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Screening of a Protein Kinase Inhibitor Library Identifies Pathways Regulating in Ureagenic Respiration by Rat Hepatocytes

Li Li[1], Robert E. Brown[1], John J. Lemasters[1,2]; [1]Departments of Drug Discovery & Biomedical Sciences, Medical University of South Carolina, Charleston, SC; [2]Institute of Theoretical and Experimental Biophysics, Pushchino, Russian Federation

Efficient detoxification of ammonia through the liver is critical to avoid ammonia accumulation in blood and prevent hepatic encephalopathy. The process of ureagenesis involves consumption of ATP and extensive exchange of molecules between the cytosol and mitochondria. In order to meet the high energy demand of ureagenesis, liver mitochondria increase O2 consumption to make ATP through oxidative phosphorylation. Here, oxygen consumption rates (OCR) by cultured rat hepatocytes were measured in a Seahorse Bioscience extracellular flux analyzer. A panel of 140 protein kinase and phosphatase inhibitors was screened to determine their effects on ureagenesis-induced mitochondrial respiration. Isolated rat hepatocytes were cultured on collagen-coated Seahorse 96-well microplates and used within 30 h. Respiration was measured in pH 7.4 Krebs-Ringer-Hepes (KRH) buffer supplemented with 5 mM NaHCO3. Inhibitors (10 μM), ureagenic substrates (3 mM NH4Cl, 5 mM ornithine and 5 mM Na-lactate) and rotenone (2 μM) were injected sequentially during measurements of OCR. Ureagenic substrates caused a 70-100% increase of OCR above rotenone sensitive basal respiration. The screening identified drug effects categorized into three main groups: 1) no change in basal respiration, no change in ureagenic respiration; 2) change in basal respiration, no change in ureagenic respiration; 3) no change in basal respiration, change in ureagenic respiration. Two groups of inhibitors in Category 3 included those affecting epidermal growth factor receptor (EGFR) and protein kinase C (PKC)-dependent pathways. EGFR inhibitors, including AG-825 (tyrosine kinase inhibitor), erbstatin and gefitinib, enhanced, whereas PKC inhibitors, including bisindolylmaleimide I, chelerythrine chloride and Gö 6983, suppressed ureagenic respiration without affecting basal respiration. Although EGF can activate PKC downstream of EGFR, our results suggest alternative pathways arising from EGFR, the elucidation of which may yield new information on the nature of the regulation of ureagenesis and mitochondrial respiration. We also found that NVP-AEW541 hydrochloride, an insulin-like growth factor-1 receptor (IGF1-R) inhibitor that blocks IGF1-R autophosphorylation, enhanced ureagenic respiration. Since Insulin can inhibit ureagenesis, this result validates our assay. In conclusion, activation of EGFR and IGF1-R inhibits ureagenic respiration, whereas PKC activation increases ureagenic respiration (NIDDK and NIAAA).

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The following people have nothing to disclose: Li Li, Robert E. Brown, John J. Lemasters

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The Gut Microbiota as a Target in T cell- mediated hepatic Injury

Birgit Schiller[1], Claudia Wegscheid[1], Laura Berkhout[1], Agnieszka E. Zarzycka[3], Ulrich Steinhoff[3], Nicole Fischer[2], Gisa Tiegs[1]; [1]Institute of Experimental Immunology and Hepatology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [2]Medical Microbiology, Virology and Hygiene, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [3]Institute for Medical Microbiology and Hygiene, University of Marburg, Marburg, Germany

Introduction The gut microbiota plays a crucial role in regulating the physiology of the host, specifically the immune system. Recent evidence suggests, that the gut microbiota is involved in liver diseases such as non-alcoholic fatty liver disease, alcoholic and viral hepatitis. However, it remains unclear whether the immunological response is modulated by the gut microbiota directly, or indirectly by its metabolites such as short chain fatty acids (SCFAs) or secondary bile salts. Both of which are important signaling molecules in the gut and in the liver. So far, little is known about the influence of gut microbiota in immune-mediated liver injury. The concanavalin A (ConA) model is a well-established mouse model of T cell mediated autoimmune hepatits. Therefore, we investigated the role of gut microbiota in ConA-induced liver injury. **Methods** Germ free C57BL/6 or broad-spectrum antibiotic treated FIRx*tiger* mice were challenged with ConA. Multiple parameters were analyzed at the initial, peak and recovery phase of ConA-mediated liver injury. Immunophenotyping was performed via flow cytometry. Microbial composition of feces was analyzed by 16S rRNA sequencing. SCFAs levels were estimated by hepatic expression levels of its receptor (e.g. GPR-43). Hepatic expression of GPR-43 as well as several regulators of bile acid metabolism were investigated by RT-PCR. The influence of SCFAs on immune cell composition was analyzed via FACS analysis after *in vitro* co-culture experiments w/o liver sinusoidal endothelial cells (LSECs). **Results** Germ free C57BL/6 as well as antibiotic treated mice were protected from ConA-induced liver injury. Antibiotic treatment reduces frequencies of $CD4^+$T cells and $IL\text{-}10^+$ regulatory T cells (Tregs) following ConA-treatment. Hepatic expression of GPR-43 was up-regulated in response to antibiotic treatment and down-regulated after ConA-challenge. The same effects was seen for cholesterol 7α-hydroxylase (Cyp7A1), which catalyzes the conversion of cholesterol to primary bile acids. The opposite effect could be determined in case of the bile acid membrane receptor TGR5. *In vitro* experiments indicate that butyrate reduces IFNγ and IL-10 production by $CD4^+$T cells in co-culture with LSECs. **Conclusion** We clearly verified a link between gut microbiota and ConA-induced liver damage. Reduction (via antibiotics) or absence (germ free mice) of gut microbiota led to ameliorated ConA-damage. This is in line with decreased Tregs in the liver, which is explained by the less severe liver damage. Our results indicate that further analysis of SCFAs and bile salt metabolism is needed to determine its specific function during pathogenesis of liver disease.

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Disparate Changes in Adaptive Immunity in Systemic vs. Portal Venous Circulation, Across the Spectrum of HCV Associated Liver Disease

Ohad Etzion[3,2], Rabab Ali[3,2], Christopher Koh[3,2], Elliot Levy[4,2], David E. Kleiner[1,2], Shakuntala Rampertaap[5,2], Sergio Rosenzweig[5,2], Varun K. Takyar[3,2], Ma Ai Thanda Han[3,2], Shilpa Lingala[3,2], Nancy Fryzek[3,2], Vanessa Haynes-Williams[3,2], Theo Heller[3,2]; [1]Laboratory of Pathology, National Cancer Institute, Bethesda, MD; [2]National Institues of Health, Bethesda, MD; [3]Liver Disease Branch, The National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; [4]Interventional Radiology, Clinical Center, Bethesda, MD; [5]Immunology Service, Clinical Center, Bethesda, MD

Background: The liver is an immune organ interposed between portal and peripheral venous circulations. Immune aberrancies including altered adaptive immune responses occur in chronic liver disease. These changes have mainly been explored in cells isolated from liver and peripheral venous blood, and their association with liver disease severity is unclear. Here, changes in T cell subset (T_{subset}) distribution in portal vs. peripheral venous blood of patients with chronic hepatitis C (cHCV) were related to disease severity. **Methods**: We prospectively studied a cohort of compensated cHCV patients. Subjects underwent percutaneous liver biopsy, direct portal vein cannulation and direct pressure (dPP) measurement. Portal and peripheral blood samples were obtained. CD4+ and CD8+ T cells were measured by multicolor flow cytometry, and categorized as naïve (CD62L+/CD45RA+), central memory (CD62L+/CD45RA-), effector memory (CD62L-/CD45RA-), or effector (CD62L-/CD45RA+) cells. Ishak fibrosis score (IF) and dPP were used as markers of liver disease severity and Spearman's rho (r) was used to correlate disease severity indicators with T_{subset} absolute counts. **Results**: Of 30 patients enrolled, 29 completed the study (mean age= 57.5, males=63.3%). IF of 0-2, 3-4 and 5-6 was found in 10, 6 and 13 patients, respectively. dPP ranged between 2-32 mm/Hg. In portal blood (n=28), CD4+ central memory T_{subset} but none of the CD8+ T_{subset}, correlated with IF (r=0.56, p=0.001). In peripheral blood (n=27), neither CD4+, nor CD8+ T_{subset} correlated with IF. With increasing dPP, portal blood derived CD4+ central memory T_{subset} trended towards significance (r=0.37, p=0.06), whereas, none of the CD8+ T_{subset} showed a significant change. Interestingly, in peripheral blood, CD4+ T_{subset} did not correlate with dPP but CD8+ effector memory T_{subset} showed a negative correlation (r= -0.38, p=0.048). **Conclusions:** CD4+ and CD8+ $T_{subsets}$ show dynamic changes across liver disease severity. Disease severity associated quantitative changes in CD8+ T_{subset} and CD4+ T_{subset} are not only distinct between portal and peripheral venous system, but the CD8+ T_{subset} changes appear to be confined to the peripheral circulation. This suggests that adaptive immune cell aberrancies in cHCV evolve with liver disease progression, and that the diseased liver contributes to these changes by affecting T cells as they transition from portal to systemic venous circulation.

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Activated Hepatic stellate cells are involved in changing the T-cell profile in chronic liver disease towards a protective phenotype

Antje Mohs[1], Nadine Hermanns[1], Kim Ohl[2], Mark V. Boekschoten[3], Thomas Longerich[4], Klaus Tenbrock[2], Francisco Javier Cubero[1], Christian Trautwein[1]; [1]Department of Medicine III, University Hospital RWTH Aachen, Aachen, Germany; [2]Department of Pediatrics, University Hospital RWTH Aachen, Aachen, Germany; [3]Nutrigenomics Consortium, TI Food & Nutrition, Wageningen, Netherlands; [4]Institute of Pathology, University Hospital RWTH Aachen, Aachen, Germany

Background & Aims: Hepatocellular carcinoma (HCC) is often based on chronic inflammation and a malignant transformation of hepatocytes, resulting in liver fibrogenesis. In this process, subsets of CD4+ T helper (Th) cells are involved, mediating pro-inflammatory (TH17) or anti-inflammatory (T regulator (Treg)) effects. T-cell specific overexpression of the cyclic adenosine monophosphate-responsive element modulator alpha (CREMα) was previously described to dispose T-lymphocytes towards a Th17 phenotype in models of systemic lupus erythematosus or lung inflammation. Additionally, an increased Th17 response is associated with a poor prognosis in patients with chronic liver disease (CLD). Therefore we investigated the relevance of Th17 cells for CLD and its implications for hepatocellular carcinoma (HCC). **Methods**: Transgenic mice overexpressing CREMa were crossed with hepatocyte-specific Nemo knockout mice ($Nemo^{\Delta hepa}$) to generate $Nemo^{\Delta hepa}$/$CREMa^{Tg}$ mice. The impact of $CREMa^{Tg}$ T-cells on $Nemo^{\Delta hepa}$ mediated CLD progression was examined. To proof the impact of $CREMa^{Tg}$ T cells, adoptive transfer of bone marrow derived cells (BMDCs) and T-cells was performed. For a comprehensive analysis of T-cell phenotype NanoString Technology™ and FACs analysis were included. **Results:** Overexpression of CREMα in T-cells of $NEMO^{\Delta hepa}$ mice diminished serum transaminase levels, associated with reduced numbers of infiltrating CD11b+ dendritic cells and CD8+ T-cells. As a consequence fibrosis and HCC development was significantly reduced. Simultaneous adoptive transfer of BMDCs and T-cells from $CREM\alpha^{Tg}$ into $Nemo^{\Delta hepa}$ mice clearly identified $CREM\alpha^{Tg}$ T-cells as essential for improving the course of CLD. Surprisingly, in this scenario, $CREM\alpha^{Tg}$ T-cells didn't show a Th17 phenotype with IL-17 production and expression of the linage marker RORγT. In contrast, hepatic T-cells were characterised by the expression of Treg-related markers like FOXP3, CTLA4 and TIM3. *In vitro*, $CREM\alpha^{Tg}$ T-cells stimulated with TGFβ and retinoic acid (RA) containing supernatant of activated HSCs, were polarised towards an anti-inflammatory Treg phenotype. Mechanistically, administration of a specific retinoic acid receptor (RAR)α inhibitor reduced FOXP3+ Treg polarisation. These findings reveal that $CREM\alpha^{Tg}$ T-cells are a prerequisite for inducing FOXP3+ Tregs. **Conclusion:** Our results demonstrate that overexpression of CREMα in T-cells changes the inflammatory milieu, attenuating initiation and progression of CLD. Unexpected, our study demonstrates that CREMα transgenic T-cells induced by HSCs shift chronic inflammation in $Nemo^{\Delta hepa}$ livers towards a protective Treg response.

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Christian Trautwein - Advisory Committees or Review Panels: Abbvie, MSD, BMS, Gilead, Bayer, AstraZeneca; Speaking and Teaching: Falk, MSD, Abbvie, BMS, Gilead

The following people have nothing to disclose: Antje Mohs, Nadine Hermanns, Kim Ohl, Mark V. Boekschoten, Thomas Longerich, Klaus Tenbrock, Francisco Javier Cubero

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Bacteria stimulate the secretion of chemokines and Th-17 polarising cytokines that may support local Th-17 responses in bile duct injury

Hannah C. Jeffery[1], Ricky H. Bhogal[1], Jane Birtwistle[2], Solomon Brown[1], Simon C. Afford[1], David H. Adams[1], Ye H. Oo[1]; [1]Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, United Kingdom; [2]Clinical Immunology, University of Birmingham, Birmingham, United Kingdom

Background. IL-17 secreting CD4 T cells (Th17) have been implicated in autoimmunity and inflammatory disease and provide a link between the innate and adaptive immune responses. IL-17-producing T cells are present around bile ducts, but their functional role and mechanism of localization is poorly understood. **Methods.** Primary human cholangiocytes were assessed for their chemokine and cytokine secretion in response to bacterial products and pro-inflammatory cytokines including IL-17. The effect of cholangiocytes on CD4 T cell differentiation and stability was assessed using cholangiocyte-conditioned media stimulated with or without IL17, TNFα and IFNγ. **Results:** E.coli and LPS treatment of cholangiocytes stimulated CCL20 secretion that was able to attract CCR6+ Th17 cells in in-vitro migration assays. Cholangiocytes secreted Th17 polarizing cytokines including IL1β, TGFβ and IL-6 when treated with IL-17 and CD4 cells showed evidence of polarisation to Th17 cells when co-cultured over 7 days with TNFα and IFNγ stimulated or IL-17 stimulated cholangiocyte supernatant. IL-17 treatment induced Stat3 dependent proliferation of cholangiocytes but no increase in ICAM-1 or VCAM-1 expression. IL-17 treatment also induced cholangiocytes to secrete IL-8 and MCP-1, which could be responsible for the recruitment of neutrophils and macrophages around the bile ducts. **Conclusions.** Cholangiocytes respond to IL-17 by proliferating and secreting Th17 polarizing cytokines, which favours the maintenance of Th17 lineage in infiltrating CD4 T cells. The secretion of CCL20 and IL-17 polarising cytokines by cholangiocytes in response to LPS and E coli suggests that the presence of bacteria or their products in inflamed portal tracts may contribute to the maintenance of this polarising microenvironment.

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The following people have nothing to disclose: Hannah C. Jeffery, Ricky H. Bhogal, Jane Birtwistle, Solomon Brown, Simon C. Afford, Ye H. Oo

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Enhanced expression of activation-induced cytidine deaminase in memory B cells provokes skewed immunoglobulin profile in advanced cirrhosis

Hiroyoshi Doi[1,2], David E. Kaplan[3], Kenichi Morikawa[4], Junichi Eguchi[5], Takayoshi Ito[5], Tatsuya Kanto[1], Hitoshi Yoshida[2]; [1]National Center Global Health and Medicine, Ichikawa, Japan; [2]Showa University, Shinagawa, Japan; [3]University of Pennsylvania, Philadelphia, PA; [4]Hokkaido University, Sapporo, Japan; [5]Showa University Koto Toyosu hospital, Toyosu, Japan

Background/Aim: It is clinically evident that patients with chronic liver disease have increased immunoglobulins compared to healthy subjects. Regardless of such conditions, patients with liver cirrhosis are immune-compromised, whose risk of severe bacterial infection is increased according to the progression of Child-Pugh status. We previously reported that peripheral CD27+ memory B-cell frequency and functions are significantly decreased in cirrhotic patients. (Hepatology 2012) We hypothesized that the dysregulation of B cell differentiation, viability and function is involved in the excessive production of "futile" immunoglobulins. We thus aimed to clarify B cell function in patients with wide range of liver diseases by analyzing the profile of serum immunoglobulin subtypes and B cell gene signatures. Method: We retrospectively analyzed IgG, IgA and IgM levels in 527 patients with liver diseases from our medical records and classified depending on etiology and Child-Pugh score. The five etiological groups are; HCV, HBV, alcohol, NAFLD and the others. Patients with autoimmune hepatic disease (AIH and PBC) were excluded. Using cryopreserved serum, we also performed the immunoglobulin isotyping with Bioplex system. We measured the mRNA levels of activation markers by real-time PCR in isolated CD27+ memory B-cells recovered from cirrhotic patients and healthy subjects. In addition, we examined the expression of activation-induced cytidine deaminase (AID), crucial for class-switch recombination and somatic hypermutation during plasma cell differentiation. Results: Cirrhotic patients have elevated serum IgG and IgA regardless of underlying etiologic change. Also, the IgG and IgA levels increased in the progression of Child-Pugh stage. Patients with advanced cirrhosis (Child-Pugh B and C) tend to have increased IgG1 frequency (p=0.0016), while relative decrease of IgG2 compared to healthy donors (HD) (p=0.0048). The expression of activation markers of memory B-cell (CD69, CD71, CD80, CD86) in the cirrhosis group was comparable with that in HD. However, AID level in memory B-cell was increased in cirrhotic patients compared to those in HD (p=0.0367). Conclusions: Cirrhotic patients with wide range of etiology show increased immunoglobulin status. Enhanced expression of AID in memory B cells and disproportional immunoglobulin profile may account for the "futile" immunoglobulin status of advanced cirrhosis.

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The following people have nothing to disclose: Hiroyoshi Doi, Kenichi Morikawa, Junichi Eguchi, Takayoshi Ito, Tatsuya Kanto, Hitoshi Yoshida

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Processing of the phagocytic cargo shapes T-cell response within the fibrotic liver

Lara Campana[1,3], Sarah E. Mok[2], Antonella Pellicoro[1], Stuart J. Forbes[2,3], John P. Iredale[4]; [1]Centre for Inflammation research, University of Edinburgh, Edinburgh, United Kingdom; [2]University of Edinburgh, Edinburgh, United Kingdom; [3]Centre for Regenerative Medicine, University of Edinburgh, EH16 5UU, United Kingdom; [4]University of Bristol, Bristol, United Kingdom

The interplay between macrophages and T cells shapes the inflammatory response. An appropriate balance of T cells is essential for the resolution of fibrosis as shown in model of organ rejection after transplantation. T-cell polarisation results after antigen presentation from professional antigen-presenting cells to CD4+ T helper lymphocytes. We induced chronic liver fibrosis by carbon tetrachloride injection in mice with defective of the last step of phagocytosis and in their wild-type counterparts. Our hypothesis is that phagocytosis is instrumental for both antigen presentation and the set-up of a correct cytokine environment for the correct T cell polarisation to occur. Increased damage was observed in mice lacking phagocytic cargo digestion, altogether with an imbalance in macrophage polarisation, tipped to a pro-inflammatory phenotype. Those findings prompted us to investigate the CD4+ T-cell response. In order to investigate it, livers were harvested at distinct time

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The interplay between macrophages and T cells shapes the inflammatory response. An appropriate balance of T cells is essential for the resolution of fibrosis as shown in model of organ rejection after transplantation. T-cell polarisation results after antigen presentation from professional antigen-presenting cells to CD4+ T helper lymphocytes. We induced chronic liver fibrosis by carbon tetrachloride injection in mice with defective of the last step of phagocytosis and in their wild-type counterparts. Our hypothesis is that phagocytosis is instrumental for both antigen presentation and the set-up of a correct cytokine environment for the correct T cell polarisation to occur. Increased damage was observed in mice lacking phagocytic cargo digestion, altogether with an imbalance in macrophage polarisation, tipped to a pro-inflammatory phenotype. Those findings prompted us to investigate the CD4+ T-cell response. In order to investigate it, livers were harvested at distinct time

points after CCl4 suspension. Analysis was carried on using qPCR and immunohistochemistry on total liver extract and liver sections respectively. This study shows that in the absence of a correct phagocytic cargo digestion an impaired Th2 response results. Defect in the production of Th2-related cytokines such as IL4 was observed in homeostatic conditions also (Il4 mRNA expression in untreated mice lacking phagocytic cargo processing *vs.* wild type mice: -4 to 5 fold), possibly pointing out to a general defect in the Th2 polarisation (Gata3 mRNA expression untreated mice lacking phagocytic cargo processing *vs.* wild type mice: -2 fold). Also, more proliferation in the non-parenchymal compartments was observed in mice lacking the last step of phagocytosis at 72h of recovery (Ki67 immunohistochemistry, 9±2 vs. 12±2 cells/field of view, 20x magnification, n=5-7 mice/group). Further investigation is required to determine the mechanism in which phagocytosis acts on the Th2 response and whether a defective phagocytosis correlates with an uncontrolled expansion of specific T-cell subtypes in the regenerating liver. Understanding the dynamics that control this relationship may have great impact on the elucidation of novel potential therapeutic targets in the scarring process.

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The following people have nothing to disclose: Lara Campana, Sarah E. Mok, Antonella Pellicoro, Stuart J. Forbes, John P. Iredale

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The role of CD151 in hepatic inflammation during chronic liver disease and HCC

Daniel A. Patten, James C. Wadkin, Sivesh K. Kathir Kamarajah, Chris J. Weston, Shishir Shetty; Centre for Liver Research, University of Birmingham, Birmingham, United Kingdom

Introduction: Unregulated inflammation of the liver drives the onset and progression of a range of aetiologically diverse chronic liver diseases and, ultimately, promotes the formation of neoplastic tumours, such as hepatocellular carcinomas (HCC). A key step in hepatic inflammation is the recruitment of leukocytes via hepatic sinusoidal endothelial cells (HSEC). CD151, a member of the tetraspanin family, has previously been shown to play a role in leukocyte recruitment to vascular endothelia; however, the presence of CD151 has not previously been explored in the hepatic sinusoidal endothelium. Consequently, an understanding CD151 expression and function in the liver could identify a new therapeutic target for limiting hepatic inflammation. **Methods:** We used immunohistochemistry, dual colour immunofluorescence co-localisation studies, qRT-PCR and western blotting to determine the cell-specific expression of CD151 in normal liver, chronic liver diseases and HCC. qRT-PCR and cell-based ELISA studies were used to determine the regulation of CD151 expression in HSEC by growth factors, proinflammatory cytokines and hepatoma cell line (HepG2) supernatant. Flow-based adhesion assays were used to study the functional role of CD151 in the adhesion of Jurkat cells, a human T cell line, to HSEC monolayers. **Results:** Increased CD151 protein expression was associated with areas of fibrosis and neovascularisation, particularly in parenchymal liver diseases, such as alcoholic liver disease (ALD) and non-alcoholic steatohepatitis (NASH), as well as in HCC. CD151 was shown to be highly expressed by HSEC *in vivo* and expression was maintained in cultured HSEC *in vitro*. The expression of CD151 in HSEC was upregulated by stimulation with HepG2 supernatant and tumourigenic growth factors, such as hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF). We also found CD151 molecules clustering around adherent T cells following capture from physiological flow by HSEC monolayers. Furthermore, function-blocking antibodies to CD151 significantly reduced adherence of T cells under flow conditions. **Conclusion:** We demonstrate, for the first time, the expression of CD151 on human sinusoidal endothelial cells and neovessels in a range of chronic liver diseases and HCC. We also demonstrate that CD151 in HSEC is maintained *in vitro* and can be upregulated by pro-tumourigenic factors and plays an important functional role in T cell adhesion to HSEC. Taken together, these findings further our understanding of hepatic inflammation and lymphocyte recruitment to the liver, during chronic disease and carcinogenesis, and could form the basis of a potential therapeutic target.

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Health gains and costs of HCV treatment: a cost effectiveness analysis of two different health policies scenarios simulated in PITER (Piattaforma Italiana per lo studio della Terapia delle Epatiti viRali) real life cohort.

Loreta A. Kondili[31], Federica Romano[12], Matteo Ruggeri[12], Stefano Rosato[31], Maurizia R. Brunetto[1], Anna Linda Zignego[2], Alessia Ciancio[6], Alfredo Di Leo[7], Giovanni Raimondo[8], Carlo Ferrari[5], Gloria Taliani[10], Guglielmo Borgia[26], Teresa A. Santantonio[3], Pierluigi Blanc[4], Giovanni B. Gaeta[11], Antonio Gasbarrini[12], Luchino Chessa[13], Elke M. Erne[14], Erica Villa[15], Donatella Ieluzzi[16], Francesco P. Russo[17], Pietro Andreone[18], Maria Vinci[20], Carmine Coppola[19], Liliana Chemello[14], Salvatore Madonia[21], Gabriella Verucchi[22], Marcello Persico[23], Massimo Zuin[24], Massimo Puoti[25], Alfredo Alberti[14], Gerardo Nardone[26], Vincenzo De Maria[27], Marco Massari[28], Giuseppe Montalto[9], Giuseppe Foti[29], Maria G. Rumi[30], Americo Cicchetti[12], Antonio Craxi[9], Stefano Vella[31]; [1]Azienda Ospedalero-Universitaria Pisana, Pisa, Italy; [2]University of Florence, Florence, Italy; [3]University of Foggia, Foggia, Italy; [4]Ospedale Santa Maria Annunziata, Florence, Italy; [5]Azienda Ospedaliero-Universitaria di Parma, Parma, Italy; [6]University of Turin, Turin, Italy; [7]University of Bari, Bari, Italy; [8]University Hospital of Messina, Messina, Italy; [9]University of Palermo, Palermo, Italy; [10]Sapienza University of Rome, Rome, Italy; [11]Second University of Naples, Naples, Italy; [12]Catholic University, Rome, Italy; [13]University of Cagliari, Cagliari, Italy; [14]University of Padua, Padua, Italy; [15]University of Modena and Reggio Emilia, Modena, Italy; [16]Azienda Ospedaliero Universitaria di Verona, Verona, Italy; [17]University Hospital of Padua, Padua, Italy; [18]University of Bologna, Bologna, Italy; [19]Gragnano Hospital, Naples, Italy; [20]Niguarda Hospital, Milan, Italy; [21]V.Cervello Hospital, Palermo, Italy; [22]Alma Mater Studiorum University of Bologna, Bologna, Italy; [23]University of Salerno, Salerno, Italy; [24]University of Milan, Milan, Italy; [25]Niguarda Ca' Granda Hospital, Milan, Italy; [26]University of Naples Federico II, Naples, Italy; [27]University Hospital Catanzaro, Catanzaro, Italy; [28]ASMN Reggio Emilia, Reggio Emilia, Italy; [29]Bianchi Malacrino-Morelli Hospital, Reggio Calabria, Italy; [30]Fondazione Ospedale Maggiore Policlinico IRCCS, University of Milan, Milan, Italy; [31]Istituto Superiore di Sanità, Rome, Italy

Background and aims: New DAA treatments for HCV infection are highly efficacious, yet costly. Nevertheless, it is time to move from treating selected prioritized patients to strategies that include treatment of all HCV infected patients. To this end a lifetime multi-cohort model of 8125 real life HCV infected patients, enrolled in the PITER cohort was used to compare two IFN free treatment's policies. **Policy 1**:**Treat all patients** of the cohort in any fibrosis stage(F0-F4)**. Policy 2**: **Treat first**: patients who are prioritized by the EASL HCV Clinical Practice Guidelines 2015; **Wait and treat**: the remaining patients when

they would reach the F3 stage. Dynamic lifetime HCV disease progression and the related costs were evaluated adapting a Markov model in a lifetime horizon from a health care system perspective. Each real life patient entered the model at the proper age and fibrosis stage and was followed in the model over a lifetime. Total medical costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs) were evaluated. Probabilistic and scenario analyses were performed. **Results:** In the base-case analysis (base price of HCV regimen: € 15,000), treating all fibrosis stages vs treating the prioritized patients first, adds: € 31,083,475 (incremental costs) and 3,497 incremental QALYs, for an ICER of € 8,893 per QALY gained. The Monte Carlo scenarios (10,000 simulations) were arranged on a cost-effectiveness plot and then reported on a cost-effectiveness acceptability curve (CEAC). ICERs (incremental costs by the incremental QALYs between Policy 1 vs Policy 2) remain cost effective (below € 40,000/QALY) in 91 % of the simulations assumed. In the scenario analysis, different ICERs were calculated for fourteen prices' combinations, differentiated by fibrosis staging and the discount rate. The base price of IFN-free treatment regimen (€ 15,000), remained unvaried on time for patients with moderate to severe liver disease stage, whereas decreasing combinations of discount prices in patients with F1/F2 and F0 stage were applied. ICER was very sensitive at price variations for patients at F0 stage. For the price levels lower than 60% and 70% of the base price, applied in patients with F1/F2 and F0 respectively, the Policy 1 resulted to be dominant (less costs and greater benefits than Policy 2); policy 1 become cost effective in 97% of the simulations and dominant in 40% of them by the sensitivity analysis. **Conclusion:** Treating HCV infection at any fibrosis stage appeared to improve health outcomes and to be cost-effective. Cost effectiveness increases significantly lowering the treatment's prices in early fibrosis stages.

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Maurizia R. Brunetto - Advisory Committees or Review Panels: Schering-Plough, Gilead, Janssen, AbbVie; Speaking and Teaching: Roche, Gilead, Bristol-Myers Squibb, Abbott, Roche, Janssen

Alfredo Di Leo - Advisory Committees or Review Panels: THD; Speaking and Teaching: Abbvie, MSD, Gilead, Roche, Italfarmaco

Giovanni Raimondo - Speaking and Teaching: BMS, Gilead, Roche, Merck, Janssen, Bayer, MSD

Carlo Ferrari - Advisory Committees or Review Panels: Gilead, Roche, Abbvie, BMS, Merck, Arrowhead; Grant/Research Support: Gilead, Roche, Janssen

Gloria Taliani - Advisory Committees or Review Panels: AbbVie, Janssen, Gilead, BMS, Merck, Roche; Speaking and Teaching: ROCHE, Merck, BMS, Gilead, Jannsen, AbbVie

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Giovanni B. Gaeta - Advisory Committees or Review Panels: Janssen, Merck, Abbvie, Roche; Speaking and Teaching: BMS, Gilead, merck

Luchino Chessa - Board Membership: Abbvie; Speaking and Teaching: BMS, Jannsen

Erica Villa - Advisory Committees or Review Panels: MSD, Abbvie, GSK, Gilead; Speaking and Teaching: Novartis

Pietro Andreone - Advisory Committees or Review Panels: Janssen-Cilag, Gilead, MSD/Schering-Plough, Abbvie, Intercept; Speaking and Teaching: Gilead, BMS

Gabriella Verucchi - Advisory Committees or Review Panels: Gilead, Abbvie, Janssen, ViiV; Speaking and Teaching: Merck&Co, Gilead, Bristol Meyers Squibb, Abbvie

Marcello Persico - Advisory Committees or Review Panels: abbvie; Grant/Research Support: gilead

Massimo Zuin - Board Membership: Abbvie; Speaking and Teaching: Roche

Massimo Puoti - Advisory Committees or Review Panels: GSK, Abbott, Janssen, MSD, Roche, Gilead Sciences, Novartis, GSK, Abbott, Janssen, MSD, Roche, Gilead Sciences, Novartis, GSK, Abbott, Janssen, MSD, Roche, Gilead Sciences, Novartis, GSK, Abbott, Janssen, MSD, Roche, Gilead Sciences, Novartis; Speaking and Teaching: BMS, BMS, BMS, BMS

Alfredo Alberti - Advisory Committees or Review Panels: Merck, roche, Gilead, Merck, roche, Gilead, Merck, roche, Gilead, Merck, roche, Gilead, Abbvie, Janssen; Grant/Research Support: Merck, gilead, Merck, gilead, Merck, gilead, Merck, gilead, Abbvie, Janssen; Speaking and Teaching: novartis, BMS, novartis, BMS, novartis, BMS, novartis, BMS

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WITHDRAWN

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Risk of incident liver cancer following HCV treatment with sofosbuvir-containing regimens

Anand P. Chokkalingam[1,2], Amanda W. Singer[1], Anu O. Osinusi[3], Diana M. Brainard[3], Laura Telep[1]; [1]Epidemiology, Gilead Sciences, Foster City, CA; [2]School of Public Health, University of California, Berkeley, Berkeley, CA; [3]Clinical Research, Gilead Sciences, Inc., Foster City, CA

Background Curative HCV treatment with IFN-based regimens has been associated with reduction in the rate of HCV-associated liver cancer. Whether achieving sustained virologic response following treatment with IFN-free direct-acting antiviral (DAA)-based regimens yields a similar benefit is unknown. The objective of this study was to examine the association of treatment completion with the DAA sofosbuvir (SOF) with risk of incident liver cancer in real-world data. **Methods** From US administrative claims data from January 1, 2010 through March 31, 2015, we identified adult HCV patients dispensed at least 12 weeks of SOF-containing therapy who had no evidence of subsequent HCV treatment (N=5,033). For comparison, we identified adult patients diagnosed with HCV without evidence of HCV treatment who had active follow-up time after SOF approval (N=69,374). All included patients had a minimum of 6 months of enrollment and no evidence of prior liver cancer at baseline. Hazard ratios (HRs) estimating risk of incident liver cancer associated with completion of SOF-containing therapy were calculated after adjustment for baseline confounders using Cox proportional hazards methods. **Results** Patients completing SOF-containing treatment were more likely to be >55 years and male, and to have cirrhosis at baseline (34.7% vs. 11.5%), than untreated HCV patients; median follow-up was shorter in SOF-completing vs. untreated patients (171 and 328 days, respectively). When stratified by baseline cirrhosis status, absolute cumulative incidence rates (95% confidence interval [CI]) were not different between SOF-completing and untreated patients: 0.77 (0.40-1.35) and 0.67 (0.60-0.75) per 100 person-years (PY), respectively among non-cirrhotics, and 3.24 (2.15-4.68) and 3.67 (3.21-4.17) per 100 PY, respectively among cirrhotics. There was no significant interaction of observed treatment effect with baseline cirrhosis (p=0.53). After adjustment for age, gender, cirrhosis, and other baseline conditions significant at p<0.10, no association was observed between SOF completion and liver cancer (HR=0.96, 95% CI: 0.69-1.34). This absence of association was observed for both IFN-free and IFN-containing SOF treatment regimens (HR=1.01 (95% CI: 0.69-1.49) and 0.87 (95% CI: 0.49-1.53), respectively). **Conclusions** In this real-world cohort study, completion of SOF-containing treatment was not independently associated

with risk of incident liver cancer, regardless of IFN co-medication. The strongest risk factors for liver cancer were baseline cirrhosis, older age, and male gender. Future cohort studies should examine longer-term liver cancer risk following completion of DAA therapy.

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Anu O. Osinusi - Employment: Gilead Sciences Inc; Stock Shareholder: Gilead Sciences Inc

Diana M. Brainard - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

Laura Telep - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

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Inter-genotypic recombinant HCV virus in Israel: prevalence and clinical implication

Mira Barak[1], Rasha N. Daniel[1,2], Orly Azulay[3], Eli Zuckerman[3]; [1]Haifa and Western Galilee Central Laboratories, Clalit Health Services, Nesher, Israel; [2]Faculty of Public Health, Haifa University, Haifa, Israel; [3]Liver Unit, Carmel Medical Center, Haifa, Israel

Background and Aims: The HCV recombinant strain (St. Petersburg variant) has been reported from several countries but its prevalence (0.5-2%) may be underestimated by the vast majority of the standard genotyping assays which are based only on the 5'(core) sequencing. So far there was no data on this recombinant virus in Israel. The clinical importance of this HCV recombinant genotype lies upon its being mistakenly identified and treated as genotype G2, a treatment which is insufficient for G1 genotype. In this study we report the first cases of recombinant strain 2/1b in Israel. An additional aim was to assess the ability of the Abbott RealTime HCV genotype II RUO (GTII) assay to detect this recombinant strain in comparison to sequence-based analyses. **Methods:** 661 stored sera samples of chronic HCV patients (viral load >10^4 unit/ml) were tested at the Central Laboratory of Haifa and Western Galilee, Clalit Health Services (2014-2015). HCV genotyping was performed in all samples using the Abbott GTII commercial kit according to the manufacturer instructions. The Abbott GTII assay amplifies and detects portions of both the 5'(core) and 3'(NS5B) regions. The samples in which 2/1b recombinant strain was detected, were further analyzed by sequence-based analyses. **Results:** Genotype distribution: G1: 441 (66.7%) [G1a 100 (15.1%), G1b 341 (51.6%)], G2: 33 (5%), G3: 155 (23.4%) and G4: 21 (3.2%) Additional 11 samples (25% of G2! and 1.7% of all 661 sera) were diagnosed as a 2/1b recombinant strain. Nine of these 11 patients were immigrants born in the former USSR. The mean age was 42 year old. Sequence-based analyses performed on 4 of these 11 samples showed that these samples are indeed recombinant genotypes 2k/1b chimera with the breaking point between NS2 and NS3. In the meanwhile, the follow -up of these patients revealed two patients who relapsed after 24 weeks of Peg/IFN therapy and other two patients showed no response. SVR was obtained in one patient after 12 weeks daclatasvir / sofosbuvir therapy. The other patients are ongoing treated by DAAs. **Conclusions:** We have found that the rate of recombinant HCV 2/1b is 1.7% of all HCV genotypes and 25% of G2 genotype tested in this study. Awareness should be raised to this possibility in patients who were identified as G2 HCV patients and it is recommended to use genotyping assays which amplify both the 5'(core) and 3'(NS5B) regions of the HCV genome. The presence of a recombinant virus may affect the outcome of the antiviral treatment.

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The following people have nothing to disclose: Mira Barak, Orly Azulay, Eli Zuckerman

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Prognostic impact of Hepatitis B and C infections in kidney recipients: control of viral replication improves patient and graft survival

Hélène Fontaine[2], Laurent Alric[3], Benjamin Legendre[1], Julien Labreuche[4], Alexandre Louvet[1], Corinne Antoine[5], Christophe M. Legendre[6], Marc Hazzan[7], Nassim Kamar[3], Sebastien Dharancy[1], Guillaume Lassailly[1], Florent Artru[1], Stanislas Pol[2], Alain Duhamel[4], Philippe Mathurin[1]; [1]Maladies de l'appareil digestif, Hôpital Huriez, Lille, France; [2]Hôpital Cochin, Paris, France; [3]Hôpital Purpan, Toulouse, France; [4]Departement de biostatistiques, Lille, France; [5]Agence de la biomedecine, Paris, France; [6]Hôpital Necker, Paris, France; [7]Hôpital Huriez, Lille, France

In kidney transplantation, before the use of antiviral therapy, HBV and HCV recipients had lower patient and graft survival than non-infected recipients. In the last two decades, nucleos(t)id analogues have been widely used for HBV patients whereas IFN-based therapy has been used for smaller proportion of HCV patients. **Aims**: 1/ to update the impact of HBV and HCV on patient and graft survival; 2/ to assess the prognostic impact of viral control (HBV or HCV). **Methods**: First, patients and graft survivals were prospectively recorded between 1993 and 2010 in the French nationwide database of kidney recipients according to serological status. Second, we calculated, based on a type I error of 0.05 and a power of 95% that a random sample of at least 580 HBV or HCV patient records should be investigated to evaluate the influence of viral control. Viral control was defined as: low DNA level upon antiviral therapy or inactive carriers for HBV patients; SVR or spontaneous viral eradication for HCV recipients. **Results:** A/ 32307 recipients, median age (47.4±14.6 years) were analyzed: 1109 (3.43 %) with positive HCV antibodies, 596 (1.84%) with positive HBsAg and 30602 (94.72 %) non infected patients. HCV kidney recipients had significantly lower 10-year patient survival (71.1±2%) than HBV (81.1±2%, p<0.0001) and non-infected recipients (84.2±3%, p<0.0001) without significant differences between HBV and non-infected recipients. They also had significantly lower 10-year graft survival (50.6±1.9%) than HBV (62.3±2.4%, p=0.0001) and non-infected (66.8.2±0.3%, p<0.0001). After adjustment on age of recipients, age of donors, time of cold ischemia, extent of HLA-B and DR matching, HCV antibodies remained an independent prognostic factor of 10-year mortality (HR :1,75; 95%CI :1.48-2.1, p<0.0001). B/ 687 patient records have been investigated. Viral control was obtained in almost all HBV recipients (95% of cases). In HCV patients, viral control was observed in 35% of cases among which 17.6% after antiviral therapy. In HCV patients, patients with viral control had higher 10-year patient (84.4±4.6% vs 68±4%, p=0.003) and graft (63.1±5.46% vs 48±3.7%, p=0.003) than those without. In multivariate analysis, HCV infection remained independently associated with mortality only in case of viral replication whereas HCV recipients with negative PCR had similar patient and graft survival than non-infected patients. **Conclusion**: Control of viral replication allows obtaining similar patient and graft survival in HBV and HCV recipients in comparison to non-infected recipients. Conversely, uncontrolled HCV infection is still associated with a decrease in patient and graft survival.

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Hélène Fontaine - Board Membership: Abbvie, Gilead, BMS, Janssen; Independent Contractor: gilead, BMS, MSD, Roche, Janssen

Laurent Alric - Board Membership: Schering Plough, Schering Plough, Schering Plough, Schering Plough; Consulting: MSD; Grant/Research Support: Abbvie; Speaking and Teaching: Roches, BMS, Gilead, Roches, BMS, Gilead, Roches, BMS, Gilead, Roches, BMS, Gilead, MSD, Abbvie

Stanislas Pol - Board Membership: Bristol-Myers-Squibb, Boehringer Ingelheim, Tibotec Janssen Cilag, Gilead, Glaxo Smith Kline, Roche, MSD, Novartis; Grant/Research Support: Gilead, Roche, MSD; Speaking and Teaching: Bristol-Myers-Squibb, Boehringer Ingelheim, Tibotec Janssen Cilag, Gilead, Roche, MSD, Novartis

Philippe Mathurin - Board Membership: MSD, Janssen-Cilag, BMS, Gilead, Abvie, Verlyx; Consulting: Roche, Bayer

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Comparing Child-Pugh, MELD and FIB-4 Scores to Predict Mortality, Hepatic Decompensation and Hepatocellular Carcinoma in HCV Infected Persons: ERCHIVES Study

Adeel A. Butt[1], Yanjie Ren[2]; [1]Division of Infectious Diseases, Weill Cornell Medical College, Mars, PA; [2]VA Pittsburgh Healthcare System, Pittsburgh, PA

Background: A relatively small proportion of HCV infected persons develop hepatic decompensation and hepatocellular carcinoma even after several years of infection. Predicting who will develop complications can help prioritize treatment decisions. Methods: In the ERCHIVES We calculated three commonly used clinical scores for liver disease severity to determine the risk of overall mortality, hepatic decompensation (HD) and hepatocellular carcinoma (HCC) 1, 3 and 5 years after diagnosis of HCV. We excluded those with HD or HCC at baseline, HIV+ or HBsAg+ and those who received HCV treatment for >28 days. Results: Among 21,327 HCV infected persons identified, <1% of those with lowest CP, MELD or FIB-4 scores develop HD, HCC or died within 1 year of HCV diagnosis. However, the proportion increases 3-6 fold for the next stratum of the score at year one and 3 fold at year 3 for the same stratum. Mortality, HD and HCC are highest in the higher strata and 5 years after diagnosis. **(Table)** Conclusions: Mortality and complications are infrequent in the first year after HCV diagnosis in persons with low liver disease severity scores, but exponentially increase with increasing time or increasing severity scores. These data may help determine the optimal time to initiate treatment to minimize mortality and liver disease complications.

Table. Proportion of persons who died, developed hepatic decompensation or hepatocellular carcinoma 1, 3 and 5 years after diagnosis of HCV infection in ERCHIVES.

	% in group N=21,327	Overall mortality %			Hepatic decompensation %			Hepatocellular Carcinoma, %		
		Year 1	Year 3	Year 5	Year 1	Year 3	Year 5	Year 1	Year 3	Year 5
Child-Pugh										
Class A	89.5	0	3.89	9.01	0.97	3.37	5.46	0.36	1.54	2.48
Class B	10.3	0	14.78	26.76	6.56	16.20	19.92	1.15	3.99	5.78
Class C	0.2	0	25.00	38.46	15.38	42.31	51.92	7.69	13.46	15.38
MELD:										
<9	79.5	0	3.42	8.10	0.84	2.95	4.91	0.33	1.45	2.30
10-19	16.9	0	11.09	20.95	5.04	13.18	16.88	1.00	3.57	5.46
20-29	3.0	0	13.13	26.74	1.27	5.54	8.39	0.79	1.90	2.85
30-39	0.6	0	12.40	22.31	2.48	6.61	7.44	0	1.65	1.65
>=40	0.06	0	8.33	8.33	16.67	25.00	25.00	0	0	8.33
FIB-4:										
<1.45	43.1	0	2.71	6.71	0.16	0.65	1.07	0.03	0.20	0.36
1.46-3.25	35.9	0	4.28	9.56	0.52	2.27	4.11	0.34	1.32	2.17
>3.25	21.0	0	11.17	21.80	6.30	17.53	24.36	1.52	6.01	9.11

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The following people have nothing to disclose: Yanjie Ren

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Elevated HCV reinfection incidence after successful treatment among HIV-infected men who have sex with men in San Diego

Antoine Chaillon[1], Natasha K. Martin[3], Thomas C. Martin[4], David L. Wyles[1], Davey M. Smith[1], Sanjay R. Mehta[1], Craig Ballard[2], Bradford Colwell[2], Francesca Torriani[1], Lucas Hill[2], Christopher Mathews[1], Charles Hicks[1], Edward R. Cachay[1]; [1]Division of Infectious Diseases, University of California San Diego, LA JOLLA, CA; [2]Skaggs School of Pharmacy, University of California San Diego, La Jolla, CA; [3]Division of Global Public Health, University of California San Diego, La Jolla, CA; [4]School of Medicine, University of California San Diego, La Jolla, CA

Background: High rates of Hepatitis C (HCV) reinfection following successful treatment among HIV-infected men who have sex with men (MSM) have been reported in Europe, but no data are available from the US. We assessed the incidence of primary HCV infection and reinfection following successful treatment among HIV positive MSM in San Diego. **Methods:** We performed a retrospective cohort analysis of HCV primary incidence and reinfection incidence after successful treatment among HIV-infected MSM during 2008-2016 at the largest HIV clinic in San Diego (UCSD Owen Clinic). Incident HCV infection was assessed among HIV-infected MSM with a negative anti-HCV test between 2008 and 2016, and defined as any positive anti-HCV or HCV-RNA test after the start of follow-up. Re-infection was defined as a positive HCV RNA PCR test after the date of sustained viral response (SVR) among HIV/HCV-coinfected MSM treated for HCV between 2008 and 2014. For the re-infection analysis patients were censored at reinfection or their last negative test before April 2016. Incidence was calculated using survival time methods. **Results:** Among 1,092 baseline negative patients between 2008 and 2016, 40 seroconversions occurred over 3,4340 person-years at risk, leading to an overall primary HCV incidence of 1.16 per 100 person-years(/100py) (95%CI 0.85,1.59). During this same time period, among 43 HIV-infected MSM who achieved SVR following HCV treatment, 3 became re-infected after a median time of 2.7 years from the date of SVR. Over 103.9 person-years of follow-up, the estimated reinfection rate was 2.89/100 py (95% CI: 0.60, 8.44). For two individuals, reinfection occurred through injecting drug use (reported sharing syringes and drug-preparation equipment since SVR). The third individual did not have any history of drug use. All three HCV re-infected patients had well controlled HIV infection. **Conclusions:** HCV reinfection incidence among HIV-infected MSM in San Diego is 2-3 fold higher than primary HCV incidence. Increased efforts at preventing reinfection post-treatment among HIV-infected MSM are required.

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Natural NS3, NS5A and NS5B HCV resistance is common in real practice, differently associated to HCV genotypes and response to NS5A inhibitors

Valeria Cento[1], Maria Chiara Sorbo[1], Ada Bertoli[1], Ilaria Lenci[2], Ennio Polilli[3], Chiara Masetti[2], Laura Gianserra[4], Elisabetta Teti[5], Elisa Biliotti[6], Carlo F. Magni[26], Marianna Aragri[1], Valeria Micheli[7], Michela Melis[8], Laura A. Nicolini[11], Simona Marenco[10], Vincenza Calvaruso[12], Stefania Paolucci[13], Fausto Baldanti[13], Filomena Morisco[14], Massimo Siciliano[15], Valeria Pace Palitti[16], Pietro Andreone[17], Bianca Bruzzone[18], Nicola Coppola[19], Tina Ruggiero[27], Miriam Lichtner[20], Barbara Menzaghi[21], Dante Romagnoli[22], Nerio Iapadre[23], Velia Chiara Di Maio[1], Francesco De Leonardis[2], Martina Milana[2], Pierluigi Cacciatore[3], Alessandro Pieri[3], Loredana Sarmati[5], Simona Landonio[26], Antonio Gasbarrini[15], Massimo Puoti[24], Antonio Craxì[12], Vincenzo Vullo[25], Adriano M. Pellicelli[9], Sergio Babudieri[8], Giuliano Rizzardini[26], Gloria Taliani[6], Massimo Andreoni[5], Caterina Pasquazzi[4], Giustino Parruti[3], Mario Angelico[2], Carlo F. Perno[1], Francesca Ceccherini-Silberstein[1]; [1]Experimental Medicine and Surgery, University of Rome "Tor Vergata", Rome, Italy; [2]Hepatology Unit, University Hospital of Rome "Tor Vergata", Rome, Italy; [3]Infectious Diseases Unit, Pescara General Hospital, Pescara, Italy; [4]Infectious Diseases Unit, Sant'Andrea Hospital – "Sapienza" University, Rome, Italy; [5]Infectious Diseases Unit, University Hospital of Rome "Tor Vergata", Rome, Italy; [6]Tropical Diseases, Umberto I Hospital –"Sapienza" University, Rome, Italy; [7]Clinical Microbiology, Virology and Bioemergencies, ASST Fatebenefratelli Sacco, Milan, Italy; [8]Clinical and Experimental Medicine, University of Sassari, Sassari, Italy; [9]Hepatology Unit, San Camillo Forlanini Hospital, Rome, Italy; [10]Division of Hepatology, IRCCS AOU San Martino - IST, Genoa, Italy; [11]Infectious Diseases Unit, IRCCS AOU San Martino - IST, Genoa, Italy; [12]Gastroenterology, "P. Giaccone" University Hospital, Palermo, Italy; [13]Molecular Virology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [14]Gastroenterology, «Federico II» University, Naples, Italy; [15]Gastroenterology, Catholic University of Rome, Rome, Italy; [16]Hepatology Unit, Pescara General Hospital, Pescara, Italy; [17]Medicine and Surgery, University of Bologna, Bologna, Italy; [18]Hygiene Unit, IRCCS AOU San Martino - IST, Genoa, Italy; [19]Infectious Diseases Unit, Second University of Naples, Naples, Italy; [20]Infectious Diseases Unit, "Sapienza" University, Latina, Italy; [21]Infectious Diseases Unit, Ospedale di circolo di Busto Arsizio, Varese, Italy; [22]Department of Biomedical, Metabolic and Neural Sciences, NOCSAE Baggiovara, Baggiovara, Italy; [23]Infectious Diseases Unit, S. Salvatore Hospital, L'Aquila, Italy; [24]Hospital Niguarda Ca'Granda, Milan, Italy; [25]Infectious Diseases Unit, Umberto I Hospital –"Sapienza" University, Rome, Italy; [26]1st Division of Infectious Diseases, ASST Fatebenefratelli Sacco, Milan, Italy; [27]Unit of Infectious Diseases, Laboratory of Microbiology and Virology, "Amedeo di Savoia" Hospital, Turin, Italy

Aim: Natural resistance-associated substitutions (RASs) are reported with highly variable prevalence across different HCV genotypes (GTs). We investigate the frequency of natural RASs, and the role of NS5A-RASs on treatment efficacy, in a large real-life database including the 4 main HCV-GTs. **Methods:** RASs in NS3 (N=1032), NS5A (N=833) and NS5B (N=496) were analysed in 1193 HCV-infected DAA-naïve patients (pts). Sanger-sequencing was performed by home-made protocols on 714 GT1a, 989 GT1b, 135 GT2c, 333 GT3a, 24 GT4a and 166 GT4d samples. RASs with fold-change $\geq$100 were defined as major. **Results:** Overall, 415/1193 (35%) pts showed natural RASs, independently by cirrhosis, but with important differences for GT/subtypes. GT1a, GT1b and GT4a frequently showed NS3 RASs (52-20-36%, respectively), with high prevalence of 80K in GT1a (17%). The 80K was never found in GT4. Major RASs D168A/E/T/V had 3% prevalence in GT2c and 4% in GT4d. Also in NS5A, GT1a, GT1b and GT4a showed the highest prevalence of RASs (10-31-38%, respectively). Major NS5A RASs were detected in 10% GT1a (28V, 30H/R, 31M, 93C/H), 9% GT1b (30R, 93H), 5% GT2c (31M, 93H), 4% GT3a (93H) and 2% GT4d (30S). The most common major NS5A RAS was 93H. In NS5B, the major sofosbuvir 282T RAS was never found, while the putative RASs 159F and 316N were exclusively detected in GT1b (13% and 19%) often in association (phy=0.67, p<0.001 by covariation analysis). Notably, the prevalence of 159F and 316N was higher in interferon+ribavirin-experienced (7-11%, respectively), than in naïve pts (3-4%; p=0.07 and p=0.02, respectively). Among 372 pts with resistance test in all 3 genes, 10% showed multiple RASs. The most prevalent association was NS3+NS5A RASs (3%, mainly GT1 and 4). Only 2 GT1b pts showed RASs on 3 drug-targets. Lastly, 138 pts treated with a NS5A-inhibitor were studied to evaluate the potential role of natural NS5A-RASs. Among 26 non-cirrhotic pts, none had major RASs, and all 4 with baseline minor NS5A RASs (GT1b: 30Q, 31M, 58S, 92T) reached a sustained viral response (SVR12). Among 112 cirrhotic pts, 4 showed major NS5A RASs (fold-change >1000). Two of them, (GT1b:93H; GT4d:30S) were treated with not-recommended regimens, without ribavirin, and experienced virological failure. On the contrary, the other 2 (GT1b:93H; GT1a:30R) received a recommended-regimen with ribavirin and reached SVR. **Conclusions:** Natural RASs are common across all HCV-GTs, and up to 10% of pts show multiple-class resistance, though only the so-called major mutations seem to have a clinical relevance. Thus, qualitative identification of only major natural RASs (rather than all) is required to properly guide DAA-based therapy.

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Dante Romagnoli - Advisory Committees or Review Panels: Abbvie

Massimo Puoti - Advisory Committees or Review Panels: GSK, Abbott, Janssen, MSD, Roche, Gilead Sciences, Novartis, GSK, Abbott, Janssen, MSD, Roche, Gilead Sciences, Novartis, GSK, Abbott, Janssen, MSD, Roche, Gilead Sciences, Novartis, GSK, Abbott, Janssen, MSD, Roche, Gilead Sciences, Novartis; Speaking and Teaching: BMS, BMS, BMS, BMS

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Mario Angelico - Advisory Committees or Review Panels: Gilead, Janssen; Grant/Research Support: Roche; Speaking and Teaching: GSK, Roche, Gilead, Novartis, BMS, Bayer

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In The Era of Highly Effective Direct Acting Anti-Viral Agents, Screening The Entire United States Population for Hepatitis C is Cost Effective

Zobair M. Younossi[2,1], Deidre Blissett[3], Rob Blissett[3], Linda Henry[4], Youssef Younossi[4], Rachel Beckerman[3], Sharon Hunt[4]; [1]Center For Liver Disease, Department of Medicine, Inova Fairfax Hospital, Falls Church, VA; [2]Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA; [3]Maple Health Group, LLC, New York, NY; [4]Center for Outcomes Research in Liver Disease, Washington, DC

BACKGROUND AND AIM: Hepatitis C virus (HCV) is the most common cause of cirrhosis, hepatocellular carcinoma (HCC) and indication for liver transplantation (LT) in the United States. Recent advances in HCV have brought about anti-HCV regimens with sustained virologic response (SVR) rates of 98%. Although general population screening has not previously been found to be cost-effective, re-assessment of this strategy for the US population must be considered. Our aim is to compare the cost effectiveness of three screening strategies for HCV: 1) Screen all (SA) 2) Screen based on Birth Cohort Screening (BCS) and 3) Screen based on risks regardless of age (HRS). **METHODS**: A decision-analytic Markov model estimated the natural history of HCV and evaluated the cost-effectiveness of three HCV screening strategies (1) SA, 2) BC and 3) HRS over a lifetime horizon for the US general population. Based on age and risk status, 16 cohorts were modelled. Health states included Fibrosis stages 0 to 4, decompensated cirrhosis, HCC, LT, post-LT, and death. The probability of progression to downstream liver-related complications was based on presence or absence of virus (SVR). HCV antibody prevalence and the % of high risk patients varied by the specific cohort. Treatment was with approved all-oral DAAs; the exact regimen and duration was based on genotype and stage of liver disease (cirrhosis and non-cirrhosis). Across all cohorts, 86% were assumed to be seen annually by a primary care provider; 76.6% of HCV Ab+ patients had detectable HCV RNA and 28% of CHC patients were aware of their infection. SVR rates, transition probabilities, utilities, and costs were derived from the literature. Incremental cost effectiveness ratios were compared between SA and the other two screening strategies. One-way sensitivity analyses tested the impact of key model drivers. **Results**: The 3 screening strategies led to identification of new cases of HCV: (SA: 1.73 million, BCS: 1.16 million and HRS: 0.38 million). The strategy to Screen All costs $294.0 billion and leads to 26.5 million QALYs while BCS and HRS cost $300.8 billion and $318.8 billion with 25.4 and 24.5 million QALYs. Compared to BCS, Screen All led to an additional 1.1 million QALYs and saved $6.78 billion while compared to HRS, SA led to 2.0 million additional QALYs and saved $24.8 billion. In this context, the SA strategy dominated both the BCS and HRS strategies with additional QALYs and cost savings. **CONCLUSIONS:** In the era of highly effective anti-viral regimens with all oral DAAs, screening the entire U.S. population and treating those with active viremia is projected to be cost-saving.

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Aberrant expression of biliary markers by hepatocytes is related to the occurrence of hepatic decompensation and hepatocellular carcinoma in HCV-related cirrhosis (ANRS CO12 CirVir prospective cohort)

Dominique Wendum[1,2], Richard Layese[3,14], Nathalie Ganne-Carrié[15,4], Valerie Bourcier[15], Fatiha Merabtene[5], Carole Cagnot[12], Emmanuel Sauce[13], Pierre Bedossa[6], Benoit Terris[7], Janick Selves[9], Paulette Bioulac-Sage[8], Nathalie Sturm[10], Christophe Sattonnet[11], Pierre Nahon[15,4], Françoise Roudot-Thoraval[3], Marianne Ziol[13,4]; [1]Anatomie Pathologique, APHP, Hôpital St Antoine, Paris, France; [2]Sorbonne Universités, UPMC Univ Paris 06, Paris, France; [3]Unité de recherche clinique, APHP, Hôpital Henri Mondor, Créteil, France; [4]Université Paris 13, Sorbonne Paris-Cité, Bobigny, France; [5]INSERM UMR_S 938 centre de recherche Saint Antoine, Paris, France; [6]Anatomie Pathologique, APHP, Hôpital Beaujon, Clichy, France; [7]Anatomie Pathologique, APHP, Hôpital Cochin, Paris, France; [8]Anatomie Pathologique, CHU Bordeaux, Bordeaux, France; [9]Anatomie Pathologique, CHU Toulouse, Toulouse, France; [10]Anatomie Pathologique, Institut de Biologie et de Pathologie, Grenoble, France; [11]Selarl Diag, Nice, France; [12]ANRS, Paris, France; [13]Anatomie Pathologique, APHP, Hôpital Jean Verdier, Bondy, France; [14]Clinical epidemiology and ageing, Université Paris Est Créteil, Créteil, France; [15]Hépatologie, APHP, Hôpital Jean Verdier, Bondy, France

Introduction: Aberrant expression of biliary markers, such as cytokeratin 7 (CK7) and epithelial cell adhesion molecule (EpCAM) is thought to reflect an abnormal regeneration recruiting hepatic progenitor cells. We aimed to describe the expression of biliary markers by hepatocytes in patients with compensated HCV-related cirrhosis and to investigate its potential influence on decompensation events and hepatocellular carcinoma occurrence. Patients and methods: Among 1323 patients with Child-Pugh A, HCV-related cirrhosis enrolled in the French prospective ANRS CO12 CirVir cohort, we selected the patients with an available liver biopsy, performed within 2 years before inclusion. Liver biopsies were re-assessed for activity grade and potential steatohepatitis. CK7 and EpCAM immunostaining was assessed independently by 2 pathologists. Biopsies were considered positive for CK7 when at least 2 foci of more than 5 hepatocytes were observed, and categorized as extensive when one or several cirrhotic nodules showed positive staining in more than 30% of hepatocyte. EpCAM was considered positive when at least one foci of hepatocyte was stained. Patients were prospectively followed. The influence of biliary markers on decompensation events (ascites, hepatic encephalopathy, gastro-intestinal bleeding) and hepatocellular carcinoma occurrence was studied using univariate analyses and Cox's multivariate analysis. Results : Among 337 patients eligible for the study (men 67%, mean age 49 y), biopsies showed CK7+ hepatocytes in 197 (58%) patients. Among them, the staining was extensive in 40 (12%). Biopsies were positive for EpCAM in 203 patients (61%). The expression of both markers was associated with with a lower platelet count, a higher AFP level and with histological steatohepatitis. During follow-up (55.2 months [36-72]), 47 patients (14%) experienced at least one decompensation event and HCC was diagnosed in 37 patients (11%). An extensive CK7 staining was independantly associated with the occurrence of a decompensation event (HR: 3.21 [1,41 ;7,29], p=0,005), along with a low albumin level and the absence of sustained virological response. EpCAM expression was independantly associated with HCC occurrence (HR : 2.40 [1,09 ;5,31],p=0,03), along with older age and low prothombin time. Steatohepatitis, observed in 42% of biopsies, was not associated with subsequent decompensation or to HCC occur-

rence. Conclusion: Aberrant expression of CK7 and EpCAM by hepatocytes, assessed on liver biopses of patients with compensated HCV-related cirrhosis, reflects a cirrhosis stage more prone to develop cirrhosis complications.

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HCV screening and infection awareness in a cohort of HIV infected and uninfected homeless and marginally housed women in San Francisco, California

Kimberly Page[1], Michelle Yu[2], Jennifer Cohen[3], Jennifer Evans[2], Martha Shumway[4], Elise Riley[5]; [1]Internal Medicine, University of New Mexico Health Sciences Center, Albuquerque, NM; [2]Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA; [3]Clinical Pharmacy, University of California San Francisco, San Francisco, CA; [4]Psychiatry, University of California San Francisco, San Francisco, CA; [5]Department of Medicine, San Francisco General Hospital, University of California San Francisco, San Francisco, CA

Hepatitis C virus (HCV) screening has taken on new importance as a result of updated guidelines and new curative therapies. Rew studies have assessed HCV in homeless populations including women. The SHADOW cohort in San Francisco recruited and studied homeless and unstably housed women; sampling was systematically conducted at free meal programs, homeless shelters, and low-cost single room occupancy hotels, and HIV-infected women were oversampled. Study inclusion criteria included female sex, age >=18 years, and a lifetime history of housing instability (slept in a public place, a shelter, or stayed with a series other people because they had no other place to sleep). In this paper, we estimated: (1) prevalence and correlates of HCV exposure; (2) the proportion who were unaware of their status; and (3) assessed correlates of both outcomes. Among 246 women, 45.9% were anti-HCV positive, of whom 61.1% were HIV coinfected. Consistent with the recruitment strategy, just over half of the sample (n=127; 51.6%) was HIV-infected. A majority (72%) of the women were in the 'baby-boomer' cohort (born between 1945 and 1965); 19% reported recent (past 6-months) injection drug use (IDU). Factors independently associated with anti-HCV positivity were: being born in 1965 or earlier (Adjusted Odds Ratio ((AOR) 3.94; 95%CI: 1.88, 8.26), a history of IDU (AOR 4.0; 95%CI: 1.68, 9.55), and number of psychiatric diagnoses (AOR 1.16; 95%CI: 1.08, 1.25). Women with symptoms of current depression had lower adjusted odds of HCV seropositivity (AOR 0.24; 95% CI: 0.12, 0.48). Overall, 26.8% reported never being HCV tested, and among anti-HCV positives, 27.4% were unaware of their status. Factors independently associated with women not knowing their HCV status (controlling for birth cohort status and IDU) included: lower income (per $100 increase), AOR; 0.78 (95%CI: 0.65, 0.94); fewer psychiatric diagnosis (per diagnosis), AOR: 0.80 (95%CI: 0.70, 0.95); and any recent cocaine use (yes vs. no), AOR; 5.63 (95%CI: 1.16, 27.36). Results fill an important gap in information regarding HCV among homeless women, and confirm the need for enhanced screening in this population where a high proportion are baby-boomers and have a history of drug use and psychiatric problems. Due to their age and risk profile, there is a high probability that women in this study have been infected for decades, and thus have significant liver disease. The association with mental illness and HCV suggests that in addition increased screening, augmenting mental health care and support may be needed to enhance treatment success.

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Improved Hepascore values in HCV accurately predicts reversal of risk of hepatocellular carcinoma, liver decompensation and liver related death.

Angus W. Jeffrey[6], Yi Huang[1,2], Bastiaan de Boer[3], Leon A. Adams[1,2], Gerry C. MacQuillan[1,2], David J. Speers[4], John Joseph[5], Gary P. Jeffrey[1,2]; [1]School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia; [2]Department of Hepatology, Sir Charles Gairdner Hospital, Perth, WA, Australia; [3]Department of Anatomical Pathology, PathWest, QEII Medical Centre, Perth, WA, Australia; [4]Department of Microbiology, PathWest, QEII Medical Centre, Perth, WA, Australia; [5]Department of Biochemistry, Pathwest, QEII Medical Centre, Perth, WA, Australia; [6]School of Medicine, The University of Notre Dame Australia, Perth, WA, Australia

Introduction: Hepascore is a serum test that provides clinically useful data regarding the stage of liver fibrosis and subsequent clinical outcomes in chronic liver disease. The aim of this study was to determine if the change in Hepascore results over time (delta Hepascore) could accurately predict the change in risk of liver related death (LRD), hepatocellular carcinoma (HCC), liver decompensation (LD) and composite endpoint (LRD, HCC, LD) in HCV infection. ***Methods:*** 353 chronic hepatitis C patients who attended the Department of Hepatology, Sir Charles Gairdner Hospital, Western Australia from 1992 to 2012 and had two or more Hepascore tests performed were studied. The ability of a baseline and delta Hepascore test to predict liver related outcomes was assessed using univariate and multivariate Cox regression, AUROC and Kaplan–Meier analysis. ***Results:*** During 1944 patient years follow up 28 (7.9%) developed hepatocellular carcinoma, liver decompensation, and/or liver related death. Baseline Hepascore ($p<0.001$) and delta Hepascore ($p=0.044$) were independently associated with the composite endpoint. A baseline Hepascore >0.75 was associated with a significant increase in LRD ($p=0.001$), LD ($p=0.004$) and HCC ($p=0.001$). Patients with a baseline Hepascore >0.75 and a subsequent improvement in delta Hepascore (>-0.1) had a significantly decreased risk of LRD ($p=0.048$), LD ($p=0.04$) and composite endpoint ($p=0.004$) compared to those with a baseline Hepascore of >0.75 and a stable Hepascore value (delta ± 0.1) or a deteriorated Hepascore value (delta >0.1). The optimum time interval between Hepascore tests was determined by comparing those with improved delta Hepascore to those with stable or worse delta Hepascore. The combination of baseline Hepascore and delta Hepascore was significantly predictive of improved liver related outcomes only when the time between tests was ≥ 1 year ($p=0.03$). ***Conclusion:*** This study showed that improved Hepascore values were significantly associated with reduced rates of liver-related mortality and morbidity. These findings have implications for patient management following HCV eradication and may determine the time for reduced need for variceal and HCC screening.

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Identification of Patient Groups Previously Not Candidates for Interferon Therapy for Chronic Hepatitis C and Implications for Planning and Budgeting for Treatment with Current Regimens

Lisa M. Nyberg[1], xia Li[3], Su-Jau Yang[3], Kevin Chiang[4], T. Craig Cheetham[3], Susan Caparosa[3], Zobair M. Younossi[2], Anders H. Nyberg[1]; [1]Kaiser Permanente, San Diego, CA; [2]Department of Medicine, Inova Fairfax Hospital, Fairfax, VA; [3]Department of Research and Evaluation, Kaiser Permanente, Pasadena, CA; [4]Pharmacy Analytical Sevices, Kaiser Permanente, Downey, CA

Background: The 2016 Global Viral Hepatitis Strategy has set a goal to eliminate chronic hepatitis C (HCV) by 2030. To attain this goal, the health care community will need to treat large numbers of patients previously diagnosed with HCV but in whom treatment was deferred due to contraindications or potential adverse effects of the previous interferon-based therapy. A better understanding of the estimated number of persons who are diagnosed but not yet treated for HCV will allow for improved planning and budgeting for future care of this large population. Objective: To analyze demographic and comorbid conditions in persons treated vs not treated for HCV with interferon-based therapy and to identify significant predictors of not receiving treatment for HCV. Methods: This is a retrospective cohort study at Kaiser Permanente Southern California (KPSC), a large Health Maintenance Organization including approximately 4 million members. Inclusion criteria: ≥ 18 years old with a diagnosis code or a positive lab test result for HCV RNA 1/1/2002-12/31/2013 and ≥ 12 months continuous membership before and after index date. Index date was defined as the date of the first treatment course or first HCV diagnosis by ICD -9 code or positive HCV RNA test. Exclusion criteria: HCV diagnosis after 1/1/2013 and/or a diagnosis of hepatocellular carcinoma (HCC) on or before index date. Diagnosis codes and/or lab tests for comorbid illnesses representing relative or absolute contraindications to HCV treatment with interferon-based therapy were determined. Multivariate logistic regression was used to determine predictors of treatment vs non-treatment. Results: 5,203 patients received treatment and 19,765 did not receive treatment. Demographics and factors associated with not receiving treatment are shown in Table 1. Conclusion: This large epidemiological study identifies the largest patient categories who remain untreated for HCV and will help in budgeting and planning for future treatment of this population with new, well tolerated therapy.

Factors associated with NOT receiving HCV

	HCV Tx - Yes	HCV Tx - No	Odds Ratio (95% CI)
N	5203	19765	
Age	49.1 (8.6)	52.3 (12.6)	1.02(1.02,1.03)
Male, N (%)	3344 (64.3%)	11648 (58.9%)	1.00
CKD	573 (11%)	3475 (17.6%)	1.72 (1.57,1.89)
PVD/Cerebral Vascular Disease	716 (13.8%)	4033 (20.4%)	1.61 (1.47,1.75)
Heart Disease	737 (14.2%)	4075 (20.6%)	1.57 (1.45,1.71)
Seizure Disorder	74 (1.4%)	368 (1.9%)	1.31 (1.02,1.69)
Non-HCC Cancer	500 (9.6%)	2403 (12.2%)	1.3 (1.18,1.44)
Diabetes	1269 (24.4%)	5252 (26.6%)	1.12 (1.05,1.2)
Lung Disease	1667 (32%)	6631 (33.5%)	1.07 (1.01,1.14)

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Serum Levels of Wisteria Floribunda Agglutinin-Positive Mac-2 Binding Protein as a Time-Dependent Predictor of Hepatocellular Carcinoma in Chronic Hepatitis C Patients

Chia-Ling Chang[3], Liang-Chun Chen[2], Hui-Han Hu[3], Yu-Ju Lin[1], Jessica Liu[3], Chin-Lan Jen[3], Chien-Yu Su[3], Cheng-Tse Chiang[3], Yong Yuan[4], Sheng-Nan Lu[5], Li-Yu Wang[5], Masaaki Korenaga[6], Masashi Mizokami[6], Chien-Jen Chen[7], Mei-Hsuan Lee[1], Hwai-I Yang[3]; [1]Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan; [2]Faculty of Medicine, National Yang-Ming University, Taipei, Taiwan; [3]Genomics Research Center, Academia Sinica, Taipei, Taiwan; [4]Global Health Economics and Outcome Research, Bristol-Myers Squibb, Princeton, NJ; [5]MacKay College of Medicine, Taipei, Taiwan; [6]The Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine,, Ichikawa, Japan; [7]Academia Sinica, Taipei, Taiwan

Background *Wisteria floribunda* agglutinin-positive Mac-2 binding protein (M2BPGi) was reported as a noninvasive marker of liver fibrosis and a predictor of hepatocellular carcinoma (HCC) in chronic hepatitis C (CHC) patients. This study aimed to assess time-dependent associations between M2BPGi and HCC development in CHC patients using samples collected during long-term follow-up. **Methods** All participants in this study were from the R.E.V.E.A.L.-HCV cohort. Serum M2BPGi levels were evaluated in a total of 1,161 samples consisted of 137 HCC cases and 725 controls. There were 82 cases and 86 controls with serial samples collected at various times throughout follow-up. Associations of M2BPGi and HCC were analyzed using multivariate logistic regression models and further stratified according to time between sample collection and HCC diagnosis. Areas under the receiver operating characteristic (AUROCs) curves were used for evaluating prediction accuracy of models that integrated M2BPGi and other risk factors in predicting HCC risk. **Results** M2BPGi levels in samples closer to HCC diagnosis were higher than that collected farther from HCC diagnosis. However, M2BPGi levels were consistently low over time in control samples. The analysis using all samples collected at various occasions showed that M2BPGi levels were associated with HCC risk in a dose-dependent manner after adjustment of gender, age, serum ALT, AST, AFP, HCV RNA levels, and HCV genotype. The adjusted odds ratio (95% CI) was 2.32 (1.57-3.43), 3.57 (1.83-6.95), and 10.36 (5.37-20.00), respectively, for M2BPGi 1-2, 2-3, and ≥3 COI compared with those with <1 COI as the referent. When stratified by time of sample collection to HCC diagnosis, associations between M2BPGi levels and HCC were strongest for the short-term period, and decreased with longer time. Compared to M2BPGi levels <1 COI, adjusted odds ratios (95% CI) for M2BPGi levels ≥3 COI were 38.6 (12.9-115.2), 7.48 (2.5-22.5), 3.95 (1.2-12.6) and 3.21 (1.0-10.3), respectively, for predicting HCC within 1-3 years, 3-6 years, 6-12 years, and ≥12 years; AUROCs incorporating M2BPGi levels and other predictors were 0.96, 0.92, 0.82 and 0.80, respectively, for prediction of HCC within 4 periods. **Conclusion** M2BPGi levels significantly predict HCC development in patients with chronic hepatitis C. The associations and prediction accuracy are stronger for samples collected closer to HCC diagnosis than those collected farther from HCC diagnosis.

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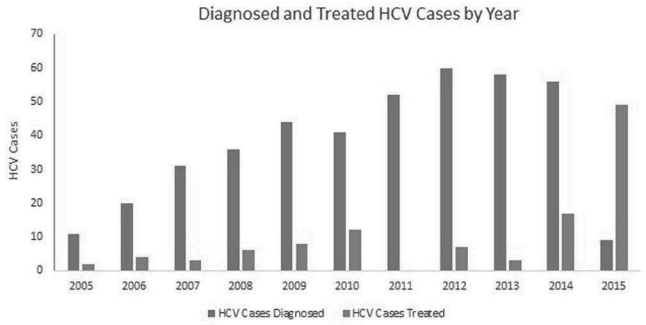
Hepatitis C Virus Testing, Prevalence, and Treatment in a Large Cohort of Treatment-Naïve, HIV-Positive Individuals

Douglas T. Dieterich[1], Cassidy Henegar[2], Jennifer Fusco[2], Philip Lackey[3]; [1]Mt. Sinai Healthcare System, New York, NY; [2]Epividian, Inc., Durham, NC; [3]Carolinas Healthcare System, Charlotte, NC

Purpose: HIV+ populations are at greater risk for HCV due to shared modes of transmission. Compared to HCV-monoinfection, HIV/HCV is more likely to result in fibrosis and cirrhosis. High rates of cure are now possible for HIV/HCV patients due to modern direct-acting antivirals (DAAs). This analysis evaluates HCV testing and treatment patterns in a real-world setting to identify opportunities for improved outcomes in coinfected patients. **Methods:** Using the OPERA database, a collaboration of caregivers at 79 clinics in 15 states, HIV+ individuals initiating HIV antiretroviral therapy (ART) for the first time between 1/1/2007 and 3/31/2015 were identified, and followed until data freeze (04/28/2016), death, or loss to follow-up. Prospectively collected data were extracted from electronic health records. **Results:** Out of 9,190 HIV+ treatment-naïve patients, 91% were evaluated for HCV prior to ART initiation; 7,837 (85.3%) were HCV antibody-negative (Ab-), 472 (5.1%) were HCV+ (by viral load, diagnosis or treatment record), and 26 (0.3%) had a history of resolved HCV. After starting ART, 4,546 (58%) of the 7,837 HCV Ab- patients were reevaluated for HCV, resulting in 101 new HCV diagnoses including 5 confirmed seroconversions. Of the 472 baseline HCV+ cases, 235 (50%) were diagnosed in the DAA era (2011 or later). Only 26% (n=123) were ever treated for HCV, most commonly after HIV ART initiation (n=109, 89%) and in the DAA era (n=86, 79%). Median time between HCV diagnosis and treatment was 29 months (IQR: 12, 69). Overall, 72% of the treated cases received DAA-based therapy, including 99% treated in 2014 or later. **Conclusion:** Most patients in this ART-naïve HIV population were evaluated for HCV. While HCV treatment was more common in the DAA era, the majority of cases remained untreated. Treatment delays were also commmon. Given the importance of controlling HCV disease progression in coinfected patients and the existence of effective therapies, greater effort should be made to treat all coinfected patients, and to continue monitoring for HCV among HIV-monoinfected patients after baseline.



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Early decrease of liver stiffness after initiation of antiviral therapy in patients with chronic hepatitis C.

Stephan Moser, Enisa Gutic, Michael Schleicher, Michael Gschwantler; 4th dept. of medicine, Wilheminenspital, Vienna, Austria

Liver elastography is widely used to assess liver fibrosis in patients with chronic hepatitis C and has also been recommended to monitor regression of liver fibrosis after successful antiviral therapy.We studied early changes of liver stiffness after initiation of antiviral treatment. The study population comprised 53 patients with chronic hepatitis C (mean age ± SD: 49.4 ± 10.7 years; METAVIR fibrosis stage F2, n=23; F3, n = 12; F4, n = 18; genotype (GT) 1, n = 32; GT3, n = 17; GT4, n = 4; mean BMI ± SD: 25.1 ± 3.8). All patients were treated with interferon-free all oral regimens. Prior to therapy and 1-6 weeks after initiation of antiviral treatment fibrosis stage was assessed by transient elastography using the Fibroscan® 502 Touch device with the M-probe (Echosens, Paris, France) and classified according to the METAVIR scoring system. Cut-off values for liver stiffness were defined as 7.1 kPa for F ≥ 2, 9.5 kPa for F ≥ 3 and 12.5 kPa for F = 4 [4]. Mean liver stiffness at baseline was 14.69 ± 11.15 kPa and decreased to 12.41 ± 9.83 kPa at follow-up Fibroscan® performed between week 1 and week 6 (p=0.006). When the same Fibroscan® cut-off values applied at baseline were applied after initiation of antiviral therapy the following results were obtained: Within 6 weeks after initiation of treatment fibrosis stage improved by at least one stage in 23/53 (43%) patients, remained stable in 28/53 (53%) and worsened in 2/53 (4%). From the 23 patients classified as F2 at baseline, 11 (48%) were classified as F0/F1 at week 1-6, 10 (43%) as F2, and 2 (9%) as F3. From the 12 patients classified as F3 at baseline, 3 (25%) were classified as F0/F1 at week 1-6, 4 (33%) as F2, and 5 (42%) as F3. From the 18 patients with F4 at baseline, 1 (6%) was classified as F0/F1 at week 1-6, 2 (11%) as F2, 2 (11%) as F3 and 13 (72%) as F4. Decrease of liver stiffness did not correlate with baseline AST (r=0.28) or ALT (r=0.04) levels. In our study a marked decrease of liver stiffness was observed within two weeks after initiation of antiviral therapy. From a pathophysiologic point of view a clinically significant decrease of liver fibrosis within such a short period of time seems impossible. We therefore assume, that the decrease is caused by resolution of the inflammatory activity within the liver. Current cut-off values for assessment of fibrosis stage in patients with chronic hepatitis C by transient elastography were obtained in patients with fibrosis *and* active inflammation. Therefore, our data clearly indicate that lower cut-off values for liver stiffness are appropriate for monitoring liver fibrosis after initiation of antiviral therapy.

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The following people have nothing to disclose: Stephan Moser, Enisa Gutic, Michael Schleicher

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Polaris Observatory - Global prevalence of hepatitis C

Sarah Blach, Chris Estes, Ivane Gamkrelidze, Jessie Gunter, Kimberly Murphy, Helen Nde, Ken Pasini, Devin M. Razavi-Shearer, Kathryn L. Razavi-Shearer, Sarah Robbins, Jonathan D. Schmelzer, Homie Razavi; Center for Disease Analysis, Louisville, CO

The 69th World Health Assembly passed a resolution to eliminate viral hepatitis by 2030. Reliable disease burden estimates

are required to develop strategies to achieve this goal. The Polaris Observatory was created to gather data and model the change in annual disease burden estimates for HBV, HCV and HDV. Disease burden models were developed for 100 countries to estimate the prevalence of HCV in 2016. The model took into consideration new infections, disease progression, mortality and cured. A Delphi process (using published literature followed by interviews with local experts) was used to gather data for 60 countries. Literature search was used for another 40 countries. The global prevalence was estimated by using regional averages for countries without data. Approximately 70 (56-90) million individuals were estimated to experience viremic HCV infection. This is lower than 2014 published estimates due to more recent (lower) prevalence estimates in African countries and a large increase in treatment. Lower estimates can also be attributed to an increase in mortality due to liver-related causes and an aging population. In 2015 alone, approximately 500 thousand individuals were treated and cured. The largest increase in treatment was in the United States (260K treated in 2015) followed by Egypt (190K) and the European Union (135K). Although this increase in treatment is a substantial step towards reducing the global burden of liver related deaths, the current treatment rate is not sufficient to achieve elimination by 2030.

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The C13-Aminopyrine Breath Test Predicts Advanced Fibrosis in Patients with Chronic Hepatitis C: A Pilot Study

Gamal Shiha[1,2], Reham Soliman[2], Seham Seif[1], Waleed Samir[2]; [1]Internal Medicine Department, Internal Medicine Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt, Mansoura, Egypt; [2]Egyptian Liver Research Institute and Hospital (ELRIAH), Mansoura, Egypt

Background and Aim: Analysis of volatile organic compounds (VOCs) in the exhaled breath can identify markers for alcoholic and nonalcoholic fatty liver disease. The aim of this pilot study was to investigate the utility of C13-Aminopyrine breath test in the diagnosis of advanced fibrosis (F3-4) in patients with chronic hepatitis C virus (HCV) infection. **Methods:** Patients undergoing liver biopsy were recruited. Fibrosis was determined by an experienced pathologist and staged according to METAVIR score. Advanced fibrosis was defined as F3-4. Exhaled breath and plasma samples were collected within 2 weeks of the biopsy, and Infra-Red Isotope Analyzer (IRIS) was used to analyze breath samples for C13 aminopyrine. **Results:** In all, 36 patients were included with a mean age of 41.6±9.4 years, 91.7% were males, and 8 (22.2%) had advanced fibrosis (F3-F4). IRIS analysis of exhaled breath revealed that patients with advanced fibrosis had significantly lower values of C13-aminopyrine compared with those without advanced fibrosis at both 30 min and 120 min; P=0.007 and P=0.004 respectively. At 30 min and 120 min, 26 (72.2%) patients and 21(58.3%) patients has levels >3.15 and > 8.25 respectively. The sensitivity, specificity, positive predictive value, and negative predictive value of the breath test at 30 min and at 120 min using the new cut-off values, compared to the standard values, are shown in the table below. The AUROC used for diagnosis of advanced fibrosis by breath test at min 30 and at 120 min were 0.81 (95% CI: 0.647-0.969; P=0.009) and 0.83 (95% CI: 0.668-0.984; P=0.005) respectively. **CONCLUSION:** C13 aminopyrine breath test is a potential biomarker for advanced fibrosis that warrants further validation. The breath test is a good negative test to detect non-severe fibrosis with the new cut-off (at 30 min: 3.15, 120 min: 8.25).

Statistic	Breath test at 30 min Range: 2.5-3.1	Breath test at 120 min Range: 3.6-4.6	Breath test at 30 min Cut-off: 3.15	Breath test at 120 min Cut-off: 8.25
Sensitivity	71.4%	37.5%	75.0%	87.5%
Specificity	79.2%	88.0%	85.7%	71.4%
PPV	50.0%	50.0%	60.0%	46.7%
NPV	90.5 %	81.5%	92.3%	95.2%
Accuracy	77.4%	75.3%	83.3%	75.0%

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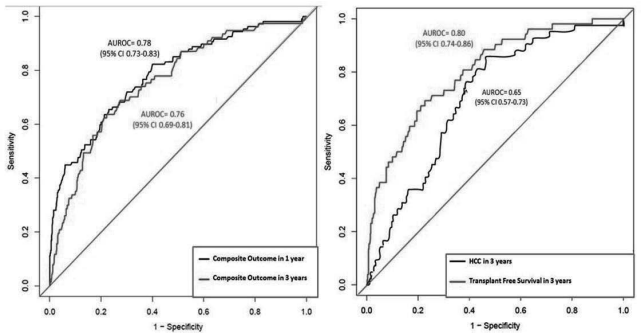
Assessing Risk of Hepatic Decompensation, Hepatocellular Carcinoma, and Transplant Free Survival for Patients with both Early Stage and Advanced Chronic Hepatitis C

Monica Konerman[1], Dongxia Lu[1], Yiwei Zhang[1], Mary Thomson[1], Ji Zhu[1], Aashesh Verma[1], Nizar Talaat[1], Peter Higgins[1], Akbar K. Waljee[1,2], Anna S. Lok[1]; [1]University of Michigan, Ann Arbor, MI; [2]Veterans Affairs Hospital, Ann Arbor, MI

Background: Despite advances in therapy, chronic hepatitis C (CHC) remains an important worldwide public health problem. The aim of this study is to externally validate a longitudinal prediction model (Konerman, Hepatology 2015) for risk of adverse clinical outcomes derived from a cohort with advanced CHC among patients (pts) with both early and advanced stage CHC. **Methods**: Adults with CHC seen in our hepatology clinic between 1/1998- 6/2014 were retrospectively analyzed. Pts with hepatic decompensation, hepatocellular carcinoma (HCC), liver transplant (LT), hepatitis B or HIV co-infection at presentation were excluded. Pts with <3years follow-up were also excluded. Outcomes included: 1) hepatic decompensation, 2) HCC and 3) LT free survival. Machine learning methods were used to predict outcomes in 1 and 3 years. **Results**: The cohort of 1007 pts had a mean age of 48.9. 61% were male, 80% were white, and 79% had genotype 1. At presentation, 73% were treatment naïve and 31% had cirrhosis. 226 pts developed an outcome over a median follow up of 6.9 years (interquartile range 4.5-10.5). The area under the receiver operating characteristic curve (AUROC) for 1 and 3 year risk prediction for a composite clinical outcome (decompensation, HCC, LT, liver-related death) was: 0.78 (95% CI 0.73-0.83) and 0.76 (95% CI 0.69-0.81). Model performance was retained when accounting for achievement of sustained virologic response (N=250) and baseline cirrhosis. Models were accurate for assessing transplant free survival but not HCC (**Figure**). Mean aspartate aminotransferase to platelet ratio index, mean maximum and baseline platelet count, and mean albumin contributed most significantly to the risk predictions. **Conclusions**: Accurate assessments for risk of clinical outcomes among pts with CHC can be obtained using routinely collected longitudinal data. These models retain their accuracy across pts with minimal or no fibrosis at baseline, different treatment exposures and varied genotypes. Given the worldwide burden of CHC, our models can convey useful prognostic information

to guide intensity of clinical monitoring and urgency of treatment.



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Association of sexual risk factors with Hepatitis C prevalence among United States non- IVDU adults 20 to 68 years old: National and Nutrition Examination survey (NHANES)

Nallely Mora[1], William H. Adams[1], Stephanie Kliethermes[1,2], Lara R. Dugas[1], Jennifer E. Layden[1,2]; [1]Public Health Sciences, Loyola University Chicago, Maywood, IL; [2]Department of Medicine, Stritch School of Medicine, Loyola University Chicago, Maywood, IL

Background: In the United States (US) major risk factors for acquiring Hepatitis C (HCV) are well known (i.e., intravenous drug users (IDU), blood transfusion prior to HCV screening 1992, HIV infected men who have sex with men). However, in 15-20% of cases, there are no identifiable risk factors. In the present study we examine the association of sexual risk factors with the risk of HCV infection among adult, non-HIV infected, non-IVDU individuals. Methods. NHANES is a population based representative survey of individuals in the US. Data from 2005 to 2012 were combined for this study. We exclude: intravenous drug users (IDU), and persons less than 20 years old or older than 68 years; and for the multivariable analysis HIV positive participants Results. The overall N was 15, 850, with an overall anti-HCV prevalence of 1.2% (95% CI, 0.9% to1.5%). Peak prevalence estimates was observed among persons 40 to 49 years of age, with a prevalence of 2.3% (1.7%-2.9%). All sexual risk factors were associated with HCV infection among non-IVDU individuals. HCV prevalence was 3.1% among non-IVDU individuals with ≥ 50 sexual partners compared to 0.7% among individuals with 0-9 partners. The HCV prevalence was 2.8% among those with Herpes (HSV), compared to 0.6% among those not infected with HSV. Among individuals with sexual debut ≤ 15, HCV prevalence was 2.6% compared to 0.9% among those with sexual debut ≥ 18 years of age. Further, the prevalence among those both HSV positive AND with sexual debut younger ≤ 15 was 4.1% (2.0- 6.1) compared to 0.3% (0.1-0.5%) for those who were HSV negative and with older sexual debut at ≥ 18 . All multi-variable analyses examining the association of sexual risk factors with HCV infection controlled for age, gender, education, poverty, ethnicity, marital status, blood transfusion, and drug use (non-IVDU). In the multiple variable models, the adjusted OR's for HSV infection compared to no HSV infection was 2.3(1.1-4.8). Lifetime partners ≥ 10 had an OR's of 2.2(1.2-4.0) compared to 0-9 lifetime partners. Finally, sexual debut≤15 carried an OR of 5.3(2.9-9.8) compared to sexual debut≥18 years of age. Among individuals both HSV positive and with early sexual debut (<15 years) the OR (95% CI) was 5.2(2.0-13.4) compared to those without HSV and later sexual debut. Conclusion. Examining risk factors among a non-IVDU population, non-HIV infected population using population based US data, we identified numerous sexual risk factors to be associated with HCV infection in both uni-and multi-variable analyses. Such data suggests that among individuals engaging in higher risk sexual behaviors, HCV may be transmitted through sexual activity.

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European mitochondrial haplogroups are associated with liver related events in HIV/HCV-coinfected patients

Salvador Resino[2], Teresa Aldámiz-Echevarría[1], María A Jiménez-Sousa[2], Pilar Miralles[1], Luz M Medrano[2], Ana Carrero[1], Cristina Diez[1], Leire Pérez-Latorre[1], José M. Bellón[3], Juan Berenguer[1]; [1]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [2]Centro Nacional de Microbiología. ISCIII, Majadahonga, Spain; [3]Fundación Investigación Biomédica Gregorio Marañón, Madrid, Spain

Mitochondria provide energy to eukaryotic cells via oxidative phosphorylation and regulate cellular survival via control of apoptosis. Mutations in the mitochondrial DNA (mtDNA) are related to many human diseases. Some of these mtDNA mutations have been acquired throughout human history by natural selection allowing subdividing the human population into a number of discrete mitochondrial clades or haplogroups defined on the basis of specific mtDNA polymorphisms. European mtDNA haplogroups have found to influence liver fibrosis progression in HIV/HCV-coinfected patients (AIDS 2011; 25: 1619-26). The aim of our study was to assess the relationship between mtDNA haplogroups and liver-related events (LRE) in HIV/HCV-coinfected patients. **Methods**: We studied clinical characteristics and outcomes of 243 HIV/HCV-coinfected patients with a baseline liver biopsy and simultaneous blood and serum samples who were followed for a median of 93 months (7.75 years). The primary endpoint was the occurrence of LRE defined as decompensation or hepatocellular carcinoma, whichever occurred first. The mtDNA genotyping was performed by Sequenom's MassARRAY platform. Univariate and multivariate Fine and Gray proportional hazards regression – taking into account death as the competing risk - were used to test the association between mtDNA haplogroups and LRE. Variables for adjustment were alcohol intake, FIB-4 score and sustained viral response (SVR). **Results***:* During follow-up, 175 patients were treated with interferon and ribavirin and 90 achieved SVR. A total of 18 patients had LRE, and 11 patients died. Out of 243 patients, 109 (47.8%) patients had mtDNA haplogroup H, and 3 (2.75%) had a LRE; whereas 25 (10.3%) patients were haplogroup T and 5 (20%) had a LRE. Haplogroup H was associated with a lower hazard of LRE in univariate analysis [subhazard ratio (SHR)=0.26 (95%CI=0.08; 0.91); *P*=0.035] and multivariate analysis [adjusted SHR (aSHR)=0.34 (95%CI=0.10; 1.19); *P*=0.092]; whereas haplogroup T was associated with a significant higher hazard of LRE in univariate analysis [SHR=3.31 (95%CI=1.03; 10.62); *P*=0.045] and multivariate analysis [aSHR=4.18 (95%CI=1.35; 12.92); *P*=0.013]. **Conclusions**: mtDNA haplogroup T was associated with an increased hazard of LRE, whereas haplogroup H was associated with a reduced hazard of LRE. These results suggest that mtDNA haplogroups are

host-related factors that influence the natural history of chronic hepatitis C in patients with HIV infection.

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Re-clearance of hepatitis C: Role of previous clearance and reinfection with a heterologous genotype

Nazrul Islam[2], Mel Krajden[1,2], Jeannie Shoveller[2,3], Paul Gustafson[2], Mark Gilbert[1], Jason Wong[1,2], Mark Tyndall[1,2], Naveed Z. Janjua[1,2]; [1]BC Centre for Disease Control, Vancouver, BC, Canada; [2]University of British Columbia, Vancouver, BC, Canada; [3]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada

Background: About 25% of individuals infected with hepatitis C virus (HCV) spontaneously clear their infection but can be at risk of reinfection. Data on spontaneous clearance of HCV after reinfection (re-clearance), particularly reinfections with a heterologous genotype, in humans are very limited. We examined HCV re-clearance in a large population-based cohort in British Columbia, Canada. **Methods**: For this analysis, we used data from the BC Hepatitis Testers Cohort that includes all individual tested for HCV between 1990 and 2013 linked with data on their medical visits, hospitalizations, and prescription drugs. We identified people with HCV reinfection who underwent follow up HCV-RNA testing (n=958; 865 cleared their first infection spontaneously while 93 achieved sustained virologic response [SVR] through treatment) to examine HCV re-clearance. Multivariable Cox proportional hazard model was used to identify potential predictors of re-clearance. **Results**: About half (48%, n=460) the participants spontaneously cleared the reinfection with an incidence rate of 16.92 (95% confidence interval [CI]: 15.41-18.53) per 100 person-years (PY). Both the proportion and the incidence rate of re-clearance (per 100 PY) in those who spontaneously cleared their first infection (proportion: 50.5%; rate: 17.8, 95%CI: 16.17-19.55) were more than twice that in those who achieved SVR through treatment (proportion: 24.7%; rate: 8.71, 95% CI: 5.52-13.07). In adjusted analysis, the likelihood of HCV re-clearance was higher among those who spontaneously cleared their first infection compared to those who achieved SVR (adjusted hazard ratio [aHR]: 1.93, 95% CI: 1.24-2.99), and lower if reinfected with a heterologous HCV genotype (aHR: 0.70, 95% CI: 0.47-1.03). **Conclusion**: Ability to spontaneously clear first infection markedly increases the likelihood of clearing subsequent infections, but does not confer protection against a heterologous virus.

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Cost-effectiveness of screening strategy of hepatitis C in France: it is time to change recommendations

Sylvie Deuffic-Burban[1,2], Alexandre Huneau[1], Adeline Verleene[1], Cécile Brouard[3], Josiane Pillonel[3], Yann Le Strat[3], Sabrina Cossais[1], Françoise Roudot-Thoraval[4], Valerie Canva-Delcambre[5], Philippe Mathurin[5,2], Daniel Dhumeaux[6], Yazdan Yazdanpanah[1,7]; [1]Inserm, IAME, UMR1137, Univ. Paris Diderot, Sorbonne Paris Cité, Paris, France; [2]Univ. Lille, Inserm, CHU Lille, U995 - LIRIC - Lille Inflammation Research International Center, Lille, France; [3]Département des Maladies Infectieuses, Santé publique France, Saint Maurice, France; [4]Service Santé Publique, Hôpital Henri Mondor, Créteil, France; [5]Service des Maladies de l'Appareil Digestif et de la Nutrition, Hôpital Huriez, CHRU Lille, Lille, France; [6]Inserm U955, Hôpital Henri-Mondor, Créteil, France; [7]Service de maladies Infectieuses et tropicales, Hôpital Bichat Claude Bernard, Paris, France

In France, recommendations for Hepatitis C Virus (HCV) screening still target only people at high risk of infection, and 40% of infected-persons remain unaware of their status. In the context of highly effective and tolerable therapies, that will be recommended for all patients in a near future, a reassessment of HCV screening strategies is needed. A cost-effectiveness study was conducted in the French general population, aged 18 to 80 years, undiagnosed for chronic hepatitis C (CHC). A Markov model simulated life expectancy in discounted quality adjusted life years (QALYs), direct lifetime discounted costs and incremental cost-effectiveness ratio (ICER) for different strategies, from 2016 until death: S1=current strategy targeting the at risk population (63% of the study population) that effectively screened 10-19% of at risk population, and 4-18% of those not at risk; S2=S1 and all men between 18 and 60 years; S3=S1 and all people between 40 and 60 years; S4=S1 and all people between 40 and 80 years; S5=all people between 18 and 80 years. We assumed that S2 to S5 reached 100% of the targeted age-cohort population. Once CHC diagnosed, treatment was initiated regardless of fibrosis either with the least or the most expensive treatment combination. We relied on published literature and on a national prevalence survey. Characteristics of undiagnosed persons in terms of fibrosis according to gender, age and alcohol consumption, and time to screening, were obtained from a previously published mathematical model. Whatever the treatment combination (Table), when we considered treatment for all, compared to the current screening strategy, adding all men aged 18-60 years was associated with the lowest ICER (27,600-31,900€/QALY). Targeting all people aged 40-80 was more effective than targeting all men aged 18-60 years and remained cost-effective (39,100-44,800€/QALY). Universal screening was even more effective than targeting all people 40-80 and remained cost-effective (40,300-46,300€/QALY). In France, although universal screening is associated with the highest costs, it is the most effective strategy and is cost-effective when treatment is initiated regardless of fibrosis.

Table - Cost-effectiveness analysis considering either the least or the most expensive treatment combination

	QALY		With the least expensive combination		With the most expensive combination	
Strategy	All (1)	HCV-RNA positive	Average lifetime cost, € (2)	ICER, €/QALY (2)/(1)	Average lifetime cost, € (3)	ICER, €/QALY (3)/(1)
S1=current strategy targeting the at risk population	15.984125	13.464796	129.22		200.81	
S3=S1 and all 40-60	15.984256	13.548011	134.61	Dominated*	206.34	Dominated*
S2=S1 and all men 18-60	15.984408	13.632313	137.02	27,600	209.83	31,900
S4=S1 and all 40-80	15.984519	13.597951	141.36	39,100	214.80	44,800
S5=S1 and all 18-80	15.984737	13.783039	150.14	40,300	224.90	46,300

*Weakly dominated strategy: higher ICER than that of a more effective alternative strategy

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Philippe Mathurin - Board Membership: MSD, Janssen-Cilag, BMS, Gilead, Abvie, Verlyx; Consulting: Roche, Bayer

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Yazdan Yazdanpanah - Board Membership: Abbvie, BMS, GILEAD, MSD, ROCHE, Johnson&Johnson, ViiVHealthcare, Pfizer, Janssen; Consulting: AbbVie, BMS, GILEAD, MSD, Roche, Johnson&Johnson, Viiv Healthcare, Pfizer, Janssen

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Impact of treatment induced vs spontaneous HCV clearance on the long term risk of hepatocellular carcinoma: BC Hepatitis Testers Cohort

Mel Krajden[1,2], Mark Tyndall[1,2], Mei Y. Chong[1], Darrel Cook[1], Jason Wong[1,2], Margot E. Kuo[1], Hasina Samji[1,2], Zahid Butt[1,2], Amanda Yu[1], Maria Alvarez[1], Ryan Woods[3], Naveed Z. Janjua[1,2]; [1]BC Centre for Disease Control, Vancouver, BC, Canada; [2]University of British Columbia, Vancouver, BC, Canada; [3]British Columbia Cancer Agency, Vancouver, BC, Canada

Background: The risk of hepatocellular carcinoma (HCC) in people who spontaneously clear HCV infection (SC), those who achieve treatment-based SVR (RxSVR), those who fail treatment (RxFail) and those with untreated chronic HCV (NoRx) is not well established. We evaluated the HCC risk in these patient groups using the BC Hepatitis Testers Cohort (BC-HTC). **Methods:** The BC-HTC includes ~1.5 million individuals tested for HCV, HIV or reported as a case of HBV, HCV, HIV or active TB between 1990–2013, linked with medical visits, hospitalizations, cancers, prescription drugs and mortality. Cumulative incidence function and multivariable Cox proportional hazard models were used to examine HCC risk in the four HCV groups (SC, RxSVR, RxFail, NoRx). **Results:** Of 46,046 eligible individuals: 12,493 were SC; 9,140 were treated of whom 5,320 (58%) were RxSVR and 3,820 (43%) were RxFail; 24,413 had chronic HCV and NoRx. The four groups were followed for a median (IQR) of 11 years: SC 10.6 (2.0-15.0); RxSVR 11.2 (7.0-14.9); RxFail 11.7 (7.9-15.0); NoRx 10.8 (6.3-17.0). The RxFail group had a higher level of cirrhosis (23% vs <9%) and diabetes (13% vs <7%) than other groups. The annual HCC incidence rate per 1,000 person-yr (PY) was 0.26 (HCC/PY=34/129,382) for SC; 1.19 (35/29,304) for RxSVR; 7.7 (170/ 22,169) for RxFail; and 1.24 (381/307,828) for NoRx. The HCC incidence rate was higher among those with cirrhosis in all groups. In the multivariable model, compared to NoRx, SC (hazard ratio (HR) = 0.24, 95%CI:0.17-0.35)) and RxSVR (HR=0.59, 95%CI:0.42-0.84) were associated with reduced HCC risk, while RxFail (HR=3.54, 95%CI:2.93-4.28) had a higher HCC risk . As expected, cirrhosis (HR=3.25, 95%CI:2.23-4.75), older age (50-59 yr: HR=4.35, 95%CI:3.58-5.28; 60+ yr: HR=9.16, 95%CI:7.27-11.54 compared to ≤49 yr), male sex (HR=2.18, 95%CI:1.79-2.66), genotype 3 vs. 1 infection (HR=1.64, 95%CI:1.34-2.02), and problematic alcohol use (HR=1.48, 95%CI:1.20-1.83) increased the adjusted HCC risk. **Conclusions:** As expected, the HCC risk for SC was low. The RxFail group had the highest HCC risk, likely reflecting a poorer prognostic profile at treatment initiation. This highlights the limited HCC prevention benefits of treating later stage disease with older interferon-based regimens even if SVR is achieved. The higher HCC risk for RxSVR compared to SC suggests that earlier HCV treatment will be required to achieve the same risk reduction observed for SC.

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Direct Medical Costs Associated with the Extrahepatic Manifestations of Hepatitis C Infection in France

Patrice P. Cacoub[1,2], Mathieu Vautier[1,2], Anne Claire Desbois[1,2], Marianne Doz[3], Antoine Lafuma[3], Zobair M. Younossi[4,5]; [1]Department of Internal Medicine and Clinical Immunology, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Paris, France; [2]Inflammation-Immunopathology-Biotherapy Department (DHU i2B), Sorbonne University, UMPC Univ Paris 06, UMR 7211, Paris, France; [3]CEMKA, Paris, France; [4]Department of Medicine, Inova Fairfax Hospital, Center for Liver Diseases, Falls Church, VA; [5]Inova Health System, Betty and Guy Beatty Center for Integrated Research, Falls Church, VA

Background Hepatitis C virus (HCV) infection is a systemic disease which is associated with both hepatic and extrahepatic manifestations (EHM). The disease burden associated with the hepatic manifestation of HCV is well documented. However, the economic impact of EHM of HCV outside the United States remains unknown. **Objective** To estimate the annual direct medical costs associated with EHM of HCV in France. **Methods** A previously validated economic model was used to estimate the annual direct medical cost associated with EHM of HCV. Prevalence of nine EHM (mixed type 2 cryoglobulinemia vasculitis, chronic kidney disease, type 2 diabetes mellitus [DM], lymphoma, lichen planus, Sjogren's syndrome, porphyria cutanea tarda, rheumatoid-like arthritis, and depression) were obtained from a recent systematic review and meta-analysis (Younossi *et al.* 2016). Per-patient-per-year (PPPY) inpatient, outpatient and medication costs to treat each of these EHM in France was obtained from the literature, from the French medico-administrative database (PMSI) or expert opinion if unavailable otherwise. Prescription drug costs were taken from the VIDAL website. All costs were adjusted to 2015 euros (€). The overall national direct medical costs associated with EHM of HCV were calculated by multiplying the total PPPY costs of each EHM by the respective prevalence rates, and then by the size of the HCV-infected population in France (INSEE; Corinne Pioch 2016). Sensitivity analysis was performed considering the 95% Confidence intervals reported in Younossi *et al.* **Results** In 2014, 192,700 individuals were estimated to be infected with HCV in France. The mean average PPPY cost of EHM was 1,354.52€. The total annual direct medical cost associated with the care of patients with the EHM of HCV

in France was estimated to be 261,016,256€. The sensitivity analyses suggested a range of 108.6 to 354.9 million euros in total cost associated with the extrahepatic manifestation of HCV. **Conclusion** Extrahepatic manifestations of HCV are quite costly and substantially add to the overall economic burden of HCV infection.

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WITHDRAWN

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What Happens After Screening and Linkage to Care? Examination of HCV Care Cascade Outcomes Among 5,000 Urban Baby Boomers Screened for HCV 2012-2014

Lesley Miller[1], Cameron B. Body[1], Brandi Park[1], Wynnetta Wimberley[1], Shelly-Ann Fluker[1], Ike S. Okosun[2]; [1]Medicine, Emory University, Atlanta, GA; [2]Epidemiology and Biostatistics, Georgia State University, Atlanta, GA

Purpose: To examine 2-year outcomes along the HCV Care Cascade among a population of over 5,000 baby boomers screened for HCV infection from 2012-2014 in an academic, primary care setting targeting underserved individuals. **Methods:** The TILT-C program, funded by the CDC, implemented baby boomer screening and linkage to care from 2012-2014 at the Grady Memorial Hospital Primary Care Center (Atlanta, GA, USA). Twenty months after the completion of the screening program, we evaluated records of the 412 patients who screened positive for HCV antibodies. Outcomes reported for the subset with chronic HCV infection included type of initial linkage to care, number of follow-up visits, number referred for antiviral treatment, reasons for non-treatment, and numbers who achieved rapid virologic response (RVR), end of treatment response (ETR) and sustained virologic response 12 weeks after completion of therapy (SVR12). **Results:** In a birth cohort population that was 92.5% African American and 53% uninsured, 412 (7.9%) of 5,239 patients screened had HCV antibodies. HCV RNA testing was completed for 92% of the antibody-positive patients, and 264 (69%) were viremic. 96% of viremic patients had an initial linkage to care visit; 43% at the onsite, primary care-based HCV clinic, 6% at the infectious disease clinic, and 47% at the primary care clinic. Subsequently, 75% of patients attended a second specialty visit, 55% a third visit, 30% a fourth, and 13% a fifth. Eighty-two patients were referred for direct acting antiviral (DAA) treatment. Reasons for non-treatment included lack of advanced fibrosis (30%), lost to follow-up (29%), awaiting newer medications (13%), and substance abuse (8%). Among the 42 patients with results available who initiated DAA therapy, 29 of 42 (69%) achieved RVR, 37 of 38 (97%) achieved ETR, and 25 of 27 (93%) achieved SVR12. **Conclusions:** Our results show that following a highly successful HCV screening and linkage to care program, there remains significant drop off along the later stages of the HCV Care Cascade. This resulted in sub-optimal numbers of patients initiating DAA therapy, despite the fact that excellent outcomes were achieved once patients initiated therapy. Our finding that lost to follow up was a significant contributor to non-treatment suggests that interventions focused on maintaining patients in care (patient navigators, case managers) could improve treatment uptake in this underserved population with high HCV prevalence.

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Diabetes Is a Risk Factor for Weight Gain among Patients Cured of HCV with Sofosbuvir/Ledipasvir

Adiba Azad, Kian Bichoupan, Sweta Chekuri, Thomas Schiano, Andrea D. Branch; Division of Liver Diseases, Icahn School of Medicine at Mount Sinai, New York, NY

Background and aim: New treatments allow an increasing number of patients to be cured of chronic hepatitis C virus (HCV) infection. Anecdotally, many patients have complained that a sustained virologic response (SVR) was accompanied by weight gain. The aim of this study was to analyze weight changes and factors associated with weight changes in patients cured of HCV through treatment with sofosbuvir (SOF)/ledipasvir (LDV). Methods: Data were collected on patients treated with SOF/LDV who achieved an SVR, and had body weight measurements recorded at baseline (within eight weeks of the start of treatment) and within four weeks of SVR. Patients without documented weights, who were on diuretics (furosemide and spironolactone), had significant ascites, and/or had co-morbidities likely to cause weight changes (e.g., malignancies) were excluded. Cirrhosis was determined by diagnostic codes. Diabetes was defined as hemoglobin A1c ≥ 6.5%. Obesity was a body mass index (BMI) ≥ 30.0. Weight changes were analyzed by paired t-tests for two intervals: baseline to SVR, and baseline to end of follow up (up to 520 days from baseline). Results: Of the 167 patients, 93 patients (56%) were male, mean age was 60 ± 11 yr. The mean weight change baseline to SVR was +2.6 ± 7.8 pounds (lb), ($p < 0.01$). Baseline to SVR, 94 patients (64%) gained weight, 43 (29%) lost weight, and 11 (7%) remained within 1 lb of baseline. The mean gain was +7 ± 5.3 lb, and the mean loss was -6.5 ± 4.9 lb. Sixty patients (41%) gained ≥ 5 lb, 23 (16%) gained ≥ 10 lb, and 11 (7%) lost ≥ 10 lb. Diabetic patients (n = 24) gained significantly more weight, 5.8 ± 7.2 lb, than non-diabetics (n = 124), 1.9 ± 7.8 lb ($p = 0.03$). There was no statistically significant difference in weight change between males and females ($p = 0.38$), patients with and without cirrhosis ($p = 0.42$), patients with and without obesity ($p = 0.90$), patients with treatment ≥ of less than 12 weeks ($p = 0.29$). Pre-treatment albumin, total cholesterol, LDL, HDL, and triglycerides did not differ significantly between patients who gained weight and those who lost weight. Among 103 patients with a second post-SVR weight measurement, the mean change was 3.7 ± 9.0 lb, ($p < 0.01$). Conclusion: 64% of patients who achieved an SVR with SOF/LDV treatment gained weight. The gain for the entire group was modest, 2.6 lb, but was greater for diabetics, 5.8 lb. Weight increases continued during follow up. To prevent excessive weight gain, patients receiving HCV treatment, especially those with diabetes, may benefit from advice about diet and exercise (DA 031095, DK 090317).

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Degree of Normalization of Hyperferritinemia by the End of IFN-free DAA for Chronic Hepatitis C Patients Is Predictive of Early Post-treatment Emergence of HCC

Po-sung Chu, Nobuhiro Nakamoto, Aya Ugamura, Hirotoshi Ebinuma, Hidetsugu Saito, Takanori Kanai; Keio University School of Medicine, Tokyo, Japan

Background and Aims: Interferon (IFN)-free direct antiviral agents (DAAs) effectively eradicate hepatitis C viruses (HCV) and rapidly improve liver residual functions. However, whether IFN-free DAAs prevent HCC primarily or secondarily is still unknown. Chronic hepatitis C (CHC) causes dysregulation of iron metabolism, which leads to moderate iron overload featured as hyperferritinemia. Iron overload is also suspected to be one of the factors favoring HCV-related hepatocellular carcinoma (HCC). However, whether IFN-free DAAs normalize HCV-related hyperferritinemia, and may ferritin be a possible predictive factor for HCC undergoing DAAs, are not yet elucidated. Methods: With the commitment of institutional review board and prior informed consents, 70 genotype 1 CHC patients undergoing IFN-free DAAs (54 with daclatasvir and asunaprevir; 18 with sofosbuvir and ledipasvir) were recruited, and laboratory data at day 0 (pre) and at the end of treatment (EOT) were analyzed. Patients with active bleeding, iron supplementation, end-stage renal disease, and women before menopause were excluded in this analysis. For HCC surveillance, patients were followed according to guidelines by AASLD/IDSA. Any HCC identified after EOT within 6 months was defined as early emergence. Results: Eight cases of early post-treatment HCC emergence were noticed (11.4%). At EOT, serum ferritin decreased significantly (199±198 IU/l vs. 91± 80 IU/l, p<0.0001), and this significant decrease was also noticed when adjusted by gender or by age. The change rate of serum ferritin (Δferritin%, compared to pre-treatment values) correlated significantly to the change rates of ALT (p< 0.0001), type 4 collagen 7s (p<0.0001), LDL (p= 0.01), albumin (p= 0.02), and γ-globulin (p= 0.03), and tended to correlate to the change rate of alpha-fetoprotein (AFP, p= 0.06). Δferritin% of cases with early post-treatment emergence of HCC was significantly lower (–31.3±30% vs. –46.5±30%, p= 0.03). In multivariate analysis, along with HCC past history, Δferritin% (p= 0.04; AUC= 0.74 at cut-off value of 49% reduction) was a significant predictive factor of early post-DAA emergence of HCC. Conclusion: Hyperferritinemia was normalized rapidly after IFN-free DAA, in accordance to HCV eradication and improvements in clinical markers for hepatic injury, hepatic stellate cell activity, lipid and protein metabolism. Δferritin% is one of the independent and significant predictive factors of early HCC emergence after IFN-free DAAs. Since obesity or excessive alcoholic intake may also cause hyperferritinemia, serum ferritin might be a useful collective predictive marker of HCC for patients who achieve SVR with IFN-free DAAs.

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A serum metabolomic analysis of HCV-infected patients successfully treated with IFN-free DAA regimens

Giorgia Ceccotti, Gaia Meoni, Leonardo Tenori, Laura Gragnani, Elisa Fognani, Elena Gianni, Claudio Luchinat, Anna Linda Zignego; University of Florence, Florence, Italy

HCV infects about 170 million of subjects worldwide. The virus has a high propensity to persist in the host, leading to cirrhosis and liver cancer. Metabolomics is the study of metabolic changes in biological systems and may identify specific profiles associated with subtle alterations induced by diseases. Few studies are available on metabolitic changes in liver injuries, and since none of which was focused on HCV-infected patients before and after reaching a SVR following treatment with direct acting antivirals (DAAs), the aim of this study was to perform a serum metabolomics analysis in this setting. Sera were collected from 52 HCV patients (18 men, mean age 65 ±9,7) successfully undergoing different IFN-free DAA regimens, before therapy (baseline) and at post-treatment week 12 (SVR12). HCV genotype was 1a/1b in 70%, 2a/2c in 23%, 3 in 4.7% and 4 in 2.3%. METAVIR score indicated F3-F4 score in 55% of patients, the remaining 45% had F0-F2. We also analyzed a small group of 12 sera from healthy subjects in order to localize them in the PLS plot respect to baseline and SVR12 as a preliminary negative control for both groups. Samples were analyzed using proton nuclear magnetic resonance spectroscopy (^{1}H-NMR). Partial Least Squares (PLS) and the canonical analysis (CA) were applied, demonstrating a significant pair-wise discrimination (96% of accuracy) for the two time-points of each patient and highlighting a metabolic shift. Several metabolites with unequivocal assignment (i.e. amino acids, organic acids, creatine, creatinine, lactate and choline) differed comparing baseline with SVR12. Baseline featured higher level of formate and acetate (p<0.05) and methionine was higher in SVR12 (p<0.05). Preliminary analysis revealed also a progressive nearing of SVR12 to the healthy fingerprint. The serum metabolomic analysis of pre- and post-treatment samples showed remarkable profile changes from baseline to SVR12. We found variations, with opposite directions, in formate (produced in adults only by hepatocytes) and methionine. These metabolites take part in biochemical ways (i.e. glucose metabolism) also involving acetate and other amino acids, going through the synthesis of folates. These alterations could be implied in the metabolic impairment previously observed in chronically infected HCV-patients. Also, since methionine is the major source of methyl groups, an understanding of its variation, could reveal important dysfunctions in liver essential pathways requiring methylation (i.e. epigenetic regulation of DNA) in HCV-related chronic infection.

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Implementing HepCure - An Innovative Web-based Toolkit for Hepatitis C to Train Primary Care Providers and Increase Patient Engagement

Ponni V. Perumalswami[1], Trang Vu[2], Brooke Wyatt[1], Korin Parrella[2], Jason Rogers[3], Jeffrey J. Weiss[2]; [1]Liver Diseases, Icahn School of Medicine at Mount Sinai, New York, NY; [2]General Internal Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; [3]Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY

Background and Aims: Primary care based models of HCV care have been successfully established although widespread adoption has been limited. There is an urgent need to scale up global training of providers for HCV. The aim of this study is to develop and operationalize HepCure (hepcure.org), a web-based application (app) offering three components: An open access toolkit (a dashboard) that enhances providers' ability to deliver guideline-based HCV care; a linked patient app that provides education, medication reminders, and a platform for tracking adherence and symptoms; and a tele-education platform for medical providers. Methods: The HepCure app is a collaboration among an academic, tertiary care medical center, the New York State (NYS) Department of Health (DOH), and community health centers in NYS. The HepCure platform captures United States Centers for Medicaid and Medicare HCV quality indicators for population health management. National HCV treatment guidance was used to provide decision support algorithms. Patient data is de-identified when cases are submitted by providers for discussion at weekly tele-education sessions with experts. Results: The HepCure Provider Dashboard (http://providers.hepcure.org) was launched in November 2014. Weekly tele-education sessions have been conducted since February 2015 (n=57) and each session has been archived with open access. There have been a total of 322 unique attendees and weekly sessions have been attended by a mean of 22 ± 9 attendees a week. The patient mobile app was launched in November 2015 to increase patient engagement and has had 546 downloads through May 2016. The primary barrier to adoption has been lack of deep integration into existing electronic health records (EHRs). HepCure is currently working with the NYS DOH to integrate HepCure into Epic and EHRs used by over 80% of community health centers in NYS. In addition, the NYS DOH HCV quality indicators (eHepQual) will be integrated into HepCure allowing for direct reporting. Conclusions: The HepCure platform brings HCV infected patients, primary care providers, and expert hepatologists together to increase treatment capacity and patient engagement with the goal of improving health outcomes. The initial implementation phase has led to the recommendation for a series of enhancements including EHR integration and creating capacity for local experts to provide case based tele-education through a hub and spoke model. These upgrades are in process along with research to evaluate the outcomes of providers and patients using HepCure. Implementation of HepCure in resource limited settings without EHRs is also being explored.

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Association of mutations at amino acids 70 and 91 of the HCV core protein with hepatocellular carcinoma risk among HALT-C trial patients

Ahmed M. Elshamy[1], Matthew Pendleton[2], Francis J. Eng[1], Erin H. Doyle[1], Ali Bashir[2], Andrea D. Branch[1]; [1]Liver Diseases, Icahn School of Medicine at Mount Sinai, New York, NY; [2]Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY

Background and aim: Amino acid mutations at positions 70 and 91 of HCV core protein are associated with an increased risk of hepatocellular carcinoma (HCC) in Asian patients infected with genotype-1b HCV. For the first time, in this study, we evaluated the prognostic significance of these mutations in a United States population. ***Methods:*** The HCV quasispecies in baseline serum samples of 90 patients with chronic genotype-1b HCV infection enrolled in the HALT-C trial were investigated using MiSeq deep sequencing. The relationship between the percentage of the quasispecies with a mutation at position 70 and/or 91 and the incidence of HCC was evaluated by receiver operating characteristic (ROC), Kaplan-Meier and multivariable Cox regression analyses. ***Results:*** In ROC analysis, quasispecies percentage cut-points ≥42% of non-arginine at position 70 (non-R^{70}) or ≥98.5% of non-leucine at position 91 (non-L^{91}) had optimal sensitivity at discerning higher or lower HCC risk. At baseline, the quasispecies of 88.5% (23/26) of the patients who later developed HCC (median follow-up, 4.4 years; range, 0.4-8.5) had ≥ 42% non-R^{70} whereas only 68.8% (44/64) of matched controls who remained HCC-free (median follow-up, 7 years; range, 2.7-8.6) had ≥ 42% non-R^{70} (P=0.06) (Fisher's exact probability test). The baseline quasispecies of 30.8% (8/26) of patients who developed HCC had ≥ 98.5% non-L^{91} whereas 54.7% (35/64) of matched controls had ≥ 98.5% non-L^{91} (P=0.06). By Kaplan-Meier analysis, HCC incidence was higher among patients with baseline non-R^{70} ≥ 42%, but the difference was not significant (P=0.08), while it was significantly lower among patients with baseline non-L^{91} ≥ 98.5% (P=0.01). Additionally, in a Cox regression model, increased HCC risk was associated with the presence of non-R^{70} ≥ 42% quasispecies at baseline [hazzard ratio (HR)=3.83, 95% confidence interval (CI)=1.02-14.3; P=0.04], higher AST/ALT ratio (HR=4.08, 95% CI=1.24-13.47; P=0.02), and higher alkaline phosphatase (HR=1.01, 95% CI=1.0-1.02; P=<0.001). Greater numbers of white blood cells were associated with reduced HCC risk (HR=0.64, 95% CI =0.45-0.89; P=0.01). ***Conclusion:*** This pilot study of United States patients adds to previous evidence that HCV core protein mutations associate with HCC risk and indicates the potential utility of HCV quasispecies analysis as a non-invasive biomarker of HCC risk.

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Less Than One Third of High Risk Patients Eligible for Hepatitis C Virus Screening Received Appropriate Testing: A Community-Based Safety-Net Hospital Experience

Brendan Campbell[1], Yael Bogler[2], Rachel Baden[2], Taft Bhuket[1], Benny Liu[1], Robert J. Wong[1]; [1]Gastroenterology and Hepatology, Alameda Health System - Highland Hospital, Oakland, CA; [2]Medicine, Alameda Health System - Highland Hospital, Oakland, CA

Background: Successful eradication of chronic hepatitis C virus (HCV) relies on effective screening programs for early

detection and linkage to care. However, awareness of HCV screening guidelines may be lacking, especially among urban safety-net populations with a high prevalence of socioeconomically disadvantaged non-English speaking minorities. Aim: To evaluate rates of HCV screening and HCV awareness among patients at high risk for chronic HCV at a diverse safety-net hospital Methods: A prospective cohort study of consecutive adults undergoing outpatient endoscopy from July 2015-March 2016 evaluated HCV screening rates among high risk patients (based on U.S. Preventative Services Task Force guidelines), with focus on birth cohort (1945-1965) and risk-based (history of drug use, incarceration, blood transfusion prior to 1992) factors. Awareness of prior HCV results and rates of accepting HCV testing were evaluated with chi-square testing and multivariate logistic regression. Results: Among 869 patients, 65.5% (n=569) were high risk for chronic HCV (51.3% male, 57.8% 1945-1965 birth cohort, 4.5% history of drug use, 6.2% history of incarceration, 5.8% blood transfusion, 9.8% HIV). Among this cohort, 30.6% received prior HCV testing, among which 36.0% were aware of test results. HCV positive patients were more likely than HCV negative patients to be aware of results (90.0% vs. 27.7%, p<0.001). Among high risk patients offered HCV testing, 83.9% accepted. Compared to non-Hispanic whites (64.0%), blacks (80.6%), Asians (89.6%), and Hispanics (93.7%) were more likely to accept testing, p<0.001. Non-English speaking patients were more likely to accept testing (91.0% vs. 77.5%, p<0.001). Patients born in 1945-1965 were less likely to accept testing (82.6% vs. 91.9%, p=0.06). On multivariate regression, blacks, Asians, and Hispanics were all significantly more likely to accept HCV testing compared to non-Hispanic whites (Table). Conclusion: Among adults presenting for outpatient endoscopy at an urban safety-net hospital, 65.4% were high risk for HCV, of which only 30.6% received prior testing. Of those that received prior testing, only 36% were aware of results. Lower rates of test acceptance among the 1945-1965 birth cohort is concerning given higher risks among this group.

Predictors of HCV Testing Acceptance

	Odds Ratio	95% CI	P-Value
Male (vs. Female)	1.61	0.86 - 3.01	0.13
1945-1965 Birth Cohort	0.34	0.10 - 1.19	0.09
Non-Hispanic White	1.00	Reference	-
Black	2.59	1.21 - 5.54	0.01
Asian	5.80	2.26 - 14.91	< 0.001
Hispanic	10.93	4.41 - 27.10	< 0.001

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Assessment of risk of acute kidney injury associated with exposure to sofosbuvir-containing HCV treatment regimens and HCV infection

Laura Telep, Andrea Brown, Diana M. Brainard, Anand P. Chokkalingam; Epidemiology, Gilead Science, Inc, Foster City, CA

BACKGROUND: The relationship between chronic kidney disease and hepatitis C virus (HCV) infection is well described, but less is known about acute kidney injury (AKI) in the HCV-infected population. In addition, the direct-acting antiviral sofosbuvir (SOF) is now widely used in the treatment of HCV. The objective of this cohort study was to characterize rates of AKI in HCV-infected patients versus patients without HCV, and to examine these rates during exposure to SOF-containing and non-SOF containing treatment regimens. METHODS: 173,677 adult patients with evidence of HCV infection were identified from a large US administrative medical claims database (claims incurred from January 1, 2010 to March 31, 2015). Data from these patients were compared with those from a random 1% sample of adult patients without evidence of HCV infection (N=529,265) from the same database. Validated administrative claim codes were used to determine first diagnosis of AKI. All included patients had at least 6 months of continuous enrollment in their medical plan prior to cohort entry and no prior AKI-related claims. Absolute rates and their corresponding exact Poisson 95% confidence intervals (CIs) were determined for each group, and adjusted incidence rate ratios (IRRs) were determined using Poisson regression. RESULTS: Among identified HCV patients, the absolute AKI rate was 2.91 per 100 person-years (PY; CI: 2.85-2.98) versus 0.40 per 100 PY (CI: 0.39-0.41) in the non-HCV population. AKI rates were higher among patients with concomitant cirrhosis and with concomitant end-stage liver disease or liver transplant (9.27 and 21.63 per 100 PY, respectively). After adjustment for age, sex, and baseline covariates including renal insufficiency and cirrhosis, HCV infection was found to be associated with an approximate 4-fold increase in risk of AKI (IRR=3.89, CI: 3.40-4.45, p<0.0001). Among HCV-infected patients receiving treatment, the absolute AKI rate during exposure to SOF-containing regimens was 4.32 per 100 PY (CI: 3.51-5.25), while the rate during exposure to alternative treatments was 3.62 per 100 PY (CI: 3.15-4.14). After adjusting for age, sex, and baseline covariates including renal insufficiency and cirrhosis, exposure to a SOF-containing regimen was associated with a non-significant reduced risk of treatment-emergent AKI events (IRR=0.81, CI: 0.63-1.04). CONCLUSIONS: The results of this real-world observational study indicate that HCV infection is independently associated with increased risk of AKI, and that there is no independent association between exposure to SOF and risk of treatment-emergent AKI. These results should be confirmed in future investigations.

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Chronological changes in FIB-4 and hepatocellular carcinoma development in patients with chronic hepatitis C after successful virus eradication

Takuya Genda, Ayato Murata, Nozomi Amano, Sho Sato, Hironori Tsuzura, Shunsuke Sato, Yutaka Narita, Yoshio Kanemitsu, Yuji Shimada, Katsuyori Iijima, Akihito Nagahara, Sumio Watanabe; Gastroenterology and Hepatology, Juntendo University Shizuoka Hospital, Izunokuni, Japan

Background and Aims: Histological hepatic fibrosis is an important predictive factor for hepatocellular carcinoma (HCC) development in patients with chronic hepatitis C (CHC). However, owing to the invasive nature of liver biopsy, several alternative fibrosis markers have been proposed. FIB-4, an index that combines standard biochemical values and age, is recognized as not only a simple and reliable alternative to liver biopsy for assessing hepatic fibrosis, but also a useful predictive marker for HCC development. Recent advances in antiviral treatment have improved the rate of sustained virological response (SVR) in patients with CHC. However, the risk of HCC development persists even in patients who achieve SVR. Achievement of SVR

results in alteration of standard biochemical values in most patients, but changes in FIB-4 and its association with HCC development after SVR have not been fully clarified. **Methods**: This study included 433 CHC patients who received interferon-based antiviral therapy and achieved SVR between 2004 and 2014. FIB-4 was estimated immediately before treatment, at 24 weeks after the end of treatment (SVR24), and at the last laboratory examination during follow-up (last visit). Multivariate Cox proportional hazard analysis was used to estimate hazard ratios (HRs) of variables for HCC development. Cumulative incidences of HCC development were evaluated using Kaplan-Meier plot analysis and the log-rank test. **Results**: During the median follow-up time of 3.2 years (range: 1.0-9.8 years), 11 of the 433 patients developed HCC. The median FIB-4 values at pretreatment, SVR24, and the last visit were 1.99, 1.71, and 1.68, respectively; the values at all the time points were significantly different from one another (P < 0.001). At each time point, patients who developed HCC had significantly higher FIB-4 than those who did not develop HCC. The areas under the receiver operator characteristic curves indicated that pretreatment FIB-4 predicted HCC development with high diagnostic accuracy (0.833) and was superior to the predictive value of FIB-4 at SVR24 (0.747) and at the last visit (0.791). Multivariate Cox proportional hazard analysis demonstrated that only pretreatment FIB-4 was significantly associated with HCC development (HR 1.58, P < 0.001). The cutoff value of pretreatment FIB-4 was identified as 2.90. The 5-year cumulative incidences of HCC development were 9.0% and 1.1% in patients with pretreatment FIB-4 ≥2.90 and <2.90, respectively (P < 0.001). **Conclusion**: Although FIB-4 decreased over time, patients with a high pretreatment FIB-4 remain at high risk of HCC development after achieving SVR.

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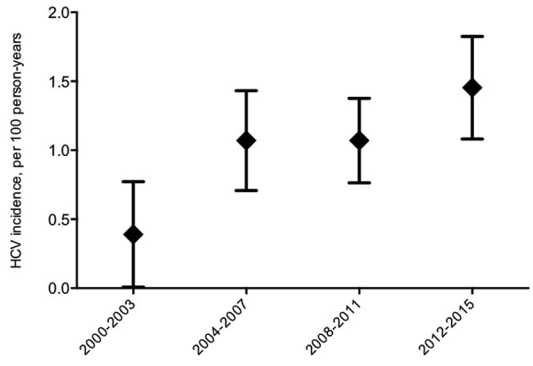
Increasing incidence of hepatitis C virus among HIV-infected men who have sex with men from 2000-2015 in San Diego: a retrospective cohort analysis

Antoine Chaillon[1], Thomas C. Martin[3], Edward R. Cachay[1], David L. Wyles[1], Davey M. Smith[1], Susan J. Little[1], Sanjay R. Mehta[1], Natasha K. Martin[2], Richard L. Garfein[2]; [1]Division of Infectious Diseases, University of California San Diego, La Jolla, CA; [2]Division of Global Public Health, University of California San Diego, La Jolla, CA; [3]School of Medicine, University of California San Diego, La Jolla, CA

Background: International reports of a hepatitis C virus (HCV) epidemic among HIV-positive men who have sex with men (HIV+ MSM) associated with recreational drug use with sex are causing concern. However, little is known about the HCV epidemic among MSM in San Diego. We assess the incidence of HCV among HIV+ MSM in San Diego. **Methods:** We performed a retrospective cohort analysis of HCV incidence among HIV+ MSM attending the largest HIV clinic in San Diego (UCSD Owen Clinic) from 2000-2015. Incident HCV infection was assessed among HIV+ MSM with a baseline negative anti-HCV test between 2000 and 2015. Incident infection was defined as any new positive anti-HCV or HCV-RNA test after the start of follow-up. Incidence was calculated using survival time methods. **Results:** Among 2,091 baseline negative patients, 141 HCV seroconversions occurred over 12,926 person-years at risk (incidence rate = 1.09/100 person-years; 95%CI 0.92-1.29). HCV incidence increased over time from 0.26/100py in 2000-2003 to 1.42/100py in 2012-2015 (Figure 1, trend test p=0.027). Individuals were tested a median of 3 times (interquartile range[IQR] 2-4) with a median testing interval of 1.2 years (IQR 0.6-2.2). Incident cases were on average 41 years in age, 11.8 years from HIV diagnosis to HCV diagnosis, and 4.9 years from first HCV negative test to HCV diagnosis. 17% (24/141) of MSM reported ever injecting drug use. HCV incidence was significantly higher (p<0.001) among MSM reporting IDU (2.6/100py, 95%CI 1.74-3.88) compared to not reporting IDU (0.97/100py, 95%CI 0.81-1.17), with no significant differences in testing rates. **Conclusions:** HCV incidence among HIV-positive MSM in San Diego is increasing, with rates similar to London and other major European cities, and double that observed in the US Multicenter AIDS Cohort Study. This study also documented HCV infection among HIV+ MSM who do not inject drugs. Further work determining the epidemic trajectory and prevention required to control the epidemic is needed.

Figure 1. HCV incidence among HIV-positive MSM in San Diego, 2000-2015



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Adherence to HCV Birth Cohort Screening Guidelines by Primary Care and Subspecialty Physicians in an Integrated Healthcare System

Amoah Yeboah-Korang[1], Mohammad Beig[1], Jay L. Goldstein[1], Amnon Sonnenberg[2], Claus Fimmel[1]; [1]Gastroenterology, NorthShore University Health System, Chicago, IL; [2]Oregon Health and Science University, Portland, OR

Purpose: Despite the 2012 CDC and 2013 USPSTF recommendations that patients born between 1945 and 1965 should receive one-time HCV antibody testing, the majority of US baby boomers have not been screened to date, indicating gaps in the implementation of the guidelines. The primary aim of this study was to compare HCV screening rates between primary care and subspecialty clinic patients in an integrated healthcare system comprising over 250,000 baby boomers. **Methods:** We identified all baby boomers presenting for at least one outpatient visit to internal or family medicine, gynecology, or other subspecialty clinics at NorthShore University HealthSystem in July 2015. Patients' electronic medical records (EMR) were searched for HCV antibody test results dating back to 2003. The frequency of HCV antibody testing was stratified by age,

gender, prior history of HCV infection, and provider specialty. The influence of patient and physician characteristics on the frequency of testing was analyzed using multivariate logistic regression. **Results:** 12,344 patients met the HCV screening criteria during the one-month sampling period. Of these, 1882 (15%) had undergone HCV antibody testing. Ninety (4.8%) screened patients were HCV antibody-positive, and 84 of 90 patients (93%) underwent follow up HCV RNA testing. HCV-RNA was detectable in 61 of 84 antibody-positive patients (73%). HCV testing was slightly less common in men (14%) than women (16%), and significantly more common in patients who were younger vs. older than age 65 (16% vs. 12%, respectively). The highest HCV screening rates were observed in gynecology clinic patients (17%), followed by internal medicine (16%), family medicine (13%), and other subspecialties including gastroenterology (10%). In the multivariate analysis all these characteristics, except gender, exerted an independent and statistically significant influence on HCV antibody testing. Among patients with a positive HCV antibody test result, the rates of HCV RNA testing were not affected by physician specialty or patient characteristics. **Conclusion:** Overall, we observed a low adherence to HCV birth cohort screening guidelines among different outpatient settings in an integrated healthcare system, as EMR-documented HCV antibody test results were found in only 15% of all eligible patients. Patients younger than age 65 were more likely to be tested than older patients, and there was significant variability between different specialty clinics, with screening rates varying from 10% to 17%. Our study identifies opportunities for increased HCV antibody screening efforts that could incorporate age- and clinic-specific practice patterns.

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HCV is an independent predictor of hospital readmission in inmates

Alysse G. Wurcel[1,2], Deirdre J. Burke[1,2], Brian Engle[2], Kathryn Noonan[4], Tamsin A. Knox[2], Arthur Y. Kim[5], Benjamin P. Linas[3]; [1]Geographic Medicine and Infectious Diseases, Tufts Medical Center, Boston, MA; [2]Public Health and Community Medicine, Tufts University School of Medicine, Boston, MA; [3]Infectious Diseases, Boston Medical Center, Boston, MA; [4]Lemuel Shattuck Hospital, Boston, MA; [5]Infectious Diseases, Massachusetts General Hospital, Boston, MA

Background: Understanding the burden of HCV-related hospitalizations in inmates is important to making rational policy about HCV treatment in prisons. We compared hospital lengths of stay and readmission by HCV infection status among inmates. **Methods:** Lemuel Shattuck Hospital (LSH) provides inpatient medical services to inmates in MA. We used billing records to develop a database of inmate discharges from LSH 2004 to 2014. Data collected included: age, race, gender, date of admission & discharge, length of stay (LOS), all reported ICD-9 codes, and disposition from hospital (died, back to prison, to another hospital). We identified HCV-infected individuals by using HCV-associated ICD-9 codes (070.41, 070.44, 070.51, 070.54, 070.70, 070.71). We compared HCV-infected to un-infected individuals. The primary outcomes were LOS and odds of readmission to LSH. Logistic regression adjusted for confounding by age, sex, race, LOS of first admission, and co-morbidities (Elixhauser index). **Results:** 4668 inmates contributed a total of 8397 discharges. 93% of inmates were male, 53% were white, median age at first hospitalization was 44 yrs (IQR 34, 52). HCV ICD-9 codes were associated with of 20% of hospitalizations. Median LOS was 5 days (IQR 2, 9). Inmates with HCV were older (46 vs. 42, p<0.001) and had longer mean LOS (6 days vs. 5 days, p<0.001). In multivariable modeling, HCV remained associated with increased odds of readmission (1.3, CI (1.1-1.6)). **Conclusion:** In MA, HCV-infection is associated with 20% of inmate admissions, a 20% increase in LOS, and a 30% increase in the odds of readmission to the hospital. Treatment may not avert all of the observed increase in hospitalization, but HCV is associated with many admissions and modest reductions in hospital utilization after SVR could help offset treatment costs.

Factors Associated with Readmission in Inmates (n = 4,668)

		N (%)	Adjusted Odds Ratio (95% CI)
HCV	No	3757 (80.5)	-
	Yes	911 (19.5)	1.32 (1.11, 1.56)
Sex	Female	347 (7.4)	-
	Male	4321 (92.6)	1.33 (1.02, 1.74)
LOS, days	<5	2678 (57.4)	-
	>5	1990 (42.6)	1.01 (0.88, 1.15)
Age, yrs	<30	754 (16.2)	-
	30-39	1022 (22.0)	1.18 (0.93, 1.50)
	40-49	1383 (29.7)	1.62 (1.30, 2.02)
	50-59	963 (20.7)	1.73 (1.36, 2.18)
	60-69	392 (8.4)	2.48 (1.87, 3.28)
	>70	137 (3.0)	4.51 (3.06, 6.65)
Race	White	2455 (52.6)	-
	Non-White	2213 (47.4)	0.80 (0.70, 0.92)
Liver Disease	No	4385 (93.9)	-
	Yes	283 (6.1)	1.46 (1.12, 1.90)
HIV	No	4420 (94.7)	-
	Yes	248 (5.3)	1.95 (1.48, 2.57)
Elixhauser Index	None	646 (13.9)	-
	1-2	2219 (47.6)	1.12 (0.91, 1.37)
	3-4	1400 (30.1)	0.99 (0.80, 1.23)
	≥5	393 (8.4)	0.86 (0.64, 1.15)

*When the Elixhauser Index variable was used in the multivariable model, HIV and Liver Disease were removed from the index.

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Hepatitis Mobile Team: a new concept for benefit toward drugs users and precarious people with hepatitis C in France

Andre Jean Remy[1,2], Hakim Bouchkira[2,1], Patrice Lamarre[2,1], Stephane Montabone[2,1]; [1]liver unit, Centre Hospitalier, Perpignan, France; [2]HEPATITIS MOBILE TEAM, PERPIGNAN, France

Introduction: Although highest european screening rate in France, 44% of patients didn't take care of hepatitis C because there were no diagnosed. Drug injection was main contamination route of hepatitis C virus (HCV) in France and western Europe since 1990. French guidelines were to treat all inmates and drug users, even fibrosis level. Access of HCV screening, care and treatment in drugs users, prisoners and homeless was low in France, less of 20%. They were considered as difficult to treat populations. . All these patients need support especially psycho-educative interventions. Hepatitis Mobile Team (HMT) was created in July 2013 to increase screening care and treatment of hepatitis B and C patients. We proposed 15 services: 1. Screening by Dried Blood Spot (DBS) HIV HBV HCV 2. Mobile Fibroscan* in different sites 3. Social screening and diagnosis (EPICES score) 4. Outreach center with specific health care workers 5 days/7 5. Free blood tests in primary care if no social insurance 6. Advanced on-site specialist consultation 7. Access to obligatory pre-treatment commissions. 8.

Individual psycho-educative sessions 9. Collective educative workshops 10. Staff training 11. Drug users prevention 12. Peer to peer program 13.Low cost specific patients mobile phones 14.Specific one day hospitalizations before and after antiviral treatment 15. Green thread: outside DBS and FIBROSCAN* in specific converted truck. Objective: increase screening care treatment access and cure of our target population. Patients and methods Target population was drugs users, prisoners, homeless, precarious people, migrants and psychiatric patients. We proposed part or all of our services to our medical and social partners. They choose only services what they need. Results: from 2013 July to 2015 December, we did 2056 DBS for 1485 people (944 HCV DBS). Our HCV active file was 244 patients included 18% of new patients screened by DBS ; 83% realized all blood tests and FIBROSCAN; 59% need treatment according to French recommendations; 50% started treatment and 49% have been cured. Quality of program for patient were free access, closeness (outside hospital), speed (of the results) and availability (of nurse and social workers). Conclusions: Specific screening, follow up and support of these difficult to treat populations are essential for increase medical management and cure of HCV patients. HMT offered complement services and not substitution of existing services. It was new useful tool to screen, diagnosis and treat these patients by outside pathway of care.

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The prediction of hepatocellular carcinoma development and overall survival in chronic hepatitis C using liver stiffness measurement: a long-term outcome study

Ryo Nakagomi, Ryosuke Tateishi, Ryota Masuzaki, Taijiro Wake, Mizuki Nishibatake, Naoto Fujiwara, Masaya Sato, Tatsuya Minami, Kenichiro Enooku, Hayato Nakagawa, Yoshinari Asaoka, Yuji Kondo, Kazuhiko Koike; Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Background and Aims: To evaluate the utility of liver stiffness measurement for the prediction of hepatocellular carcinoma (HCC) development and survival in chronic hepatitis C patients. Method: We enrolled 1,130 patients in whom liver stiffness was measured using FibroScan® at the authors' hospital from December 2004 to December 2015. We excluded patients who had already achieved sustained virological response (SVR) at the initial liver stiffness measurement. We assessed HCC development and overall survival based on liver stiffness using Kaplan-Meier method. Results: The patients consists of 493 males and 637 females with median age of 64. Liver stiffness at the enrollment was ≤5 kPa in 235, 5.1–10 kPa in 454, 10.1–15 kPa in 190, 15.1–20 kPa in 96, 20.1–25 kPa in 57, and >25 kPa in 98, respectively. During the mean follow-up period of 6.6 years, HCC developed in 191 patients. The cumulative incidence rates of HCC at 1, 2, 3, 5, 7, and 10 years were 1.9%, 4.9%, 7.4%, 12.1%, 17.3%, and 23.3%, respectively. Cumulative HCC incidence rates at 5 years were 1.7% in those with ≤5 kPa, 3.3% in 5.1–10 kPa, 16.4% in 10.1–15 kPa, 25.4% in 15.1–20 kPa, 38.4% in 20.1–25 kPa, and 43.2% in >25 kPa, respectively (P <0.001). During the study period, 101 patients died. The cause of death was liver cancer in 30, liver failure in 17, gastrointestinal bleeding in 7, and others in 47. Overall survival rates at 1, 2, 3, 5, 7, and 10 years were 99.9%, 99.5%, 98.8%, 96.8%, 93.0%, and 86.7%, respectively. Ten-year survival rates were 99.3% in those with ≤5 kPa, 95.7% in 5.1–10 kPa, 81.7% in 10.1–15 kPa, 80.9% in 15.1–20 kPa, 64.5% in 20.1–25 kPa, and 48.3% in >25 kPa, respectively (P <0.001). Conclusions: Liver stiffness can predict long-term outcomes over 5 years in chronic hepatitis C patients.

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Hepatitis C Virus Seroprevalence Survey in the Country of Georgia

Liesl Hagan[1], Ana Kasradze[2], Stephanie Salyer[3], Amiran Gamkrelidze[2], Maia Alkhazashvili[2], Gvantsa Chanturia[2], Nazi Chitadze[2], Roena Sukhiashvili[2], Marina Shakhnazarova[2], Curtis Blanton[3], Steven Russell[3], Giorgi Kuchukhidze[2], Davit Baliashvili[2], Susan Hariri[1], Jan Drobeniuc[1], Paata Imnadze[2], Juliette Morgan[3], Francisco Averhoff[1]; [1]Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, GA; [2]National Center for Disease Control, Tbilisi, Georgia; [3]Division of Global Health Protection, Centers for Disease Control and Prevention, Atlanta, GA

Purpose: Georgia is the first country in the world to adopt a national HCV elimination goal, set for 2020. This abstract presents results from Georgia's first nationally representative hepatitis C virus (HCV) seroprevalence survey, which will be used to monitor progress toward HCV elimination. **Methods:** A cross-sectional, nationally representative seroprevalence survey of 7,000 individuals aged ≥18 years was conducted in Georgia from May-August 2015 using a stratified, multi-stage cluster design. After giving informed consent, participants provided epidemiologic data including demographics, medical history, knowledge of HCV transmission and prevention methods, and HCV-related risk factors. Blood specimens were collected from participants and tested for antibodies to HCV, and for HCV RNA. Data were weighted based on probability of selection and calibrated using census data on sex, age, and geography. Descriptive statistics were computed. **Results:** Nationally, HCV seroprevalence was 7.7% (95% CI: 6.7-8.9), and prevalence of chronic HCV infection was 5.4% (95% CI: 4.6-6.4). Seroprevalence was 9.4% (95% CI: 6.9-12.6) in the capital city (Tbilisi), 9.5% (95% CI: 8.0-11.3) in urban areas overall, and 5.4% (95% CI: 4.4-6.7) in rural areas. Seroprevalence was highest among persons aged 40-49 years (14.0%, 95% CI: 11.1-17.6), males (12.1%, 95% CI: 10.2-14.3), and persons reporting a history of injection drug use (IDU) (66.5%, 95% CI: 56.0-75.6), incarceration (42.0%, 95% CI: 32.8-51.7), or blood transfusion before and after Georgia began testing donor blood for HCV in 1997 (25.3%, 95% CI: 16.2-37.3; 17.4%, 95% CI: 10.7-27.1, respectively). A majority of respondents demonstrated knowledge that HCV can be transmitted through infected blood (56.1%, 95% CI: 53.9-58.3) or by sharing needles or syringes (52.3%, 95% CI: 50.0-54.6), and that HCV can be prevented by avoiding needle sharing (54.1%, 95% CI: 51.9-56.3) and avoiding unsterile/used medical devices (50.0%, 95% CI: 47.4-51.7). Less than half (38.9%) of seropositive respondents were aware of their infection, and 11.8% reported initiating treatment prior to the availability of all-oral,

direct-acting antiviral drug regimens in Georgia. **Conclusions:** HCV seroprevalence in Georgia is high overall, exceeding 50% among persons reporting IDU, and is higher in urban than in rural settings. Among those who tested HCV antibody-positive, awareness of infection was low, and most had not been treated. Knowledge of current nationwide HCV prevalence and associated risk factors will inform implementation of prevention, screening, and treatment strategies and will establish a baseline to track progress toward elimination over time.

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Predictors of Treatment Failure Among Irish Individuals Infected with Hepatitis C Virus.

Jonathan Dean, Martha Neary, Suzie Coughlan, Cillian F. De Gascun; National Virus Reference Laboratory, University College Dublin, Dublin, Ireland

Introduction With the increasing number of licensed direct-acting antivirals (DAA) for the treatment of chronic HCV infection, choosing the right treatment regimen for the right patient has become paramount. We believe baseline sequencing for the presence of resistance-associated substitutions (RAS) is an important contributor to this decision-making process. In the present study in an Irish cohort, we performed a retrospective analysis on all HCV samples received for drug resistance testing at the Irish National Virus Reference Laboratory between September 2014 and May 2016. Particular attention was paid to patients who experienced virological failure in an attempt to identify predictors of failure. **Methods** Sanger sequence data covering the HCV NS3 protease coding region were obtained for 682 samples received during the study period. Sequence data for the NS5A and NS5B regions in some samples were also obtained. The rs12989860 single nucleotide polymorphism site was examined by allelic discrimination real-time PCR. **Results** Analysis of the NS3 viral sequences demonstrated that 85.5% (583/682) were HCV subtype 1a, 14.2% (97/682) subtype 1b and 0.3% (2/682) subtype 1c infections. RAS proven to reduce susceptibility to NS3 inhibitor treatment were detected in 45.9% of cases (313/682). Although the vast majority of all RAS detected were found in subtype 1a viruses, 7.2% (7/97) subtype 1b samples also contained one or more RAS. The Q80K polymorphism was found in 313/583 (57.3%) of HCV subtype 1a, and almost exclusively in clade 1 (242/443; 54.6%) versus clade 2 viruses (2/140; 1.4%). Among the cohort of patients who experienced virological failure whilst on treatment, RAS could be detected in 11/17 (64.7%) patients for whom sequence could be generated. These included V36M/L (6/11; 54.5%), Q80K (5/11; 45.5%), R155K/T (3/11; 27.3%) and T54S (1/11; 9.1%). The majority of these patients were found to possess the deleterious "T" single nucleotide polymorphism (SNP) at the rs12989860 site within the interleukin-28B gene locus. Nine of eleven patients with detected RAS were found to also be either CT or TT at rs12989860, one patient was CC at this SNP. Preliminary data from patients experiencing treatment failure on NS5A/B inhibitors also indicate the presence of RAS in 4 of 7 individuals. **Discussion** The high incidence of RAS within HCV NS3 protease sequences, the detection of RAS in NS5A sequences, and the apparent risk of treatment failure, albeit in a small number of patients, when the RAS are present, highlights the importance of sequencing these viruses prior to commencing treatment with protease inhibitors, and the need to identify additional predictors of failure.

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Spontaneous Clearance of Chronic HCV Infection is More Frequent in HIV/HCV Coinfection and in HCV Genotype 2 and 3

Varun Jain[1,2], Diana Otero[1,2], Tatjana Gavrancic[1,2], Qing Liu[1,2], Sonja Marcus[3], Norbert Bräu[1,2]; [1]Medical Program, James J. Peters VA Medical Center, Bronx, NY; [2]Dept. of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; [3]Research Program, James J. Peters VA Medical Center, Bronx, NY

BACKGROUND: In acute hepatitis C virus (HCV) infection, 25-40% of patients clear the infection spontaneously through immunological mechanisms. Spontaneous clearance of chronic HCV infection without antiviral therapy has been described only in rare case reports. The frequency of such clearance is unknown as is the influence of HIV coinfection. METHODS: The HCV Clinical Case Registry of a single tertiary care facility was reviewed for all quantitative plasma HCV RNA levels measured from 1997 – 2015 (19 years). Patients with at least one HCV RNA ≥3,000 IU/ml and no evidence of acute infection were included as chronically infected. Cases of spontaneous clearance were defined as at least one HCV RNA <43 IU/ml or undetectable preceded by at least one HCV RNA ≥3,000 IU/mL with no antiviral therapy in the time interval between measures. RESULTS: Among 3,018 chronically HCV-infected patients, 13 (0.43%; 95% confidence interval, 0.23% – 0.74%) experienced spontaneous clearance. Five of the 13 patients were HIV/HCV-coinfected, all of them with suppressed HIV RNA <400 copies/ml on antiretroviral therapy and a median CD4+ cell count of 444/mm3 (range, 198 – 708). No patient was hepatitis B virus /HCV-coinfected (HBsAg+), three had compensated cirrhosis, and one had a prior liver transplantation with HCV recurrence. Among HIV/HCV-coinfected patients, the frequency of spontaneous clearance was 1.07% (5 of 469; 95% C.I., 0.35% – 2.47%), while in HCV-monoinfected patients, the rate was 0.31% (8 of 2,549; 95% C.I., 0.14% – 0.62%). The risk ratio for spontaneous HCV clearance in HIV/HCV coinfection over HCV monoinfection was 3.40 (95% C.I., 1.12 – 10.3, p=0.031). The rate of spontaneous clearance in chronic HCV genotype 1 (GT-1) infection was 0.16% (95% C.I., 0.03% - 0.46%), for GT-2 it was 1.06% (95% C.I., 0.13% - 3.79%), and for GT-3 it was 2.74% (95% C.I., 0.33% - 9.6%). The risk ratio for GT-2 over GT-1 was 6.8 (95% C.I., 3.0 – 102.5, p=0.002), and for GT-3 over GT-1 it was 17.4 (95% C.I., 3.0 – 102.5, p=0.002). CONCLUSION: Spontaneous clearance of chronic HCV infection without antiviral therapy is rare and occurs in about 0.4% of patients. Clearance is significantly more common in HIV/HCV-coinfected than in HCV-monoinfected patients and in GT-2 and GT-3 patients compared to GT-1.

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WITHDRAWN

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Project ITTREAT (Integrated Community Based Test – Stage-Treat) HCV Service for People who Inject Drugs (PWID)

Margaret O'Sullivan[2], Hugh Williams[3], Anna-Marie Jones[4], Sumita Verma[1,2]; [1]Brighton and Sussex Medical School, Brighton, United Kingdom; [2]Gastroenterology and Hepatology, Brighton and Sussex University Hospital, Brighton, United Kingdom; [3]Psychiatry, Surrey and Borders Partnership Trust, Brighton, United Kingdom; [4]Susssex Partnership NHS Trust, Brighton, United Kingdom

Objective/aims: Majority (90%) of HCV positive individuals in England are people who inject drugs (PWID) with poor engagement with health services. Our on going study assesses feasibility of non-invasive detection, staging and treatment of HCV. related chronic liver disease in the community. **Methods:** Four-year prospective study (Dec 2013-Nov 2017) conducted at a large substance misuse service in SE England. Individuals offered dry blood spot testing (DBST), mobile transient elastography (TE), HCV treatment (including DAA) and qualitative interviews with recent addition of patient reported outcomes (SF-12v2, SFLDQOL) and health economics (EQ-5D-5L). **Results:** To date, 391 individuals recruited, 81% males with mean age of 40.0 yrs. (sd 9.8). There was high prevalence of injecting drug use (IDU) [274 (70%)], alcohol use [336 (86%)] and psychiatric illness [174 (45%)]. Uptake of DBST was 49% (n=190); prior testing being the main reason for declining. Prevalence of positive serological markers/PCR were: HBcAb 20% (n=71), HCV antibody 53% (n=200), HCV PCR 82% (163/200); genotypes 1=71 (44%) and 3= 79 (48%). On logistic regression, independent predictors of a positive HCV serology were if ever injected (OR 8.5, 95% CI 4.2-17.4); positive HBcAb (OR 3.5 95% CI 1.9-6.6) and a psychiatric diagnosis (OR 2.1, 95% CI 1.3-3.5). Of those with a positive HCV PCR (n=163), 132 (81%) underwent TE [mean LSM kPa 9.9 (sd 10.3), 59 (36%) having LSM $\geq$ 7.5 kPa, 32 (20%) having cirrhosis (LSM $\geq$12 kPa). There was a significant association between a positive HCV serology and LSM $\geq$7.5 kPa: 72% of those with LSM<7.5 were positive compared to 98% with LSM $\geq$ 7.5 (p<0.001). None had had prior HCV treatment. Forty-eight (29%) were not treatment candidates (chaotic lifestyle). Of the remaining (n=115), 50 commenced treatment. Characteristics of treated cohort were: age 45 yrs. (sd 10.2), 92% male, > 80% having substance/alcohol use, 86% undergoing TE, genotypes (1 = 41%, 3= (55%), treatment received: INF/RBV 32%, INF+DAA=38% and DAA 30% and treatment outcomes were: 35 (70%) SVR/EOTR, nine (18%) on-going treatment, six (12%) NR (included four RR). Twenty- two have had pre-treatment questionnaires done. **Conclusions:** Prevalence of positive HCV serological markers remain high in PWID, which might explain the almost 40% prevalence of significant hepatic fibrosis. Compliance in this difficult to engage cohort was ~ 90% with HCV treatment outcomes comparable to secondary care. Our on going prospective study endorses the success of this novel, easy to replicate "one-stop" community based HCV treatment model with onsite mobile TE.

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Role of primary T cell immunodeficiency and Hepatitis B on spontaneous clearance of Hepatitis C

Nazrul Islam[1,2], Mel Krajden[2,3], Mark Gilbert[2,4], Paul Gustafson[5], Mark Tyndall[1,2], Naveed Z. Janjua[1,2]; [1]School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada; [2]British Columbia Centre for Disease Control, Vancouver, BC, Canada; [3]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada; [4]Ontario HIV Treatment Network, Toronto, ON, Canada; [5]Department of Statistics, University of British Columbia, Vancouver, BC, Canada

Background: T-cell host immune response against hepatitis C virus (HCV) has been suggested to play important role in determining HCV outcomes which has not been examined in population-based cohort studies. Concurrent hepatitis B (HBV) infection has been found a significant predictor of spontaneous clearance of HCV in high-risk population. This study examined the effect of these two along with other factors on the spontaneous clearance of HCV in a population-based cohort in British Columbia, Canada. **Methods**: The BC Hepatitis Testers Cohort (BC-HTC) includes all individual tested for HCV between 1990 and 2013 linked with data on their medical visits, hospitalizations, and prescription drugs. HCV positive individuals with at least one valid HCV PCR test on or after HCV diagnosis (n=46,783) were included in this study. To examine factors associated with the spontaneous clearance of HCV, we fitted multivariable logistic regression on the full sample, and Cox proportional hazard model on the seroconverters i.e. HCV negative individuals who subsequently became HCV positive (n=6,238). **Results**: Spontaneous clearance was observed in 25.1% (n=11,737) of those tested for HCV. After adjusting for potential confounders, the odds of spontaneous clearance of HCV was lower in people with pre-existing primary T-cell immunodeficiency (adjusted odds ratio [aOR]: 0.55, 95% CI: 0.32-0.94), and higher in females (aOR: 1.61, 95% CI: 1.54-1.68), in those with pre-existing HBV (aOR: 2.26, 95% CI: 1.89-2.71), and in HCV infections with genotype-3 (aOR: 2.23, 95% CI: 1.74-2.86, compared to genotype-1). **Conclusion**: Spontaneous clearance was lower for people with primary T-cell immunodeficiency while it was higher among females, those with pre-existing HBV, and HCV infections with genotype-3.

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Hepatitis C virus exposure, infection and associated risk behaviours in two maximum-security prisons in New South Wales, Australia

Behzad Hajarizadeh[1], Jason Grebely[1], Marianne Byrne[1], Philippa Marks[1], Tony Butler[1], Janaki Amin[1], Peter Vickerman[2], Natasha K. Martin[2,3], John G. McHutchison[4], Diana M. Brainard[4], Carla Treloar[5], Andrew R. Lloyd[1], Gregory Dore[1]; [1]Kirby Institute, UNSW Australia (University of New South Wales), Sydney, NSW, Australia; [2]School of Social and Community Medicine, University of Bristol, Bristol, United Kingdom; [3]Division of Global Public Health, University of California San Diego, San Diego, CA; [4]Gilead Sciences, Inc, Foster City, CA; [5]Centre for Social Research in Health, UNSW Australia (University of New South Wales), Sydney, NSW, Australia

Background: The Surveillance and Treatment of Prisoners with hepatitis C (SToP-C) study is evaluating the impact of rapid

scale-up of interferon-free HCV therapy on HCV transmission in prisons in New South Wales, Australia. This analysis characterises HCV epidemiology and risk behaviours among prisoners in two maximum-security prisons in SToP-C study. **Methods:** Data for this analysis includes prisoners enrolled from two maximum-security prisons between October 2014 and March 2016. All prisoners over the age of 18 were eligible to participate. At enrolment, participants received testing for HCV antibodies/RNA and completed a detailed survey, including injecting behaviours. Injecting behaviours by HCV infection/exposure status were evaluated. **Results:** In March 2016, 393 prisoners were enrolled (Prison A: n=308; Prison B: n=85). The median age was 34 years (Q1-Q3: 27, 44). The median duration of stay at the current prison at the time of enrolment was 2 years (Q1-Q3: 0.9, 5). Overall, 54% (n=213) were HCV antibody negative (Ab-), 18% (n=69) were HCV antibody positive/HCV RNA negative (Ab+/RNA-; including 19 with self-reported previous HCV treatment), and 28% (n=111) were HCV RNA positive (RNA+). Injecting illicit drugs during the current imprisonment was reported in 78% (83/111) of those RNA+, and 67% (46/69) of those Ab+/RNA-, compared with 11% (24/213) of those Ab- (P<0.001). Injecting in the previous month was reported by 49% (54/111) of those RNA+, and 32% (22/69) of those Ab+/RNA-, compared with 4% (8/213) of those Ab- (P<0.001). Among those injecting in the previous month, 86% (n=72) reported sharing injecting equipment. **Conclusion:** A high proportion of prisoners with HCV infection from maximum-security prisons reported injecting risk behaviours. Among prisoners at risk of HCV, those with previous HCV exposure and clearance were more likely to report high risk injecting than those with no previous exposure, suggesting the risk for re-infection and the need for increased prevention activities. Surveillance of HCV incidence should focus on detecting both HCV re-infection and primary infection.

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Divergency of liver and spleen stiffness dynamics 24 weeks after end of interferon-free treatment in patients with hepatitis C virus (HCV)-associated cirrhosis and sustained virologic response

Viola Knop[1], Daniel Hoppe[1], Tania M. Welzel[1], Johannes Vermehren[1], Eva Herrmann[2], Annika Vermehren[1], Mireen Friedrich-Rust[1], Christoph Sarrazin[1], Stefan Zeuzem[1], Martin W. Welker[1]; [1]Universitätsklinik Frankfurt, Frankfurt, Germany; [2]Institut für Biostatistik und mathematische Modellierung, Goethe-Universität, Frankfurt, Germany

Background Regression of cirrhosis and portal hypertension (PT) is a major goal in treatment of patients with hepatitis C virus (HCV) associated cirrhosis. Improvement of Child-Pugh-Turcotte (CPT)- and model of end stage liver disease (MELD)-scores were consistently observed in current trials investigating direct antiviral agents (DAA)-based treatment in HCV associated cirrhosis. However, persistence of PT has been reported despite sustained virologic response (SVR) and improvement in CTP/MELD-score. In the current study, we prospectively evaluated dynamics of liver and spleen stiffness in patients with HCV associated cirrhosis and SVR after DAA-based antiviral treatment. Methods A total of 54 patients (69% male) with HCV associated cirrhosis and SVR after DAA-based antiviral treatment were included. Liver and spleen stiffness was assessed at baseline (BL), end of treatment (EOT), and 24 weeks after EOT (FU24) by transient elastography of the liver (L-TE) as well as acoustic radiation force impulse (ARFI) of the liver (L-ARFI) and spleen (S-ARFI). Biochemical, virological and clinical data were obtained in parallel. Results There was a significant reduction of liver stiffness between BL [median (range), 32.5 (9.1-75) kPa] and EOT [median (range), 21.3 (6.7-73.5) kPa; p<0.0001) as well as between BL and FU24 [median (range), 21.2 (5.4-70) kPa; p<0001)] by L-TE. Liver stiffness assessed by L-ARFI significantly decreased between BL [median (range), 2.7 (1.2-4.1) m/s] and FU24 [median (range), 2.4 (1.2-3.9) m/s; p=0.002), while spleen stiffness assessed by S-ARFI did not decrease significantly between B, EOT and FU24. Improvement of liver stiffness was more pronounced between BL and EOT than between EOT and FU24. In addition, a significant improvement of MELD-score between BL [median (range), 9 (6-17)] and FU24 [median (range), 8 (6-18)] was observed (p=0.01)]. Conclusion Liver, but not spleen elastography improved significantly in patients with HCV associated cirrhosis and SVR after DAA-based antiviral therapy. As this effect was mainly associated with the first 12-24 weeks of treatment, it must be discussed to which amount improvement of liver stiffness was associated with decrease of hepatic necroinflammation or regression of fibrosis and portal hypertension. Studies investigating only dynamics of CTP- and MELD-score or liver stiffness may overestimate the degree of putative regression of cirrhosis.

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Chronic Hepatitis C Virus Infection Increases Risk of Cardiovascular Disease and Chronic Kidney Disease in the United States

Haesuk Park[1], Wei Wang[1], Chao Chen[1], David R. Nelson[2,3]; [1]College of Pharmacy, University of Florida, Gainesville, FL; [2]College of Medicine, University of Florida, Gainesville, FL; [3]Clinical and Translational Science Institute (CTSI), University of Florida, Gainesville, FL

Background: Hepatitis C Virus (HCV) infection is a major cause of chronic liver disease and associated with several extra-hepatic manifestations. Several studies have demonstrated significant associations among HCV infection and insulin resistance,

chronic kidney disease (CKD), and cardiovascular diseases (CVD). Conducted in Taiwan, it is unclear whether the results of these studies apply to US population given differences in prevailing genotype, level of comorbidities, and observed differences in the natural history of HCV. **Objective:** To assess the risk of CKD and CVD associated with chronic HCV infection in the U.S. **Methods:** A retrospective cohort analysis of the Truven Health MarketScan Database (2008 - 2014) was conducted. Patients aged >=18 years with newly diagnosed HCV infection (ICD-9: 070.44, 070.54, V02.62, 070.70, 070.71) were identified (HCV cohort). Outcomes included the incidence of CKD and CVD (coronary heart disease, cerebrovascular disease, peripheral arterial disease or congestive heart failure). Patients were excluded if they had experienced an outcome during 1 year prior to the first diagnosis of HCV. We matched the HCV cohort 1:3 with patients without HCV infection (non-HCV cohort) using propensity score matching. Follow-up continued until each study outcome, end of enrollment, or 31 December 2014, whichever comes first. We used Cox proportional hazards models to compare the risk of developing CKD and CVD between HCV and non-HCV cohorts. Additional covariates adjusted in the model included alcohol/drug abuse disorders, HIV/AIDS, disease-modifying medications, hepatitis B virus, cirrhosis, and so on. **Results:** The mean follow-up time was 1.96 – 2.24 years. The overall incidence rates of CKD were 114 and 43 per 10,000 person-years in the HCV (72213 patients) and the non-HCV cohorts (216639 patients), respectively. The overall incidence rates of CVD were 55 and 29 per 10,000 person-years in the HCV (59212 patients) and the non-HCV cohorts (177637 patients), respectively. In multivariate adjusted models, HCV infection was associated with 2.2 fold higher incidence of CKD (hazard ratio (HR): 2.22; 95% confidence interval (CI): 2.01-2.38) and an almost two fold higher incidence of CVD (HR:1.91; 95% CI:1.85-1.97). **Conclusions:** The analysis of a large US administrative claim database suggests that patients with HCV infection are at greater risk of developing CKD and CVD than individuals without HCV infection. Future studies are needed to investigate whether sustained virologic response to all-oral direct-acting antivirals alters the risk for development and/or progression of renal disease and cardiovascular outcomes.

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Hepatitis B and C prevalence and epidemiology among women in Spain

Jose Antonio Munoz-Gamez[1,2], Javier Salmeron[1,3], Angeles Ruiz-Extremera[1,3]; [1]Hospital Universitario San Cecilio e ibs. GRANADA, Complejo Hospitales Universitarios de Granada, Granada, Spain; [2]ibs.GRANADA, Instituto de Investigación Biosanitaria de Granada, Granada, Spain; [3]CIBERehd, Ciber de Enfermedades Hepaticas y Digestivas, Granada, Spain

Background: Hepatitis C and B virus infections are highly prevalent worldwide and the main causes of liver disease both in children and in adults. The vertical transmission of HCV is a major route of HCV infection in children (>90%). In Spain, there has been a marked increase in the immigrant population in recent years and this may have changed the prevalence of HCV and HBV in pregnancy. The objective is to determine the prevalence and epidemiology of HCV and HBV in pregnant women in Spain. **Methods:** A prospective cohort study was conducted at 10 National Spanish Hospitals. 25,000 women (18-42 years old), followed up in these Centers from January till October 2015, were enrolled. Prevalence of HCV (anti-HCV+) and HBV (HBsAg+) was determined in this cohort and in a sub-group of pregnant mothers. Moreover, we studied the epidemiology of the HBV/HCV infection among pregnant mothers. **Results:** Overall HBV prevalence was 0.57% (0.55-0.77; 25,289 women) and for HCV was 0.66% (0.55-0.77; 21,379 women). The prevalence of these viral hepatitis was higher among women over 25 years of age. However, the prevalence for HBV and HCV differ significantly between both groups (HBV and HCV prevalence in pregnant women: 0.42% and 0.21% respectively vs the prevalence of these viral hepatitis among women in fertile age: 0.99% and 0.80% respectively; p<0,05). Co-infection data were: HBV/HCV: 0.036%, HBV/HIV: 0.04% and HCV/HIV: 0.08%. Caucasian and Chinese population were predominant in HBV prevalence whereas Caucasian, Latin and Gypsy population were in HCV. In relation to the country of origin, the VHB infected women were from: Spain (65%) and Eastern Europe (28%), and the HCV women were form: Spain (36%), Asia (25%, mainly China), Eastern Europe (16%), Africa (12%) and the South America (11%). The main risk factors for HBV infections were: vertical transmission (50%), presence of tattoo (18%) and personal antecedents of surgery (10%). However, for HCV infections were: the use of parenteral drugs, (56%), surgery (25%), tattoo (18%) and personal antecedents of transfusion (15%). **Conclusions:** An important percentage of women infected with these viruses are immigrant population. The difference in HBV/HCV prevalence between pregnant and fertile age women may be due to: 1) the fertile age group had a high number of women with high risk to infection and 2) in relation to the HCV prevalence, HCV screening in Spain is not universal during the gestation and therefore it is performance mainly on high-risk women. The women over 25 years of age have an increased risk to viral hepatitis infection due to lack of prophylactic cares for HBV and to lack of HCV blood screening until 1990.

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Hepatitis C SVR is not affected by the metabolic syndrome or diabetes in patients treated at a single VA hospital clinic

Jihane Benhammou[1], Christine Y. Yu[1], Jenna K. Kawamoto[2], Vivek Dixit[2], Neville Pimstone[2], Alan J. Sheinbaum[2], Joseph R. Pisegna[2]; [1]UCLA, Santa Monica, CA; [2]VA Greater Los Angeles, Los Angeles, CA

Background: Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide. Metabolic Syndrome (MS) is highly prevalent within the VA patient population and represents a heterogeneous group of patient with the potential for a genetic basis, especially in certain ethnic patient populations. The increasing prevalence of this disorder can increase the likelihood for the progression to fibrosis, cirrhosis and hepatocellular carcinoma. The risk of progression from chronic HCV infection to cirrhosis is highly variable, and many factors such as components of the MS are believed to accelerate disease progression and impact the likelihood of sustained virological response (SVR). MS has been thought to decrease the efficacy of antiviral therapies for chronic hepatitis C. Newer hepatitis C treatment regimens are being used within the VA healthcare system and could affect HCV outcome in patients with MS. **Aim:** To evaluate if the presence of meta-

bolic syndrome could overcome HCV treatment resistance in the era of direct-acting antivirals (DAA). **Methods:** All patients undergoing HCV antiviral therapy with direct-acting antivirals from 2014-2016 were pooled for this analysis which was performed at the VA Greater Los Angeles HCS. We analyzed the SVR in a cohort of 1205 veterans with HCV with or without DM2, dyslipidemia, and hypertension as identified by ICD-9 code or if the patients were currently on therapy. **Results:** SVR results in HCV treated patients with DM2, dyslipidemia and hypertension. Total number of DAA treated patients was 1205. **Conclusion:** These data suggest that the presence of metabolic syndrome does not adversely impact the antiviral treatment responses with the newer anti-viral drugs. The importance of attaining SVR and reversal of progression of fibrosis remains to be evaluated.

SVR 4 or 12		
DM2+	58	163
DM2-	56	516
DM2+, dyslipidemia	59	129
DM2-, dyslipidemia	58.5	217
DM2+, dyslipidemia, HTN	58	117
DM2+, dyslipidemia, HTN	59	168

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Prevalence of Hepatitis E Virus Infection in HCV and HCV/HIV Coinfected Patients

Kenneth E. Sherman[1], Susan D. Rouster[1], Mohamed Tarek M. Shata[1], Norah Terrault[2], Jason Blackard[1], Shyam Kottilil[3]; [1]Department of Medicine, University of Cincinnati, Cincinnati, OH; [2]University of California- San Francisco, San Francisco, CA; [3]Institute of Human Virology, University of Maryland, Baltimore, MD

Background: Hepatitis E virus (HEV) is an endemic, primarily zoonotic infection in the U.S. and Western Europe. Recent data from NHANES suggests that approximately 11% of the population has been exposed as evidenced by serologic testing. Some series have described higher rates of infection in those with HCV and/or HIV. We sought to evaluate the cross-sectional prevalence of HEV in a large cohort of HCV and HCV/HIV coinfected patients. Methods: Serum samples were obtained from the HCVRES and HEPPRO Cohorts. These longitudinal cohorts were developed from HCV mono-infected and HCV/HIV coinfected persons seeking care at clinical facilities in the District of Columbia and surrounding environs. Samples collected at or near the baseline enrollment period were evaluated. HEV IgG was evaluated using a sensitive ELISA assay (Wantai, Beijing, China), and the test was performed according to the manufacturer's instructions. Positives were confirmed by repeat duplicate testing as recommended by the manufacturer. Parametric and non-parametric testing was performed using Statistix 10.0. Results: 355 individuals – including 184 HCV mono-infected and 171 HCV/HIV co-infected – were tested for anti-HEV IgG. The mean age was 56 years (range 21-82 years), 76% were male, and 78% were black. The median CD4 was 711 cells/mm^3 (range 62-2328 cell/mm^3) and was lower in HIV+ (mean= 595) vs HIV- enrollees (mean=983). Overall, anti-HEV IgG was detected and confirmed in 18.6%. The proportions of confirmed cases were statistically similar regardless of HIV status (21.1% HCV vs 16.4% HCV/HIV, p = n.s.). Anti-HEV prevalence was not affected by sex, race, or ethnicity in univariate analysis. HEV IgG was significantly more common in older (≥60) vs. younger (<60) participants (p = 0.0097). There was a modest inverse correlation between CD4 count and HEV IgG OD/Cutoff ratio (r = -0.32), and subjects with CD4<200 (AIDS definition) had HEV IgG OD/Cutoff ratios significantly lower (mean 5.6) than those with higher CD4 counts (mean=11.9) among anti-HEV IgG positive persons (p = 0.019). Conclusion: HEV exposure is higher in those with HCV and/or HIV than has been reported in general population surveys. Older HCV mono-infected and HCV/HIV co-infected persons are more likely to be exposed. However, HCV/HIV co-infected patients with low CD4 have less robust immune response as evidenced by lower antibody titers. We speculate that this may lead to increased proportions of false negative results in this subgroup. Further evaluation of qualitative profiling of antibodies to HEV including determination of binding avidity are indicated.

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An outbreak of Acute Hepatitis C (AHC) transmitted by IV injection during computerized tomography (CT)

Orlev Levy-Nissenbaum[1], Eyal Shteyer[2], Inna Gafanovich[2], Dana G. Wolf[3], Heftziba Ivgi[4], Ilana Dery[2], Rima Barsuk[3], Daniela Armoni[2], Michal C. Eliav[2], Yizhak Skorochod[2], Gabriel S. Breuer[2], Ran Tur-Kaspa[5], Yonit Wiener-Well[6], Scott Cotler[7], Harel Dahari[7], Yoav Lurie[2]; [1]Life sceinces, Seminar Hakibutzim College Israel, Ramat Aviv, Israel; [2]Liver Unit, Shaare Zedek Medical Center, Jerusalem, Israel; [3]Clinical Virology Unit, Hadassah Hebrew University Medical Center, Jerusalem, Israel; [4]Immunology Unit, Shaare Zedek Medical Center, Jerusalem, Israel; [5]Bar-Ilan University School of Medicine, Liver Institute Rabin Medical Center, Bar-Ilan, Israel; [6]Infectious disease Unit, Shaare Zedek Medical Center, Jerusalem, Israel; [7]The Program for Experimental and Theoretical Modeling, Division of Hepatology, Department of Medicine, Loyola University Medical Center, Maywood, IL

Background: The incidence of acute hepatitis C (AHC) is declining worldwide. However, almost 30 years after the identification of the hepatitis C virus (HCV), new cases still occur. Since acute HCV infection is generally asymptomatic, it is seldom diagnosed. Thus, the specific mode of transmission, number of patients exposed, source of infection as well as the clinical and laboratory course of a given case can rarely be ascertained in real time. We describe an outbreak of AHC wherein all these parameters are known. **Case reports:** Three patients presented to our medical center with new onset jaundice between April 25th and May 9th 2016 (Table 1). AHC was diagnosed, and a review of the patient's histories identified a common potential source of exposure. All had CT scanning with IV contrast in one community imaging center on March 17th 2016. The last patient to undergo a CT at that center on March 16th was a known chronic hepatitis C patient. Health authorities were notified, and patients were summoned for testing. All 12 who had a CT with contrast on that day, were found to be positive for HCV RNA. Seven out of the 12 are treated in our medical center and described here (Table 1). Patients 1-4 were followed-up closely and their viral load declined significantly without antiviral treatment Patient number 5 is undergoing workup for a lung

mass and deferred treatment. Patients 6 and 7 are treated with DAA because of patient's preference, and non declining viral load, respectively. **Conclusions:** Iatrogenic acute hepatitis C still occurs due to a combination of technical [*e.g.*, multi-dose vials] and human factors.Given that AHC rarely leads to fulminant hepatic failure, knowing the exact date of infection and close monitoring of the viral load presented a unique opportunity to follow the patients and their viral load closely. In anticipation of spontaneous viral clearance, treatment should be offered only when viral load does not decline. Thus, every effort should be made to ascertain the date of infection and to contact all patients potentially exposed. We aim to quantitate the clinical observation that more severe AHC leads to a greater chance of spontaneous recovery.

Table 1: Clinical data of the seven AHC patients treated at SZMC

#	Patient Age	Days post exposure	Genotype	HCV Ab	HCV RNA levels at diagnosis [IU/ml]	Last HCV RNA Levels [IU/ml]	Bilirubin Total - Admission levels [mg/dL]	Bilirubin Total - Max levels [mg/dL]	ALT - Max levels [X ULN]	Treatment
1	31	39	1b	+	3,749,887	84	16.2	24.1	32.69	-
2	80	49	1b	+	283,904	47	13.5	24.5	42.49	-
3	16	53	1b	+	2,629,902	133	4.2	5.5	43.25	-
4	25	53	1b	+	8,230152	<30 borderline	1.3	1.8	23.28	-
5	72	53	ND (low viral load)	-	14,661	3,294	0.6	0.6	3.07	-
6	75	54	1b	-	7,414,650	1,408	1.0	1.7	21.80	+
7	71	54	1b	-	817,310	235	0.6	1.5	14.80	+

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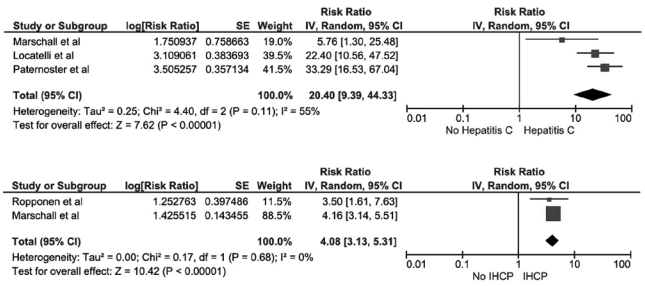
Hepatitis C Infection and Intrahepatic Cholestasis of Pregnancy: A Systematic Review and Meta-analysis

Karn Wijarnpreecha[1], Charat Thongprayoon[1], Sikarin Upala[1,2], Anawin Sanguankeo[1,2], Patompong Ungprasert[3], Wisit Cheungpasitporn[3]; [1]Internal Medicine, Bassett Medical Center and Columbia University College of Physicians and Surgeons, Cooperstown, NY; [2]Department of Preventive and Social Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [3]Department of Internal Medicine, Mayo Clinic, Rochester, MN

Background/Objectives: Hepatitis C virus (HCV) infection is a major cause of cirrhosis worldwide. Several studies have linked HCV infection to a higher risk of developing intrahepatic cholestasis of pregnancy (ICP), but the results were inconsistent. This meta-analysis was conducted with the aim to assess the associations between ICP and HCV infection before and after the diagnosis of ICP. *Methods*: This study consists of two meta-analyses. A literature search was performed using MEDLINE and EMBASE from inception to January 2016. The first study included observational studies that reported relative risks, odds ratios, or hazard ratios of the associations between HCV infection and risk of ICP. The second analysis included studies comparing the risk of later HCV infection in ICP patients with those without ICP. Pooled risk ratios (RR) and 95% confidence intervals (CI) were calculated using a random-effect, generic inverse variance method. *Results*: Three studies were included in the first analysis. The pooled RR of ICP in HCV-infected pregnant women compared to non-HCV pregnant women was 20.40 (95% CI, 9.39-44.33, I^2 =55%). Two studies were included in the second analysis. The pooled RR of later HCV infection among ICP patients compared to non-ICP patients was 4.08 (95% CI, 3.13-5.31, I^2=0%). *Conclusions*: Our study demonstrated an increased risk of ICP among HCV-infected pregnant women and also increased risk of later HCV infection among ICP patients. Physicians should be aware of this association, and we strongly suggest testing for hepatitis C in women with signs of ICP.

Forest plot of the included studies of the associations between hepatitis C infection and risk of intrahepatic cholestasis of pregnancy (Top).

Forest plot of the included studies of the associations between intrahepatic cholestasis of pregnancy and risk of later hepatitis C infection (Below).



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Estimation of liver fibrosis by the use of non-commercial serum scores in comparison to transient elastography in HCV patients receiving direct acting antiviral treatment

Wolf Peter Hofmann[1], Peter Buggisch[2], Hartwig H. Klinker[3], Stefan Mauss[4], Rainer Günther[5], Holger Hinrichsen[6], Dietrich Hueppe[7], Heike Pfeiffer-Vornkahl[8], Karl-Georg Simon[9], Thomas Berg[10], Michael P. Manns[11], Mireen Friedrich-Rust[12], German Hepatitis C-Registry[13]; [1]Gastro Study Center Berlin, Berlin, Germany; [2]ifi-institute for interdisciplinary medicine, Hamburg, Germany; [3]University Hospital of Würzburg, Würzburg, Germany; [4]Center for HIV and Hepatogastroenterology, Duesseldorf, Germany; [5]Universitätsklinikum Schleswig-Holstein (UKSH), Campus Kiel, Kiel, Germany; [6]Leberstudienzentrum Kiel GbR, Kiel, Germany; [7]Center of Gastroenterology, Herne, Germany; [8]e.factum GmbH, Butzbach, Germany; [9]MVZ Dr. Eisenbach Dr.Simon Dr.Schwarz GbR, Leverkusen, Germany; [10]Department of Hepatology, University Hospital Leipzig, Leipzig, Germany; [11]Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [12]Department of Internal Medicine I, J.W.Goethe University Hospital, Frankfurt, Germany; [13]Leberstiftungs-GmbH Deutschland, Hannover, Germany

Introduction: Treatment decision making with direct acting antivirals (DAA) in patients with chronic hepatitis C (CHC) is mainly based on baseline HCV RNA concentration, the HCV genotype and the presence or absence of liver cirrhosis. Since estimation of liver fibrosis by histology results has low acceptance, transient elastography (TE) and serum scores are often used in addition to clinical findings. Here, we assessed the diagnostic accuracy of a panel of non-commercial serum scores in comparison to TE. **Methods:** The DHC-R (Deutsches Hepatitis C-Register, German Hepatitis C-Registry) is a national multicenter real-world cohort including approx. 9,300 patients. Patients are treated at the discretion of the physician. Data are collected by a web-based system. Data quality is analyzed by plausibility checks and on site monitoring. This data analysis is based on 6,034 patients who were observed for at least 40 weeks after initiation of antiviral treatment. Valid data on TE were available for 1,742 patients. In those patients, the

non-commercial serum sores APRI score and FORNS index were calculated and the diagnostic accuracy was compared to FS results. **Results:** As estimated by TE, 625 (35.9%) patients had no significant fibrosis (SF) (<7,1kPa), 530 (30.4%) patients had SF (>7.1kPa) and 587 (33.7%) patients had liver cirrhosis (>12.5kPa). Patients with liver cirrhosis were more frequently men, were older, had a higher BMI, had a longer estimated duration of disease and were more likely treatment-experienced. SVR rates following different DAA regimens with or without ribavirin for 8 – 24 weeks were 98.2%, 96.8%, and 92.4% for patients with no SF, SF, and cirrhosis, respectively. For discrimination of SF, AUROCS were: 0.791 (APRI score), 0.840 (FORNS index). For discrimination of cirrhosis, AUROC was 0.879 (APRI score). **Conclusions:** In our national multicenter real world cohort, significant fibrosis and cirrhosis were predicted with accuracy between 79-84% and 87% with non-commercial serum scores as compared to FS results. Our data support the use of serum scores when TE is not available for accurate cirrhosis estimation. SVR rates in patients with cirrhosis were numerically lower with current DAA regimens.

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Holger Hinrichsen - Advisory Committees or Review Panels: BMS, Janssen, Gilead, Abbvie; Speaking and Teaching: MSD

Dietrich Hueppe - Advisory Committees or Review Panels: Roche, MSD, Novatis, Gilead, BMS, Janssen, AbbVie

Heike Pfeiffer-Vornkahl - Employment: efactum GmbH

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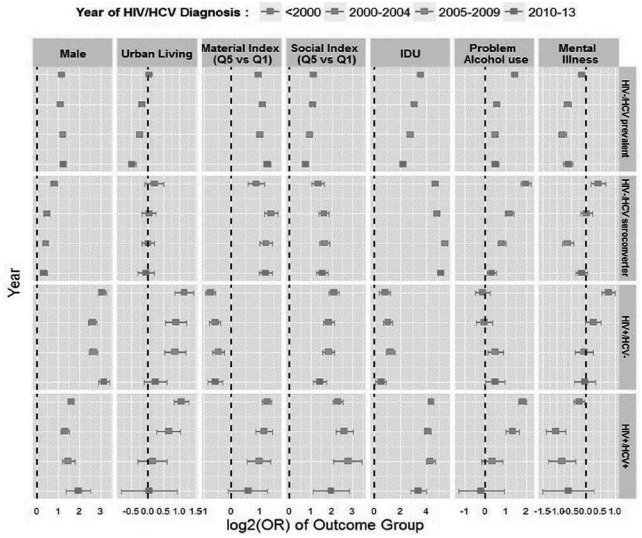
Social disparities and co-evolution of HIV/HCV infections, mental disorders and substance use: the British Columbia Hepatitis Testers Cohort (BC-HTC)

Zahid Butt[1], Nabin Shrestha[1], Margot E. Kuo[2], Dionne Gesink[3], Mark Gilbert[4,2], Jason Wong[2], Amanda Yu[2], Maria Alvarez[5], Hasina Samji[2], Jane A. Buxton[1,6], James C. Johnston[7], Victoria Cook[7], David Roth[7], Theodora B. Consolacion[2], Michelle Murti[8,9], Gina Ogilvie[1,6], Robert Balshaw[6], Mark Tyndall[6,1], Mel Krajden[6], Naveed Z. Janjua[2,1]; [1]School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada; [2]Clinical Prevention Services, BCCDC, Vancouver, BC, Canada; [3]Epidemiology, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada; [4]Ontario HIV Treatment Network, Toronto, ON, Canada; [5]Epidemiology and Surveillance, BC Centre for Disease Control, Vancouver, BC, Canada; [6]BC Centre for Disease Control, Vancouver, BC, Canada; [7]TB Services, BC Centre for Disease Control, Vancouver, BC, Canada; [8]Fraser Health, Surrey, BC, Canada; [9]University of British Columbia, Vancouver, BC, Canada

We examined the coevolution of HIV and HCV infections, mental illnesses, substance use and disparities over time in BC during 1990-2013 using the BC Hepatitis Testers Cohort (BC-HTC). The BC-HTC includes ~1.5 million individuals tested for HCV or HIV, or reported as a case of HCV, HIV, HBV, or tuberculosis linked to administrative healthcare databases. We classified individuals into HIV-/HCV-, HIV+/HCV-, HIV-/HCV+ seroconverters, HIV-/HCV+ prevalent, and HIV+/HCV+. Of 1.37 million eligible individuals, 4.1% were prevalent HCV infection, 0.5% HIV-monoinfected, 0.3% HIV/HCV co-infected and 0.5% were HCV seroconverters. Overall, HIV monoinfected individuals lived in urban areas (92%), had low injection drug use (IDU, 4%), problem alcohol use (4%) and were materially more privileged than other groups. HIV/HCV co-infected and HCV seroconverters were materially most deprived (14%, 12%), had higher IDU (34%, 53%), problem alcohol use (15%, 17%) and major mental illnesses (12%, 21%). HIV, HCV and HIV/HCV co-infection began to increase in rural areas after 2004. Material deprivation, IDU and opioid substitution therapy increased overtime among seroconverters. Multivariable multinomial regression models mirrored descriptive trends. Overtime, odds of IDU declined among HCV prevalent and HIV monoinfected individuals but not in seroconverters. Decline in odds of problem alcohol use were observed in seroconverters and coinfected individuals overtime (Figure 1). Results could inform optimal alignment of prevention, care and support services for HIV and HCV infected population within the context of changing epidemiology, disparities and risk profiles of these groups.

Adjusted log odds ratios of risk factors for HIV/HCV groups by time periods



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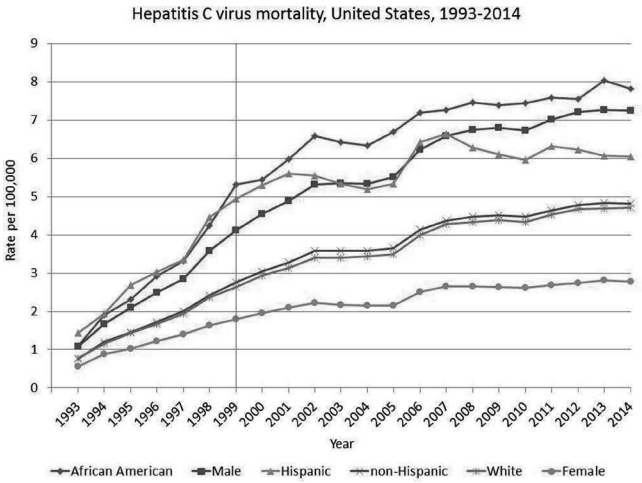
The Burden of Viral Hepatitis B and C Infection in the United States Population

Aynur Unalp-Arida[1], Constance E. Ruhl[2]; [1]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; [2]Social & Scientific Systems, Inc., Silver Spring, MD

Chronic liver disease and cirrhosis was the 12th leading cause of death in the U.S. in 2014. Viral hepatitis leads to significant morbidity and mortality. We used national databases to update estimates of the viral hepatitis burden in the U.S. **Methods:** The National Ambulatory and Hospital Ambulatory Medical Care Surveys, Nationwide Inpatient Sample, and Vital Statistics of the U.S. databases were used to estimate medical care and mortality with a primary or other diagnosis of viral hepatitis B or C. Rates were age-adjusted and shown per 100,000 population for the most recent year available. **Results:** Hepatitis C contributed to 1.8 million ambulatory visits, 606,000 hospital discharges, and 20,000 deaths. Ambulatory visit and hospital discharge rates were higher in middle compared with older age, and among men and African Americans compared with women and whites, respectively. Both rates increased significantly from 1993 to 2013; however, greater availability of treatment options might have contributed to this rise. Mortality rates were higher in middle compared with older age, and among men compared with women (7.2 vs. 2.8) and African Americans compared with whites (7.8 vs. 4.7). The mortality rate increased in the overall population by 6-fold from 1993 to 2014 (0.8 to 4.9) and in demographic subgroups (Figure). Hepatitis B contributed to 462,000 ambulatory visits, 72,000 hospital discharges, and 2,000 deaths. Ambulatory visit and hospital discharge rates were higher in middle compared with older age, and along with mortality rates were higher among men, African Americans, and non-Hispanics compared with women, whites, and Hispanics, respectively. Both medical care rates doubled from 1993 to 2013; in contrast, mortality rates declined by one third. **Conclusions:** The viral hepatitis burden in the U.S. today primarily reflects that of hepatitis C and is greater among men and African Americans.



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Age and Region specific Prevalence of Hepatitis C Virus in Ghana: A population-based Study

Stephanie Kliethermes[1,2], Jason Gantenberg[1], Nallely Mora[1], Richard O. Phillips[3], Ohene Opare-Sem[4], Dorcas Owusu[4], Jennifer E. Layden[1,2]; [1]Public Health Sciences, Loyola University Chicago, Maywood, IL; [2]Department of Medicine, Stritch School of Medicine, Maywood, IL; [3]Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; [4]KNUST, Kumasi, Ghana

Purpose: This population-based study sought to determine age- and region-specific Hepatitis C Virus (HCV) estimates in Ghana, where lack of available data and assessment has led to uncertainty regarding the burden of disease. Methods: The study sample consisted of 2985 individuals currently located in the Ashanti region of Ghana. Study participants completed a survey and an Oraquick rapid screen assay for HCV status. Those with positive screening tests underwent confirmatory testing with a CIA HCV antibody assay to confirm seropositivity. Age, gender, and region of origin were identified for each participant. Bayesian logistic regression was used to obtain odds ratios for assessing risk of HCV and age- and region-specific prevalence estimates. Median posterior estimates are reported with 95% highest posterior density (HPD) credible intervals. Results: The average age of participants was 31.3 (range: 3-103) years, and 70% of subjects were women. Children under the age of 15 comprised 22% of the sample, and 59% of individuals originated from the Ashanti region, 18% from northern regions, and 23% from other regions of Ghana. Compared to Ashanti-born subjects, the age-adjusted odds of HCV infection were 15.6 (HPD: 2.7–38.0), 22.9 (HPD: 9.2–44.8), and 18.6 (HPD: 5.3–39.4) higher for those originating from the Northern, Upper West, and Upper East regions, respectively. These odds corresponded to HCV prevalence estimates of 4.3% (95% HPD: 1.1%–9.0%), 6.1% (HPD: 3.7%–9.1%), and 5.0% (HPD: 2.0%–8.8%) in the Northern, Upper West, and Upper East regions, compared to 0.3% in Ashanti. After adjusting for region of origin, the lowest prevalence was in the 0–14 (0.9%; HPD: 0.4%–1.5%) and 15–24 (0.4%; HPD: 0.1%–1.0%) age groups, respectively. Beginning at age 25, region-adjusted prevalence increased to 1.9% (HPD: 0.8%–

3.3%) and peaked at 3.3% (HPD: 1.0%–6.5%) among 55–64 year olds before declining to 1.9% (HPD: 0.3%–5.1%) in individuals 65 and older. A sub-analysis involving only subjects originally from the northern regions (Northern, Upper West, Upper East) suggested age-specific prevalence may be even higher in the North, with prevalence estimates of 6.9% (HPD: 3.0%–11.6%) among 25–34 year olds and increasing to 12.6% (HPD: 4.5%–23.2%) among individuals 55–64 years old. Conclusion: Significant age and regional differences in HCV prevalence exist in Ghana, with higher prevalence among individuals originating from the northern regions and among individuals ages 25–64, with very few cases observed among participants less than 25 years of age. Such findings suggest either an age cohort effect or transmission exposures that are low in childhood and increase with age.

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Association between Liver stiffness measurement and serum Wisteria floribunda agglutinin-positive Mac-2 binding protein among Japanese patients with hepatitis B, C and NAFLD/NASH

Shinjiro Uchida, Kazumi Yamasaki, Kohei Hayashi, Yuki Kugiyama, Shigemune Bekki, Satoru Hashimoto, Akira Saeki, Shinya Nagaoka, Seigo Abiru, Atsumasa Komori, Hiroshi Yatsuhashi; National Hospital Organization, Nagasaki Medical Center, Omura, Japan

Background As optimal management of chronic liver disease depends on the degree of liver fibrosis, accurate, but non-invasive evaluation of liver fibrosis is of importance. Though liver stiffness measurement (LSM) using Fibroscan and serum Wisteria floribunda agglutinin-positive Mac2 binding protein (M2BPGi) were novel, noninvasive, and reliable technique to assess the degree of liver fibrosis, trans-etiological comparison between two parameters has not yet been available in the literature. The aims of this study were to assess the correlation between LSM and serum M2BPGi levels among Japanese patients with hepatitis B, C and NAFLD. Methods A total of 1,347 patients who underwent LSM between 2012 and 2015 at our hospital were reviewed. 224 patients whose LSM value were invalid or failure were excluded. Among the remaining 1123 patients, 782 patients (282 patients infected with HBV, 450 patients infected with HCV, and 50 patients with NAFLD) were enrolled in this study. Serum WFA(+)M2BP, aspartate transaminase to platelet ratio index (APRI), and fibrosis index to platelet ratio index (FIB4) were simultaneously measured and calculated on the occasion of LCM. Results The baseline characteristics of eligible patients were 393(50.3%) male with a median age of 64.5 years. The median value of LSM, M2BPGi, APRI, and FIB4 were 5.6 kPa (2.3- 75.0), 0.9 COI (0.1-21.0), 0.5 (0.1- 9.1), and 2.1(0.2-23.9), respectively. Positive correlations between LSM and M2BPGi level (R2=0.46, p<0.001), APRI (R2=0.43, p<0.001), and FIB4 (R2=0.32, p<0.001) were observed; multiple linear regression analysis revealed M2BPGi level as the most significantly associated factor (effect size=0.46, p<0.001). Correlation coefficient between LSM and each fibrosis marker were as follows, in ascending order; HBV (R2=0.16, p<0.01), NAFLD (R2=0.46, p<0.01), and HCV (R2=0.53, p<0.001). The diagnostic performance of M2BPGi, APRI and FIB4 were evaluated using receiving operating characteristic curve analysis; AUC of M2BPGi, APRI and FIB4 were 0.83, 0.83, 0.78 in LSM level ≥7, 0.89, 0.88, 0.85 in LSM level ≥10, 0.89, 0.88, 0.85 LSM level ≥13, respectively. The optimal cutoff values of M2BPGi which best predicted LSM level ≥7 and ≥13 were 1.4 and 2.7, respectively. The optimal cutoff values of M2BPGi which best predicted LSM level ≥7 in distinct etiologies (HBV, NAFLD, and HCV) were 0.9, 1.0 and 2.0, respectively. Conclusions LSM values measured by Fibroscan were closely correlated with serum M2BPGi levels, compared to either APRI or FIB4, especially in hepatitis C patients. Consideration of the etiology of liver diseases is required with regard to the prediction of LSM by M2BPGi cutoff values.

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Association of low-density lipoprotein cholesterol with spontaneous clearance in HCV-infected patients

Karina Gonzalez-Aldaco[1,2], Sonia Roman[1,2], Nora A Fierro[1,2], Erika Martinez-Lopez[1,2], Rafael Torres-Valadez[1,2], Maria Elena Trujillo-Trujillo[1,2], Arturo Panduro[1,2]; [1]University of Guadalajara, Jalisco, Mexico; [2]Molecular Biology in Medicine, Civil Hospital of Guadalajara, Guadalajara, Mexico

Background. Host, viral and environmental interactions play a major role in the clinical outcomes of HCV infection. Spontaneous clearance (SC) may be associated with immunological mechanisms, as well as genetic and metabolic factors related with serum lipids. Therefore, Apolipoprotein E (*ApoE*) isoforms interacting with low-density lipoprotein cholesterol (LDL-c) could alter the course of the disease. **Aim.** To analyze the anthropometric, metabolic and lipid alterations of SC patients and the association of *ApoE* alleles and LDL-c with SC. **Methods.** Totally, 299 treatment-naïve, anti-HCV positive patients were included. Patients were classified in chronic hepatitis (CH) (n=206) who had at least two detectable viral loads (VL), and SC (n=93) after two undetectable VL in the last 12 months. A clinical record was elaborated for all participants. Body mass index (BMI) was evaluated by electric bioimpedance (InBody 3.0). Biochemical tests were accessed by dry chemistry assay. VL was determined by COBAS® TaqMan 48 HCV test. Liver damage was evaluated by transitional elastography, and *ApoE* genotypes were identified by TaqMan Real-Time PCR. **Results.** No statistical differences were detected in age, gender, and risk factors for HCV infection between groups. However, BMI was higher in SC than CH, predominating more CH patients with normal weight than SC (36.6% *vs.* 19.5% p=0.007). Total cholesterol (CHol) and hypercholesterolemia (>200 mg/dl) was higher in SC than CH patients (184.1 ± 43.3 mg/dL *vs.* 148.1 ± 43.3 mg/dL, p<0.001 and 32.6% *vs.* 9.8% p<0.001, respectively). No significant differences were detected in insulin resistance and type 2 diabetes between SC and CH groups (55.4% *vs.* 43.5% p=0.072; 14.1% *vs.* 7.8% p=0.183, respectively). Liver damage was detected (37.5%,18/48) in SC patients despite the low levels of ALT and AST (below 50 IU/mL each). The *ApoE* e4 allele frequency was significantly higher in the SC patients compared to CH group (p=0.042). Also, in the *e4* allele subgroup, total CHol and LDL-c values were higher in patients with SC compared to CH patients (193 ± 42 mg/dL and 125.2 ± 35.9 mg/dL *vs.* 160.5 ± 45 mg/dL and 101.9 ± 42.4 mg/dL, respectively). LDL-c, *e4* allele and BMI were associated with SC (OR=0.20, 95% CI 0.10-0.41, p<0.001; OR=0.55, 95% CI 0.313-0.987, p=0.042; OR=0.37, 95% CI 0.18-0.76, p=0.007), whereas ALT was associated as a risk

factor for CH (OR=5.67, 95% CI 2.69-11.97, p>0.001). **Conclusions.** LDL-c, *e4* allele, and BMI were independent factors for SC. Cholesterol and LDL-c levels modulated by genetics or dietary factors may influence the natural history and long-term outcome of HCV infection.

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Higher liver volume is a non-invasive indicator of hepatic reserve in cirrhotic patients with HCV infection

Roberta K. Sefcik[1], Jasnit Makkar[2], Joshua Hartman[3], Kian Bichoupan[3], James F. Crismale[3], Neal M. Patel[3], Sweta Chekuri[3], Sara C. Lewis[2], Bachir Taouli[2], Thomas Schiano[3], Andrea D. Branch[3]; [1]Department of Medical Education, Icahn School of Medicine at Mount Sinai, New York, NY; [2]Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, NY; [3]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY

Background: New treatments for HCV allow the majority of patients to achieve a sustained virological response (SVR); however, many patients with advanced liver disease continue to have impaired liver function. Non-invasive tests are needed to predict their clinical course. Many centers routinely perform CT/MRI imaging on patients with advanced liver disease, providing data that can be used to calculate liver and spleen volumes. Aim: To assess pre-treatment liver volume as a predictor of post-SVR liver function. Methods: The study group was comprised of cirrhotic patients who achieved an SVR and who had impaired liver function, defined as serum albumin < 3.4 g/dL, prior to the start of treatment. Pre-treatment liver and spleen volumes were calculated from CT/MRI images obtained within one year of the start of HCV treatment and were adjusted for ideal body weight using Vitrea software. Demographic, anthropometric and other medical record data were collected pre- and post-SVR. Logistic regression was used to identify factors associated with recovery of liver function, defined as a post-SVR albumin level ≥ 3.4 g/dL. Results: The median pre-treatment age of the 49 patients was 61 years (IQR: 56 - 65) (n=49); albumin, 3.0 g/dL (2.8 - 3.2); MELD score, 14 (IQR: 11 - 15); liver volume, 1264 mL (1078 - 1555); and spleen volume, 537 mL (366 - 839). Liver function returned to normal in 59% (29/49) of the patients. Recovery (albumin normalization) was significantly related to higher liver volume pre-treatment [odds ratio (OR): 1.2 per mL/kg, p=0.008], lower spleen volume (OR: 0.89 for every mL/kg, p=0.032), and lower MELD score (OR=0.56 for every 1-unit increase in MELD score, p=0.002). In a subgroup-analysis of 28 patients with a pre-treatment albumin ≤ 3.0 g/dL, liver function returned to normal in 14 (50%). There was a strong trend toward an association between recovery and higher liver volume (OR: 1.2 per mL/kg, p=0.07) and lower spleen volume (OR: 0.84 per mL/kg, p=0.06). Recovery was significantly related to lower MELD score (OR: 0.62 for every 1-unit increase in MELD score, p=0.04). Quality control tests performed on liver explants (n=16) and spleen explants (n=8) of known volume revealed that liver and spleen volume computed from CT/MRI accurately estimated liver weight (median error = 6.1%, IQR: 3.5% - 12%) and spleen weight (median error = 15%, IQR: 4.4% - 33%), validating the approach. Conclusions: Liver and spleen volumes may be sensitive, non-invasive prognostic indicators of liver functional status in the growing number of patients with advanced liver disease who achieve an SVR. Acknowledgements: DA 031095, DK 090317.

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Cross-sectional Study of Chronic Kidney Disease Prevalence in association with Monoinfected patients Hepatitis C virus in ANRS CO-22 Hepather cohort

Hélène Fontaine[1,2], Eric Thervet[3,4], Vincent Bonnemains[5], Laurent Alric[6,7], Jean-Jacques Boffa[8], Philippe Mathurin[9], Bénédicte Stengel[10], Fabrice Carrat[5,11], Stanislas Pol[1,2], Linda Wittkop[12]; [1]Hepatology Unit, Cochin Hospital, Assistance Publique des Hôpitaux de Paris, Paris, France; [2]INSERM U-818 and USM20, Institut Pasteur, Paris, France; [3]Nephrology Unit, HEGP, APHP, Paris, France; [4]INSERM UMR970-PARCC, Paris Descartes University, Paris, France; [5]UPMC Univ Paris 06, INSERM, Institut Pierre Louis d'épidémiologie et de Santé Publique (IPLESP UMRS 1136), Sorbonne Universités, Paris, France; [6]Internal Medecine-Digestive Department, CHU Purpan, Purpan, France; [7]UMR152, IRD, Toulouse 3 University, Purpan, France; [8]Nephrology Department, Tenon Hospital, Paris, France; [9]Department of Hepatology and Gastroenterology, CHRU Claude Huriez, Lille, France; [10]U1018,Centre for Epidemiology and Population Health - Renal and Cardiovascular, INSERM, Villejuif, France; [11]Unité de Santé Publique, Assistance Publique-Hôpitaux de Paris, Hôpital Saint Antoine, Paris, France; [12]Inserm U897, Centre of Epidemiology and Biostatistics, ISPED Bordeaux School of Public Health, CHU de Bordeaux, University Bordeaux Segalen, Bordeaux, France

Background: Patients with chronic HCV infection have an increased risk of chronic kidney disease (CKD) and kidney failure. Hepatitis C virus (HCV) is also more common in CKD patients than in the general population. The purpose of this study was to estimate the prevalence of CKD (stage ≥3) in HCV infected patients and to look for correlation with the liver disease severity. Patients and methods : We analyzed the estimated glomerular filtration rate (eGFR) using CKDEPI formula in patients with a positive virus C serology in a multicenter observational prospective national cohort Hepather CO-22 (n = 20802). Exclusion criteria was kidney transplant recipient. Results : The analysis included 8571 patients (pts) from HCV 12 456 pts. The characteristics were: 56% men;57 ± 20 years;30% hypertensive;HCV since 17 ± 13 years;detectable HCV RNA in 96%;genotype 1, 2, 3, 4 and 5/6/7 in 66%, 6%, 13%, 13% and 2%, respectively;40% of cirrhotic patients (96% Child A and MELD average 8 ± 3);and 59% previously treated with anti-viral combination C (including an association with interferon and ribavirin 67%). The prevalence of an eGFR≤60 ml/min at inclusion was 6.3%. In univariate analysis, risk factors were sex, age, BMI, duration of infection, HCV treatment, diabetes, hypertension, high cholesterol, level of education, a history of heart disease, liver transplantation, the genotype (without influence of the stage of fibrosis, cirrhosis and Child score). In multivariate analysis, predictors of IRC were [Table 1] Conclusion : In ANRS C0-22 HEPATHER cohort, the CKD prevalence was 7.3% and was associated with age, hypertension, diabetes, hypercholesterolemia, and history of cardiac disease but not the severity of the liver disease (cirrhosis, Child and MELD scores). Longitudinal analysis will analyze the effect of anti-viral combinations on long-term renal function based on the usual nephropathy risk factors.

Table 1

Covariate	OR (CI 95%)	P
Age (every 10 yrs)	1,7 (1,6-1,9)	< 0.01
HBP	4,4 (3,4-5,6)	< 0.01
Diabetes mellitus	1,8 (1,0-2,4)	< 0.03
PMH of cardiopathy	1,6 (1,0-2,4)	< 0.03
Hypercholesterolemia	1,4 (1,0-1,9)	< 0.04

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Prevalence of naturally occurring HCV NS5A resistance-associated substitutions by high-resolution sequencing technology in treatment naive genotype 1 patients

Qian Chen[1,2], Maria Buti[3,4], Maria Eugenia Soria[1], Josep Gregori[1,4], Celia Perales[1,5], Francisco Rodriguez-Frias[2,4], Damir Garcia-Cehic[1,4], Maria Homs[2,4], David Tabernero[2,4], Leonardo Nieto[2], Rafael Esteban[3,4], Juan I. Esteban[3,4], Josep Quer[1,4]; [1]Liver Diseases Unit, Vall d'Hebron Research Institute, Barcelona, Spain; [2]Departments of Biochemistry and Microbiology, Hospital Universitari Vall d'Hebron, Barcelona, Spain; [3]Liver Unit, Hospital Universitari Vall d'Hebron, Barcelona, Spain; [4]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Barcelona, Spain; [5]Centro de Biología Molecular Severo Ochoa (CSIC-UAM), Consejo Superior de Investigaciones Científicas, Madrid, Spain

Background Since the development of direct acting antivirals (DAAs), sustained virologic response (SVR) rates in chronic Hepatitis C patients have increased dramatically with DAAs combination therapies. However, the presence of resistance-associated substitutions (RAS) with decreased susceptibility to DAAs within the viral quasispecies prior to therapy is considered as the main responsible of treatment failure and viral relapse. Currently, testing for RAS prior to first-line DAA therapy is only recommended by clinical guidelines, for GT 1a patients (-Q80K) in Simeprevir based regimens and Elbasvir-based treatment. In the present work we have analyzed the baseline prevalence of NS5A RAS among 1a and 1b treatment naïve patients in our geographic area by massive parallel sequencing using 454/GS-Junior platform. Methods A total of 50 samples from treatment naïve chronic HCV patients have been selected, 18 G1a and 32 G1b. A fragment of 437nts of NS5A region have been amplified and sequenced using 454/GS-Junior sequencing platform and compared to consensus sequences provided by Los Alamos Sequence Database. The cutoff of detection was 1%. The following RAS mutations have been considered in the present study: G1a (M28, L31, H58, E62, Y93) and G1b (L28, R30, L31, P58, Y93). Results Overall, RAS at NS5A regions have been detected in 50% of G1 patients (44% G1a and 53% G1b). 16.7% G1a and 28.1% G1b patients present RAS with frequency above 15%. The most prevalent RAS in G1a was M28V/T followed by H58R, L31M and Y93H. For subtype 1b the most prevalent substitution was Y93H followed by R30H/Q, L31M and P58S. The frequency of RAS ranged from 0.47% to 99.57% in G1a patients and from 0.44% to 100% in G1b. Interestingly, 11.1% of G1a and 28.1% of G1b patients have Y93H substitution at baseline, which has been associated with reduced susceptibility to Daclatasvir, Ledipasvir and Ombitasvir. In G1a samples Y93H is observed as a minority mutant while in G1b, 22% of the Y93H carriers showed the mutation in 100% of sequences. Conclusions High-resolution HCV-sequencing technology is a good tool to study RAS. This methodology reveals a high prevalence of RAS in NS5A region in Spain, however, the clinical significance of each variant is dependent of the frequency and the type of RAS, and in this sense, Y93H has shown higher level of DAA resistance than other substitutions. Besides, here we show that the prevalence of each RAS is subtype-dependent, and for instance Y93H is more prevalent in subtype 1b compared with 1a. It is still unknown which is the minimal frequency at which a minority RAS is clinically relevant.

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Clearance of the hepatitis C virus without treatment occurs more often than traditionally reported

Gia Tyson, Philip Oravetz, Susan Montz, Shobha Joshi, George Therapondos, Natalie H. Bzowej, Aldo Russo, Nigel Girgrah; Ochsner Health System, New Orleans, LA

Introduction: Hepatitis C virus (HCV) infection is the most common chronic blood borne infection in the United States and accounts for significant morbidity and mortality. There have been increasing efforts to perform birth cohort screening to get this high risk group diagnosed and treated for HCV. It is usually reported that 75-85% of people exposed to HCV develop chronic infection. Our group conducted a study to determine if the traditionally reported rates of developing chronic HCV are consistent with rates of chronic HCV we see in the era of birth cohort screening. **Methods:** Our health system consists of 15 hospitals and 63 health centers. The electronic medical record, Epic, was integrated into the entire health system by January 2014. Therefore, from January 2014- June 2016 we have been able to collect data on all patients within the health system born between 1945-1965 who have been screened for HCV with HCV antibody (Ab) testing. We then identified those who were tested for HCV RNA. We calculated the percentage of patients HCV Ab+, then calculated the percentage of patients HCV RNA+. **Results:** In 2014, there were 20,171 patients who were screened for HCV, of which 968 (4.8%) tested positive. There were 778 (80.4%) patients with HCV RNA tests, of which 495 (63.6%) tested positive for chronic infection. In 2015, there were 21,053 patients screened for HCV, of which 1,092 (5.2%) tested positive. There were 634 (58.1%) patients with HCV RNA tests, of which 367 (57.9%) tested positive. In the first 6 months of 2016, there were 9,070 patients who were screened for HCV, of which 414 (4.6%) tested positive. There were 174 (42.0%) patients with HCV RNA tests, of which 73 (42.0%) tested positive. **Conclusion:** Based on our large health system 42-64% of patients born between 1945-1965 develop chronic HCV infection of those exposed to HCV; therefore, 36-58% of patients exposed to HCV clear virus without treatment. This percentage of clearance is higher than the typically reported 15-25% of patients who clear HCV without treatment. It is likely that spontaneous clearance of HCV is more common than previously expected.

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Is cirrhosis reversible in patients with hepatitis C and decompensated liver disease? Explant histology in patients with sustained virologic response

Allison Kwong[1], W. Ray Kim[1], John Higgins[2]; [1]Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA; [2]Pathology, Stanford University, Stanford, CA

Background/Aim: With the advent of highly effective antiviral therapy against hepatitis C virus (HCV) infection, patients with decompensated cirrhosis are able to achieve sustained virologic response (SVR). There is widespread optimism that eradication of HCV would lead to reversal of cirrhosis, thus obviating the need for liver transplantation (LTx). Explants from LTx recipients present an opportunity to accurately assess histological changes of the liver after SVR in patients with already advanced liver disease. **Methods:** Institutional databases and medical records were reviewed to identify adult liver transplant recipients with HCV. Patients were divided into (1) SVR versus (2) non-SVR groups, the latter being defined as viremia at the time of LTx. Patients were stratified by presence of HCC. Explant liver specimens were retrieved and reviewed by a single pathologist. Fibrosis stage, grade of inflammation, nodule size, and overall histological description were compared between the two groups. **Results:** Of the 349 adult patients who underwent LTx between 2011 and 2016, 149 had a primary diagnosis of HCV. 30 patients achieved SVR prior to LTx. Of the remaining patients (non-SVR), 30 were selected and matched by age, MELD categories and year of transplantation. To date, five SVR explants have been reviewed and characterized completely (Table 1). All patients exhibited advanced, stage 4 fibrosis with varying degrees of inflammation (grade 0-2) and nodule size, regardless of how recently they achieved SVR. The study is ongoing, and complete data in SVR and non-SVR patients will be available at the time of presentation. **Conclusion:** Although the sample size to date is small, marked regression of cirrhosis was not observed. HCV patients with decompensated liver disease may have cirrhosis that is too far advanced to regress. Complete analysis of the study samples may suggest that HCV therapy in LTx candidates should be individualized. For some patients, postponement of antiviral therapy until post-LTx may be advantageous, particularly in regions with a high median MELD score.

Table 1. Explant characteristics in 5 selected patients with HCV cirrhosis and SVR.

Patient	Age (years)	Sex	MELD at LTx	SVR4 (time prior to LTx)	Inflammation grade	Fibrosis stage	Nodule size	History of alcohol use
1	57	F	42	294 days	0	4b	Large	No
2	70	M	39	unknown (years)	1	3-4a	Large	No
3	64	M	17	5 days	1	4a	Small	No
4	56	F	29	> 10 years	1	4b	Small	Yes
5	54	M	41	unknown (years)	2	4c	Large	Yes

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Excess risk of extrahepatic cancers among hepatitis C virus infected

Fatma M. Shebl; CDE, Yale School of Public Health, New Haven, CT

Background: Approximately 5 million Americans live with hepatitis C virus (HCV) infection. Since 2010, the incidence of acute HCV infection is rising. Therefore, it is expected to observe an increase in HCV-related morbidity and mortality, including cancer. Excess risk of liver cancer among HCV-infected is well documented. However, the excess risk of other extrahepatic cancers are less documented. Of the extrahepatic cancers, non-Hodgkin lymphoma, thyroid, pancreatic and multiple myeloma have been observed. Therefore, we examined risk of extrahepatic cancers as well as the possible mediating mechanisms among HCV-infected subjects compared to non-HCV-infected. Methods: The Surveillance, Epidemiology, and End Results (SEER) Medicare-linked (SEER-Medicare) database was used to assess cancer risk among 65 years and older in the United States. We used HCV ICD-9 codes to classify subjects as HCV positive if their claims included any of the following: 070.41, 070.44, 070.51, 070.54, 070.70, 070.71, or V02.62. The study included 1,029,695 cancer cases as well as 100,000 frequency matched controls. We used unconditional logistic regression to calculate adjusted odds ratios (ORs) and 95% confidence intervals (CI) adjusting for the matching variables including age, sex, and calendar year. For each cancer, we examined the cancer-specific mediating mechanisms using structural equation modeling (SEM). Results: In the multivariable model, individuals with HCV infection had higher likelihood of overall cancer [OR (95% CI); 1.39 (1.23, 1.57)], lip cancer 2.00 (1.05, 3.80), stomach 1.33 (1.04, 1.72), anorectal 2.20 (1.30, 3.72), intrahepatic cancers 3.21 (1.90, 5.44), NHL 1.46 (1.22, 1.75), acute myeloid leukemia 1.64 (1.15, 2.33), non-epithelial skin cancer 1.73 (1.05, 2.84), and pancreatic cancer 1.36(1.09-1.69). Diabetes was the main mediator through which HCV infection might operate. Other mediators included pancreatitis for pancreatic cancer and peptic ulcer for stomach cancer. Conclusion: HCV is a potential risk factor for several inflammation-related and immune-related types of cancer. The associations of HCV infection and cancers are partially mediated by diabetes, and other cancer-specific factors such as pancreatitis and peptic ulcer. Further studies are needed to identify the mechanisms by which HCV infection may induce extrahepatic cancers.

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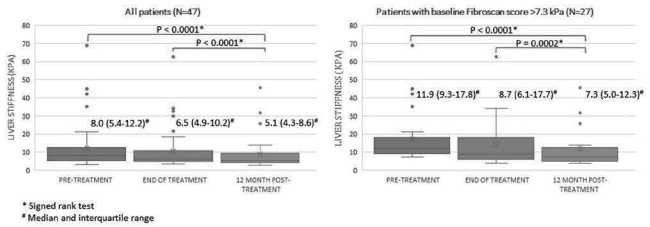
Direct Acting Anti-Viral (DAA) Therapy for Chronic Hepatitis C Virus (HCV) Infection Is Associated with Regression of Liver Fibrosis, Assessed by Serial Transient Elastography (Fibroscan)

Justin Chan[1,2], Neliswa Gogela[5], Hui Zheng[3,2], Sara Lammert[1,2], Tokunbo Ajayi[4,2], Zachary Fricker[4,2], Arthur Y. Kim[1,2], Gregory K. Robbins[1,2], Raymond T. Chung[4,2]; [1]Infectious Diseases Unit, Massachusetts General Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Biostatistics Center, Massachusetts General Hospital, Boston, MA; [4]Department of Medicine, Massachusetts General Hospital, Boston, MA; [5]Division of Hepatology, University of Cape Town, Cape Town, South Africa

Background: Liver fibrosis stage determines clinical outcomes from chronic HCV infection. Those who achieved sustained virologic response (SVR) with interferon-based therapies had

regression of fibrosis over time. This study aimed to assess the effect of HCV DAA therapy on changes in liver fibrosis, using transient elastography (Fibroscan). **Methods:** Patients being treated with DAA therapy for chronic HCV were enrolled in this prospective cohort study. We performed pre-treatment baseline Fibroscans, then repeat scans at end of treatment (EOT) and 12 months post-treatment. The primary outcome was significant improvement in liver fibrosis (>30% decrease in Fibroscan score 12 months after treatment), relative to baseline. Multivariable logistic regression analysis was used to control for confounding. Signed rank test was used to assess change in liver stiffness measurement (LSM) between time points. **Results:** Of the 47 patients who have completed the protocol, 27 (57.4%) had significant baseline liver fibrosis (LSM >7.3 kPa), and 27 (57.4%) were treatment-experienced. SVR rate was 95.7%. The primary outcome of >30% improvement in LSM was met in 24 (51.1%) patients. The 2 relapsers did not reach this outcome. Of those with baseline Metavir stage ≥F3 (LSM >8.5 kPa), 9/23 (39.1%) improved to <F2 (LSM ≤7.3 kPa) (cutoffs from reference 1). Baseline LSM >7.3 kPa was associated with reaching the primary outcome, and remained significant after controlling for BMI and elevated ALT (OR=8.8; 95% CI 1.9-37.2). In this subgroup (baseline LSM >7.3 kPa), median intra-patient change in LSM between pre-treatment and 12 months post-treatment was -4.5 kPa (IQR -7.1, -2.0; P<0.0001). **Conclusions:** Treatment of chronic HCV with DAAs leads to clinically relevant reduction in liver fibrosis over the first year post-treatment, measured by Fibroscan, even after controlling for BMI and elevated ALT. This outcome was more likely in those with baseline significant liver fibrosis, with some experiencing improved Metavir fibrosis stage. **Reference:** 1. Tapper EB, Castera L, Afdhal NH. Clin Gastroenterol Hepatol 2015;13:27–36.

Figure. Distribution of Fibroscan Scores by Time



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Direct-acting antiviral treatment patterns among hepatitis C patients with advanced chronic kidney disease: a retrospective cohort study

Amanda W. Singer, Brian L. McNabb, Anu O. Osinusi, Diana M. Brainard, Marcus Littman, Anne-Ruth van Troostenburg de Bruyn, Anand P. Chokkalingam; Gilead Sciences, Foster City, CA

Background: Patients with chronic hepatitis C virus (HCV) infections and advanced chronic kidney disease (CKD) have faced substantial barriers to treatment. There are limited data on current HCV treatment patterns with direct-acting antiviral (DAA) therapies in patients with HCV and advanced CKD. We examined US administrative claims data to characterize treatment uptake among patients with HCV and advanced CKD in the DAA era. **Methods:** All patients with chronic HCV and a claim for advanced CKD (stages IV or V or end stage renal disease) enrolled between January 2010 and March 2015 were included. Differences in the treated and untreated advanced CKD populations at baseline (i.e. prior to or up to one year following first HCV claim) were analyzed by chi-square tests. The proportion of advanced CKD patients initiating treatment and the distribution of treatment regimens was examined per calendar year for 2012-2014. **Results:** 179,804 adult patients with chronic HCV were identified, of which 15.2% received any anti-HCV treatment during the observation period. 3.3% of total HCV patients (N=5857) had a diagnosis of advanced CKD; most were between the ages of 45 and 64 years (75.7%) and male (69.5%), and 41.6% had a claim for dialysis at baseline. 9.3% of advanced CKD patients (N=545) ever received anti-HCV treatment; of these, 303 had an advanced CKD claim prior to treatment start. Compared to untreated advanced CKD patients, advanced CKD patients treated for HCV were more likely to be under 65 years of age, male, and have a diagnosis of cirrhosis; and were less likely to have diagnoses of anemia or type 2 diabetes or to have received dialysis at baseline. Treatment uptake and median duration by year is shown below. In 2012 and 2013, the most common regimens among treated advanced CKD patients were ribavirin (RBV) + interferon (IFN) (2012: 50.0%; 2013: 39.0%) and telaprevir + RBV + IFN (2012: 25.0%; 2013: 17.1%). In 2014, 92.4% of treated patients received a sofosbuvir (SOF)-containing regimen, including SOF + simeprevir (35.3%), SOF + RBV (22.9%), and ledipasvir/SOF (18.2%). **Conclusion:** A growing number of patients with chronic HCV and advanced CKD are treated for HCV despite recognized treatment limitations in this population. Treatment uptake has increased with greater availability of DAAs, with the majority of treated patients receiving SOF-based regimens in 2014.

Year	2012	2013	2014
Total number of advanced CKD patients	2966	3012	2805
Number (%) of patients treated for HCV	40 (1.3)	41 (1.4)	170 (6.1)
Median (range) duration of treatment in days	104 (28-578)	93 (28-337)	84 (6-246)

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Brian L. McNabb - Consulting: DocMatter; Employment: Gilead Sciences Inc.

Anu O. Osinusi - Employment: Gilead Sciences Inc; Stock Shareholder: Gilead Sciences Inc

Diana M. Brainard - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

Marcus Littman - Employment: Gilead Sciences, Inc.; Management Position: Gilead Sciences, Inc.; Stock Shareholder: Gilead Sciences, Inc.

Anne-Ruth van Troostenburg de Bruyn - Consulting: King's College London; Employment: Gilead Sciences International Ltd; Stock Shareholder: Gilead Sciences

Anand P. Chokkalingam - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

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Is there any place for non-invasive markers of fibrosis predicting the development of complications in patients with Child-Pugh A post hepatitis C cirrhosis (ANRS CO12 CirVir prospective cohort)?

Jean-Pierre H. Zarski[1,2], Sandra David-tchouda[6,5], Candice Trocme[4], Marie Noelle Hilleret[1,2], Jennifer Margier[6,5], Carole Cagnot[7], Françoise Roudot-Thoraval[3], Pierre Nahon[3]; [1]Gastroenterology and Hepatology, CHU de grenoble, Grenoble, France; [2]CRI INSERM U-823, Grenoble, France; [3]Statistiques, CHU de creteil, Creteil, France; [4]Biochimie, CHU de Grenoble, Grenoble, France; [5]CIC 1406 INSERM, Grenoble, France; [6]Universite Grenoble Alpes, TIMC-Imag UMR 5525, Grenoble, France; [7]ANRS, Paris, France

There are no specific marker predicting the development of any complication in patients with Child-Pugh A post hepatitis C cirrhosis, sustained virological response excepted. The aim of the study was to analyze the place of surrogate markers of fibrosis in a french national multicenter prospective cohort of HCV-infected patients with biopsy-proven cirrhosis (ANRS CO12 CIRVIR) included in 35 centers in order to predict the development of complications especially HCC. This study was a case control study ratio (1/4), the main events were collected on a 36 month period and were HCC, ascites, digestive hemorrage. Actitest-Fibrotest, Fibrometer 3G, performed independently in one lab, and fibroscan were analysed every 6 months between months 0 to 36. Our multivariate analysis took into account confounding factors, matching and changes in markers with time (conditional logistic regression and mixed-effects model). We included 136 cases (74/136 had HCC) and 270 controls (cirrhotic patient without any liver related events). In all groups mean age was 58±10 years, 65% were males .The 2 groups were comparable for comorbidities (diabetes, kidney failure, HA, dyslipidemia) and all viral factors, except for SVR (66.8% vs 29.1%, p <0.001), and lab data (bilirubin, gammaGT, platelets, TP). Results were systematically adjusted on SVR. From D0 onwards, a significant difference between cases and controls was systematically found for the mean marker scores and persisted between D0 and M36: Fibrotest: 0.72±0.18 vs 0.84±0.10; Fibrometer 3G (fibrosis: 0.72±0.13 vs 0.94±0.06, 0.85±0.13 vs 0.94±0.06;); and FibroScan: 17.0±11.2 vs 22.5±12.8 (p<0.0001). This significant difference was found in SVR patients except for Fibroscan. The kinetics between D0 and M36 showed few clinically relevant changes, thus multivariate exploration of the predictive value of the tests was carried out for D0. After adjusting for SVR, all markers remained associated with the occurrence of a complication. To conclude, all surrogates markers of fibrosis are able to early predict the occurrence of complications especially HCC in patients with post hepatitis C cirrhosis. Markers kinetic do not give any additional information. We hereby propose to monitor more accurately patients with high initial values, threshold remaining to be determined.

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Marie Noelle Hilleret - Speaking and Teaching: BMS, GILEAD, ABBVIE

Françoise Roudot-Thoraval - Advisory Committees or Review Panels: Roche, gilead; Consulting: LFB biomedicaments; Speaking and Teaching: gilead, Janssen, BMS, Roche, Abbvie

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Flow Mediated Dilation may be an indirect measure of liver stiffness in HCV genotype 1 related chronic hepatitis

Tommaso Bucci, Mario Masarone, Andrea Aglitti, Rosa Caruso, Pasqualina Di Siervi, Marie Francoise Tripodi, Marcello Persico; Medicina Interna ed Epatologia, Università degli studi di Salerno, Salerno, Italy

Introduction: Brachial Flow Mediated Dilation (FMD) is a well-known non-invasive method to assess endothelial function. In chronic liver disease, endothelial function was shown impaired suggesting a significant correlation among liver damage, sinusoidal endothelial function and liver stiffness. **Aim and Methods:**To investigate the relationship between endothelial function and liver stiffness we performed a cross-sectional study including 100 consecutive HCV Genotype 1 patients who underwent a complete clinical and laboratory screening for HCV infection. Liver stiffness was assessed by transient-elastography (TE). FMD and Carotid Intima-Media Thickness (c-IMT) were evaluated by 2-d ultrasound. Mean age was 62±12,5 years and 41,8% were woman. Based on TE score and according to liver fibrosis (Metavir score) patients were grouped as it follows: F0:14%; F1:19%; F2:10%; F3:20%; F4:37%. **Results** show a significant inverse linear correlation between FMD and TE until the value of 20kPa of stiffness (p<0,001). For TE higher than 20kPa the correlation shown not significant although the tendency of FMD enhancement was of note. In the whole population with Spearman test, FMD was inversely correlated with TE (p<0.001), age (p=0.002), male sex (p=0.002), GGT (p=0.035), low PLT (p=0.001), APRI (p<0.001), c-IMT (p=0.003) and directly with unconjugated bilirubin (p=0.014). At the multivariate regression analysis only TE (p<0.001), c-IMT (p=0.003) were inversely, and unconjugated bilirubin (p=0.031) directly, associated with FMD. Further sub analysis was conducted in patients with TE>20kPa (n=30) and <20kPa (n=70). In patients with TE>20 kPa at the multivariate analysis only unconjugated bilirubin (p=0.031) and low albumin (p=0.012) were directly correlated with FMD. While in the group with TE <20 kPa the only independent factors inversely associated with FMD were TE (p=0.017) and c-IMT (p=0.001). **In conclusion** an impaired FMD is significantly associated to a worst TE in chronic HCV related hepatitis. In patients with sickest disease, the liver failure, surprisingly, seems to be associated with a reconstituted endothelial function.

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Risk of colonic neoplasia in patients with chronic hepatitis C

Matthew Conti[1], John E. Poulos[2], Valentin Milanov[3]; [1]School of Osteopathic Medicine, Campbell University, Buies Creek, NC; [2]Fayetteville Gastroenterology Associates, Fayetteville, NC; [3]Mathematics and Computer Science, Fayetteville State University, Fayetteville, NC

Introduction- Evidence indicates that patients with chronic hepatitis C (CHC) have an increased risk of neoplasia. Data from tertiary referral centers suggests that HCV may be an independent risk factor for colonic neoplasia. However, the link between colon cancer and CHC in a community setting has not been extensively studied. Goal- The goal of this study was to determine if patients with CHC undergoing colonoscopies have

an increased risk of colonic neoplasia. Methods- Colonoscopy data were retrospectively collected and compared for patients with CHC and controls who underwent screening (N=370) and surveillance (N=126) between 1993 and 2016. Patients were matched for age, sex, and race. Data based on polyp size and histology was collected. Regression analysis was applied. Results- The screening data consists of 185 patients with CHC and 185 non-hepatitis controls. The surveillance data consists of 67 CHC and 59 patients without chronic liver disease. Analysis of screening data indicated that patients with CHC had a greater number of adenomas in comparison to controls (70% vs 45%; p<0.001, respectively). A trend towards advanced neoplasia was seen in the CHC group (8% vs 4%; p<0.15). Patients with CHC had a greater number of polyps larger than 0.75 cm in comparison to controls (31% vs 19%; p< 0.05, respectively). Regression analysis indicated the independent risk factors of CHC and male sex for the development of colonic neoplasia. The odds of having polyps in CHC patients was 55% higher than the odds of having polyps for controls (odds ratio 3.55, 95% confidence interval [CI]: 2.16, 5.94). For the surveillance data, the total number of patients with polyps was higher in the CHC group than controls (70% vs 47%, p<0.05). There was a higher proportion of patients with tubular adenomas in the CHC group. (61% vs 46%, p=0.12). There was a trend for patients with CHC having polyps larger than 0.75 cm in comparison to controls (25% vs 19%, p=NS). For surveillance data, regression analysis revealed CHC as an independent risk for the development of colonic neoplasia. The odds of having polyps for CHC patients were 227% higher than the odds for control patients (odds ratio 3.27, 95% CI: 1.37, 8.25). Conclusion- This study concludes an association between HCV infection and increased numbers of polyps and more advanced neoplasia in patients undergoing screening colonoscopy. CHC patients undergoing surveillance had a greater odds of polyp formation than controls. Further research should determine if this high risk population should undergo screening at an earlier age and/or at decreased intervals.

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Clinical evaluation of liver fibrosis and hepatocarcinogenesis using a novel glycobiomarker *Wisteria floribunda* agglutinin+ - Mac-2 binding protein (M2BPGi)

Takako Inoue[1], Yuji Tsuzuki[1,3], Etsuko Iio[2], Kumiko Ohne[1], Noboru Shinkai[3], Tomoyuki Ohike[1], Takaaki Goto[1], Shigeru Sato[1], Yasuhito Tanaka[1,3]; [1]Clinical Laboratory, Nagoya City University Hospital, Nagoya, Japan; [2]Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; [3]Department of Virology and Liver Unit, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Background: Recently, a novel glycobiomarker *Wisteria floribunda* agglutinin+ - Mac-2 binding protein (M2BPGi) has been available for evaluation of liver fibrosis. The aim of this study was to assess the association between serum M2BPGi level and 1) progression of fibrosis and hepatocarcinogenesis, and 2) cumulative survival rate and carcinogenesis rate in patients with hepatitis C virus (HCV). **Methods:** This study protocol was approved by the appropriate institutional ethics review committees. Serum M2BPGi levels were measured by HISCL M2BPGi (Sysmex Co., Japan) from 128 HCV-infected patients who were histopathologically diagnosed as F3 or F4 in our hospital from January 1998 to August 2014. All F4 patients were diagnosed as Child-Pugh Class A. The numbers of F3 or F4 patients were 44 (non-hepatocellular carcinoma [HCC]/HCC=30/14) and 84 (non-HCC/HCC=49/35), respectively. The median age was 65 (29-85) and male was 74 (57.8%). Seventy-nine patients without HCC at baseline were analyzed for survival and carcinogenesis rates during a median of 51 months (1-195). For statistical analyses, chi-square test or Mann-Whitney U test were used. Both cumulative survival rate and carcinogenesis rate were calculated by the Kaplan-Meier method. **Results:** 1) Serum M2BPGi levels (C.O.I) were significantly higher in patients with F4 (non-HCC/HCC=7.2 [0.9-19.3]/7.0 [0.5-39.2]) than F3 (non-HCC/HCC= 2.0 [0.5-14.0] /3.5 [1.0-8.4]) (p<0.001). In F3 and F4, serum M2BPGi levels did not differ significantly between patients with HCC and without HCC. 2) In F3 or F4 patients without HCC (n=79), five/eight years survival rates of high M2BPGi group (≥4, n=39) were 78%/48%, respectively, whereas those of intermediate M2BPGi (1-4, n=33) were 100%/82%, respectively. No one died in patients with low M2BPGi (<1, n=7). The survival rate differed significantly among the three groups (p=0.0041). HCC incidence in patients with high M2BPGi was higher than in those with low M2BPGi (p=0.0019). Cumulative carcinogenesis rates in patients with high M2BPGi were 48.7% after 4 years, contrasted with 16.9% in patients with intermediate M2BPGi and 0% in patients with low M2BPGi. The cumulative carcinogenesis rate differed significantly among the three groups (p = 0.002). All of the 7 patients without HCC who died within 60 months were diagnosed as F4 with high M2BPGi (16.3 [7.7-18.9]), and the period before dying was 29 months (3-58). **Conclusions:** Serum M2BPGi is useful for diagnosis of F4 despite the existence of HCC, and the patients with high M2BPGi had poor prognosis. Assessing serum M2BPGi would be diagnostic utility for predicting carcinogenesis and survival in patients with advanced fibrosis.

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Viral eradication reduces all-cause mortality in chronic hepatitis C patients with advanced liver fibrosis: a propensity score analysis

Toshifumi Tada[1], Takashi Kumada[1], Hidenori Toyoda[1], Natsuko Kobayashi[1], Junko Tanaka[2]; [1]Ogaki Municipal Hospital, Ogaki, Japan; [2]Hiroshima Univiersity, Hiroshima, Japan

Background & Aims Eradication of hepatitis C virus (HCV) by interferon (IFN)-based therapy has been reported to reduce all-cause mortality rates in patients with chronic HCV (CHC) infection. However, the impact of HCV eradication on non–liver-related mortality including the causes of death has not been sufficiently investigated in CHC patients with advanced liver fibrosis. **Methods** We enrolled 784 CHC patients with advanced liver fibrosis (APRI>1). Causes of death, incidence of hepatocellular carcinoma (HCC), and all-cause mortality including non–liver-related diseases, were analyzed. **Results** Of these 784 patients, 170 achieved sustained virological response (SVR) (eradication of HCV) by IFN-based therapy (IFN-SVR) or 614 did not receive IFN-based therapy (non-IFN patients) (Cohort 1); of these, 130 were selected from IFN-SVR (n=65) and non-IFN (n=65) groups using propensity score matching (Cohort 2).The median follow-up duration was 10.3 years. In Cohort 1 patients, mortality rates from non–liver-re-

lated diseases were 63.6% (7/11) in IFN-SVR patients and 36.3% (95/262) in non-IFN patients, respectively. In Cohort 2 patients, mortality rates from non–liver-related diseases were 66.7% (2/3) in IFN-SVR patients and 56.0% (14/25) in non-IFN patients, respectively. The eradication of HCV reduced all-cause mortality (hazard ratio (HR), 0.105; 95% confidence interval (CI), 0.032–0.349) including non–liver-related mortality (HR, 0.147; 95% CI, 0.034–0.635), and the incidence of HCC (HR, 0.195; 95% CI, 0.083–0.454). **Conclusions** Eradication of HCV reduced not only liver-related mortality but also non–liver-related mortality in CHC patients with advanced liver fibrosis.

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Per-contact infectivity of HCV infection and reinfection in association with receptive needle sharing exposures in a prospective cohort of young injection drug users in San Francisco, CA

Yuridia Leyva[1], Kimberly Page[1], Stephen Shiboski[3], Judith A. Hahn[4], Jennifer Evans[5], Erik Erhardt[2]; [1]Internal Medicine, University of New Mexico Health Sciences Center, Albuquerque, NM; [2]Mathematics & Statistics, University of New Mexico, Albuquerque, NM; [3]Department of Epidemiology & Biostatistics, University of California, San Francisco, San Francisco, CA; [4]Medicine, University of California-San Francisco School of Medicine, San Francisco, CA; [5]Department of Epidemiology & Biostatistics, University of California San Francisco, San Francisco, CA

Sharing needles and ancillary injection drug equipment places people who inject drugs (PWID) at risk for hepatitis C virus (HCV), a highly infectious blood-borne infection. The availability of data on HCV infectivity in the context of injecting with another person's previously used needle is limited. Our goal was to estimate the per-contact probability of HCV infection and reinfection accompanying injection with previously used needles, classified as receptive needle sharing (RNS). A probabilistic exposure model linking observed HCV infection outcomes to self-reported RNS exposure was applied to data from the UFO Study, a prospective observational cohort study of 784 active PWID under age 30 who were surveyed and tested quarterly for HCV between 2003-2008 and 2010-2014 in San Francisco, California. For each participant, the first survey with an HCV-negative status up through the first survey with an HCV-positive status was selected, returning 118 participants in the analysis. A maximum likelihood estimate considering RNS yields a per-contact HCV infectivity ranging between 0.89% and 1.62% among HCV susceptible groups. Table 1 shows the per-contact probability of HCV (and 95% bootstrap confidence intervals) among the different susceptible groups who became infected or reinfected at least once. The strengths of this study include the ability to assess infectivity specifically from data on *receptive* needle sharing contacts (vs. 'sharing needles'), as well as the short (3-month) recall and HCV testing periods to ascertain these exposure and outcome events. These factors likely account for the higher infectivity estimates than found by others of 0.57% (95% CI 0.32%, 1.05%) (Boelen et al. 2014). This analysis fills an important gap in information due to its focus on per-contact probability of HCV in association with RNS, a primary route of HCV transmission among PWID. Results can inform models and research on the impact of prevention scale up and population level impact. Reducing RNS and frequency of RNS will contribute to reducing the spread of HCV.

Per-contact probability of HCV acquisition associated with RNS

Group	n	Infectivity	95% CI
Subjects with primary infection only	101	0.89%	(0.20%, 2.27%)
Reinfected subjects only	17	1.62%	(0.44%, 8.14%)
Participants with primary infection or reinfection	118	1.12%	(0.48%, 2.36%)

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Predicting Hepatocellular Carcinoma in Hepatitis C Patients by Analysis of APRI Score Progression Pattern

Jeremy M. Mason[1], Peter Richardson[2], Fasiha Kanwal[2], Paul K. Newton[3], Peter Kuhn[1], Jennifer R. Kramer[2]; [1]Biological Sciences, University of Southern California, Los Angeles, CA; [2]Michael E. DeBakey VA Medical Center and Baylor College of Medicine, Houston, TX; [3]Aerospace and Mechanical Engineering, University of Southern California, Los Angeles, CA

Background Approximately 2-6% of hepatitis C virus (HCV) patients with cirrhosis will develop hepatocellular carcinoma (HCC) in their lifetime. The aspartate aminotransferase to platelet ratio index (APRI) score is a non-invasive measure of fibrosis that can be used to determine the risk of advanced liver disease. While APRI scores can fluctuate over the course of the disease and appear random, we explored the possibility that specific patterns can be used as diagnostic measures in certain groups of HCV patients. **Methods** Using the Veteran Health Administration HCV Clinical Case Registry, we isolated a set of 34,268 HCV patients (17,134 HCV antibody+ and RNA+ cases propensity matched to 17,134 HCV antibody+ and RNA-). Patients were required to have a minimum of two APRI scores in separate years and no prior existing evidence of cirrhosis or HCC. For each year in the study, we classify each patient using lab data based on their median APRI score in that year or ICD-9 code into 8 clinical stages including APRI: 0-1, APRI: 1-1.77, APRI: > 1.77, compensated cirrhosis, decompensated cirrhosis, HCC, transplant (post-transplant care), and death. Data and models are analyzed on a webpage that has the capability of displaying multiple interactive figures of patient subgroups (e.g. age, race, gender, alcohol abuse, etc.) for side-by-side comparisons. **Results** Based on the defined stages recorded in each year, we illustrated disease progression for the population as tree ring diagrams spanning a 14 year period, overall and by subgroups. For example, we analyzed age groups of 20-49, 50-64, and 65-100 y/o and observed that while many of the older population died early on in the study, the middle population had more distinct pathways (304 paths compared to 218 in the younger and 157 in the older). Based on these stage progression paths, we created Markov chain models that are used to run Monte Carlo simulations to simulate HCV progression to advanced liver disease. We found that the younger population had greater probabilities of fluctuating APRI scores before progression to advance liver disease, and that this can be used as a measure to predict future outcomes. **Conclusions** APRI scores are a powerful diagnostic tool for measuring progression to advanced liver disease, and the patterns that emerge in fluctuating scores are easily viewed as tree ring diagrams. Modeling this progression as a Markov process provides a unique and novel way of predicting future liver disease outcomes in HCV patients. By more accurately predicting these outcomes in specific patient groups, we can ultimately improve HCV patient care and reduce costs associated with unnecessary treatments.

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Defining HCV-Related Cirrhosis Clusters in Alabama using Geospatial Methods

Omar T. Sims[1], Krishna V. Venkata[2], Justin X. Moore[3], Sumant Arora[2], Mohamed G. Shoreibah[4], Omar I. Massoud[4]; [1]Department of Social Work; Department of Health Behavior; Center for AIDS Research; Comprehensive Center for Healthy Aging, The University of Alabama at Birmingham, Birmingham, AL; [2]Department of Medicine, The University of Alabama at Birmingham, Birmingham, AL; [3]Department of Epidemiology; Department of Emergency Medicine; Comprehensive Cancer Center, The University of Alabama at Birmingham, Birmingham, AL; [4]Division of Gastroenterology & Hepatology, The University of Alabama at Birmingham, Birmingham, AL

BACKGROUD AND AIMS: Geospatial analysis is a novel epidemiologic approach that can be used to identify and map geographic disease cluster areas and describe demographic characteristics of those areas. There are scant studies on the use of geospatial analysis in hepatitis C (HCV) research. We sought to determine the geographic distribution of HCV-related cirrhosis cases by Alabama three-digit zip codes, and determine patient-level and community-level factors associated with higher HCV-related cirrhosis rates. **METHODS:** We obtained data from 738 HCV-infected patients who presented for care at UAB's Liver Center from January 2015 through December 2015. We performed three-geospatial analysis: Empirical Bayes [EB], Local Moran's I [LISA], and Getis Ord Gi* [Gi*]. We considered three-digit zip code areas to be "Clustered" if they were identified as high risk or cirrhosis hot spots using two or more of the geospatial metrics (i.e., LISA, Gi*, or EB rates). All other three-zip code areas were classified as "Non-Clustered". **RESULTS:** The prevalence of HCV-related cirrhosis was 33% (247/738). There were a total of 88 HCV-related cirrhosis cases within the Clustered areas, and 159 cases within the Non-Clustered areas. The cirrhosis Clustered region had a higher cirrhosis event rate (9.40 per 100,000 persons; 95% CI: 7.60 – 11.50) compared with the Non-Clustered (4.10 per 100,000 persons; 95% CI: 3.50 – 4.80). The Clustered communities were located in central Alabama with the city of Birmingham at the centroid point of the strong cirrhosis clustering. Event rates for the 350 (10.40 per 100,000 persons; 95% CI: 7.80 – 13.90) and 352 (8.50 per 100,000 persons; 95% CI: 6.30 – 11.50) Birmingham zip codes were among the highest between Alabama three-digit zip codes. Patients who lived in cirrhosis Clustered communities were more likely to be of Black race (45.80% vs. 20.45%, p <0.01), report active drug use (13.99% vs. 10.40%, p = 0.05), and no tobacco use (43.01% vs. 32.96%, p < 0.01) when compared with patients who lived in the Non-Clustered communities. Clustered communities had higher education (p < 0.01). Non-Clustered communities had a larger proportion of individuals living above the poverty threshold (21.85% vs. 19.80% for PIR 1 – 2, 5.83% vs. 5.53% for PIR >2, p <0.01) when compared with Clustered communities. **CONCLUSION:** This study supports the use of geospatial analysis as a tool for identifying geographic distribution of HCV-related cirrhosis hot spots. Future studies are needed to investigate underlying causes of non-random cirrhosis clustering in the metropolitan Birmingham area.

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Comparing APRI and FibroScan score for pre-treatment assessment of HCV-related liver disease in community settings

Joseph S. Doyle[1,2], David M. Iser[2,3], Amanda J. Wade[1], Alex J. Thompson[3,4], Margaret Hellard[1,2]; [1]Population Health, Burnet Institute, Melbourne, VIC, Australia; [2]Infectious Diseases, Alfred Health, Melbourne, VIC, Australia; [3]Gastroenterology, St Vincent's Hospital Melbourne, Melbourne, VIC, Australia; [4]Medicine, University of Melbourne, Melbourne, VIC, Australia

Background Fibrosis assessment prior to hepatitis C (HCV) treatment is recommended, however access to elastography is limited by resources in many settings, even in high-income countries. This study aims to assess whether routine blood tests can be used to triage need for non-invasive fibrosis assessment in a community-based cohort of people who inject drugs (PWID). **Methods** The HCV Treatment And Prevention (TAP) Study examines the feasibility of community-based HCV treatment for PWID using oral sofosbuvir/ledipasvir ±ribavirin in Melbourne. Haematological, biochemical and fibrosis assessment using transient elastography (FibroScan™) were performed at screening. The AST:Platelet Ratio Index (APRI) was calculated and compared with valid FibroScan scores (10 readings >60% success; <30% IQR/median) at screening. Cirrhosis (Ishak F4) was defined as FibroScan score ≥12.5kPa. Negative (NPV) and positive predictive values (PPV) were calculated for predicting cirrhosis at high (2.0) and low (1.0) APRI. **Results** Of participants screened to date, APRI was calculable in 114/118, and valid FibroScan was available among 99/114. Participants were 67% male, median age 37 years (IQR 33—44 years), with median body mass index 23.1 (IQR 20.9—26.4). Median APRI was 0.54 (IQR 0.29—0.98). Median FibroScan score was 5.6kPa (IQR 4.5—6.8kPa); 7% and 12% had liver stiffness ≥12.5kPa and ≥9.5kPa, respectively. Two individuals had discrepant APRI<1.0 and FibroScan>12.5kPa score: both were male, aged 32 and 35 years old, with BMI 27.5 and 22.5, and ALT 74U/l and 70U/l, respectively. Using an APRI cut off of 1.0, NPV for cirrhosis was 96% (70/73; 95%CI 89—99%), and PPV was 19% (5/26). Using an APRI cut off of 2.0, NPV for cirrhosis was 94% (88/94) and PPV was 40% (2/5). **Conclusions** A low APRI score (<1.0) may be an acceptable community screening test to exclude cirrhosis where FibroScan is unavailable. Use of APRI may facilitate treatment initiation in such settings. APRI threshold >1.0 should not be used to diagnose cirrhosis.

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Genetic characteristics and transmission pattern of HCV genotype 1a in Okinawa island, the south of Japan

Kunikazu Hoshino[1], Masaya Sugiyama[1], Tatsuji Maeshiro[2], Tomoko Date[1], Hirotaka Shoji[1], Yohei Mano[1], Hiroyoshi Doi[1], Sachiyo Yoshio[1], Tatsuya Kanto[1], Masashi Mizokami[1]; [1]National Center for Global Health and Medicine, Ichikawa, Japan; [2]Department of Infectious, Respiratory, and Digestive Medicine, University of the Ryukyus, Nishihara, Japan

BACKGROUND/AIM: The distribution of hepatitis C virus (HCV) genotypes varies according to ethnic and geographic differences in the world. HCV genotype 1b (GT-1b) is the most prevailing type in Japan, while the prevalence of HCV GT-1a is rare in the mainland of Japan. In contrast, Okinawa island, which is located in the south of Japan, has the history of US military occupation after the World War II. The prevalence of GT-1a in Okinawa is reported to be higher than that in the mainland, the reasons of which may be influenced by geographical, historical and social backgrounds. We aimed to elucidate the route and timescale of transmission of HCV GT-1a by clarifying genetic features of HCV GT-1a in Okinawa island using whole genome sequencing of HCV and subsequent phylogenetic analysis. **PATIENTS/METHODS:** In this study, 10 patients with HCV GT-1a infection determined by serological test were enrolled, who were born and bred in Okinawa island (mean age, 58.4 years; 6 male and 4 female). We performed whole HCV genome sequencing covering the region from Core to NS5B using several pairs of primer. For phylogenetic analyses, the obtained sequence was aligned using MAFFT with a set of global references retrieved from HCV database. Phylogenetic trees were constructed with 6-parameter method and bootstrapped 1,000 times to confirm the reliability of the phylogenetic tree by Neighbor-Joining method using MEGA v7. **RESULTS:** We successfully obtained full genome sequences of HCV GT-1a from all of the samples. In phylogenetic analyses, these sequences were clustered into HCV GT-1a group consisting of US strains but not Asian cluster, suggesting that a possible route of transmission was from US. To estimate the epidemic period of HCV GT-1a in Okinawa, we performed phylodynamic analysis using all samples. The time of spreading of HCV GT-1a was estimated around the Viet Nam War. Several routes of HCV Gt-1a infection were observed because a specific cluster consisting of Okinawa samples was not observed in the phylogenetic tree. **CONCLUSION:** In Okinawa, HCV GT-1a was estimated to be introduced from US, spreading of which was accelerated by the increase of intravenous drug users (IVDU) during Viet Nam War. In the present, as HCV infection risk via medical activity was exceedingly zero in Japan, educational activity to take a screening test for HCV infection patients was also needed to reduce chronic hepatitis C patients.

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Non-invasive assessment of liver fibrosis and cirrhosis regression in chronic hepatitis C patients treated with pan-oral direct-acting antivirals

Guofeng Chen[1], Dong Ji[1,2], Lei Lu[3], Yudong Wang[3], Jing Chen[3], Cheng Wang[3,4], Qing Shao[1], Bing Li[1], April Wong[3], Vanessa Wu[3], George Lau[3,1]; [1]Second Liver Cirrhosis Diagnosis and Treatment Center, 302 Hospital, Beijing, China; [2]Liver Failure Treatment and Research Center, 302 Hospital, Beijing, China; [3]Division of Gastroenterology & Hepatology, Humanity & Health Medical Centre, Hong Kong, Hong Kong; [4]State Key Laboratory of Organ Failure Research, Guangdong Provincial Key Laboratory of Viral Hepatitis Research, Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, China

Background and Aim In the era of direct-acting antivirals (DAAs), sustained virological response (SVR) rates in patients with chronic hepatitis C (CHC) are remarkably increased. However, whether DAAs therapies can improve liver histology is still largely unknown. We aim to evaluate the impact of DAA therapies on liver fibrosis and cirrhosis non-invasively by liver stiffness measurement (LSM). **Methods** One hundred and seventy-five Chinese patients with genotype 1 CHC were included in this study, which were treated with pan-oral DAAs for 12 weeks (Group 1), including ledipasvir (90 mg)/sofosbuvir (400 mg) (n=123), daclatasvir (60 mg)/sofosbuvir (400 mg) (n=50) and paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus dasabuvir (250 mg) (n=2). Fifty-five age and gender matched patients treated with long-term pegylated interferon (PEG-IFN) based therapies (median treatment duration: 60 weeks) were enrolled as the control group (Group 2). The median follow-up duration for Group 1 and 2 were 44 weeks and 46 weeks respectively. LSM was measured at baseline, the end-of-treatment and the end of follow-up by transient elastography (TE). Advanced liver fibrosis or cirrhosis (F≥3) is defined by LSM>9.5 kPa. **Results** One hundred and seventy-two patients in Group 1 (172/175, 98.3%) achieved SVR at the end of follow-up, which was significantly higher than that of Group 2 (42/55, 76.4%) (p<0.001). Median LSM decreased significantly from baseline to the end-of-treatment in both groups (Group 1: 12.5 vs. 10.6 kPa, p<0.001; Group 2: 15.2 vs. 12.1 kPa, p<0.001). Median LSM also decreased significantly during the follow-up in Group 1 (10.6 vs. 8.7 kPa, p<0.001), but not in Group 2 (12.1 vs. 13.2 kPa, p=0.378). The median LSM reduction from the baseline to the end of follow-up in Group 1 was 1.8 kPa, which was equivalent to the median LSM reduction in Group 2 (2.4 kPa, p=0.08). In Group 1, there were 105 (60.0%) patients had advanced liver fibrosis or cirrhosis (F≥3) at baseline, which significantly reduced to 54.3% (95/175, p<0.001) at the end-of-treatment and further significantly reduced to 46.3% (81/175, p<0.001) at the end of follow-up. Similarly, patients with advanced fibrosis and cirrhosis at baseline in Group 2 (41/55, 74.5%) were also significantly reduced to 61.8% (34/55, p<0.001) after PEG-IFN treatment, but there is no significant change from the end-of-treatment to the end of follow-up (65.4%, p=0.378). **Conclusion** Liver fibrosis and cirrhosis significantly regressed during the treatment and follow-up of DAA therapies in genotype 1 CHC patients. The impacts of 12-week DAAs therapies on liver stiffness were equivalent to long-term PEG-IFN treatment.

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New blood test multi-targeted for liver fibrosis outperforms all other blood tests and even elastography in chronic liver diseases

Paul Cales[1], Jerome Boursier[1], Oberti Frederic[1], Valerie Moal[2], Isabelle Fouchard-Hubert[1], Sandrine Bertrais[3], Gilles Hunault[3], Marie Christine Rousselet[4]; [1]Hepatology Department, Centre Hospitalier Universitaire d' Angers, Angers Cedex 9, France; [2]Biochemistry, CHU, Angers, France; [3]HIFIH laboratory, Angers University, Angers, France; [4]Pathology, CHU, Angers, France

Fibrosis blood test construction is classically limited to a unique diagnostic target: significant fibrosis. Yet, these single-target tests are commonly used for other diagnostic targets like cirrhosis. Therefore, our aim was to improve the accuracy of non-invasive fibrosis staging by targeting biomarkers for all diagnostic targets using a new statistical method. **Methods**. 2589 patients were included: 1012 with chronic hepatitis C (CHC) in a derivation population and 1577 in 5 validation populations of different etiologies (CHC, chronic hepatitis B, HIV/CHC, NAFLD, alcoholic liver disease) using Metavir fibrosis stages (F) by liver biopsy as reference. FibroMeter biomarkers were statistically combined against as many fibrosis targets as made possible by Metavir staging. Several statistical functions were successively used to provide a unique score ranging from 0 to 1 as in classical fibrosis scores. This new score was called multi-target FibroMeter^{V2G} (MFM^{V2G}). Accuracy was evaluated primarily by the Obuchowski index discriminating all Metavir stages and secondarily by AUROCs for binary diagnostic targets and by correct classification rates in fibrosis classifications (into 6 fibrosis classes from F0/1 to F4). **Results.** In the derivation CHC population, the Obuchowski index (0.853) and AUROC for cirrhosis (0.929) of MFM^{V2G} were significantly superior to those of single-target (F≥2) FibroMeter^{V2G} (0.843 and 0.907, respectively, p<0.001). MFM^{V2G} classification was more accurate (92.3%) than FibroMeter^{V2G} classification (87.6%, p<0.001). In the CHC validation population (641 patients), the Obuchowski index and AUROC for cirrhosis of MFM^{V2G} were significantly superior to those of all other single-target classical blood tests: FibroMeter^{V2G}, CirrhoMeter^{V2G}, APRI, Fib4, Fibrotest, Hepascore and Zeng score. MFM^{V2G} was also globally superior to untargeted Fibroscan according to the Obuchowski index: 0.797 vs 0.766, respectively, but this was not significant (p=0.178). Similarly, their AUROCs for cirrhosis were not significantly different, MFM^{V2G}: 0.880, Fibroscan: 0.897, p=0.090. MFM^{V2G} classification remained more accurate (88.0%) than FibroMeter^{V2G} classification (83.6%, p<0.001). Most of these results were confirmed in other etiologies. ***Conclusion:*** Multi-targeting biomarkers improves the accuracy of non-invasive fibrosis staging in a highly significant manner compared to classical single-target blood tests, matching liver elastography even for cirrhosis diagnosis.

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Cost and effectiveness of hepatitis C virus cryoglobulinemia vasculitis (HCV-CryoVas) treatment in the era of direct acting antivirals (DAA) in a tertiary French center

Patrice P. Cacoub[1,2], Mathieu Vautier[1,2], Anne Claire Desbois[1,2], Marianne Doz[3], Antoine Lafuma[3]; [1]Department of Internal Medicine and Clinical Immunology, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Paris, France; [2]Inflammation-Immunopathology-Biotherapy Department (DHU i2B), Sorbonne University, UMPC Univ Paris 06, UMR 7211, Paris, France; [3]CEMKA, Paris, France

Background Accounting for the economic burden of extrahepatic manifestations is essential for a more accurate correct quantification of the benefits of treatment of HCV. HCV infection is the main cause of cryoglobulinemia vasculitis (CryoVas). Evolution in HCV treatment has allowed for changes in the management of CryoVas. **Objective** To estimate the effectiveness and costs of HCV-CryoVas treatment in the direct acting antiviral (DAA) era and compare to those in the pre-DAA era, in a tertiary national reference French center. **Methods** A chart review of HCV-CryoVas patients treated from 1996 to 2015 was performed. Patients were divided in two groups according to the first HCV treatment (group 1: interferon (IFN) ± ribavirin (RBV) or pegIFN+RBV, group 2: HCV treatment with DAA). Main clinic-biological characteristics were assessed at diagnosis, before and following the first anti-viral session. Effectiveness was evaluated in three dimensions: (1) Clinical response (CR) - improvement of all or some of the organs affected by CryoVas at baseline, and the absence of clinical relapse, (2) Immunological response (IR) – decrease >50% or the absence of cryoglobulinemia after treatment, (3) Sustained virological response (SVR) - negative viremia post-treatment. For cost analyses, all resources used for each patient were collected including HCV treatments, non-viral drugs, dialysis, duration of hospitalizations and rehabilitation care for CryoVas. **Results** 201 patients with CryoVas were treated at the center since 1996. 107 (53%) women, mean age at CryoVas diagnosis 59 ± 13 years, F3/F4 Metavir score in 69 (37%), and main genotypes were 1 (64%), 2 (12%) and 4 (11%). Main CryoVas symptoms were neuropathy (76%), purpura (69%), arthralgia (50%), glomerulonephritis (33%), and sicca syndrome (10%), with a mean of 4.9 extrahepatic CryoVas manifestations per patient. Cryoglobulinemia was positive in 185 (92%), type 2 Ig Mk (72%), and at a mean level of 1.2 g/L. There were no statistically significant differences in baseline characteristics between the groups. CR improved from 79% to 96%, IR from 77% to 89% and SVR from 43% to 75%. HCV drug cost increased from 11,941€ to 57,669€, the mean total cost increased less (63,433€ to 90,377€) due to a decrease in both hospitalization costs (33,591€ to 21,347€), in non-antiviral treatments (17,899€ to 11,397€). **Conclusion** In this large cohort of HCV-CryoVas patients, improved antiviral effectiveness and safety of HCV drugs in the DAA era resulted in higher rates of clinical and immunological responses of CryoVas and a significant reduction in hospitalization and non-antiviral treatment costs.

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High Prevalence of Steatosis and Association with Advanced Fibrosis in Patients with Chronic Hepatitis C

Alex Myint[1], Priyanka Ancharya[2], Hector E. Nazario[3]; [1]Gastroenterology, Methodist Dallas Medical Center, Dallas, TX; [2]Clinical Research Institute, Methodist Health System, Dallas, TX; [3]The Liver Institute at Methodist Dallas Medical Center, Dallas, TX

Background Hepatic steatosis is the defining feature of non-alcoholic fatty liver disease (NAFLD) and has been associated with chronic hepatitis C infection (CHC), particularly genotype 3. Both diseases are associated with liver fibrosis and cirrhosis. Previous studies have suggested an association of higher degrees of steatosis in CHC patients with more advanced fibrosis. We aim to investigate how the prevalence of steatosis and non-alcoholic steatohepatitis (NASH) have changed as obesity has become more prevalent and how their presence affects fibrosis in CHC. **Methods** We conducted a retrospective review of 857 patients who had native liver biopsy for CHC at a tertiary referral center between 2011-2015. Repeat biopsies and those without evidence of CHC were excluded. Variables collected include age, sex, Batts-Ludwig score, degree of steatosis, histologic features, BMI, HCV genotype, LFTs, platelet count, presence of comorbidities and alcohol abuse within 6 months of biopsy. Analysis was performed using STATA version 14 and SPSS version 21. **Results** Overall, 58.95% of patients had steatosis & 10.82% had steatosis >30%. 3.97% of the overall population had NASH. Patients with NASH had a statistically significant higher prevalence of genotype 3 and elevated transaminases compared to those without NASH. Additionally, Hispanics had a statistically higher prevalence of NASH(OR=3.50;95% CI=1.39-8.50), but not steatosis, compared to other races. There was no increased prevalence of genotype 3 infection for Hispanics. There was no difference in age, BMI, diabetes, hypertension, hyperlipidemia or CV disease. The presence of steatosis was associated with higher rates of advanced fibrosis (OR = 1.98; 95% CI=1.43-2.76). High percentage of steatosis(>30%) (OR = 2.76; 95% CI=1.60-4.77) and presence of SH (OR=2.94; 95% CI = 1.34-6.64) were associated with higher rates of advanced fibrosis compared to those without steatosis. **Conclusions** Steatosis is highly prevalent in those with chronic CHC. Coexistent NASH/CHC existed in a small number of those undergoing biopsy, but higher rates of NASH/CHC are seen in Hispanics and those with genotype 3. Both steatosis and NASH are associated with advanced fibrosis with a 2 and 3 fold increase in risk, respectively. CHC patients with steatosis/NASH may merit CHC treatment sooner and closer liver monitoring ***post-CHC treatment*** due to risks of advancing fibrosis from steatosis/NASH.

Steatosis	Age (years)	BMI (kg/m^2)	Genotype 3 (%)	Hispanic (%)	Advanced Fibrosis (%)	OR for Advanced Fibrosis
No	54.47	29.96	2.32	10.47	35.47	N/A
Yes	55.22	30.75	6.94	10.27	52.16	1.98(1.43-2.76)
NASH	53.03	32.29	16.67	12.50	61.76	2.94(1.34-6.64)

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Use of an EHR Clinical Decision Support Tool for HCV Birth Cohort Screening: A Single Center Experience

David N. Fitch, Ajay Dharod, Claudia Campos, Marina Nunez; Internal Medicine, Wake Forest Baptist Health, Winston Salem, NC

BACKGROUND: The U.S. Preventive Services Task Force (USPSTF) recommended in June 2013 that all patients born between 1945 and 1965 receive one-time screening for hepatitis C. Data evaluating the implementation of birth cohort HCV screening in clinical practice is scarce and interventions to improve it are not yet common practice. We sought to implement an electronic health record (EHR) clinical decision support (CDS) tool for HCV birth cohort screening in the clinic sites at our medical center, and to evaluate its effect. METHODS: The study was conducted at 2 general internal medicine clinics affiliated with Wake Forest Baptist Medical Center. They serve primarily underrepresented minorities (~46% AA, ~15% Hispanic/Other, ~39% White) with a large uninsured or Medicaid population. The Department of Medicine Informatics Team designed a clinical decision support tool to identify individuals in the birth cohort (1945-1965) without previous anti-HCV antibody (Ab) in the EHR who were established with a PCP. The CDS consists of a HCV screening reminder and user design for automatic provider ordering for anti-HCV Ab. Data on anti-HCV Ab and HCV RNA tests in the eligible population were recorded from EHR implementation date (10/1/2012). Data was analyzed at three different time points: 12/31/14 (end of historical period), 7/1/15 (EHR CDS implementation) and 12/31/15 (CDS period). RESULTS: The population eligible for birth-cohort screening increased over the three periods as did the proportion of patients tested for anti-HCV Ab: 854/4,355 (20%) historical, 1220/4,994 (24%) by July 2015, and 1,700/5,578 (30%) by December 2015. There was a statistically significant decline in the proportion tested patients with a positive anti-HCV Ab result: 59/480 (12%) in CDS period compared to prior, 218/1220 (18%); p=0.005. HCV RNA confirmatory testing tended to increase after CDS implementation (79% compared to 73% prior). The CDS tool was used to order the anti-HCV Ab in 166/480 (35%) of the patients screened in the CDS period. CONCLUSIONS: Within a short period of time and despite partial use, 6 months after CDS implementation there was a modest increase in HCV birth cohort screening. In addition, negative anti-HCV Ab results increased during the CDS period. Given the high prevalence of anti-HCV positivity in our population we believe continued use of the CDS, with added education reinforcement, will help uncover HCV infections that otherwise may have remained undiagnosed.

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Chronic Hepatitis C Virus Infection and Cancer Risks: A Population-based Cohort Study

Phyo T. Htoo[2], Jean Marie Arduino[3], Jinghua He[1]; [1]PharmacoEpidemiology, Merck & Co. Inc, North WAles, PA; [2]Gillings School of Global Public Health, University of North Carolina at Chapel Hill, CHAPEL HILL, NC; [3]Merck & Co., Inc, North Wales, PA

OBJECTIVE: Chronic hepatitis C virus (HCV) infection has been associated with the incidence of various cancers but few studies were done in the U.S. large healthcare setting. We aim to assess the incidence of common cancer sites among chronic HCV versus non-HCV and Surveillance, Epidemiology, and End Results (SEER) general population. **METHODS:** We conducted a cohort study on 18+ year old Humana commercial insurance and Medicare advantage beneficiaries 2007-2015. Chronic hepatitis C virus (HCV) patients were identified by medical claims of at least 2 ICD-9-CM diagnoses within 6 months. Patients were required to have a 12-month baseline of continuous insurance prior to the first HCV diagnosis. Patients with prevalent HCV or cancer diagnoses during this period were excluded. All patients have healthcare utilization during base-

line to reduce detection bias. We identified cancer outcomes of interest with a validated algorithm: 2+ ICD-9-CM diagnoses within 6 months. Incident rates in the HCV cohort were estimated by standardizing for age and sex against 2000 U.S. census population and compared with rates in the non-HCV cohort and SEER 18 areas 2007-2013, also standardized against the same population. Non-HCV cohort includes patients with no HCV diagnoses by the start of follow up, which is one of the healthcare utilization dates. **RESULTS:** HCV patients are younger (mean age 60) compared to non-HCV patients (mean age 65) and crude incident rates are mostly similar to non-HCV rates. After standardizing for age and sex, incident rates increased substantially and the standardized rates are significantly higher for HCV vs. non-HCV with rate ratios, RR (95% confidence intervals) of 1.81 (1.22, 2.69) for lung, 27.20 (17.80, 41.55) for liver, and 1.71 (0.92, 3.18) for pancreatic cancers. Rates are similar in both cohorts for other cancers with RR (95% CI) of 1.18 (0.72, 1.94) for colorectal cancer, 1.02 (0.49, 2.12) for non-Hodgkin's lymphoma (NHL), 0.85 (0.48, 1.15) for breast, 0.73 (0.46, 1.15) for prostate, 0.79 (0.36, 1.76) for leukemia, 0.72 (0.40, 1.29) for bladder and 1.11 (0.59, 2.07) for renal. There is lower incidence of thyroid cancer for HCV vs. non-HCV with RR 0.35 (0.14, 0.90). Analyses of SEER rates are also consistent: HCV patients having higher rates of colorectal, lung, liver, renal, pancreatic cancers and NHL vs. SEER general population. **CONCLUSION:** Chronic HCV is associated with higher incidence of common cancer sites versus non-HCV or SEER general population, adjusted for age and sex. Confounding by comorbidities, social or behavioral risk factors cannot be excluded.

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The following people have nothing to disclose: Phyo T. Htoo

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Versant HCV Genotype 2.0 assay (LiPA) misclassifies the circulating HCV recombinant RF1_2k/1b in genotype 2 patients

Hans Orlent[1,4], Wim Schuermans[5], Elizaveta Padalko[5], Isabelle Desombere[2], Patrick Descheemaeker[3], Hans Van Vlierberghe[4], Marijke Reynders[3]; [1]Gastroenterology and Hepatology, AZ St Jan Brugge Oostende, Brugge, Belgium; [2]Center for Vaccinology, Ghent University and Hospital, Ghent, Belgium; [3]Laboratory Medicine, Clinical Microbiology, AZ Sint Jan Brugge Oostende, Brugge, Belgium; [4]Gastroenterology and Hepatology, Ghent University and Hospital, Ghent, Belgium; [5]Clinical Chemistry, Microbiology and Immunology, Ghent University and Hospital, Ghent, Belgium

Introduction and aims: The accuracy of the Versant HCV Genotype 2.0 Line Probe Assay (LiPA) to identify the subtype diversity within genotype 2 has been reported to be suboptimal. The aim of the present study was to characterize the HCV subtype diversity of patient samples previously labeled as HCV genotype 2 with the Versant HCV Genotype 2.0 LiPA. **Methods:** 89 consecutive HCV-RNA samples stored in the UZ Gent HCV-RNA bank with genotype 2 status as determined with the Versant HCV Genotype 2.0 Assay (LiPA) were re-genotyped with the HCV NS5B sequencing reference method (Murphy et al., 2007). Concordance for genotype group and subtype between both typing methods was calculated. The results of genotypes and subtypes obtained by NS5B sequencing were considered the reference genotypes. **Results:** The HCV polymerase region (NS5B) was successfully sequenced in 86/89 (97%) genotype 2 samples. The two genotyping methods resulted in concordant genotype and subtype in 10/86 samples (12 %). 55/86 (64%) samples were incompletely genotyped with LiPA (exact genotype result with an unidentified subtype or with an absence of discrimination between two subtypes). Both methods failed to assign a subtype in 8/86 (9 %) samples. 13/86 (15%) samples were misclassified with LiPA (wrong genotype or correct genotype associated with a wrong subtype). The circulating HCV recombinant form RF1_2k/1b was detected with the HCV NS5B sequencing reference method in 11 of these samples (11/86 (13%)). 9/11 (82%) of these had been labeled as "2a or 2c" with the LiPA 2.0 method. **Conclusions:** Direct sequencing of the HCV NS5B polymerase region revealed the presence of the recombinant form RF1_2k/1b in 13% of samples, the majority of which had been labeled as genotype "2a or c" with Versant HCV Genotype -LiPA 2.O. The impact on choice of optimal antiviral treatment regimen and patient care of these findings needs to be evaluated further.

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Regression of Liver Fibrosis Stage in Chronic Hepatitis C Infected Patients After Achieving Sustained Virologic Response Using Direct-Acting Antivirals as Demonstrated by Elastography

Ahmad S. Alawad[2], Masato Yoneda[2,3], Tiffannia Grant[2], Emmanuel Thomas[1], Eugene R. Schiff[2]; [1]Schiff Center for Liver Diseases, Syllvester Comprehensive Cancer Center, Department of Cell Biology, University of Miami Miller School of Medicine, Miami, FL; [2]Schiff Center for Liver Diseases, University of Miami Miller School of Medicine, Miami, FL; [3]Department of Hepatology, Yokohama City University, Yokohama, Japan

Background: Cirrhosis due to HCV infection has been associated with increased risk for hepatocellular carcinoma. The aim of our study was to assess changes in liver transient elastography (TE) and fibrosis-4 (FIB-4) score in patients with chronic hepatitis C (CHC) who achieved sustained viral response (SVR). **Methods:** Our retrospective prospective study included 60 patients with CHC and a baseline liver biopsy who achieved SVR after treatment with DAA regimens and had a pretreatment TE study and at least one follow up TE measurement at 24 weeks or later post end of treatment response (EOTR). The estimated stage of liver fibrosis based on TE was categorized as F0-F2 (≤9.4kpa), or F3 (9.5 – 12.4 Kpa), or F4/cirrhotics (TE ≥12.5 kpa). **Results:** Median age was 62 y/o, 56% were male, and the median BMI was 26.8 kg/m2. The median baseline TE for the entire cohort was 11.9 Kpa (range 3.8 to 65.2) and at follow up, TE decreased to 7.35 Kpa (range 2.9 to 34.8) with a median change in TE of -3.4 Kpa (range -35.3 to +1, p=7.355e-11). At baseline, 45% of the entire cohort were cirrhotic (78% Childs-Pugh A) with median TE of 16.3 Kpa and FIB4 of 4.85. Follow up median TE done in the cirrhotic population after median time of 39 weeks post EOTR decreased to 11.7 Kpa and FIB4 was 2.3. The median change of TE in cirrhotic patients was -6.5 kpa (range -35.3 to +1, p=1.043e-7) and for FIB4 was -1.97 (range -17.47 to -0.33, p=1.49e-8). Non-cirrhotic patients (TE≤12.4) comprised 55% of the entire cohort and their median change of TE was -2.4 Kpa (range -6.4 to 0.7, p=1.539e-6) and FIB4 was -0.68 (range -2.8 to 0.41, p=2.987e-6). 48% of the entire cohort down-staged their liver fibrosis as determined by TE. In the cirrhotic group, 59% of the patients had a drop in their stage of liver fibrosis {F4

to F0-2 (11/27 patients), F4 to F3 (5/27 patients)} and there was no correlation in Childs-Pugh Score and failure to achieve improvement in fibrosis stage. 82% of patients that were baseline F3 had a drop in their stage of liver fibrosis {F3 to F0-2 (13/16 patients)}. In a multiple logistic regression analysis for factors associated with down-staging in liver fibrosis, we found that patients who were treatment naïve were more likely to improve their fibrosis stage (OR 5.73, p=0.033). **Conclusion:** Liver fibrosis stage, as determined by TE, improved after achieving SVR with DAA treatments in most patients. The significant drop in TE measurement post SVR was also correlated with a significant drop in FIB4. Although cirrhotic patients had a more significant drop in their median TE when compared to non-cirrhotic patients, they had a lower probability of improving their fibrosis stage.

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Leveraging the EHR to Eliminate HCV: Automated Birth Cohort Prompting Within a Large Healthcare System

Alexander Geboy[1], Whitney L. Nichols[1], Idene E. Perez[1], Stephen J. Fernandez[1], Peter Basch[1,2], Dawn A. Fishbein[1]; [1]MedStar Health Research Institute, Washington, DC; [2]MedStar Health, Columbia, MD

Hepatitis C (HCV) is the most common blood-borne infection in the US. The Birth Cohort (BC) (b. 1945-1965) accounts for 75% of all US chronic infection. It is estimated that at least 50% of those with HCV are unaware of their condition. Improved identification, testing and linkage to care protocols within large health care systems is paramount. Thus, an automated MedStar-wide Electronic Health Record EHR-based testing protocol for identifying BC HCV infection was implemented. METHODOLOGY: In January 2015, a MedStar-wide HepC Linkage to Care Navigation program was established with Gilead FOCUS funding. An automated MedStar-wide HCV BC EHR-based testing protocol in Primary Care Clinics was created and went live in Centricity on July 1, 2015. It has six discrete clinical decision support options. Providers enter a separate screen and opt-in for an HCV Ab with reflex test. A biostatistician extracted HCV testing data via SQL, compiled it in SAS and then exported it to Excel for analysis. A descriptive analysis follows. RESULTS: Between July 1, 2015 and May 1, 2016, testing occurred at approximately 76 primary provider locations and 350 providers. Overall, 10% (n=6,462) of the 67,997 BC patients with a visit during the period were tested, with 3.1% (n=202) testing HCV Ab positive (HCV Ab+). Mean age of all patients was 59 $\pm$ 5.7 years; 58% (n=3,720) were women, 38% (n=2,440) had public insurance, and 45% (n=2702) were black (b/AA). More men than women (62% (n=125)) were HCV Ab+ (OR 2.3 [CI_{95} 1.7-3.0]). B/AAs accounted for 55% (n=112) of those HCV Ab+ (7.5% of all b/AA men, 2.3% of all b/AA women), and were more likely to be HCV Ab+ than any other race or ethnicity (OR 2.0 [CI_{95} 1.2-3.2]). Overall, 90.6% (183/202) of those HCV Ab+ were RNA tested, 32% (n=58/183) were found to be HCV RNA positive, or 1% of overall HCV tests (n=58/6,462). CONCLUSION: The BC testing rate for MedStar Health was less than expected at 10%, though the HCV Ab+ rate of 3.1% is similar to the 3.25% CDC BC estimate. This is perhaps due to low protocol adherence, testing those with possible lower infection risk, and regional testing differences between urban and non-urban sites. Interestingly, though overall positivity is below the 7.4% previously reported at MedStar Washington Hospital Center, the current rate alone remained high at 6%. Work is underway to increase testing education and implement geocoding analysis to understand variability in the testing and positive rates. This protocol has the potential to provide essential intelligence on the magnitude and distribution of HCV within different regions of Washington DC and Maryland and significantly impact the push to eliminate HCV.

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Regression of Liver Fibrosis assessed by non-invasive methods in Patients with Chronic Hepatitis C who Achieved Sustained Virologic Response after DAAs Treatment

Yana Davidov[1], Yeroham Kleinbaum[2], Oranit Cohen-Ezra[1], Ella Veitsman[1], Tania Berdichevski[1], Peretz Weiss[1], Sima Katshereginsky[2], Hasid Avishag[1], Keren Tsaraf[1], Ziv Ben Ari[1,3]; [1]Liver Disease Center, Sheba Medical Center, Ramat Gan, Israel; [2]Deparmtent of Radiology, Sheba Medical Center, Ramat Gan, Israel, Ramat gan, Israel; [3]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Background: Interferon-induced SVR in patient with HCV has been associated with a reduced rate of liver-related morbidity and mortality. Non-invasive methods for the assessment of liver fibrosis stage are frequently being used. We propose that cure of HCV following DAAs therapy (defined as SVR of at least 12 weeks) can lead to regression of liver fibrosis (using non-invasive measures). Prospective assessment of the development of cirrhosis related complications and baseline predictors of liver fibrosis regression were determined. **Methods**: We conducted a retrospective/prospective study of HCV patients who achieved SVR after DAAs treatment (86 % Abbvie 3D regimen) with baseline liver fibrosis stage F1-4. The fibrosis stage was determined using: elastography (shear wave, Aixplorer SuperSonic Imagine, France) or Fibrotest© (BioPredictive, France) as well as the APRI score, and FIB-4 at baseline, 6, 12, and 24 months and each year up to 60 months after end of treatment. **Results:** A total of 130 patients were enrolled, 58 (48% female, mean age 60± 10 years, BMI 27.6±4.0,hypertension 41%, DM 17%, Dyslipidemia 12%) are currently eligible for analysis. The median follow up period was 9 months (IQR 7-10). Of the 33 patients who had cirrhosis (F4) at baseline, 14 (52.4%) demonstrated improvement (defined as a change in fibrosis stage ≥1). Of the 17 patients with F3, 12 (70.6%) demonstrated improvement. NO changes in fibrosis score F1-2 ?? The median (IQR) elastography score decreased significantly from 10.88 (9.4-16.4) Kpa to 9.7 (6.7-13.0) Kpa (p>0.0001). Baseline spleen enlargement (p> 0.001), BMI (p=0.035), bilirubin level (p=0.012), and hypertension (p=0.05) were negatively associated with improvement in fibrosis stage. In multivariate analysis enlarged spleen was the only predictor of fibrosis stages no regression. Baseline age, sex, genotype, history of previous antiviral treatment, other comorbidities (DM, Dyslipidemia), ALT, AST, platelets, INR, albumin, creatinine, esophageal varices, APRI, and FIB4 were not predictors of fibrosis regression. **Conclusions:** The majority of our subjects

(44.8%) demonstrated improvement in liver fibrosis stage by non-invasive methods. Some of the clinical parameters were negative predictors of liver fibrosis regression. Longer follow up period is required to determine the impact of the DAAs treatment in HCV patients.

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WITHDRAWN

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Stage 3-4 Fibrosis does not guarantee access to direct-acting antivirals in patients with state-funded insurance: An analysis of a HCV referral program

Patricia Santos, Ronald Racho, Moaz Abdelwadoud, Megan Cooper, Candice B. Kuns-Adkins, Jens Rosenau, Anna Christina Dela Cruz; Division of Digestive Diseases and Nutrition, University of Kentucky, Lexington, KY

Background: Hepatitis C (HCV) treatment guidelines recommend prioritizing patients with advanced fibrosis. However, strict insurance requirements of abstinence from illicit drug use may limit access to treatment. Objective: We aim to identify socioeconomic barriers to treatment initiation in HCV patients with advanced fibrosis. Methods: 1,048 new patients were evaluated for HCV treatment at the University of Kentucky Liver Clinic from July 1, 2014 to June 30, 2015. 103 patients (10%) had a FibroSure™ suggesting stage 3-4 fibrosis were included in the cohort for analysis. Patients who had cirrhosis were compensated. Demographic, clinical and socio-economic data, such as insurance, proximity of residence to the clinic, drug and alcohol use, history of incarceration were collected and compared between patients who were treated versus those not treated or had delayed treatment (i.e. treated started beyond 6months after initial visit). Multivariate logistic regression was done to evaluate factors predicting treatment delay and non-initiation. Results: The mean interval between initial consult to treatment start was 165 days (5 months). Among the 103, 49 (48%) were treated with direct-acting antivirals (DAAs) within 6 months, and 54 (52%) had delayed (mean of 10 months) initiation of treatment (n=20) or did not receive treatment (n=34). The mean age was 53 (± 9). Seventy five percent were male, 58% were estimated to live within 60 miles from the clinic, 57% had a history of incarceration, 80% a remote history of illicit drug use, and 45% a remote history of alcohol abuse. Between the treated and delayed/not-treated groups, there were no significant differences in these factors. The two groups, however, differ in insurance type, with the treated group more likely to have a non-Medicaid insurance than the delayed/not-treated group (67% vs. 32%, $p<0.001$). The patients who had delayed or no treatment had higher rates of recent history of illicit drug use (68% vs. 32%, $p<0.03$) and positive urine drug screen on evaluation (63% vs 38%, $p<0.03$). On multivariate analysis, the insurance type was the only significant predictor of treatment initiation, with patients on non-Medicaid insurance having 4x higher likelihood to start treatment within 6 months vs. those on Medicaid (OR 3.9, 95% CI 1.6-9.5, $p<0.005$). Conclusion: Despite the emergence of highly effective HCV DAAs, there remains barriers to treatment initiation in patients with advanced fibrosis. Patients with non-Medicaid insurance are more likely to receive prompt treatment compared to those with Medicaid.

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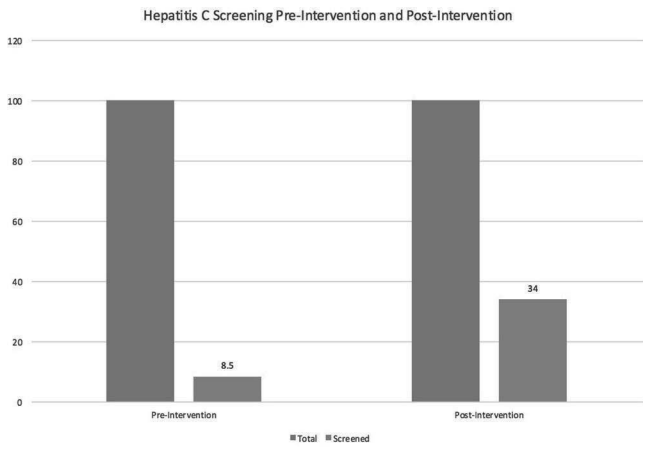
Hepatitis C Screening: The Downstream Dissemination of Evolving Guidelines in a Resident Continuity Clinic

Ali Aamar, Kamraan Madhani, Prabhdeep Singh, David Chia; Internal Medicine, Yale-Waterbury Hospital, Waterbury, CT

Background:In 2012 the CDC published guidelines supporting one-time screening for hepatitis C (HCV) in all persons born between 1945-65. It is estimated that 75% of adults infected with HCV fall within this cohort. Furthermore, it is projected that this preventative health intervention would lead to the diagnosis of 800,000 unknown cases and the prevention of 120,000 deaths. Aim:The primary objectives were to measure adherence to HCV screening in a continuity practice staffed by internal medicine residents and to measure the effect of interventions to enhance HCV screening. Methods:We performed a retrospective chart review of a random sample of patients born between 1945-1965. In order to meet inclusion criteria, the patients must have had an HCV status that was unknown and must have been seen by a primary care provider ≥ 2 times between January 1 and December 31, 2013. After initial data was extracted, providers were given reminders for HCV screening guidelines through emails, lectures and conferences. Chart review of patients was done to measure improvement in HCV screening rate after the intervention. Data was analyzed using chi-squared testing. Results:Out of 294 patients reviewed before intervention, 200 met inclusion criteria. Only 17 (8.5%) patients were offered screening for HCV. After intervention, 100 patients met the inclusion criteria. 34 patients were screened for HCV. Screening rate increased by 325 percent after the intervention. Conclusion: Adherence to HCV screening guidelines in a resident continuity practice prior to any educational intervention was low at 8.5 percent. Regular reminders through emails, conferences and lectures can increase the awareness and improve screening rate. In our resident continuity practice, HCV screening rate improved by 325% by increasing awareness of the HCV screening guidelines through regular reminders and education of house staff.

HCV screening rate, before and after intervention



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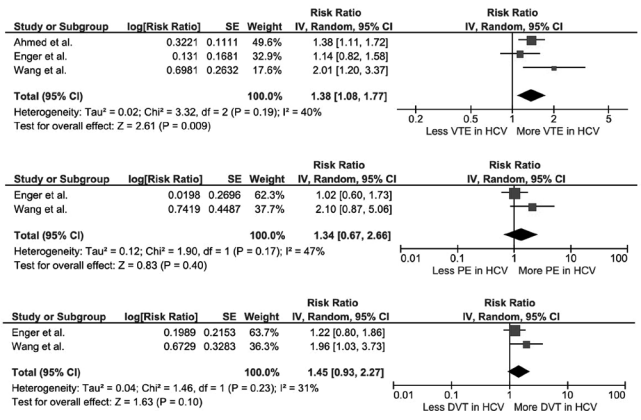
828

Hepatitis C Virus infection and Risk of Venous Thromboembolism: A Systematic Review and Meta-analysis

Karn Wijarnpreecha[1], Charat Thongprayoon[1], Panadeekarn Panjawatanan[2], Patompong Ungprasert[3,4]; [1]Internal Medicine, Bassett Medical Center and Columbia University College of Physicians and Surgeons, Cooperstown, NY; [2]Department of Biochemistry, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [3]Department of Internal Medicine, Division of Rheumatology, Mayo Clinic, Rochester, MN; [4]Department of Medicine, Division of Rheumatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Background/Objectives: Hepatitis C virus (HCV) infection is one of the leading causes of cirrhosis. As a result of chronic inflammatory response to the virus, HCV-infected patients may be at a higher risk of venous thromboembolism (VTE). However, the data on this association is unclear. This systematic review and meta-analysis was conducted with the aims to summarize all available evidence. *Methods*: A literature search was performed using MEDLINE and EMBASE from inception to April 2016. Studies that reported relative risks, odd ratios, or hazard ratios comparing the risk of VTE among HCV-infected patients versus subjects without HCV infection were included. Pooled risk ratios (RR) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method. *Results*: Three studies met our eligibility criteria and were included in analysis. The pooled RR of VTE in HCV-infected patients versus subjects without HCV infection was 1.38 (95% CI, 1.08-1.77, I^2 =40%). Subgroup analysis showed that risk was increased for both pulmonary embolism (PE) and deep venous thrombosis (DVT) even though without adequate power to demonstrate statistical significance (Poole RR of 1.34, 95% CI, 0.67-2.66 for PE and pooled RR 1.45, 95% CI, 0.93-2.77 for DVT). *Conclusions*: Our study demonstrated a significantly increased risk of VTE among HCV-infected patients. Further studies are required to clarify how this risk should be addressed in clinical practice.

Forest plot of the included studies hepatitis C infection and risk of venous thromboembolism (Top), pulmonary embolism (Middle), and deep venous thrombosis (Bottom)



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To determine the order of influence that patient demographics and clinical conditions have on access to new Direct Acting Antiviral Agents (DAAs) in the EU5

Jason Katz, Sarah Brown, Mohammed Aiyaz, Elizabeth Baynton, Sabina Heinz; Ipsos Healthcare, New York, NY

Background and Aims: Over the last two years, The European Medicines Agency has approved highly effective Direct Acting Antiviral (DAA) regimens for the treatment of Hepatitis C. Access to the revolutionary DAAs, sofosbuvir (and/or ledipasvir), daclatasvir, or ombitasvir/paritaprevir/ ritonavir with/ without dasabuvir is not pervasive; there remains country level differences due in some part to variations in national level insurance and country-manufacturer dealings. Apart from these variables, patient level factors also influence access. The aim of this study was to analyze and order the influence of residency, demographics and clinical conditions on access to DAAs using recent patient chart audit data and Chi-squared Automatic Interaction Detection (CHAID). Method: Ipsos' HCV Therapy Monitor, running since 2006 in the EU, reports on ~240 physicians per quarter across Italy, Spain, France, United Kingdom, and Germany. Physicians provide patient demographic, disease and treatment data on HCV patients seen within each period. The EU Therapy Monitor Q2-Q4 2015 data and a CHAID analysis were used to create a decision tree. The tree determines the hierarchy of influence that viral load, comorbidities, country, substance abuse, and fibrosis score has on patient access to DAAs. Results: The CHAID analysis split the data by fibrosis level, revealing that fibrosis had the strongest impact on DAA access. Country and substance abuse status were, in most cases, the next most influential variables on treatment access. When focusing on F2 patients in Germany and Spain, those not abusing substances had a ~80% and ~60% chance of DAA access, whilst F2 abusers in Germany and Spain had a lower chance at ~50% and 5%, respectively. A similar trend persisted throughout the individual fibrosis level cohorts apart from cirrhotic patients, where clinical characteristics had a greater influence than residency. Conclusion: The decision tree revealed that treatment access is significantly dependent on fibrosis, country and substance abuse, with viral load and comorbidities playing a lesser role. All EU5 countries have similar fibrosis level adjudication, but then experience minor divergence in how substance abuse status is integrated in access decisions. The difference in treatment rates between abusers and non-abusers diminishes from F0-F4. Abusers are commonly denied because of the non-compliance risk, yet denying access now leaves the potential for future strain on payer systems.

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The new Aptima HCV Quant Dx Real-time TMA assay accurately quantifies Hepatitis C virus genotype 1-6 RNA

Stephane Chevaliez[1], Fabienne Dubernet[1], Claude Dauvillier[1], Christophe Hezode[2], Jean-Michel Pawlotsky[1]; [1]Virology & INSERM Unit U955, Henri Mondor University Hospital, Creteil, France; [2]Hepatology, Henri Mondor, Creteil, France

Background: Sensitive and accurate hepatitis C virus (HCV) RNA detection and quantification is essential for the management of chronic hepatitis C therapy. Currently available platforms and assays are usually batched and require at least one

full day of work to complete the analyses. **Objective:** The aim of this study was to evaluate the ability of the newly developed Aptima HCV Quant Dx assay (Hologic Inc., San Diego, CA), a transcription-mediated amplification (TMA)-based assay making use of the fully automated Panther system, that eliminates the need for batch processing and automates all aspects of nucleic acid testing in a single step, to accurately detect and quantify HCV RNA in a large series of patients infected with different HCV genotypes. **Results:** The limit of detection was estimated to be 2.3 IU/mL. The specificity of the assay was 98.6% (95% confidence interval: 96.1%-99.5%). Intra-assay and inter-assay coefficients of variation ranged from 0.09% to 5.61%, and 1.05% to 3.65%, respectively. The study of serum specimens from patients infected with HCV genotypes 1 to 6 showed a satisfactory relationship between HCV RNA levels measured by the Aptima HCV Quant Dx assay, and both real-time PCR comparators [Abbott RealTime HCV (Abbott Molecular, Des Plaines, IL) and Cobas AmpliPrep/Cobas TaqMan HCV Test, version 2.0 (CAP/CTM HCV v2.0, Roche Molecular Systems, Pleasanton, CA), assays]. **Conclusion:** The new Aptima HCV Quant Dx assay is sensitive, reasonably specific and reproducible and accurately quantifies HCV RNA in serum samples from patients with chronic HCV infection, including patients on antiviral treatment. Quantification is linear over the full dynamic range of quantification, which covers values observed in both untreated and treated patients with chronic HCV infection. The Aptima HCV Quant Dx assay can thus be confidently used to detect and quantify HCV RNA in both clinical trials with new anti-HCV drugs and clinical practice in Europe and the US.

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Jean-Michel Pawlotsky - Advisory Committees or Review Panels: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck; Grant/Research Support: Gilead; Speaking and Teaching: Bristol-Myers Squibb, Gilead, Merck, Janssen, Gilead

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Minimal Risk of Hepatitis B Virus Reactivation in Hepatitis B Virus Surface Antigen-Negative Chronic Hepatitis C Patients Receiving Direct Acting Antiviral Agents

Chen-Hua Liu[1], Chun-Jen Liu[1], Tung-Hung Su[1], Yu-Jen Fang[2], Hung-Chih Yang[1], Pei-Jer Chen[1], Ding-Shinn Chen[1], Jia-Horng Kao[1]; [1]Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [2]Internal Medicine, National Taiwan University Hospital, Yun-Lin Branch, Douliou, Taiwan

Background: Little is known about the risk of hepatitis B virus (HBV) reactivation in hepatitis C virus (HCV)-infected patients receiving interferon (IFN)-free direct acting antiviral agents (DAAs). **Methods:** HCV-infected patients receiving 12 weeks of IFN-free DAA therapies were consecutively enrolled. The baseline, on-treatment, and off-therapy HBV DNA, HBV surface antigen (HBsAg), HBV surface antibody (anti-HBs), and alanine aminotransferase (ALT) were serially examined. HBV reactivation was defined as detectable serum HBV DNA following baseline undetectable HBV DNA, or an increase of ≥ 1 $\log_{10}$ IU/mL HBV DNA compared to baseline detectable HBV DNA. Significant HBV-related ALT flare was defined as ALT ≥ 5 times upper limit of normal (ULN) or ALT ≥ 2 times of the baseline level with concomitant HBV DNA > 2,000 IU/mL. HBV-related hepatic decompensation was defined as significant HBV-related ALT flare combined with jaundice, coagulopathy, hepatic encephalopathy or ascites. **Results:** Of the 103 patients enrolled, 3 (2.9%) had HBV reactivation, but none of them had significant HBV-related ALT flare or hepatic decompensation. Of 6 HBsAg-positive patients, 3 (50%) had HBV reactivation. In the remaining 97 HBsAg-negative patients, none had HBV reactivation after DAA therapy. In patients with baseline HBsAg negativity with/without anti-HBs positivity, there were no changes of HBV serological markers. **Conclusions:** The risk of HBV reactivation was low in HCV-infected patients receiving IFN-free DAA treatment, and HBV reactivation was limited to HBV/HCV-coinfected patients. Furthermore, the risk of HBV-related ALT flares or hepatic decompensation is also minimal in those with HBV reactivation.

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High presence of HCV genotype 4d in HIV/HCV co-infected HIV / HCV patients in España.LOST G4

Enrique Ortega Gonzalez[1], Miguel A. von Wichmann[2], Maria Alma Bracho[3], Victor Asensi[4], Jose Antonio Mira[5], Rafael Granados[6], Marisa Montes[7], Livia Giner[8], Carlos Martin[9], Antonio Rivero-Juárez[10], Francisco Arnaiz de las Revillas[11], Juan Berenguer[12], Cristina Tural[13], Francisco Vera[14], Juan Luis Gomez-Sirvent[15], Jose Antonio Oteo[16], Elisa Martínez[17], Antonio Aguilera[18], Luis Morano[19], Jorge Navarro[20], Roberto Oropesa[21], Javier Moreno[22], Purificacion Rubio-Cuevas[23]; [1]Infeccious disease, Consorcio Hospital General Universitario, Valencia, Spain; [2]Infectous Disease, 2 Hospital Universitario Donostiarra-OSI Donostialdea, San Sebastian, Spain; [3]3 Unidad Mixta Infección y Salud Pública FISABIO-Universitat de Valencia, Valencia, Spain; [4]Infectious Disease, Hospital Universitario central de Asturias, Oviedo, Spain; [5]Internal Medicine, Hospital Universitario Virgen de Valme, Sevilla, Spain; [6]Internal Medicine, Hospital Universitario Dr. Negrin, Las Palmas, Spain; [7]HIV Unit, Hospital Universitario La Paz Madrid, IdiPaz, Madrid, Spain; [8]Infectious Disease, Hospital General Universitario Alicante, Alicante, Spain; [9]Internal Medicine, Complejo Hospitalario de Cáceres, Caceres, Spain; [10]IMIBIC, Hospital Universitario Reina Sofía, Universidad de Córdoba, Cordoba, Spain; [11]Infectious Disease, Hospital Universitario Marqués de Valdecilla, Universidad de Cantabria, Santander, Spain; [12]Infectious Disease, Hospital Gregorio Marañón, Madrid, Madrid, Spain; [13]Infectious Disease, Hospital Germans Trias i Pujol, Badalona, BAdalona, Spain; [14]Infectious Disease, Hospital Virgen del Rosell, Cartagena, Cartagena, Spain; [15]Infectious Disease, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Tenerife, Spain; [16]Internal Medicine, Hospital de La Rioja y Complejo Hospitalario San Millán-San Pedro-de La Rioja, Logroño, Spain; [17]Internal Medicine, 17 Complejo Hospitalario Universitario de Albacete, Albacete, Spain; [18]Microbiologia, Hospital Clínico Universitario de Santiago de Compostela, Santiago De Compostela, Spain; [19]Infectious Disease, Hospital Universitario Álvaro Cunqueiro, Vigo, Vigo, Spain; [20]Infectious Disease, Hospital Universitari Vall d'Hebron, Barcelona;, Barcelona, Spain; [21]Internal Medicine, Hospital Can Misses, Ibiza, Ibiza, Spain; [22]Infectious Disease, Hospital Miguel Servet, Zaragoza., Zaragoza, Spain; [23]Infectious Disease, Hospital Genral Universitario Valencia, Valencia, Spain

Introduction Information about the epidemiology and the impact of HCV genotype 4 (G4) in HCV/HIV patients in Spain is scarce. There is no data available on the number and spread of HCV G4 lineages. **Design and Setting** In order to determine the prevalence and distribution pattern of HCV G4 in

HCV/HIV co-infected individuals, a multicenter, retrospective, observational cohort study was conducted in 21 Spanish hospitals. A descriptive epidemiological analysis on a random sample of cases was performed. A portion of the HCV NS5B region (796 nucleotides) was amplified and sequenced in 207 associated plasma samples. HCV subtyping was performed by using the COMET HCV online tool and compared with our subtyping system based on phylogenetic reconstruction. A maximum-likelihood phylogenetic tree with bootstrap support for branches built with RAxML was used for detection of clusters of sequences. **Results** Within the initial cohort of 24,539 HIV-infected patients, 6,047 individuals were HIV/HCV co-infected and 1,148 of them presented VHC G4 (20%). Characteristics: Average age 50, male (75%), injection drug user with more than 20 years of estimated time of infection and stage of hepatic fibrosis greater than or equal to F2 (55%). In most regions the prevalence of HCV G4 exceeded that of G3. Within HCV G4, average prevalences of subtypes 4d and 4a were 79% and 21%, respectively. A south-north distribution pattern of HCV G4 subtypes was detected. The proportion of patients with HCV 4d is mainly present in the north of Spain while subtype G4a tends to increase from the north to south with a presence greater than or equal or G4d in southern Spain. In addition, we have detected a significant cluster of subtype 4d formed by 8 sequences from Madrid and one from Canary Islands that share a recent common ancestor. Moreover, these 9 genetically close sequences along with 20 sequences belonging to Dutch HCV/HIV co-infected individuals from a study published in 2009, also formed a significant cluster. This clustering suggests that transnational transmission networks of HCV associated with risk factors can be detected by using this methodology. In contrast, no significant clusters were found among subtype 4a sequences. **Conclusions** There is a high percentage of HCV/HIV co-infection (24.64%) in Spanish patients with a high prevalence of HCV G4 (20%). The predominant subtype is 4d (71%), especially in northern Spain. Conversely, subtype 4a has a presence similar or greater than subtype 4d in southern Spain and Canary Islands. Phylogenetic analysis detected a group of closely related subtype 4d sequences that suggests the existence of transmission networks of HCV/HIV associated to risk factors.

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Screening for Hepatitis C in Baby Boomer Population Using EMR Pop-Up and Targeted Mailing from Primary Care Physicians in a Single Community Teaching Hospital

Paul J. Thuluvath[1,2], Harris Feldman[1], Asher Horowitz[1], George Lowe[1]; [1]Institute for Digestive Health & Liver Diseases, Mercy Medical Center, Baltimore, MD; [2]Medicine & Surgery, University of Maryland School of Medicine, Baltimore, MD

In inner cities, the prevalence rates of HCV are thought to be very high, but diagnosis and linkage to care has been sub-optimal. CDC estimates those Baby Boomers, born between 1945 and 1965, account for more than 75 percent of Americans with Hepatitis C. However, screening of this population has been dismal despite the recommendations from CDC, USPSTF, and CMS. Our institution provide primary healthcare to 33,736 baby boomers via 41 primary care physicians, but only less than 10% of population at risk was screened, prior to our intervention, 2 years after CDC published the recommendations. **Objectives**: The objective of our study was to improve the HCV screening of baby boom generation. **Methods**: We used a 2 pronged approach. We created a 'pop-up' in EMR prompting primary care physicians to order the screening test when patients visited them. We also sent letters to patients explaining the rationale for screening along with an order form for the blood test. The letters were sent out only after approval by the primary care physician, and were addressed to the patient and signed by the primary care physician. Patients who were found to be positive for HCV were educated and linked to care by dedicated coordinators. We collected the numbers of completed orders by 'pop-up' prompting and through letters using EMR. To improve the disease awareness, we also conducted CME events for primary care physicians, and additionally, coordinators met with their office staff and provided education material. **Results:** In this ongoing study, we have mailed letters to 10,189 patients of 14 primary care physicians in the first 12 months. During this period, the screening rates increased by over 300% compared to previous 12 months. 1,167 patients were screened through the mailed orders, and 26 patients were found to HCV antibody; 25 of these patients have been tested for HCV RNA, and only 10 were positive for HCV RNA (0.86% of total screened). Additionally, 1,404 patients were screened through the EMR pop-up, identifying another 18 with HCV antibody; all of these positive patients were tested for HCV RNA, and 6 were positive for HCV RNA (0.43% of total screened). Of those screened through the pop-up, about 28% had also received a letter. **Conclusion:** The use of automated processes incorporated into electronic medical record systems, can be an effective way of increasing screening rates for viral infections. This in combination with a targeted mailing campaign can expand the ability of primary care physicians to test their patients, and identify infected individuals. The prevalence rate of HCV in baby boom generation at our institution appears to be lower than previously reported.

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The role of community-based hepatitis C testing in reaching young, at-risk adults

Jeffrey Hom[2], Michelle Dougherty[1], Lora Magaldi[1], Carla Coleman[1], Ta-wanda Preston[1], Stacey Trooskin[1]; [1]Medicine, Drexel University, Philadelphia, PA; [2]University of Pennsylvania, Philadelphia, PA

BACKGROUND: While adults born between 1945-1965 constitute the largest group of people in the United States with chronic hepatitis C infection (HCV), young adults, particularly with a history of injection drug use, are increasingly diagnosed. Unfortunately, young adults are known to have low levels of engagement with the health care system where HCV testing is offered. We sought to describe the characteristics of young adults receiving HCV testing through the 'C' a Difference program, an academic-community partnership that provides free HCV testing in three community organizations. METHODS: Participants were recruited through a convenience sample of

adults presenting for HCV testing at one of three community health programs in Philadelphia, Pennsylvania, between June 2014 and December 2015. Participants completed a survey at the time of HCV testing that included questions on risk factors, primary care and prior HCV testing. Descriptive statistics were performed on survey data, with comparisons made between young adults (ages 18-35) and older adults. RESULTS: During the study period 2131 adults, of whom 761 (36%) were young adults, presented to one of the community health programs. Among the 1511 (71%) adults who consented to the study and completed the survey 534 (35%) were young adults. Compared to older adults, the young adults in our sample were less likely to have been incarcerated (47% vs 60%, p<0.001) and more likely to have a tattoo from an unregulated setting (36% vs 21%, p<0.001). Young adults were also more likely than older adults to use prescription drugs (23% vs 14%, p<0.001), while older adults were more likely to use crack (36% vs 12%, p<0.001) and cocaine (37% vs 18%, p<0.001). Despite several risk factors young adults were less likely than older adults to be insured (68% vs 77%, p=0.001) or have primary care (60% vs 69%, p<0.001). Rates of prior HCV testing were similar between the two groups, with 36% of young adults and 35% of older adults reporting prior testing (p=0.424). Among those who had been previously tested, young adults were more likely to have been tested at a location other than their PCP's office (58% vs 43%, p=0.001). Among the 303 young adults who had not been previously tested either in a PCP office or elsewhere 11 (4%) were found to be positive through 'C' a Difference. CONCLUSION: This study suggests that community-based programs are an important site for engaging and testing young adults who are at risk for HCV and who may not have access to regular health care. With the epidemiology of HCV revealing a rise of cases among young adults, support is warranted to promote testing in locations frequented by this group.

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Effect of Direct Acting Antiviral Hepatitis C Drugs on Fibrosis Stage Over Time Using APRI and FIB-4 Scores

Whitney L. Nichols, Alexander Geboy, Sameer Desale, Idene E. Perez, Dawn A. Fishbein; Medstar Health Research Institution, Washington, DC

Few studies have evaluated possible regression of liver fibrosis (LF) and cirrhosis (LC) after cure of chronic hepatitis C (HCV). Past limitations included the lack of efficacy of interferon-based drugs. This study examines effects of sustained virologic response (SVR) from new Direct Acting Antivirals(DAAs) on changes in LF or LC using non-invasive tests, fibrosis-4 (FIB-4) and aspartate amino transferase to platelet ratio index (APRI). Methods: A retrospective cohort study was conducted using clinical data from HCV patients from January 2014 to April 2016 at MedStar Washington Hospital Center comparing FIB-4/APRI scores in patients during and after DAA therapy who achieved SVR and those not treated. Safety labs were collected from treatment group at baseline, 4 weeks, end of treatment and 12 weeks after treatment; and from untreated patients at 4 equivalent time points. Chi-Square and Wilcoxon Tests were used to assess correlations between covariates. Multivariate logistic regression was used to assess correlations between FIB-4 and APRI. Results: Of the 149 patients treated, mean age was 61.4 ± 6 years, 60% were male, and 89% were black. There were no statistically significant differences between treated and controls regarding sex, and race/ethnicity; age was significantly older in the treated group (p<0.009). The majority were HCV mono-infected and previously treatment naïve, though the latter had less patients treated (75.2 v 87.5% [p=0.006]). Regarding FIB-4: At baseline, there were more LF/LC patients in the treatment group (79.1 v 62.5% [p=0.002]); FIB-4 scores were significantly higher in controls compared to the treatment group at time 2, 3, and 4 (p=0.04, 0.007, and 0.03 respectively). Regarding APRI: At baseline, there were fewer LF/LC patients in treatment group (30.2 v 38.8% [p=0.12]) but this was not statistically significant; APRI scores were significantly higher in controls compared to the treatment group at time 2, 3, and 4 (all p <0.0001). For APRI staging of LC vs. non-LC, the odds for developing LC at time 3 were 3.7 times higher for non-treated (OR_{adj} 3.7 [CI_{95}1.5-9.6]). For FIB-4 staging of LC vs. non-LC, odds for developing LC at times 3 and 4 were 2.13 and 3.04 times higher respectively, (ORs_{adj} 2.1 [CI_{95}1.1-4.2], 3.0 [CI_{95}1.4-6.7]). APRI and FIB-4 scores have been validated as non-invasive markers of liver disease. They have not been examined for those treated with new DAAs and achieved SVR. Our study shows that FIB-4 and APRI scores improved, even in those with advanced disease, compared to those not treated during the same period. This is further evidence that achieving SVR may lead to improvement in liver disease.

Disclosures:

Dawn A. Fishbein - Advisory Committees or Review Panels: BMS, Gilead; Grant/Research Support: Gilead; Stock Shareholder: Gilead, Abbvie

The following people have nothing to disclose: Whitney L. Nichols, Alexander Geboy, Sameer Desale, Idene E. Perez

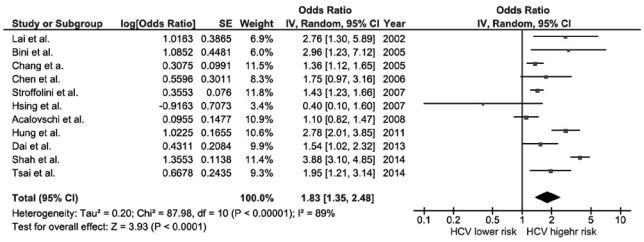
836
Hepatitis C Virus infection and Risk of Gallstones: A Systematic Review and Meta-analysis

Karn Wijarnpreecha[1], Charat Thongprayoon[1], Panadeekarn Panjawatanan[2], Natasorn Lekuthai[3], Patompong Ungprasert[4,3]; [1]Internal Medicine, Bassett Medical Center and Columbia University College of Physicians and Surgeons, Cooperstown, NY; [2]Biochemistry, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [3]Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [4]Medicine, Mayo Clinic, Rochester, MN

Background/Objectives: Gallstones and its complications are one of the most common hepatobiliary tract diseases. Several epidemiologic studies have suggested that patients with hepatitis C virus (HCV) infection might be at an increased risk of gallstones. However, the data on this relationship remain inconclusive. This meta-analysis was conducted with the aims to summarize all available evidence. *Methods*: A literature search was performed using MEDLINE and EMBASE database from inception to May 2016. Studies that reported relative risks, odd ratios, or hazard ratios comparing the risk of gallstones among HCV-infected patients versus subjects without HCV infection were included. Pooled odds ratio (OR) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method. *Results*: Eleven studies met our eligibility criteria and were included in analysis. The pooled OR of gallstones in HCV-infected patients versus subjects without HCV infection was 1.83 (95% CI, 1.35-2.48, I^2 =89%). Subgroup analysis showed that significant risk was increased for both

male (Pooled OR of 2.07, 95% CI, 1.14-3.76) and female (Pooled OR of 3.00, 95% CI, 2.16-4.17). *Conclusions*: Our study demonstrated a significantly increased risk of gallstones among HCV-infected patients. Further studies are required to clarify how this risk should be addressed in clinical picture.

Forest plot of the included studies hepatitis C infection and risk of gallstones



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837

Clinical evaluation of a newly developed chemiluminescence enzyme immunoassay for HCV core antigen

Takako Inoue[1], Tomoyuki Ohike[1], Takaaki Goto[1], Kumiko Ohne[1], Yuji Tsuzuki[1,2], Shigeru Sato[1], Yasuhito Tanaka[1,2]; [1]Clinical Laboratory, Nagoya City University Hospital, Nagoya, Japan; [2]Department of Virology & Liver unit, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Background: The quantification of hepatitis C virus core antigen (HCV Ag) in serum is useful to estimate viral replication. A newly developed and fully automated chemiluminescence enzyme immunoassay (CLEIA) for HCV Ag will be available in Japan. The aim of this study is to compare the new HCV Ag assay with conventional ones and to evaluate its clinical utility. **Methods:** This study protocol was approved by the appropriate institutional ethics review committees. The new HCV Ag assay (Lumipulse Presto HCV Ag [LP-Presto HCV Ag] [Fujirebio, Inc.]) was compared with two conventional assays (Lumipulse Ortho HCV Ag [LP-Ortho HCV Ag] [Fujirebio, Inc.] and Architect HCV Ag [Abbott Japan]). 1) A total of 220 frozen sera (83 were positive and 137 were negative by LP Ortho HCV Ag) in our hospital, and a total of 206 fresh sera which were negative by LP-Ortho HCV Ag obtained on the day when the examination was performed were used in this study. As basic examinations, reproducibility, stability, and quantitation limit were examined. Correlation and concordance rates between LP-Presto HCV Ag and conventional assays were performed. Specificity test for LP-Presto HCV Ag were examined. 2) A total of 42 frozen sera with hypergammaglobulinemia which were negative by LP-Ortho HCV Ag were measured by LP-Presto HCV Ag. **Results:** 1) Reproducibility, stability, and quantitation limit of LP-Presto HCV Ag were all supportive results to efficacy. In the 83 cases positive by LP-Ortho HCV Ag, correlation was found with LP-Ortho HCV Ag (y=1.023x+131.5, r=0.967), and with Architect HCV Ag (y=1.381x-56.76, r=0.941). There were 1 discrepancy between Lumipulse Presto and LP-Ortho HCV Ag, and 2 discrepancies between Lumipulse Presto and Architect HCV Ag. The concordance rates were 98.8% between Lumipulse Presto and LP-Ortho HCV Ag, and 97.6% between Lumipulse Presto and Architect HCV Ag. In the 133 cases negative by LP-Ortho HCV Ag, there were no discrepancies. A total of 137 frozen samples and 206 fresh samples negative by LP-Ortho HCV Ag were negative by LP-Presto HCV Ag under the cutoff value 20 fmol/L. Meanwhile, there was 1 discrepancy between these assays under the cutoff value 10 fmol/L. 2) Of the 42 frozen samples with hypergammaglobulinemia and negative by LP-Ortho HCV Ag, 41 samples were negative and one sample (IgG 7,125 mg/dL) showed false-positive by LP-Presto HCV Ag. **Conclusions:** The results of basic examinations and specificity test are reliable, and the concordance rates with conventional assays are high. The nonspecific reaction caused by hypergammaglobulinemia is found to be reduced. The new assay "Lumipulse Presto HCV Ag" can be used with high clinical efficiency.

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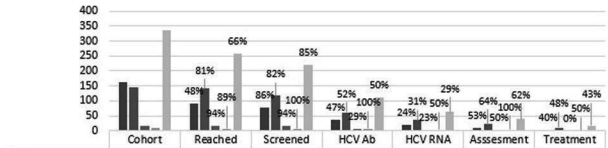
Case Management to Improve Uptake for Screening and Therapy of Hepatitis C viral infection in People Who Inject Drugs.

Rob Bielen[2], Rita Verrando[3], Joris Penders[4], Els Oris[4], Frederik Nevens[5], Geert Robaeys[6,1]; [1]Faculty of Medicine and Life sciences, Hasselt University, Tongeren, Belgium; [2]Faculty of Medicine and Life sciences, Hasselt University, Hasselt, Belgium; [3]Centra voor Alcohol en andere Drugproblemen, Hasselt, Belgium; [4]Department of Clinical Biology, Ziekenhuis Oost-Limburg, Genk, Belgium; [5]Department of Gastro-Enterology and Hepatology, University Hospitals KULeuven, Leuven, Belgium; [6]Department of Gastro-Enterology and Hepatology, Ziekenhuis Oost-Limburg, Genk, Belgium

Introduction Hepatitis C viral infection (HCV) has become a curable disease due to the development of direct acting antivirals (DAA). Therefore, the World Health Organization (WHO) has set a target to eliminate HCV. The largest group at risk for HCV at present are people who inject drugs (PWID), especially in the western world. Due to various barriers, this risk group is still underserved for HCV. Our goal was to study if a case management policy could improve uptake for screening and treatment for HCV in PWID. **Methods** We performed a prospective, interventional cohort study, evaluating the effect of case management on screening and treatment for HCV in PWID in an opiate substitution treatment (OST) setting in Limburg (Belgium). The goal was to address the PWID at this setting and to provide all the steps of the continuum of care, proposed by Meyer JP et al. (*Int J Drug Policy*, 2015). The cohort existed of four groups of PWID: firstly, a large group who received methadone at their local pharmacy. A second large group received methadone at the OST setting. Thirdly a smaller a group who were active users in a needle exchange program. And finally a small group who were recruited after referral to the hospital (former PWID). **Results** The results are presented in Figure 1. In all of the groups more than 80% of the cases were screened, except in the pharmacy group: these presented only a few times a year in the OST setting which could explain the lower screening rate. However, when addressed, more than 85% of the PWID in the pharmacy group were tested. In our PWID cohort, approximately 29% was HCV RNA positive. From these chronically infected PWID, 62% were assessed for treatment. 95% of them were eligible for antiviral treatment. However, treatment could only be started within the Belgian reimbursement criteria (requirement of F3 or F4 Metavir fibrosis score). As such, 51% were ruled out for therapy at present and treatment was started in 43%. **Conclusion** Case management is an effective way to screen a well-defined cohort of high-risk individuals for HCV and also improves treatment uptake.

♦ Denotes AASLD Presidential Poster of Distinction

Figure 1: Outcome of Case Management on the uptake for screening and treatment for HCV in a PWID cohort in Limburg (Belgium)



	Cohort	Reached	Screened	HCV Ab	HCV RNA	Asssesment	Treatment
Pharmacy	163	92	78	37	19	10	4
OST center	144	142	117	61	36	23	11
Needle exchange	18	17	17	5	4	2	0
Former PWID	9	8	8	8	4	4	2
Total	334	259	220	111	63	39	17

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Frederik Nevens - Consulting: MSD, CAF, Intercept, Gore, BMS, Abbvie, Novartis, Durect, Janssens-Cilag, Ono Pharma, Promethera Biosciences; Grant/Research Support: Ferring, Roche, Astellas, Novartis, Janssen-Cilag, Abbvie

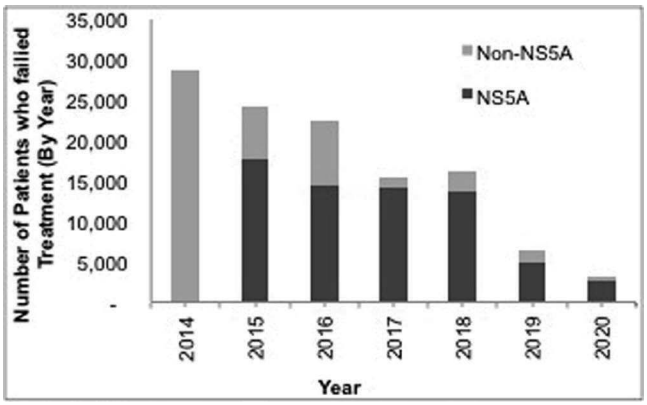
Geert Robaeys - Advisory Committees or Review Panels: MSD, Janssens, Gilead, Abbvie, BMS

The following people have nothing to disclose: Rob Bielen, Rita Verrando, Joris Penders, Els Oris

839
Patients who Fail Treatment in the era of DAAs: Projections from HEP-SIM Model

Jagpreet Chhatwal[1], Qiushi Chen[4], Turgay Ayer[4], Fasiha Kanwal[5,6], Kris V. Kowdley[2], Xiaojie Wang[4], Mark S. Roberts[7], Stuart C. Gordon[3]; [1]Institute for Technology Assessment, Massachusetts General Hospital, Harvard Medical School, Boston, MA; [2]Swedish Medical Center, Seattle, WA; [3]Henry Ford Hospital, Detroit, MI; [4]Georgia Institute of Technology, Atlanta, GA; [5]Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX; [6]Baylor College of Medicine, Houston, TX; [7]University of Pittsburgh, Pittsburgh, PA

Purpose: The introduction of oral direct-acting antivirals (DAAs) has dramatically changed the landscape of HCV treatment. Many more patients are eligible for therapy due to the absence of interferon and ribavirin, and real-world effectiveness mirrors the results of Phase 3 clinical trials. Our objective was to quantify the number of HCV (GT 1-6) patient population who fail on currently approved oral DAAs (including NS5A vs. non-NS5A failures) over time in the U.S. **Methods**: We used our Hepatitis C Disease Burden Simulation model (HEP-SIM), which was previously validated with NHANES and CDC studies and used to project changes in HCV prevalence in the U.S. We simulated the current clinical management of HCV including the birth-cohort and risk-based screening. Using market research data from IMS and IPSOS, we modeled DAA treatment in different waves starting with the launch of 1st-generation DAAs in 2011, followed by 2nd-generation DAAs including sofosbuvir, simeprevir and ledipasvir in 2014, and multiple NS5A-inhibitor containing DAAs in 2015. SVR rates were obtained from real-world TRIO and TARGET datasets. Within our model, patients who failed an NS5A were not eligible for NS5A re-treatment until 2018, unless they were cirrhotic. We projected the number of patients undergoing treatment between 2014 and 2020; and the number of patients who failed DAAs (NS5A and non-NS5A). **Results**: We estimated that 1.41 million patients would receive treatment with 2nd-generation DAAs from 2014 to 2020. Of these, 117,000 would fail to achieve SVR with DAAs, of which 58% are NS5A inhibitors failures (Figure 1). The characteristics of patients who fail on DAAs were: 51% cirrhosis, 72% GT1, 14% GT2, 9% GT3, and 5% GT4-6. **Conclusions**: Even in the era of highly efficacious DAAs, a significant number of patients will fail to achieve SVR and will have limited re-treatment options. This population represents a group with significant unmet medical need. Safe and effective therapies are needed for this population to prevent the long-term sequelae of HCV.



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Kris V. Kowdley - Advisory Committees or Review Panels: Abbvie, Enanta, Gilead, Intercept, Merck, Novartis, Trio Health, Verylx; Grant/Research Support: Abbvie, Evidera, Galectin, Gilead, Immuron, Intercept, Merck, NGM Biopharma, Novartis, Tobira, Trio Health; Speaking and Teaching: Gilead, Intercept

Stuart C. Gordon - Advisory Committees or Review Panels: Gilead, AbbVie, Merck, Intercept; Consulting: CVS Caremark; Grant/Research Support: Cymba Bay, Gilead, BMS, AbbVie, Intercept, Conatus, Exalenz, Merck; Speaking and Teaching: Gilead, Intercept

The following people have nothing to disclose: Qiushi Chen, Turgay Ayer, Fasiha Kanwal, Xiaojie Wang, Mark S. Roberts

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Risk of hepatitis C virus related hepatocellular carcinoma between subjects with spontaneous and treatment-induced viral clearance

Ming-Lung Yu[1], Chung-Feng Huang[1], Chia-Yen Dai[1], Jee-Fu Huang[1], Mei-Hsuan Lee[2], Wan-Long Chuang[1]; [1]Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, Kaohsiung, Taiwan; [2]Institute of Clinical Medicine, National Yang-Ming University, Taiwan, Taipei, Taiwan

Background/Aims Both spontaneous hepatitis C virus (HCV) clearance and the achievement of sustained virological response (SVR) by means of anti-viral therapy greatly reduce the incidence of hepatocellular carcinoma (HCC) development. The current study aimed to compare the risk of HCC between the two patient groups **Methods** A total of 313 subjects with spontaneous HCV clearance (SC) and 564 age- and sex-matched patients in the treatment-induced SVR group were enrolled for analysis. **Results** Nineteen (2.17%) of the 877 patients developed HCC during 6,963 person-years of follow-up. Fourteen (2.48%) SVR patients and 5 (1.6 %) SC patients developed HCC (P=0.004). Cox regression analysis of factors predictive of HCC included SVR (versus SC: hazard ratio [HR]/ 95% confidence interval [CI]: 5.83/1.27-26.88), diabetes (HR/CI:3.41/1.21-9.58), and age (HR/CI: 1.07/1.01-1.14).Of the 564 SVR patients, eleven (5.88 %) of the 187 patients with fibrosis stage 2-4 (F2-4) and 2 (0.88 %) of the 226 patients with F01 developed HCC (P=0.01). Compared to SC subjects, only SVR patients with F2-4 (P<0.001) but not F0-1(P=0.60) had a higher risk of HCC development. Cox-regression analysis using liver fibrosis as a variable demonstrated that factors associated with HCC included SVR with F2-4 (versus SC: HR/CI: 10.06/2.20-45.98), diabetes (HR/CI:3.23/1.14-9.19), and age (HR/CI: 1.08 1.02-1.15). **Conclusions** Compared to

subjects with spontaneous viral clearance, subjects with antiviral treatment-induced HCV viral clearance remain at high risk for HCC development, especially if they have significant hepatic fibrosis. These results may provide important information for decision-making regarding the prioritization of current direct antiviral agents in resource-limited countries.

Disclosures:

Ming-Lung Yu - Advisory Committees or Review Panels: ABBOTT, MSD, ABBVIE, GILEAD, J&J, ROCHE, BMS; Consulting: MSD, ABBVIE, GILEAD, J&J, ROCHE, BMS; Grant/Research Support: ABBOTT, ROCHE, MSD, ABBVIE, GILEAD, ABBVIE, GILEAD, ROCHE, BMS; Speaking and Teaching: ABBOTT, ROCHE, MSD, GILEAD, BMS, GSK

Wan-Long Chuang - Advisory Committees or Review Panels: Gilead, Abbvie, Roche, PharmaEssentia; Speaking and Teaching: Gilead, Roche, BMS, MSD, PharmaEssentia

The following people have nothing to disclose: Chung-Feng Huang, Chia-Yen Dai, Jee-Fu Huang, Mei-Hsuan Lee

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Cryoglobulins and autoantibodies clearance in a cohort of HIV/HCV co-infected subjects treated with different anti-HCV direct-acting agents.

Roberto Rossotti; Infectious Diseases, "Niguarda Cà Granda" Hospital, Milan, Italy

Background. HIV and HCV infections are characterized by chronic immune system activation that leads to immunologic dysregulation and exhaustion. This study assessed the evolution of inflammation parameters in HIV/HCV subjects treated with different anti-HCV regimens. **Methods.** Co-infected individuals who started an interferon-free treatment were included in the analysis. Data about leukocytes, inflammation markers, cryoglobulins and autoantibodies were collected at baseline and 12 weeks after end of treatment. Descriptive statistics, Chi-square and Wilcoxon tests were used. **Results.** 64 HIV/HCV patients (males 76.6%, median age 52 years) achieved SVR12 after a treatment with different regimens, mainly sofosbuvir-based (21.8% with SOF and ribavirin, 45.3% in combination with daclatasvir, 17.2% with ledipasvir, 9.4% with simeprevir), 6.3% with 3D. The majority was infected by genotype 3 (37.5%) and was cirrhotic (68.8%). None had a diagnosis of autoimmune disease, 3 subjects had cryoglobulins-related kidney damage. There is a trend in Neutrophils increase, while no change was observed in Leukocytes, CD4+ and CD4/CD8 ratio. Ferritin and cryoglobulins positivity decrease significantly. Anti-thyroglobulin, c-ANCA and p-ANCA decrease significantly. ANA positivity remains stable, but fluorescence changed: there is a trend in anti ring/rod (anti-RR) antibodies increase. **Conclusions.** This analysis showed that achieving an SVR partially improves immunologic parameters within a short follow up: immunologic response in terms of cryoglobulins clearance was significant. ANA showed a change in fluorescence was registered: anti-RR antibodies are considered to be interferon-induced, while in co-infected subjects they were already present at baseline and increased with virologic clearance even without interferon, thus suggesting a virological clearance-mediated instead of a drug-induced effect.

Table 1. Comparison of immune-related.

	Baseline	12 weeks post-treatment	p
Leukocytes x10³/mL, median [IQR]	4.91 [3.60-6.87]	5.34 [4.92-6.97]	NS
Neutrophils x10³/mL, median [IQR]/%	2.42 [1.78-3.53]/53.7	3.08 [1.31-2.35]/55.5	0.055/NS
Lymphocytes x10³/mL, median [IQR]/%	1.78 [1.21-2.17]/33.6	1.71 [1.31-2.35]/30.5	NS/NS
CD4+ Lymphocytes µL, median [IQR]/%	409 [295-592]/23.7	424 [294-565]/23.8	NS/NS
CD8+ Lymphocytes µL, median [IQR]	723 [507-1092]	874 [550-1263]	NS
CD4/CD8 ratio	0.54	0.52	NS
CRP mg/dL, median	0.1	0.1	NS
Ferritin ng/mL, median	198	121	**0.041**
C3 mg/dL, median	98.3	100.6	NS
C4 mg/dL, median	14.6	16.2	NS
Rheumatoid Factor UI/mL, median	10	8	NS
Cryoglobulins positivity, %	73.7	26.9	**<0.001**
– Quantifiable cryocrit, %	54.8	42.9	NS
– Cryocrit, median	1	2.8	NS
– Monoclonal cryoglob., %	42.9	66.7	NS
Anti-thyroglobulin Ab UI/mL, median	15	12	**<0.001**
Anti-thyroid peroxydase Ab UI/mL, median	8	8	NS
ANCA screening positivity, %	8.3	11.1	NS
c-ANCA positivity, %	35.6	0	**<0.001**
p-ANCA positivity, %	35.6	3.8	**<0.001**
ASMA positivity, %	20.7	33.3	NS
AMA positivity, %	0	0	=
Anti-LKM Ab positivity, %	0	0	=
Anti-DNA Ab positivity, %	5.0	0	NS
ANA positivity, %	52.5	51.0	NS
– Anti-RR positivity, %	16.1	42.9	0.053

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The following people have nothing to disclose: Roberto Rossotti

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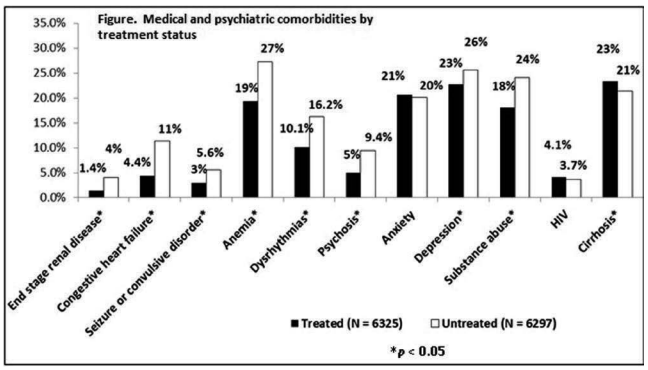
Higher Prevalence of Existing Comorbidities and Medication Use in Untreated Patients with Chronic Hepatitis C (CHC) compared to Treated Patients: A Population-Based Study in Post- Oral Direct-Acting Antivirals (DAAs) Era

Philip Vutien[1,2], Nhu (Josephine) Q. Tran[3], Felix Cao[3], Vincent Peichel[3], Mindie H. Nguyen[1]; [1]Division of Gastroenterology and Hepatology, Stanford University Medical Center, Palo Alto, CA; [2]Rush University Medical Center, Chicago, IL; [3]Optum, Eden Prairie, MN

Background: Over 75% of patients living with CHC in the US were born between 1945 and 1965. As this population ages, the increasing rates of medical comorbidities will make CHC management more challenging. In addition related medications and drug-drug interactions may complicate the use of cytochrome P-450 metabolized DAAs. **Objective:** To measure the prevalence of comorbidities and medications that may be barriers towards initiating DAAs in a large U.S. cohort with CHC. **Methods:** We identified from Optum Insight's insurance claims database CHC patients by ICD-9 code from 1/1/2011 to 9/30/2015. Our treatment group consisted of patients receiving DAA prescriptions after 11/1/2013. Any patients treated prior to 11/1/2013 were excluded from the study. Medical comorbidities were defined by ICD-9 codes. **Results:** In total, 12,622 insured CHC patients were included: 6,325 treated and 6,297 untreated patients. The majority were male (61%) and had Medicare part-D (66.8%). By medical comorbidities (Figure), untreated patients were more likely to have end stage renal disease (4% vs. 1.4% treated, OR = 2.9, p <0.001), congestive heart failure (11.4% vs. 4.4% treated, OR = 2.8, $p < 0.001$), and seizure disorder (5.6% vs 3% treated, OR = 1.9, $p < 0.001$). Untreated patients were also more likely to have active or prior episodes of psychosis (9.4% vs. 5% treated, OR = 2, $p < 0.001$) and were more likely to be prescribed a medication with potentially severe drug-drug interaction to DAAs (24.7% vs. 21.5% treated, $p < 0.001$) including anticonvulsants (1.7% untreated vs. 0.9% treated, $p < 0.001$). **Conclusion:** In a largely Medicare U.S. cohort of CHC patients, the prevalence of certain major comorbidities and concomitant medications was higher in untreated CHC patients compared to treated patients. The presence of major comorbidities and/or concomitant medications with major drug-drug interactions

with anti-HCV medications may be a barrier to anti-HCV therapy, and treatment prior to development of such comorbidities and related medications may help improve the overall treatment rate for CHC.



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Foundation for a Clinical Intervention on Hepatitis C: A 2015 Survey of New York City Hospitals' Capacity to Cure

Ryan Duerme, Shale Maulana, Jessie Schwartz, Nirah Johnson, Eric J. Rude, Fabienne Laraque; Viral hepatitis/BCD, NYC DOHMH, Long Island City, NY

BACKGROUND: In New York City (NYC), many of the estimated 146,500 residents with chronic hepatitis C (HCV) will likely seek care at one of NYC's 34 acute care hospitals' outpatient clinics. Data on the capacity of hospitals to provide HCV screening, diagnosis, and treatment are limited. Given the changing landscape of HCV treatment and the complexity of the NYC hospital-based healthcare system, an understanding of gaps related to HCV care is needed to tailor interventions. To that end, the NYC Health Department conducted a needs assessment of hospitals on their capacity for HCV screening, diagnosis, and treatment. **METHODS**: The Health Department developed and administered a survey on facility-level practices related to HCV screening, diagnosis, and treatment capacity to NYC acute care hospitals. Clinical representatives from the hospitals were recruited through email and site visits. Responses were collected through paper surveys and SurveyMonkey.com from July 8, 2015 – September 30, 2015. Descriptive analysis was conducted using Survey Monkey and Excel. **RESULTS**: Twenty-seven hospitals completed the survey (79% response rate). *Screening*: Of the 23 hospitals responding to this question, 18 (78%) indicated that most of their patients have risk factors for HCV infection. Eighteen (67%) of the 27 sites also reported that their hospital's electronic health record system had an age-based screening alert for high-risk patients born from 1945-1965, yet only 10 (37%) reported screening 50% or more of this cohort . *Diagnosis*: Eleven (41%) sites reported no challenges to providing RNA testing in-house, but only 5 (19%) had implemented HCV antibody-to-RNA reflex testing. *Treatment*: With the exception of one facility, all hospitals indicated being able to provide HCV treatment in-house. However, only 9 (33%) and 6 (22%) respondents indicated that HCV treatment was available in their primary care clinics for mono-infected and HIV/HCV co-infected patients, respectively. Most patients were cared for in infectious diseases and gastroenterology clinics. Finally, of the 26 hospitals responding to this question, 16 (62%) indicated denial of medication coverage by health insurances was a barrier to HCV treatment. **CONCLUSION**: This survey provided an understanding of practice and gaps in HCV care capacity among acute care hospital clinics in NYC. Low rates of screening, confirmatory testing, along with limited provider capacity in primary care settings and barriers to securing treatment were reported. This information is being used to guide the work of the HCV Clinical Network and develop interventions to address these gaps.

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The following people have nothing to disclose: Ryan Duerme, Shale Maulana, Jessie Schwartz, Nirah Johnson, Eric J. Rude, Fabienne Laraque

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Performance Evaluation of the new real-time PCR-based cobas HCV assay for use on the cobas 6800/8800 systems for the detection and quantification of HCV RNA

Johannes Vermehren[1], Caterina Berkowski[1], Benjamin Maasoumy[2], Veronique Michel-Treil[3], Enrique Marino[4], Ed G. Marins[4], Heiner Wedemeyer[2], Christoph Sarrazin[1]; [1]Medizinische Klinik 1, Universitätsklinikum Frankfurt, Frankfurt, Germany; [2]Medizinische Hochschule Hannover, Hannover, Germany; [3]Covance Central Laboratory Services, Geneva, Switzerland; [4]Roche Molecular Diagnostics, Pleasanton, CA

Background and Aim: Quantification of HCV RNA during antiviral therapy is essential for the guidance of treatment duration, to decide on futility and to determine sustained response. The aim of this study was to evaluate the performance of the recently FDA-approved real-time PCR HCV RNA assay cobas® HCV for use on the cobas® 6800/8800 systems (cobas HCV; Roche Diagnostics). **Methods:** Analytical sensitivity and linearity at lower concentrations (5-1000 IU/mL) were assessed by cobas HCV using WHO standard traceable panels representing HCV genotypes (GT) 1-4 and compared with two established HCV RNA assays, COBAS® AmpliPrep/COBAS® TaqMan® HCV test v2.0 (CAP/CTM) and COBAS® TaqMan® HCV test v2.0 for Use with the High Pure System (HPS/CTM). In addition, pairwise assay comparisons were performed using clinical serum samples (n=245) representing HCV GT1. Concordance of baseline samples was assessed using the 6 million IU/mL cut-off which is used to tailor treatment duration in non-cirrhotic, treatment-naïve GT1 patients receiving ledipasvir/sofosbuvir. **Results:** The analytical sensitivity of cobas HCV was 8.2 IU/mL (95% CI: 6.7-14.4) in samples representing GT 1, and 6.3, 6.1 and 13.7 IU/mL in GT 2, 3 and 4, respectively. cobas HCV was mostly linear at low HCV RNA concentrations with a mean observed log difference of 0.18 in samples containing GT1 (all differences between expected and observed results were <0.3 log IU/ml). Pairwise comparison of quantifiable GT 1 samples showed excellent agreement between cobas HCV and CAP/CTM (mean difference, 0.085; 95% CI: 0.06, 0.11), and cobas HCV vs. HPS/CTM (mean difference, -0.095; 95% CI: -0.119, -0.072). Using the concordance in baseline samples between cobas HCV vs. CAP/CTM and cobas HCV vs. HPS/CTM was 97% and 96%, respectively, with respect to the 6 million IU/mL cut-off. **Conclusions:** cobas HCV is highly sensitive and linear at the low end of the dynamic range in GTs 1-4. cobas HCV shows excellent correlation and a high level of concordance at the 6 million cut-off with CAP/CTM and HPS/CTM in clinical samples of patients with HCV GT1.

Disclosures:

Johannes Vermehren - Advisory Committees or Review Panels: AbbVie, Abbott; Speaking and Teaching: AbbVie, Bristol-Myers Squibb, Gilead, Medtronic

Benjamin Maasoumy - Advisory Committees or Review Panels: Abbott Molecular, Janssen-Cilaq; Grant/Research Support: Abbott Molecular, Roche Diagnostics; Speaking and Teaching: MSD/Merck, Roche Diagnostics, Roche Pharma, Janssen-Cilaq, Fujirebio, BMS, AbbVie

Enrique Marino - Employment: Roche Molecular Systems, Inc

Ed G. Marins - Employment: Roche Molecular Systems

Heiner Wedemeyer - Advisory Committees or Review Panels: Transgene, MSD, Roche, Gilead, Abbott, BMS, Falk, Abbvie, Novartis, GSK, Roche Diagnostics, Eiger; Consulting: MyrGmbH; Grant/Research Support: MSD, Novartis, Gilead, Roche, Abbott, Roche Diagnostics; Speaking and Teaching: BMS, MSD, Novartis, ITF, Abbvie, Gilead

Christoph Sarrazin - Advisory Committees or Review Panels: Bristol-Myers Squibb, Janssen, Merck/MSD, Gilead, Roche, Abbvie, Janssen, Merck/MSD; Consulting: Merck/MSD, Merck/MSD; Grant/Research Support: Abbott, Roche, Merck/MSD, Gilead, Janssen, Abbott, Roche, Merck/MSD, Qiagen; Speaking and Teaching: Gilead, Novartis, Abbott, Roche, Merck/MSD, Janssen, Siemens, Falk, Abbvie, Bristol-Myers Squibb, Achillion, Abbott, Roche, Merck/MSD, Janssen

The following people have nothing to disclose: Caterina Berkowski, Veronique Michel-Treil

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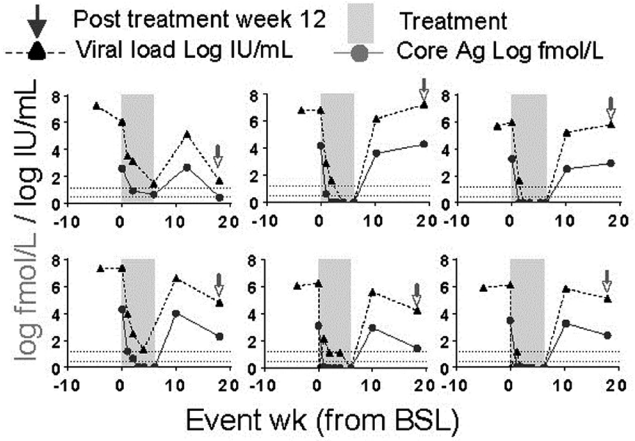
Hepatitis C virus core antigen: A simplified treatment monitoring tool among those with recent Hepatitis C virus infection, including for post-treatment relapse

Francois Lamoury[1], Behzad Hajarizadeh[1], Marianne Martinello[1], Angelica Soker[1], Danica Martinez[1], Philip Cunningham[2], Gavin A. Cloherty[3], Pip Marks[1], Gail Matthews[1], Janaki Amin[1], Jason Grebely[1], Gregory Dore[1], Tanya L. Applegate[1]; [1]The Kirby Institute, University of New South Wales, Sydney, NSW, Australia; [2]St Vincent's Applied Medical Research, St Vincent's Hospital Sydney, Sydney, NSW, Australia; [3]Abbott Virology, Abbott Laboratories, North Chicago, IL

Background: Simplified, affordable diagnostic tools are essential to facilitate global access to hepatitis C virus (HCV) treatment. This study evaluated the clinical performance of HCV core antigen (HCVcAg) detection as an alternative to RNA testing in plasma to monitor HCV treatment efficacy in recent infection. **Methods:** Participants with recent HCV infection (duration of infection ≤12months) who completed 6 weeks of sofosbuvir+ribavirin in DARE-C II were assessed at week 1, 2, 3, 4, end of treatment (ETR) and post-treatment week 4, week 12 and week 24. HCV RNA and HCVcAg were quantified by AmpliPrep/COBAS Taqman assay (Roche) and ARCHITECT HCV Ag (Abbott Diagnostics). The sensitivity and specificity of HCVcAg assay (>3fmol/L) were calculated for quantifiable HCV RNA (>15IU/mL). **Results:** 124 longitudinal samples in 18 treated participants were available for HCV RNA and HCVcAg testing, including baseline (n=18), ETR (n=16), post-treatment week 12 (n=18). Overall, HCVcAg demonstrated a sensitivity of 74.1% (95% CI 60.7-84.4) and a specificity of 98.5% (95% CI 90.7-99.9) compared with HCV RNA. At pre-treatment, HCVcAg was detected in 89% samples, demonstrating a sensitivity of 88.9% (95% CI 63.9-98.1). Two baseline HCVcAg non-reactive samples had quantifiable HCV RNA at 33 and 150IU/mL. At ETR, RNA and HCVcAg were detected in 13% and 6% samples, respectively (sensitivity 50%, 95% CI 2.7-97.3; specificity 100%, 95% CI 73.2-100%). At post-treatment week 12, RNA and HCVcAg were detected in 72% and 61% samples, respectively (sensitivity 84.6%, 95% CI 53.7-97.3; specificity 100%, 95% CI 46.3-100% CI). Two post-treatment week 12 non-reactive HCVcAg results had quantifiable HCV RNA at 50 and 2533IU/mL. **Conclusion:** This study demonstrates core antigen provides high specificity when compared with HCV RNA. The potential clinical utility of HCV core antigen requires further evaluation, particularly in the context of low HCV RNA levels.



Disclosures:

Gavin A. Cloherty - Employment: Abbott Laboratories; Stock Shareholder: Abbott Laboratories

Jason Grebely - Advisory Committees or Review Panels: Merck, Gilead; Grant/Research Support: Merck, Gilead, Abbvie, BMS

Gregory Dore - Board Membership: Gilead, Merck, Abbvie, Bristol-Myers Squibb; Grant/Research Support: Gilead, Merck, Abbvie, Bristol-Myers Squibb; Speaking and Teaching: Gilead, Merck, Abbvie, Bristol-Myers Squibb

The following people have nothing to disclose: Francois Lamoury, Behzad Hajarizadeh, Marianne Martinello, Angelica Soker, Danica Martinez, Philip Cunningham, Pip Marks, Gail Matthews, Janaki Amin, Tanya L. Applegate

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Integrated Resistance Analyses of HCV-infected Patients treated with Sofosbuvir, Velpatasvir and Voxilaprevir for 8 and 12 weeks from Phase 2 Studies

Nancy Reau[2], Mindie H. Nguyen[3], Kris V. Kowdley[4], Edward J. Gane[5], Hadas Dvory-Sobol[1], Evguenia S. Svarovskaia[1], Jenny C. Yang[1], Luisa M. Stamm[1], Diana M. Brainard[1], Michael D. Miller[1], Hongmei Mo[1], Eric Lawitz[6], Paul Y. Kwo[8], Michael P. Curry[9], Ira M. Jacobson[7]; [1]Gilead Sciences, Inc., Foster City, CA; [2]Rush University Medical Center, Chicago, IL; [3]Stanford University Medical Center, Palo Alto, CA; [4]Swedish Medical Center, Seattle, WA; [5]Auckland City Hospital, New Zealand Liver Transplant Unit, Auckland, New Zealand; [6]University of Texas Health Sciences Center, Texas Liver Institute, San Antonio, TX; [7]Mount Sinai Beth Israel, New York, NY; [8]Indiana University School of Medicine, Indianapolis, IN; [9]Beth Israel Deaconess Medical Center, Boston, MA

Background: In 4 Phase 2 studies, the combination of sofosbuvir (SOF), velpatasvir (VEL), and voxilaprevir (VOX) that target distinct HCV proteins, NS5B, NS5A, and NS3/4A, respectively, demonstrated high efficacy in genotype (GT) 1-6 HCV infected patients who were DAA-naïve or DAA-experienced with durations of 8 or 12 weeks. Here, we evaluate the effect of baseline resistance associated substitutions (RASs) on treatment outcome and emergence of RASs in patients who experience virologic failure. **Methods**: NS3, NS5A, and NS5B deep sequencing was performed at baseline for all patients (N=262; 145 GT1a, 31 GT1b, 23 GT2, 54 GT3, 7 GT4, 2 GT6) and at the time of virologic failure. Results are reported using a 15% cutoff. **Results**: At baseline, 141/262 (54%) patients had RASs in at least one of the NS3 and/or NS5A viral genes (23% NS3, 18% NS5A, 13% NS3/NS5A). NS5A RASs were observed more commonly in NS5A inhibitor-experienced patients (40/46, 87%) than DAA-experienced patients who had not previously received a NS5A inhibitor (18/81, 22%). In DAA-naïve patients treated for 8 weeks, 97% achieved SVR12 with similar SVR12 rates observed in patients without (79/81, 98%) or with (52/54, 96%) RASs. In NS5A inhibitor-experienced patients, all (46/46, 100%) achieved

SVR12 and in non-NS5A inhibitor DAA-experienced patients, all but 1 patient (80/81, 99%) with a NS5A RAS achieved SVR12. Overall, 91% of patients with NS5A Y93 RASs at baseline achieved SVR12 (21/23). Thirteen (5%) patients had NS5B nucleoside inhibitor (NI) RASs, including 5 with L159F, all achieved SVR12. Of the 5 patients who relapsed, none had treatment emergent NS5A and NS5B RASs. One patient who relapsed had treatment-emergent NS3 Q80R (which confers no phenotypic change to VOX). **Conclusions:** Baseline RASs had no impact on the virologic response in DAA-naïve and DAA-experienced patients following treatment with SOF, VEL, and VOX for 8 or 12 weeks, respectively. Viral relapse was not associated with emergence of viral resistance.

SVR12 in Patients With or Without Baseline RASs

	DAA-Naïve Patients	NS5A inhibitor-Experienced Patients	Non-NS5A inhibitor DAA-Experienced Patients
RASs	SOF/VEL/+VOX 8 Weeks (N=135)	SOF/VEL/+VOX 12 Weeks (N=46)	SOF/VEL/+VOX 12 Weeks (N=81)
No NS3 or NS5A RAS	79/81 (98%)	4/4 (100%)	36/36 (100%)
Any NS3 or NS5A RAS	52/54 (96%)	42/42 (100%)	44/45 (98%)
- NS3 RAS	29/30 (97%)	2/2 (100%)	27/27 (100%)
- NS5A RAS	15/16 (94%)	19/19 (100%)	11/12 (92%)
- NS3 and NS5A RASs	8/8 (100%)	21/21 (100%)	6/6 (100%)

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Nancy Reau - Advisory Committees or Review Panels: Jannsen, Merck, AbbVie, Intercept, Salix, BMS, Gilead; Grant/Research Support: Gilead, Intercept, AbbVie

Mindie H. Nguyen - Advisory Committees or Review Panels: Bristol-Myers Squibb, Gilead; Consulting: Gilead Sciences, Inc.; Grant/Research Support: Gilead Sciences, Inc., Bristol-Myers Squibb

Kris V. Kowdley - Advisory Committees or Review Panels: Abbvie, Enanta, Gilead, Intercept, Merck, Novartis, Trio Health, Verylx; Grant/Research Support: Abbvie, Evidera, Galectin, Gilead, Immuron, Intercept, Merck, NGM Biopharma, Novartis, Tobira, Trio Health; Speaking and Teaching: Gilead, Intercept

Edward J. Gane - Advisory Committees or Review Panels: AbbVie, Janssen, Gilead Sciences, Achillion, Merck; Speaking and Teaching: AbbVie, Gilead Sciences, Merck, Alnylam

Hadas Dvory-Sobol - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

Evguenia S. Svarovskaia - Employment: Gilead Sciences Inc; Stock Shareholder: Gilead Sciences Inc

Jenny C. Yang - Employment: Gilead Sciences, Inc

Luisa M. Stamm - Employment: Gilead Sciences

Diana M. Brainard - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

Michael D. Miller - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

Hongmei Mo - Employment: Gilead Science Inc

Eric Lawitz - Advisory Committees or Review Panels: AbbVie, Achillion Pharmaceuticals, Regulus, Theravance, Enanta, Idenix Pharmaceuticals, Janssen, Merck & Co, Novartis, Gilead; Grant/Research Support: AbbVie, Achillion Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Idenix Pharmaceuticals, Intercept Pharmaceuticals, Janssen, Merck & Co, Novartis, Nitto Denko, Theravance, Salix, Enanta; Speaking and Teaching: Gilead, Janssen, AbbVie, Bristol Meyers Squibb, Merck, intercept

Paul Y. Kwo - Advisory Committees or Review Panels: Abbott, Abbvie, BMS, Gilead, Janssen, Merck, Alnylam, Quest, CVS, Innovio; Grant/Research Support: Abbvie, BMS, Gilead, Merck, Janssen, Esai, Cepheid, Conatus

Michael P. Curry - Consulting: Alexion, Bristol Meyers Squib, Abbvie; Grant/Research Support: Gilead Sciences, Conatus

Ira M. Jacobson - Consulting: AbbVie, Achillion, Bristol Myers Squibb, Intercept, Gilead, Janssen, Merck, Trek; Grant/Research Support: AbbVie, Bristol Myers Squibb, Gilead, Janssen, Merck; Speaking and Teaching: AbbVie, Bristol Myers Squibb, Gilead, Janssen

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Six weeks of sofosbuvir/ledipasvir treatment of acute hepatitis C virus genotype 1 monoinfection: Final results of the The German HepNet Acute HCV IV Study

Katja Deterding[1,2], Christoph D. Spinner[3], Eckart Schott[4], Tania M. Welzel[5], Guido Gerken[6], Hartwig H. Klinker[7], Ulrich Spengler[8], Johannes Wiegand[9], Julian Schulze zur Wiesch[10], Anita Pathil[11], Markus Cornberg[1,12], Andreas Umgelter[3], Caroline Zöllner[4], Stefan Zeuzem[5], Armin Papkalla[13], Kristina Weber[14], Svenja Hardtke[12], Heiko von der Leyen[13], Armin Koch[14], Dorothee von Witzendorff[12], Michael P. Manns[1,12], Heiner Wedemeyer[1,12]; [1]Hannover Medical School, Hannover, Germany; [2]HepNet Study-House, project of the German Liver Foundation, Hannover, Germany; [3]University Hospital Klinikum rechts der Isar, Munich, Germany; [4]Charité Universitätsmedizin Berlin, Berlin, Germany; [5]University Hospital Frankfurt, Frankfurt, Germany; [6]University Hospital Essen, Essen, Germany; [7]University of Würzburg Medical Center, Würzburg, Germany; [8]University Hospital Bonn, Bonn, Germany; [9]University of Leipzig, Leipzig, Germany; [10]University Hospital Hamburg-Eppendorf, Hamburg, Germany; [11]University Clinic of Heidelberg, Heidelberg, Germany; [12]HepNet Study-House, project of the German Liver Foundation, German Centre for Infection Research (DZIF), Hannover, Germany; [13]Hannover Clinical Trial Center GmbH, Hannover, Germany; [14]Department of Biostatistics, Hannover, Germany

Background: Early treatment of acute hepatitis C virus (HCV) infection with interferon alfa monotherapy is highly effective but is associated with frequent unfavorable side effects. There is no fully published study yet exploring the safety, efficacy and required treatment duration of interferon free treatment of acute hepatitis C virus monoinfection. Preliminary reports suggested that ledipasvir/sofosbuvir therapy is effective in acute hepatitis C but relapses were reported in HIV-coinfected patients after 6 weeks of treatment. Methods: The German HepNet Acute HCV IV Study was designed as a single arm, prospective multicenter pilot study to evaluate the efficacy and safety of treatment with sofosbuvir plus ledipasvir (SOF/LDV) for 6 weeks without ribavirin in patients with acute genotype 1 HCV monoinfection. We here report the final 24 weeks post treatment results. Results: Twenty patients were included by 10 centers (60% male, mean age 46±12 years; 11 patients HCV genotype 1a, 9 patients genotype 1b). The main risk factors for HCV infection were sexual transmission (n=11) and medical procedures/needle stick injuries (n=5). Median alanine aminotransferase (ALT) and median bilirubin levels before start of antiviral treatment were 225 U/l (range 32-2716) and 13.6 µmol/l (range 5.13-111), respectively. ALT levels rapidly declined during therapy and values normalized already by treatment weeks 2 in 9 patients and by week 4 in 17 patients. HCV RNA was undetectable by the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test v2.0 by weeks 2, 4 and 6 in 8, 13, and 20 patients, respectively. SVR-12 was 100% and 18 patients have already completed FU-week 24 and all remained HCV-RNA negative. Conclusion: Treatment for 6 weeks with LDV/SOF was well tolerated and highly effective in HCV genotype 1 monoinfected patients with acute hepatitis C. Virological response was durable after therapy for at least 24 weeks. A rapid improvement in biochemical disease activity was observed during therapy. Short-duration treatment of acute hepatitis C could prevent the spread of HCV in high risk populations and may be cost-saving as compared to treatment of chronic hepatitis C.

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Katja Deterding - Speaking and Teaching: AbbVie, MSD/Merck, Gilead

Christoph D. Spinner - Advisory Committees or Review Panels: Gilead Sciences; Grant/Research Support: Gilead Sciences

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Eckart Schott - Advisory Committees or Review Panels: Gilead, Roche, Bayer, BMS, Abbvie, Janssen, MSD; Speaking and Teaching: Gilead, Novartis, Roche, MSD, Bayer, Falk, BMS, Janssen, Abbvie

Tania M. Welzel - Advisory Committees or Review Panels: Novartis, Janssen, Gilead, Abbvie, Boehringer-Ingelheim+, BMS

Hartwig H. Klinker - Advisory Committees or Review Panels: AbbVie, BMS, Gilead, Hexal, Janssen, MSD; Grant/Research Support: AbbVie, BMS, Gilead, Janssen, MSD, Arrowhead, Novartis; Speaking and Teaching: AbbVie, BMS, Gilead, Janssen, MSD

Anita Pathil - Speaking and Teaching: AbbVie, BMS, Gilead

Markus Cornberg - Advisory Committees or Review Panels: Merck (MSD Germamny), Roche, Gilead, Novartis, Abbvie, Janssen Cilag, BMS; Grant/Research Support: Merck (MSD Germamny), Roche; Speaking and Teaching: Merck (MSD Germamny), Roche, Gilead, BMS, Novartis, Falk, Abbvie

Andreas Umgelter - Speaking and Teaching: Gilead, BMS

Stefan Zeuzem - Consulting: Abbvie, Bristol-Myers Squibb Co., Gilead, Merck & Co., Janssen

Michael P. Manns - Consulting: Roche, BMS, Gilead, Boehringer Ingelheim, Novartis, Enyo Pharma, Eiger, GSK, Merck/MSD, Janssen, Medgenics, Biotest, AbbVie; Grant/Research Support: Merck/MSD, Roche, Gilead, Novartis, Boehringer Ingelheim, BMS, AbbVie, Janssen; Speaking and Teaching: Merck/MSD, Roche, BMS, Gilead, Janssen, GSK, Novartis, AbbVie

Heiner Wedemeyer - Advisory Committees or Review Panels: Transgene, MSD, Roche, Gilead, Abbott, BMS, Falk, Abbvie, Novartis, GSK, Roche Diagnostics, Eiger; Consulting: MyrGmbH; Grant/Research Support: MSD, Novartis, Gilead, Roche, Abbott, Roche Diagnostics; Speaking and Teaching: BMS, MSD, Novartis, ITF, Abbvie, Gilead

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Cost Effectiveness Analysis of Pre vs. Post LT Treatment with All Oral Direct Acting Antivirals in Hepatitis C Patients with Decompensated Cirrhosis in the US

Sammy Saab[1], Stevan A. Gonzalez[2], Ryan B. Perumpail[3], George Cholankeril[4], Aijaz Ahmed[3], Zobair M. Younossi[5]; [1]UCLA, Los Angeles, CA; [2]Baylor Health, Fort Worth, TX; [3]Stanford University Medical Center, Palo Alto, CA; [4]Roger Williams Medical Center, Providence, RI; [5]Inova Fairfax Hospital, Falls Church, VA

Background and Objective: Selected all-oral direct acting antivirals (DAAs) have been shown to have high safety and efficacy in treating Hepatitis C (HCV) patients with decompensated cirrhosis (DCC). However, there is limited empirical evidence comparing the health and economic outcomes associated with treating patients pre- vs. post-liver transplant (LT). The objective of this study was to analyze the cost-effectiveness of pre- vs. post LT treatment with an all-oral DAA regimen among patients with DCC waitlisted (WL) for LT. **Methods:** We constructed a decision-analytic Markov model of the natural disease progression of HCV in patients with decompensated cirrhosis (DCC) waitlisted (WL) for LT. The model followed a hypothetical cohort of 1,000 patients with a mean age of 50 over a lifetime horizon from a third-party US payer perspective, and estimated their health and cost outcomes based on pre- vs. post-LT treatment with an oral DAA. Health states and natural history pre-LT were stratified by MELD score and SVR. Transition probabilities and utilities were based on the literature and hepatologist consensus. SVR rates were sourced from ASTRAL-4 and SOLAR-1, -2. Costs were sourced from RedBook, Medicare fee schedules, and published literature. **Results:** The post-LT treatment arm had a mean time on WL of 0.94 years and a 27.6% probability of death on the WL, vs. 2.05 years (+117.5%) and 26.2% (-5.1%) in the pre-LT arm. Over the model time horizon, the post-LT treatment arm yielded 629 patients with SVRs, 7 patients with HCC, and 679 liver-related deaths, vs. 902 (+43.4%), 5 (+35.8%) and 607 (-10.7%) in the pre-LT arm. The pre-LT treatment strategy resulted in 10.2 per-patient quality-adjusted life years (QALYs), 12.0 per patient life years (LYs), and $262,846 per patient lifetime costs vs. 9.0, 11.3, and $253,713 in the post-LT arm. Therefore, pre-LT treatment was found to be the most cost-effective, with an ICER of $7,593. Based on one-way deterministic sensitivity analysis, our results were most sensitive to the utility of patients post-LT, treatment SVR rates, and LT costs. **Conclusion:** The timing of antiviral treatment for HCV patients with DCC relative to LT is an important area of clinical and policy research. Our results indicate that pre-LT treatment with a highly effective, all-oral DAA regimen is the most cost-effective strategy for the treatment of HCV patients with DCC waitlisted for LT.

Disclosures:

Sammy Saab - Advisory Committees or Review Panels: BMS, Gilead, Merck, Janssen; Grant/Research Support: Gilead; Speaking and Teaching: BMS, Gilead, Merck, Janssen, Salix, Onyx, Bayer, Janssen; Stock Shareholder: Achillion, Johnson and Johnson, BMS, Gilead

Stevan A. Gonzalez - Speaking and Teaching: Gilead, Salix, AbbVie, Merck

Aijaz Ahmed - Consulting: Bristol-Myers Squibb, Gilead Sciences Inc., Roche, AbbVie, Shire, Janssen pharmaceuticals; Grant/Research Support: Gilead Sciences Inc.

The following people have nothing to disclose: Ryan B. Perumpail, George Cholankeril, Zobair M. Younossi

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Analysis of HCV Variants in the MAGELLAN-1 Part 1 Study: ABT-493 and ABT-530 Combination Therapy of Genotype 1-Infected Patients Who Had Failed Prior Direct Acting Antiviral-Containing Regimens

Teresa Ng, Tami Pilot-Matias, Rakesh Tripathi, Gretja Schnell, Thomas Reisch, Jill Beyer, Tanya Dekhtyar, Armen Asatryan, Federico Mensa, Jens Kort, Christine Collins; AbbVie, North Chicago, IL

Background: ABT-493 (NS3/4A protease inhibitor [PI] identified by AbbVie and Enanta) and ABT-530 (NS5A inhibitor) are next generation HCV direct-acting antiviral agents (DAAs). Co-administration of ABT-493 + ABT-530 achieved a high sustained virologic response 12 (SVR12) rate in DAA-naïve patients with HCV genotype (GT) 1-6 infection, as well as GT1-infected patients who had previously failed a DAA-containing regimen. In this report we present the characterization of variants detected in samples from subjects enrolled in Part 1 of the MAGELLAN-1 study: treatment with ABT-493 + ABT-530 ± RBV for 12 weeks in non-cirrhotic GT1-infected patients who had previously failed regimens containing a PI and/or NS5A inhibitor, ± an NS5B polymerase inhibitor. Methods: Next generation sequencing (NGS) was performed on HCV NS3/4A and NS5A genes from all baseline samples and the first available sample after virologic failure with HCV RNA ≥1000 IU/mL. Sequencing results at 1% and 15% detection cutoffs were examined for the presence of resistance-associated variants (RAVs) in the NS3 and NS5A genes. Results: NGS (with 1% cutoff) of baseline samples from all patients (n=50) identified RAVs in 41 (82%) patients: 15 (30%) in NS3 only, 10 (20%) in NS5A only, and 16 (32%) in both targets. In 90% (37/41) of these samples, the RAVs were also present using an NGS detection cutoff of 15%. These DAA-experienced patient cohorts had broad representation of baseline variants at key resistance-associated positions, including those at NS3 V36, Q80, R155, and D168, as well as NS5A M28, Q30, L31, and Y93. All patients with baseline variants at position Y93 in NS5A that confer high level of resistance to currently approved NS5A inhibitors achieved SVR12 (n=10). Of the 2 out of 50 (4%) patients who experienced virologic failure, 1 patient had baseline NS3 (Y56H and D168A/T) and NS5A (M28V and Q30L/R) RAVs, and the other patient had baseline RAVs in NS5A (L31M and H58D) only. Conclusions: The combination

of ABT-493 and ABT-530 demonstrated potent antiviral activity and a high barrier to resistance in non-cirrhotic HCV GT1-infected patients who had previously failed a DAA-containing regimen, regardless of the diverse profile and high prevalence of baseline NS3 and/or NS5A RAVs among these patients. These promising results support the study of this combination regimen in a larger cohort of DAA-experienced patients.

Disclosures:

Teresa Ng - Employment: AbbVie; Patent Held/Filed: AbbVie; Stock Shareholder: AbbVie

Tami Pilot-Matias - Employment: AbbVie; Stock Shareholder: Abbott

Rakesh Tripathi - Employment: AbbVie; Stock Shareholder: AbbVie

Gretja Schnell - Employment: AbbVie Inc.; Stock Shareholder: AbbVie Inc.

Thomas Reisch - Employment: Abbvie; Stock Shareholder: Abbvie

Jill Beyer - Employment: Abbvie; Stock Shareholder: Abbvie

Tanya Dekhtyar - Employment: Abbvie; Stock Shareholder: Abbvie

Armen Asatryan - Employment: AbbVie

Federico Mensa - Employment: Abbvie; Stock Shareholder: Abbvie

Jens Kort - Employment: AbbVie; Stock Shareholder: AbbVie

Christine Collins - Employment: AbbVie

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A Decision Analytic Markov Model to Evaluate the Health Outcomes of Sofosbuvir/Velpatasvir for Patients with Chronic Hepatitis C Virus Genotypes 1 to 6 and Decompensated Cirrhosis in the US

Aijaz Ahmed[1], Sammy Saab[2], Stuart C. Gordon[3], Douglas T. Dieterich[4], Robert J. Wong[1], Kimberly Ann Brown[3], Marcelo Kugelmas[5], Zobair M. Younossi[6]; [1]Stanford University Medical Center, Stanford, CA; [2]UCLA, Los Angeles, CA; [3]Henry Ford Hospital, Detroit, MI; [4]Icahn School of Medicine, New York, NY; [5]South Denver Gastroenterology, Englewood, CO; [6]Inova Fairfax Hospital, Falls Church, VA

BACKGROUND AND AIM: Chronic hepatitis C virus (CHC) patients with decompensated cirrhosis (DCC) awaiting transplant have limited treatment options and are at high risk for liver-related comorbidity and increased mortality. The new oral single tablet regimen of sofosbuvir/velpatasvir (SOF/VEL) has been shown to have excellent efficacy and safety in this population. A decision-analytic Markov model evaluated the health outcomes of SOF/VEL compared with current treatment options in DCC. **METHODS**: The analysis modeled a cohort of 10,000 CHC DCC genotype (GT) 1-6 patients with an average age of 52 from a US third-party payer perspective over a lifetime horizon. Pre-transplant treatment with SOF/VEL for 12 weeks (W) with ribavirin (R) was compared with ledipasvir/sofosbuvir (LDV/SOF) 12W+R and 24W+/-R, SOF+ daclatasvir (DCV) for 12W+R or 24W, and no treatment (NT). Sustained virologic response (SVR) rates were extrapolated from ASTRAL-4, SOLAR-1, -2, and ALLY-1. Transition probabilities and utilities were based on a literature review and consensus by a panel of hepatologists. **RESULTS**: The SOF/VEL regimen resulted in the best health outcomes in terms of the lowest number of hepatocellular carcinoma (HCC) cases, liver transplants (LT), and liver-related deaths compared with all comparators in GT 1, 2, 3, and 5/6 (Table 1). In GT4, SOF+DCV was associated with slightly fewer liver-related complications, particularly for HCC and LT. **CONCLUSIONS**: Compared to currently available options including SOF+DCV, LDV/SOF and NT, SOF/VEL demonstrated better overall health outcomes in DCC patients, leading to fewer cases of liver-related complications. Further, SOF/VEL is the only available pan-genotypic, all-oral, once-daily single tablet regimen for CHC patients, simplifying treatment across GTs.

Table 1: Projected health outcomes per 10,000 patients for SOF/VEL vs. comparators

		SVR	Cases of HCC	No. of LTs	Liver-related deaths
GT1	SOF/VEL	96.1%	343	660	4719
	LDV/SOF	81.2%	426	777	5430
	SOF+DCV	87.0%	394	732	5156
	NT	0.0%	889	1417	9315
GT2	SOF/VEL	100%	321	629	4531
	SOF+DCV	79.1%	427	1239	5480
	NT	0.0%	889	1417	9315
GT3	SOF/VEL	84.6%	503	744	5274
	SOF+DCV	67.3%	710	875	6117
	NT	0.0%	1512	1378	9356
GT4	SOF/VEL	94.3%	353	675	4806
	LDV/SOF	79.7%	435	789	5501
	SOF+DCV	98.9%	327	638	4584
	NT	0.0%	889	1417	9315
GT5/6	SOF/VEL	94.3%	353	675	4806
	NT	0.0%	889	1417	9315

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Aijaz Ahmed - Consulting: Bristol-Myers Squibb, Gilead Sciences Inc., Roche, AbbVie, Shire, Janssen pharmaceuticals; Grant/Research Support: Gilead Sciences Inc.

Sammy Saab - Advisory Committees or Review Panels: BMS, Gilead, Merck, Janssen; Grant/Research Support: Gilead; Speaking and Teaching: BMS, Gilead, Merck, Janssen, Salix, Onyx, Bayer, Janssen; Stock Shareholder: Achillion, Johnson and Johnson, BMS, Gilead

Stuart C. Gordon - Advisory Committees or Review Panels: Gilead, AbbVie, Merck, Intercept; Consulting: CVS Caremark; Grant/Research Support: Cymba Bay, Gilead, BMS, AbbVie, Intercept, Conatus, Exalenz, Merck; Speaking and Teaching: Gilead, Intercept

Douglas T. Dieterich - Advisory Committees or Review Panels: Gilead, BMS, Abbvie, Janssen, Merck, Achillion

Robert J. Wong - Advisory Committees or Review Panels: Gilead; Grant/Research Support: Gilead

Kimberly Ann Brown - Advisory Committees or Review Panels: CLDF, gilead, abbvie, janssen, Merck, BMS, Janssen; Grant/Research Support: Gilead, abbvie, janssen, duke medical research, Merck; Speaking and Teaching: CLDF

Marcelo Kugelmas - Advisory Committees or Review Panels: Merck, Abbvie, Janssen, Salix; Consulting: Abbvie, Merck, Gilead, Janssen; Grant/Research Support: roche, Intercept, Hologic, Gilead, Janssen, Roche, Anadys, Salix, abbvie; Speaking and Teaching: Abbvie, Gilead, Merck, Janssen, Salix

The following people have nothing to disclose: Zobair M. Younossi

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Final Results from Phase 3 Portion in Phase 2/3 Study of Elbasvir / Grazoprevir in Hepatitis C Genotype 1 Infected Japanese Patients

Fumitaka Suzuki[1], Yoshiyasu Karino[2], Kazuaki Chayama[3], Norifumi Kawada[4], Takeshi Okanoue[5], Yoshito Itoh[6], Satoshi Mochida[7], Hidenori Toyoda[8], Hitoshi Yoshiji[9], Shintaro Takaki[10], Naoyoshi Yatsuzuka[11], Etsuo Yodoya[11], Go Fujimoto[11], Janice Wahl[12], Michael Robertson[12], Stuart Black[12], Hiromitsu Kumada[1]; [1]Department of Hepatology, Toranomon Hospital, Tokyo, Japan; [2]Department of Gastroenterology, Sapporo Kosei General Hospital, Hokkaido, Japan; [3]Department of Gastroenterology and Metabolism, Hiroshima University, Hiroshima, Japan; [4]Department of Hepatology, Osaka City University Medical School, Osaka, Japan; [5]Department of Gastroenterology and Hepatology, Saiseikai Suita Hospital, Osaka, Japan; [6]Department of Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Kyoto, Japan; [7]Department of Gastroenterology & Hepatology, Saitama Medical University, Saitama, Japan; [8]Department of Gastroenterology, Ogaki Municipal Hospital, Ogaki, Japan; [9]Third Department of Internal Medicine, Nara Medical University, Nara, Japan; [10]Department of Gastroenterology/Liver Center, Hiroshima Red Cross Hospital and Atomic-bomb Survivors Hospital, Hiroshima, Japan; [11]MSD K.K., Tokyo, Japan; [12]Merck & Co., Inc., Kenilworth, NJ

Introduction: This phase 3 portion of a phase 2/3 study assessed an all-oral, once-daily regimen of elbasvir (EBR,

MK-8742; HCV NS5A inhibitor) in combination with grazoprevir (GZR, MK-5172; HCV NS3/4A protease inhibitor) in treatment-naïve or IFN-experienced Japanese patients with or without compensated cirrhosis with HCV genotype 1 (GT1) infection. **Methods:** HCV GT1-infected non-cirrhotic patients were randomized to immediate treatment with EBR/GZR (50mg/100mg) once daily for 12 weeks or deferred treatment (placebo for 12 weeks followed by active dosing for 12 weeks). Compensated cirrhotic patients were assigned to receive open-label EBR/GZR (50mg/100mg). The primary efficacy endpoint was sustained virologic response (SVR) at follow-up week (FU) 12 (SVR12; COBAS TaqMan v2.0 [lower limit of quantitation < 1.2 Log IU/mL]) in the EBR/GZR arm. Safety was evaluated with comparison of adverse events and laboratory abnormalities during treatment through FU4 in the immediate and deferred treatment arms. **Results:** 336 patients randomized (non-cirrhotics: 227 received EBR/GZR and 74 received placebo, 36% male, mean age 61, and 98% GT1b; cirrhotics: n=35, 51% male, mean age 65, and 97% GT1b). SVR12 on EBR/GZR was 96% (219/227) among non-cirrhotics and 97% (34/35) among cirrhotics. In the EBR/GZR non-cirrhotic arm 4% (8/227) did not achieve SVR12; 3 patients withdrew from the study before FU12 and 5 subjects relapsed. In the cirrhotic arm 3% (1/35) experienced relapse. During the initial treatment period through FU4, at least one AE occurred in 147 (65%) and 50 (68%) patients in the EBR/GZR non-cirrhotic and placebo arms, respectively, and in 28 (80%) of cirrhotics. Serious AEs occurred in 11 (5%) and in 1 (1%) of the EBR/GZR non-cirrhotic and placebo patients, respectively, and in no cirrhotic patients. Grade 3 and Grade 4 ALT elevations were observed for 1.3% (3/227) and 0.4% (1/227) in the EBR/GZR arm, but not in the placebo arm. Grade 3 ALT elevations were observed for 5.7% (2/35) in the cirrhotic arm, but no patient had a Grade 4 ALT elevation. The most common AEs were nasopharyngitis (15%) and ALT increased (5.7%) in EBR/GZR arm, and nasopharyngitis (14%) and ALT/AST increased (14%) in the cirrhotic arm. SVR12 data from deferred treatment and SVR24 data will be also presented at the meeting. **Conclusions:** Once-daily EBR/GZR for 12 weeks was highly effective and generally well tolerated in non-cirrhotic and compensated cirrhotic Japanese patients with HCV G1-infection.

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Fumitaka Suzuki - Speaking and Teaching: BMS

Yoshiyasu Karino - Speaking and Teaching: BMS KK

Kazuaki Chayama - Advisory Committees or Review Panels: Mitsubishi Tanabe, Taisho Toyama; Consulting: AbbVie; Grant/Research Support: Ajinomoto, AbbVie, Aska, Asstellas, Aska, Bristol Squibb, Daiichi Sankyo, Dainippon Sumitomo, Daiichi Sankyo, Eisai, GlaxoSmithKline, Mitsubishi Tanabe, Nippon Kayaku, Otsuka, Sogo Rinsho MV©dv©fi, Taiho, Takeda, Toray, Torii, Tsumura, Zeria; Speaking and Teaching: Abbott, AbbVie, Ajinomoto, Astellas, AstraZeneca, Bayer, Bristol Squibb, Chugai, Dainippon Sumitomo, Eidia, Eisai, Gilead, GlaxoSmithKline, JIMRO, Johnson & Johnson, Mitsubishi Tanabe

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Naoyoshi Yatsuzuka - Employment: MSD K.K.

Etsuo Yodoya - Employment: MSD K.K.

Go Fujimoto - Employment: MSD K.K.; Stock Shareholder: Merck

Janice Wahl - Employment: Merck & Co,

Michael Robertson - Employment: Merck; Stock Shareholder: Merck

Stuart Black - Employment: Merck

Hiromitsu Kumada - Speaking and Teaching: Bristol-Myers Squibb,Pharma International, MSD, Abbvie, Glaxosmithkline, Gilead Sciences, Diainippon Sumitomo Pharma

The following people have nothing to disclose: Takeshi Okanoue, Hidenori Toyoda, Hitoshi Yoshiji, Shintaro Takaki

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Pharmacokinetics of Sofosbuvir/Velpatasvir and Tenofovir in Subjects with HCV/HIV Coinfection Using Boosted or Unboosted Antiretroviral Regimens

Erik Mogalian[1], Vinay Daryani[1], Anu O. Osinusi[1], John McNally[1], Liyun Ni[1], David L. Wyles[5], Norbert Bräu[3,4], Mark S. Sulkowski[2], John Ling[1], Anita Mathias[1]; [1]Gilead Sciences, Inc, Foster City, CA; [2]Johns Hopkins University School of Medicine, Baltimore, MD; [3]Veteran Affairs Medical Center, New York, NY; [4]Icahn School of Medicine at Mount Sinai, New York, NY; [5]University of California, San Diego, Division of Infectious Diseases, San Diego, CA

Background: Administration of the pangenotypic fixed-dose combination of sofosbuvir (SOF)/velpatasvir (VEL) 400/100 mg once-daily for 12 weeks resulted in an overall SVR12 rate of 95% (99/104) in HCV/HIV co-infected subjects (ASTRAL-5), which included subjects on boosted (cobicistat- or ritonavir-containing) or unboosted antiretroviral (ARV) regimens. Pharmacokinetic (PK) data were collected to evaluate the relationship between exposure and extrinsic/intrinsic variables, treatment outcome, and to compare PK in co-infected and HCV mono-infected subjects. **Methods:** The study population included HCV/HIV co-infected subjects (N=106) receiving SOF/VEL 400/100 mg for 12 weeks on a stable ARV regimen including various combinations of: abacavir, atazanavir, cobicistat, darunavir, elvitegravir, emtricitabine, lamivudine, lopinavir, raltegravir, rilpivirine, ritonavir, and tenofovir disoproxil fumarate (TDF). The PK of SOF, GS-331007, VEL, and tenofovir (TFV) were evaluated in all subjects with measurable plasma concentrations using previously established population PK models. The PK of SOF, GS-331007, and VEL in HCV/HIV co-infected subjects was compared across ARV regimen, treatment outcome, and to subjects with HCV monoinfection. The PK of TFV was compared across ARV regimens (boosted vs. unboosted). **Results:** Exposures of SOF, GS-331007, and VEL were similar across ARV regimens, and were similar to exposures observed in the HCV mono-infected population (90% CI range: 0.76 to 1.10). Mean TFV exposure was similar following administration of SOF/VEL with a boosted (AUC_{tau}: 3740 h*ng/mL; n=56) or unboosted (AUC_{tau}: 3590 h*ng/mL; n=35) regimen, and was similar to mean TFV AUC observed following TDF administration as part of boosted regimens in HIV mono-infected subjects (mean TFV AUC range: 3110 to 4630 h*ng/mL). **Conclusions:** Pharmacokinetic results in addition to safety and efficacy data support the use of SOF/VEL 400/100 mg for 12 weeks in subjects with HCV/HIV co-infection. Tenofovir exposures (administered as TDF) were consistent with those observed following administration of boosted regimens to HIV mono-infected subjects.

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Erik Mogalian - Employment: Gilead Sciences, Inc; Stock Shareholder: Gilead Sciences, Inc

Vinay Daryani - Employment: Gilead Sciences, Inc.

Anu O. Osinusi - Employment: Gilead Sciences Inc; Stock Shareholder: Gilead Sciences Inc

John McNally - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

David L. Wyles - Advisory Committees or Review Panels: Bristol Myers Squibb, Gilead, Merck, AbbVie; Grant/Research Support: Gilead, Merck, Bristol Myers Squibb, AbbVie, Tacere

Mark S. Sulkowski - Advisory Committees or Review Panels: Merck, AbbVie, Janssen, Gilead, Trek, Cocrystal; Grant/Research Support: Merck, AbbVie, Janssen, Gilead

Anita Mathias - Employment: Gilead Sciences Inc.,

The following people have nothing to disclose: Liyun Ni, Norbert Bräu, John Ling

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Prevalence and Impact of Baseline Resistance-Associated Variants on the Efficacy of Elbasvir / Grazoprevir in Hepatitis C Genotype 1 Infected Japanese Patients

Yoshito Itoh[1], Fumitaka Suzuki[2], Yoshiyasu Karino[3], Kazuaki Chayama[4], Naoyoshi Yatsuzuka[5], Etsuo Yodoya[5], Go Fujimoto[5], Stuart Black[6], Ernest Asante-Appiah[6], Janice Wahl[6], Michael Robertson[6], Hiromitsu Kumada[2]; [1]Department of Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Kyoto, Japan; [2]Department of Hepatology, Toranomon Hospital, Tokyo, Japan; [3]Department of Gastroenterology, Sapporo Kosei General Hospital, Hokkaido, Japan; [4]Department of Gastroenterology and Metabolism, Hiroshima University, Hiroshima, Japan; [5]MSD K.K., Tokyo, Japan; [6]Merck & Co., Inc., Kenilworth, NJ

Introduction: A Phase 2/3 clinical study was conducted to evaluate efficacy and safety of elbasvir (EBR, MK-8742; HCV NS5A inhibitor (NS5A I)) and grazoprevir (GZR, MK-5172; HCV NS3/4A protease inhibitor (NS3/4A PI)) in treatment-naïve or -IFN experienced Japanese patients with or without compensated cirrhosis with HCV genotype 1 (GT1) infection. Study results showed that once daily co-administration of EBR/GZR for 12 weeks is highly effective and well tolerated in HCV GT1-infected Japanese patients. The prevalence of HCV NS3 or NS5A resistance-associated variants (RAVs) at baseline (BL) and their impact on SVR were also assessed in the study. **Methods:** Population sequencing of NS3/4A and NS5A was performed on BL samples from all patients and on samples (viral load >3 Log IU/mL) from patients who met the criteria for virologic failure (VF). RAVs of interest that confer resistance to the NS3 protease inhibitor class include those at positions: 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170 and 175. RAVs of interest that confer resistance to the NS5A inhibitor class include those at positions: 28, 30, 31, 58 and 93. In addition, selected samples were analyzed by clonal sequencing (≥40 clones, cutoff:5%); baseline samples from all patients and samples from VF patients in the phase 3 program were analyzed by next generation sequencing (NGS, cutoff:1%,15%). The resistance analysis population (RAP) excluded non-VFs (2 early discontinuations (ED) and 1 lost to follow-up (LTFU)) as well as all patients in the placebo arm. **Results:** 324 patients received active study drug: 319 (98%) had GT1b and 5 (2%) had GT1a. 61/62 (98%, VF:1) and 253/262 (97%, VF:6, ED:2, LTFU:1) patients achieved SVR12 in the phase 2 and 3 portions of the study, respectively. The prevalence of BL NS3 RAVs was 32% (103/321). All 103 patients achieved SVR12 including 5 patients (2%) with the BL D168E RAV. The prevalence of BL NS5A RAVs was 18% (58/321); 4% (13/321) at L31I/M/V and 14% (44/321) at Y93C/H. SVR12 was achieved in 93% (54/58) of patients with BL NS5A RAVs and 99% (260/263) of patients without BL NS5A RAVs. SVR12 was achieved in 92% (12/13) patients with BL L31I/M/V RAVs and 93% (41/44) patients with BL Y93C/H RAVs. No treatment-emergent NS3 RAVs were observed in the 7 VF. Treatment-emergent NS5A RAVs were observed in 6/7 VF including 4 patients who had BL NS5A RAVs that were still present at time of failure. **Conclusions:** The prevalence of NS3 and NS5A RAVs that confer potency losses to various NS3/4A PIs and NS5A Is at baseline was 32% and 18%, respectively. The presence of these BL RAVs had no clinically remarkable impact on SVR12 in this Japanese phase 2/3 study.

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Fumitaka Suzuki - Speaking and Teaching: BMS

Yoshiyasu Karino - Speaking and Teaching: BMS KK

Kazuaki Chayama - Advisory Committees or Review Panels: Mitsubishi Tanabe, Taisho Toyama; Consulting: AbbVie; Grant/Research Support: Ajinomoto, AbbVie, Aska, Asstellas, Aska, Bristol Squibb, Daiichi Sankyo, Dainippon Sumitomo, Daiichi Sankyo, Eisai, GlaxoSmithKline, Mitsubishi Tanabe, Nippon Kayaku, Otsuka, Sogo Rinsho Mv©dv©fi, Taiho, Takeda, Toray, Torii, Tsumura, Zeria; Speaking and Teaching: Abbott, AbbVie, Ajinomoto, Astellas, AstraZeneca, Bayer, Bristol Squibb, Chugai, Dainippon Sumitomo, Eidia, Eisai, Gilead, GlaxoSmithKline, JIMRO, Johnson & Johnson, Mitsubishi Tanabe

Naoyoshi Yatsuzuka - Employment: MSD K.K.

Etsuo Yodoya - Employment: MSD K.K.

Go Fujimoto - Employment: MSD K.K.; Stock Shareholder: Merck

Stuart Black - Employment: Merck

Ernest Asante-Appiah - Employment: Merck

Janice Wahl - Employment: Merck & Co,

Michael Robertson - Employment: Merck; Stock Shareholder: Merck

Hiromitsu Kumada - Speaking and Teaching: Bristol-Myers Squibb,Pharma International, MSD, Abbvie, Glaxosmithkline, Gilead Sciences, Diainippon Sumitomo Pharma

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Drug-drug interactions between direct acting antivirals ABT-493 and ABT-530 with angiotensin II receptor blockers (losartan or valsartan)

Matthew P. Kosloski, Sandeep Dutta, Qi Jiang, Betty Yao, Armen Asatryan, Federico Mensa, Jens Kort, Wei Liu; AbbVie, North Chicago, IL

Purpose: The direct acting antiviral (DAA) combination of ABT-493 (NS3/4A protease inhibitor discovered by AbbVie and Enanta) + ABT-530 (NS5A inhibitor) achieved high sustained virologic response rates across chronic hepatitis C virus (HCV) genotype 1-6 infection in Phase 2 studies with a favorable safety profile. Angiotensin II receptor blockers (ARBs) are used in the treatment of hypertension and other cardiovascular indications, and are commonly administered in HCV infected subjects with such comorbidities. Pharmacokinetics, safety, and tolerability of ABT-493 + ABT-530 coadministered with losartan or valsartan were evaluated to assess the drug-drug interaction potential of these agents. **Methods:** This was an open-label one-sequence crossover study. Healthy adult subjects received single doses of losartan 50 mg (n=12) or valsartan 80 mg (n=12) alone and in combination with ABT-493 300 mg QD + ABT-530 120 mg QD. Intensive blood sampling for determination of losartan, losartan carboxylic acid metabolite, valsartan, ABT-493 and ABT-530 concentrations was performed and pharmacokinetic parameters (maximum observed concentration [C_{max}], area under the concentration-time curve [AUC_{inf} or AUC_{24}] and/or trough concentration [C_{24}]) were estimated. The effect of ABT-493 + ABT-530 on the pharmacokinetics of losartan or valsartan and vice versa, were assessed by a repeated-measures analysis using SAS. Safety was evaluated by assessment of adverse events, vital signs, ECGs, and clinical laboratory tests. **Results:** Exposures were higher for losartan (↑C_{max} 151% and ↑AUC_{inf} 56%) when administered with multiple doses of ABT-493 + ABT-530, relative to losartan alone; losartan active carboxylic metabolite C_{max} was 118% higher, while AUC_{inf} was similar (≤ 14% difference). Exposures of val-

sartan were slightly higher (↑C_{max} 36% and ↑AUC_{inf} 31%) when administered with ABT-493 + ABT-530. Exposures of ABT-493 and ABT-530 (C_{max}, AUC_{24}, and C_{24}) were similar with or without losartan or valsartan (≤ 23% difference). No serious adverse events occurred in the study. There was no pattern to the adverse events reported. No clinically significant vital signs, ECGs, or laboratory abnormalities were observed in the study. **Conclusions:** ABT-493 + ABT-530 increased losartan and valsartan exposures. ABT-493 and ABT-530 exposures were not affected by losartan or valsartan. Consistent with losartan and valsartan label recommendations for similar magnitudes of exposure increases caused by other drugs or in special populations, no dose adjustment is required when ABT-493 and ABT-530 are coadministered with losartan or valsartan.

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Matthew P. Kosloski - Employment: AbbVie

Sandeep Dutta - Employment: AbbVie

Qi Jiang - Employment: AbbVie Inc.

Betty Yao - Employment: AbbVie

Armen Asatryan - Employment: AbbVie

Federico Mensa - Employment: Abbvie; Stock Shareholder: Abbvie

Jens Kort - Employment: AbbVie; Stock Shareholder: AbbVie

Wei Liu - Employment: AbbVie

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Hemodialysis does not affect the pharmacokinetics of ABT-493 or ABT-530

Matthew P. Kosloski, Sandeep Dutta, Weihan Zhao, David Pugatch, Federico Mensa, Jens Kort, Wei Liu; AbbVie, North Chicago, IL

Purpose: The direct acting antiviral (DAA) combination of ABT-493 (NS3/4A protease inhibitor discovered by AbbVie and Enanta) + ABT-530 (NS5A inhibitor) demonstrated favorable safety profiles and high sustained virologic response rates across chronic hepatitis C (HCV) genotype 1-6 infection in Phase 2 studies. It has been previously demonstrated that no dose adjustment is needed for administration of this combination in subjects with mild, moderate, or severe renal impairment, or with end-stage renal disease (ESRD) not on dialysis. This study evaluated the pharmacokinetics and safety of ABT-493 and ABT-530 when administered in ESRD dialysis-dependent subjects under dialysis and non-dialysis conditions. **Methods:** In this open-label study, N=8 subjects on hemodialysis for ≥ 1 month received single doses of ABT-493 300 mg + ABT-530 120 mg in Period 1 three hours prior to initiating a hemodialysis session and in Period 2 on the day prior to scheduled hemodialysis. A washout of ≥ 7 days separated dosing in each period. Intensive blood sampling for determination of ABT-493 and ABT-530 concentrations was performed for 24 hours following each dose and pharmacokinetic parameters (maximum observed concentration [C_{max}], area under the concentration-time curve [AUC_t], clearance [CL], and clearance due to dialysis [CL_D]) were estimated. Additionally, arterial (predialyzer) and venous (postdialyzer) blood samples were collected during dialysis. The effect of dialysis on ABT-493 and ABT-530 pharmacokinetics was assessed by a repeated-measures analysis. Safety was evaluated throughout the study with assessment of adverse events, vital signs, ECGs and clinical laboratory tests. **Results:** Peak plasma concentrations of ABT-493 and ABT-530 were both reached during dialysis. The mean dialysis duration was 3.95 hours. C_{max} and AUC_t were similar for ABT-493 (≤ 7% difference) and ABT-530 (≤ 18% difference) under dialysis conditions compared to non-dialysis days. ABT-493 and ABT-530 arterial and venous concentration profiles were similar during dialysis. CL_D represented a minimal portion of total drug clearance for ABT-493 (< 1%) and ABT-530 (< 0.005%). No serious adverse events occurred in the study. No clinically significant vital signs, ECG or laboratory measurements were observed during the course of the study. **Conclusions:** ABT-493 and ABT-530 exposures were not affected by dialysis. No dose-adjustment is needed when ABT-493 + ABT-530 are administered in subjects with renal impairment, with or without dialysis.

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Matthew P. Kosloski - Employment: AbbVie

Sandeep Dutta - Employment: AbbVie

Weihan Zhao - Employment: AbbVie, Inc; Stock Shareholder: AbbVie, Inc, United Airlines, American Airlines, Procter & Gamble

Federico Mensa - Employment: Abbvie; Stock Shareholder: Abbvie

Jens Kort - Employment: AbbVie; Stock Shareholder: AbbVie

Wei Liu - Employment: AbbVie

The following people have nothing to disclose: David Pugatch

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A Decision Analytic Markov Model to Evaluate the Health Outcomes of Sofosbuvir/Velpatasvir for Patients with Chronic Hepatitis C Virus Genotype 1 Infection in the US

Zobair M. Younossi[1], Stuart C. Gordon[2], Douglas T. Dieterich[3], Robert Wong[6], Kimberly Ann Brown[2], Marcelo Kugelmas[4], Sammy Saab[5], Aijaz Ahmed[6]; [1]Inova Fairfax Hospital, Falls Church, VA; [2]Henry Ford Hospital, Detroit, MI; [3]Icahn School of Medicine at Mount Sinai, New York, NY; [4]South Denver Gastroenterology, Denver, CO; [5]UCLA, Los Angeles, CA; [6]Stanford University Medical Center, Palo Alto, CA

BACKGROUND AND AIM: Sofosbuvir / velpatasvir (SOF/VEL) is an oral single tablet regimen that has been shown in the clinical trial setting to have excellent efficacy and tolerability in treatment-naïve (TN) and treatment-experienced (TE) patients with chronic hepatitis C virus (HCV) genotype 1 (GT1). A decision-analytic Markov model evaluated the health outcomes of SOF/VEL compared with current treatment options for GT1. **METHODS**: The analysis modeled two cohorts of 10,000 chronic HCV GT1 patients (non-cirrhotic (NC); cirrhotic (CC)) with an average age of 52 from a US third-party payer perspective over a lifetime horizon. 70% of each cohort was TN. SOF/VEL for 12W was compared with LDV/SOF for 8W, 12W +/- ribavirin (RBV), and 24W, elbasvir/grazoprevir (EBR/GRZ) +/- RBV for 12W or 16W, and no treatment (NT). Sustained virologic response (SVR) rates were extrapolated from Phase III clinical trials and stratified by baseline NS5A resistance associated variant for EBR/GRZ. Transition probabilities and utilities were based on a literature review and consensus by a panel of hepatologists. **RESULTS**: Initiation of SOF/VEL in GT1 patients resulted in the best health outcomes in terms of the lowest numbers of patients with liver-related complications compared with EBR/GRZ, LDV/SOF, and NT (Table 1). Results were consistent across patient subpopulations, including TN, peginterferon+ribavirin (PR)-TE, PR+protease inhibitor-TE, NC, and CC. **CONCLUSIONS**: Compared to EBR/GRZ and LDV/SOF, SOF/VEL demonstrated better overall health outcomes in GT1, with reductions up to 58%, 47% and 54% in cases of decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), and liver transplant (LT), respectively. Our results highlight the longer-term benefits of treating chronic HCV with SOF/VEL versus currently available options.

Table 1: Projected health outcomes per 10,000 patients for SOF/VEL vs. comparator regimens in HCV GT1 patients

		SOF/VEL	LDV/SOF	EBR/GRZ	NT
SVR rate	NC	98.2%	96.9%	95.8%	0%
	CC	99.3%	93.0%	96.9%	0%
Cases of DCC	NC	58.6	97.4	138.5	3,212.3
	CC	3,287.1	3,412.7	3,335.7	5,166.2
Cases of HCC	NC	66.6	95.4	125.6	2,403.1
	CC	673.6	863.4	746.8	3,571.8
LTs	NC	10.9	17.1	23.8	528.0
	CC	203.1	247.7	220.3	902.5

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Douglas T. Dieterich - Advisory Committees or Review Panels: Gilead, BMS, Abbvie, Janssen, Merck, Achillion

Robert Wong - Advisory Committees or Review Panels: Gilead; Grant/Research Support: Gilead

Kimberly Ann Brown - Advisory Committees or Review Panels: CLDF, gilead, abbvie, janssen, Merck, BMS, Janssen; Grant/Research Support: Gilead, abbvie, janssen, duke medical research, Merck; Speaking and Teaching: CLDF

Marcelo Kugelmas - Advisory Committees or Review Panels: Merck, Abbvie, Janssen, Salix; Consulting: Abbvie, Merck, Gilead, Janssen; Grant/Research Support: roche, Intercept, Hologic, Gilead, Janssen, Roche, Anadys, Salix, abbvie; Speaking and Teaching: Abbvie, Gilead, Merck, Janssen, Salix

Sammy Saab - Advisory Committees or Review Panels: BMS, Gilead, Merck, Janssen; Grant/Research Support: Gilead; Speaking and Teaching: BMS, Gilead, Merck, Janssen, Salix, Onyx, Bayer, Janssen; Stock Shareholder: Achillion, Johnson and Johnson, BMS, Gilead

Aijaz Ahmed - Consulting: Bristol-Myers Squibb, Gilead Sciences Inc., Roche, AbbVie, Shire, Janssen pharmaceuticals; Grant/Research Support: Gilead Sciences Inc.

The following people have nothing to disclose: Zobair M. Younossi

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Gender Differences in Patients Treated for HCV: Efficacy and Safety of Sofosbuvir/Velpatasvir in Women

Tram T. Tran[1], Jordan J. Feld[2], Graham R. Foster[3], Sarjita Naik[4], Edward S. Eggleton[4], Jie Zhang[4], Macky Natha[4], Joseph Llewellyn[4], Bruce Kreter[4], Diana M. Brainard[4], David L. Wyles[5], Mark S. Sulkowski[6], Shari S. Rogal[7]; [1]Cedars-Sinai Medical Center, Los Angeles, CA; [2]University of Toronto, Toronto, ON, Canada; [3]Queen Marys, University of London, London, United Kingdom; [4]Gilead Sciences, Foster City, CA; [5]University of California San Diego, San Diego, CA; [6]Johns Hopkins University, Baltimore, MD; [7]VA Pittsburgh Healthcare System, Pittsburgh, PA

BACKGROUND: Gender differences in both safety and efficacy have been reported for interferon-based HCV treatments. Data in large cohorts of women with HCV treated with direct acting antivirals are lacking. The aim of this analysis was to evaluate the influence of gender on the efficacy and safety of the RBV-free regimen of SOF/VEL 400/100 mg in patients with HCV genotypes (GT) 1-6. METHODS: This secondary analysis included patients enrolled in ASTRAL 1, 2, 3, or 5, all who received SOF/VEL 400/100 mg daily for 12 weeks. Patients with decompensated liver disease (ASTRAL 4) were excluded from this analysis. In ASTRAL 5, the HIV/HCV co-infected study, 14% of patients enrolled were women and 86% were men. Demographics, sustained virological response at 12 weeks (SVR12) and adverse events (AEs) were assessed by gender using Fisher's exact and Chi-square tests. RESULTS: Overall, 1,141 patients were treated with SOF/VEL in the Phase III ASTRAL 1, 2, 3, and 5 trials. The overall SVR12 in women was 99% and the relapse rate was <1% (3/421). In men, the overall SVR12 was 97% and the relapse rate was 2% (12/721). Demographics, SVR12, and AEs by gender are described in Table 1. Women reported higher rates nausea, headache, and nasopharyngitis than men. Further analysis of AEs in women will be done. However, treatment was generally well tolerated in women and men, and discontinuation rates were very low. CONCLUSIONS: In this pooled analysis, the once daily, single tablet regimen of SOF/VEL 400/100 mg for 12 weeks was highly efficacious regardless of GT or gender and is a safe, RBV-free option for women of all ages with HCV.

Table 1.

	Women (n=420)	Men (n=721)	p value
Demographics			
Mean Age (SD)	53 (11.6)	53 (10.3)	0.78
Mean BMI (SD)	26.5 (5.9)	27 (4.4)	<0.001
Black	34 (8.1%)	75 (10.4%)	0.20
Treatment experienced	103 (24.5%)	219 (30.4%)	0.034
Cirrhosis	72 (17.1%)	167 (23.2%)	0.016
Overall SVR12			
GT 1a	80/83 (96%)	189/193 (98%)	0.68
GT 1b	62/62 (100%)	66/68 (97%)	0.50
GT 2	95/95 (100%)	153/154 (99%)	1.00
GT 3	105/107 (98%)	170/182 (93%)	0.09
GT 4	31/31 (100%)	89/90 (99%)	1.00
GT 5	21/21 (100%)	13/14 (93%)	0.40
GT 6	21/21 (100%)	20/20 (100%)	N/A
AEs			
Headache	133 (31.7%)	177 (24.5%)	0.011
Nausea	78 (18.6%)	64 (8.9%)	<0.001
Nasopharyngitis	61 (14.5%)	65 (9%)	0.006
Insomnia	41 (9.8%)	53 (7.4%)	0.18
Treatment discontinuations	1 (0.2%)	3 (0.4%)	1.00

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Jordan J. Feld - Advisory Committees or Review Panels: Merck, Gilead, AbbVie, Bristol Myers Squibb; Grant/Research Support: AbbVie, Janssen, Gilead, Merck, Regulus

Graham R. Foster - Advisory Committees or Review Panels: GlaxoSmithKline, Novartis, Boehringer Ingelheim, Tibotec, Gilead, Janssen, Idenix, GlaxoSmithKline, Novartis, Roche, Tibotec, Chughai, Gilead, Merck, Janssen, Idenix, BMS, Alnylam; Board Membership: Boehringer Ingelheim; Grant/Research Support: Roche, Chughai, Springbank; Speaking and Teaching: Roche, Gilead, Tibotec, Merck, BMS, Boehringer Ingelheim, Gilead, Janssen

Sarjita Naik - Employment: Gilead Sciences

Macky Natha - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

Joseph Llewellyn - Employment: Gilead Sciences

Bruce Kreter - Employment: Gilead Sciences; Stock Shareholder: Bristol-Myers Squibb, Merck, Pfizer, Roche, Achillion, Celgene

Diana M. Brainard - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

David L. Wyles - Advisory Committees or Review Panels: Bristol Myers Squibb, Gilead, Merck, AbbVie; Grant/Research Support: Gilead, Merck, Bristol Myers Squibb, AbbVie, Tacere

Mark S. Sulkowski - Advisory Committees or Review Panels: Merck, AbbVie, Janssen, Gilead, Trek, Cocrystal; Grant/Research Support: Merck, AbbVie, Janssen, Gilead

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A Decision Analytic Markov Model to Evaluate the Health Outcomes of Sofosbuvir/Velpatasvir for Patients with Chronic Hepatitis C Virus Genotype 2 and 3 Infection in the US

Stuart C. Gordon[1], Aijaz Ahmed[2], Marcelo Kugelmas[3], Douglas T. Dieterich[4], Robert Wong[2], Kimberly Ann Brown[1], Sammy Saab[5], Zobair M. Younossi[6]; [1]Henry Ford Hospital, Detroit, MI; [2]Stanford University Medical Center, Palo Alto, CA; [3]South Denver Gastroenterology, Denver, CO; [4]Icahn School of Medicine at Mount Sinai, New York, NY; [5]UCLA, Los Angeles, CA; [6]Inova Fairfax Hospital, Falls Church, VA

BACKGROUND AND AIM: The new oral single tablet regimen sofosbuvir / velpatasvir (SOF/VEL) has shown excellent

efficacy and safety in patients with hepatitis C virus (HCV) genotypes (GT) 2 and 3. In particular, GT3 patients are considered difficult-to-treat populations with limited treatment options. A decision-analytic Markov model evaluated health outcomes with SOF/VEL in GT2 and 3 compared with current recommended alternatives with high real-world utilization. **METHODS**: The analysis modeled cohorts of 10,000 chronic HCV GT2 or GT3 patients with a mean age of 52 years from a US third-party payer perspective over a lifetime horizon. 15% and 21% were cirrhotic (CC) and 10% and 40% were treatment-experienced (TE) in GT2 and GT3, respectively. In GT2, SOF/VEL was compared to SOF+ribavirin (R) and no treatment (NT); in GT3, SOF/VEL was compared to SOF+daclatasvir (DCV)+/-R and NT. Sustained virologic response (SVR) rates were based on Phase III clinical trials. Transition probabilities and utilities were based on a literature review and consensus by a panel of hepatologists. **RESULTS**: The SOF/VEL regimen resulted in the best health outcomes in terms of the lowest numbers of decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), and liver transplants (LT) when compared with all other comparators (Table 1). Results were consistent across patient subpopulations, including treatment naïve, peginterferon+ribavirin-TE, SOF+R-TE, non-cirrhotics, and cirrhotics. **CONCLUSION** These results demonstrate that SOF/VEL is highly effective in HCV GT2 and GT3 patients, leading to the fewest cases of liver-related complications vs. SOF+R and SOF+DCV. Furthermore, SOF/VEL provides a RBV-free option for GT2 and GT3, and is the only available pan-genotypic, all-oral, once-daily single tablet regimen for chronic HCV, simplifying treatment across GTs. Although studies report that efficacy and adherence rates for all-oral single tablet regimens are similar in real-world and clinical trial settings, additional analyses are necessary to determine the impact of real-world utilization

Table 1: Projected health outcomes per 10,000 patients for SOF/VEL vs. comparator regimens in HCV GT2 and GT3 patients

	GT2			GT3		
	SOF/VEL	SOF+R[1]	NT	SOF/VEL	SOF+DCV[2]	NT
SVR	99.16%	96.45%	0.00%	95.13%	89.8%	0%
CASES OF:						
CC	46.62	27.83	5481.99	257.35	526.06	6485.33
DCC	516.93	566.89	3505.42	673.00	884.01	4453.33
HCC	138.84	221.64	2578.38	303.38	536.35	3729.06
LT	35.69	55.27	584.15	68.22	114.71	785.93
Liver-related deaths	303.70	462.52	4888.57	583.80	982.85	6738.39

[1] SOF+DCV is substituted where SOF+R is not recommended in TE-SOF+R; [2]Average across 12+R, 24W and 24W+R

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Marcelo Kugelmas - Advisory Committees or Review Panels: Merck, Abbvie, Janssen, Salix; Consulting: Abbvie, Merck, Gilead, Janssen; Grant/Research Support: roche, Intercept, Hologic, Gilead, Janssen, Roche, Anadys, Salix, abbvie; Speaking and Teaching: Abbvie, Gilead, Merck, Janssen, Salix

Douglas T. Dieterich - Advisory Committees or Review Panels: Gilead, BMS, Abbvie, Janssen, Merck, Achillion

Robert Wong - Advisory Committees or Review Panels: Gilead; Grant/Research Support: Gilead

Kimberly Ann Brown - Advisory Committees or Review Panels: CLDF, gilead, abbvie, janssen, Merck, BMS, Janssen; Grant/Research Support: Gilead, abbvie, janssen, duke medical research, Merck; Speaking and Teaching: CLDF

Sammy Saab - Advisory Committees or Review Panels: BMS, Gilead, Merck, Janssen; Grant/Research Support: Gilead; Speaking and Teaching: BMS, Gilead, Merck, Janssen, Salix, Onyx, Bayer, Janssen; Stock Shareholder: Achillion, Johnson and Johnson, BMS, Gilead

The following people have nothing to disclose: Zobair M. Younossi

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Direct-Acting Antiviral Therapy and Purgatory MELD: Fact or Fiction?

George Cholankeril[1,2], Ryan B. Perumpail[3], Eric R. Yoo[4], Menghan Hu[5], Aijaz Ahmed[3], Sammy Saab[6], Stevan A. Gonzalez[7], Rachel Beckerman[8]; [1]Internal Medicine, Roger Williams Medical Center, Providence, RI; [2]Internal Medicine, Boston University School of Medicine, Boston, MA; [3]Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA; [4]Medicine, University of Illinois College of Medicine, Chicago, IL; [5]Biostatistics, Brown University School of Public Health, Providence, RI; [6]Medicine and Surgery, UCLA, Los Angeles, CA; [7]Transplant Hepatology, Simmons Transplant Institute, Baylor All Saints Medical Center, Fort Worth, TX; [8]Maple Health Group, New York, NY

Background: In the era of direct-acting antiviral therapy (DAA) for chronic hepatitis C (HCV), the decision to treat HCV liver transplant (LT) waitlist candidates has been controversial. It is thought that by treating these candidates prior to LT, their Model End-Stage Disease (MELD) score may improve and thereby place them in a "purgatory MELD," which would reduce their likelihood of receiving a LT. No data have been reported to determine if "purgatory MELD" does indeed exist. **Methods:** Using the United Network for Organ Sharing (UNOS) database, we compared HCV LT waitlist candidates 18 months before (pre-DAA: May 2012 to October 2013) and after (post-DAA: January 2014 to June 2015) FDA approval of DAA agents (November to December 2013). We determined rates for transplant and death using removal codes for deceased donor transplant, death, and too sick to transplant. All statistical analyses were performed using SAS 9.4. **Results:** Overall there were a total of 20,411 HCV waitlist LT candidates, 10,606 candidates in pre-DAA period and 9,805 candidates in post-DAA period. Compared to pre-DAA period, HCV waitlist LT candidates during the post-DAA had a significantly lower rate of removal due to death (11.5 % to 7.4%, $p < 0.01$) and too sick to transplant (11.3% to 7.9 %, $p < 0.01$) (Table). Post-DAA HCV waitlist LT candidates did however have a significantly lower rate of liver transplantation (38.7% to 29.9%, $p < 0.01$). **Discussion:** Although post-DAA HCV LT waitlist candidates had a lower likelihood of receiving a transplant, their likelihood of dying on the waitlist was significantly lower. Further data needs to be evaluated to determine the role of "purgatory MELD" within this population.

Table. HCV liver transplant waitlist candidate transplant and death rates, pre-DAA versus post-DAA.

Reason for Removal	Pre-DAA n=10,606	Post-DAA n=9,805	p-value
Death	1220 (11.5%)	729 (7.4%)	< 0.01
Too Sick to Transplant	1200 (11.3%)	776 (7.9%)	< 0.01
Death + Too Sick	2420 (22.8%)	1505 (15.3%)	< 0.01
Transplanted	4127 (38.9%)	2930 (29.9%)	< 0.01

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Stevan A. Gonzalez - Speaking and Teaching: Gilead, Salix, AbbVie, Merck

Rachel Beckerman - Consulting: Gilead Sciences

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Hepatocellular carcinoma development in hepatitis C virus patients who achieved sustained viral response by interferon therapy and direct anti-viral agents therapy

Yuko Nagaoki, Hiroshi Aikata, Tomoki Kobayashi, Tomokazu Kawaoka, Masataka Tsuge, Akira Hiramatsu, Michio Imamura, Yoshiiku Kawakami, Kazuaki Chayama; Hiroshima University, Hiroshima, Japan

Background We assessed risk factors for the development of hepatocellular carcinoma (HCC) following successful eradication of hepatitis C virus (HCV) with interferon therapy and direct anti-viral agents (DAA) therapy in cohort study. *Methods* We retrospectively evaluated patients who achieved SVR by oral DAA interferon-free regimens; daclatasvir/asunaprevir (DCV/ASV, n=150) and by pegylated-interferon plus ribavirin (Peg-IFN/RBV, n=201). In all patients, the background was chronic hepatitis or cirrhosis caused by HCV genotype 1b, received HCC surveillance by tumor markers (AFP, DCP), ultrasonography and/or dynamic computed tomography at least biannually and with no evidence of HCC development prior to HCV eradication and within a year following eradication. During the observation period (median 46 months: range 12-160), 10 (3%) of 351 patients developed HCC after HCV eradication. After 29 months from HCV eradication to HCC development, 1 (7%) of DAA-treated patients developed HCC. The 3- and 5-year cumulative HCC development rates were 5% and 0%,respectively, in the DAA group, and 7% and 13 % in the Peg-IFN/RBV group (p=0.353), treatment regimen was not associated with development of HCC after HCV eradication. As independent risk factors for HCC development, multivariate analysis identified male gender (HR, 0.12: 95%CI, 0.015-927: P=0.047), advanced fibrosis stage (F3/4) (HR, 8.5: 95%CI, 2.0-35.2: P=0.003) and heavy alcohol intake (HR, 4.6: 95%CI, 1.1-18.9: P=0.003). Serum AFP level was measured before treatment, 1, and 2 years after anti-viral treatment. We excluded from this analysis those patients who developed HCC during the follow-up. The baseline AFP level was 16 (1-343) ng/ml in the DAA group, which was higher than that of the Peg-IFN/RBV group [9 (2-87) ng/ml]. The AFP level gradually decreased in both groups after anti-viral therapy and was similar at 1 and 2 years after the start of anti-viral therapy (p value not significant). *Conclusions* We demonstrated in the present study that the rate of HCC development was reduced in patients infected with HCV genotype 1b, after achieving SVR with DAA-based regimen. The impact of DAA-based treatment was similar to that of IFN-based treatment with regard to HCC risk reduction in patients who achieved SVR.

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Clinical And Immunological Effect Of Direct Acting Antivirals In Patients With Hepatitis C Virus-Associated Cryoglobulinemic Vasculitis

Martin S. Bonacci[1], José Hernández-Rodríguez[2], María-Carlota Londoño[1], Zoe Mariño[1], Patricia Gonzalez[1], José M. Sánchez-Tapias[1], Manel Ramos Casal[3], Xavier Forns[1], Sabela Lens[1]; [1]Hepatology, Hospital Clinic CIBERhed, Barcelona, Spain; [2]Vasculitis Research Unit.Department of Autoimmune Diseases, Hospital Clinic, Barcelona, Spain; [3]Laboratory of Systemic Autoimmune Diseases "Josep Font", CELLEX, Department of Systemic Autoimmune Diseases, Hospital Clinic of Barcelona, IDIBAPS,Barcelona, Spain, Hospital Clinic, Barcelona, Spain

Background: Although current direct acting antivirals (DAAs) have taken a big step forward in HCV therapy, experience in patients with HCV-cryoglobulinemic vasculitis (CV) is limited. **Aim:** To evaluate clinical and immunological outcomes in HCV-CV subjects treated with oral DAAs 12 weeks after the end of therapy. **Methods**: Prospective observational study of HCV-patients with circulating cryoglobulins who received DAAs therapy. Patients were grouped in two cohorts: asymptomatic with cryoglobulins (ACC) and patients with CV (HCV-CV). Complete immunological response (CIR) was defined by complement normalization and cryoglobulins negativization 12 weeks after therapy (FU12). Among those with HCV-VC, clinical remission was considered complete if BVAS v3 score=0 or all affected organs improved and partial if BVAS v3<50% of entry score. **Results:** 65 Caucasian patients were included, 36HCV-CV and 29 ACC. No significant differences were observed between groups regarding age (median 61 years), viral-genotype (83% G1b), null-responders (50%) or antiviral therapy [3D (33%) and LDV/SOF (29%)]. Female gender was more common in HCV-CV group (72% vs. 48%), and cirrhosis in ACC group (69%vs 47%). HCV-CV patients showed significantly elevated rheumatoid factor (RF) (80 vs 20 IU/mL;p=0.01), lower C4 complement fraction (0.02 vs 0.06 g/L;p=0.01) and slightly higher cryoglobulins (3vs2.3 %;p=0.1). Among HCV-CV, the most common manifestations were asthenia(70%), purpura(66%), polyneuropathy(50%), arthralgia(31%) and renal involvement(22%). Twelve patients received glucocorticoids and 2 rituximab. SVR12 rate was 92% (HCV-CV:92% and ACC:93%). At FU12, cryoglobulins and C4 improved equally in both groups, but RF decrease was greater in HCV-CV (-25 vs. 0 IU,p=0.03). CIR was achieved in 42% without significant differences between groups(36% and 48%). A cryocrit >2,7%(median)at baseline was associated to non-CIR (OR=6.7[2.2-20.1];p=0.01). Despite the persistence of cryoglobulins and abnormal C4 in 50% of HCV–CV patients, 29 (80%) patients achieved clinical remission (complete in 69% and partial in 11%). Median BVAS. v3 score decreased from 6 to 0 (p<0.01), with a resolution of purpura and arthralgia in 28/32 (90%) plus improvement of renal and neurological symptoms in 6/8 (75%) and 14/18 (77%), respectively. Glucocorticoid dosage could be reduced in 75% of patients. **Conclusions**: Despite a short follow-up, 42% of patients with HCV and circulating cryoglobulins achieved a CIR after SVR. Baseline cryocrit >2.7% was the only independent factor related to non-immunological response. However, SVR12 was associated with clinical improvement in a significant proportion of HCV-CV patients (80%).

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Sofosbuvir and Ribavirin is safe and effective therapy in chronic hepatitis C patients with end-stage renal disease on haemodialysis

Sumanlata Nayak[1], Manoj Sharma[2], Rajendra P. Mathur[1], Prem prakash Varma[1], Ekta Gupta[3], Ashok Choudhary[2], Kapil D. Jamwal[2], Rakhi Maiwall[2], Guresh Kumar[2], Ankit Bhardwaj[2], Shiv K. Sarin[2]; [1]nephrology, institute of liver and biliary sciences, N.Delhi, India; [2]Hepatology, Institute of liver and biliary sciences, Delhi, India; [3]virology, ilbs, New Delhi, India

Chronic hepatitis C virus [HCV] infection is more prevalent in patients with advanced chronic kidney disease on Hemodialysis(HD) as compared to the general population. Direct acting antiviral (DAAs) have been very effective in chronic hepatitis C. However, treatment of HCV in patients with advanced CKD on HD remains a major challenge due to the lack of reported efficacy and safety data of DAAs in this population. We investigated the efficacy and safety of Sofosbuvir (SOF) and Ribavirin (RBV) in chronic HCV infected CKD patients on HD. **Patients and methods:** Patients with CKD on HD having chronic HCV infection, were prospectively enrolled between September 2015 –June 2016 to receive SOF with RBV for 24 weeks. Prior to starting treatment each patient was informed that the use of sofosbuvir is not commercially approved in individuals with severe renal impairment. All patients consented to the off-label use of SOF, understanding that safety and efficacy under such circumstances is unknown. Patients were started on SOF 400 mg daily and RBV at 200 mg once to thrice weekly (as per tolerability of patients and serial Hb values). Treatment-induced anaemia was managed with erythropoietin (EPO) and iron. Safety and efficacy data were collected; including SVR12 and SVR24 data for all patients after completing therapy. **Results:** 48 patients have been enrolled, with mean age of 42.79 ±10.98 yrs. HCV genotype 1 was present in 28(58.3%) and genotype 3 in 20 (41.7%) patients. 39% patients have completed 24 weeks of therapy. The virological cure was achieved in 19/19 (100%) of patients who have completed 24 weeks. Those who have reached 12 weeks & 24 weeks post-treatment had 100 % SVR at 12 & 24 Wk. Mean drop in haemoglobin was 1.12 g/dl. 34% patients required adjustment in ribavirin dosage and increase in erythropoietin dose. 25% patients needed blood transfusion and 3 patients discontinued ribavirin due to persistent low haemoglobin. **Conclusions**: Sofosbuvir plus ribavirin therapy, given for 24 weeks appears to be well tolerated in patients with ESRD on HD with 100% SVR at 12 weeks.

Baseline demographics	All patients (n=48)
Mean age (yrs)	42.79 ±10.978
Sex (n)M/F	32/16
HCV Genotype 1(%)	28(58.3%)
Genotype 3(%)	20 (41.7%)
Treatment experienced (%)	12(25%)
Treatment naïve(%)	36(75%)
Mean baseline Hb (gm/dl)	10.489+1.64
Mean baseline ALT(mg/dl)	20.7±12.23
Mean baseline AST(mg/dl)	35.89+16.00
Mean baseline total bilirubin(mg/dl)	.8167±.43148
Mean INR	1.07± .16

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Effect of eradication of hepatitis C virus for liver stiffness measurement using acoustic radiation force impulse elastography in patients with a sustained virological response

Yoshihiko Tachi; Gastroenterology, Komaki city hospital, Komaki, Japan

Abstract Background : Acoustic radiation force impulse (ARFI) elastography is a non-invasive method for measuring liver stiffness. However, there are no reports evaluating the value of ARFI elastography for liver fibrosis in chronic hepatitis C patients with a sustained virological response (SVR). **Aims:** To investigate the diagnostic performance of ARFI elastography and the effect of the duration after eradication of HCV for the liver stiffness using AFRI elastography in hepatitis C virus (HCV) infected patients with an SVR. **Methods:** In this prospective study, we enrolled 336 patients: 121 HCVpatients with an SVR (44.6% women) and 215 patients with HCV (47.9% women). A needle liver biopsy was performed for all patients. ARFI elastography measurements of all patients were performed on the same day of liver biopsy. The post-SVR biopsy was performed 5.9 ± 1.8 years after the end of the therapy. **Results:** The diagnostic accuracies expressed as areas under the receiver operating characteristic curves for ARFI elastography in HCV patients with an SVR and those in patients with HCV were 0.818 and 0.875 for the diagnosis of significant fibrosis (≥F2), 0.909 and 0.888 for the diagnosis of severe fibrosis (≥F3), and 0.981 and 0.890 for the diagnosis of liver cirrhosis (F4), respectively. The respective mean LS values as assessed using ARFI elastography (m/s) for fibrosis stages F0-1, F2, F3,and F4 were 1.10 ± 0.23, 1.22 ± 0.22, 1.35 ± 0.42, and 2.16 ± 0.64 in patients with SVR, and 1.23 ± 0.26, 1.55 ± 0.50, 1.90 ± 0.70, and 2.27 ± 0.58 in patients with HCV infection. The mean LS values as assessed using ARFI elastography were markedly lower in patients with SVR compared with those in patients with HCV infection with regard to the same stage of fibrosis. The mean LS values as assessed using ARFI elastography were compared among patients with HCV, patients with short-term SVR (observation period after SVR< 5.9 years), and patients with long-term SVR (observation period after SVR ≥ 5.9 years) for each fibrosis stage. The respective mean LS values as assessed using ARFI elastography (m/s) for fibrosis stages F0–1, F2–3,and F4 were 1.22 ± 0.26, 1.70 ± 0.61, and 2.27

± 0.58 in patients with HCV, 1.15 ± 0.26, 1.32 ± 0.28, and 2.12 ± 0.53 in patients with short-term SVR, and 1.06 ± 0.20, 1.06 ± 0.22, and 2.24 ± 0.86 in patients with long-term SVR. In patients with F0–1, F2–3, a significant decrease in LS values was observed according to observation period after SVR . **Conclusions:**The liver stiffness values were lower in patients with SVR compared with those in patients with HCV at the same stage of fibrosis. The liver stiffness values were affected by the duration after SVR.

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The Safety and Tolerability of Sofosbuvir/Velpatasvir with Weight Based Ribavirin in Patients with Child-Pugh Class B Cirrhosis in the ASTRAL-4 study

Michael R. Charlton[1], Robert S. Brown[2], Gregory T. Everson[3], Mitchell L. Shiffman[4], Myron J. Tong[5], Mark S. Sulkowski[6], Di An[7], Lingling Han[7], Anu O. Osinusi[7], John McNally[7], Diana M. Brainard[7], Mani Subramanian[7], Jacqueline G. O'Leary[8], Michael P. Curry[9]; [1]Intermountain Medical Center, Murray, UT; [2]Weill Cornell Medical College, NewYork, NY; [3]School of Medicine, University of Colorado Denver, Aurora, CO; [4]Liver Institute of Virginia, Richmond, VA; [5]Huntington Medical Research Institute, Pasadena, CA; [6]Johns Hopkins University, Baltimore, MD; [7]Gilead Sciences, Foster City, CA; [8]Baylor University Medical Center, Dallas, TX; [9]Beth Israel Deaconess Medical Center, Boston, MA

Introduction In the ASTRAL-4 study, HCV infected patients with Child-Pugh B cirrhosis achieved an SVR12 of 96% after 12 weeks of sofosbuvir/velpatasvir (SOF/VEL) and ribavirin (RBV). In contrast with other regimens evaluated in patients with decompensated cirrhosis where RBV dosing was 600 mg/day, weight based RBV dosing (1000-1200 mg/day) was used in the ASTRAL-4 study. This analysis compares the safety and tolerability of SOF/VEL and weight based ribavirin dosing to the safety and tolerability of ledipasvir/sofosbuvir (LDV/SOF) and RBV 600 mg as reported in the SOLAR-1and -2 studies. Methods: Treatment-emergent adverse events and laboratory abnormalities were compared between patients with CPT-B cirrhosis (pretransplant) treated with SOF/VEL with weight-based RBV for 12 weeks in the ASTRAL-4 study and patients treated with LDV/SOF with 600 mg RBV for 12 weeks in the SOLAR-1 and SOLAR-2 studies. The tolerability of RBV was assessed by review of RBV dose modification, dose reductions and discontinuations. Results: Patients treated with SOF/VEL and weight-based RBV had a lower incidence of adverse events (90.8%) compared with patients treated with LDV/SOF and 600 mg RBV (96.6%). However for both regimens most adverse events were mild or moderate in severity and only one patient treated with SOF/VEL with weight-based RBV and one patient treated with LDV/SOF with 600mg RBV had a treatment related serious adverse event. Three patients who received SOF/VEL and weight-based RBV died and one patient who received LDV/SOF with 600mg RBV died; no deaths were assessed as treatment related. Table 1 presents a summary of postbaseline hemoglobin and RBV dose modifications. There was a higher incidence of RBV dose reductions, interruptions and modifications among patients treated with SOF/VEL and weight based RBV compared with patients treated LDV/SOF and 600mg RBV. Conclusions The higher incidence of hemoglobin reductions in HCV infected patients with CPT-B cirrhosis treated with SOF/VEL with weight based RBV compared with patients treated with LDV/SOF with 600 mg RBV was managed with more frequent dose modification of RBV without discontinuation of treatment. This group of patients should be treated by providers experienced in the care of patients with advanced liver disease and the management of RBV associated toxicities.

Hemoglobin and Ribavirin Dose Modifications	ASTRAL-4 CPT-B SOF/VEL+RBV 12 Weeks (N = 87)	SOLAR 1,2 CPT-B LDV/SOF+RBV 12 Weeks (N=58)
Hemoglobin < 10 g/dL, n (%)	20 (23.0)	6 (10.3)
Hemoglobin < 8.5 g/dL, n (%)	6 (6.9)	1 (1.7)
Ribavirin dose reductions, n (%)	33 (37.9)	9 (15.5)
Ribavirin dose interruptions (>3 days), n (%)	4 (4.6)	0
Ribavirin dose discontinuations, n (%)	15 (17.2)	1 (1.7)

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Michael R. Charlton - Consulting: Gilead Sciences; Grant/Research Support: GIlead Sciences, Merck, Janssen, AbbVie, Novartis, Intercept

Robert S. Brown - Advisory Committees or Review Panels: Vital Therapies; Consulting: Gilead, Janssen, Abbvie, Merck, BMS

Gregory T. Everson - Advisory Committees or Review Panels: Roche/Genentech, Abbvie, Galectin, Bristol-Myers Squibb, HepC Connection, BioTest, Gilead, Merck; Board Membership: HepQuant LLC, PSC Partners, HepQuant LLC; Consulting: Abbvie, BMS, Gilead, Bristol-Myers Squibb; Grant/Research Support: Roche/Genentech, Abbvie, Bristol-Myers Squibb, Merck, PSC Partners, Gilead; Management Position: HepQuant LLC, HepQuant LLC; Patent Held/Filed: Univ of Colorado; Speaking and Teaching: Abbvie

Mitchell L. Shiffman - Advisory Committees or Review Panels: Merck, Gilead, Bristol-Myers-Squibb, Abbvie; Grant/Research Support: conatus, Immuron, Merck, Gilead, Galactin, Bristol-Myers-Squibb, Abbvie, Beckman-Coulter, NGMBio, Intercept, Novartis, Eisai, Shire; Speaking and Teaching: Merck, Gilead, Bristol-Myers-Squibb, Abbvie, Intercept

Myron J. Tong - Speaking and Teaching: BMS, Gilead, Genentech

Mark S. Sulkowski - Advisory Committees or Review Panels: Merck, AbbVie, Janssen, Gilead, Trek, Cocrystal; Grant/Research Support: Merck, AbbVie, Janssen, Gilead

Di An - Employment: Gilead Sciences, Inc.

Anu O. Osinusi - Employment: Gilead Sciences Inc; Stock Shareholder: Gilead Sciences Inc

John McNally - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

Diana M. Brainard - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

Jacqueline G. O'Leary - Advisory Committees or Review Panels: Gilead, Intercept, Novartis; Consulting: Abbvie, Fish & Richarson PC; Grant/Research Support: Fisher Scientific; Speaking and Teaching: Gilead, Abbvie, Merck, Astellas; Stock Shareholder: Medfusion

Michael P. Curry - Consulting: Alexion, Bristol Meyers Squib, Abbvie; Grant/Research Support: Gilead Sciences, Conatus

The following people have nothing to disclose: Lingling Han, Mani Subramanian

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Long-Term Clinical Outcomes in HCV Genotype 1-Infected Patients Receiving Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir ± Ribavirin: First interim Safety and Efficacy Results from TOPAZ-I

Kosh Agarwal[1], Emily O. Dumas[2], Giovanni B. Gaeta[3], Sam Lee[4], Adrian Streinu-Cercel[5], Eckart Schott[6], Raul J. Andrade[7], Alma M. Perez[8], Jacob George[9,14], Igor G. Bakulin[10], Rui T. Marinho[11], Resat Ozaras[12], Mariem Charafeddine[2], Li Liu[2], Tami Pilot-Matias[2], Kevin Howieson[2], Melannie Co[2], Daniel E. Cohen[2], Fabien Zoulim[13]; [1]Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, United Kingdom; [2]AbbVie Inc., North Chicago, IL; [3]Second University of Naples, Naples, Italy; [4]University of Calgary, Alberta, AB, Canada; [5]Carol Davila University of Medicine and Pharmacy, National Institute for Infectious Diseases "Prof. Dr. Matei Bals", Bucharest, Romania; [6]Charité Universtätsmedizin Berlin, Berlin, Germany; [7]University Hospital of Málaga, IBIMA, CIBERehd, Andalusia, Spain; [8]Centro de Investifaciòn Farmaceutica Especializada s.ç, Jalisco, Mexico; [9]Westmead Hospital, Westmead Institute for Medical Research, Westmead, Sydney, NSW, Australia; [10]Central Scientific Research Institute for Gastroenterology, Moscow, Russian Federation; [11]Hospital Santa Maria, Medical School of Lisbon, Lisbon, Portugal; [12]Department of Infectious Diseases, Cerrahpasa Medical School, Istanbul University, Istanbul, Turkey; [13]Institut National de la Santé et de la Recherche Médicale, Paris, France; [14]University of Sydney, Sydney, NSW, Australia

Introduction: In phase 3 trials, the 3 direct-acting antiviral (3-DAA) regimen of ombitasvir/paritaprevir/ritonavir (paritaprevir identified by AbbVie and Enanta) and dasabuvir ± ribavirin (RBV) achieved high sustained virologic (SVR) rates with a favorable safety profile in >2300 HCV patients, including those with compensated cirrhosis. TOPAZ-I evaluates the impact of SVR12 on long-term progression of liver disease over 5 years' post-treatment (PT) follow-up in patients with chronic HCV GT1 infection receiving 3-DAA ± RBV. **Methods:** TOPAZ-I is an on-going phase 3b, international, multicenter, open label study which enrolled HCV GT1-infected treatment-naive or interferon-experienced patients without cirrhosis or with compensated cirrhosis across 187 centers in 27 countries. Patients were to receive 3-DAA ± RBV for 12 or 24 weeks, based on subtype and cirrhosis status, as consistent with the approved local labels. First interim results include SVR12 (HCV RNA < LLOQ 12 weeks PT), safety and clinical outcomes. Change in liver fibrosis from baseline was evaluated by FibroScan®. **Results:** 1564 patients received study drug (50% male; 97% White, 15% compensated cirrhosis). 79% (1228/1564) of patients reached SVR12 time point. ITT SVR12 was achieved in 97% (1190/1228) of patients who reached PTW12; 95% and 97% in patients with and without cirrhosis, respectively. In patients who achieved SVR12, mean FibroScan® scores improved over time, with greatest improvements seen in patients with cirrhosis (mean kPa change from baseline to PTW12: F0–F1 = –0.55, F2 = –1.64, F3 = –2.75, F4 = –6.45). In total, 66% (1024/1564) patients experienced an AE, with fatigue (18%), headache (17%), nausea (11%), pruritus (11%), and insomnia (11%) occurring in >10% of patients. The majority of AEs were mild/moderate in severity, 37 (2%) patients experienced serious AEs, 6 (0.4%) patients discontinued study drug due to AEs. Grade 3-4 laboratory abnormalities were rare. Clinical outcomes are reported in the table. **Conclusions:** Data from this large study confirm the efficacy and safety results observed in registrational trials of 3-DAA ± RBV in HCV GT1-infected patients. Preliminary data show a beneficial impact on liver fibrosis; clinical outcomes were infrequent. Updated safety, efficacy and clinical outcomes will be presented.

Patients with clinical outcomes, n (%)	3-DAA±RBV (N=1564)
Any clinical outcome	9 (0.6)
Death*	2 (0.1)
Liver decompensation-related events†	6 (0.4)
Liver transplantation	0
HCC	2 (0.1)

*n=1 pneumonia leading to hepatic decompensation and multiple organ failure; n=1 ischemic heart disease
†Includes ascites, variceal bleeding, or hepatic encephalopathy

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Kosh Agarwal - Advisory Committees or Review Panels: Gilead, BMS, Novartis, Janssen, AbbVie; Consulting: MSD, Janssen, Achillion, Intercept; Grant/Research Support: Roche, Gilead, BMS, Arbutus; Speaking and Teaching: Astellas, Gilead, BMS, GSK

Emily O. Dumas - Employment: AbbVie; Stock Shareholder: AbbVie

Giovanni B. Gaeta - Advisory Committees or Review Panels: Janssen, Merck, Abbvie, Roche; Speaking and Teaching: BMS, Gilead, merck

Sam Lee - Employment

Eckart Schott - Advisory Committees or Review Panels: Gilead, Roche, Bayer, BMS, Abbvie, Janssen, MSD; Speaking and Teaching: Gilead, Novartis, Roche, MSD, Bayer, Falk, BMS, Janssen, Abbvie

Alma M. Perez - Advisory Committees or Review Panels: GILEAD, LA ROCHE, ABBVIE, MSD; Grant/Research Support: JANSSEN; Speaking and Teaching: GILEAD, LA ROCHE, ABBVIE, JANSSEN, BMS, MSD

Jacob George - Advisory Committees or Review Panels: Pharmaxis, BMS, MSD, Gilead, Janssen, Abbvie; Grant/Research Support: MSD

Rui T. Marinho - Advisory Committees or Review Panels: Abbvie, MSD, BMS, Janssen, Bayer

Mariem Charafeddine - Employment: AbbVie Ltd; Stock Shareholder: AbbVie Ltd

Tami Pilot-Matias - Employment: AbbVie; Stock Shareholder: Abbott

Kevin Howieson - Employment: AbbVie

Daniel E. Cohen - Employment: AbbVie; Stock Shareholder: AbbVie

Fabien Zoulim - Advisory Committees or Review Panels: Janssen, Gilead, Novira, Abbvie, Arbutus, Transgene; Consulting: Roche; Grant/Research Support: Novartis, Gilead, Scynexis, Roche, Novira, Assemblypharm, Janssen; Speaking and Teaching: Bristol Myers Squibb, Gilead

The following people have nothing to disclose: Adrian Streinu-Cercel, Raul J. Andrade, Igor G. Bakulin, Resat Ozaras, Li Liu, Melannie Co

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Combined resistance, demographic, and phylogenetic analyses of HCV genotype 4-infected patients treated with ombitasvir/paritaprevir/r ± ribavirin in the PEARL-I and AGATE-1 studies

Gretja Schnell, Rakesh Tripathi, Jill Beyer, Thomas Reisch, Coleen Hall, Yao Yu, Niloufar Mobashery, Tami Pilot-Matias, Christine Collins; AbbVie Inc., North Chicago, IL

Background: An HCV regimen containing ombitasvir (NS5A inhibitor) and paritaprevir (NS3 protease inhibitor identified by AbbVie and Enanta) with ritonavir [OBV/PTV/r] plus ribavirin (RBV) is highly efficacious for the treatment of HCV genotype (GT) 4 infection. We utilized a large dataset of NS5A sequences containing diverse HCV GT4 subtypes isolated from patients treated with OBV/PTV/r ± RBV to assess genetic diversity by geographic region, analyze patient demographics and baseline sequence variability across GT4 subtypes, and report the development of viral resistance in virologic failure (VF) patients. **Methods:** The full-length NS5A gene was sequenced by population or next-generation sequencing (NGS) from the baseline samples of 132 non-cirrhotic (PEARL-I) or 118 cirrhotic (AGATE-1) GT4-infected patients. NS5A sequences were included in a phylogenetic analysis to assess genetic relationships among and within GT4 subtypes by country. The prevalence of baseline polymorphisms and treatment-emergent resistance-associated variants (RAVs) in NS5A were analyzed. **Results:** Sixteen GT4 subtypes were identified in the combined dataset (4a, 4b, 4c, 4d, 4e, 4f, 4h, 4k, 4l, 4n, 4o, 4p, 4q, 4r, 4t, 4). Subtype prevalence varied by country of enrollment, and in study AGATE-1 the subtype prevalence by country of

origin was closely associated with the reported distribution of GT4 subtypes in Africa, Europe, and North America. A phylogenetic analysis of NS5A sequences revealed two sequence clusters within subtype 4a which correlated with the country of origin for each sample; one cluster contained sequences from Egypt and the Middle East, while the second cluster contained sequences originating from Europe. Baseline demographics analyses also revealed that the distribution of patient race was significantly different across GT4 subtypes 4a, 4d, and non-4a/4d. Baseline amino acid variability in NS5A was frequently detected across GT4 subtypes but had no impact on treatment outcome. Overall 5 out of 255 patients experienced VF, of which 1 was infected with GT4a and 4 were infected with GT4d, and the predominant RAVs at the time of failure were D168V in NS3/4A and L28I/S/V or Y93H in NS5A. **Conclusions:** Overall, high response rates were observed among patients infected with 16 HCV GT4 subtypes with no impact of NS5A baseline polymorphisms on treatment outcome. GT4 subtype distribution differed based on patient demographics and geography. Two phylogenetic clusters within subtype 4a were found to segregate by country of origin and suggest a genetically distinct strain of 4a circulating in Egypt versus Europe.

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Gretja Schnell - Employment: AbbVie Inc.; Stock Shareholder: AbbVie Inc.

Rakesh Tripathi - Employment: AbbVie; Stock Shareholder: AbbVie

Jill Beyer - Employment: Abbvie; Stock Shareholder: Abbvie

Thomas Reisch - Employment: Abbvie; Stock Shareholder: Abbvie

Coleen Hall - Employment: AbbVie; Stock Shareholder: AbbVie

Yao Yu - Employment: Abbvie

Niloufar Mobashery - Employment: Abbvie; Stock Shareholder: abbvie

Tami Pilot-Matias - Employment: AbbVie; Stock Shareholder: Abbott

Christine Collins - Employment: AbbVie

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Safety of Sofosbuvir-Based Regimens for the Treatment of Chronic HCV Infection in Patients with Mild or Moderate Renal Impairment

Francois Durand[2], Stephen Pianko[3], Liyun Ni[1], Shampa De-Oertel[1], John McNally[1], Diana M. Brainard[1], John G. McHutchison[1], Eugene R. Schiff[4], Massimo Colombo[5]; [1]Gilead Sciences, Inc, Foster City, CA; [2]AP-HP Hôpital Beajon, Clichy, France; [3]Monash Medical Center, Clayton, VIC, Australia; [4]Schiff Center for Liver Disease, University of Miami, Miami, FL; [5]Gastroenterology, IRCCS Maggiore Hospital University of Milan, Milan, Italy

Background: The major metabolite of sofosbuvir (SOF), GS-331007, is cleared renally and accumulates in severe renal impairment or end stage renal disease. Although these populations were excluded from most Phase 2 and 3 clinical trials, patients with mild and moderate renal impairment were enrolled. This retrospective analysis presents the safety profile of SOF-based therapies in these groups. **Methods**: Safety data from patients with or without compensated cirrhosis enrolled in 48 Phase 2 or 3 studies of SOF+RBV, LDV/SOF±RBV, and SOF/VEL±RBV were assessed according to +/-RBV and degree of renal impairment: normal renal function (estimated glomerular filtration rate [eGFR; using the Cockcroft-Gault equation] >80 ml/min), mild renal impairment (eGFR 50-80 mL/min), or moderate renal impairment (eGFR 30-49 mL/min). **Results:** 11,111 patients were included in this analysis; 2,186 (20%) had mild or moderate renal impairment at baseline. Mean eGFR was 119, 69, and 44 mL/min for patients with normal renal function (n=8925), mild (n=2043), or moderate (n=143) renal impairment, respectively. Baseline characteristics were generally similar across groups, except patients with impaired renal function were older. Table 1 provides a summary of adverse events (AEs). Patients receiving RBV had higher rates of Grade 3-4 AEs, SAEs, and discontinuations as compared to patients not receiving RBV; this difference was more pronounced among those with renal impairment. Among patients not receiving RBV, there were similar rates of Grade 3-4 AEs and discontinuations due to AE across groups. Patients with moderate renal impairment had higher rates of SAEs but most were not treatment-related. **Conclusions:** Treatment with SOF-based regimens was well-tolerated in patients with mild or moderate renal impairment. Differences were seen in RBV tolerability between patients with moderate renal impairment, compared to those with no or mild renal impairment.

Overall Summary of Safety in Patients Treated with a SOF-containing Regimen According to Renal Function and the Presence of RBV

Subjects Experiencing Adverse Events N (%)	Normal Renal Function +RBV n=5863	Normal Renal Function -RBV n=3062	Mild Renal Impairment +RBV N=1239	Mild Renal Impairment -RBV N=804	Moderate Renal Impairment +RBV N=93	Moderate Renal Impairment -RBV N=50
Gr 3-4 AE	401 (7)	109 (4)	125 (10)	25 (3)	30 (32)	3 (6)
SAE	232 (4)	96 (3)	79 (6)	23 (3)	24 (26)	6 (12)
Treatment-Related SAE	37 (0.6)	8 (0.3)	13 (1)	1 (0.1)	9 (10)	1 (2)
Treatment Discontinuation due to AE	112 (2)	12 (0.4)	46 (4)	0	16 (17)	0
Death	17 (0.3)	5 (0.2)	7 (0.6)	3 (0.4)	4 (4)	0

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Francois Durand - Advisory Committees or Review Panels: Astellas, Novartis, BMS; Speaking and Teaching: Gilead

Stephen Pianko - Advisory Committees or Review Panels: Roche, Novartis, GILEAD, Roche, Novartis; Consulting: GILEAD; Speaking and Teaching: JANSSEN, BMS

Shampa De-Oertel - Employment: Gilead Sciences, Inc; Stock Shareholder: Gilead Sciences, Inc

John McNally - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

Diana M. Brainard - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

John G. McHutchison - Employment: gilead; Stock Shareholder: gilead

Eugene R. Schiff - Advisory Committees or Review Panels: Bristol Myers Squibb, Gilead, Merck, Janssen, Salix Pharmaceutical, Pfizer, Arrowhead, Astrazeneca, CVS; Consulting: Acorda; Grant/Research Support: Bristol Myers Squibb, ABBVIE, Gilead, Merck, Conatus, Medmira, Roche Molecular, Janssen, Orasure Technologies, Discovery Life Sciences, Siemens, Beckman Coulter, Siemens, Ortho JNH, Intercept, Beckman

Massimo Colombo - Advisory Committees or Review Panels: Gilead Sciences, Abbvie, BMS, Bayer, Merck; Speaking and Teaching: Gilead Sciences, Abbvie, BMS, Bayer, Merck, Janssen, Sanofi, Vertex

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♦ Denotes AASLD Presidential Poster of Distinction

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Safety and Tolerability of Direct Acting Antiviral Agents (DAAs) Used in Usual Clinical Practice: HCV-TARGET International Consortium

Michael W. Fried[1], K. Rajender Reddy[4], Mitchell L. Shiffman[5], Stefan Zeuzem[6], Norah Terrault[8], Alexander Kuo[7], Paul J. Pockros[9], Mark S. Sulkowski[11], Michael P. Manns[12], Jacqueline G. O'Leary[10], Lucy Akushevich[1], Monika Vainorius[1], David R. Nelson[3], Joseph K. Lim[2]; [1]University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]School of Medicine, Yale, New Haven, CT; [3]Medicine, University of Florida, Gainesville, FL; [4]Hepatology, University of Pennsylvania, Philadelphia, PA; [5]Liver Institute of Virginia, Bon Secours, Richmond, VA; [6]Medicine, Goethe University Hospital, Frankfurt, Germany; [7]Medicine, University of California San Diego, San Diego, CA; [8]Medicine, University of California, San Francisco, San Francisco, CA; [9]Medicine, Liver Disease Center Scripps Clinic, La Jolla, CA; [10]Medicine, Baylor, Dallas, TX; [11]Medicine, Johns Hopkins, Baltimore, MD; [12]Medicine, Hannover Medical School, Hannover, Germany

DAAs have an outstanding safety profile in phase III trials. Post-marketing surveillance has generated additional safety warnings about drug interactions and restricted use in decompensated cirrhosis. **Aim:** To evaluate detailed safety data across a broad spectrum of patients treated with DAAs in usual clinical practice. **Methods:** Patients enrolled in HCV-TARGET were treated according to regional standards of care at academic (n=38) and community medical centers (n=13) in North America (n=47) and Europe (n=4). Detailed information on demographics, clinical course, and adverse events (AEs) was abstracted from medical records into a centralized data core. Data monitors systematically reviewed data for accuracy. **Results:** From Jan 2014 to May 2016, 5590 patients (pts) were treated with oral DAAs including 2483 (44%) pts with cirrhosis of whom 1145 (46.1%) had evidence of prior hepatic decompensation. Regimens included SOF+RBV (n=782), SOF+SMV+/- RBV (n=1213), LDV/SOF+/-RBV (n=2542), PrOD+/-RBV (n=656), PrO+/-RBV (n=13) and SOF+DCV+/-RBV (n=384). Therapy was completed in 4971 (89%). Early discontinuation due to AEs occurred in 101 (1.8%), and was higher among RBV-containing vs RBV-free regimens (55/2097, 2.6%) vs (46/3493, 1.3%). Deaths were reported in 39 pts from a variety of causes. An increase in bilirubin of ≥ 3mg/dl over baseline ($bilirubin_{\Delta 3}$) occurred in 110/4678 (2.4%) pts with evaluable data, of whom 25 (22.7%) prematurely discontinued treatment. Severe $bilirubin_{\Delta 5}$ (≥5mg/dl above baseline) occurred in 48 pts, of whom only 3 (6.3%) had concomitant ALT elevation, and 9 (18.8%) died. 32 pts had $bilirubin_{\Delta 3}$ associated with biliary tract disease, sepsis, or transplantation. In multivariable logistic analyses excluding those patients, cirrhosis, prior hepatic decompensation, low albumin, and higher baseline bilirubin were associated with $bilirubin_{\Delta}$ during treatment. De novo hepatic decompensation occurred in 41/1338 (3.1%) previously compensated cirrhotic pts whereas secondary decompensating events among those with a prior history of decompensation was higher (198/1145, 17.3%). Ribavirin use was associated with secondary hepatic decompensation in the latter group, (OR 2.82, 95% CI 1.96-4.12, p<0.01). **Conclusions:** The event rate for hyperbilirubinemia and decompensation was low, even among patients with advanced cirrhosis, and infrequently led to premature discontinuation of therapy. Features of advanced cirrhosis were associated with increased risk for AEs. Of note, ribavirin independently increases risk of hepatic decompensation. Severe hyperbilirubinemia and clinical sequelae usually occur in the absence of ALT elevations and deserve further scrutiny.

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Michael W. Fried - Consulting: Merck, Abbvie, Janssen, Bristol Myers Squibb, Gilead; Grant/Research Support: Merck, AbbVie, Janssen, Bristol Myers Squibb, Gilead; Stock Shareholder: TARGET PharmaSolutions

K. Rajender Reddy - Advisory Committees or Review Panels: Merck, Janssen, BMS, Abbvie, Gilead; Grant/Research Support: Merck, BMS, Gilead, Janssen, Abbvie

Mitchell L. Shiffman - Advisory Committees or Review Panels: Merck, Gilead, Bristol-Myers-Squibb, Abbvie; Grant/Research Support: conatus, Immuron, Merck, Gilead, Galactin, Bristol-Myers-Squibb, Abbvie, Beckman-Coulter, NGMBio, Intercept, Novartis, Eisai, Shire; Speaking and Teaching: Merck, Gilead, Bristol-Myers-Squibb, Abbvie, Intercept

Stefan Zeuzem - Consulting: Abbvie, Bristol-Myers Squibb Co., Gilead, Merck & Co., Janssen

Norah Terrault - Advisory Committees or Review Panels: Eisai, Biotest; Consulting: BMS, Merck, Achillion, CoCrystal; Grant/Research Support: Eisai, Biotest, Vertex, Gilead, AbbVie, Novartis, Merck

Paul J. Pockros - Advisory Committees or Review Panels: Janssen, Merck, BMS, Gilead, AbbVie; Consulting: Lumena, Beckman Coulter; Grant/Research Support: Intercept, Janssen, BMS, Gilead, Lumena, Beckman Coulter, AbbVie, RMS, Merck; Speaking and Teaching: AbbVie, Janssen, Gilead

Mark S. Sulkowski - Advisory Committees or Review Panels: Merck, AbbVie, Janssen, Gilead, Trek, Cocrystal; Grant/Research Support: Merck, AbbVie, Janssen, Gilead

Michael P. Manns - Consulting: Roche, BMS, Gilead, Boehringer Ingelheim, Novartis, Enyo Pharma, Eiger, GSK, Merck/MSD, Janssen, Medgenics, Biotest, AbbVie; Grant/Research Support: Merck/MSD, Roche, Gilead, Novartis, Boehringer Ingelheim, BMS, AbbVie, Janssen; Speaking and Teaching: Merck/MSD, Roche, BMS, Gilead, Janssen, GSK, Novartis, AbbVie

Jacqueline G. O'Leary - Advisory Committees or Review Panels: Gilead, Intercept, Novartis; Consulting: Abbvie, Fish & Richarson PC; Grant/Research Support: Fisher Scientific; Speaking and Teaching: Gilead, Abbvie, Merck, Astellas; Stock Shareholder: Medfusion

David R. Nelson - Grant/Research Support: Abbvie, BMS, Gilead, Merck, Janssen

Joseph K. Lim - Consulting: Bristol Myers Squibb, Gilead; Grant/Research Support: Bristol Myers Squibb, Gilead

The following people have nothing to disclose: Alexander Kuo, Lucy Akushevich, Monika Vainorius

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Concomitant Proton Pump Inhibitor Use Does Not Reduce the Efficacy of Elbasvir/Grazoprevir

Nancy Reau[1], Michael Robertson[2], Hwa-Ping Feng[2], Luzelena Caro[2], Wendy W. Yeh[2], Bach-Yen T. Nguyen[2], Janice Wahl[2], Eliav Barr[2], Peggy Hwang[2], Stephanie O. Klopfer[2]; [1]Rush University Medical Center, Chicago, IL; [2]Merck & Co., Inc., Kenilworth, NJ

Background: It is estimated that up to one-third of hepatitis-C virus (HCV)-infected patients use proton pump inhibitors (PPIs) and other acid reducing agents. Concomitant PPI use with some NS5A inhibitors impacts the pharmacokinetics (PK) of direct-acting antiviral agents (DAAs), potentially reducing efficacy. Phase I study results demonstrated no effect of PPI use on the PK of the fixed-dose combination of elbasvir/grazoprevir (EBR/GZR) in healthy volunteers. This *post hoc* analysis of studies in the Phase 3 clinical program of EBR/GZR assessed the 12-week sustained viral response (SVR12) in subjects with self-reported PPI use and the PK of EBR/GZR in these patients. **Methods**: Data were derived from six Phase 3 EBR/GZR trials with treatment-naïve or treatment experienced GT1/4-infected subjects, with or without cirrhosis. Analyses were done in the modified Full Analysis Set population (excludes administrative discontinuations). Self-reported baseline PPI use was defined as ≥7 consecutive days of use between Day -7 and Day 7. Bivariate analyses assessed PPI use and other factors associated with SVR, with gender, age (continuous and dichotomous), cirrhosis status, prior treatment status, baseline HCV RNA (continuous and dichotomous), HCV genotype, and baseline resistance associated variants as variables in the models. **Results**: Overall, 12% (162/1322) of EBR/GZR-treated subjects reported baseline use of PPIs. Of those, 155/162 (96%) achieved SVR12. In

patients without PPI use, 1129/1160 (97%) achieved SVR12. PPI use was not a predictive factor in achieving SVR12 based on a univariate analysis (p = 0.188). In the bivariate models, none of the interaction terms was statistically significant, indicating that any potential effects of PPI were consistent across the factors considered. In addition, PPI usage was not a statistically significant effect, regardless of adjustment for the factors considered. From 3 of the 6 studies for which population PK data were available, the estimated AUC and Cmax values for EBR were comparable among patients with and without reported PPI use (table). **Conclusions**: These results demonstrate that PPIs use with EBR/GZR has no clinically significant effect on SVR12 rates in GT1/4-infected patients with and without cirrhosis.

	SVR12 Achieved?	Baseline PPI Use	Baseline PPI Use GM (95% CI)	No Baseline PPI Use	No Baseline PPI Use GM (95% CI)
EBR GM AUC0-24*, nM•Hr	Yes	n=81	2732.8 (2523.3, 2959.6)	n=617	2331.0 (2264.7, 2399.4)
EBR GM AUC0-24*, nM•Hr	No	n=5	1941.8 (1368.8, 2754.7)	n=19	2030.3 (1696.9, 2429.3)
EBR GM Cmax*, nM	Yes	n=81	165.6 (153.6, 178.6)	n=617	148.6 (144.6, 152.7)
EBR GM Cmax*, nM	No	n=5	121.4 (88.4, 166.7)	n=19	133.1 (113.1, 156.6)

AUC=area under the curve; GM=geometric mean

*Estimated using population PK modeling

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Nancy Reau - Advisory Committees or Review Panels: Jannsen, Merck, AbbVie, Intercept, Salix, BMS, Gilead; Grant/Research Support: Gilead, Intercept, AbbVie

Michael Robertson - Employment: Merck; Stock Shareholder: Merck

Hwa-Ping Feng - Employment: Merck

Luzelena Caro - Employment: Merck & Co., Inc.

Wendy W. Yeh - Employment: Merck

Bach-Yen T. Nguyen - Employment: Merck

Janice Wahl - Employment: Merck & Co,

Eliav Barr - Employment: Merck; Stock Shareholder: Merck

Peggy Hwang - Employment: Merck, Merck

Stephanie O. Klopfer - Employment: Merck & Co., Inc.

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Protease inhibitor resistance remains even after mutant strains become undetectable using ultra-deep sequencing

Hiromi Kan[1,2], Michio Imamura[1,2], Nobuhiko Hiraga[1,2], C. Nelson Hayes[1,2], Takuro Uchida[1,2], Eisuke Miyaki[1,2], Masataka Tsuge[1,2], Hiromi Abe-Chayama[1,2], Hiroshi Aikata[1,2], Daiki Miki[1,2], Hidenori Ochi[1,2], Yuji Ishida[3], Chise Tateno[3], Kazuaki Chayama[1,2]; [1]Department of Gastroenterology and Metabolism, Applied Life Sciences, Institute of Biomedical & Health Sciences, Hiroshima University, Hiroshima, Japan; [2]Liver Research Project Center, Hiroshima University, Hiroshima, Japan; [3]PhoenixBio Co., Ltd., Higashihiroshima, Japan

Background: Although treatment-emergent NS3/4A protease inhibitor (PI)-resistant variants typically decrease in frequency after cessation of PI therapy in chronic hepatitis C patients, susceptibility to PIs in patients who have previously failed to respond to PI therapy has not been addressed. ***Methods***: A total of 406 genotype 1 chronic hepatitis C patients who had detectable drug resistant-associated variants (RAVs) in neither HCV NS5A-L31 nor -Y93 prior to the treatment as determined by Invader assay were treated with daclatasvir plus asunaprevir. Human hepatocyte chimeric mice were injected with serum samples obtained either from treatment-naïve patients or daclatasvir plus asunaprevir non-responders, then treated with simeprevir and sofosbuvir or telaprevir. The nucleotide and amino acid sequences of resistance-associated regions of NS3 and NS5A were determined by deep sequencing. ***Results***: Sustained virological response (SVR) was achieved in 95.0% (377 out of 397) of DAA treatment-naïve patients, whereas in only 33.3% (3 out of 9) of patients who experienced simeprevir plus PEG-IFN/RBV treatment failure (*P = 0.0001*). Multivariate logistic regression analysis identified history of simeprevir treatment (odds ratio, 56.6 for absence; *P*<0.001) as an independent predictor for SVR. After viral breakthrough with daclatasvir and asunaprevir treatment, NS5A-L31/Y93 RAVs persisted at high frequencies. In contrast, deep sequencing analysis showed that the frequency of NS3-D168 RAVs gradually decreased and were completely replaced by wild-type after cessation of therapy. Mice injected with serum from a DAA-naïve patient or the daclatasvir plus asunaprevir non-responder were treated with simeprevir alone or sofosbuvir in combination with either simeprevir or telaprevir. Both simperevir alone and simperevir plus sofosbuvir treatments resulted in a rapid emergence of the NS3-D168 mutation at significantly higher frequencies in mice injected with serum from the daclatasvir and asunaprevir non-responder compared to mice injected with serum from the DAA naïve patient. In contrast to sofosbuvir plus simeprevir treatment, sofosbuvir plus telaprevir treatment reduced serum HCV RNA levels sustainably, and emergence of NS3-D168 RAVs was suppressed in mice injected with serum from the daclatasvir and asunaprevir non-responder. ***Conclusions*:** Virological response to daclatasvir plus asunaprevir treatment was low in patients with simeprevir plus PEG-IFN/RBV treatment failure. PI resistance remains even after disappearance of mutant strains by ultra-deep sequencing. DAA combination therapy without NS3/4A PIs is recommended for patients who failed NS3/4A PI treatment.

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Michio Imamura - Grant/Research Support: Bristol-Meyers Squibb; Speaking and Teaching: Bristol-Meyers Squibb

Yuji Ishida - Employment: PhoenixBio Co., Ltd.

Chise Tateno - Board Membership: PhoenixBio Co., Ltd.

Kazuaki Chayama - Advisory Committees or Review Panels: Mitsubishi Tanabe, Taisho Toyama; Consulting: AbbVie; Grant/Research Support: Ajinomoto, AbbVie, Aska, Asstellas, Aska, Bristol Squibb, Daiichi Sankyo, Dainippon Sumitomo, Daiichi Sankyo, Eisai, GlaxoSmithKline, Mitsubishi Tanabe, Nippon Kayaku, Otsuka, Sogo Rinsho M√©d√©fi, Taiho, Takeda, Toray, Torii, Tsumura, Zeria; Speaking and Teaching: Abbott, AbbVie, Ajinomoto, Astellas, AstraZeneca, Bayer, Bristol Squibb, Chugai, Dainippon Sumitomo, Eidia, Eisai, Gilead, GlaxoSmithKline, JIMRO, Johnson & Johnson, Mitsubishi Tanabe

The following people have nothing to disclose: Hiromi Kan, Nobuhiko Hiraga, C. Nelson Hayes, Takuro Uchida, Eisuke Miyaki, Masataka Tsuge, Hiromi Abe-Chayama, Hiroshi Aikata, Daiki Miki, Hidenori Ochi

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HCV reinfection and injecting risk behavior following elbasvir/grazoprevir treatment in patients on opioid agonist therapy: Co-STAR Three Year Follow-up Study

Gregory Dore[1], Jason Grebely[1], Frederick Altice[2], Alain H. Litwin[3], Olav Dalgard[4], Edward J. Gane[5], Oren Shibolet[6], Anne Luetkemeyer[7], Ronald Nahass[8], Cheng-Yuan Peng[9], Brian Conway[10], David M. Iser[11], Hsueh-cheng Huang[12], Isaias N. Gendrano[12], Michelle M. Kelly[12], Peggy Hwang[12], Michael Robertson[12], Janice Wahl[12], Eliav Barr[12], Heather L. Platt[12]; [1]UNSW Australia, Sydney, NSW, Australia; [2]Yale University, New Haven, CT; [3]Albert Einstein/Montefiore Medical Center, Bronx, NY; [4]Akershus University, Oslo, Norway; [5]Aukland City Hospital, Aukland, New Zealand; [6]Liver Unit, Department of Gastroenterology, Tel-Aviv Medical Center and Tel-Aviv University, Tel-Aviv, Israel; [7]University of California, San Francisco, CA; [8]ID Care, Hillsboro, NJ; [9]China Medical University Hospital, Taichung, Taiwan; [10]Vancouver Infectious Diseases Centre, Vancouver, BC, Canada; [11]St. Vincent's Hospital, Melborne, VIC, Australia; [12]Merck & Co., Inc., Kenilworth, NJ

Background/Purpose: High rates of efficacy were observed in Co-STAR, a Phase 3 trial of 12 weeks of elbasvir/grazoprevir (EBR; HCV NS5A inhibitor) / GZR; HCV NS3/4A protease inhibitor) in patients on opioid agonist therapy (OAT). HCV reinfection was observed in 6/296 (2%) of patients between the end of treatment (EOT) and follow-up week 24. The aim of the Co-STAR Three Year Follow-up Study (3YFU) is to evaluate HCV reinfection and injecting risk behaviors in patients treated with EBR/GZR. **Methods**: This 3 year observational cohort study enrolled patients who received at least one dose of EBR/GZR in the Phase 3 trial. Every 6 months, patients are tested for HCV RNA and if detected, viral genotype and sequencing are performed. Patients complete a questionnaire to assess drug use. **Results**: Of 296 patients treated in Co-STAR, 185 patients (63%) were enrolled in the 3YFU. Patients who enrolled in the 3YFU were generally representative of the parent trial: average age, 49 years; males, 76%, white race, 79%; GT1a, 73%; GT1b, 19%; GT4, 7%; GT6, 1%. Sixty percent and 58% of patients in the 3YFU study and the Phase 3 trial had a positive urine drug screen (UDS) result at enrollment, respectively. The median time from EOT to the first visit during the 3YFU was 330 days (range: 206-485). In addition to the 6 reinfections observed between EOT and follow-up week 24, two viral recurrences were identified at the first visit in the 3YFU. One patient had GT1a at baseline: the patient reported non-injection drug use (intranasal cocaine, inhaled amphetamines, inhaled cannabinoids) at follow-up, GT3 was identified, and opiates and cannabinoids were detected by UDS. One patient had GT1b at baseline, had HCV RNA (258 IU/mL) detected at the first visit; however, the genotype was unable to be determined due to low viral load, no drug use was reported by the patient for the previous 6 months, and no drugs besides OAT were detected by UDS; this patient is not considered a reinfection while additional follow-up is pending. Of the 185 patients in the 3YFU, 108 (58%) reported any drug use (non-injecting or injecting) in the past 6 months. Injecting drug use in the past 6 months was reported by 47 (25%) patients. Among those reporting injecting drug use in the past 6 months (n=47 patients), injected drugs included heroin (n=34; 72%), amphetamines (n=8; 17%), cocaine (n=7; 15%), and other opioids (n=7; 15%). **Conclusion**: HCV reinfection among patients on opioid agonist therapy following elbasvir/grazoprevir treatment is uncommon despite ongoing drug use. Additional follow-up is ongoing.

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Gregory Dore - Board Membership: Gilead, Merck, Abbvie, Bristol-Myers Squibb; Grant/Research Support: Gilead, Merck, Abbvie, Bristol-Myers Squibb; Speaking and Teaching: Gilead, Merck, Abbvie, Bristol-Myers Squibb

Jason Grebely - Advisory Committees or Review Panels: Merck, Gilead; Grant/Research Support: Merck, Gilead, Abbvie, BMS

Frederick Altice - Grant/Research Support: Gileaad, NIH, NIDA, SAMHSA, HRSA; Speaking and Teaching: Merck, Bristol Myers Squibb, Gilead, Rush Practice Point Communications

Alain H. Litwin - Advisory Committees or Review Panels: Merck, Gilead, BMS, Janssen; Grant/Research Support: Merck, Gilead

Olav Dalgard - Advisory Committees or Review Panels: MSD, Janssen Cilag, Medivir, Gilead, Abbvie; Grant/Research Support: MSD, Medivir, Gilead, Abbvie

Edward J. Gane - Advisory Committees or Review Panels: AbbVie, Janssen, Gilead Sciences, Achillion, Merck; Speaking and Teaching: AbbVie, Gilead Sciences, Merck, Alnylam

Anne Luetkemeyer - Grant/Research Support: Gilead, Abbvie, Bristol Myers Squibb, Merck

Ronald Nahass - Advisory Committees or Review Panels: Gilead, Merck, Janssen, BMS; Grant/Research Support: Gilead, Merck, Janssen, BMS

Cheng-Yuan Peng - Advisory Committees or Review Panels: AbbVie, BMS, Gilead, MSD, Roche

Brian Conway - Advisory Committees or Review Panels: AbbVie, Gilead, Merck; Grant/Research Support: AbbVie, Gilead, Merck, Pendopharm, Jannsen; Speaking and Teaching: AbbVie, Gilead, Merck

David M. Iser - Speaking and Teaching: AbbVie, Bristol Myers Squibb, Gilead, Janssen, Merck, Roche

Hsueh-cheng Huang - Employment: Merck; Stock Shareholder: Merck

Isaias N. Gendrano - Employment: Merck Sharp & Dohme Corp; Stock Shareholder: Merck Sharp & Dohme Corp

Peggy Hwang - Employment: Merck, Merck

Michael Robertson - Employment: Merck; Stock Shareholder: Merck

Janice Wahl - Employment: Merck & Co,

Eliav Barr - Employment: Merck; Stock Shareholder: Merck

Heather L. Platt - Employment: Merck

The following people have nothing to disclose: Oren Shibolet, Michelle M. Kelly

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GEODE-II: Efficacy and Safety of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir with Low-Dose Ribavirin QD in Patients with Genotype 1a Chronic Hepatitis C Virus Infection without Cirrhosis

Fred Poordad[1], Shahriar Sedghi[2], Paul J. Pockros[12], Natarajan Ravendhran[3], Robert Reindollar[4], Michael R. Lucey[5], Michael S. Epstein[6], Leslie Bank[7], David E. Bernstein[8], Roger Trinh[9], Preethi Krishnan[9], Tami Pilot-Matias[9], Akshanth R. Polepally[9], Rajvineeth K. Pothacamury[9], Kristina Unnebrink[10], Marisol Martinez[9], David R. Nelson[11]; [1]Texas Liver Institute, University of Texas Health Science Center, San Antonio, TX; [2]Associate Professor of Medicine and Surgery, Mercer University School of Medicine, Macon, GA; [3]Digestive Disease Associates, Baltimore, MD; [4]Piedmont Healthcare/Carolinas Center for Liver Disease, Statesville, NC; [5]Division of Gastroenterology/Hepatology, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI; [6]Anne Arundel Medical Center, Digestive Disorders Associates, Annapolis, MD; [7]Principal Investigator, Regional Clinical Research Inc., Endwell, NY; [8]Hofstra Northwell School of Medicine, Manhasset, NY; [9]AbbVie Inc., North Chicago, IL; [10]AbbVie Deutschland GmbH&Co KG, Ludwigshafen, Germany; [11]Department of Medicine, University of Florida, Gainesvillle, FL; [12]Division of Gastroenterology/Hepatology, Scripps Clinic, La Jolla, CA

BACKGROUND: Ribavirin (RBV) is a component of guidelines-recommended treatment regimens for certain patient populations with hepatitis C virus (HCV) infection, and is known to cause decreases in hemoglobin and/or elevations of indirect bilirubin. RBV is typically administered at a weight-based daily dosage of 1000–1200 mg. In this study, we investigated the safety and efficacy of the direct-acting antiviral agents (DAAs) ombitasvir/paritaprevir (identified by AbbVie and Enanta)/ritonavir (OBV/PTV/r) plus dasabuvir (DSV) with a fixed low dose of RBV in patients with genotype 1a (GT1a) chronic HCV

infection without cirrhosis. **METHODS:** GEODE-II is a Phase 3, open-label, multi-center study designed to evaluate the safety and efficacy of OBV/PTV/r+DSV co-administered with low-dose RBV (600 mg QD) for 12 weeks in GT1a HCV-infected patients without cirrhosis, who are either HCV treatment-naïve (TN) or treatment-experienced (TE) to previous interferon (IFN) or pegylated IFN ± RBV therapy. Efficacy is assessed by sustained virologic response at post-treatment week 12 (SVR12) compared with historic SVR12 rates for the same regimen coadministered with weight based RBV. Safety is assessed in all patients receiving at least 1 dose of study drugs. Results will be presented for the intent-to-treat (ITT) and modified (m) ITT (excluding discontinuations due to non-viral failures and non-drug related AEs) populations. **RESULTS:** A total of 105 patients (52% female, 86% white) were enrolled in this study, of whom 89% were TN. As of the data cut-off date (May 11, 2016) 79 patients reached the end of treatment. The SVR4 rate was 94% for the 71 ITT patients who reached post-treatment week 4. AEs were mostly mild or moderate in severity, with fatigue (25%), headache (13%) and insomnia (11%) the most frequently reported. One patient had a breakthrough, 1 patient relapsed, 3 patients discontinued study drug for non-viral failures and 1 patient was discontinued due to a drug related AE. No subjects required RBV dose reduction as per protocol. Grade 1 hemoglobin-level abnormalities were reported in 15/104 patients (14%) during the treatment period, while both grade 1 (n=9, 9%) and grade 2 (n=5, 5%) elevated total bilirubin levels were reported. Full safety data and SVR12 rates will be available at the meeting. **CONCLUSIONS:** Preliminary data from this ongoing study demonstrate an SVR4 rate of 94% in the ITT population. The regimen was well tolerated and hemoglobin and bilirubin abnormalities were observed infrequently. These preliminary results suggest that the use of low-dose RBV with the 3-DAA regimen may be sufficient for most patients to achieve SVR while reducing RBV-related AEs.

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Fred Poordad - Advisory Committees or Review Panels: Abbott/Abbvie, Achillion, BMS, Inhibitex, Boeheringer Ingelheim, Pfizer, Genentech, Idenix, Gilead, Merck, Vertex, Salix, Janssen, Novartis; Grant/Research Support: Abbvie, Anadys, Achillion, BMS, Boehringer Ingelheim, Genentech, Idenix, Gilead, Merck, Pharmassett, Vertex, Salix, Tibotec/Janssen, Novartis

Paul J. Pockros - Advisory Committees or Review Panels: Janssen, Merck, BMS, Gilead, AbbVie; Consulting: Lumena, Beckman Coulter; Grant/Research Support: Intercept, Janssen, BMS, Gilead, Lumena, Beckman Coulter, AbbVie, RMS, Merck; Speaking and Teaching: AbbVie, Janssen, Gilead

Natarajan Ravendhran - Grant/Research Support: BMS, GILEAD, merck, Abbvie, Salix; Speaking and Teaching: onyx, salix, Gilead, Abbvie

Michael R. Lucey - Grant/Research Support: Abbvie, Gilead

Michael S. Epstein - Advisory Committees or Review Panels: Aspire Bariatrics; Consulting: abbvie, Eli Lilly, IMHEALTHSCIENCE

Leslie Bank - Grant/Research Support: AbbVie Virology, Gilead, Merck, BMS; Speaking and Teaching: AbbVie Immunology, Gilead, Merck, BMS

David E. Bernstein - Consulting: abbvie, Merck, Janssen; Grant/Research Support: GIlead, abbvie, BMS, Janssen; Speaking and Teaching: Gilead

Preethi Krishnan - Employment: AbbVie Inc

Tami Pilot-Matias - Employment: AbbVie; Stock Shareholder: Abbott

Akshanth R. Polepally - Employment: AbbVie

Kristina Unnebrink - Employment: AbbVie; Stock Shareholder: AbbVie

Marisol Martinez - Employment: Abbvie; Stock Shareholder: Abbvie

David R. Nelson - Grant/Research Support: Abbvie, BMS, Gilead, Merck, Janssen

The following people have nothing to disclose: Shahriar Sedghi, Robert Reindollar, Roger Trinh, Rajvineeth K. Pothacamury

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ONYX-I: Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir in Asian Adults with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection - A Randomized, Double-Blind, Placebo-Controlled Study

Lai Wei[1], Jinlin Hou[2], Yan Luo[3], Jeong Heo[4], Chi-Jen Chu[5], Zhongping Duan[6], Mong Cho[7], Jun Cheng[8], Jun Li[9], Jidong Jia[10], Xinyan Zhang[3], Tami Pilot-Matias[3], Niloufar Mobashery[3], Wan-Long Chuang[11]; [1]Peking University Peoples Hospital, Beijing, China; [2]Nanfang Hospital, Guangzhou, China; [3]AbbVie Inc., North Chicago, IL; [4]Department of Internal Medicine, College of Medicine, Pusan National University and Medical Research Institute, Pusan National University Hospital, Busan, Korea (the Republic of); [5]Taipei Veterans General Hospital, Taipei City, Taiwan; [6]Beijing Youan Hospital Capital Medical University, Beijing, China; [7]Pusan National University Yangsan Hospital, Yangsan, Korea (the Republic of); [8]Beijing Di Tan Hospital, Capital Medical University, Beijing, China; [9]Jiangsu Province Hospital, Nanjing, China; [10]Beijing Friendship Hospital, Capital Medical University, Beijing, China; [11]Kaohsiung Medical University, Kaohsiung City, Taiwan

BACKGROUND: Previous multinational Phase 3 studies have demonstrated that treatment with the direct-acting antiviral agents (DAAs) ombitasvir/paritaprevir (identified by AbbVie and Enanta)/ritonavir (OBV/PTV/r) and dasabuvir (DSV) was well tolerated and achieved sustained virologic response at post-treatment week 12 (SVR12) in 100% of patients infected with genotype 1b (GT1b) hepatitis C virus (HCV) without cirrhosis. Despite these findings, interferon (IFN)/peglated IFN (pegIFN) and ribavirin (RBV) are still the current standard of care in some Asian countries where GT1b HCV infection has high prevalence. The present study evaluated the safety and efficacy of OBV/PTV/r plus DSV in adults with chronic GT1b HCV infection in Mainland China, Taiwan, and South Korea. **METHODS:** In this Phase 3, randomized, double-blind, placebo-controlled study, the safety and efficacy of OBV/PTV/r + DSV administered for 12 weeks were evaluated in treatment-naïve and treatment-experienced (IFN/pegIFN and RBV), non-cirrhotic adults with chronic GT1b HCV infection. Patients in Arm A received the active drugs during the 12 weeks of double-blind period, while patients in Arm B received the placebo during the same period followed by the active drug treatment during the 12 weeks of open-label period. Efficacy will be assessed by comparing the Arm A SVR12 rate with the historical SVR rate of telaprevir plus pegIFN and RBV. Safety is assessed in all patients who received at least 1 dose of study drugs. **RESULTS:** A total of 650 patients (Mainland China: 410; South Korea: 120; Taiwan: 120) were randomized 1:1 to Arms A and B. All patients were Asian, 54% were female and 44% were treatment experienced. As of the data cut-off date (May 5, 2016), all South Korean and Taiwanese Arm A patients reached post-treatment week 4 achieving an SVR4 rate of 100%. Some of the Chinese patients have not yet reached post-treatment week 4. Most treatment emergent adverse events (AEs) for patients receiving the active drug were mild in severity. The most common AEs (Arm A, B) were upper respiratory tract infection (9%, 9%), headache (5%, 4%) and dizziness (5%, 4%). Nine patients had serious AEs during the double-blind treatment (7 in Arm A; 2 in Arm B) with only one case (in Arm A) being drug related, resulting in alanine aminotransferase elevation. Two patients in Arm B discontinued treatment. **CONCLUSIONS:** Preliminary data from this ongoing study demonstrated a 100% SVR4 rate in HCV GT1b-infected Korean and Taiwanese patients treated with OBV/PTV/r + DSV for 12 weeks. The regimen was well tolerated with mostly mild AEs reported. SVR12 rates from the entire study will be reported at the conference.

Disclosures:

Jinlin Hou - Consulting: Roche, Novartis, GSK, BMS, Abbovir; Grant/Research Support: Roche, Novartis, GSK

Yan Luo - Employment: AbbVie; Stock Shareholder: AbbVie

Jeong Heo - Advisory Committees or Review Panels: Abbvie, Gilead; Grant/Research Support: BMS, Roche, GSK, Sillajen

Chi-Jen Chu - Advisory Committees or Review Panels: Gilead; Speaking and Teaching: BMS, Merck, Abbvie, Roche

Jidong Jia - Consulting: Abbie, BMS, GSK, Novartis, Roche

Xinyan Zhang - Employment: AbbVie

Tami Pilot-Matias - Employment: AbbVie; Stock Shareholder: Abbott

Niloufar Mobashery - Employment: Abbvie; Stock Shareholder: abbvie

Wan-Long Chuang - Advisory Committees or Review Panels: Gilead, Abbvie, Roche, PharmaEssentia; Speaking and Teaching: Gilead, Roche, BMS, MSD, PharmaEssentia

The following people have nothing to disclose: Lai Wei, Zhongping Duan, Mong Cho, Jun Cheng, Jun Li

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High Efficacy in Patients With Chronic Hepatitis C Virus (HCV) Genotype (GT)1b Infection Treatment With Elbasvir/Grazoprevir for 12 Weeks: An Integrated Analysis

Stefan Zeuzem[1], Lawrence Serfaty[2], John M. Vierling[3], Wendy Cheng[4], Jacob George[5,6], Jan Sperl[7], Simone I. Strasser[8], Hiromitsu Kumada[9], Peggy Hwang[10], Michael Robertson[10], Janice Wahl[10], Eliav Barr[10], Rohit Talwani[10], Heather L. Platt[10]; [1]Department of Internal Medicine I, J.W. Goethe University Hospital, Frankfurt, Germany; [2]Saint-Antoine Hospital, Paris, France; [3]Baylor College of Medicine, Houston, TX; [4]Royal Perth Hospital, Perth, WA, Australia; [5]Westmead Institute for Medical Research, Westmead Hospital, Sydney, NSW, Australia; [6]University of Sydney, Sydney, NSW, Australia; [7]Institute for Clinical and Experimental Medicine, Prague, Czech Republic; [8]Royal Prince Alfred Hospital, Sydney, NSW, Australia; [9]Toranomon Hospital, Tokyo, Japan; [10]Merck & Co., Inc., Kenilworth, NJ

GT1b is the most common HCV genotype globally, accounting for the largest proportion of infections in Europe, Latin America, Russia, Turkey, and East Asia. We report the efficacy of 12 weeks of once-daily elbasvir/grazoprevir (50 mg/100 mg) (NS5A inhibitor/NS3/4 protease inhibitor) in HCV GT1b-infected patients enrolled in the clinical development program. This analysis of treatment-naïve and treatment-experienced GT1b-infected patients used data pooled from 11 trials involving 30 countries and included 1070 patients with/without cirrhosis, chronic kidney disease (CKD), and HIV co-infection. Cirrhosis (F4, compensated) was confirmed by either liver biopsy or noninvasive tests. Patients with Stage 4 or Stage 5 CKD on hemodialysis were included. HIV/HCV co-infected patients were required to be on a stable antiretroviral regimen (ARV) (tenofovir or abacavir, emtricitabine or lamivudine, and either raltegrevir, dolutegravir, or rilpivirine) with CD4 >200/μL and HIV viral load undetectable, or if not on ARVs, have CD4 >500/μL and viral load <50,000 IU/mL. The primary endpoint was the proportion of patients with HCV RNA below the lower limit of quantitation 12 weeks after treatment (SVR12). Efficacy data are presented for the full analysis set (FAS), which includes all patients who received at least one dose of study medication, and for the per-protocol (PP) population, which excludes nonvirologic failures. A total of 1,070 patients were included in the analysis. Mean patient age was 53.7 years (range, 19-80); 50% were male; 47% were white, 43% were Asian, and 9% were black or African American; 20% were treatment-experienced; 39% had a baseline viral load >2,000,000 IU/mL; and 18% had evidence of cirrhosis. SVR12 was 97% (1040/1070) in the FAS; 15 patients (1.4%) were categorized as virologic failures and 15 (1.4%) were categorized as nonvirologic failures (lost-to-follow-up or withdrawal). Excluding the nonvirologic failures, SVR12 was 99% (1040/1055) in the PP analysis. There were no notable differences in subgroup analyses: SVR12 was 97% in both treatment-naïve and treatment-experienced patients; 99% in cirrhotics and 97% in noncirrhotics; 98% in patients with a baseline viral load <2,000,000 IU/mL and 97% in patients with a baseline viral >2,000,000 IU/mL; 94% in HIV/HCV co-infected patients; and 100% and 95% in patients with Stage 4 or 5 CKD, respectively. High efficacy was achieved in the GT1b-infected population treated with elbasvir/grazoprevir for 12 weeks, with comparable efficacy across subgroups, including those with cirrhosis, high baseline viral load, and prior treatment failures.

Disclosures:

Stefan Zeuzem - Consulting: Abbvie, Bristol-Myers Squibb Co., Gilead, Merck & Co., Janssen

Lawrence Serfaty - Advisory Committees or Review Panels: MSD, Janssen, Roche, Gilead, BMS, Abbvie; Speaking and Teaching: Aptalis

John M. Vierling - Advisory Committees or Review Panels: Abbvie, Bristol-Meyers-Squibb, Gilead, Hyperion, Intercept, Janssen, Novartis, Merck, Sundise, HepQuant, Salix, Immuron, Exalenz, Chronic Liver Disease Foundation; Board Membership: Clinical Research Centers of America, LLC; Grant/Research Support: Abbvie, Bristol-Meyers-Squibb, Eisai, Gilead, Hyperion, Intercept, Janssen, Novartis, Merck, Sundise, Ocera, Mochida, Immuron, Exalenz, Conatus; Speaking and Teaching: GALA, Chronic Liver Disease Foundation, ViralEd, Chronic Liver Disease Foundation, Clinical Care Options

Jacob George - Advisory Committees or Review Panels: Pharmaxis, BMS, MSD, Gilead, Janssen, Abbvie; Grant/Research Support: MSD

Jan Sperl - Advisory Committees or Review Panels: MSD, Abbvie, Gilead, Janssen; Grant/Research Support: Gilead, Janssen; Speaking and Teaching: MSD, BMS, Abbvie, Gilead, Janssen

Simone I. Strasser - Advisory Committees or Review Panels: AbbVie, MSD, Bristol-Myers Squibb, Gilead, Norgine, Bayer Healthcare; Speaking and Teaching: Roche Products Australia, Bayer Healthcare, Bristol-Myers Squibb, MSD, Gilead, Abbvie

Hiromitsu Kumada - Speaking and Teaching: Bristol-Myers Squibb,Pharma International, MSD, Abbvie, Glaxosmithkline, Gilead Sciences, Diainippon Sumitomo Pharma

Peggy Hwang - Employment: Merck, Merck

Michael Robertson - Employment: Merck; Stock Shareholder: Merck

Janice Wahl - Employment: Merck & Co,

Eliav Barr - Employment: Merck; Stock Shareholder: Merck

Rohit Talwani - Employment: Merck

Heather L. Platt - Employment: Merck

The following people have nothing to disclose: Wendy Cheng

875 ♦

ONYX-II: Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir Coadministered with Ribavirin in Asian Adults with Genotype 1b Chronic Hepatitis C Virus Infection and Compensated Cirrhosis

Lai Wei[1], Qui-Qiang Wang[2], Yan Luo[3], Chi-Jen Chu[4], Seung Woon Paik[5], Jinlin Hou[6], Jun Cheng[7], Qing Xie[8], Zhongping Duan[9], Jia-Horng Kao[10], Bo Fu[3], Niloufar Mobashery[3], Jeong Heo[11]; [1]Peking University Peoples Hospital, Beijing, China; [2]Peking University First Hospital, Beijing, China; [3]AbbVie Inc., North Chicago, IL; [4]Taipei Veterans General Hospital, Taipei City, Taiwan; [5]Samsung Medical Center, Seoul, Korea (the Republic of); [6]Nanfang Hospital of Southern Medical University, Guangzhou, China; [7]Beijing Di Tan Hospital, Capital Medical University, Beijing, China; [8]Ruijin Hospital Shanghai Jiaotong, University School of Medicine, Shanghai, China; [9]Beijing Youan Hospital Capital Medical University, Beijing, China; [10]National Taiwan University Hospital, Zhongzheng District, Taiwan; [11]Department of Internal Medicine, College of Medicine, Pusan National University and Medical Research Institute, Pusan National University Hospital, Busan, Korea (the Republic of)

BACKGROUND: Previous multinational Phase 3 studies have demonstrated that treatment with the direct-acting antiviral agents (DAAs) ombitasvir/paritaprevir (identified by AbbVie and Enanta)/ritonavir (OBV/PTV/r) and dasabuvir (DSV) ± ribavirin (RBV) was well tolerated and achieved sustained virologic response at post-treatment week 12 (SVR12) in 100% of patients infected with genotype 1b (GT1b) hepatitis C virus (HCV) and with compensated cirrhosis. Despite these findings, interferon (IFN)/peglated IFN (pegIFN) and ribavirin (RBV) are still the current standard of care in some Asian countries where GT1b HCV infection has high prevalence. The present study is evaluating the safety and efficacy of OBV/PTV/r plus DSV coadministered with RBV in adults with chronic GT1b HCV infection and compensated cirrhosis in Mainland China, South Korea and Taiwan. **METHODS:** In this phase 3, open-label, multi-center study, the safety and efficacy of OBV/PTV/r plus DSV and RBV administered for 12 weeks were evaluated in treatment-naïve and treatment experienced (IFN/pegIFN and RBV) adults with GT1b HCV Infection and compensated cirrhosis (fibrosis stage = F4). Efficacy was assessed by sustained virologic response at post treatment week 12 (SVR12) compared with the historical SVR rates of telaprevir plus pegIFN and RBV. Safety and efficacy were assessed in all patients receiving at least 1 dose of study drugs. **RESULTS:** A total of 104 patients (62% female, 100% Asian, 58% treatment-experienced) were enrolled from Mainland China (n=63), South Korea (n=21) and Taiwan (n=20). All patients had chronic GT1b HCV infection and compensated cirrhosis. As of the data cut-off date (May 5, 2016), post-treatment week 4 data were available for 102 patients achieving an SVR4 rate of 100%. Most Treatment Emergent Adverse Events (TEAEs) were mild in severity. The most common TEAEs (≥10%) were increased blood bilirubin levels (23%), pruritus (15%), anemia (12%), asthenia (12%) and dizziness (11%). Four patients had serious TEAEs and all were assessed as not being related to the DAA regimen (one was assessed as being possibly related to RBV). One patient who achieved SVR4 discontinued treatment due to drug-related TEAEs after 22 days of dosing (due to elevations in alanine aminotransferase, aspartate aminotransferase and blood bilirubin). **CONCLUSIONS:** High SVR4 rates (100%) were achieved in HCV GT1b-infected Asian patients with compensated cirrhosis who were treated with OBV/PTV/r plus DSV and RBV for 12 weeks. The regimen was well tolerated with mostly mild TEAEs reported. SVR12 rates from the entire study will be reported at the conference.

♦ Denotes AASLD Presidential Poster of Distinction

Disclosures:

Yan Luo - Employment: AbbVie; Stock Shareholder: AbbVie

Chi-Jen Chu - Advisory Committees or Review Panels: Gilead; Speaking and Teaching: BMS, Merck, Abbvie, Roche

Jinlin Hou - Consulting: Roche, Novartis, GSK, BMS, Abbovir; Grant/Research Support: Roche, Novartis, GSK

Bo Fu - Employment: AbbVie

Niloufar Mobashery - Employment: Abbvie; Stock Shareholder: abbvie

Jeong Heo - Advisory Committees or Review Panels: Abbvie, Gilead; Grant/Research Support: BMS, Roche, GSK, Sillajen

The following people have nothing to disclose: Lai Wei, Qui-Qiang Wang, Seung Woon Paik, Jun Cheng, Qing Xie, Zhongping Duan, Jia-Horng Kao

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Long-term follow-up of patients with chronic HCV infection treated with daclatasvir-based regimens in phase 2 and 3 studies

K. Rajender Reddy[1], Stanislas Pol[2], Paul J. Thuluvath[3], Hiromitsu Kumada[4], Joji Toyota[5], Kazuaki Chayama[6], James Levin[7], Eric Lawitz[8], Adrian Gadano[9], Wayne Ghesquiere[10], Guido Gerken[11], Maurizia R. Brunetto[12], Cheng-Yuan Peng[13], Marcelo O. Silva[14], Simone I. Strasser[15], Jeong Heo[16], Fiona McPhee[17], Zhaohui Liu[18], Rong Yang[19], Misti Linaberry[19], Stephanie Noviello[19]; [1]University of Pennsylvania, Philadelphia, NJ; [2]Hôpital Cochin, Paris, France; [3]Mercy Medical Center, Baltimore, MD; [4]Toranomon Hospital, Tokyo, Japan; [5]Sapporo-Kosei General Hospital, Sapporo, Japan; [6]Hiroshima University, Hiroshima, Japan; [7]Dean Foundation for Health, Research and Education, Madison, WI; [8]Texas Liver Institute and the University of Texas Health Science Center, San Antonio, TX; [9]Hospital Italiano de Buenos Aires-Argentina, Buenos Aires, Argentina; [10]Vancouver Island Health Authority and University of British Columbia, Victoria, BC, Canada; [11]University of Duisburg-Essen, Essen, Germany; [12]University Hospital, Pisa, Italy; [13]School of Medicine, China Medical University, Taichung, Taiwan; [14]Hospital Universitario Austral, Buenos Aires, Argentina; [15]Royal Prince Alfred Hospital, Sydney, NSW, Australia; [16]College of Medicine, Pusan National University and Medical Research Institue, Pusan National University Hospital, Busan, Korea (the Republic of); [17]Bristol-Myers Squibb, Wallingford, CT; [18]Bristol-Myers Squibb, Hopewell, NJ; [19]Bristol-Myers Squibb, Princeton, NJ

Background: Combinations of daclatasvir (DCV), a pangenotypic NS5A inhibitor, with other antivirals and/or peginterferon/ribavirin (pegIFN/RBV) were assessed in multiple phase 2 and 3 clinical studies. Here we report interim long-term follow-up analyses of these studies (study AI444-046), including response durability, safety, and resistance. Methods: This ongoing observational study is monitoring patients for 3 years after receiving treatment in parent studies with DCV+sofosbuvir (SOF) ±RBV, DCV+asunaprevir (ASV), DCV+ASV+beclabuvir (BCV) ±RBV, DCV+pegIFN/RBV, or DCV+ASV+pegIFN/RBV. Patients were enrolled within 6 months of parent study completion or protocol availability, and evaluated at annual to semi-annual visits for HCV RNA levels, hepatic disease progression and decompensation events, and persistence of NS5A and NS3 resistance variants. Results: This analysis includes 893 patients treated with pegIFN-free DCV regimens and 610 treated with pegIFN-containing regimens. Patients were 60% male, 18% aged ≥65 years, 87% HCV genotype-1, and 18% cirrhotic. Overall, 1329/1489 evaluable patients achieved SVR12 in parent studies; 1316/1329 (99%) maintained SVR at their most recent long-term follow-up visit. Twelve patients relapsed after achieving SVR12 (9 on/before and 3 after posttreatment week 24); 1 patient was reinfected. Relapses after SVR12 were less frequent after treatment with all-oral regimens (3/842, 0.4%) vs pegIFN-based regimens (9/487, 2%). 34/1503 patients (2%) reported hepatic disease progres-

sion events during long-term follow-up; HCC (n=15), cirrhosis (n=8), and HCC+cirrhosis (n=2) were most common. 13 of these 34 patients did not achieve SVR12 in the parent study; 21/34 achieved and maintained SVR12. Among patients with virologic failure being monitored for up to 42 months post-treatment, replacement of NS5A and NS3 variants by wild-type sequences was observed in 27/157 (17%) and 29/41 (71%) patients, respectively. Conclusions: This interim analysis indicates that SVR12 achieved with DCV-based regimens is durable during long-term posttreatment follow-up, with infrequent liver disease progression or HCC development. Further follow-up of patients treated with DCV-containing regimens is ongoing.

Parameter	DCV+SOF ±RBV N=237	DCV+ASV N=389	DCV+ASV +BCV±RBV N=267	DCV +pegIFN/RBV N=411	DCV+ASV +pegIFN/RBV N=199
Median wks follow-up after SVR12	44.1	113.6	63.0	163.4	113.1
SVR12 in parent study, n/N(%)	232/237 (98)	350/384 (91)	260/267 (97)	297/404 (74)	190/197 (96)
SVR maintained, n/N(%)	232/232 (100)	349/350 (>99)	257/260 (99)	291/297 (98)	187/190 (98)
Relapse after SVR12, n/N(%)	0	1/350 (<1)	2/260 (<1)	6/297 (2)	3/190 (2)
Hepatic disease progression	4 (2)	11 (3)	4 (1)	12 (3)	3 (2)

Disclosures:

K. Rajender Reddy - Advisory Committees or Review Panels: Merck, Janssen, BMS, Abbvie, Gilead; Grant/Research Support: Merck, BMS, Gilead, Janssen, Abbvie

Stanislas Pol - Board Membership: Bristol-Myers-Squibb, Boehringer Ingelheim, Tibotec Janssen Cilag, Gilead, Glaxo Smith Kline, Roche, MSD, Novartis; Grant/Research Support: Gilead, Roche, MSD; Speaking and Teaching: Bristol-Myers-Squibb, Boehringer Ingelheim, Tibotec Janssen Cilag, Gilead, Roche, MSD, Novartis

Paul J. Thuluvath - Advisory Committees or Review Panels: Abbvie, Gilead; Grant/Research Support: Gilead, AbbVie, BMS, Isai, Salix; Speaking and Teaching: AbbVie, Bayer/Onyx, Gilead

Hiromitsu Kumada - Speaking and Teaching: Bristol-Myers Squibb,Pharma International, MSD, Abbvie, Glaxosmithkline, Gilead Sciences, Diainippon Sumitomo Pharma

Kazuaki Chayama - Grant/Research Support: Ajinomoto, Astellas, Asuka, MSD, Bayer, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Nihon Kayaku, Nihon Shinyaku, Kowa, Mitsubishi Tanabe, Nippon Eli Lily, Roche, Otsuka, Takeda, Toray, Torii, Tsumura, Zeria; Speaking and Teaching: Bristol-Myers Squibb, Abbvie, Ajinomoto, Abbott, Astellas, AstraZeneca, Asuka, Chugai, Dainippon Sumitomo, Johnson and Johnson, Jimuro, Miyarisan, Nihon Kayaku, Nihon Shinyaku, Olympus, MSD

James Levin - Advisory Committees or Review Panels: Gilead, Merck; Grant/Research Support: Gilead, Merck, BMS, Abbvie; Speaking and Teaching: BMS, Gilead, Merck, Abbvie

Eric Lawitz - Advisory Committees or Review Panels: AbbVie, Achillion Pharmaceuticals, Regulus, Theravance, Enanta, Idenix Pharmaceuticals, Janssen, Merck & Co, Novartis, Gilead; Grant/Research Support: AbbVie, Achillion Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmith-Kline, Idenix Pharmaceuticals, Intercept Pharmaceuticals, Janssen, Merck & Co, Novartis, Nitto Denko, Theravance, Salix, Enanta; Speaking and Teaching: Gilead, Janssen, AbbVie, Bristol Meyers Squibb, Merck, intercept

Maurizia R. Brunetto - Advisory Committees or Review Panels: Schering-Plough, Gilead, Janssen, AbbVie; Speaking and Teaching: Roche, Gilead, Bristol-Myers Squibb, Abbott, Roche, Janssen

Cheng-Yuan Peng - Advisory Committees or Review Panels: AbbVie, BMS, Gilead, MSD, Roche

Marcelo O. Silva - Advisory Committees or Review Panels: MSD, AbbVie; Grant/Research Support: BMS, MSD, Bayer; Speaking and Teaching: BMS, AbbVie

Simone I. Strasser - Advisory Committees or Review Panels: AbbVie, MSD, Bristol-Myers Squibb, Gilead, Norgine, Bayer Healthcare; Speaking and Teaching: Roche Products Australia, Bayer Healthcare, Bristol-Myers Squibb, MSD, Gilead, Abbvie

Jeong Heo - Advisory Committees or Review Panels: Abbvie, Gilead; Grant/Research Support: BMS, Roche, GSK, Sillajen

Fiona McPhee - Employment: Bristol-Myers Squibb

Rong Yang - Employment: BMS; Stock Shareholder: BMS

Misti Linaberry - Employment: BMS

Stephanie Noviello - Consulting: Merck/Schering-Plough; Employment: Bristol-Myers Squibb, Merck/Schering-Plough; Stock Shareholder: Merck/Schering-Plough, J&J, Bristol-Myers Squibb

The following people have nothing to disclose: Joji Toyota, Adrian Gadano, Wayne Ghesquiere, Guido Gerken, Zhaohui Liu

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Treating non-cirrhotic Hepatitis C patients in the UK is a cost-saving intervention.

*Lucile Marié***[1], Ines Guerra[2], Mark Nelson[3], Sanjay Bhagani[4]; [1]Mapi, Nanterre, France; [2]Mapi, Uxbridge, United Kingdom; [3]Chelsea and Westminster Hospital, London, United Kingdom; [4]Royal Free Hospital, London, United Kingdom*

Purpose: The aim of this study is to assess the cost-effectiveness of treating chronic hepatitis C (HCV) infected patients at a non-cirrhotic stage compared to treating these patients when they develop cirrhosis. **Methods:** A Markov model was developed to follow a cohort of 10,000 treatment-naïve patients for a lifetime (100 years of age). Two strategies were compared: treating all patients independently of their fibrosis stage versus only treating cirrhotic patients. The analysis was performed on the general patient population. Age, the distribution of patients between the different fibrosis stages and costs were reflective of the UK setting. Patients were treated with ledipasvir/sofosbuvir (LDV/SOF) for 8 weeks in the non-cirrhotic stages (F0 to F3) and with LDV/SOF for 12 weeks in the cirrhotic stage. The model structure is based on the models submitted to the National Institute for Health and Care Excellence (NICE) for HCV during previous health technology appraisals. Sustained virological response rates, transition probabilities, costs and utilities were obtained from the literature and the clinical trials of LDV/SOF. Costs and outcomes were discounted at 3.5% as recommended by NICE. Re-infection was included in sensitivity analysis, as well as the proportion of patients re-treated after re-infection. Both deterministic and probabilistic sensitivity analyses were conducted, investigating different ranges of the parameters and alternative values collected from the literature. Onward transmission was not considered in the analysis. **Results:** Long-term costs are lower and quality-adjusted life years (QALYs) gained are higher if treatment starts at earlier stages of the disease. The results of the analysis therefore show that treating all fibrosis stages is cost-saving (-£1,396/QALY). The cost per cure for treating all patients is £34,164 versus £32,568 for F4. Furthermore, treating patients earlier generates fewer cases of decompensated cirrhosis, hepatocellular carcinoma, liver transplants and saves lives. All results are robust to sensitivity analysis. **Conclusion:** This analysis demonstrates that treating HCV in early fibrosis stages, including F0 and F1, is cost-saving in the UK. Therefore, treating patients as soon as they are diagnosed with HCV will not only generates savings, but will also reduce the burden on HCV.

Disclosures:

Lucile Marié - Employment: Mapi

Ines Guerra - Consulting: Gilead

Mark Nelson - Advisory Committees or Review Panels: Janssen, MSD, BMS, ABBVIE, Viiv, Gilead; Consulting: Janssen, MSD, BMS, ABBVIE, Viiv, Gilead; Grant/Research Support: Boehringer Ingelheim, Janssen, MSD, BMS, ABBVIE, Viiv, Gilead, Roche; Speaking and Teaching: GSK, Janssen, MSD, BMS, Abbott, Viiv, Gilead

Sanjay Bhagani - Advisory Committees or Review Panels: BMS, MSD, Abbvie, Jannsen, Gilead Sciences; Speaking and Teaching: BMS, Gilead Sciences, MSD, Jannsen, Abbvie

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Pharmacokinetics of Once Daily Sofosbuvir or Ledipasvir/Sofosbuvir in HCV-Infected Pediatrics Aged 6 to <12 Years Old

Kimberly L. Garrison[1], Anita Mathias[1], Kathryn Kersey[1], Bittoo Kanwar[1], Liyun Ni[1], Anant Jain[1], John Ling[1], Regino P. Gonzalez-Peralta[2], Karen F. Murray[3], C-H Lin[4], Mary Suzanne Whitworth[5], Jessica Wen[6], Kathleen B. Schwarz[7], William Balistreri[8]; [1]Gilead Sciences, Inc., Foster City, CA; [2]University of Florida, Gainesville, FL; [3]Seattle Children's Hospital, Seattle, WA; [4]Children's Hospital Los Angeles, Los Angeles, CA; [5]Cook Children's Health Care System, Fort Worth, TX; [6]The Children's Hospital of Philadelphia, Philadelphia, PA; [7]Johns Hopkins University School of Medicine, Baltimore, MD; [8]Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Background Sofosbuvir (SOF) and ledipasvir/sofosbuvir (LDV/SOF) are approved for treatment of chronic HCV infection in adults. The safety and efficacy of SOF + ribavirin (RBV) and LDV/SOF are being assessed in adolescents receiving the adult dose. The pharmacokinetics (PK) of lower doses of SOF and LDV/SOF were evaluated in HCV-infected children (6 to <12 y) to confirm the appropriateness of predicted doses in this population. **Methods** HCV-infected children (6 to <12 y, weight ≥17 to <45 kg at screening) received SOF 200 mg QD +RBV for 7 days (N=10) or LDV/SOF 45 mg/200 mg QD for 10 days (N=10) with intensive PK assessments done on Day 7 or 10, respectively (PK lead-in); 2 additional patients in each cohort inadvertently received adult doses SOF 400 mg or LDV/SOF 90 mg/400 mg for 3 to 46 days. Upon completing the PK lead-in, patients continued SOF+RBV for 12 or 24 weeks (GT-2 or GT-3, respectively) or LDV/SOF for 12 wks (GT-1). SOF, GS-331007 (major circulating metabolite) and LDV PK parameters were compared via ANOVA to exposures in Phase 2/3 SOF or LDV/SOF adult clinical programs with predefined equivalence bounds of 50-200%. Safety was assessed throughout the study. **Results** All patients completed PK assessments. At screening, median (range) age (y) for patients (4 male, 8 female) on SOF+RBV was 8.5 (6, 11), weight (kg) was 31 (18, 45). Median (range) age and weight for LDV/SOF patients (8 male, 4 female) were 9 (6, 11) and 33 (20, 41), respectively. Study treatments were well tolerated. SOF and LDV/SOF exposures were similar between pediatric and Phase 2/3 populations (Table 1). **Conclusion** Study treatments were well tolerated. SOF 200 mg +RBV or LDV/SOF 45 mg/200 mg provided comparable exposures to those observed in adults, and these data support the ongoing evaluation of these doses in children 6 to <12 y.

Table 1. Steady-state exposure of SOF, GS-331007 and LDV

	SOF		
PK Parameter* Mean(%CV)	6 to <12 y *N=12*	Ph 2/3 Pop *N=1695*†	GLSM %Ratio (90%CI)
SOF			
AUC_{tau} *ng*h/mL*	977 (52.8)	1030 (36.5)	88.7 (75.2,105)
C_{max} *ng/mL*	635 (50.9)	511 (32.5)	115 (95.1,139)
GS-331007			
AUC_{tau} *ng*h/mL*	6250 (25.4)	7120 (30.7)	89.2 (76.8,104)
C_{max} *ng/mL*	865 (26.5)	582 (36.3)	154 (128,185)
	LDV/SOF		
	6 to <12 y *N=12*	Ph 2/3 Pop *N=2113*‡	GLSM %Ratio (90%CI)
LDV			
AUC_{tau} *ng*h/mL*	7520 (58.0)	8530 (60.8)	86.9 (66.5,114)
C_{max} *ng/mL*	432 (51.3)	364 (51.4)	116 (92.1,147)
C_{tau} *ng/mL*	248 (67.5)	247 (59.2)	91.1 (69.5,120)
SOF			
AUC_{tau} *ng*h/mL*	1600 (29.7)	1380 (34.0)	116 (101,133)
C_{max} *ng/mL*	906 (36.0)	659 (34.0)	139 (116,167)
GS-331007			
AUC_{tau} *ng*h/mL*	8140 (31.6)	12500 (29.2)	65.2 (56.9,74.7)
C_{max} *ng/mL*	772 (24.4)	736 (28.2)	106 (92.8,122)

*PK parameters presented to 3 sig fig and dose-adjusted as appropriate; †N=838 (SOF); ‡N=1542 (SOF)

Disclosures:

Kimberly L. Garrison - Employment: Gilead Sciences, Inc; Stock Shareholder: Gilead Sciences, Inc

Anita Mathias - Employment: Gilead Sciences Inc.,

Kathryn Kersey - Employment: Gilead Sciences, Inc; Stock Shareholder: Gilead Sciences, Inc

Bittoo Kanwar - Employment: Gilead Sciences

Regino P. Gonzalez-Peralta - Advisory Committees or Review Panels: Shire; Consulting: Roche; Grant/Research Support: Abbvie, Gilead, Bristol Myers-Squibb, Schering-Plough (Merck), Sucampo

Karen F. Murray - Grant/Research Support: Gilead; Stock Shareholder: Merck

Jessica Wen - Grant/Research Support: Gilead, BMS, Abbvie, Novartis

Kathleen B. Schwarz - Advisory Committees or Review Panels: Alexion; Grant/Research Support: Bristol-Myers Squibb, Gilead, Roche/Genentech, Roche

William Balistreri - Grant/Research Support: Gilead

The following people have nothing to disclose: Liyun Ni, Anant Jain, John Ling, C-H Lin, Mary Suzanne Whitworth

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Ledipasvir/Sofosbuvir in Egyptian Patients with Chronic Genotype 4 HCV Infection

Gamal Shiha[1], Imam Waked[2], Reham Soliman[1], Wael Abdelrazek[2], Mohamed Hassany[3], Rabab F. Omar[4], Waleed Samir[1], Talaat Zakareya[2], Radi Hammad[3], Sherief Musa[4], Kathryn Kersey[5], Sophia Lu[5], Benedetta Massetto[5], Diana M. Brainard[5], John G. McHutchison[5], Wahid H. Doss[3], Gamal E. Esmat[4]; [1]Egyptian Liver Research Institute and Hospital, Mansoura, Egypt; [2]National Liver Institute, Menoufiya, Egypt; [3]National Hepatology and Tropical Medicine Research Institute, Cairo, Egypt; [4]Cairo University, Cairo, Egypt; [5]Gilead Sciences, Inc., Foster City, CA

Background: Egypt has the highest prevalence of chronic hepatitis C virus (HCV) infection in the world, and more than 90% of patients are infected with genotype (GT) 4 virus. Ledipasvir/sofosbuvir (LDV/SOF) for 12 weeks resulted in a SVR12 rate of 93% (41/44) in a phase 2 study conducted in France. The aims of this ongoing study are to evaluate the safety and efficacy of LDV/SOF ± ribavirin (RBV) in treatment-naïve (TN) and –experienced (TE) patients in Egypt with chronic genotype (GT) 4 HCV infection. **Methods:** TN patients were randomized to 8 or 12 weeks of LDV/SOF± RBV and IFN-experienced patients were randomized to 12 weeks of LDV/SOF±RBV. Randomization was stratified by cirrhosis status. SOF-experienced patients receive 12 weeks LDV/SOF+RBV. The primary endpoint is SVR12. Secondary endpoints include SVR4, safety and, tolerability. **Results**: 170 GT4 TN Egyptian patients were enrolled and treated; 54% were male, mean (range) age 42 (21, 74), mean (range) BMI 30.4 (21.0, 50.0) kg/m^2, 18% had compensated cirrhosis, and 78% had IL28B non-CC genotype. 74 IFN-experienced and 10 SOF-experienced patients have been enrolled to date; 76% were male, mean (range) age 50 (23, 74), mean (range) BMI kg/m^2 29.3 (19.1, 50.0), 27% had compensated cirrhosis, and 84% had IL28B non-CC genotype. SVR4 rates are summarized below. In total, 6 TN patients did not achieve SVR4 due to relapse (4), rebound (n=1), and early study discontinuation (n=1); all TE patients to date have achieved SVR4. SVR12 data for all groups will be presented. The most common AEs (>10% of patients in any treatment group) are headache and fatigue. Serious AEs have been reported for 4 patients: 3 with injuries (2 road traffic accidents, 1 arm fracture), and 1 with atypical chest pain. None of the SAEs was considered related to study drug and 1 (road traffic accident) led to treatment discontinuation. **Conclusions:** These preliminary results support the use of LDV/SOF for 12 weeks in patients with genotype 4 HCV and the potential utility of LDV/SOF for 8 weeks in those who are treatment-naïve.

Preliminary SVR4 rates (%; n/N) in patients with GT4 HCV who have reached 4 weeks post-treatment

	LDV/SOF 8 weeks	LDV/SOF+RBV 8 weeks	LDV/SOF 12 weeks	LDV/SOF+RBV 12 weeks
Treatment-naive				
Overall	95 (41/43)	95 (40/42)	98 (42/43)	98 (41/42)
No cirrhosis	97 (35/36)	97 (34/35)	100 (34/34)	97 (33/34)
Cirrhosis	86 (6/7)	86 (6/7)	89 (8/9)	100 (8/8)
Treatment-experienced				
Overall	NA	NA	100 (17/17)	100 (24/24)*
No cirrhosis			100 (11/11)	100 (17/17)
Cirrhosis			100 (6/6)	100 (7/7)

*18 IFN-experienced and 6 SOF-experienced patients;

NA=not applicable

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Imam Waked - Advisory Committees or Review Panels: Janssen; Speaking and Teaching: Hoffman L Roche, BMS, Gilead, AbbVie

Mohamed Hassany - Grant/Research Support: Gilead Sc, Abbvie, Janssen ; Speaking and Teaching: Abbvie

Talaat Zakareya - Grant/Research Support: Gilead sciences, Inc.

Radi Hammad - Grant/Research Support: Gilead Sciences,Inc, Janssen Pharmaceuticals, Inc.

Kathryn Kersey - Employment: Gilead Sciences, Inc; Stock Shareholder: Gilead Sciences, Inc

Benedetta Massetto - Employment: Gilead Sciences, Inc.; Stock Shareholder: Gilead Sciences, Inc

Diana M. Brainard - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

John G. McHutchison - Employment: gilead; Stock Shareholder: gilead

Gamal E. Esmat - Advisory Committees or Review Panels: MSD &BMS companies, MSD &BMS companies, Abbvie; Grant/Research Support: Gilead Sc, Abbvie ; Speaking and Teaching: Roche & GSK companies, Roche & GSK companies, Gilead Sc, Abbvie

The following people have nothing to disclose: Gamal Shiha, Reham Soliman, Wael Abdelrazek, Rabab F. Omar, Waleed Samir, Sherief Musa, Sophia Lu, Wahid H. Doss

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Long-Term Follow-up of Patients with Chronic HCV Infection and Compensated or Decompensated Cirrhosis Following Treatment with Sofosbuvir-Based Regimens

Andrew J. Muir[1], Maria Buti[2], Ronald Nahass[3], Kosh Agarwal[4], Edward J. Gane[5], Simone I. Strasser[6], Alessandra Mangia[7], Jose L. Calleja[8], Kathryn Kersey[9], Stephanie Moody[10], Diana M. Brainard[9], Paul Marotta[11], Marc Bourlière[12], Bruce Bacon[13], Bradley Freilich[14], Michael P. Curry[15]; [1]Duke University, Durham, NC; [2]Hospital Valle Hebron and Ciberehd del Institut Carlos III, Barcelona, Spain; [3]ID CARE, Hillsborough, NJ; [4]Kings College Hospital, London, United Kingdom; [5]Auckland Clinical Studies Ltd, Auckland, New Zealand; [6]Royal Prince Alfred Hospital, Camperdown, NSW, Australia; [7]Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Italy; [8]Hospital Puerta de Hierro Majadahonda, Madrid, Spain; [9]Gilead Sciences, Inc., Foster City, CA; [10]PharPoint, Durham, NC; [11]London Health Sciences Centre, London, ON, Canada; [12]Hôpital-Saint Joseph, Marseille, France; [13]St Louis University Hospital, St Louis, MO; [14]Kansas City Research Institute, Kansas City, MO; [15]Beth Israel Deaconess Medical Center, Boston, MA

Background and Aims: Significant advances in the treatment of chronic hepatitis C have been made with direct acting antiviral (DAA) regimens. While sustained virologic response (SVR) rates may now be achieved in most patients, data on long term virologic and clinical outcomes with these regimens are needed. A recent report suggested HCC incidence may not be reduced after successful DAA therapy. The objective of this ongoing registry study is to evaluate long term outcomes in patients with cirrhosis who achieved SVR following treatment with a sofosbuvir- (SOF) based regimen. Methods: Patients with compensated or decompensated cirrhosis who achieved SVR after receiving a SOF-based regimen are eligible for enrollment. Patients may enroll within 60 weeks of completing a treatment study or transfer from another SVR registry study, or within 2 years of achieving SVR following treatment in a clinical practice setting. Patients return for visits every 24 weeks for 5 years. Durability of SVR and clinical outcomes (decompensation, HCC, transplantation, and liver-related death) and laboratory parameters relating to disease progression/regression are followed in all patients. Results: 859 patients have been enrolled as of 17 May 2016. Mean age (range) is 59 (33, 83), 68% are male, and mean (range) MELD score at baseline was 8 (6, 21) and 12 (6, 24) in those with CPT A and CPT B or C cirrhosis, respectively. Median (range) time since end of treatment for clinical study patients was 373 (15, 1215) days. At baseline, SVR was maintained in 99.9% of patients (838/839); 1% (9/845) had HCC. Table 1 shows changes in pretreatment CPT class to start of the registry study for those who had decompensated cirrhosis pre-treatment. Change in laboratory parameters and time to event for clinical signs through Week 72 of the registry study will be presented. Conclusions: At baseline of this registry study, SVR was maintained in 99.9% of patients with cirrhosis post-treatment with a SOF-based regimen. In patients with decompensated cirrhosis pretreatment, CPT class improved at entry into the registry study (from CPT B to A or from CPT C to B or A) in 65% and was unchanged in 35%. This ongoing study will provide information on whether achieving SVR following treatment with an HCV DAA regimen will improve longer term liver function and reduce the rate of liver-related complications, including HCC.

Table 1. Number (%) of patients with CPT B or C cirrhosis prior to treatment with SOF-based regimen by CPT class at baseline of registry study

		CPT Class at Registry Study Baseline		
		CPT A	CPT B	CPT C
Pretreatment CPT Class	CPT B (N=133)	83 (62)	50 (38)	0
	CPT C (N=15)	6 (40)	8 (53)	1 (7)

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Andrew J. Muir - Advisory Committees or Review Panels: Abbvie, BMS, Gilead, Janssen, Merck; Consulting: Shire, Inovia Pharmaceuticals, Intercept, Portola Pharmaceuticals; Grant/Research Support: Abbvie, BMS, Gilead, Janssen, Merck, Hologic, Intercept, NGM Biopharm, Roche

Maria Buti - Advisory Committees or Review Panels: Gilead, Janssen, MSD; Grant/Research Support: Gilead, Janssen; Speaking and Teaching: Gilead, Janssen, BMS

Ronald Nahass - Advisory Committees or Review Panels: Gilead, Merck, Janssen, BMS; Grant/Research Support: Gilead, Merck, Janssen, BMS

Kosh Agarwal - Advisory Committees or Review Panels: Gilead, BMS, Novartis, Janssen, AbbVie; Consulting: MSD, Janssen, Achillion, Intercept; Grant/Research Support: Roche, Gilead, BMS, Arbutus; Speaking and Teaching: Astellas, Gilead, BMS, GSK

Edward J. Gane - Advisory Committees or Review Panels: AbbVie, Janssen, Gilead Sciences, Achillion, Merck; Speaking and Teaching: AbbVie, Gilead Sciences, Merck, Alnylam

Simone I. Strasser - Advisory Committees or Review Panels: AbbVie, MSD, Bristol-Myers Squibb, Gilead, Norgine, Bayer Healthcare; Speaking and Teaching: Roche Products Australia, Bayer Healthcare, Bristol-Myers Squibb, MSD, Gilead, Abbvie

Alessandra Mangia - Advisory Committees or Review Panels: Gilead Sciences, BMS, Shering-Plough, MSD, Boheringer, BMS; Board Membership: MSD; Grant/Research Support: Janssen, Janssen, Gilead; Speaking and Teaching: ROCHE

Jose L. Calleja - Advisory Committees or Review Panels: Gilead, Abbvie ; Speaking and Teaching: Abbvie, Gilead, Janssen, BMS

Kathryn Kersey - Employment: Gilead Sciences, Inc; Stock Shareholder: Gilead Sciences, Inc

Diana M. Brainard - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

Marc Bourlière - Advisory Committees or Review Panels: Schering-Plough, Bohringer inghelmein, Schering-Plough, Bohringer inghelmein, Transgene; Board Membership: Bristol-Myers Squibb, Gilead, Idenix; Consulting: Roche, Novartis, Tibotec, Abott, glaxo smith kline, Merck, Bristol-Myers Squibb, Novartis, Tibotec, Abott, glaxo smith kline; Speaking and Teaching: Gilead, Roche, Merck, Bristol-Myers Squibb

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Bruce Bacon - Advisory Committees or Review Panels: Gilead, Bristol-Meyers Squibb, ISIS, Abbvie, Janssen; Consulting: Merck; Grant/Research Support: Merck, Gilead, Bristol-Meyers Squibb, Abbvie; Speaking and Teaching: Merck, Gilead, Abbvie, Salix, Janssen

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Michael P. Curry - Consulting: Alexion, Bristol Meyers Squib, Abbvie; Grant/Research Support: Gilead Sciences, Conatus

The following people have nothing to disclose: Stephanie Moody, Paul Marotta

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Variables associated with treatment outcomes for hepatitis C genotype 1 infection with direct acting antivirals (DAA): Data from the German Hepatitis C-Registry (DHC-R)

Stefan Mauss[1], Peter Buggisch[5], Klaus H. Boeker[7], Eckart Schott[10], Hartwig H. Klinker[9], Rainer Günther[8], Heike Pfeiffer-Vornkahl[6], Thomas Berg[3], Christoph Sarrazin[4], Dietrich Hueppe[11], Michael P. Manns[2], German Hepatitis C-Registry[12]; [1]Center for HIV and Hepatogastroenterology, Duesseldorf, Germany; [2]Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hanover, Germany; [3]Dept.of Gastroenterology and Rheumatology, University Hospital Leipzig, Leipzig, Germany; [4]J.W. Goethe University Frankfurt, Frankfurt, Germany; [5]ifi-institute for interdisciplinary medicine, Hamburg, Germany; [6]e.factum GmbH, Butzbach, Germany; [7]Center of Hepatology, Hanover, Germany; [8]Universitätsklinikum Schleswig-Holstein (UKSH), Campus Kiel, Kiel, Germany; [9]University Hospital Würzburg, Wuerzburg, Germany; [10]Charité Campus Virchow-Klinikum (CVK), Berlin, Germany; [11]Center of Gastroenterology, Herne, Germany; [12]Leberstiftungs-GmbH Deutschland, Hanover, Germany

Introduction: In pivotal studies with modern direct acting antivirals (DAA) SVR rates in HCV genotype 1 (GT1) are >90%. However these data have to be replicated in less well controlled settings including patients more difficult to treat. **Methods:** The German Hepatitis C Registry is a national multicentre real-world cohort. Patients are treated at the discretion of the physician. Data are collected by a web-based system. Data quality is analyzed by plausibility checks and on site monitoring. This data analysis is based on 6,034 patients who were observed for at least 40 weeks after initiation of antiviral treatment. **Results:** Between 2/2014 and 5/2015, 5,110 patients with GT1 have been enrolled. SVR12 data are available for 3,439 patients at the time of analysis. Demographics: 56% male, median age 55 years, 98% Caucasian, 52% treatment experienced, 30% liver cirrhosis, 10% HCV-RNA >6 Mio IU/mL. Comorbidities were reported for 75% of the patients in the cohort: cardiovascular 27%, psychiatric 15%, drug abuse 13%, diabetes 10%, thyroid dysfunction 10% being the most frequent. Patients treated with one of the approved regimens for GT1 were analysed (table 1). SVR12 overall in GT1a was 91% and in GT1b 93%. In multivariate analysis adjusting for age, sex, platelets, cirrhosis, HCV RNA, GT1a/1b and treatment regime, SVR12 was associated with the choice of antiviral regimen (OR 1.48 (1.37-1.60); p<0.001), cirrhosis (OR 0.60 (0.45-0.80); p<0.001) and higher age (OR 1.49 (1.08-2.07); p<0.05). HIV-coinfected patients (n=247) had an overall SVR12 of 93% not substantially different from HCV-monoinfected patients. Adverse events were reported by 53% of patients with fatigue (23%), headache (16%), nausea (7%) and insomnia (6%) being the most frequent. Serious adverse event were observed in 3% and 16 patients (0.3%) died. **Conclusions:** Data from this real life cohort show SVR 12 rates close to those obtained in clinical studies. Choice of antiviral therapy was associated with treatment outcome. In addition higher age was a positive factor and presence of cirrhosis a negative factor for achieving SVR12. Dropout rates were low confirming good adherence of patients with these regimens.

Table 1. Treatment regimens and SVR12 data of patients with HCV GT1 (ITT)

Treatment regimen	Cirrhotics (%)	SVR, ITT n/total (%)	Lost/no data n/total (%)	Discontin. n/total (%)	Relapse/NR n/total (%)
PegIFN+RBV+SOF	21.9	274/328 (84)	17/328 (5)	1/328 (<1)	36/328 (11)
SIM+SOF±RBV	61.3	245/284 (86)	13/284 (5)	2/284 (<1)	24/284 (8)
SOF+DCV±RBV	45.1	502/528 (95)	11/528 (2)	3/528 (<1)	12/528 (2)
SOF/LDV±RBV	22.8	1,734/1,836 (94)	57/1,836 (3)	15/1,836 (<1)	30/1,836 (2)
OBV/PTV/r+DSV±RBV	28.4	367/390 (94)	7/390 (2)	10/390 (3)	6/390 (2)

Disclosures:

Stefan Mauss - Advisory Committees or Review Panels: BMS, AbbVie, ViiV, Gilead; Speaking and Teaching: BMS, AbbVie, Janssen, Gilead, MSD

Peter Buggisch - Advisory Committees or Review Panels: Janssen, AbbVie, BMS; Speaking and Teaching: Falk, MSD, Gilead, Merz Pharma

Klaus H. Boeker - Consulting: Janssen; Speaking and Teaching: MSD, Roche, Gilead, BMS, Falk Foundation, Novartis, AbbVie

Eckart Schott - Advisory Committees or Review Panels: Gilead, Roche, Bayer, BMS, Abbvie, Janssen, MSD; Speaking and Teaching: Gilead, Novartis, Roche, MSD, Bayer, Falk, BMS, Janssen, Abbvie

Hartwig H. Klinker - Advisory Committees or Review Panels: AbbVie, BMS, Gilead, Hexal, Janssen, MSD; Grant/Research Support: AbbVie, BMS, Gilead, Janssen, MSD, Arrowhead, Novartis; Speaking and Teaching: AbbVIe, BMS, Gilead, Janssen, MSD

Rainer Günther - Speaking and Teaching: Roche Pharma AG, Gilead, AbbVie

Heike Pfeiffer-Vornkahl - Employment: efactum GmbH

Thomas Berg - Advisory Committees or Review Panels: Gilead, BMS, Roche, Tibotec, Vertex, Jannsen, Novartis, Abbott, Merck, Abbvie; Consulting: Gilead, BMS, Roche, Tibotec; Vertex, Janssen; Grant/Research Support: Gilead, BMS, Roche, Tibotec; Vertex, Jannssen, Merck/MSD, Boehringer Ingelheim, Novartis, Abbvie; Speaking and Teaching: Gilead, BMS, Roche, Tibotec; Vertex, Janssen, Merck/MSD, Novartis, Merck, Bayer, Abbvie

Christoph Sarrazin - Advisory Committees or Review Panels: Bristol-Myers Squibb, Janssen, Merck/MSD, Gilead, Roche, Abbvie, Janssen, Merck/MSD; Consulting: Merck/MSD, Merck/MSD; Grant/Research Support: Abbott, Roche, Merck/MSD, Gilead, Janssen, Abbott, Roche, Merck/MSD, Qiagen; Speaking and Teaching: Gilead, Novartis, Abbott, Roche, Merck/MSD, Janssen, Siemens, Falk, Abbvie, Bristol-Myers Squibb, Achillion, Abbott, Roche, Merck/MSD, Janssen

Dietrich Hueppe - Advisory Committees or Review Panels: Roche, MSD, Novatis, Gilead, BMS, Janssen, AbbVie

Michael P. Manns - Consulting: Roche, BMS, Gilead, Boehringer Ingelheim, Novartis, Enyo Pharma, Eiger, GSK, Merck/MSD, Janssen, Medgenics, Biotest, AbbVie; Grant/Research Support: Merck/MSD, Roche, Gilead, Novartis, Boehringer Ingelheim, BMS, AbbVie, Janssen; Speaking and Teaching: Merck/MSD, Roche, BMS, Gilead, Janssen, GSK, Novartis, AbbVie

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Treatment of HCV in the Department of Corrections (DOC) in the era of Oral Direct Acting Antivirals (DAA)

Richard K. Sterling, Reena Cherian, Lewis Shawn, Ravi Chhatrala, Anas Alsaleh, Kathleen Genther, Carloyn Driscoll, Kelly Martin, Scott C. Matherly, Mohammad Siddiqui, Velimir A. Luketic, R. Todd Stravitz, Puneet Puri, Hannah Lee, Paula G. Smith, Arun J. Sanyal; Virginia Commonwealth University, Richmond, VA

Chronic HCV is prevalent in the DOC. Although SVR with DAA treatment (tx) is high, feasibility and SVR of patients (pt) in the DOC are unknown. We compared SVR12 in the Virginia DOC with DAAs through telemedicine to HCV pts in our privately-insured and indigent clinics treated with Ledipasvir/Sofosbuvir. **Methods**: DOC pts were evaluated via telemedicine for disease severity and appropriateness for tx following AASLD-IDSA Guidelines. Those with decompensated cirrhosis, significant co-morbidities, or those with less than 9 months on their sen-

tence we excluded. Demographic, baseline labs, HIV and prior tx status (naïve (TN) or experienced (TE)), % advanced fibrosis (AF, bridging fibrosis/cirrhosis), duration of tx, use of ribavirin (RBV), and SVR12 (the primary outcome) were recorded. We compared SVR12 in our DOC pts to 2 control groups: our privately-insured and indigent tx clinics during the same time period by the same providers. We excluded those with non-genotype (GT)1 (n= 45) and those GT1 treated with other DAAs (n=16). **Results:** 255 consecutive pts were included: 50 DOC pts were compared to 161 private and 44 indigent pts who had SVR12 data available. The characteristics of our populations and SVR12 are shown in the table. Those in the DOC were younger, male, TN, had AF, received RBV and 12 weeks of tx. SVR12 was 98% in the DOC and similar to our indigent (98%) compared to our private clinics (89%; p=.02) even when those who were lost to follow up were excluded (SVR12 91%). Multiple logistic regression identified treatment clinic (p=.02) and FIB-4 (.0002) as predictors of lack of SVR12 with no impact of race, gender, age, duration or prior tx history, RBV use, or HIV. **Conclusions:** Tx of HCV in the DOC by telemedicine with DAA is not only feasible, but has a very high SVR12. The higher SVR12 in the DOC compared to our private clinic may be due to directly observed therapy or differences in pt characteristics (lower FIB-4, a marker of disease severity). Additional data with longer follow up in the DOC are needed.

Characteristic	DOC (n=50)	Private (n=161)	Indigent (n=44)	p
Age	54±7	59±8	56±7	<.0001
% Male	96	65	56	<.0001
% White	66	53	43	.19
% AF	100	89	72	.005
FIB-4	3.9±2.2	5.5±4.3	4.8±4.2	.04
% TE/TN	16/84	50/50	27/73	<.0001
% HIV+	4	10	0	<.0001
% RBV use	88	36	25	<.0001
% 12 weeks	100	78	98	.0003
% SVR	98	89	98	.02
% lost to f/u	0	4	0	

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Velimir A. Luketic - Advisory Committees or Review Panels: GSK; Grant/Research Support: INTERCEPT, LUMENA/SHIRE, MERCK, GILEAD, GENFIT, BMS, ABVIE, NGM

Arun J. Sanyal - Advisory Committees or Review Panels: Bristol Myers, Gilead, Genfit, Abbott, Ikaria, Exhalenz, Pfizer, Novartis; Consulting: Salix, Immuron, Exhalenz, Nimbus, Genentech, Echosens, Takeda, Merck, Enanta, Zafgen, JD Pharma, Islet Sciences, Hemoshear; Grant/Research Support: Salix, Genentech, Intercept, Ikaria, Takeda, GalMed, Novartis, Gilead, Tobira; Independent Contractor: UpToDate, Elsevier; Management Position: Sanyal Biotechnology

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8 weeks treatment under real life conditions with Ledipasvir/Sofosbuvir in HIV co-infected treatment-naïve HCV genotype 1 patients demonstrates similar results to mono-infected HCV patients: data from the German Hepatitis C-Registry (DHC-R)

Peter Buggisch[1], Klaus H. Boeker[2], Rainer Günther[3], Gerlinde Teuber[4], Hartwig H. Klinker[5], Anita Pathil[6], Stefan Christensen[7], Heike Pfeiffer-Vornkahl[8], Karl-Georg Simon[9], Claus Niederau[10], Heiner Wedemeyer[11], Stefan Zeuzem[12], German Hepatitis C-Registry[13]; [1]ifi-institute for interdisciplinary medicine, Hamburg, Germany; [2]Center of Hepatology, Hannover, Germany; [3]Department of Internal Medicine I, UK S-H, Campus Kiel, Kiel, Germany; [4]Center of Hepatology, Frankfurt, Germany; [5]University Hospital Würzburg, Würzburg, Germany; [6]Internal Medicine IV, Gastroenterology and Hepatology, University Clinic of Heidelberg, Heidelberg, Germany; [7]Center for interdisciplinary Medicine (CIM), Muenster, Germany; [8]e.factum GmbH, Butzbach, Germany; [9]MVZ Dr.Eisenbach Dr.Simon Dr.Schwarz GbR, Leverkusen, Germany; [10]St. Josef-Hospital, Katholisches Klinikum Oberhausen, Oberhausen, Germany; [11]Gastroenterology,Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [12]Department of Internal Medicine I, J.W. Goethe University Hospital, Frankfurt, Germany; [13]Leberstiftungs-GmbH Deutschland, Hannover, Germany

Introduction: Ledipasvir/Sofosbuvir (LDV/SOF) for 8-24 weeks is approved for the treatment of chronic hepatitis C. In the ION-3 study 8 weeks of LDV/SOF was non-inferior to 12 wks in previously untreated GT1 patients without cirrhosis. Although the number of patients eligible for 8 weeks according to the summary of product characteristics (SmPC) is high, a large proportion of patients still receives a longer treatment duration. One of the reasons might be the uncertainty whether 8 weeks treatment duration is sufficient in harder to cure populations as HIV co-infected patients, patients on opioid substitution treatment (OST) or older patients (> 70 yrs.). Aim of this analysis was to evaluate the virologic response rates of 8 wks treatment under real world conditions in these patients. **Methods:** The German Hepatitis C registry is a national multicenter cohort. Patients are treated at the discretion of the physician. Data are collected by a web-based data system and confirmed by plausibility checks and on site monitoring. In this analysis data of patients with 8 or 12 wks treatment with LDV/SOF and available SVR12 data (data cut 2/2016) were included. Baseline characteristics, prior treatment history, safety and effectiveness were investigated. **Results:** 831 (433 female) pts were treated for 8 weeks. The mean (SD) age was 50.2 (12.9) yrs. In 37% the fibrosis stage was evaluated by elastography (Fibroscan®), the mean (SD) stiffness value was 6.5 kPa (2.4). 674 pts reached the SVR 12 time point and were included in the analysis. Genotype distribution was 99.1% for GT1 and 0.9% for GT4. Baseline viral load was > 6 Mio IU/mL in 2,7%, 8,6% were treatment experienced and 2.5% had liver cirrhosis and were treated for 8 weeks despite these characteristics. The overall SVR 12 rate was 93% (ITT) and 98% (PP). 59 (8.8%) pts had HIV co-infection. SVR 12 in this group was 93.2% (ITT) and 96.6% (PP), only 2 viral relapses occurred. 72 pts received OST, only 1 pt developed viral relapse. 5 pts discontinued therapy and 5 were lost to follow up, thus, SVR12 was 84.7% (ITT) and 98.6% (PP) compared to 94.5% (ITT) and 97.9% (PP) without OST. 48 pts were >70 yrs. with SVR12 rates of 95.8% (ITT) and 97.9% (PP). 65 pts who were pretreated achieved SVR12 rates of 90.8% (ITT) and 95.2% (PP). **Conclusions:** Under real world conditions, 8 wks LDV/SOF achieves very high SVR rates in heterogeneous groups like HIV co-infected pts and in other so called harder to cure populations.

Disclosures:

Peter Buggisch - Advisory Committees or Review Panels: Janssen, AbbVie, BMS; Speaking and Teaching: Falk, MSD, Gilead, Merz Pharma

Klaus H. Boeker - Consulting: Janssen; Speaking and Teaching: MSD, Roche, Gilead, BMS, Falk Foundation, Novartis, AbbVie

Rainer Günther - Speaking and Teaching: Roche Pharma AG, Gilead, AbbVie

Gerlinde Teuber - Advisory Committees or Review Panels: MSD, Gilead, Abbvie; Grant/Research Support: Gilead, Abbvie, Falk; Speaking and Teaching: MSD, Gilead, BMS, Abbvie, Janssen

Hartwig H. Klinker - Advisory Committees or Review Panels: AbbVie, BMS, Gilead, Hexal, Janssen, MSD; Grant/Research Support: AbbVie, BMS, Gilead, Janssen, MSD, Arrowhead, Novartis; Speaking and Teaching: AbbVIe, BMS, Gilead, Janssen, MSD

Anita Pathil - Speaking and Teaching: AbbVie, BMS, Gilead

Stefan Christensen - Advisory Committees or Review Panels: BMS, Abbvie, Janssen, ViiV, Gilead, MSD; Speaking and Teaching: Gilead, MSD, Abbvie, BMS, Janssen

Heike Pfeiffer-Vornkahl - Employment: efactum GmbH

Karl-Georg Simon - Advisory Committees or Review Panels: AbbVie, BMS, JANSSEN, MSD; Speaking and Teaching: AbbVie, BMS, FALK, GILEAD, JANSSEN, NORGINE, MERZ, MSD

Claus Niederau - Advisory Committees or Review Panels: MSD, Abbvie, Jannsen, Gilead; Consulting: MSD; Grant/Research Support: MSD; Speaking and Teaching: MSD, Abbvie, BMS, Roche, Gilead

Heiner Wedemeyer - Advisory Committees or Review Panels: Transgene, MSD, Roche, Gilead, Abbott, BMS, Falk, Abbvie, Novartis, GSK, Roche Diagnostics, Eiger; Consulting: MyrGmbH; Grant/Research Support: MSD, Novartis, Gilead, Roche, Abbott, Roche Diagnostics; Speaking and Teaching: BMS, MSD, Novartis, ITF, Abbvie, Gilead

Stefan Zeuzem - Consulting: Abbvie, Bristol-Myers Squibb Co., Gilead, Merck & Co., Janssen

German Hepatitis C-Registry - Grant/Research Support: AbbVie Deutschland GmbH & Co. KG, Bristol-Myers Squibb GmbH & Co. KGaA, Gilead Sciences GmbH, Janssen-Cilag GmbH, MSD Sharp & Dohme GmbH, Roche Pharma AG

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WITHDRAWN

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QUARTZ II-III: Final Efficacy and Safety Results in Patients with HCV Genotype 2 or 3 Infection Treated With Ombitasvir/Paritaprevir/Ritonavir and Sofosbuvir With or Without Ribavirin

Stephen Shafran[1], David Shaw[6], Mariem Charafeddine[5], Kosh Agarwal[2], Graham R. Foster[3], Manal Abunimeh[5], Bo Fu[5], Tami Pilot-Matias[5], Rajvineeth K. Pothacamury[5], Eric Cohen[5], Daniel E. Cohen[5], Edward J. Gane[4]; [1]University of Alberta, Edmonton, AB, Canada; [2]Kings College Hospital, London, United Kingdom; [3]Barts Health, Queen Mary University of London, London, United Kingdom; [4]Liver Unit, Auckland City Hospital, Auckland, New Zealand; [5]AbbVie, Inc., North Chicago, IL; [6]Royal Adelaide Hospital, Adelaide, SA, Australia

Background Hepatitis C virus (HCV) genotypes (GT) 2 and 3 account for an estimated 40% of global HCV infections. GT3 is the most difficult to cure with direct-acting antiviral (DAA) therapy, especially in patients with cirrhosis or prior treatment failure. We previously presented safety and efficacy of ombitasvir (NS5A inhibitor) co-formulated with the protease inhibitor paritaprevir (identified by Abbvie and Enanta) and ritonavir (OBV/PTV/r; 2D) plus sofosbuvir (SOF) ± ribavirin (RBV) in 20 GT3-infected patients (QUARTZ-II/III Arms A and B). Here we investigate the safety and efficacy of 6- and 8-week treatment durations of 2D+SOF+RBV in 18 GT2-infected patients, and assess 12-week 2D+SOF± RBV in 20 additional GT3-infected patients, including those with cirrhosis. **Methods** QUARTZ II-III (NCT02292719) is an open-label, multicenter study. GT2-infected patients received OBV/PTV/r 50/150/100mg + SOF 400mg ± weight-based RBV for 8 (Arm C) or 6 (Arm D) weeks. GT3-infected patients with cirrhosis (Arm E) received 2D+SOF+RBV for 12 weeks; GT3-infected patients without cirrhosis received 2D+SOF with (Arm B) or without (Arms A+F) RBV for 12 weeks. The primary efficacy endpoint is the percentage of patients achieving SVR12. **Results** The study enrolled 70 patients. Table 1 shows select baseline demographics, efficacy, & safety data for 54 patients. As of post-treatment week 4 (PTW4), 35/37 (95%) patients with available data had HCV RNA<LLOQ. Two GT2-infected patients, one each in Arm C (8 weeks) and Arm D (6 weeks), experienced relapse at PTW4. To date, there have been no virologic failures in patients with GT3 infection, regardless of cirrhosis status. The most common AEs were fatigue (42%), headache (36%), nausea (24%), and diarrhea (20%). No serious AEs were related to DAAs and no DAA-related AEs led to discontinuation of study drug. **Conclusions** 2D+SOF±RBV was well tolerated in patients with GT2 or 3 infection, and most patients achieved SVR4. Complete SVR12, resistance, and safety data will be presented.

Table 1.Baseline Demographics, Safety and SVR4

	Arm C: GT2 + RBV 8 Weeks N = 10	Arm D: GT2 + RBV 6 Weeks N = 8	Arm E: GT3 Cirrhosis + RBV 12 Weeks N = 17	Arm A+F: GT3 No RBV 12 Weeks N = 19
Male, n (%)	5 (50)	5 (63)	8 (47)	13 (68)
White race, n (%)	10 (100)	6 (75)	13 (76)	16 (84)
Treatment-experienced, n (%)	2 (20)	2 (25)	14 (58)	9 (47)
SVR4 n/N, (%)	9/10 (90)	3/4 (75)	8/8 (100)	15/15 (100)
Any AE	10 (100)	8 (100)	15 (88)	16 (84)
Serious AE	1 (10)	0	2 (12)	0
AE leading to RBV dose reduction	2 (20)	0	2 (12)	-
Bilirubin Grade 3 (3 × ULN)	0	0	1 (6)	0
Alanine aminotransferase Grade 3 (>5 × ULN)[1]	1 (10)	0	2 (12)	0
Aspartate aminotransferase Grade 3 (>5 × ULN)[1]	0	0	1 (6)	0

GT, genotype; RBV, ribavirin; AE, adverse event; ULN, upper limit of normal
[1]Post-nadir

Disclosures:

Stephen Shafran - Advisory Committees or Review Panels: Bristol-Myers Squibb, Gilead Sciences, Merck; Grant/Research Support: AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck; Speaking and Teaching: Pfizer

Mariem Charafeddine - Employment: AbbVie Ltd; Stock Shareholder: AbbVie Ltd

Kosh Agarwal - Advisory Committees or Review Panels: Gilead, BMS, Novartis, Janssen, AbbVie; Consulting: MSD, Janssen, Achillion, Intercept; Grant/Research Support: Roche, Gilead, BMS, Arbutus; Speaking and Teaching: Astellas, Gilead, BMS, GSK

Graham R. Foster - Advisory Committees or Review Panels: GlaxoSmithKline, Novartis, Boehringer Ingelheim, Tibotec, Gilead, Janssen, Idenix, GlaxoSmithKline, Novartis, Roche, Tibotec, Chughai, Gilead, Merck, Janssen, Idenix, BMS, Alnylam; Board Membership: Boehringer Ingelheim; Grant/Research Support: Roche, Chughai, Springbank; Speaking and Teaching: Roche, Gilead, Tibotec, Merck, BMS, Boehringer Ingelheim, Gilead, Janssen

Manal Abunimeh - Employment: AbbVie

Bo Fu - Employment: AbbVie

Tami Pilot-Matias - Employment: AbbVie; Stock Shareholder: Abbott

Daniel E. Cohen - Employment: AbbVie; Stock Shareholder: AbbVie

Edward J. Gane - Advisory Committees or Review Panels: AbbVie, Janssen, Gilead Sciences, Achillion, Merck; Speaking and Teaching: AbbVie, Gilead Sciences, Merck, Alnylam

The following people have nothing to disclose: David Shaw, Rajvineeth K. Pothacamury, Eric Cohen

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RUBY-I: Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir with or without Ribavirin in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection with Severe Renal Impairment or End-Stage Renal Disease

John M. Vierling[1], Eric Lawitz[2], K. Rajender Reddy[3], Eric Cohen[4], Nyingi Kemmer[5], Giuseppe Morelli[6], Philippe J. Zamor[7], Michael Bennett[8], David E. Bernstein[9], Kris V. Kowdley[10], Parvez S. Mantry[11], Paul J. Pockros[12], David L. Wyles[13], Sonal Kumar[14], Kalyan R. Bhamidimarri[15], Daniel E. Cohen[4], Tami Pilot-Matias[4], Wangang Xie[4], Thomas Podsadecki[4], Tarek I. Hassanein[16]; [1]Baylor-St. Luke's Medical Center/St. Luke's Advanced Liver Therapies, Houston, TX; [2]The Texas Liver Institute, University of Texas Health Science Center, San Antonio, TX; [3]University of Pennsylvania, Philadelphia, PA; [4]AbbVie Inc., North Chicago, IL; [5]Tampa General Medical Group, Tampa, FL; [6]University of Florida Health Science Center, Gainesville, FL; [7]Carolinas Medical Center, Charlotte, NC; [8]Medical Associates Research Group, San Diego, CA; [9]North Shore University Hospital, Manhasset, NY; [10]Swedish Medical Center, Seattle, WA; [11]The Liver Institute at Methodist Dallas, Dallas, TX; [12]Scripps Clinic, Scripps Clinic, LaJolla, CA; [13]University of California San Diego, LaJolla, CA; [14]Weill Cornell Medical College, New York, NY; [15]University of Miami, Miami, FL; [16]Southern California GI and Liver Centers and Southern California Research Center, Coronado, CA

BACKGROUND: Combinations of direct acting antiviral agents (DAAs) have demonstrated high rates of sustained virologic response (SVR) in patients with chronic hepatitis C virus (HCV) infection in compensated cirrhotics and non-cirrhotics. However, clinical data are limited for DAAs in patients with comorbid renal dysfunction. RUBY-I is a phase 3b, open-label, multi-center study assessing the safety and efficacy of OBV/PTV/r + DSV ± RBV in GT1 HCV-infected patients with severe renal impairment or end-stage renal disease, including dialysis. Results from the first cohort were previously presented; here we present safety and efficacy data from the second cohort (Arms C-E), including patients with compensated cirrhosis. **METHODS:** Participants were either treatment naïve (TN) or treatment experienced (TE) with IFN/pegIFN and RBV. Patients with GT1a HCV infection and fibrosis stages <F4 were assigned to Arm C and received the 3-DAA regimen with RBV 200 mg QD for 12 weeks, while those with fibrosis stage F4 were assigned to Arm D and treated with the same regimen for 24 weeks. Patients with GT1b HCV infection with fibrosis stages F0-F4 were assigned to Arm E and treated with the 3-DAA regimen without RBV for 12 weeks. Efficacy is assessed by SVR at post-treatment week 12 (SVR12). Safety is assessed in all patients who received at least 1 dose of the study drugs. **RESULTS:** A total of 48 patients with chronic HCV infection (31% with and 69% without cirrhosis) and with severe renal impairment or end stage renal disease were enrolled in this cohort: 28 in Arm C, 9 in Arm D and 11 in Arm E. Among them, 83% were male and 54% were black. All patients had either stage 4 (17%) or 5 chronic kidney disease, including 69% on hemodialysis. As of the data cut-off date (May 5, 2016), SVR4 was achieved in 29/31 (94%) patients (16/17, 2/3 and 11/11 in Arms C, D and E, respectively) in the intent-to-treat population. Both patients not achieving SVR4 prematurely discontinued treatment. Most treatment emergent adverse events (AEs) were mild or moderate in severity, with anemia (27%), decreased hemoglobin (23%) and fatigue (21%) the most frequently reported. Ten patients experienced serious AEs and one patient discontinued treatment in each of Arms C and D. **CONCLUSIONS:** Preliminary data from this ongoing study demonstrated an SVR4 rate of 94%. Most AEs were mild or moderate in severity. These results support the use of this regimen in patients with advanced renal disease, for whom treatment options are limited.

Disclosures:

John M. Vierling - Advisory Committees or Review Panels: Abbvie, Bristol-Meyers-Squibb, Gilead, Hyperion, Intercept, Janssen, Novartis, Merck, Sundise, HepQuant, Salix, Immuron, Exalenz, Chronic Liver Disease Foundation; Board Membership: Clinical Research Centers of America, LLC; Grant/Research Support: Abbvie, Bristol-Meyers-Squibb, Eisai, Gilead, Hyperion, Intercept, Janssen, Novartis, Merck, Sundise, Ocera, Mochida, Immuron, Exalenz, Conatus; Speaking and Teaching: GALA, Chronic Liver Disease Foundation, ViralEd, Chronic Liver Disease Foundation, Clinical Care Options

Eric Lawitz - Advisory Committees or Review Panels: AbbVie, Achillion Pharmaceuticals, Regulus, Theravance, Enanta, Idenix Pharmaceuticals, Janssen, Merck & Co, Novartis, Gilead; Grant/Research Support: AbbVie, Achillion Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmith-Kline, Idenix Pharmaceuticals, Intercept Pharmaceuticals, Janssen, Merck & Co, Novartis, Nitto Denko, Theravance, Salix, Enanta; Speaking and Teaching: Gilead, Janssen, AbbVie, Bristol Meyers Squibb, Merck, intercept

K. Rajender Reddy - Advisory Committees or Review Panels: Merck, Janssen, BMS, Abbvie, Gilead; Grant/Research Support: Merck, BMS, Gilead, Janssen, Abbvie

Philippe J. Zamor - Advisory Committees or Review Panels: Bristol Myers Squibb, Gilead; Grant/Research Support: Gilead, AbbVie, Merck; Speaking and Teaching: Bristol Myers Squibb, Gilead, AbbVie

David E. Bernstein - Consulting: abbvie, Merck, Janssen; Grant/Research Support: GIlead, abbvie, BMS, Janssen; Speaking and Teaching: Gilead

Kris V. Kowdley - Advisory Committees or Review Panels: Abbvie, Enanta, Gilead, Intercept, Merck, Novartis, Trio Health, Verylx; Grant/Research Support: Abbvie, Evidera, Galectin, Gilead, Immuron, Intercept, Merck, NGM Biopharma, Novartis, Tobira, Trio Health; Speaking and Teaching: Gilead, Intercept

Parvez S. Mantry - Consulting: Salix, Gilead, Janssen, Abbvie, BMS; Grant/Research Support: Salix, Merck, Gilead, Boehringer-Ingelheim, Mass Biologics, Vital Therapies, Santaris, mass biologics, Bristol-Myers Squibb, Abbive, Bayer-Onyx, Shinogi, Tacere, Intercept; Speaking and Teaching: Gilead, Janssen, Salix

Paul J. Pockros - Advisory Committees or Review Panels: Janssen, Merck, BMS, Gilead, AbbVie; Consulting: Lumena, Beckman Coulter; Grant/Research Support: Intercept, Janssen, BMS, Gilead, Lumena, Beckman Coulter, AbbVie, RMS, Merck; Speaking and Teaching: AbbVie, Janssen, Gilead

David L. Wyles - Advisory Committees or Review Panels: Bristol Myers Squibb, Gilead, Merck, AbbVie; Grant/Research Support: Gilead, Merck, Bristol Myers Squibb, AbbVie, Tacere

Sonal Kumar - Advisory Committees or Review Panels: Gilead, Intercept, Abbvie; Speaking and Teaching: Intercept, Gilead

Kalyan R. Bhamidimarri - Advisory Committees or Review Panels: Gilead, Bristol Myers Squibb, Salix; Speaking and Teaching: Alexion

Daniel E. Cohen - Employment: AbbVie; Stock Shareholder: AbbVie

Tami Pilot-Matias - Employment: AbbVie; Stock Shareholder: Abbott

Wangang Xie - Employment: AbbVie

Thomas Podsadecki - Employment: AbbVie; Stock Shareholder: AbbVie

Tarek I. Hassanein - Advisory Committees or Review Panels: AbbVie Pharmaceuticals, Bristol-Myers Squibb, Trek Therapeutics; Grant/Research Support: AbbVie Pharmaceuticals, Obalon, Bristol-Myers Squibb, Eiasi Pharmaceuticals, Gilead Sciences, Merck Sharp & Dohme, NGM BioPharmaceuticals, Ocera Therapeutics, Salix Pharmaceuticals, Sundise, TaiGen Biotechnology, Vital Therapies, Tobria, Shinoghi & Co. Ltd, La Jolla Pharmaceuticals, Trek Therapeutics, Novo Nordisk, Intercept; Speaking and Teaching: Baxter, Bristol-Myers Squibb, Gilead Sciences, Salix Pharmaceuticals, AbbVie Pharmaceuticals

The following people have nothing to disclose: Eric Cohen, Nyingi Kemmer, Giuseppe Morelli, Michael Bennett

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Frequency and severity of biochemical abnormalities with paritaprevir/ritonavir/ombitasvir +/- ribavirin in a real-world cohort of HCV Genotype 1 patients – predictors and clinical significance

John Lubel[1,6], Joanne Mitchell[2], Stephen Pianko[3], Alex J. Thompson[4,5], David M. Iser[4], Alessia Gazzola[2], Sarah Chivers[6], Gauri Mishra[3], John Gough[4], Simone I. Strasser[7], Gregory Dore[8], Katherine A. Stuart[9], Jacob George[10,11], Edmund Tse[12], Amany Zekry[13], Miriam Levy[14], Gerry C. MacQuillan[15], Vince Fragomeli[16], Paul Gow[17], Brenda Morales[17], Joe Sasadeusz[18], Saroj Nazareth[19], Steven J. Bollipo[20], Tracey L. Jones[20], Amanda J. Wade[21], Stuart K. Roberts[2]; [1]Gastroenterology and Hepatology, Eastern Health, Melbourne, VIC, Australia; [2]Gastroenterology, Alfred Health, Melbourne, VIC, Australia; [3]Gastroenterology, Monash Health, Melbourne, VIC, Australia; [4]Gastroenterology, St Vincent's Hospital, Melbourne, VIC, Australia; [5]University of Melbourne, Melbourne, VIC, Australia; [6]Eastern Health Clinical School, Monash University, Melbourne, VIC, Australia; [7]AW Morrow Gastroenterology and Liver Centre, Royal Prince Alfred Hospital, Sydney, NSW, Australia; [8]HIV, Immunology, Infectious Diseases Department, St Vincent's Hospital, Sydney, NSW, Australia; [9]Gastroenterology, Princess Alexandra Hospital, Brisbane, QLD, Australia; [10]Storr Liver Centre, Westmead Institute for Medical Research, Sydney, NSW, Australia; [11]University of Sydney, Sydney, NSW, Australia; [12]Gastroenterology, Royal Adelaide Hospital, Adelaide, VIC, Australia; [13]Gastroenterology, St Georges Hospital, Sydney, NSW, Australia; [14]Gastroenterology, Liverpool Hospital, Sydney, NSW, Australia; [15]Gastroenterology, Sir Charles Gairdner Hospital, Perth, WA, Australia; [16]Gastroenterology, Nepean Hospital, Sydney, NSW, Australia; [17]Victorian Liver Transplant Unit, Austin Health, Melbourne, VIC, Australia; [18]VIDS and Peter Doherty Institute, Royal Melbourne Hospital, Melbourne, VIC, Australia; [19]Gastroenterology, Royal Perth Hospital, Perth, WA, Australia; [20]Gastroenterology, John Hunter Hospital, Newcastle, NSW, Australia; [21]Infectious Diseases, Barwon Health, Geelong, VIC, Australia

Background and Aims In October 2015 the FDA released a warning on the use of ritonavir-boosted paritaprevir, with ombitasvir and dasabuvir (PrOD) +/- ribavirin in patients with cirrhosis. Consequently PrOD is now contraindicated in patients with Child-Turcotte Pugh class B/C hepatic impairment. Both hyperbilirubinemia and elevated ALT concentrations have been observed during therapy but the severity and clinical significance of these abnormalities in a real-world setting have not been reported. The aims of this study were to characterize the bilirubin and ALT changes observed during PrOD therapy in a large real-world population and to determine the impact of these changes on outcome (SVR12 and early discontinuation of therapy). **Methods** Patients who participated in an Australian compassionate access program to treat hepatitis C between October 2014 and July 2015 were included in the analysis if they received at least one dose of PrOD. Elevations in bilirubin were characterized in accordance with the Common Terminology Criteria for Adverse Events (CTCAE v4.0). **Results** There were 461 patients included in this analysis. The majority had cirrhosis (74%). In the 88% of cirrhotic patients with complete response data, the SVR12 was 95.5%. Hyperbilirubinemia on PrOD was very common with elevated values ≥ 2mg/dL (34μmol/L) occurring in 45.1 % of subjects (Table 1). A small proportion of patients had mild elevation (≥2mg/dL in 6.5%) prior to comemncing. In the 9 patients that experienced elevations in bilirubin >10 mg/dL, all were cirrhotic, 89% developed hyperbilirubinemia within the first 4 weeks of therapy and 78% ceased therapy early (mean 4.79 weeks ± 1.5). In most instances the ALT diminished on PrOD (88%, mean 58 IU/L ±4.4), however in 11 patients (2.4%) there was an increase in ALT of at least 100 IU/L from baseline. This was not associated with hyperbilirubinemia and 73% were cirrhotic with SVR12 of 80%. **Conclusions** In this real-world study of HCV genotype 1 patients mostly with cirrhosis, SVR12 rates were excellent. Hyperbilirubinemia occurred commonly but in most instances the abnormality was only mild-moderate and did not lead to discontinuation or significantly impact upon SVR 12. In a small proportion of patients the bilirubin exceeded 10mg/dL and this frequently resulted in early discontinuation.

Maximum bilirubin increase on PrOD

Maximum bilirubin (mg/dL)	n, percent (%)
2-3 mg/dL	106 (23.0%)
3-5 mg/dL	73 (15.5%)
5-10 mg/dL	20 (4.3%)
>10 mg/dL	9 (2.0%)
TOTAL	45.1 %

Disclosures:

John Lubel - Advisory Committees or Review Panels: Gilead, Abbvie, Bayer; Grant/Research Support: BMS, MSD, Abbvie; Speaking and Teaching: Gilead, Abbvie, BMS, Jansen, Roche

Stephen Pianko - Advisory Committees or Review Panels: Roche, Novartis, GILEAD, Roche, Novartis; Consulting: GILEAD; Speaking and Teaching: JANSSEN, BMS

Alex J. Thompson - Advisory Committees or Review Panels: Gilead, Abbvie, BMS, Merck, Spring Bank Pharmaceuticals, Arrowhead, Roche; Grant/Research Support: Gilead, Abbvie, BMS, Merck; Speaking and Teaching: Roche, Gilead, Abbvie, BMS

David M. Iser - Speaking and Teaching: AbbVie, Bristol Myers Squibb, Gilead, Janssen, Merck, Roche

Simone I. Strasser - Advisory Committees or Review Panels: AbbVie, MSD, Bristol-Myers Squibb, Gilead, Norgine, Bayer Healthcare; Speaking and Teaching: Roche Products Australia, Bayer Healthcare, Bristol-Myers Squibb, MSD, Gilead, Abbvie

Gregory Dore - Board Membership: Gilead, Merck, Abbvie, Bristol-Myers Squibb; Grant/Research Support: Gilead, Merck, Abbvie, Bristol-Myers Squibb; Speaking and Teaching: Gilead, Merck, Abbvie, Bristol-Myers Squibb

Katherine A. Stuart - Advisory Committees or Review Panels: Gilead, Bayer, AbbVie; Grant/Research Support: Roche

Jacob George - Advisory Committees or Review Panels: Pharmaxis, BMS, MSD, Gilead, Janssen, Abbvie; Grant/Research Support: MSD

Amany Zekry - Advisory Committees or Review Panels: GILEAD, BMS, MSD, Abbvie

Miriam Levy - Advisory Committees or Review Panels: Bayer; Grant/Research Support: Gilead

Vince Fragomeli - Advisory Committees or Review Panels: Roche, MSD, Jansen

Brenda Morales - Advisory Committees or Review Panels: MSD, Jansen, Roche, Abbvie, BMS

Joe Sasadeusz - Advisory Committees or Review Panels: Merck, Gilead, BMS; Grant/Research Support: Roche, Gilead, Avvbie; Speaking and Teaching: Gilaed, Merck, BMS, Merck

Amanda J. Wade - Grant/Research Support: AbbVie

Stuart K. Roberts - Board Membership: AbbVie, Gilead

The following people have nothing to disclose: Joanne Mitchell, Alessia Gazzola, Sarah Chivers, Gauri Mishra, John Gough, Edmund Tse, Gerry C. MacQuillan, Paul Gow, Saroj Nazareth, Steven J. Bollipo, Tracey L. Jones

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Reduced ITPase Activity Protects Against Ribavirin-Induced Anemia, but does not Predict Virologic Response in Interferon-free, Ribavirin Containing Regimens

Aparna Vasanthakumar[1], Manal Abunimeh[2], Jonas Soderholm[2], Justin W. Davis[1], Emily O. Dumas[2], Daniel E. Cohen[2], Jeffrey F. Waring[1], Martin Lagging[3]; [1]Pharmacogenetics and Pharmacogenomics, AbbVie, North Chicago, IL; [2]AbbVie, North Chicago, IL; [3]Division of Infectious Disease, Univ. Gothenberg, Gothenburg, Sweden

Background: Genetic variants of the inosine triphosphatase (*ITPA*) gene that confer reduced ITPase activity have been

associated with protection against ribavirin-induced hemolytic anemia in peginterferon (IFN)/ribavirin-based treatment of hepatitis C virus (HCV). Studies in patients treated with IFN/ribavirin have shown improved treatment efficacy in patients with reduced ITPase activity. Ribavirin has been an important component of IFN-containing regimens, and is currently recommended in combination with several IFN-free regimens for treatment of HCV infections. In the present study, genetic analyses were conducted to interrogate the effect of these *ITPA* variants on anemia, platelet counts, and virologic response in HCV genotype 1a-infected subjects treated with the direct-acting antiviral (DAA) regimen of ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin. **Methods:** DNA samples were obtained from appropriately consented subjects enrolled in the PEARL-IV study (NCT01833533) and analyzed for *ITPA* variants rs7270101 and rs1127354 using pyrosequencing. **Results:** Reduction in ITPase activity protected against ribavirin-induced anemia, an effect that was more significant when gender was added as a covariate in the analyses. Male subjects with lower ITPase activity were protected against ribavirin-induced anemia (Hb change -0.92 g/dL in low ITPase vs. -2.65 g/dL in high ITPase; p=0.0013), whereas no such significant association was noted among female subjects (-0.92 g/dL in low ITPase vs. -1.7 g/dL in high ITPase; NS). ITPase activity did not have a significant impact on platelet counts overall; however female subjects with lower ITPase activity had a significantly higher incidence of thrombocytosis (32.63 $x10^9$/L in low ITPase vs 1.46 $x10^9$/L in high ITPase; p=0.016). No association was noted between ITPase activity reduction and Hb levels or platelet counts in patients treated without ribavirin. Reduction in ITPase activity had no impact on virologic response to DAA treatment, viral kinetics, or baseline IP-10 levels. **Conclusions:** Our study demonstrates that genetic variants in *ITPA* that associate with reduced activity may help predict anemia in chronic hepatitis C patients treated with IFN-free regimens containing ribavirin. This may be particularly helpful in the contexts of subjects with difficult to treat HCV infection, such as patients with cirrhosis for who ribavirin-containing regimens are recommended. In contrast to some of the studies that analyzed IFN-containing regimens, our study showed no impact of ITPase activity reduction on treatment outcome or relapse rates in DAA-based regimens.

Disclosures:

Manal Abunimeh - Employment: AbbVie

Jonas Soderholm - Employment: AbbVie

Justin W. Davis - Employment: abbvie

Emily O. Dumas - Employment: AbbVie; Stock Shareholder: AbbVie

Daniel E. Cohen - Employment: AbbVie; Stock Shareholder: AbbVie

Jeffrey F. Waring - Employment: AbbVie; Patent Held/Filed: AbbVie; Stock Shareholder: AbbVie

Martin Lagging - Advisory Committees or Review Panels: MSD, AbbVie, Gilead, Medivir, BMS; Speaking and Teaching: MSD, AbbVie, Gilead, Medivir, BMS

The following people have nothing to disclose: Aparna Vasanthakumar

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Elbasvir/Grazoprevir (EBR/GZR) Does Not Worsen Renal Function in Patients With Hepatitis C Virus (HCV) Infection and Pre-existing Renal Disease

K. Rajender Reddy[1], David Roth[2], Annette Bruchfeld[3], Peggy Hwang[4], Barbara Haber[4], Bach-Yen T. Nguyen[4], Eliav Barr[4], Janice Wahl[4], Wayne Greaves[4]; [1]University of Pennsylvania Hospital, Philadelphia, PA; [2]University of Miami Miller School of Medicine, Miami, FL; [3]Karolinska Institute, Stockholm, Sweden; [4]Merck & Co., Inc., Kenilworth, NJ

Decreased estimated glomerular filtration rate (eGFR) has been reported in patients with HCV infection receiving direct-acting antiviral agents. EBR/GZR was safe and efficacious in patients with chronic kidney disease stage 4/5 (CKD 4/5) in the C-SURFER study. The aim of this analysis was to evaluate the impact of EBR/GZR on eGFR in patients with less severe CKD. We analyzed a pooled dataset of 1689 patients who received EBR/GZR (50 mg/100 mg) with or without ribavirin (RBV) for 8 (n=91, 5%), 12 (n=1238, 73%), 16 (n=211, 12%), or 18 (n=149, 9%) weeks (656 patients [39%] received RBV). Patients were treatment-naïve or treatment-experienced, and included cirrhotics and those with HIV co-infection. Creatinine values were assessed at baseline and ≥1 post-baseline timepoint. eGFR was calculated using the Modified Diet in Renal Disease equation at baseline, end of treatment, and 12 weeks post-therapy. Of the 1689 patients evaluated, 32 had CKD 3 (eGFR <60 mL/min/1.73 m^2 to ≥30 mL/min/1.73 m^2) and 1657 had eGFR ≥60 mL/min/1.73 m^2 (**Table**). Demographics were similar in both groups except for a higher proportion of HIV–co-infected patients in the CKD 3 group (41% vs. 17%). Patients with CKD 3 and those with eGFR >60 mL/min/1.73 m^2 at baseline did not show any decrease in eGFR during treatment or follow-up. EBR/GZR did not affect eGFR in patients with pre-existing eGFR ≥60 mL/min/1.73 m^2 or those with CKD3. Treatment duration, RBV co-administration, cirrhosis, or HIV coinfection did not adversely affect renal outcome.

Patient Demographics and On-Treatment Change in eGFR

	Baseline eGFR <60 to ≥30 mL/min/1.73 m^2 n=32	Baseline eGFR ≥60 mL/min/1.73 m^2 n=1657
Mean age, years (range)	58.5 (32-82)	52.5 (18-79)
Male, n (%)	15 (47)	1023 (62)
Treatment-naïve, n (%)	25 (78)	1018 (61)
Cirrhotic, n (%)	8 (25)	449 (27)
Mean baseline viral load, IU/mL	3,344,605	4,030,364
Treatment duration, n (%)		
8 weeks	1 (3)	90 (5)
12 weeks	26 (81)	1212 (73)
16 weeks	2 (6)	209 (13)
18 weeks	3 (9)	146 (9)
Ribavirin in treatment regimen, n (%)	10 (31)	646 (39)
HIV co-infected, n (%)	13 (41)	285 (17)
Baseline MDRD eGFR†, mL/min/1.73 m^2 (range)	56 (45-59)	100 (61-364)
End-of-treatment MDRD eGFR, mL/min/1.73 m^2 (range)	58 (41-78)	97 (44-228)‡
MDRD eGFR at 12 weeks FU, mL/min/1.73 m^2 (range)	59 (38-78)	100 (48-364)¶

FU, follow-up. MDRD, Modification of Diet in Renal Disease.
† Median eGFR (range).
‡ Based on n = 1653.
¶ Based on n = 1590.

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David Roth - Advisory Committees or Review Panels: Merck, Sharp and Dome; Consulting: Merck, Sharp and Dome

Peggy Hwang - Employment: Merck, Merck

Barbara Haber - Employment: Merck & Co., Inc.

Bach-Yen T. Nguyen - Employment: Merck

Eliav Barr - Employment: Merck; Stock Shareholder: Merck

Janice Wahl - Employment: Merck & Co,

Wayne Greaves - Employment: Merck

The following people have nothing to disclose: Annette Bruchfeld

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High Sustained Virological Response Rates using Legally Imported, Generic Direct Acting Antiviral Treatment for Hepatitis C

James A. Freeman[2], Richard Sallie[3], Adam Kennedy[4], Greg Jeffreys[5], Anna Savage[6], Andrew M. Hill[1]; [1]Pharmacology, University of Liverpool, Liverpool, United Kingdom; [2]FixHepC, GP2U Telehealth, Hobart, TAS, Australia; [3]Hepatology, Nedlands Medical Centre, Nedlands, WA, Australia; [4]Kingswood Pharmacy, Kingswood, NSW, Australia; [5]University of Tasmania, Hobart, TAS, Australia; [6]Faculty of Medicine, Imperial College, London, United Kingdom

Introduction: High prices of Direct Acting Antivirals (DAAs) can prevent access to treatment. Generic versions of sofosbuvir, daclatasvir and ledipasvir are being mass produced for prices under 1% of the current US retail price. Patients have the legal right to import 3 months of treatment into Australia, UK, New Zealand and many other countries provided it is for their personal use. Worldwide, several thousand patients are being treated with legally imported Direct Acting Antivirals. There are Hepatitis C Buyers Clubs established in Russia, USA, Australia, SE Asia and the UK. This analysis assessed the efficacy and safety of generic DAAs accessed via these personal importation rules, through the FixHepC Buyers Club. **Methods:** Sofosbuvir (SOF), ledipasvir (LDV) and daclatasvir (DCV) were imported from generic companies in India, China and Bangladesh. Selection of DAAs and treatment duration depended on baseline HCV Genotype and fibrosis stage. To provision patient safety, these generic DAAs were evaluated for quality using High Precision Liquid Chromatograhy (HPLC) and Nuclear Magnetic Resonance (NMR). Patients were evaluated pre-treatment, during treatment and then for SVR 4 and 12. Adverse events were recorded. This analysis includes data from 481 patients from two clinics. Through the FixHepC Buyers Club, patients were treated in the USA, Europe, Australia, New Zealand and SE Asia. Summary SVR rates were compared with equivalent data from the original Phase 3 trials of SOF/LDV and SOF/DCV. **Results:** Of the 481 patients treated, 252 received SOF/LDV, 226 SOF/DCV and 3 SOF/RBV. Overall, the patients were 55% male with a mean age of 55 years; 30% had cirrhosis; 65% were Genotype 1 and the mean baseline HCV RNA was 6.48 log10 IU/mL. During the first four weeks of treatment, the viral decay kinetics of HCV RNA in the first weeks of treatment were similar to results from the original Phase 2 studies of SOF/DCV and SOF/LDV. Based on currently available data, the percentage with HCV RNA <LLOQ was 320/322 (99.4%) at end of treatment (EOT), 141/152 (92.8%) at SVR 4 and 102/112 (91.1%) at SVR12. In Genotype 1 the SVR4 rates were 93.2% (69/74) with SOF/LDV and 97.5% (39/40) with SOF/DCV. These SVR rates were consistent with results from the original trials of these DAA combinations. **Conclusions:** In this analysis, treatment with legally imported generic DAAs achieved overall SVR12 rates of 91.1% and these rates are comparable to those seen in Phase 3 trials of the branded treatments. Mass treatment with the current generic DAAs is a feasible, low-cost option where high prices prevent access to branded treatment.

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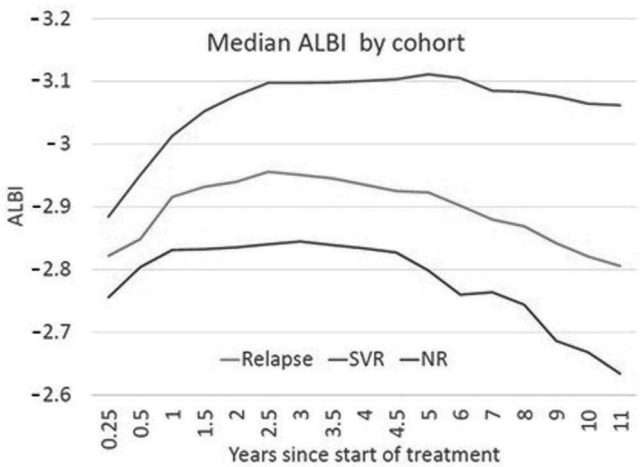
Long-term impact of response to interferon-based therapy in patients with chronic HCV in relation to liver function, survival and cause of death

Philip J. Johnson[1], Emily de Groot[2], Sarah Berhane[1], Toshifumi Tada[3], Takashi Kumada[3], Hidenori Toyoda[3]; [1]Molecular & Clinical Cancer Medicine, University of Liverpool, UK, Liverpool, United Kingdom; [2]University of St. Andrews, St. Andrews, United Kingdom; [3]Ogaki Municipal Hospital, Gifu, Japan

Purpose:. Among patients with chronic HCV**,** there is little information on the benefit of achieving SVR in terms of liver function in comparison to non-responders. Here we assess liver function by the recently devised ALBI score[1]. ***Methods:*** 1118 patients were followed-up for a median 8.9 years (95% CI 8.5 – 9.2) and classified as achieving SVR (59%), relapse (24%) or no response (NR 17%) having received interferon based therapy. ***Results.*** Differences in liver function in each group was evident by the end of treatment improving in all, but falling off rapidly in NR and relapse cohorts (figure). Survival was better in those with SVR (92% for SVR and 76% for non-SVR respectively at 15 years, p<0.0001). Fibrosis, as assessed by the FIB-4 index, progressed significantly in the R and NR groups. HCC was the major cause of death (47%), the great majority (90%) occurring among the non-SVR group. Overall 5.4% from those who died (or 0.6% overall) were recorded as dying from liver failure. ***Conclusions.*** Within the timeframe of this study SVR is associated with improved liver function and less progression of fibrosis but any improvement in survival appears to be largely as a result of reduction in HCC development. Reference: [1]Johnson PJ et al., J. Clin. Oncol. 2014.

Changes in ALBI score according to treatment response. Lower scores on the vertical axis indicate better liver function



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♦ Denotes AASLD Presidential Poster of Distinction

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Real World Effectiveness of Ledipasvir/Sofosbuvir (LDV/SOF) in Patients Coinfected With HCV and HIV-1: A Comparative Analysis of Clinical Trials with Four Real World Cohorts

Susanna Naggie[1], Eric Rosenthal[2], Sarah Kattakuzhy[3], Justin McGinnis[4], Sarjita Naik[5], Macky Natha[5], Joseph Llewellyn[5], Richard Haubrich[5], Anu O. Osinusi[5], Luisa M. Stamm[5], Curtis Cooper[6], Douglas T. Dieterich[7], Mark S. Sulkowski[8]; [1]Duke University, Durham, NC; [2]University Hospital Archet, Nice, France; [3]NIH, Rockville, MD; [4]University of Southern California, Los Angeles, CA; [5]Gilead Sciences, Foster City, CA; [6]Ottawa Hospital, Ottawa, ON, Canada; [7]Mt Sinai School of Medicine, New York, NY; [8]Johns Hopkins University, Baltimore, MD

BACKGROUND and AIMS: In clinical trials, SOF-based regimens have performed similarly in patients with HIV/HCV co-infection and HCV mono-infection. Recent reports suggest HCV monoinfected patients achieve similar SVR rates with SOF-based regimens in real world cohorts (RWC) as those observed in clinical trials, however this has not yet been demonstrated in HIV/HCV co-infected patients. The aim of this study was to compare the efficacy of the single tablet regimen of ledipasvir/sofosbuvir (LDV/SOF) in HCV genotype 1 patients with HIV/HCV co-infection in clinical trials to the effectiveness in RWC. METHODS: In this analysis, data from three clinical trials of LDV/SOF in HIV/HCV co-infected patients is compared to four RWC. RWC were selected based on willingness to participate and had at least 50 HIV/HCV co-infected patients. The clinical trials include data from ERADICATE, ION-4, and ANRS HC31 SOFTRIH study. The RWC include HCV-TRIO, ASCEND, Portugal, and Veterans Affairs (USC) and represent diverse patient populations from Europe and U.S. including academic centers, urban primary care settings and the Veterans Health Administration. Baseline characteristics and efficacy were analyzed. RESULTS: The clinical trials enrolled 445 patients with the following baseline characteristics: male (79%), black (40%), and cirrhosis (20%). The RWC studies enrolled 733 patients with the following overall baseline characteristics: male (79%), black (41%), and cirrhosis (30%) in those that reported demographics. Patients enrolled in the clinical trials were treated with 12 or 24 weeks of LDV/SOF with an overall SVR12 rate of 97%. In the RWC, patients were treated with 8, 12, or 24 weeks of LDV/SOF ± RBV and the overall SVR12 was 95%. The individual study results are presented in Table 1. CONCLUSIONS: Real world data in HIV/HCV co-infected patients correlates closely with data seen in the clinical trials. SVR rates were high across all populations including black race and treatment experienced patients with cirrhosis. This analysis demonstrates that SVR rates from RWC are generalizable from clinical trials.

Table 1. Clinical trials and RWC with LDV/SOF ± RBV in HIV/HCV co-infection

		N	SVR12, n/N (%)
Clinical Trials	ERADICATE	50	49/50 (98%)
	ION-4	327	314/327 (96%)
	SOFTRIH	68†	65/65 (100%)
Real World Cohorts	TRIO*	150	147/150 (98%)
	ASCEND	88	80/88 (91%)
	Portugal	287	279/287 (97%)
	Veterans Affairs, USC*	208	193/208 (93%)

† 65 patients were evaluable for virological efficacy.

*Contains patients treated for 8 weeks.

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Susanna Naggie - Advisory Committees or Review Panels: Merck; Grant/Research Support: Tacere, Gilead, AbbVie, BMS, Jenssen, Merck

Eric Rosenthal - Board Membership: gilead, msd, Abbvie

Justin McGinnis - Consulting: Gilead; Grant/Research Support: AbbVie

Sarjita Naik - Employment: Gilead Sciences

Macky Natha - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

Joseph Llewellyn - Employment: Gilead Sciences

Richard Haubrich - Employment: Gilead

Anu O. Osinusi - Employment: Gilead Sciences Inc; Stock Shareholder: Gilead Sciences Inc

Luisa M. Stamm - Employment: Gilead Sciences

Curtis Cooper - Advisory Committees or Review Panels: Gilead, Abbvie, MERCK; Grant/Research Support: MERCK, Gilead, Abbvie; Speaking and Teaching: MERCK, Abbvie, Gilead

Douglas T. Dieterich - Advisory Committees or Review Panels: Gilead, BMS, Abbvie, Janssen, Merck, Achillion

Mark S. Sulkowski - Advisory Committees or Review Panels: Merck, AbbVie, Janssen, Gilead, Trek, Cocrystal; Grant/Research Support: Merck, AbbVie, Janssen, Gilead

The following people have nothing to disclose: Sarah Kattakuzhy

893

New resistance-associated variants and failure of dual oral therapy with daclatasvir and asunaprevir

Seiichi Mawatari, Akihiro Moriuchi, Sho Ijuin, Haruka Sakae, Oki Taniyama, Kazuaki Tabu, Akihiko Oshige, Kohei Oda, Tsutomu Tamai, Akio Ido; Digestive and Lifestyle Diseases, Department of Human and Environmental Sciences, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan

OBJECTIVES: In Japan, dual oral therapy with daclatasvir (DCV) and asunaprevir (ASV) is the first interferon (IFN) -free therapy approved for patients with hepatitis C virus (HCV) genotype 1b infection in July 2014. Combination therapy with DCV and ASV has been primarily used in patients without NS5A L31 or Y93 resistance-associated variants (RAVs) prior to treatment. In this study, we examined the characteristics of patients without baseline L31 or Y93 RAVs who failed to achieve HCV eradication with DCV+ASV therapy and identified new baseline NS5A RAVs that are closely associated with failure of combination therapy. METHODS: A total of 335 patients with HCV genotype 1b infection with no NS5A L31, NS5A Y93, or NS3 D168 RAVs prior to DCV+ASV therapy were enrolled. RAVs were evaluated using the direct sequence method. RESULTS: Patient age ranged from 34 to 86 years (median, 70), 216 patients (65%) were female, and 107 (32%) patients had cirrhosis. One hundred eighty patients (54%) had prior IFN-based therapy, of whom 101 (56%) received pegylated-IFN+ribavirin treatment. Sustained virologic response at 12 weeks (SVR12) was achieved in 297 patients (89%). The rate of SVR12 in patients with cirrhosis or HCV RNA ≥6.2 logIU/mL was lower than in patients with chronic hepatitis or HCV RNA <6.2 logIU/mL (83% vs 91%, and 86% vs 92%, respectively). Patients with NS5A Q24, L28, and/or R30 RAVs had a significantly lower SVR12 rate compared with patients without these RAVs (67% vs 92%, p<0.001). The coexistence of NS5A F37 and Q54 RAVs was closely associated with treatment failure (with both RAVs, 80%; without both RAV, 92%, p=0.004). Although 43 patients had adverse events resulting in cessation of DCV+ASV therapy, all patients receiving DCV+ASV for more than six weeks, and those with ALT elevation, achieved SVR12. Multivariate analysis showed that NS5A Q24, L28, and/or R30 RAVs (odds ratios, 8.021; 95% confidence interval, 3.193–20.150), coexistence of F37 and Q54 (4.429; 1.936–10.132), discontinuation of therapy as a result of adverse events (5.403; 1.799–16.227), and grade 2 or higher ALT elevation (0.104; 0.012–0.913) were significantly associated with virologic failure. Pretreatment coexistence of NS5A Q24, L28, R30, F37, or Q54 RAVs was present in 28 of 29 (96.6%) patients with

virologic failure. CONCLUSION: In patients without NS5A L31 or Y93 RAVs, the virological effect of DCV+ASV therapy was associated with baseline NS5A Q24, L28, and/or R30 RAVs and coexistence of F37 and Q54 RAVs. These results indicate that coexistence of baseline RAVs other than NS5A L31 and Y93 affects the antiviral effect of DCV+ASV therapy.

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Retreatment of Patients Who Failed Direct-acting Antiviral (DAA) Therapies: Real World Experience from a Large European Hepatitis C Resistance Database

Johannes Vermehren[1], Julia Dietz[1], Simone Susser[1], Thomas von Hahn[2], Joerg Petersen[3], Holger Hinrichsen[4], Ulrich Spengler[5], Stefan Mauss[6], Christoph P. Berg[7], Stefan Zeuzem[1], Christoph Sarrazin[1]; [1]Medizinische Klinik 1, Universitätsklinikum Frankfurt, Frankfurt am Main, Germany; [2]Medizinische Hochschule Hannover, Hannover, Germany; [3]ifi-Institut für Interdisziplinäre Medizin, Hamburg, Germany; [4]Gastroenterologische Gemeinschaftspraxis, Kiel, Germany; [5]Universitätsklinikum Bonn, Bonn, Germany; [6]Medizinisches Versorgungszentrum, Düsseldorf, Germany; [7]Universitätsklinikum Tübingen, Tübingen, Germany

Background Treatment with direct antiviral agents (DAAs) achieved high sustained virologic response (SVR) rates across a broad range of patients with chronic hepatitis C virus (HCV) infection. Presence of baseline resistance-associated variants (RAVs) has been associated with reduced SVR rates depending on the DAA regimen. There are few data on retreatment after DAA failure. However, AASLD guidelines recommend a switch to another DAA drug class, the addition of ribavirin and treatment extension to 24 weeks. In addition, testing for RAVs is recommended prior to initiating retreatment. **Methods** Patients with failure to currently approved DAA combination therapies were drawn from a large resistance database comprising more than 3900 patients. Post failure serum samples were analyzed for the presence of RAVs by direct sequencing of the NS3, NS5A and NS4B genes. Patients with urgent reasons were retreated based on the RAV analysis and guideline recommendations. **Results** In total, 456 patients with failure to different DAA combinations were analyzed. All currently approved DAA therapies were affected by treatment failure. These include ledipasvir/sofosbuvir ±ribavirin (RBV) (n=178), simeprevir/sofosbuvir ±RBV (n=63), daclatasvir/sofosbuvir ±RBV (n=70), sofosbuvir/RBV (n=93; genotypes 2/3 only), and paritaprevir/ombitasvir and dasabuvir ±RBV (3D; n=52). RAVs were detected in 90% of genotype (GT) 1 failures and 39% of patients with GT3, including 3 patients with the NS5B RAV S282T (GT1b: n=1; GT3: n=2). Retreatment was initiated in 73 (16%) of GT1/3 patients of whom 74% had cirrhosis. The majority of retreated patients had failed simeprevir/sofosbuvir. For retreatment, either ledipasvir/sofosbuvir or the 3D regimen were chosen. So far, 43 of GT1/ GT3 patients have completed follow-up and 89% of these patients achieved SVR. **Conclusion** Retreatment was started in only a small subgroup of DAA failures, mainly due to the lack of approved regimens. By using an individualized treatment approach based on post-failure RAV analysis and switching to another regimen with a different DAA target, SVR can be achieved in the majority of DAA failures.

Disclosures:

Johannes Vermehren - Advisory Committees or Review Panels: AbbVie, Abbott; Speaking and Teaching: AbbVie, Bristol-Myers Squibb, Gilead, Medtronic

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Holger Hinrichsen - Advisory Committees or Review Panels: BMS, Janssen, Gilead, Abbvie; Speaking and Teaching: MSD

Stefan Mauss - Advisory Committees or Review Panels: BMS, AbbVie, ViiV, Gilead; Speaking and Teaching: BMS, AbbVie, Janssen, Gilead, MSD

Stefan Zeuzem - Consulting: Abbvie, Bristol-Myers Squibb Co., Gilead, Merck & Co., Janssen

Christoph Sarrazin - Advisory Committees or Review Panels: Bristol-Myers Squibb, Janssen, Merck/MSD, Gilead, Roche, Abbvie, Janssen, Merck/MSD; Consulting: Merck/MSD, Merck/MSD; Grant/Research Support: Abbott, Roche, Merck/MSD, Gilead, Janssen, Abbott, Roche, Merck/MSD, Qiagen; Speaking and Teaching: Gilead, Novartis, Abbott, Roche, Merck/MSD, Janssen, Siemens, Falk, Abbvie, Bristol-Myers Squibb, Achillion, Abbott, Roche, Merck/MSD, Janssen

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Outcomes of Sofosbuvir and Daclatasvir rescue therapy in decompensated Hepatitis C cirrhotics with MELD ≥ 15: final results of the Australian TOSCAR study

Geoff McCaughan[2], Phoebe A. Thwaites[1], Stuart K. Roberts[3], Simone I. Strasser[2], Paul Gow[1], Alan J. Wigg[4], Caroline Tallis[8], Gary P. Jeffrey[7], Jacob George[6], Alex J. Thompson[5], Joanne Mitchell[3], Susan Mason[2], Brenda Morales[1], Peter W. Angus[1]; [1]Victorian Liver Transplant Unit, Melbourne, VIC, Australia; [2]Australian National Liver Transplant Unit, Sydney, NSW, Australia; [3]Alfred Health, Melbourne, VIC, Australia; [4]South Australian Liver Transplant Unit, Adelaide, SA, Australia; [5]St Vincent's Hospital, Melbourne, VIC, Australia; [6]Westmead Hospital, Sydney, NSW, Australia; [7]Western Australian Liver Transplant Unit, Perth, WA, Australia; [8]Queensland Liver Transplant Unit, Brisbane, QLD, Australia

Introduction: Antiviral therapy for hepatitis C (HCV) has the potential to improve liver function in patients with decompensated HCV cirrhosis who are candidates for liver transplant. However, data on treatment outcomes in this population are limited. **Methods:** We prospectively collected data on all patients who satisfied the current minimum criterion for transplantation in decompensated cirrhosis in Australia (MELD ≥15) who commenced combination therapy with sofosbuvir and daclatasvir (sof/dac) with or without ribavirin (riba) for 24 weeks under the Australian Patient Supply Program (TOSCAR) and analysed outcomes including SVR12, death and transplant. **Results:** The study included 110 patients (M/F, 80/30; mean ± standard deviation (SD) age, 55.9 ± 7.7 years; mean ± SD Child Pugh Score (CPS), 10.0 ± 1.5) whom were followed for at least 36 weeks from commencement of treatment. Genotypes were predominantly 1 and 3. 108 patients received sof/dac and two received sof/dac/riba. Forty-three patients (39%) had failed previous therapy. Seventy-eight patients completed 24 weeks of therapy, of whom three were transplanted during follow up. SVR12 was achieved in 60 patients (76.9%) (genotype 1 (n=34), SVR12=79.4%; genotype 2 (n=2), SVR12 = 100%; genotype 3 (n=38), SVR12 = 63.2%; genotype 4 (n=4), SVR12 = 100%), while 17 patients relapsed (21.8%) and one patient was lost to follow up. Thirty-two patients failed to complete therapy due to death (n=11, 10%), transplant (n=18, 16%) or adverse events (n=3, 3%). Overall, the mean MELD and CP scores of the 110 patients in the study fell from 17.0 to 15.7 (p=0.03) and 10.0 to 8.5 (p<0.01), respectively from baseline. In those patients who completed treatment, mean MELD and CPS fell from 16.8 to 14.3 (p<0.01) and 9.7 to 8.1 (p<0.01), respectively. In those who died or were transplanted (due to liver failure), mean MELD increased from

18.0 to 21.0 at death or transplant (p=0.045) while mean CPS remained unchanged (10.7 to 10.3, p=0.27). Overall, 59 (76%) patients achieved an improvement in both MELD and CP scores with treatment. In patients with MELD ≥ 20 at entry (n=16), 69% died or required rescue liver transplantation whilst on treatment compared to 16% in patients with MELD < 20 (p<0.0001). **Conclusions**: SVR12 rates in HCV positive patients with advanced liver disease treated with sofosbuvir and daclatasvir (with/without ribavirin) are reduced compared to other patient groups. Although treatment improves MELD and CP scores in most patients, a significant proportion will die or require rescue transplantation and in those with MELD ≥ 20 it may be better to delay treatment until the post-transplant period.

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Geoff McCaughan - Advisory Committees or Review Panels: Gilead, ABBVIE

Stuart K. Roberts - Board Membership: AbbVie, Gilead

Simone I. Strasser - Advisory Committees or Review Panels: AbbVie, MSD, Bristol-Myers Squibb, Gilead, Norgine, Bayer Healthcare; Speaking and Teaching: Roche Products Australia, Bayer Healthcare, Bristol-Myers Squibb, MSD, Gilead, Abbvie

Caroline Tallis - Advisory Committees or Review Panels: BMS; Speaking and Teaching: Gilead

Jacob George - Advisory Committees or Review Panels: Pharmaxis, BMS, MSD, Gilead, Janssen, Abbvie; Grant/Research Support: MSD

Alex J. Thompson - Advisory Committees or Review Panels: Gilead, Abbvie, BMS, Merck, Spring Bank Pharmaceuticals, Arrowhead, Roche; Grant/Research Support: Gilead, Abbvie, BMS, Merck; Speaking and Teaching: Roche, Gilead, Abbvie, BMS

Susan Mason - Advisory Committees or Review Panels: Janssen, MSD, BMS, Gilead Sciences; Grant/Research Support: Janssen, MSD; Speaking and Teaching: ASHM

Brenda Morales - Advisory Committees or Review Panels: MSD, Jansen, Roche, Abbvie, BMS

Peter W. Angus - Advisory Committees or Review Panels: Gilead Sciences, BMS, Bayer; Grant/Research Support: Gilead sciences

The following people have nothing to disclose: Phoebe A. Thwaites, Paul Gow, Alan J. Wigg, Gary P. Jeffrey, Joanne Mitchell

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Does successful viral eradication translate into beneficial long-term clinical outcome of patients with advanced liver disease due to hepatitis C after DAA therapy?

Karin Kozbial[1], Stephan Moser[2], Remy Schwarzer[3], Ramona Al Zoairy[4], Rudolf E. Stauber[5], Hermann Laferl[6], Andreas Maieron[3], Heinz M. Zoller[4], Sandra Beinhardt[1], Albert Stättermayer[1], Rafael Stern[1], Petra E. Steindl-Munda[1], Michael P. Strasser[7], Markus Peck-Radosavljevic[1], Ivo Graziadei[8], Michael H. Trauner[1], Harald Hofer[1], Peter Ferenci[1]; [1]Internal Medicine III, Gastroenterology and Hepatology, Medical University of Vienna, Vienna, Austria; [2]Internal Medicine IV, Gastroenterology and Hepatology, Wilhelminenspital, Vienna, Austria; [3]Internal Medicine IV, Elisabethinen Krankenhaus Linz, Linz, Austria; [4]Internal Medicine II, Medical University Innsbruck, Innsbruck, Austria; [5]Internal Medicine, Medical University of Graz, Graz, Austria; [6]4th Med. Dpt. of Infectious Diseases and Tropical Medicine, Kaiser Franz Joseph Spital, Vienna, Austria; [7]Internal Medicine I, Paracelsus Medical University, Salzburg, Austria; [8]Department for Internal Medicine, Landeskrankenhaus Hall in Tirol, Hall in Tirol, Austria

Background and aims: Interferon (IFN)-free antiviral treatment with DAAs is very effective to cure HCV infection, but the long-term outcome of patients is unknown. AURIC (AUstrian Ribavirin [RBV]/Interferon free Cohort; ClinicalTrials.gov, NCT02628717) is a "real world" study including patients with advanced liver disease (F3/F4) without evidence of hepatocellular carcinoma (HCC) treated with IFN/RBV free DAA combinations. In this study patients' outcomes were evaluated after at least 48 weeks of treatment free follow up. **Methods:** Of the 484 patients in AURIC 456 (94.2%) had a sustained virological response after 12 weeks (SVR12) of follow up, 20 relapsed (4.1%) and 8 were lost to follow up. At the time of abstract submission, 191 SVR12 patients completed at least 48 weeks of treatment free follow up (m/f=112/79; mean age 57.8±10.4yrs; genotype [GT]-1:170, GT-3:7; GT-4:14; F3:41 F4:150; Child Pugh Score[CPS] A:117, B:27, C:6; treatment: sofosbuvir[SOF]+daclatasvir[DCV]:85, DCV+simeprevir[SMV]:83, SOF+ledipasvir:19, SMV+DCV:1, 3D:3). **Results:** SVR was durable during follow up. CPS improved in 22 patients (CPS-B to A: 19, C to A:1, C to B: 2) and worsened in 6 (A to B: 3, A to C:1 B to C: 2). Eleven patients (5.5%) had liver related events: 7 ascites, 3 hepatic encephalopathy and one had a variceal hemorrhage. Five patients were transplanted after end of therapy (EoT) due to decompensated liver cirrhosis or occurrence of a de novo HCC, one them died due to thrombotic complications. Three patients were delisted due to clinical improvement. Seven additional patients died: five related to liver disease, three due to nonhepatic diseases. As reported previously, HCC was diagnosed in 13 (6.8%) patients during follow-up (m/f=9/4, mean age 65.4±6.5yrs, GT-1:12; GT-4:1; CPS at baseline:A:7, B:3, C:1, F3:2). Overall, platelet count (plts) and serum albumin (alb) improved from baseline (BL) to EoT, and furthermore from EoT to FUP48 (plts: BL: 133 vs. EoT:142G/L, vs. SVR 48: 152G/L; alb: 39.4 vs. 41.0 g/L, vs. 42.7g/L, all: p<0.005). **Conclusion**: Clinical condition and laboratory markers of liver function improved in most patients with cirrhosis after successful DAA therapy; however morbidity and mortality rate remains substantial. Furthermore, an unexpectedly high rate of HCC was observed shortly after EoT implicating the need of vigorous surveillance after achieving SVR in patients with cirrhosis.

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Rudolf E. Stauber - Advisory Committees or Review Panels: Gilead, MSD, BMS; Grant/Research Support: AbbVie

Hermann Laferl - Advisory Committees or Review Panels: Janssen; Grant/Research Support: Gilead, AbbVie, Roche; Speaking and Teaching: Gilead

Andreas Maieron - Advisory Committees or Review Panels: MSD, Jannsen, BMS, Bv∂hringer Ingelheim, Gilead, Abbvie ; Grant/Research Support: Roche; Speaking and Teaching: Roche, MSD, Jannsen, Gilead, Abbvie

Markus Peck-Radosavljevic - Advisory Committees or Review Panels: Bayer, Intercept, Gilead, Janssen, BMS, AbbVie; Consulting: Bayer, Shionogi, Boehringer-Ingelheim, ONO Pharma, Eli Lilly, AbbVie; Grant/Research Support: Bayer, Gilead, MSD, AbbVie; Speaking and Teaching: Bayer, Gilead, MSD, AbbVie

Ivo Graziadei - Advisory Committees or Review Panels: Gilead, AbbVie, MSD, Janssen, BMS; Speaking and Teaching: Gilead, AbbVie, MSD, BMS

Michael H. Trauner - Consulting: Albireo, Falk, Phenex, Gilead, Novartis, MSD; Grant/Research Support: Falk, Albireo, Intercept

Harald Hofer - Advisory Committees or Review Panels: Gilead, Abbvie; Speaking and Teaching: Janssen, BMS, Gilead, Abbvie

Peter Ferenci - Advisory Committees or Review Panels: Idenix, Gilead, MSD, Janssen, Salix, AbbVie, BMS, Wilson Therapeutics; Patent Held/Filed: Madaus Rottapharm; Speaking and Teaching: Gilead, Roche

The following people have nothing to disclose: Karin Kozbial, Stephan Moser, Remy Schwarzer, Ramona Al Zoairy, Heinz M. Zoller, Sandra Beinhardt, Albert Stättermayer, Rafael Stern, Petra E. Steindl-Munda, Michael P. Strasser

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Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir Plus Ribavirin in Daily Practice Hepatitis C Virus Genotype 1- or 4-Infected Patients with Compensated Cirrhosis

Salvatore Petta[1], Marco Marzioni[2], Pierluigi Russo[3], Alessio Aghemo[4], Alfredo Alberti[5], Antonio Ascione[6], Andrea Antinori[7], Raffaele Bruno[8], Savino Bruno[9], Antonio Chirianni[10], Giovanni B. Gaeta[11], Edoardo G. Giannini[12], Manuela Merli[13], Vincenzo Messina[14], Simona Montilla[3], Carlo F. Perno[15], Massimo Puoti[16], Giovanni Raimondo[17], Maria Rendina[18], Francesca Ceccherini-Silberstein[15], Erica Villa[19], Anna Linda Zignego[20], Luca Pani[3], Antonio Craxì[1]; [1]Cattedra ed U.O.C. di Gastroenterologia ed Epatologia, Palermo, Italy; [2]Clinic of Gastroenterology and Hepatology, Università Politecnica delle Marche, Ancona, Italy, Ancona, Italy; [3]Italian Medicines Agency, Roma, Italy; [4]UO Gastroenterologia ed Epatologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Italy, Milan, Italy; [5]Department of Molecular Medicine, University of Padova, Padova, Italy, Padova, Italy; [6]Centro per le malattie del Fegato- Ospedale Fatebenefratelli - Napoli, Italy, Napoli, Italy; [7]National Institute for Infectious Diseases "Lazzaro Spallanzani" IRCCS, Roma, Italy., Roma, Italy; [8]Dipartimento Malattie infettive - Fondazione IRCCS Policlinico San Matteo Pavia Italia - Università degli studi di Pavia, Italy, Pavia, Italy; [9]Humanitas University and Humanitas Research Hospital Rozzano, Milano, Milano, Italy; [10]U.O.C. Infezioni sistemiche e dell'immunodepresso. A.O. Ospedali dei Colli Napoli, Italy, Napoli, Italy; [11]Infectious Diseases and Viral Hepatitis, Second University of Naples, Italy, Napoli, Italy; [12]Gastroenterology Unit, Department of Internal Medicine, University of Genoa, Genoa, Italy, Genova, Italy; [13]Gastroenterology Department of Clinical Medicine, Sapienza University of Rome, Italy, Roma, Italy; [14]Infectious Diseases Unit, AORN Sant'Anna e San Sebastiano, Caserta, Italy, Caserta, Italy; [15]Department of Experimental Medicine and Surgery, University of Rome Tor Vergata, Italy, Roma, Italy; [16]Department of Infectious Diseases, AO Niguarda Ca' Granda, Milano, Italy, Milano, Italy; [17]Division of Clinical and Molecular Hepatology, Department of Clinical and Experimental Medicine, University Hospital of Messina, Italy, Messina, Italy; [18]Gastroenterology and digestive Endoscopy, University Hospital Policlinico Bari, Italy, Bari, Italy; [19]Division of Gastroenterology, Azienda Ospedaliero-Universitaria Policlinico di Modena, Italy Università degli Studi di Modena e Reggio Emilia, Via del Pozzo 71, 41124 Modena, Italy, Modena, Italy; [20]Anna Linda Zignego, Interdepartmental Centre MASVE, Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy, Firenze, Italy

Background Compassionate-use programs for direct-acting antivirals (DAAs) for chronic hepatitis C virus (HCV) infection provide access to DAAs pending approval and provide real-world data on the effectiveness and safety of these regimens. We collected data from a compassionate-use nationwide program (promoted by the Italian Medicines Agency) to provide access to the 3-DAA regimen of ombitasvir, paritaprevir, with the pharmacokinetic enhancer ritonavir, and dasabuvir (OBV/PTV/r + DSV), with ribavirin (RBV) for GT1 infection and the 2-DAA regimen of OBV/PTV/r + RBV for GT4 infection in patients with cirrhosis at high risk of decompensation. **Methods** HCV GT1-infected patients with cirrhosis at high risk of decompensation received once-daily co-formulated OBV/PTV/r (25/150/100 mg) and twice-daily dasabuvir (250 mg) for 12 (GT1b) or 24 (GT1a) weeks; GT4-infected patients received co-formulated OBV/PTV/r (25/150/100 mg) for 24 weeks. The primary efficacy endpoint was sustained virologic response at week 12 post-treatment. Univariate and multivariate logistic regression were used to identify baseline characteristics associated with SVR12. Adverse events were recorded throughout the study. **Results** The overall SVR12 rate was 95.5% (728/762) among cirrhotic patients who received OBV/PTV/r ± DSV + RBV therapy for 12 or 24 weeks. Logistic regression analyses identified that bilirubin <2 mg/d (OR: 4.76; 95% CI: 1.83–12.3; p=0.001) and marginally albumin ≥3.5 g/dL (OR: 2.36; 95% CI: 0.96–6.16; p=0.07) were associated with SVR12. 3.4% of patients discontinued treatment due to adverse events. **Conclusions** Our findings suggest that the safety and effectiveness of OBV/PTV/r ± DSV + RBV in real-life use in patients with HCV genotype 1 or 4 infection and cirrhosis at high risk of decompensation are similar to those reported in clinical trials.

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Alessio Aghemo - Advisory Committees or Review Panels: Abbvie, Gilead; Grant/Research Support: Gilead; Speaking and Teaching: Abbvie, Gilead, MSD, Janssen, BMS

Alfredo Alberti - Advisory Committees or Review Panels: Merck, roche, Gilead, Merck, roche, Gilead, Merck, roche, Gilead, Merck, roche, Gilead, Abbvie, Janssen; Grant/Research Support: Merck, gilead, Merck, gilead, Merck, gilead, Merck, gilead, Abbvie, Janssen; Speaking and Teaching: novartis, BMS, novartis, BMS, novartis, BMS, novartis, BMS

Andrea Antinori - Consulting: Bristol Myers Squibb, Gilead, Merck, Janssen-Cilag, Abbie, ViiV; Grant/Research Support: Gilead, Bristol Myers Squibb, Janssen-Cilag, ViiV

Giovanni B. Gaeta - Advisory Committees or Review Panels: Janssen, Merck, Abbvie, Roche; Speaking and Teaching: BMS, Gilead, merck

Edoardo G. Giannini - Advisory Committees or Review Panels: GlaxoSmithKline, Gilead; Consulting: 4-SC; Grant/Research Support: GlaxoSmithKline, 4-SC; Speaking and Teaching: GlaxoSmithKline, MSD, Roche, Gilead, Bayer, BMS, Janssen, Novartis

Massimo Puoti - Advisory Committees or Review Panels: GSK, Abbott, Janssen, MSD, Roche, Gilead Sciences, Novartis, GSK, Abbott, Janssen, MSD, Roche, Gilead Sciences, Novartis, GSK, Abbott, Janssen, MSD, Roche, Gilead Sciences, Novartis, GSK, Abbott, Janssen, MSD, Roche, Gilead Sciences, Novartis; Speaking and Teaching: BMS, BMS, BMS, BMS

Giovanni Raimondo - Speaking and Teaching: BMS, Gilead, Roche, Merck, Janssen, Bayer, MSD

Francesca Ceccherini-Silberstein - Speaking and Teaching: Merck Sharp & Dohme, Gilead, Janssen, Abbvie, ViiV, Roche diagnosticis, BMS

Erica Villa - Advisory Committees or Review Panels: MSD, Abbvie, GSK, Gilead; Speaking and Teaching: Novartis

The following people have nothing to disclose: Salvatore Petta, Marco Marzioni, Pierluigi Russo, Antonio Ascione, Raffaele Bruno, Savino Bruno, Antonio Chirianni, Manuela Merli, Vincenzo Messina, Simona Montilla, Carlo F. Perno, Maria Rendina, Anna Linda Zignego, Luca Pani, Antonio Craxì

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Retreatment Of HCV DAA Failures In Real Life: HCV Infection May Be Always Curable

Denis Ouzan[1], Guillaume Pénaranda[2], Gaelle Le Folgoc[3], Christophe Renou[4], Michel Antoni[5], Patrick Delasalle[6], Thierry Fontanges[7], Patricia Cerdan[8], Pierre Toulemonde[9], Sylvain Beorchia[10], Nathalie Boyer[11], Bertrand Hanslik[12], Philippe Halfon[2,13], Marc Bourlière[3]; [1]Department of Hepatologie, Institut Arnault Tzanck, Saint-Laurent-du-Var, France; [2]Laboratoire Alphabio, Marseille, France; [3]Hôpital Saint-Joseph, Marseille, France; [4]Hôpital d'Hyères, Hyères, France; [5]Private Practice, Orange, France; [6]Clinique du Palais, Grasse, France; [7]Private Practice, Bourgoin-Jallieu, France; [8]Private Practice, Nîmes, France; [9]Private Practice, Toulouse, France; [10]Private Practice, Lyon, France; [11]Private Practice, Nanterre, France; [12]Private Practice, Montpellier, France; [13]Hôpital Européen, Marseille, France

Introduction: Retreatment options in experienced patients to new Direct Acting Antivirals (DAA) are not yet well defined. The aim of this study was to analyze the retreatment of patient who failed to a first course of regimen containing new DDA **Patients & Methods**: Two cohorts of patients treated with new DAA in real life for HCV infection (AVDLIB 1:186 patients and AVDLIB 2: 190 patients) were constituted since January 2014 to September 2015. Overall 376 patients were exposed to sofosbuvir (SOF) containing regimen (SOF+ Ribavirin (RBV), SOF+PEGIFN +RBV, SOF +Simeprevir (SIM) ± RBV, SOF+ Daclatasvir

(DAC) ± RBV, SOF+ Ledipasvir (LDV) ± RBV) and 20 exposed to Viekirax± Exviera regimen. **Results**: Among these 376 patents, 20 (5%) relapsed (16 in AVDLIB1 and 4 in AVDLIB2 IFN free regimen). There were 18 males; fibrosis stage was F3 in 2 patients and F4 in 18 patients; HCV genotype repartition G1/G2/G3/G4 was12/3/3/2, respectively. All relapsers but one received a second course of DDA recorded in 18/19 patients. The treatment of relapsers was as follow: one patient received a Viekirax+RBV 12 weeks course after SOF /PEGINF/RBV failure, 12 patients received SOF+DAC+RBV mostly during 24 weeks after SOF+PEGIFN+RBV n=8 and SOF+RBV n=4 failures, 2 patients received SOF+LED during 12 weeks after SOF+RBV and SOF+PEG+RBV failures, 2 patients received SOF+SIM +RBV during 24 weeks after SOF/PEG/RBV and SOF+LED failure and one patient received SOF+Elbasvir+Grazoprevir+RBV during 16 weeks after SOF+LED failure. NS5A RAVs with high level of cross-resistance among NS5A inhibitors were found at the time of viral failure in two patients. SVR 12 was available in 14/18 patients and all of them achieved SVR 12.The results of the 4 remaining patients will be available at the time of the meeting **Conclusion**: This study showed that retreatment of patients who previously failed to DAA first course therapy is highly efficient: a SVR of 100% was observed in patients retreated with SOF or Viekirax based-therapy, and for whom a post-treatment follow-up of at least 12 weeks is available. Second line DAA therapy, ideally with no cross-resistance with the DAAs already administered, should be the solution to cure all HCV infected patients.

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Bertrand Hanslik - Board Membership: MSD, Janssen, Mayoli, Gilead, Intercept; Speaking and Teaching: Roche, Aptalis, BMS, Echosens

Marc Bourlière - Advisory Committees or Review Panels: Schering-Plough, Bohringer inghelmein, Schering-Plough, Bohringer inghelmein, Transgene; Board Membership: Bristol-Myers Squibb, Gilead, Idenix; Consulting: Roche, Novartis, Tibotec, Abott, glaxo smith kline, Merck, Bristol-Myers Squibb, Novartis, Tibotec, Abott, glaxo smith kline; Speaking and Teaching: Gilead, Roche, Merck, Bristol-Myers Squibb

The following people have nothing to disclose: Denis Ouzan, Guillaume Pénaranda, Gaelle Le Folgoc, Christophe Renou, Michel Antoni, Patrick Delasalle, Thierry Fontanges, Patricia Cerdan, Pierre Toulemonde, Sylvain Beorchia, Nathalie Boyer, Philippe Halfon

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Factors Associated with Persistent Alanine Aminotransferase Elevation in Patients Treated with Ledipasvir/Sofosbuvir or Sofosbuvir/Velpatasvir

Tania M. Welzel[2], Paul Y. Kwo[3], Ira M. Jacobson[7], Jie Zhang[1], Shampa De-Oertel[1], John McNally[1], Diana M. Brainard[1], John G. McHutchison[1], Keyur Patel[4], Mark S. Sulkowski[5], Graham R. Foster[6]; [1]Gilead Sciences, Inc, Foster City, CA; [2]Medizinische Klinik 1, Universitätsklinikum Frankfurt, Frankfurt, Germany; [3]Division of Gastroenterology and Hepatology, Indiana University School of Medicine, Indianapolis, IN; [4]Toronto Center for Liver Disease, University Health Network, Toronto, ON, Canada; [5]Johns Hopkins University, Boston, MA; [6]Queen Mary University, London, United Kingdom; [7]Mt. Sinai Beth Israel Hospital, New York, NY

Background: Normalization of ALT levels coincides with virologic suppression in most HCV-infected patients treated with DAAs. The aim of this analysis was to characterize baseline (BL) factors of patients with persistently elevated ALT at the end of treatment (EOT). **Methods**: Patients from safety analysis sets of the LDV/SOF±RBV Phase 3 ION 1-3 trials and SOF/VEL ASTRAL1-3 trials (n=3394) were included in this analysis if they were treated for at least 8 weeks and had both BL and EOT data available. Elevated ALT was defined as ALT greater than upper limit of normal (ULN) as defined by the central laboratory. **Results:** Overall, 73% (2487/3394) of patients had received at least 8 weeks of treatment and had elevated ALT at BL. The majority had ALT normalization after initiation of LDV/SOF±RBV or SOF/VEL, but 8% (200/2487) had elevated ALT at EOT. Compared to patients with ALT normalization, patients who continued to have elevated ALT at EOT had higher rates of cirrhosis and the co-morbid conditions cholelithiasis, hepatic steatosis, diabetes mellitus, or hypertension; were more likely to be taking β blocking agents or diabetes medications; and had higher BMI and hemoglobin A1c values at baseline. A multivariate regression analysis will be presented, as well as analyses using AASLD thresholds for ALT values. Efficacy was similar between groups with nearly all patients with elevated BL ALT reaching HCV RNA < LLOQ by Week 4 of treatment. SVR12 was achieved in 96% (2193/2287) of patients with ALT normalization and 97% (193/200) for patients with elevated ALT at EOT. **Conclusions** LDV/SOF and SOF/VEL were highly efficacious in patients with elevated ALT at BL, regardless of whether ALT normalized by EOT. Patients with elevated ALT levels prior to HCV treatment, who do not have rapid and sustained normalization of transaminases, should be evaluated for other hepatobiliary or metabolic conditions that may contribute to liver inflammation which does not resolve with viral suppression.

Baseline Characteristics of Patients with Elevated Baseline ALT Treated with LDV/SOF or SOF/VEL

	ALT Elevated at BL and EOT (n=200)	ALT Normalized at EOT (n=2287)
Age, mean	52	53
Male, n (%)	133 (67)	1396 (61)
BMI, mean	29.0	27.2
BMI ≥30 kg/m2, n (%)	73 (37)	555 (24)
Hemoglobin A1C (%), mean	5.7	5.5
Hb A1C ≥6.5, n (%)	29 (15)	139 (6)
HCV RNA, log10, mean	6.3	6.4
Cirrhosis, n (%)	83 (42)	425 (19)
IL28 CC, n (%)	57 (29)	689 (30)
ALT (U/L), mean	142	92
AST (U/L), mean	107	70

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Tania M. Welzel - Advisory Committees or Review Panels: Novartis, Janssen, Gilead, Abbvie, Boehringer-Ingelheim+, BMS

Paul Y. Kwo - Advisory Committees or Review Panels: Abbott, Abbvie, BMS, Gilead, Janssen, Merck, Alnylam, Quest, CVS, Innovio; Grant/Research Support: Abbvie, BMS, Gilead, Merck, Janssen, Esai, Cepheid, Conatus

Ira M. Jacobson - Consulting: AbbVie, Achillion, Bristol Myers Squibb, Intercept, Gilead, Janssen, Merck, Trek; Grant/Research Support: AbbVie, Bristol Myers Squibb, Gilead, Janssen, Merck; Speaking and Teaching: AbbVie, Bristol Myers Squibb, Gilead, Janssen

Shampa De-Oertel - Employment: Gilead Sciences, Inc; Stock Shareholder: Gilead Sciences, Inc

John McNally - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

Diana M. Brainard - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

John G. McHutchison - Employment: gilead; Stock Shareholder: gilead

Mark S. Sulkowski - Advisory Committees or Review Panels: Merck, AbbVie, Janssen, Gilead, Trek, Cocrystal; Grant/Research Support: Merck, AbbVie, Janssen, Gilead

Graham R. Foster - Advisory Committees or Review Panels: GlaxoSmithKline, Novartis, Boehringer Ingelheim, Tibotec, Gilead, Janssen, Idenix, GlaxoSmithKline, Novartis, Roche, Tibotec, Chughai, Gilead, Merck, Janssen, Idenix, BMS, Alnylam; Board Membership: Boehringer Ingelheim; Grant/Research Support: Roche, Chughai, Springbank; Speaking and Teaching: Roche, Gilead, Tibotec, Merck, BMS, Boehringer Ingelheim, Gilead, Janssen

The following people have nothing to disclose: Jie Zhang, Keyur Patel

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Daclatasvir Plus Sofosbuvir Plus RIbavirin in HCV Genotype 3 Infected Patients with Cirrhosis Child A: A Randomized Trial for 16 or 24 Weeks (NCT #02304159)

Tarek I. Hassanein, Yasmeen Esshaki, Catherine Hill, Renee Pozza, Jennifer Higham, B K. Luvisa, Anna Marie Hefner; Southern California Research Center, Coronado, CA

BACKGROUND: HCV genotype 3 is still the challenging genotype. With current standard therapy the relapse rates are still considered high, particularly in patients with cirrhosis. The combination of Daclatasvir and Sofosbuvir with or without Ribavirin for 12 or 16 weeks have shown slightly improved SVR rates and lower relapse rates using weight-based dosing of Ribavirin. The goal of our study is to explore the efficacy of 16 weeks versus 24 weeks of Daclatasvir/Sofosbuvir/Ribavirin in cirrhotic patients with HCV genotype 3, and to explore the importance of the initial Ribavirin dosing. **METHODS:** 49 subjects were screened into the study. 39 were randomized into two arms (16 weeks versus 24 weeks) in 1:1 ratio using IVRS. Baseline demographics and viral parameters were similar in both arms. The mean age was 55.4 ± 7 years; 22 males; 21 non-Hispanics. 28 patients were treatment naïve and 11 patients were experienced to Peg/RBV therapy. Cirrhosis was confirmed in all patients by Fibroscan. **RESULTS:** 39 patients were randomized into the study, and 32 patients completed the course of therapy. 7 patients are still on treatment. 100% of the patients who completed therapy achieved EOT viral negativity. In the 16-week group, SVR^{12} was 91.6% with only one patient relapse. This patient had over 90% adherence to the medication regimen and was recieving 1200 mg/day RIbvirian. SVR^{12} in the 24-week group was 100% in the patients who finished the study (17/17). Ribavirin dose started at 800 mg/day in 25 patients and 1000-1200 mg/day in 14 patients. Three patients in each group required a decrease in their Ribavirin dose due to anemia. The starting dose of Ribavirin did not impact the SVR^{12}. **CONCLUSION:** The combination of Daclatasvir/Sofosbuvir/Ribavirin is recommended for HCV genotype 3 patients. In cirrhotic patients our study shows 1) 16-week treatment achieved 91.6% SVR^{12} with only one relapse; 2) 24-week treatment achieved 100% SVR^{12}; 3) there was no significant difference in SVR between the two arms; 4) 800 mg/day of Ribavirin achieved the same viral response as weight-based Ribavirin; 5) 16- and 24-week treatment was well tolerated in patients with cirrhosis.

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The following people have nothing to disclose: Yasmeen Esshaki, Catherine Hill, Renee Pozza, Jennifer Higham, B K. Luvisa, Anna Marie Hefner

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High Rates of Sustained Virologic Response among HCV Infected Native Americans Treated with Direct Acting Anti-Virals

Jorge Mera[2], Kartik Joshi[1], Karla A. Thornton[3], Terry D. Box[4], John D. Scott[5], Paulina Deming[3], Miranda L. Sedillo[3], Crystal David[2], Robert Gish[1], Whitney Essex[2], Jennifer Shade[2], Richard Manch[1], Anita Kohli[1]; [1]St. Joseph's Hospital and Medical Center, Phoenix, AZ; [2]Divison of Infectious Disease, Cherokee Nation W.W. Hastings Hospital, Tahlequah, OK; [3]Division of Infectious Diseases, University of New Mexico, Albuquerque, NM; [4]Division of Gastroenterology, University of Utah, Salt Lake City, UT; [5]Infectious Diseases, University of Washington, Seattle, WA

Introduction: One quarter of HCV infected patients in the U.S. are not served by mainstream healthcare systems, including Native Americans, the incarcerated, and the homeless. Data on the efficacy of DAA therapies in these vulnerable populations is limited. Our aim was to determine the efficacy of DAA therapies and predictors of treatment response among Native Americans infected with chronic HCV. ***Methods:*** All Native American patients with chronic HCV treated at a specialty clinic or by primary care clinicians through the ECHO (Extension for Community Healthcare Outcomes) (ECHO) model who completed treatment with directly acting antiviral (DAA) therapies from 11/4/2011-9/30/2015 were identified. Data on demographics, baseline laboratory values, treatment regimen, genotype, and viral load were systematically abstracted into a standardized database. In 191 patients (86%), data on psychiatric disease, HCV risk factors, and concomitant nonalcoholic fatty liver disease (NAFLD) was also collected. ***Results:*** 222 Native American patients were included and eligible for analysis. The majority of patients (n=163, 73%) were infected with HCV genotype 1; genotype 1a was the most common subtype (n=137, 62%), while genotype 2 and 3 represented 16% (n=26) and 10% (n=23) of the cohort. 37% (n=83) of patients had cirrhosis. Treatment regimens included sofosbuvir (SOF)/ledipasvir (LDV) (n=137), SOF/ribavirin (RBV) (n=63), simeprevir (SIM)/SOF (n=6), SIM/SOF/RBV (n=5), SOF/pegylated-interferon (PEG)/RBV (n=5), SOF/LDV/RBV (n=4), and paritaprevir/ritonavir/ombitasvir/dasabuvir ± RBV (n=2). Among patients with data, 35% (n=67) were actively using marijuana, opiates, benzodiazepines, amphetamines, and barbiturates and 26% (n=49) were diagnosed with nonalcoholic fatty liver disease (NAFLD). Overall, 84% (n=187) of patients achieved SVR12. When all missing patients (n=16) were excluded, SVR12 increased to 91%. Among the missing patients, 46% were active drug users, 69% had psychiatric disease, and 46% had cirrhosis. Nineteen patients (9%) relapsed; of whom, 8 (42%) were cirrhotic and 16% (n=3) were previously treated. SVR12 was similar in cirrhotic (83%) vs. non-cirrhotic patients (85%), active drug users (82%) vs. non/former users (87%), and concomitant NAFLD, HCV (90%) vs. non-NAFLD, HCV patients (84%). ***Conclusions:*** Overall, there was a high cure rate of HCV in Native Americans being treated with DAA regimens. Patients with cirrhosis, concomitant NAFLD, and even active drug use, all achieved high rates of SVR12. Given the efficacy of DAA treatment in this vulnerable, understudied population, more steps need to be taken to increase treatment availability.

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Jorge Mera - Advisory Committees or Review Panels: gilead; Board Membership: CDC/HRSA; Grant/Research Support: AIDS AND EDUCATION TRAINING CENTER, Indian Health Services, Oklahoma University Health Science Center

Terry D. Box - Advisory Committees or Review Panels: Gilead, AbbVie, Salix, BMS; Grant/Research Support: Gilead, Merck, Intercept, BMS, AbbVie, Salix, Boehringer Ingelheim, ikaria; Speaking and Teaching: Gilead, Merck, AbbVie, Intercept, Salix

John D. Scott - Advisory Committees or Review Panels: Tacere Therapeutics; Grant/Research Support: Merck

Robert Gish - Advisory Committees or Review Panels: Gilead, AbbVie, Arrowhead, Ionis, MERCK; Consulting: Eiger, Genentech, MERCK; Speaking and Teaching: Gilead, AbbVie, MERCk; Stock Shareholder: Arrowhead

Richard Manch - Speaking and Teaching: Gilead, Abbvie, Merck, BMS, Salix, Bayer, Intercept

Anita Kohli - Advisory Committees or Review Panels: Gilead, Alexion; Speaking and Teaching: Merck

The following people have nothing to disclose: Kartik Joshi, Karla A. Thornton, Paulina Deming, Miranda L. Sedillo, Crystal David, Whitney Essex, Jennifer Shade

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Does Paritaprevir/ritonavir, Ombitasvir, Dasabuvir Combination Increase the Risk of Hepatic Decompensation and Renal Insufficiency in Patients with Cirrhosis?

Adeel A. Butt[1], Yanjie Ren[2], Kristen M. Marks[1], Obaid S. Shaikh[2], Kenneth E. Sherman[3]; [1]Division of Infectious Diseases, Weill Cornell Medical College, Mars, PA; [2]VA Pittsburgh Healthcare System, Pittsburgh, PA; [3]University of Cincinnatti, Cincinnatti, OH

Background: DAA regimens have been associated with hepatic decompensation (HD), especially in patients with pre-treatment cirrhosis, but large scale studies are not available to quantify the risk. **Methods:** In the ERCHIVES database, we analyzed those treated with a Paritaprevir/ritonavir, Ombitasvir, Dasabuvir (PrOD) regimen for hepatic decompensation (HD), and worsening renal function and compared them with those who received sofosbuvir/simeprevir (SOF/SIM) or sofosbuvir/ledipasvir (SOF/LDV)regimen. Participants were followed up to 12 weeks post-treatment. We excluded those with HIV, HBsAg+ and pre-existing diagnosis of HD and hepatocellular carcinoma **Results:** Of 3,728 persons on PrOD, 1,578 on SOF/SIM and 10,440 on SOF/LDV, cirrhosis was present at baseline in 23%, 45% and 26% respectively. There were 15 HD events in the PrOD, 24 in the SOF/SIM and 52 in the SOF/LDV group. Incidence rates [95% CI] of HD/1,000 treatments initiated were 10.6[5.89,17.36] for the PrOD group, 32.4[20.74,48.16] for the SOF/SIM group and 13.0[9.74,17.10] for the SOF/LDV group. Among those with baseline cirrhosis, these rates were 36.9[19.1,64.5], 61.8[38.2,94.5] and 41.1[29.9,55.2] respectively, while among those without cirrhosis at baseline, these rates were 2.7[0.6,8.0], 7.5[1.5,21.8] and 2.7[1.2,5.4] respectively. Advanced fibrosis was associated with increased risk of HD in all groups. There were no deaths. Proportion of persons with eGFR increase >30ml/min/1.73m^2 was higher among the PrOD group, but presence of cirrhosis did not appear to affect this. **Conclusions:** The overall incidence of HD in persons treated with PrOD regimen, on treatment and up to 12 weeks after completion of treatment, was comparable to those treated with SOF/LDV regimen, and was lower than among those treated with a SOF/SIM regimen. Such risk was predominantly observed in those with cirrhosis at baseline.

Table. Incidence rates and number of events by treatment regimen and severity of liver disease.

		Incidence rate [95% CI] per 1,000 treatments initiated N			
		Hepatic decompensation	P-value*	eGFR increase >30ml/min/1.73m²	P-value*
Overall	PrOD	10.60 [5.89,17.36] 15	--	31.49 [22.97, 42.14] 45	--
	SOF/SIM	32.37 [20.74,48.16] 24	<0.01	4.01[0.83, 11.71] 3	<0.01
	SOF/LDV	13.04 [9.74,17.10] 52	0.46	10.25 [7.36, 13.91] 41	<0.01
With cirrhosis	PrOD	36.91 [19.07,64.46] 12	--	42.70 [23.35,71.65] 14	--
	SOF/SIM	61.79 [38.25,94.46] 21	0.15	8.68 [1.79,25.36] 3	0.01
	SOF/LDV	41.12 [29.88,55.21] 44	0.74	17.60 [10.60,27.48] 19	0.01
Without cirrhosis	PrOD	2.73 [0.56,7.97] 3	--	28.16 [19.13,39.96] 31	--
	SOF/SIM	7.47 [1.54,21.83] 3	0.22	0	-
	SOF/LDV	2.74 [1.18,5.40] 8	0.99	7.54 [4.72,11.41] 22	<0.01
MELD 1-9	PrOD	7.72[3.53,14.65] 9	--	23.95 [15.91,34.61] 28	--
	SOF/SIM	27.74[15.86,45.06] 16	0.31	1.72 [0.04, 9.58] 1	<0.01
	SOF/LDV	11.29[7.95,15.56] 37	<0.01	8.22 [5.41,11.95] 27	<0.01
MELD >=10	PrOD	27.48[10.09,59.82] 6	--	63.88 [34.92, 107.18] 14	--
	SOF/SIM	53.68[23.17,105.76] 8	0.21	13.24 [1.60, 47.81] 2	0.04
	SOF/LDV	25.18[14.09,41.53] 15	0.86	21.70 [11.56, 37.11] 13	<0.01

*P-value for comparison with PrOD regimen; PrOD, paritaprevir/ritonavir, ombitasvir, dasabuvir; SOF, sofosbuvir; SIM, simeprevir; LDV, ledipasvir; eGFR, estimated glomerular filtration rate calculated using the CKD-EPI equation; INR, international normalized ratio.

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The following people have nothing to disclose: Yanjie Ren

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Real World Efficacy of Antiviral Treatment in Chronic Hepatitis C Genotype 3 Infection: Data from the German Hepatitis C-Registry (DHC-R)

Markus Cornberg[1], Joerg Petersen[2], Andreas Schober[3], Guenther Schmutz[4], Klaus H. Boeker[5], Ralph Link[6], Stefan Christensen[7], Karl-Georg Buescher[8], Heike Pfeiffer-Vornkahl[9], Michael P. Manns[1], Christoph Sarrazin[10], Dietrich Hueppe[11], Thomas Berg[12], Claus Niederau[13], German Hepatitis C-Registry[14]; [1]Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [2]ifi-institute for interdisciplinary medicine, Hamburg, Germany; [3]Center of Hepatology, Göttingen, Germany; [4]Center for HIV and Hepatogastroenterology, Duesseldorf, Germany; [5]Center of Hepatology, Hannover, Germany; [6]MVZ-Offenburg, Offenburg, Germany; [7]Center for interdisciplinary Medicine (CIM), Muenster, Germany; [8]Center of Hepatology, Bottrop, Germany; [9]e.factum GmbH, Butzbach, Germany; [10]J. W. Goethe-University Hospital, Frankfurt, Germany; [11]Center of Gastroenterology, Herne, Germany; [12]Department of Hepatology, University Hospital Leipzig, Leipzig, Germany; [13]St. Josef-Hospital, Katholisches Klinikum Oberhausen, Oberhausen, Germany; [14]Leberstiftungs-GmbH Deutschland, Hannover, Germany

Introduction: Treatment of HCV genotype 3 (GT3) is still more challenging compared to HCV genotype 1. Sustained virological response (SVR) rates for GT3 with the first approved IFN free regimen sofosbuvir (SOF)+ribavirin (RBV) are not satisfactory in patients with cirrhosis. Further treatment options include pegylated interferon (PegIFN)+SOF+RBV for 12 weeks, SOF+ledipasvir (LDV) or SOF+daclatasvir (DCV)±RBV for 12-24 weeks. Data from large cohorts and the real-world are still limited. **Methods:** The DHC-R (Deutsches Hepatitis C-Register, German Hepatitis C-Registry) is a national multicenter real-world cohort including >9,300 patients. Patients are treated at the discretion of the physician. Data are collected by a web-based system. Data quality is analyzed by plausibility checks and on-site monitoring. This analysis is based on 6,034 patients observed for at least 40 weeks after initiation

of antiviral treatment. **Results:** Between 2/2014 and 5/2015, 1,074 patients with GT3 have been enrolled. Treatment has been initiated in 864 patients (70.3% male, median age 46.5 years, 34.7% treatment experienced, 33.2% with liver cirrhosis, 14.2% with platelets <90/nl, 11.6% with a HCV-RNA >6 Mio IU/mL, 46.5% with a HCV-RNA <0.8 Mio IU/mL). In 2/2016 a total of 591 patients reached the SVR12 follow-up, but SVR12 data were missing from 31 patients and another 38 patients were not included in the per protocol analysis. Treatment regimens and SVR are shown in table 1. **Conclusions:** ITT-SVR was <80% for SOF+RBV or SOF+LDV highlighting the need for better options in GT3 patients. PegIFN based therapy was still often used (>30%) and in combination with SOF+RBV associated with high SVR in compensated disease. However, side effects have to be considered. DCV+SOF±RBV have already been used in about 1/4 of patients with SVR around 90% even in difficult-to-treat patients.

Table 1. Overview of SVR in different treatment groups

Regimens	pts who started treatment n	% of all treatments	% cirrhosis in treatment group*	% early termination of therapy#	SVR12 ITT n/total	SVR12 ITT* %	SVR12 PP n/total	SVR12 PP %
PegIFN+RBV	92	10.6	1.5	19.7	33/59	56.9	32/41	78.0
PegIFN+RBV+SOF	202	23.4	21.8	4.3	164/182	90.1	160/167	95.8
SOF+RBV	245	28.4	28.1	8.4	115/156	73.7	112/133	84.2
SOF+DCV±RBV	201	23.3	43.6	6.1	121/135	89.6	119/127	93.7
SOF/LDV±RBV	115	13.3	64.0	5.3	40/53	75.5	40/47	85.1
Other	9	1.0	14.3	0	7/7	100.0	7/7	100.0
Total	864	100	33.2	7.4	480/591	81.2	470/522	90.0

*Presence of cirrhosis, early termination of therapy, ITT-SVR12, and PP-SVR12 were all significantly associated with the type of treatment (p<0.05 by analysis of variance, respectively).
#Early termination of therapy due to an SAE was reported only in 3 patients among all treatment groups (n= 1 in the group receiving PegIFN+RBV+SOF and 2 in the groups receiving DAC+SOF±RBV).

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Markus Cornberg - Advisory Committees or Review Panels: Merck (MSD Germamny), Roche, Gilead, Novartis, Abbvie, Janssen Cilag, BMS; Grant/Research Support: Merck (MSD Germamny), Roche; Speaking and Teaching: Merck (MSD Germamny), Roche, Gilead, BMS, Novartis, Falk, Abbvie

Joerg Petersen - Advisory Committees or Review Panels: Bristol-Myers Squibb, Gilead, Novartis, Merck, Bristol-Myers Squibb, Gilead, Novartis, Merck; Grant/Research Support: Roche, GlaxoSmithKline, Roche, GlaxoSmithKline; Speaking and Teaching: Abbott, Tibotec, Merck, Abbott, Tibotec, Merck

Klaus H. Boeker - Consulting: Janssen; Speaking and Teaching: MSD, Roche, Gilead, BMS, Falk Foundation, Novartis, AbbVie

Stefan Christensen - Advisory Committees or Review Panels: BMS, Abbvie, Janssen, ViiV, Gilead, MSD; Speaking and Teaching: Gilead, MSD, Abbvie, BMS, Janssen

Heike Pfeiffer-Vornkahl - Employment: efactum GmbH

Michael P. Manns - Consulting: Roche, BMS, Gilead, Boehringer Ingelheim, Novartis, Enyo Pharma, Eiger, GSK, Merck/MSD, Janssen, Medgenics, Biotest, AbbVie; Grant/Research Support: Merck/MSD, Roche, Gilead, Novartis, Boehringer Ingelheim, BMS, AbbVie, Janssen; Speaking and Teaching: Merck/MSD, Roche, BMS, Gilead, Janssen, GSK, Novartis, AbbVie

Christoph Sarrazin - Advisory Committees or Review Panels: Bristol-Myers Squibb, Janssen, Merck/MSD, Gilead, Roche, Abbvie, Janssen, Merck/MSD; Consulting: Merck/MSD, Merck/MSD; Grant/Research Support: Abbott, Roche, Merck/MSD, Gilead, Janssen, Abbott, Roche, Merck/MSD, Qiagen; Speaking and Teaching: Gilead, Novartis, Abbott, Roche, Merck/MSD, Janssen, Siemens, Falk, Abbvie, Bristol-Myers Squibb, Achillion, Abbott, Roche, Merck/MSD, Janssen

Dietrich Hueppe - Advisory Committees or Review Panels: Roche, MSD, Novatis, Gilead, BMS, Janssen, AbbVie

Thomas Berg - Advisory Committees or Review Panels: Gilead, BMS, Roche, Tibotec, Vertex, Jannsen, Novartis, Abbott, Merck, Abbvie; Consulting: Gilead, BMS, Roche, Tibotec; Vertex, Janssen; Grant/Research Support: Gilead, BMS, Roche, Tibotec; Vertex, Jannssen, Merck/MSD, Boehringer Ingelheim, Novartis, Abbvie; Speaking and Teaching: Gilead, BMS, Roche, Tibotec; Vertex, Janssen, Merck/MSD, Novartis, Merck, Bayer, Abbvie

Claus Niederau - Advisory Committees or Review Panels: MSD, Abbvie, Jannsen, Gilead; Consulting: MSD; Grant/Research Support: MSD; Speaking and Teaching: MSD, Abbvie, BMS, Roche, Gilead

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Safety and efficacy of IFN- free antiviral therapies in advanced HCV- associated liver cirrhosis: Results from the German Hepatitis C-Registry (DHC-R)

Katja Deterding[1], Joerg Petersen[2], Hartwig H. Klinker[3], Karl-Georg Simon[4], Klaus H. Boeker[5], Eckart Schott[6], Tim Zimmermann[7], Markus Cornberg[1], Rainer Günther[8], Heike Pfeiffer-Vornkahl[9], Christoph Sarrazin[10], Michael P. Manns[1], Dietrich Hueppe[11], Heiner Wedemeyer[1], Thomas Berg[12], German Hepatitis C-Registry[13]; [1]Gastroenterology, Hepatology und Endocrinology, Hannover Medical School, Hannover, Germany; [2]ifi-institute for interdisciplinary medicine, Hamburg, Germany; [3]University Hospital Würzburg, Würzburg, Germany; [4]MVZ Dr.Eisenbach Dr.Simon Dr.Schwarz GbR, Leverkusen, Germany; [5]Center of Hepatology, Hannover, Germany; [6]Charité Campus Virchow-Klinikum (CVK), Berlin, Germany; [7]I. Dept. of Medicine, Johannes Gutenberg University Mainz, Mainz, Germany; [8]Department of Internal Medicine I, UK S-H, Campus Kiel, Kiel, Germany; [9]e.factum GmbH, Butzbach, Germany; [10]J. W. Goethe-University Hospital, Frankfurt, Germany; [11]Center of Gastroenterology, Herne, Germany; [12]Department of Hepatology, University Hospital Leipzig, Leipzig, Germany; [13]Leberstiftungs-GmbH Deutschland, Hannover, Germany

Introduction: Direct-acting antiviral (DAA) regimens improved the efficacy of chronic HCV treatment. Phase 3 trials suggested lower response rates in patients with liver cirrhosis. However, there is limited information on the efficacy of DAA therapies in interferon-ineligible patients with advanced cirrhosis. To what extent liver function improves in cirrhotic patients receiving interferon-free therapies is unknown. **Methods:** The DHC-R (Deutsches Hepatitis C-Register, German Hepatitis C-Registry) is a national multicenter real-world cohort including approx. 9,300 patients. Patients are treated at the discretion of a physician. Data are collected by a web-based system. Data quality is analyzed by plausibility checks and on site monitoring. This data analysis is based on 6,034 patients who were observed for at least 40 weeks after initiation of antiviral treatment. Patients with advanced liver cirrhosis, defined by at least one of the following criteria: FibroScan >20kPa, thrombocytes <90,000/µl, albumin <35g/l or signs of liver decompensation, were analyzed. **Results:** 763 patients had advanced liver cirrhosis (median MELD-Score 9; range 6-32), 632 patients with FU week 12 were included. The majority of patients was infected with HCV-genotype 1 (n=592); HCV-genotypes 2, 3, 4 and 6 were present in 17, 124, 28 and 1 patient, respectively. Patients received different treatment regimens. Overall, SVR was achieved in 88.0% of the patients (ITT). SVR rates according to the regimen ranged from 66 to 100%. DAA therapy lead to SVR rates (ITT) of 91.1%, 80.0%, 72.7% and 82.6% for HCV- genotype 1 (n =460), 2 (n =12), 3 (n=64) and 4 (n=19), respectively. Liver function parameters including albumin, bilirubin and prothrombin time improved in the majority of patients during antiviral therapy/follow-up. The median platelet count, as a clinical marker of portal hypertension, increased from 88,000/µl at baseline to 111,000/µl during follow-up (p<0.05). Creatinine levels were stable during antiviral treatment. SAEs were reported in 8.1% and 6 patients died during the observation period. **Conclusions:** This real-world cohort confirms that DAA treatment is feasible in patients with advanced liver cirrhosis leading to a restoration of liver function. A broad spectrum of individual treatment regimens was applied reflecting individualization of treatment in this difficult-to-treat cohort.

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Katja Deterding - Speaking and Teaching: AbbVie, MSD/Merck, Gilead

Joerg Petersen - Advisory Committees or Review Panels: Bristol-Myers Squibb, Gilead, Novartis, Merck, Bristol-Myers Squibb, Gilead, Novartis, Merck; Grant/Research Support: Roche, GlaxoSmithKline, Roche, GlaxoSmithKline; Speaking and Teaching: Abbott, Tibotec, Merck, Abbott, Tibotec, Merck

Hartwig H. Klinker - Advisory Committees or Review Panels: AbbVie, BMS, Gilead, Hexal, Janssen, MSD; Grant/Research Support: AbbVie, BMS, Gilead, Janssen, MSD, Arrowhead, Novartis; Speaking and Teaching: AbbVIe, BMS, Gilead, Janssen, MSD

Karl-Georg Simon - Advisory Committees or Review Panels: AbbVie, BMS, JANSSEN, MSD; Speaking and Teaching: AbbVie, BMS, FALK, GILEAD, JANSSEN, NORGINE, MERZ, MSD

Klaus H. Boeker - Consulting: Janssen; Speaking and Teaching: MSD, Roche, Gilead, BMS, Falk Foundation, Novartis, AbbVie

Eckart Schott - Advisory Committees or Review Panels: Gilead, Roche, Bayer, BMS, Abbvie, Janssen, MSD; Speaking and Teaching: Gilead, Novartis, Roche, MSD, Bayer, Falk, BMS, Janssen, Abbvie

Tim Zimmermann - Advisory Committees or Review Panels: Abbvie; Speaking and Teaching: BMS

Markus Cornberg - Advisory Committees or Review Panels: Merck (MSD Germamny), Roche, Gilead, Novartis, Abbvie, Janssen Cilag, BMS; Grant/Research Support: Merck (MSD Germamny), Roche; Speaking and Teaching: Merck (MSD Germamny), Roche, Gilead, BMS, Novartis, Falk, Abbvie

Rainer Günther - Speaking and Teaching: Roche Pharma AG, Gilead, AbbVie

Heike Pfeiffer-Vornkahl - Employment: efactum GmbH

Christoph Sarrazin - Advisory Committees or Review Panels: Bristol-Myers Squibb, Janssen, Merck/MSD, Gilead, Roche, Abbvie, Janssen, Merck/MSD; Consulting: Merck/MSD, Merck/MSD; Grant/Research Support: Abbott, Roche, Merck/MSD, Gilead, Janssen, Abbott, Roche, Merck/MSD, Qiagen; Speaking and Teaching: Gilead, Novartis, Abbott, Roche, Merck/MSD, Janssen, Siemens, Falk, Abbvie, Bristol-Myers Squibb, Achillion, Abbott, Roche, Merck/MSD, Janssen

Michael P. Manns - Consulting: Roche, BMS, Gilead, Boehringer Ingelheim, Novartis, Enyo Pharma, Eiger, GSK, Merck/MSD, Janssen, Medgenics, Biotest, AbbVie; Grant/Research Support: Merck/MSD, Roche, Gilead, Novartis, Boehringer Ingelheim, BMS, AbbVie, Janssen; Speaking and Teaching: Merck/MSD, Roche, BMS, Gilead, Janssen, GSK, Novartis, AbbVie

Dietrich Hueppe - Advisory Committees or Review Panels: Roche, MSD, Novatis, Gilead, BMS, Janssen, AbbVie

Heiner Wedemeyer - Advisory Committees or Review Panels: Transgene, MSD, Roche, Gilead, Abbott, BMS, Falk, Abbvie, Novartis, GSK, Roche Diagnostics, Eiger; Consulting: MyrGmbH; Grant/Research Support: MSD, Novartis, Gilead, Roche, Abbott, Roche Diagnostics; Speaking and Teaching: BMS, MSD, Novartis, ITF, Abbvie, Gilead

Thomas Berg - Advisory Committees or Review Panels: Gilead, BMS, Roche, Tibotec, Vertex, Jannsen, Novartis, Abbott, Merck, Abbvie; Consulting: Gilead, BMS, Roche, Tibotec; Vertex, Janssen; Grant/Research Support: Gilead, BMS, Roche, Tibotec; Vertex, Jannssen, Merck/MSD, Boehringer Ingelheim, Novartis, Abbvie; Speaking and Teaching: Gilead, BMS, Roche, Tibotec; Vertex, Janssen, Merck/MSD, Novartis, Merck, Bayer, Abbvie

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Safety And Efficacy Of The Combination Ombitasvir/ Paritaprevir/Ritonavir ± Dasabuvir In Hcv Genotype 1- Or 4-Mono-Infected Patients From The French Anrs CO22 Hepather Cohort

Hélène Fontaine[1], Christophe Hezode[2], Françoise Roudot-Thoraval[2], Stanislas Pol[1]; [1]Hop Cochin, Paris, France; [2]Hop H Mondor, Creteil, France

Background Data on real-life use of direct acting antivirals (DAAs) in the treatment of chronic hepatitis C are scarce. We report the real-life results of the ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) ± dasabuvir (DSV) combination in HCV genotype-1 or 4-infected patients. **Methods** ANRS CO22 HEPATHER « Therapeutic options for hepatitis B and C: a French cohort » is a multicenter observational cohort which aims to include 15 000 HCV- and 10 000 HBV-infected patients (ClinicalTrials.gov, NCT01953458). We selected all cohort participants (n=277) with a HCV genotype 1 (n=223/80.5%) or genotype 4 (n=54/19.5%) infection who initiated a combination of PTV/r 150/100 mg/d and OBV 25 mg/d with (GT1) or without (GT4) DSV 500 mg/d, with (n= 137) or without (n= 140) ribavirin (RBV) (1-1.2 g/d) before October 1st, 2015. The mean age was 58 years, cirrhosis F4 and F3 fibrosis was present in 52/94 (18.8/33.9%) patients, respectively and the duration of therapy was mainly 12 weeks. The main endpoint criteria was sustained virological response (SVR12) defined by the undetectability of HCV RNA 12 weeks after the last treatment intake. **Findings:** Population characteristics and SVR4 and SVR12 are presented in the Table A SVR4 and a SVR12 was obtained in 96/101 (95 %) and 88/91 (96.7 %) of patients. **Interpretation:** In real life setting, the OBV/PTV/r+/-DSV combination is associated with a high rate of SVR12, higher than 92 %, in patients infected by genotype 1 or 4. Results on all patients treated with OBV/PTV/r+/-DSV and included in the cohort will be presented. Failure associated factors will be analyzed.

Population description, SVR4, and SVR12

	OBV/PTV/r+DSV RBV N = 84	OBV/PTV/r+DSV N = 131	OBV/PTV/r N = 9	OBV/PTV/r RBV N = 53
Genotype 1, n (%)	80 (95)	130 (99)	6 (67)	7 (13)
Genotype 4, n (%)	4 (5	1 (1)	3 (33)	46 (83)
Mean age (years)	60	60	61	53
Male, n (%)	55 (65)	60 (46)	4 (44)	30 (57)
Severe fibrosis (F3-F4), n (%)	60 (71)	54 (41)	5 (56)	27 (51)
Treatment experienced, n (%)	47 (56)	55 (42)	3 (33)	26 (47)
SVR4, n/n (%)	41/44 (93,2)	41/44 (93,2)	1/1 (100)	24/24 (100)
SVR12, n/n (%)	36/38 (94,7)	26/27 (92,3)	1/1 (100)	25/25 (100)

Disclosures:

Hélène Fontaine - Board Membership: Abbvie, Gilead, BMS, Janssen; Independent Contractor: gilead, BMS, MSD, Roche, Janssen

Christophe Hezode - Speaking and Teaching: Roche, BMS, MSD, Janssen, abbvie, Gilead

Françoise Roudot-Thoraval - Advisory Committees or Review Panels: Roche, gilead; Consulting: LFB biomedicaments; Speaking and Teaching: gilead, Janssen, BMS, Roche, Abbvie

Stanislas Pol - Board Membership: Bristol-Myers-Squibb, Boehringer Ingelheim, Tibotec Janssen Cilag, Gilead, Glaxo Smith Kline, Roche, MSD, Novartis; Grant/Research Support: Gilead, Roche, MSD; Speaking and Teaching: Bristol-Myers-Squibb, Boehringer Ingelheim, Tibotec Janssen Cilag, Gilead, Roche, MSD, Novartis

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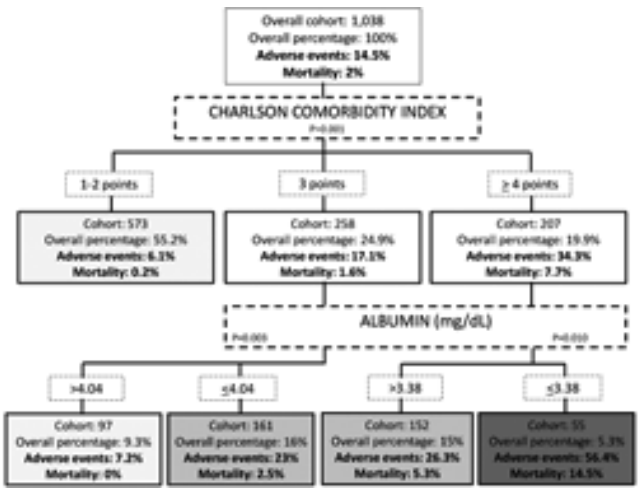
Charlson Comorbidity Index predicts the overall benefit of IFN-free therapy in hepatitis (HepCom Study)

Javier Ampuero[1,2], Carlota Jimeno[3], Rosa Quiles[4], Nieves Palomo[5], Guillermo Ontanilla[1], Jose Miguel Rosales-Zabal[6], Susana Llerena[7], Patricia Cordero[1], Francisco Javier Serrano[8], A. Ortega[9], Marta Hernández[10], Martin S. Bonacci[11], Moises Diago[12], Blanca Figueruela[3], Xavier Forns[11], Jose L. Calleja[10], Raul J. Andrade[9], Manuel De la Mata[8], Isabel Carmona[1], Javier Crespo[7], J. M. Navarro[6], Juan Manuel Pascasio[1], Maria Buti[5], Javier Salmeron[4], Manuel Romero-Gomez[1,2]; [1]Intercentre Unit of Digestive Diseases, Virgen del Rocío - Virgen Macarena University Hospitals, Sevilla, Spain; [2]Ciberehd, Institute of Biomedicine of Sevilla, Sevilla, Spain; [3]Valme University Hospital, Sevilla, Spain; [4]Ciberehd, San Cecilio University Hospital, Granada, Spain; [5]Ciberehd, Vall d'Hebrón University Hospital, Barcelona, Spain; [6]Agencia Sanitaria Costa del Sol Hospital, Marbella, Spain; [7]Marqués de Valdecilla University Hospital, Santander, Spain; [8]Reina Sofía University Hospital, Córdoba, Spain; [9]Virgen de la Victoria University Hospital, Málaga, Spain; [10]Puerta de Hierro University Hospital, Majadahonda, Madrid, Spain; [11]IDIBAPS, Ciberehd, Clinic University Hospital, Barcelona, Spain; [12]General University Hospital, Valencia, Spain

Background: The advent of new direct-acting antivirals has dramatically increased the SVR rates in Hepatitis C (HCV), with fewer adverse effects. However, the eradication of the virus could not be associated with a better prognosis in all

patients. Aim: To assess the impact of basal comorbidities on the overall benefit of HCV patients treated with IFN-free therapies. Methods: Multicenter study including prospectively 1,038 HCV patients (cirrhosis 71%) treated with IFN-free therapies. Basal comorbidities were evaluated by: a) Charlson Comorbidity Index (CCI) (Charlson, 1987); b) Modified Charlson Comorbidity Index (mCCI) (Berkman, 1992); c) CirCom Index (Jepsen, 2014). Liver and non-liver related life-threatening and serious adverse events were collected within the first year of treatment. Results: Adverse events were found in 14.5% (150/1,038) of overall cohort, with 2% (21/1,038) of deaths, during 7.5±3.1 months of follow-up. CCI (3.4±1.7 *vs.* 2.2±1.6; p=0.0001), mCCI (0.9±1 *vs.* 0.4±0.8; p=0.0001) and CirCom (0.7±0.9 *vs.* 0.3±0.6; p=0.0001) were higher in patients suffering from adverse events. Age, platelet count, creatinine, albumin and total bilirubin, as well as the presence of cirrhosis were also related to adverse events. An algorithm to predict and identify low-, moderate- and high-risk groups was constructed using CRT growing method (**Figure**). These groups were subsequently introduced in Kaplan-Meier curve for adverse events (logRank 135.318; p<0.0001) and mortality (logRank 72.134; p<0.0001). Conclusion: HCV patients showing higher basal comorbidities showed more risk of suffering poor prognosis. A rapid and objective algorithm, including Charlson Comorbidity Index, helps to identify patients with increased rates of mortality and adverse events within first months of antiviral therapy. Thus, we could determine the overall benefit of DAA therapy beyond of the eradication of the virus.



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Xavier Forns - Consulting: Jansen, Abbvie; Grant/Research Support: Jansen, Abbvie

Jose L. Calleja - Advisory Committees or Review Panels: Gilead, Abbvie ; Speaking and Teaching: Abbvie, Gilead, Janssen, BMS

Javier Crespo - Advisory Committees or Review Panels: Abbvie, Janssen, BMS; Grant/Research Support: MSD, Gilead

Maria Buti - Advisory Committees or Review Panels: Gilead, Janssen, MSD; Grant/Research Support: Gilead, Janssen; Speaking and Teaching: Gilead, Janssen, BMS

The following people have nothing to disclose: Javier Ampuero, Carlota Jimeno, Rosa Quiles, Nieves Palomo, Guillermo Ontanilla, Jose Miguel Rosales-Zabal, Susana Llerena, Patricia Cordero, Francisco Javier Serrano, A. Ortega, Marta Hernández, Martin S. Bonacci, Moises Diago, Blanca Figueruela, Raul J. Andrade, Manuel De la Mata, Isabel Carmona, J. M. Navarro, Juan Manuel Pascasio, Javier Salmeron, Manuel Romero-Gomez

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SVR12 rates under DAA-based HCV therapy from the National German Cohort Study: Does HIV co-infection impair the response to DAA combination therapy?

Jürgen K. Rockstroh[1], Thomas Lutz[2], Stefan Mauss[3], Christiane Cordes[4], Heribert Hillenbrand[5], Arend Moll[6], Heike Pfeiffer-Vornkahl[7], Markus Cornberg[8], Michael P. Manns[8], Axel Baumgarten[9], German Hepatitis C-Registry[10]; [1]Department of Internal Medicine I, Bonn University, Bonn, Germany; [2]Infektiologikum, Frankfut, Germany; [3]Center for HIV and Hepatogastroenterology, Duesseldorf, Germany; [4]Practice for Infectiology, Berlin, Germany; [5]PraxisCityOst, Berlin, Germany; [6]Praxiszentrum Kaiserdamm, Berlin, Germany; [7]e.factum GmbH, Butzbach, Germany; [8]Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [9]Center for infectious diseases, Berlin, Germany; [10]Leberstiftungs-GmbH Deutschland, Hannover, Germany

Introduction: More recently, cohort analyses have claimed that HIV co-infection independently impairs the response to direct-acting antiviral (DAA)-based therapy against chronic hepatitis C (HCV) in real life cohorts (1). The aim of this study was therefore to compare SVR12 rates between HIV/HCV co-infected and HCV mono-infected subjects from the National German HCV cohort. **Methods:** The DHC-R (Deutsches Hepatitis C-Register, German Hepatitis C-Registry) is a national multicenter real-world cohort including approx. 9,300 patients. Patients are treated at the discretion of the physician. Data are collected by a web-based system. Data quality is analyzed by plausibility checks and on site monitoring. This data analysis is based on 6,034 patients who were observed for at least 40 weeks after initiation of antiviral HCV treatment. **Results:** Overall, 459 HIV/HCV co-infected and 5,411 HCV mono-infected subjects were included into this analysis. Baseline characteristics for both groups are shown in Table 1. Overall, SVR12 rates across all genotypes in the ITT analysis were comparable between HCV mono- and HIV/HCV co-infected individuals with 90.9% and 91.9% (SVR12 92.3% vs 92.6% for GT1 and 83.7% vs 88.9% for GT3), respectively. Neither treatment duration nor ribavirin use were different between both groups. Also no difference in HCV SVR12 rate was observed between cirrhotic patients with and without HIV co-infection (89.7% vs 87.9%). Also in the subset of GT1 patients receiving 8 weeks of Ledipasvir/sofosbuvir no difference in SVR12 rates was noted between HIV- and HIV+ HCV patients (93,7% (n=478) vs. 95,8% (n=46)). Number of treatment discontinuations was low for both groups with 2.3 and 1.6%, accordingly. **Conclusions:** This analysis from a large national real-life patient cohort finds no difference in HCV cure rates between HIV/HCV and HCV mono-infected patients and therefore supports current HCV guidelines which no longer see a need to consider HIV co-infected individuals as a special patient population. Neukam K et al., HIV coinfection impairs response to DAA-based HCV therapy. EASL 2016; Abstract: LBP513

Baseline characteristics	HCV mono infection (n=5,411)	HIV/HCV coinfection (n=459)
Male (%)	56.9	85.4
Age (mean ± SD)	53.9 ± 12.4	46.8 ± 8.7
Cirrhosis (%)	30.8	19.2
Genotype (GT) 1/1a (%)	78.0/30.2	79.9/64.3
Genotype 3 (%)	13.8	13.1
HCV Treatment-naive	49.7	52.1
Treatment regimens		
LDV/SOF ± RBV // DAC/SOF ± RBV for GT1 (%)	56.0//13.3	56.8//10.4
SOF/RBV // SOF/IFN/RBV // SOF/DAC for GT3 (%)	31.1//26.7//13.3	52.0//12.0//8.0

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Jürgen K. Rockstroh - Advisory Committees or Review Panels: Abbvie, Cipla, BMS, Merck, Roche, Tibotec, Abbvie, Bionor, Tobira, ViiV, Abbott, Gilead, Janssen; Consulting: Novartis; Grant/Research Support: Gilead, Merck; Speaking and Teaching: BMS, Merck, Siemens, Tibotec, Gilead, Janssen, ViiV

Stefan Mauss - Advisory Committees or Review Panels: BMS, AbbVie, ViiV, Gilead; Speaking and Teaching: BMS, AbbVie, Janssen, Gilead, MSD

Heike Pfeiffer-Vornkahl - Employment: efactum GmbH

Markus Cornberg - Advisory Committees or Review Panels: Merck (MSD Germamny), Roche, Gilead, Novartis, Abbvie, Janssen Cilag, BMS; Grant/Research Support: Merck (MSD Germamny), Roche; Speaking and Teaching: Merck (MSD Germamny), Roche, Gilead, BMS, Novartis, Falk, Abbvie

Michael P. Manns - Consulting: Roche, BMS, Gilead, Boehringer Ingelheim, Novartis, Enyo Pharma, Eiger, GSK, Merck/MSD, Janssen, Medgenics, Biotest, AbbVie; Grant/Research Support: Merck/MSD, Roche, Gilead, Novartis, Boehringer Ingelheim, BMS, AbbVie, Janssen; Speaking and Teaching: Merck/MSD, Roche, BMS, Gilead, Janssen, GSK, Novartis, AbbVie

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The following people have nothing to disclose: Thomas Lutz, Christiane Cordes, Heribert Hillenbrand, Arend Moll, Axel Baumgarten

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Sofosbuvir + Peginterferon + Ribavirin for 12 Weeks in Genotype 3 HCV Infected Patients and Treatment-Experienced Cirrhotic Patients with Genotype 2 HCV Who Did Not Achieve SVR after 16 or 24 Weeks of Sofosbuvir + Ribavirin

Kosh Agarwal[1], Michael Schultz[2], Stephen Pianko[3], Leslie Bank[4], Jane Collier[5], Jacob George[6], Matthew Priest[7], Stephen D. Ryder[8], Blaire E. Burman[9], Kuldeep Cheent[10], Matthew Cramp[11], Daniel M. Forton[12], Barbara A. Leggett[13], Gerry C. MacQuillan[14], Alnoor Ramji[15], Paul Richardson[16], Michael J. Ryan[17], Nigel Stace[18], Amany Zekry[19], Donald L. Zogg[20], Eleanor Barnes[21], Diana M. Brainard[22], Benedetta Massetto[22], Frances Chen[22], John G. McHutchison[22], Mani Subramanian[22], Eric M. Yoshida[23], Graham R. Foster[24]; [1]King's College Hospital, London, United Kingdom; [2]Dunedin Hospital, Dunedin, New Zealand; [3]Monash Medical Centre, Melbourne, VIC, Australia; [4]Gastreontorology Department, Binghmanton, NY; [5]John Radcliffe Hospital, Radcliffe, United Kingdom; [6]Storr Liver Centre, Westmead Millennium Institute for Medical Research, University of Sydney and Westmead Hospital, Sydney, NSW, Australia; [7]Gartnavel General Hospital, Glasgow, United Kingdom; [8]Nottingham University Hospitals NHS Trust and NIHR Biomedical Research Unit, Nottingham, United Kingdom; [9]Virginia Mason Medical Center, Seattle, WA; [10]Frimley Park Hospital, Frimley, United Kingdom; [11]South West Liver Unit, Derriford Hospital, Plymouth, United Kingdom; [12]St George's Hospital University of London, London, United Kingdom; [13]Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia; [14]Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [15]Gastroenterology Research Institute, Vancouver, BC, Canada; [16]Royal Liverpool Hospital, Liverpool, United Kingdom; [17]Digestive and Liver Disease Center, Norfolk, VA; [18]Wellington Hospital, Wellington, New Zealand; [19]St George Hospital, Sydney, NSW, Australia; [20]Minnesota Gastroenterology, Saint Paul, MN; [21]Nuffield Department of Medicine, Oxford NHIR BRC, Oxford, United Kingdom; [22]Gilead Sciences, Foster City, CA; [23]University of British Columbia, Division of Gastroenterology, Vancouver, BC, Canada; [24]Queen Mary University of London, Barts Health, London, United Kingdom

Background and Aims: Retreatment options for direct-acting antiviral (DAA)-experienced genotype 2 or 3 HCV-infected patients are limited. Treatment-experienced (TE) patients with genotype (GT) 2 HCV and cirrhosis, and treatment-naïve (TN) and TE patients with GT3 HCV with and without cirrhosis who relapsed following SOF+RBV treatment in the Phase 3 Boson study were offered retreatment with SOF+PegIFN+RBV for 12 weeks. **Methods:** Thirty patients received open-label SOF 400mg+PegIFN+RBV for 12 weeks. PegIFN was administered as 180 μg s.c weekly injection, and RBV was administered orally 1000-1200 mg in a divided daily dose. The primary endpoint was SVR12. **Results:** Of these 30 patients, 90% were male, all but one (97%) had GT3 HCV infection, 43% had cirrhosis. All patients completed the treatment period per protocol. Overall, SVR12 was achieved by 80% (24/30). Among patients with GT3 HCV infection, 83% (24/29) achieved SVR12, SVR12 rates were higher among those without cirrhosis (88%) than those with cirrhosis (75%), and among those previously treated for 24 weeks (100%) than 16 weeks (74%) (Table).The single GT2 patient relapsed at post-treatment Week 4 visit. Prior to retreatment, 4 of the 30 patients had NS5B nucleoside inhibitor RASs (N142T n=1, L159F n=2, V321 n=1) and all achieved SVR12 after retreatment.The most common adverse events were fatigue, headache, nausea, myalgia, pyrexia, influenza-like illness, pruritus, and rash. No patient experienced an AE leading to study drug discontinuation. One patient experienced an SAE of shoulder pain one day after treatment completion that was assessed as not related to study drug by the investigator. **Conclusions:** SOF+PegIFN+RBV provided a high rate of SVR12 in non-cirrhotic patients with GT3 HCV infection who relapsed following SOF+RBV therapy. However, PegIFN based regimens are not favored by patients and highly effective and well tolerated IFN free regimens for treatment of GT3 HCV are needed.

SVR12 rates in GT3 patients, by cirrhosis status and prior regimen

SVR % (n/N)	SOF+PegIFN+RBV N=29
Overall	83 (24/29)
Cirrhotic	75 (9/12)
SOF+RBV 16 weeks	67 (6/9)
SOF+RBV 24 weeks	100 (3/3)
Non cirrhotic	88 (15/17)
SOF+RBV 16 weeks	80 (8/10)
SOF+RBV 24 weeks	100 (7/7)

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Kosh Agarwal - Advisory Committees or Review Panels: Gilead, BMS, Novartis, Janssen, AbbVie; Consulting: MSD, Janssen, Achillion, Intercept; Grant/Research Support: Roche, Gilead, BMS, Arbutus; Speaking and Teaching: Astellas, Gilead, BMS, GSK

Stephen Pianko - Advisory Committees or Review Panels: Roche, Novartis, GILEAD, Roche, Novartis; Consulting: GILEAD; Speaking and Teaching: JANSSEN, BMS

Leslie Bank - Grant/Research Support: AbbVie Virology, Gilead, Merck, BMS; Speaking and Teaching: AbbVie Immunology, Gilead, Merck, BMS

Jacob George - Advisory Committees or Review Panels: Pharmaxis, BMS, MSD, Gilead, Janssen, Abbvie; Grant/Research Support: MSD

Stephen D. Ryder - Advisory Committees or Review Panels: Abbvie, Gilead, MSD, MBS, Norgine

Matthew Cramp - Advisory Committees or Review Panels: Gilead, AbbVie, BMS, Merck, Janssen; Grant/Research Support: Gilead, AbbVie, BMS, Merck, Janssen; Speaking and Teaching: Gilead, AbbVie, BMS, Merck, Janssen

Daniel M. Forton - Advisory Committees or Review Panels: Gilead, Merck, Abbvie; Speaking and Teaching: Janssen, BMS

Barbara A. Leggett - Advisory Committees or Review Panels: MSD, MSD, MSD, MSD, BMS, Abbvie; Speaking and Teaching: Roche, Roche, Roche, Roche, Gilead

Alnoor Ramji - Advisory Committees or Review Panels: BMS, Merck, Gilead, Janssen, Lupin, Boehringer Ingelheim; Grant/Research Support: BMS, Abbvie, Merck, Gilead, Vertex, Novartis, Boehringer Ingelheim

Michael J. Ryan - Advisory Committees or Review Panels: gilead; Speaking and Teaching: gilead

Amany Zekry - Advisory Committees or Review Panels: GILEAD, BMS, MSD, Abbvie

Diana M. Brainard - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

Benedetta Massetto - Employment: Gilead Sciences, Inc.; Stock Shareholder: Gilead Sciences, Inc

John G. McHutchison - Employment: gilead; Stock Shareholder: gilead

Eric M. Yoshida - Advisory Committees or Review Panels: Gilead Sciences Inc; Grant/Research Support: Abbvie, Merck Inc, Springbank, Jannsen Inc, Gilead Sciences Inc, Intercept; Speaking and Teaching: Gilead Sciences Inc, Merck Canada, Celgene Canada, Merck Inc

Graham R. Foster - Advisory Committees or Review Panels: GlaxoSmithKline, Novartis, Boehringer Ingelheim, Tibotec, Gilead, Janssen, Idenix, GlaxoSmith-Kline, Novartis, Roche, Tibotec, Chughai, Gilead, Merck, Janssen, Idenix, BMS, Alnylam; Board Membership: Boehringer Ingelheim; Grant/Research Support: Roche, Chughai, Springbank; Speaking and Teaching: Roche, Gilead, Tibotec, Merck, BMS, Boehringer Ingelheim, Gilead, Janssen

The following people have nothing to disclose: Michael Schultz, Jane Collier, Matthew Priest, Blaire E. Burman, Kuldeep Cheent, Gerry C. MacQuillan, Paul Richardson, Nigel Stace, Donald L. Zogg, Eleanor Barnes, Frances Chen, Mani Subramanian

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Predictors of Improvement in Glomerular Filtration Rate Among Patients Treated with Ombitasvir/Paritaprevir/r and Dasabuvir with or without RBV

David E. Bernstein[1], Albert Tran[2], Paul Martin[3], Kris V. Kowdley[4], Marc Bourlière[5], Mark S. Sulkowski[6], Paul J. Pockros[7], Lois M. Larsen[8], Diana L. Shuster[8], Daniel E. Cohen[8], Boris Renjifo[8], Ira M. Jacobson[9]; [1]Department of Medicine, Hofstra Northwell School of Medicine, Manhasset, NY; [2]University Hospital of Nice, Digestive Centre, Nice, France; [3]Division of Hepatology, School of Medicine, University of Miami, Miami, FL; [4]Swedish Medical Centre, Seattle, WA; [5]Hôpital Saint Joseph, Marseilles, France; [6]Viral Hepatitis Center, Johns Hopkins University, Baltimore, MD; [7]Scripps Clinic and Scripps Translational Science Institute, La Jolla, CA; [8]AbbVie Inc., North Chicago, IL; [9]Mount Sinai Beth Israel, New York, NY

Introduction: HCV infection is associated with an increased risk of chronic kidney disease (CKD), and management of HCV in patients with advanced CKD remains a challenge. We previously reported that treatment of HCV GT1-infected patients with ombitasvir, paritaprevir (identified by AbbVie and Enanta) with the pharmacokinetic enhancer ritonavir, and dasabuvir (OBV/PTV/r + DSV) ± RBV was not associated with overall changes in renal function. However we observed a mean gain in eGFR following treatment in patients with baseline (BL) eGFR 60–≤ 90 (+1.3 mL) or ≤ 60 mL/min/1.73 m^2 (+6.0 mL). This analysis investigated BL patient characteristics and laboratory predictors for eGFR improvement with OBV/PTV/r + DSV ± RBV. **Methods:** Renal function was categorized by eGFR using the MDRD equation and patients were grouped according to BL eGFR: > 90, 60–90, or < 60 mL/min/1.73 m^2. Analysis included patients treated with OBV/PTV/r + DSV ± RBV in 9 trials: SAPPHIRE-I/II; TURQUOISE-II/III; TOPAZ-II; PEARL-II/III/IV; and RUBY-I (excluding patients on dialysis). BL factors associated with a ≥ 10 mL/min/1.73 m^2 increase in eGFR were examined by stepwise logistic regression. The primary model excluded two studies (RUBY-I and TURQUOISE-III) that did not include BL urinalysis. Additional models included these studies and explored other degrees of change in eGFR. **Results:** BL characteristics are shown in **Table 1**. In the primary model, a ≥ 10 mL/min/1.73 m^2 increase in eGFR was associated with BL proteinuria (OR 1.647; 95% CI 1.320–2.054; p<0.001), history of diabetes (OR 1.512; 95% CI 1.059–2.161; p=0.023), BMI (OR 0.948; 95% CI 0.926–0.971; p<0.001), and Black race (OR 0.596; 95% CI 0.384–0.923; p=0.021). **Conclusion:** BL proteinuria, history of diabetes, lower BMI, and non-Black race were identified as predictors of an eGFR increase of ≥10 mL/min/1.73 m^2 after OBV/PTV/r + DSV ± RBV treatment. Longer follow-up is needed to confirm any beneficial effect on renal function or possible clinical outcomes associated with eradication of HCV with this treatment.

Baseline characteristics

Characteristic	eGFR, mL/min/1.73 m2		
	<60 N=82	60-90 N=1479	>90 N=1172
Age, years, mean ± SD	59.9 ± 6.6	54.8 ± 9.7	49.1 ± 11.6
Race, n (%) White race Black race Asian race Other	 72 (88) 9 (11) 1 (1) 0	 1348 (91) 99 (7) 19 (1) 13 (0.9)	 1026 (88) 110 (9) 18 (2) 18 (2)
BMI, kg/m2, mean ± SD	28.0 ± 4.8	26.7 ± 4.3	27.0 ± 4.9
Fibrosis stage, n (%) F0-1 F2 F3 F4	 37 (45) 11 (13) 7 (9) 27 (33)	 793 (54) 229 (16) 190 (13) 265 (18)	 650 (56) 145 (12) 112 (10) 264 (23)
History of diabetes, n (%)	10 (12)	119 (8)	97 (8)
History of hypertension, n (%)	41 (50)	467 (32)	291 (25)
BL proteinuria, n/N (%)*	21/67 (31)	325/1449 (22)	277/1151 (24)

* Excludes RUBY-I and TURQUOISE-III.

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David E. Bernstein - Consulting: abbvie, Merck, Janssen; Grant/Research Support: GIlead, abbvie, BMS, Janssen; Speaking and Teaching: Gilead

Paul Martin - Advisory Committees or Review Panels: BMS; Grant/Research Support: Merck, Gilead, Janssen, Abbvie

Kris V. Kowdley - Advisory Committees or Review Panels: Abbvie, Enanta, Gilead, Intercept, Merck, Novartis, Trio Health, Verylx; Grant/Research Support: Abbvie, Evidera, Galectin, Gilead, Immuron, Intercept, Merck, NGM Biopharma, Novartis, Tobira, Trio Health; Speaking and Teaching: Gilead, Intercept

Marc Bourlière - Advisory Committees or Review Panels: Schering-Plough, Bohringer inghelmein, Schering-Plough, Bohringer inghelmein, Transgene; Board Membership: Bristol-Myers Squibb, Gilead, Idenix; Consulting: Roche, Novartis, Tibotec, Abott, glaxo smith kline, Merck, Bristol-Myers Squibb, Novartis, Tibotec, Abott, glaxo smith kline; Speaking and Teaching: Gilead, Roche, Merck, Bristol-Myers Squibb

Mark S. Sulkowski - Advisory Committees or Review Panels: Merck, AbbVie, Janssen, Gilead, Trek, Cocrystal; Grant/Research Support: Merck, AbbVie, Janssen, Gilead

Paul J. Pockros - Advisory Committees or Review Panels: Janssen, Merck, BMS, Gilead, AbbVie; Consulting: Lumena, Beckman Coulter; Grant/Research Support: Intercept, Janssen, BMS, Gilead, Lumena, Beckman Coulter, AbbVie, RMS, Merck; Speaking and Teaching: AbbVie, Janssen, Gilead

Lois M. Larsen - Employment: AbbVie; Stock Shareholder: AbbVie

Diana L. Shuster - Employment: AbbVie

Daniel E. Cohen - Employment: AbbVie; Stock Shareholder: AbbVie

Boris Renjifo - Employment: AbbVie; Stock Shareholder: AbbVie

Ira M. Jacobson - Consulting: AbbVie, Achillion, Bristol Myers Squibb, Intercept, Gilead, Janssen, Merck, Trek; Grant/Research Support: AbbVie, Bristol Myers Squibb, Gilead, Janssen, Merck; Speaking and Teaching: AbbVie, Bristol Myers Squibb, Gilead, Janssen

The following people have nothing to disclose: Albert Tran

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Belgian Experience with Direct Acting Antivirals in People Who Inject Drugs.

Rob Bielen[1], Hans Van Vlierberghe[2], Stefan Bourgeois[3], Christophe Moreno[4], Thomas Vanwollegem[5], Wim Verlinden[5], Jean-Pierre Mulkay[6], Jochen Decaestecker[7,9], Mike Cool[8,9], Chantal de Galocsy[10], Lode Van Overbeke[11], Filip Janssens[12,9], Christophe Van Steenkiste[13,2], François D'heygere[14], Wilfried Cools[15], Frederik Nevens[9], Geert Robaeys[16,1]; [1]Faculty of Medicine and Life sciences, Hasselt University, Tongeren, Belgium; [2]Department of Hepatology and Gastro-Enterology, University Hospitals Gent, Gent, Belgium; [3]Department of Gastro-Enterology and Hepatology, ZNA Stuivenberg, Antwerp, Belgium; [4]Department of Gastro-Enterology and Hepatopancreatology, Erasme Hospital, Brussels, Belgium; [5]Department of Gastro-Enterology and Hepatology, University Hospitals UZAntwerpen, Antwerp, Belgium; [6]Department of Gastro-Enterology and Hepatology, Hôpital Saint-Pierre, Brussels, Belgium; [7]Department of Gastro-Enterology and Hepatology, AZ Delta, Roeselare, Belgium; [8]Department of Gastro-Enterology and Hepatology, AZ Damiaan, Oostende, Belgium; [9]Department of Gastro-Enterology and Hepatology, University Hospitals KULeuven, Leuven, Belgium; [10]Department of Gastro-Enterology and Hepatology, Hôpital HIS Bracops, Brussels, Belgium; [11]Department of Gastro-Enterology and Hepatology, AZ Sint Maarten, Mechelen, Belgium; [12]Department of Gastro-Enterology and Hepatology, Jessa Hospital, Hasselt, Belgium; [13]Department of Gastro-Enterology and Hepatology, AZ Maria Middelares, Gent, Belgium; [14]Department of Gastro-Enterology and Hepatology, AZ Groeninge, Kortrijk, Belgium; [15]Faculty of Sciences, Mathematics and Statistics, Centre for Statistics, Hasselt Universlty, Hasselt, Belgium; [16]Department of Gastro-Enterology and Hepatology, Ziekenhuis Oost-Limburg, Genk, Belgium

Introduction Hepatitis C viral infection (HCV) remains one of the main causes of chronic liver disease worldwide. It has now become a curable disease due to the development of direct acting antivirals (DAA). Therefore, the WHO has set a target to eliminate HCV completely. To reach this target, people who inject drugs (PWID) need to be treated as they are the largest risk group for HCV in the Western world. Furthermore, treatment of HCV in PWID is recommended by the treatment guidelines. The aim was to study the uptake and outcome of treatment for HCV in PWID and the general population. **Method** We performed a Belgian, nation-wide, retrospective cohort study in 12 hospitals. All patients who were treated in these hospitals with simeprevir-sofosbuvir, daclatasvir-sofosbuvir, or ombitasvir/paritaprevir ritonavir – dasabuvir between December 2013 and November 2015 were included. These regimens were chosen based on the Belgian reimbursement criteria. All centers were experienced in treating HCV infected PWID. In case antiviral treatment was started, data were collected in a central database. PWID were subdivided in active users, defined by drug use during therapy with DAA, and former PWID. A PWID was defined by someone who used intravenous drugs at least once. **Results** The study population consisted of 419 patients: 111 PWID, subdivided in 23 active users and 88 former PWID, and 308 non-PWID treated with one of the above DAA regimens ± ribavirin. PWID (active and former) were younger (p=0.001), predominantly male (p=0.001), had a lower BMI (p=0.006), abused more alcohol (p=0.001), used more benzodiazepines (p=0.001) and were more infected with genotype 1a, 3 and 4 (p=0.001). Active PWID were less treatment experienced (p=0.05) and used less comedications (p=0.043). There were no differences in fibrosis score (F3, F4) (p=0.454) between all groups. PWID had a similar rate of side-effects (p=0.961). There was a trend towards more psychological complaints in PWID (p=0.051). Similar rates of treatment completion (p=0.095) and SVR (p=0.372) were achieved irrespective of active substance abuse. **Conclusion** Although DAA are safe and effective also in (active) drug users, PWID are still highly underrepresented in a Belgian treatment cohort, even the era of new DAA therapy. As this risk-group is at the heart of the HCV epidemic, more efforts are necessary to reach this group.

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Alcohol use and hepatitis C virus treatment outcomes among 15,151 patients receiving direct antiviral agents

Judith Tsui[1], Emily Williams[2], Pamela Green[2], Kristin Berry[2], Feng Su[1], George N. Ioannou[1,2]; [1]University of Washington, Seattle, WA; [2]Veterans Affairs Puget Sound Healthcare System, Seattle, WA

Background: Whether alcohol use negatively impacts hepatitis C virus (HCV) treatment outcomes in the era of direct antiviral agents (DAAs) is unknown. Alcohol Use Disorders Identification Test Consumption (AUDIT-C) questionnaires have been recommended to be administered annually in the VA since 2008 to screen for unhealthy alcohol use. This study examined associations between levels of drinking ascertained by screening AUDIT-C questionnaires administered within one year prior to DAAs and response to DAAs in the national Veterans Affairs (VA) healthcare system. **Methods**: Out of 17,487 patients who initiated HCV DAAs during the 18-month period from January 1, 2014 to June 30, 2015, 15,151 (87%) had completed an AUDIT-C questionnaire within one year prior to initiating therapy and comprised the final study sample. DAAs included: sofosbuvir (SOF), ledipasvir/sofosbuvir (LDV/SOF) or ombitasvir-paritaprevir-ritonavir, and dasabuvir (PrOD). Sustained virologic response (SVR) was defined as a viral load below the limit of quantification performed ≥12 weeks after the end of treatment. AUDIT-C scores were categorized as 0 (abstinence), 1–3 (low-level drinking) and 4–12 (unhealthy drinking) in men or 0, 1-2 and 3-12 in women. Rates of SVR and 95% confidence intervals were calculated and we performed multiple logistic regression models, with and without imputing missing SVR data. **Results**: The sample was mostly male (96.7%), 28.9% were black, 30% had cirrhosis, mean age was 61±7 years and the distribution of HCV genotypes was 1 (79.8%), 2 (12.5%), 3 (7.0%) and 4 (0.8%). Alcohol abstinence was reported in 10,387 (68.5%), low-level drinking in 3422 (22.6%) and unhealthy drinking in 1342 (8.9%). There were no significant differences in SVR rates between abstinent (SVR 91%, 95% CI 91-92%), low-level drinking (SVR 93%, 95% CI 92-94%) or unhealthy drinking (SVR 91%, 95% 89-92) categories in the entire sample, or among subgroups defined by HCV genotype, cirrhosis, or HIV status. AUDIT-C categories were not significantly associated with SVR after adjustment for most important predictors of SVR in multivariable logistic regres-

sion models. **Conclusions**: A substantial proportion (31.5%) of HCV-infected patients treated with DAAs in 2014-15 reported not being abstinent from alcohol based on a screening AUDIT-C questionnaire performed within a year prior to initiating DAAs. However, rates of SVR were high, even among persons with low-level and unhealthy alcohol use and AUDIT-C score was not associated with SVR.

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Impact of Sustained Virological Response to Direct Acting Antivirals on Insulin Resistance in Patients with Chronic HCV

Mostafa G. Elhelbawy, Ayman Alsebaey, Wael Abdel-Razek, Mohammed Saad Hashem, Hassan A. El Shennawy, Imam Waked; Hepatology, National Liver Institute, Menoufiya, Egypt

Introduction: Insulin resistance (IR) is a common complication in patients with chronic HCV. The change in IR after treatment with direct acting antivirals (DAAs) is not known. **Aim:** To assess the impact of response to DAAs on the IR status in patients with chronic HCV. **Methods:** Five hundred and eighteen patients (366 treatment-naïve and 152 pegylated interferon (PEG) and ribavirin (RBV) experienced) with positive HCV RNA for more than 6 months were enrolled. Patients with uncontrolled diabetes or other comorbidities, hepatic or extrahepatic malignancy, decompensated liver disease, or prior non-response to DAAs were excluded. The Homeostatic Model Assessment (HOMA) was calculated before and 12 weeks after treatment and IR was defined as HOMA>1.9. Patients were treated according the treating physician's choice, and received one of the following DAAs protocols; 12 weeks of ombitasvir/ritonavir/paritaprevir/RBV (n=28), sofosbuvir (SOF)/simeprevir (n=37), SOF/ravidasvir (n=101), SOF/PEG/RBV (n=195) or 24 weeks of SOF/RBV (n=157). **Results:** Patients' age was 50.7±10.4 years. They were mostly males (n=395, 76.3%), non-diabetics (n=390, 75.3%), non-F4 fibrosis (n=274, 52.9%) and most with pre-treatment IR (n=415, 80.4%). Sustained virological response at 12 weeks post-treatment (SVR12) was achieved in 471 patients (90.9%). There was no significant difference in pre-treatment HOMA between responders and non-responders (3.8±2.6 vs. 4.5±3.3 respectively, p=0.122). HOMA improved significantly more in patients with SVR than in non-responders (median decrease (IQR) = -1.09 (1.8) vs. -0.08 (2.26), p=0.002). The number of patients with IR decreased significantly in patients who achieved SVR (table) much more than in non-responders (p<0.0001). All treatment protocols were associated with comparable HOMA improvement (p=0.222). Significant predictors of SVR12 included age <50 years (p=0.038; OR: 2.1, 95% CI: 1.042-4.226), serum albumin ≥3.5 g/dL (p=0.035; OR: 2.14, 95% CI: 1.057-4.338) and liver stiffness <10 kPa (p=0.017; OR: 2.59, 95% CI: 1.183-5.682) but not pre-treatment IR (p=0.075; 95% CI: 0.838-1.009) **Conclusion:** Insulin resistance improves significantly in patients who achieve an SVR with different DAA regimens.

Number of Patients with IR Before and After Therapy

	Responders (SVR12)		Non-Responders	
	Pre treatment	Post treatment	Pre treatment	Post treatment
Patients with IR (#(%))	375 (80%)	206 (44.1%)	40 (85.1%)	37 (80.4%)
Patients without IR (#(%))	94 (20%)	261 (55.9%)	7 (14.9%)	9 (19.6%)
p	<0.0001		0.551	

IR, insulin resistance; SVR, sustained virological response.

Patients with IR in responders vs. non-responders: pre treatment: p=0.562, post treatment: p<0.0001

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Directly observed therapy of chronic hepatitis C with interferon-free all-oral regimens at a low-threshold drug treatment facility is highly effective for treatment of patients with borderline compliance receiving opioid substitution therapy

Stephan Moser[1], Angelika Schütz[2], Katharina Marchart[2], Gerhard Rechberger[3], Doris Kalchbrenner[3], Sabrina Ambrosch[2], Julian Luhn[2], Enisa Gutic[1], Hans Haltmayer[2], Michael Gschwantler[1]; [1]Department of Internal Medicine IV, Wilhelminenspital, Vienna, Austria; [2]Ambulatorium Suchthilfe Wien, Suchthilfe Wien gGmbH, Vienna, Austria; [3]Verein Dialog Wien, Vienna, Austria

Background: An important subgroup of people who inject drugs (PWID) receives opioid substitution therapy (OST) under direct observation of a physician or nurse at a low-threshold drug treatment facility or pharmacy on a daily basis. Most of these patients suffer from psychiatric comorbidities and are reluctant or unable to go to specialized hepatitis centers. Our hypothesis was that chronic hepatitis C in these difficult-to-treat patients could be optimally managed if modern, interferon-free regimens were applied together with OST under direct observation of a physician or nurse at a low-threshold drug treatment facility. **Methods:** Fifty-nine PWID with chronic hepatitis C and borderline compliance (male/female: 47/12; mean age: 39.1 ± 9.8 years; genotype (GT) 1/3/4: 46/12/1) started interferon-free treatment of chronic hepatitis C at the "Ambulatorium Suchthilfe Wien" – a low-threshold drug treatment facility in Vienna, Austria. Four patients were coinfected with HIV and 15 had liver cirrhosis. Patients received antiviral treatment together with OST under direct observation of a physician or nurse. Treatment-naïve GT1-patients without cirrhosis were treated with sofosbuvir/ledipasvir for eight weeks. For the other patients, the individual treatment regimen was selected according to GT, fibrosis stage, pretreatment, HIV-status and current reimbursement policy of insurances. **Results:** Following this concept of directly observed therapy, adherence to antiviral therapy was excellent: Only two scheduled dates, out of 3.662 dates (0.06%), for ingestion of the antiviral therapy in combination with OST were missed by the 59 patients. Till now, 29 patients (male/female: 24/5; mean age: 39.1 ± 7.0 years; GT1/3/4: 23/5/1; liver cirrhosis present in 8 patients) have completed treatment and a 12-week follow-up period. Virologic healing of hepatitis C infection (sustained virologic response, SVR12) could be confirmed in all 29 patients (SVR12 rate: 100%). **Conclusion:** Directly observed therapy of chronic hepatitis C with interferon-free all-oral regimens at a low-threshold drug treatment facility represents a promising new concept for treatment of patients with borderline compliance receiving OST. By this concept chronic hepatitis C can be cured in a group of difficult-to-treat patients, who are unable to be treated at hepatologic centers. It should be stressed that successful treatment of these patients is not only beneficial for themselves but also for the general population because further transmission of the virus may be prevented.

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Efficacy and Safety of DAAs therapy in Hepatitis C: A Multicenter Real-world Cohort of Chronic Hepatitis C Patients.

Tatsuya Ide[1], Yuichiro Eguchi[3], Masaru Harada[2], Yuichi Honma[2], Shinji Iwane[3], Michiaki Okada[3], Teruko Arinaga-Hino[1], Miyajima Ichiro[1], Ogata Kei[1], Reiichiro Kuwahara[1], Keisuke Amano[1], Takuji Torimura[1]; [1]Division of Gastroenterology,, Kurume University School of Medicine, Kurume, Japan; [2]The Third Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyusyu, Japan; [3]Hepatology, Saga Medical School, Saga, Japan

Purpose: In clinical trials, direct-acting antivirals (DAA) display efficacy rates of 90-99% against chronic hepatitis C (CHC), but it is unclear whether similar results are seen in routine practice. Our goal is to verify the efficacy and safety of DAAs treatment for CHC in a multicenter real-world patients cohort from Japan. Methods: We prospectively enrolled 2,192 consecutive CHC patients in whom 24 weeks' daclatasvir and asunaprevir (DCV/ASV) (n=1,057), 12 weeks' sofosbuvir and ledipasvir (SOF/LDV) (n=701) for genotype 1 disease, or 12 weeks' sofosbuvir and ribavirin (SOF/RBV) (n=434) for genotype 2 disease was initiated during the period from September 2014 to April 2016. Results: 960 patients (43.8%) were male, and the patients' mean age was 66.8 (range: 19-89) years. In addition, 766 patients (34.9%) had been pretreated with interferon–based regimens. Liver cirrhosis was observed in 478 patients (21.8%), and 275 patients (12.5%) had a history of hepatocellular carcinoma. Among the patients treated with DCV/ASV, the treatment discontinuation rate due to adverse events was 4.8% (40/834). The most common reason for discontinuation was increased alanine transaminase levels. The 12-week sustained viral response (SVR12) rate was 89.0% (738/872). The SVR rates of the patients with and without cirrhosis were 89.0% (235/264) and 90.1% (548/608) (p=0.6), respectively. The absence of NS5A-Y93 variants and not having been treated with simeprevir were found to be significantly associated with a SVR (p<0.001). Among the patients treated with SOF/LDV, treatment discontinuation was only necessary in two patients (due to esophagitis and pneumonia, respectively), and the SVR4 or 12 rate was 99.1% (318/321). One patient with cirrhosis and NS5A-L31 and Y93 variants relapsed after the therapy. Among the patients treated with SOF/RBV, the treatment discontinuation rate was 1.7% (5/291), and the SVR4 or 12 rate was 96.2% (280/291). Of the 11 patients who did not achieve a SVR, 8 completed the treatment. Of these 8 patients, 4 were cirrhotic, and the RBV dose was reduced in 3 patients. Cirrhosis was found to be significantly associated with a non-SVR (p=0.03). Conclusion: This cohort, which included a substantial proportion of cirrhotic patients, generally exhibited high response rates. HCV variants were associated with a non-SVR among patients that were treated with DCV/ASV, and cirrhosis was associated with a reduction in the SVR rate among patients that were treated with SOF-based regimens.

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Decreased health resource utilization by peri-transplant (PT) HCV patients after successful direct acting antiviral (DAA) therapy

Suman Verma[1], Graham R. Foster[2], Matthew D. Sadler[1], Michael A. Heneghan[1], William Irving[3], Aisling B. Considine[1], Kate Childs[1], Abid Suddle[1], Ivana Carey[1], Kosh Agarwal[1]; [1]Institute of Liver Studies, King's College Hospital, London, United Kingdom; [2]The Blizard Institute, Queen Mary University of London, London, United Kingdom; [3]NIHR Nottingham Digestive Diseases Biomedical Research Unit, University Hospital Nottingham, Nottingham, United Kingdom

Introduction DAA therapies in patients with advanced liver disease are effective and safe. However, impact on natural history and health economic benefits of treating this advanced, PT population remain unclear. This study assessed healthcare resource utilization from a clinical and cost perspective during, and 6 months (mths) post, DAA therapy compared to untreated HCV patients accepted onto the UK transplant waiting list. **Methods** The NHS England Expanded Access Program (EAP) enabled provision of 12 weeks therapy with Sofosbuvir (SOF) and an NS5A inhibitor, (Ledipasvir or Daclatasvir at clinicians discretion),+/- ribavirin (RBV) to a cohort of HCV positive patients with advanced, decompensated liver disease (Childs Pugh (CP) B7 and above). Of these, 178 patients fulfilled the NHSBT criteria for liver transplantation (LT), with 78 treated at King's College Hospital (KCH) (median CP B7, range B7-C13). Data collection on clinical interventions, support and ancillary therapies was prospective for the duration of therapy and 6 mths post. Additionally, similar data were collected from a comparable retrospective 'control' cohort of 40 untreated HCV KCH patients meeting the NHSBT criteria with CP≥B7 (median B7, range B7-C10) from inclusion onto the LT waiting list, until LT or death (majority within 9 mths) **Results** During DAA therapy minimal blood product and phone call support were needed (24 phone calls to nurse specialists and 44 to consultants, mean 11.5 and 11.6 mins respectively). Of the KCH EAP patients, 85% achieved SVR, with 27 patients at 6 mths follow-up having complete resolution of the decompensation present at treatment initiation (ascites and encephalopathy). 13.6% with SVR were transplanted, 2.9% delisted and 3% died (due to overdose or progression) compared to 56% transplanted, 11% delisted and 33% deaths in the control cohort. Clinical deterioration and worsening MELD necessitated more control cohort patients to be prioritized whilst on the waiting list. This was reflected in the duration of emergency admissions (encephalopathy; sepsis/SBP and variceal bleed) to ITU (mean 0.45 days for patients with SVR *vs* 2.05 for control cohort) and to wards (mean 1.66 *vs* 19.82 days respectively). Overall a mean cost saving of £8473 per successfully treated patient was identified. **Discussion** This early analysis of health resource usage by PT patients treated with SOF and NS5A inhibitor +/- RBV demonstrates benefits in survival, quality of life and health resource utilization in this challenging cohort. Full health resource usage data from 178 PT EAP patients will be presented. The longer term impact of successful DAA therapy on natural history is still unclear.

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A program of Testing and Treat Intended to Eliminate Hepatitis C in a Prison: The JAILFREE-C study

Susana LLerena[1,2], Carmen Cobo[3], Silvia Alvarez[1,2], Angel Estebanez-Gallo[1,2], Miguel M. Soler[3], Jose Ramon Pallas[3], Santiago Echevarria[1,2], Ana Sáez[1,2], Jesus Agüero[1,2], Natalia Chueca[4], Raul Pellon[1,2], Juan Crespo[1,2], Antonio Cuadrado[1,2], Federico García[4], Javier Crespo[1,2]; [1]Gastroenterology and Hepatology Unit., University Hospital Marqués de Valdecilla/Instituto de investigación Marqués de Valdecilla (IDIVAL), Santander, Spain; [2]Department of Molecular Biology, Radiology and Medicine, University of Cantabria, Santander, Spain; [3]Medical Service, El Dueso Penitentiary Centre, Santoña, Spain; [4]Microbiology Unit, Complejo Hospitalario Universitario Granada-Hospital San Cecilio, Instituto de Investigación Biosanitaria IBS, Granada, Spain

Thanks to the National Strategy Plan for tackle Hepatitis C in Spain (2015/16), around 50,000 infected patients are to be cured, mainly F3-F4 and as general population. However, that Plan also considers as a priority the infected patients in prisons. Accordingly we planned a project in a Northern region of Spain (Cantabria) with 600k inhabitants and focused to the regional long-stay prison of El Dueso. Our objectives were to: 1) Perform a systematic screening and evaluation of infections related to blood-borne viruses, 2) Evaluate the efficacy and safety of an IFN-free antiviral regimen, including the impact on the rates of reinfections at short/long term. Methods: The project was planned to start in 1Q 2016 following 3 consecutive phases: 1) viral testing and characterization, 2) treatment of HCV infected inmates, 3) follow-up of patients for 30 months. All new entries in the prison are to be tested immediately and treatment initiated in the first week if HCV-positive. The list of variables to be analyzed include: 1) Demographics, clinical, and virological variables, including NS5a baseline resistance and deep analysis of nucleotide sequence quasispecies complexity of HVR1 region, 2) Endothelial dysfunction and neurocognitive function tests before treatment and 6 months after, 3) Efficacy, safety and QoL throughout the study, and 4) Rates of persistent HCV infection, reinfection and super-infection. Results: Up to now 436 inmates have been included being full tested for blood-borne viruses. The majority of inmates were male (98%) with a median age of 59 yrs. Seventy patients were anti-HCV positive (16%), of these 52 (74%) were HCV RNA positive. HCV genotypes were GT3 (56%), GT1 (36%), and GT4 (8%). Seven patients were HIV-coinfected (13%), and none HBV-coinfected. Fibrosis distribution was: F0-1 51.9%; F2 11.5%; F3 13.4% and F4 23%. The mean MELD score was 8. All viremic patients have been treated with LDV/SOF+/-RBV 12 wks (49 patients) or 8 wks (3 patients). All patients achieved EOT response. No serious AEs were reported and no patients discontinued due to AEs. Baseline NS5A RAS were found in 19% of the patients and were more frequent in HCV GT3 (36%). Viral diversity of the HVR1 region was high, irrespective of the HCV genotype. In 4Q 2016 SVR12 will be available for all treated inmates, including the remaining variables of this long-term study. Conclusions: In this Spanish prison the HCV prevalence is x15 times the described in the general population, showing a different profile of HCV genotypes and a high viral diversity in HVR1. An elimination program of this nature is intended as a pilot experience that could be extended to other prisons.

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Influence of ITPase activity on decreases of hemoglobin during treatment with Interferon-free DAA-based and ribavirin in HCV-related cirrhosis

Nicola Coppola[1], Stefania De Pascalis[1], Vincenzo Messina[2], Giovanni Di Caprio[1], Salvatore Martini[1], Giorgio de Stefano[3], Mario Starace[1], Gianfranca Stornaiuolo[1], Vincenzo Sangiovanni[3], Maria Stanzione[1], Rosa Zampino[1], Federica Calò[1], Luca Rinaldi[1], Marcello Persico[4], Alessandro Federico[1], Antonio Riccardo Buonomo[5], Guglielmo Borgia[5], Giovanni B. Gaeta[1], Pietro Filippini[1,2], Ivan Gentile[5]; [1]Second University of Naples, Naples, Italy; [2]Infectious Diseases, AO CAserta, Caserta, Italy; [3]AO dei Colli, Naples, Italy; [4]Internal Medicine, University of Salerno, Salerno, Italy; [5]University Federico II of Naples, Naples, Italy

BACKGROUND: The aim of the present study was to investigate the association between theinosinetriphosphatase (ITPA) activity and the degree of anemia occurring during DAA/RBV-based therapy in patients with cirrhosis. **METHODS:**In a multicentric, prospective study we enrolled 227 patients with HCV-related cirrhosis treated with DAA and RBV [median age 66 years (IQR 57–71), 52.9% male, median BMI 26.4 (IQR 23.9–28.4), 4.5% withChild B cirrhosis, 6.6% post-liver transplants, 2.7% HIV]. HCV genotype 1a was identified in 10.2%,1bin 58.2%, 2 in 23.6%, 3 in 7.1% and 4 in 0.9%. The median of baseline hemoglobin levels were 14.1 g/dl (IQR 12.9-15.0). Seventy-two (32%) patients were treated with Sofosbuvir(SOF) plus RBV, 25.4% withOmbitasvir, Paritaprevir, Ritonavirand Dasabuvirplus RBV, 22.2% withSOF+Simeprevirplus RBV, 10.2% with SOF+Ledipasvir plus RBV, 8% with SOF+Daclatasvir plus RBV and 2.2% whit Ombitasvir, Paritaprevir, Ritonavir plus RBV. The median dose of RBV/mg/kg was 12.9 (IQR 11.6-14.6).All patients were screened for both the rs1127354 and rs7270101ITPA single nucleotide polymorphisms using a direct sequencing. The predicted ITPA activity was based in according to previous study (Thompson 2010). **RESULT.** One-hundred fifty (66.1%) patients (Group 1) had a normal (100%)ITPase activity, 48 (21.1%; Group 2) had moderate (60%)activityand 29 (12.8%; Group 3) minimal (≤30%)activity.In the three groups the decline of hemoglobin was evaluated from baseline to day 15 (delta 15) and to day 30 (delta 30) of treatment. In Group 1 the delta 15 and 30 were respectively -1.26 (SD ±0.97) and -1.9 (±1.2), decays more severe than those observed in group 2(-0,7±0.99; p=0.006 and -1.5±1.4; p=0.10, respectively) and in group3(-0.36±0.53;p=0.000; and -0.6±0.74;p=0.000). Also the prevalence ofanemia-related events (reduction of RBV dose and/oruse of erythropoietin and/or of blood transfusions)was more frequently observed in group 1 (12.7% at day 15 and 28.7% at day 30) than in group 2 (6.3% and 25%, respectively) and group 3(3.4% and 6.9%,p=0.047).A logistic regression analysis including the ITPA activity, age, sex, dose of Ribavirin andeGFRidentified the the ITPA activity and the dose of ribavirinas the only independent predictors of anemia-related

events (OR:4.66, IC 95%:1.12-19.31,p=0.03; OR:1.25, IC 95%:1.11-1.89,p<0.001; respectively) **CONCLUSION.** This study suggests that the polymorphisms in the ITPA gene influences the severity of anemia during the first month of a DAA-based treatment in HCV-related cirrhosis. Thus, ITPA polymorphism may drive the use of RBV in difficult-to-treat patients, such as cirrhotic and/or non responder patients

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Hepatitis B reactivation after interferon-based therapy versus pan-oral direct acting antiviral agents in chronic hepatitis C patients co-infected with hepatitis B virus: a systematic review and meta-analysis

Cheng Wang[1,2], Bing Li[3], Jing Chen[1], Huiming Liu[4], Dong Ji[3,5], Qing Shao[3], Xiaoyong Zhang[2], Vanessa Wu[1], Yudong Wang[1], Lei Lu[1], Jian Sun[2], Jinlin Hou[2], Guofeng Chen[3], George Lau[1,3]; [1]Division of Gastroenterology & Hepatology, Humanity & Health Medical Centre, Hong Kong, Hong Kong; [2]State Key Laboratory of Organ Failure Research, Guangdong Provincial Key Laboratory of Viral Hepatitis Research, Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, China; [3]Second Liver Cirrhosis Diagnosis and Treatment Center, 302 Hospital, Beijing, China; [4]Department of Medicine, Xixi Hosipital, Hangzhou, China; [5]Liver failure treatment and research centre, 302 Hospital, Beijing, China

Background and Aims: Hepatitis due to hepatitis B virus (HBV) reactivation has been reported in chronic hepatitis C (CHC) patients coinfected HBV, treated with either interferon-based therapy or pan-oral direct acting antivirals (DAAs). We compare the rate of hepatitis due to HBV reactivation and HCV sustained virologic response (SVR) in CHC patients co-infected with HBV, treated with interferon-based therapy versus DAAs. **Methods:** A systematic search of English literature from Jan 1st 1990 to Dec 31st 2015 in Pubmed, Embase, Ovid, and Cochrane databases was conducted in March 2016. Two independent reviewers systematically identified studies that examined the efficacy and safety of HCV antiviral therapies in HBV/HCV co-infected patients. A meta-analysis was conducted using a random effects model to assess the primary outcome (HBV reactivation rate and incidence of hepatitis due to HBV reactivation) and secondary outcomes (HCV SVR rate for 24 weeks in patients treated with interferon and for 12 weeks in patients treated with DAAs). Case reports were included in the systematic review but excluded in the meta-analysis. Meta-analysis was done by Stata 13. **Results:** The search yielded 35 studies involving 1121 CHC patients. Majority of the studies (n=30) were using interferon. All studies reported SVR rates, 26 studies reported HBV reactivation, and 22 studies reported occurrence of hepatitis due to HBV reactivation. Excluding results from case reports, the overall SVR rate was 47% in HBV/HCV co-infected patients, and the SVR rate was lower in patients treated with interferon (43%) than those treated with DAAs (100%, p<0.001). The overall HBV reactivation rate was 12.3% and no difference in HBV reactivation was observed in patients treated with interferon (12.4%) and those treated with DAAs (12.2%, p=0.90). Overall incidence of hepatitis due to HBV reactivation was 0.3% (0-1.1% in patients treated with interferon vs. 0.2-33.2% in those treated with DAAs, p=0.02). Most cases of HBV reactivation occurred during the follow-up of interferon treatment (3 weeks to 72 months post-treatment) while all cases were observed during DAAs treatment (4 to 11 weeks during treatment). **Conclusions:** In CHC patients co-infected with HBV, HCV SVR rate was higher in those treated with DAAs than those treated with interferon. Though there was no difference in HBV reactivation rates between DAAs and interferon based therapies, incidence of hepatitis due to HBV reactivation was higher in DAA treatment and HBV reactivation occurred much earlier in patients treated with DAAs than those treated with interferon.

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Improvement of carotid intima-media thickness and ankle-brachial index in patients with hepatitis C virus after IFN-free treatment.

Rocío Muñoz[1], Javier Ampuero[1], Raquel Millán[1], Maria del Carmen Rico[1], Mercedes Romera[3], Carlota Jimeno[2], Antonio Gil-Gómez[1], Manuel Romero-Gomez[1]; [1]Translational research in liver and digestive diseases, Institute of Biomedicine of Seville- University Hospital Virgen del Rocio., Seville, Spain; [2]Digestive disease, University Hospital Virgen del Valme, Seville, Spain; [3]Neurology, University Hospital Virgen del Valme, Seville, Spain

Background: Associations have been found between HCV infection and systemic atherosclerosis, endothelial dysfunction and hypertension. The carotid intima-media thickness (CIMT) is currently one of the most widely used noninvasive measures of atherosclerosis. The ankle brachial index (ABI) is a sensitive tool for peripheral artery disease and can also be used to assess systemic atherosclerosis. Aim: To analyze the impact of IFN-free treatment on the cardiovascular risk in HCV mono-infected patients. Methods: We recruited prospectively 82 consecutive patients eligible for direct-acting antivirals. We measured the cardiovascular risk according to: a) carotid intima-media thickness (CIMT), >0.9mm was considered pathological; b) ankle-brachial index (ABI), <0.9 was considered pathological. We classified patients in two groups accordingly: a) non-improvement/worsening CV risk group, showing pathological CIMT or ABI after the treatment; b) improvement/non-worsening CV risk group, showing normal CIMT or ABI after the treatment. In addition, we obtained biochemical parameters at baseline and at 12 weeks after finishing the treatment. Results: We obtained 30 patients with paired CV risk assessment, before and after the treatment. At baseline, 45.5% (10/22) of patients showed pathological ABI, decreasing up to 27.3% (6/22) at week 12 (p=ns). We also found an improvement in CIMT; 12% (3/25) at baseline *vs.* 8% (2/25) at week 12 showed a pathological CIMT. Combining both tests, 60% (12/20) of patients showed pathological CIMT or ABI at baseline and this value decreased to 35% (7/20) at week 12 (p=ns). Patients who responded to the treatment, in terms of CV risk, had a worse baseline profile of soluble biomarkers (**Table**). Conclusion: These preliminary results (ongoing study) showed that patients with basal pro-atherogenic conditions had a greater

improvement in cardiovascular risk assessed by ankle-brachial index and carotid intima-media thickness.

Baseline Characteristics

	Non improvement/ Worsening	Improvement/ non worsening	p value
Abdominal circumference (cms)	93.33±9.36	102.9±49.47	0.023
TG (mg/dL)	68.62±27.86	114± 43.64	0.009
HOMA index	3.31±1.83	5.33± 2.88	0.076
LPa (mg/dL)	3.67±3.20	10.71± 12.67	0.357
BMI (kg/m2)	25.85±2.87	28.28± 3.67	0.108
Microalbuminuria (mcg/mL)	4.33±1.49	9.85±8.13	0.186
Endothelial microparticles (U/μL)	434.63±220.30	1111.11±1065.49	0.035

Data are shown as mean ± SD. variables were analyzed with Mann–Whitney U tests.

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Reduction of liver stiffness by direct-acting antivirals for chronic hepatitis C

Naoto Kawabe, Toshiki Kan, Tomoki Takamura, Sayuri Nomura, Senju Hashimoto, Michihito Murao, Takuji Nakano, Kazunori Nakaoka, Masashi Ohki, Ochi Yuka, Takamitsu Kurashita, Aiko Fukui, Toru Nishikawa, Keisuke Osakabe, Naohiro Ichino, Kentaro Yoshioka; Department of Liver, Biliary Tract and Pancreas Diseases, Fujita Health University School of Medicine, Toyoake, Japan

Background and Aim: Liver stiffness (LS) by transient elastography (TE) and velocity of shear wave (Vs) by acoustic radiation force impulse (ARFI) have been reported to correlate with fibrosis stages in various liver diseases. The aim of the present study was to evaluate the effect of direct-acting antivirals (DAAs) on LS and Vs in chronic hepatitis C (CHC). **Methods:** LS (kPa) and Vs (m/s) were measured in 582 patients with CHC. The changes of LS and Vs were assessed in 300 patients treated with DAAs. 125 patients were treated with daclatasvir (DCV) and asunaprevir (ASV), 115 with sofosbuvir (SOF) and ledipasvir (LDV) for HCV genotype 1, and 60 with SOF and ribavirin (RBV) for genotype 2. **Results:** DCV/ASV, SOF/LDV, SOF/RBV treatments achieved high rates of sustained virologic response (SVR) (89, 95, 97%, respectively). LS significantly decreased and Vs did not significantly decrease at end of treatment (EOT) (10.0, p=0.0005; 1.76, p=0.11), LS and Vs significantly decreased at 6 months after EOT (10.3, p<0.0001; 1.69, p<0.0001) and at 12 months after EOT (12.3, p=0.0034; 1.98, p=0.0062), compared with baseline (12.7, 1.86) in patients with DCV/ASV. LS decreased in tendency (10.2, p=0.081) but Vs did not significantly decrease (1.62) at EOT compared with baseline (12.0, 1.60) in patients with SOF/LDV. LS significantly decreased (10.0, p=0.0097) but Vs did not significantly decrease (1.75) at 6 months after EOT compared with baseline (11.1, 1.63) in patients with SOF/RBV. Fibrosis stages were deduced from Vs values according to cut-off values for fibrosis stages in patients with DCV/ASV. The cutoff values determined by ROC analysis were 1.28 for F2, 1.44 for F3, and 1.73 for F4 in 108 patients who underwent liver biopsy. Two points or greater reduction of deduced stage was observed in 19% of patients with DCV/ASV, whose pretreatment deduced stages were F3-F4. Higher platelets counts, lower total bilirubin levels, and lower gamma globulin levels were significantly associated with a 2-point or greater reduction of deduced fibrosis stage. LS and Vs at baseline did not predict SVR in each treatment. **Conclusions:** The reduction of LS was observed in patients with DAAs, and can be attributed to regression of liver fibrosis and inflammation. The reduction of Vs was slower than that of LS. This finding may be attributed to the stronger association of LS with inflammation compared with that of Vs. The significant reduction of deduced fibrosis stage was observed in those with milder fibrosis which was indicated by higher platelets counts, lower total bilirubin levels and gamma globulin levels. TE and ARFI were useful for evaluating the effect of DAAs in CHC.

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Four weeks of sofosbuvir, ledipasvir and ribavirin with or without interferon give high cure rates in drug users with hepatitis C - a randomized controlled trial (4WIDUC)

Anne L. Øvrehus[1], Inge Birkemose[2], Dorte Kinggaard Holm[3], Belinda K. Moessner[1], Henrik Krarup[4], Peer B. Christensen[1]; [1]Department of Infectious Diseases, Odense University Hospital, Odense, Denmark; [2]Odense Drug Treatment Center, Odense, Denmark; [3]Department of Clinical Immunology, Odense University Hospital, Odense, Denmark; [4]Department of Clinical Biochemistry, Aalborg University Hospital, Aalborg, Denmark

Background and aims People who inject drugs (PWID) are the driving force of chronic hepatitis C (CHC) in the western world, but treatment uptake has been low in. Direct acting antivirals (DAA's) cures more than 90% of patients. Outreach treatment programs at drug treatment centers (DTC's) are feasible but shorter treatment duration is desirable. Four week DAA trials have been disappointing so far. We hypothesise that maintaining ribavirin (RBV) in a 4 week DAA regimen and adding pegylated-interferon 2 alpha(PEG 2a) could give high cure rates in drug users. Method The study was conducted at one DTC. Thirty two patients were randomized 1:1 to either LDV/SOF+RBV or LDV/SOF/RBV+PEG 2a for 4 weeks. RBV was dosed weight based and PEG 2a at 180 ug weekly. Main inclusion criteria: Treatment naïve patient with CHC (all genotypes), in opium substitution therapy(OST) p, age< 50 years, weight<100 kg, viral load<2mill IU/ml and liver stiffness measure(LSM)< 8 kPa. Subjects were allowed any kind of concomitant drug or alcohol use but should be compliant to their OST program. Primary endpoint was sustained virological response at week 12 after end of treatment (SVR 12) in the intention to treat (ITT) population. Results Forty seven persons were screened, and 32 initiated treatment. At date of submission SVR 12 in the ITT population was 92 % (12/13) in the interferon arm and 77% (10/13) in the interferon free arm. One virological relaps was detected. The remaining three failures were due to lost to follow-up or premature withdrawel from therapy. The PP SVR12 is so far 100% in the interferon arm and 91% in the interferon free arm.Full SVR 12 data will be presented at the meeting. Conclusion 4 weeks of sofosbuvir, ledipasvir and ribavirin with or without interferon was highly effective in curing CHC in this hard to reach but easy to treat population of non-cirrhotic drug users on OST with only one virological relapse detected in a PP patient. Delivering treatment at a DTC concurrently with OST was feasible and the SVR rates suggest this short regiment to be evaluated in larger trials.

Results

Variables	4 weeks LDV/SOF/RBV +PEG 2a n= 16	4 weeks LDV/SOF/RBV n= 16
Age, median (range)	39 (27-48)	38 (22-46)
Sex (male/female)	14/2	11/5
Genotype 1a+b/2/3	4/0/12	9/1/6
Weight in kilograms, median (IQR)	76 (66,5-82,5)	75 (68-86)
IL28b subtype CC/nonCC	3/13	6/9 – 1 pending
Viral load ($x10^3$IU/ml) at screening, mean(range)	352 (16,5-1140)	241 (7,44-1730)
Fibroscan in kPa, median(range)	5,1 (3,5-7,9)	5,3 (3,6-7,9)
Alcohol overuse past year yes/no	7/9	3/13
Years since start injecting, median (IQR)	18 (12-23)	14 (6-20)
Active injecting yes/no	6/10	6/10
Results		
ITT SVR 12/Patients at time point	12/13	10/13
ITT SVR 4/Patients at time point	15/16	13/16
Per Protocol SVR 12	12/12	10/11

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Ledipasvir/Sofosbuvir Fixed-Dose Combination (LDV/SOF FDC) for 8 Weeks for Treatment-Naïve, Non-cirrhotic Hepatitis C Genotype 6 (HCV-6) and for 12 Weeks for Those With Cirrhosis and/or Prior Treatment Failure: An Open-Labeled Clinical Trial

Mindie H. Nguyen[1], Huy N. Trinh[2], Son T. Do[3], Thuan Nguyen[4]; [1]Division of Gastroenterology and Hepatology, Stanford University Medical Center, Palo Alto, CA; [2]San Jose Gastroenterology, San Jose, CA; [3]Digestive Health Associates of Texas, Plano, TX; [4]Liver and Digestive Consultants, Houston, TX

Background: HCV affects approximately 30 million persons in Southeast Asia where HCV-6 is one of the most prevalent genotypes. Treatment data is limited for HCV-6, especially with new direct acting antiviral (DAA) agents. LDV/SOF FDC for 12 weeks has been shown to be effective for multiple HCV genotypes including treatment-naïve HCV-6. Our goal is to examine treatment outcomes in a diverse HCV-6 population. **Methods:** We prospectively enrolled 60 HCV-6 patients at four medical centers in California and Texas, USA. All patients received LDV 90mg/SOF 400 mg in a single tablet regimen orally once a day for 8 weeks if they were treatment-naïve and did not have cirrhosis or for 12 weeks if they had cirrhosis (treatment-naïve and experienced) or treatment-experienced (cirrhosis and non-cirrhosis). Patients with prior solid organ transplantation were excluded. Primary outcome was sustained virological response 12 weeks after therapy (SVR12). Secondary outcomes were adverse events (AE). All patients gave written consent. **Results:** Overall mean age was 58±10 and 58% were male. All patients were Asian and foreign-born. The 8-week group included 20 patients (33.3%) and the 12-week included 40 patients (66.7%). There were no statistically significant differences in baseline clinical and laboratory characteristics other than cirrhosis status and prior treatment history between the two groups. Baseline HCV RNA level was 6.43±0.73 log IU/mL and the distribution of HCV-6 subtypes were 23% HCV-6a/b, 37% HCV-6c, and 4% HCV-6m. Baseline platelet count was 191±67 overall, 208±53 for 8-week group and 182±73 for the 12-week group (p=0.16). There were two patients with decompensation (5.0%), 3 patients with liver cancer (7.5%), and 14 with prior treatment (35.0%) in the 12-week group. Currently, SVR12 were available for 59 patients (of 60). SVR12 was 95.0% for the 8-week group (19/20) and 94.9% for the 12-week group (37/39). All patients completed the intended treatment duration. There were two treatment-unrelated SAEs (*H. pylori*-related bleeding gastric ulcer and leg fracture due to mechanical fall), and both patients achieved SVR12. AEs included fatigue (5%), insomnia (3%), headache (1.7%), and nausea (1.7%). **Conclusion:** In this largest clinical trial of HCV-6 to date with LDV/SOF FDC orally once daily or with DAAs in general, LDV/SOF FDC for 8 weeks was safe and effective for patients without cirrhosis or prior treatment failure (SVR12=95.0%), and LDV/SOF FDC for 12 weeks was also safe and effective for patients with cirrhosis and/or prior treatment failure, including patients with hepatic decompensation and liver cancer (SVR 12=94.9%).

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Son T. Do - Advisory Committees or Review Panels: gilead, Asian Health Foundation; Speaking and Teaching: gilead, Asian Health Foundation

Thuan Nguyen - Speaking and Teaching: Gilead, Abbvie

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Project INSPIRE: a Comprehensive Care Coordination Program for HCV-Infected Patients

Marie P. Bresnahan, Mary Ford, Payal Desai, Nicolette G. Gantt, Fabienne Laraque; Viral Hepatitis Program, New York City Department of Health and Mental Hygiene, Queens, NY

Background New York City (NYC) Health Department has an established Care Coordination Protocol and Heath Promotion Manual for HIV-infected persons. Infection with the Hepatitis C Virus (HCV) is a complex disease often occurring in patients with substance abuse, HIV, and mental illness, making treatment in a supported setting critical. Project INSPIRE, a Round II Healthcare Innovation Award from the Centers for Medicaid and Medicare Services, was designed by the Health Department to implement and test a comprehensive care coordination protocol and health promotion curriculum adapted from HIV and tailored for HCV. **Primary Aim** To demonstrate a model of service delivery and payment that can reduce morbidity and death from chronic illnesses and reduce costs associated with its complications, using chronic HCV infection as a case study. **Methods** Established care coordination protocols and health promotion materials used for HIV/AIDS were adapted for use with patients with HCV infection with the overall goal of improving HCV cure rates and patient self-sufficiency. The protocol includes: comprehensive assessment, care plan, health promotion, treatment readiness counseling, alcohol and drug counseling and medication adherance support. Health promotion sessions are designed to provide information on HCV infection, treatment for HCV, liver health, alcohol and drug use, and how to avoid re-infection. A robust monitoring and evaluation framework is being used to evaluate the program including monthly data feedback reports, fidelity analysis, clinical outcomes analysis, comparison with a control group, and cost analysis. **Results** INSPIRE was implemented at 12 outpatient clinics, serving high need patients, with a high level of fidelity to the protocol. Among the 1,805 participants enrolled by April 30, 2016, most reached key milestones within 30 days of enrollment including completing a comprehensive assessment (83%), attending their first clinical appointment for HCV care (90%), and receiving a medical evaluation (79%). Over 95% of participants who initiated treatment have received alcohol counseling, health promotion, treatment readiness counseling, and medication coordination. Two-thirds (66%) of participants received their first health promotion session within 15 days of

enrollment.The project was implemented at two major medical centers, and starting many on treatment with the expectation that the vast majority will be cured. Over the next year, a plan to disseminate the care coordination protocol and health promotion materials will be developed and the costs of care coordination will be calculated and integrated into a payment model.

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Sofosbuvir/Ledipasvir plus Ribavirin achieves high SVR12 in genotype-3 patients with compensated cirrhosis and similar to Sofosbuvir plus Daclatasvir. A multicentre real life cohort

Mar Riveiro-Barciela[1,2], Sonia Alonso[3], Inmaculada Fernandez[19], Diego Rincón[20], Yolanda Real[4], Javier Crespo[5], Francisco Gea[6], Antonio Olveira[7], Jose L. Calleja[8], Benjamin Polo Lorduy[9], Jose Antonio Carrion[10], Juan Arenas[11], Maria Jose Devesa[12], Carme Baliellas[13], Angeles Castro[14], Manuel Romero-Gomez[15], Rafael Granados[16], Juan Manuel Pascasio[17], Martin Prieto[18], Javier Salmeron[21], Ester Badia[22], Jose M. Moreno[23], Xavier Forns[24], Juan Turnes[25], Jose Luis Montero[26], Rafael Esteban[1,2], Conrado M. Fernández-Rodríguez[3]; [1]Liver Unit, Internal Medicine Department, Vall d'Hebron hospital, Barcelona, Spain; [2]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain; [3]Gastroenterology, Hospital Universitario Fundación Alcorcón, Madrid, Spain; [4]Hospital Universitario La Princesa, Madrid, Spain; [5]Gastroenterology, Hospital Marqués de Valdecilla, Santander, Spain; [6]Hospital Universitario Ramón y Cajal, Madrid, Spain; [7]Hospital Universitario La Paz, Madrid, Spain; [8]Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain; [9]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [10]Hospital del Mar, Barcelona, Spain; [11]Hospital Universitario Donostia, Donostia, Spain; [12]Hospital Universitario Clínico San Carlos, Madrid, Spain; [13]Hospital Universitari de Bellvitge, Barcelona, Spain; [14]Hospital Universitario de A Coruña, A Coruña, Spain; [15]Hospital Virgen de Valme, Sevilla, Spain; [16]H. U. de Gran Canaria Dr. Negrín, Gran Canaria, Spain; [17]H. U. Virgen del Rocío, Sevilla, Spain; [18]HU La Fe, Valencia, Spain; [19]Hospital Universitario 12 de Octubre, Madrid, Spain; [20]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [21]H. U. San Cecilio, Granada, Spain; [22]Hospital Universitario de Burgos, Burgos, Spain; [23]C. H. U. de Albacete, Albacete, Spain; [24]Hospital Clínic, Barcelona, Spain; [25]Complejo Hospitalario de Pontevedra, Pontevedra, Spain; [26]H. Reina Sofia, Córdoba, Spain

Background and aims: Current antiviral therapy for HCV genotype (GT) 3-associated cirrhosis achieves suboptimal sustained virological response (SVR) rates. Daclatasvir (DCV) + Sofosbuvir (SOF) ± ribavirin (RBV) is the only all-oral recommended option due to lower SVR rates of SOF/LDV in patients with cirrhosis. We aimed to evaluate the efficacy and safety of 12 and 24-week SOF+DCV or SOF/LDV ± RBV in a real-life cohort of GT3 patients with cirrhosis. **Patients and methods**: Multicenter observational study from two different databases: HepaC-AEEH and Community of Madrid Regional registry. All HCV-cirrhotic patients mono-infected by GT3 and treated with SOF plus a NS5A inhibitor (DCV or LDV) ± RBV between May 2014 and October 2015 were included. **Results**: 282 patients were included: 83% male, age 54 years (26-82), 124 (44%) treatment-experienced, 48 (17%) decompensated, 130 (46%) FibroScan >20 kPa and 65 (23%) MELD score>10. 195 (69%) received SOF+DCV and 87 (31%) SOF/LDV. Overall, 88% received RBV. The addition of RBV and extension to 24 weeks were higher in the SOF/LDV group (95% vs. 84%, p=0.004; 83% vs. 62%, p<0.001). A higher percentage of decompensated patients were treated with DCV (21% vs. 10%, p=0.029). 208 patients have reached week 12 of follow-up. Overall SVR12 was 93.8% (195/208), 94% with SOF+DCV and 93.5% with SOF/LDV. SVR12 rates are summarized in table. 13 failures were observed (9 relapses, 1 virological failure, 3 deaths). Previous treatment did not impact on SVR. Platelet <75,000/mL was the only factor associated with nonSVR12 (RR: 3.50; 95%CI 1,23-9,94; p=0.019). In patients with MELD <10 or albumin >3.5 mg/dL, type of NS5A inhibitor did not impact on SVR12 (93% vs 97%, RR 0.96, 95%CI 0.89-1.04; 93% vs 96%, RR 0.97, 95%CI 0.90-1.05, respectively). Only 16 patients (5.7%) presented serious adverse events (SAE), including 3 deaths (1.1%) and 6 discontinuations (3.2%). Percentage of SAEs and deaths was higher in decompensated patients (18% vs. 3.1%, p<0.001, 4% vs. 0.4%, p=0.08). SVR12 of all cohort will be presented at the meeting. **Conclusions**: SOF/LDV+RBV achieved high SVR12 rates in GT3 patients with compensated cirrhosis, similar to SOF+DCV, both with low rates of serious adverse events.

		SVR n (%)	95 CI
SOF+DCV+RBV	Child A	82/87 (94,2%)	0,87-0,98
SOF+DCV+RBV	Child B/C	17/18 (94,4%)	0,72-0,99
SOF+DCV	Child A	10/11 (91,0%)	0,58-0,99
SOF+DCV	Child B/C	14/15 (93,3%)	0,68-0,99
SOF/LDV+RBV	Child A	61/64 (95,3%)	0,86-0,99
SOF/LDV+RBV	Child B/C	7/9 (77,7%)	0,39-0,97
SOF/LDV	Child A	4/4 (100%)	0,39-1
SOF/LDV	Child B/C	0/0	NA

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Sonia Alonso - Consulting: Abbvie, Gilead; Speaking and Teaching: Abbvie, Bayer, MSD

Javier Crespo - Advisory Committees or Review Panels: Abbvie, Janssen, BMS; Grant/Research Support: MSD, Gilead

Antonio Olveira - Consulting: MSD; Speaking and Teaching: Abbvie, Gilead, MSD

Jose L. Calleja - Advisory Committees or Review Panels: Gilead, Abbvie ; Speaking and Teaching: Abbvie, Gilead, Janssen, BMS

Juan Arenas - Advisory Committees or Review Panels: Abbvie; Speaking and Teaching: MSD, BMS, Gilead

Rafael Granados - Advisory Committees or Review Panels: Abbvie; Consulting: Janssen; Speaking and Teaching: Abbive, Janssen, Gilead

Martin Prieto - Advisory Committees or Review Panels: Gilead, Abbvie, Bristol

Xavier Forns - Consulting: gilead, abbvie, jansen

Juan Turnes - Advisory Committees or Review Panels: Gilead, Abbvie, Janssen, BMS; Speaking and Teaching: MSD, Gilead, Janssen, BMS, Abbvie

Rafael Esteban - Speaking and Teaching: MSD, BMS, Novartis, Gilead, Glaxo, MSD, BMS, Novartis, Gilead, Glaxo, Janssen

The following people have nothing to disclose: Mar Riveiro-Barciela, Inmaculada Fernandez, Diego Rincón, Yolanda Real, Francisco Gea, Benjamin Polo Lorduy, Jose Antonio Carrion, Maria Jose Devesa, Carme Baliellas, Angeles Castro, Manuel Romero-Gomez, Juan Manuel Pascasio, Javier Salmeron, Ester Badia, Jose M. Moreno, Jose Luis Montero, Conrado M. Fernández-Rodríguez

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Sofosbuvir and NS5A inhibitors without Ribavirin during 12 weeks are efficient to treat hepatitis C recurrence after liver transplantation only in genotype 1. Results from the CO23 ANRS CUPILT study.

Pauline Houssel-Debry[1], Audrey Coilly[2], Claire Fougerou-Leurent[26], Caroline Jezequel[1], Christophe Duvoux[3], Victor de Ledinghen[4], Sylvie Radenne[5], Nassim Kamar[6], Vincent Leroy[7], Vincent Di Martino[8], Louis d'Alteroche[9], Valerie Canva-Delcambre[10], Filomena Conti[11], Jérôme Dumortier[12], Helene Montialoux[13], Pascal Lebray[14], Danielle Botta-Fridlund[15], Rodolphe Anty[16], Christophe Moreno[17], Christine Silvain[18], Camille Besch[19], Philippe Perré[20], Claire Francoz[21], Armand Abergel[22], François Habersetzer[23], Maryline Debette-Gratien[24], Alexandra Rohel[25], Alpha Diallo[25], Emilie Rossignol[26], Hélène Danjou[26], Aurelie Veislinger[26], Jean-Charles Duclos-Vallee[2], Georges-Philippe Pageaux[27]; [1]Liver diseases Unit, University Hospital Pontchaillou, Rennes, France; [2]Centre Hépato-Biliaire, University Hospital Paul-Brousse, Villejuif, France; [3]Hepatogastroenterology Unit, University Hospital Henri-Mondor, Creteil, France; [4]Hepatogastroenterology Unit, University Hospital Haut-Lévêque, Bordeaux, France; [5]Hepatogastroenterology Unit, University Hospital Croix-Rousse, Lyon, France; [6]Nephrology, Hypertension and Dialysis Unit, University Hospital Rangueil, Toulouse, France; [7]Hepatogastroenterology Unit, University Hospital Michallon, Grenoble, France; [8]Hepatology Unit, University Hospital Minjoz, Besançon, France; [9]Hepatogastroenterology Unit, University Hospital Trousseau, Tours, France; [10]Digestive tract Diseases Unit, University Hospital Huriez, Lille, France; [11]Hepatobiliary surgery and liver transplantation Unit, University Hospital Pitié-Salpêtrière, Paris, France; [12]Digestive tract diseases Department, University Hospital Edouard Herriot, Lyon, France; [13]Hepatogastroenterology Unit, University Hospital Charles Nicolle, Rouen, France; [14]Hepatogastroenterology Unit, University Hospital Pitié-Salpêtrière, Paris, France; [15]Hepatogastroenterology Unit, University Hospital La Timone, Marseille, France; [16]Hepatogastroenterology Unit, University Hospital Archet, Nice, France; [17]Hepatogastroenterology University Hospital Erasme, Université Libre de Bruxelles, Bruxelles, Belgium; [18]Hepatogastroenterology Unit, University Hospital Milétrie, Poitiers, France; [19]Transplantation, hepatic and endocrine surgery Unit, University Hospital Hautepierre, Strasbourg, France; [20]: Internal Medicine unit, Vendée Departmental Hospital, La Roche sur Yon, France; [21]Hepatology unit, University Hospital Beaujon, Clichy, France; [22]Digestive Department, University Hospital Estaing, Clermont-Ferrand, France; [23]Hepatogastroenterology Unit, University Hospital Nouvel hôpital civil, Strasbourg, France; [24]Hepatogastroenterology Unit et Nutrition, University Hospital Dupuytren, Limoges, France; [25]ANRS (France REcherche Nord&Sud Sida-hiv Hépatites), Paris, France; [26]Pharmacology Unit, University hospital Pontchaillou, Rennes, France; et INSERM, CIC 1414 Clinical Investigation Centre, Rennes, France; [27]Hepatogastroenterology and Liver transplantation Department, University Hospital Saint Eloi, Montpellier, France

(a) Sofosbuvir (SOF) with NS5A inhibitors has shown efficacy to treat hepatitis C (HCV) recurrence after liver transplantation (LT). But the duration of treatment and the utility of ribavirin (RBV) are not clear in this population. We aimed to assess which patients can be treated with SOF + NS5A inhibitors-based regimens without RBV during 12 weeks after LT. (b) From October 2013 to October 2015, 699 liver transplant recipients with HCV recurrence have been enrolled in the prospective multicentric ANRS CO23 CUPILT cohort. In the present study, we selected patients receiving SOF and NS5A inhibitor +/- RBV and followed at least 12 weeks after treatment discontinuation. The primary efficacy end point was a sustained virological response 12 weeks after the end of treatment (SVR12). We identified four groups of patients according to treatment' regimens and duration: SOF+NS5A±RBV during 12 or 24 weeks. Logistic regression with adjustment was used. (c) Among the 699 patients, 386 fulfilled the inclusion criteria. The main characteristics were as follows: 75.1% genotype 1 and 15% genotype 3 (G3), 62.2% treatment-naïve, and when treated, 43.8% were non-responders. Fibrosis stage was F3/F4 in 155 patients (40.2%). In the cirrhosis group (23.1%), 56 patients were Child Pugh (CPT) A (73.7%), 18 CPT B (23.7%) and 2 patients CPT C (2.6%). One hundred and fourty-three patients were treated during 12 weeks (105 (27.2%) without RBV; 38 (9.8%) with RBV) and 243 patients were treated during 24 weeks (176 (45.6%) without RBV; 67 (17.4%) with RBV).The mean RBV dose was 760 ± 254 mg/d. The rate of F3-F4 fibrosis stage (47.7%, p=0.0006), previously treated (45.3%, p=0.0008) and non-responders patients (19.3%, p=0.0442) was higher in 24 weeks treatment groups. The SVR12 was 97.1%, 100%, 98.9%, 95.5% in the 12 weeks without RBV group, the 12 weeks with RBV group, the 24 weeks without RBV group and the 24 weeks with RBV group, respectively (p=0.27). Only 8 patients had treatment failure. By multivariate analysis, the factors such fibrosis stage, previous treatment, HCV genotype, HCV viral load at baseline did not influence the rate of SVR12 among the four study groups (p=0.38). However the risk of failure was higher in G3 group (OR= 4.92, (1.19 – 20.20) and others genotype (2, 4, 5) group (5.31, (1.22 – 23.10)) (p= 0.03). The rate of haematological adverse events was higher in the RBV group: anemia 57% (p<0.0001), blood transfusion 56% (p0.02). (d) SOF+NS5A inhibitors without RBV regimen during 12 weeks was efficient to treat HCV recurrence after liver transplantation including F3-F4 and previously treated patients. In G3 patients, 24 weeks of treatement is suggested.

Disclosures:

Pauline Houssel-Debry - Speaking and Teaching: NOVARTIS, ASTELLAS, GILEAD

Caroline Jezequel - Speaking and Teaching: Gilead, MSD

Christophe Duvoux - Advisory Committees or Review Panels: Novartis, Roche, Novartis, Roche, Novartis, Roche, Chiesi; Speaking and Teaching: Astellas, Astellas, Astellas, Astellas

Victor de Ledinghen - Board Membership: Janssen, Gilead, BMS, Abbvie, Intercept Pharma, Supersonic Imagine; Grant/Research Support: Supersonic Imagine; Speaking and Teaching: AbbVie, Merck, BMS, Gilead

Vincent Leroy - Board Membership: Abbvie, BMS, Gilead; Consulting: Janssen, MSD; Speaking and Teaching: Abbvie, BMS, Gilead, Janssen, MSD

Vincent Di Martino - Advisory Committees or Review Panels: Gilead, France, Abbvie, BMS France; Board Membership: MSD France; Consulting: Gilead, France; Speaking and Teaching: Janssen, BMS France, Gilead France

Jérôme Dumortier - Board Membership: Novartis, Astellas, Roche, Gilead; Consulting: Novartis; Grant/Research Support: Novartis, Astellas, Roche, MSD, GSK, Gilead

Helene Montialoux - Consulting: GILEAD

Pascal Lebray - Grant/Research Support: Schering-Plough, Schering-Plough, Schering-Plough, Schering-Plough; Speaking and Teaching: Gilead, Gilead, Gilead, Gilead

Danielle Botta-Fridlund - Consulting: GILEAD, ABBVIE, BMS, MSD

Christophe Moreno - Consulting: Abbvie, Janssen, Gilead, BMS, MSD; Grant/Research Support: Janssen, Gilead, Roche, Astellas, Abbvie

François Habersetzer - Board Membership: Gilead, BMS; Speaking and Teaching: Gilead, BMS

Jean-Charles Duclos-Vallee - Consulting: Astellas, BMS, Gilead, Janssen, Abbvie, Novartis, Roche

Georges-Philippe Pageaux - Board Membership: Astellas, BMS; Speaking and Teaching: Gilead, BMS, Novartis, MSD

The following people have nothing to disclose: Audrey Coilly, Claire Fougerou-Leurent, Sylvie Radenne, Nassim Kamar, Louis d'Alteroche, Valerie Canva-Delcambre, Filomena Conti, Rodolphe Anty, Christine Silvain, Camille Besch, Philippe Perré, Claire Francoz, Armand Abergel, Maryline Debette-Gratien, Alexandra Rohel, Alpha Diallo, Emilie Rossignol, Hélène Danjou, Aurelie Veislinger

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Direct-Acting Antiviral Therapy Outcomes in Canadian Chronic Hepatitis C Telemedicine Patients

Holly Hatashita, Parmvir Parmar, Daniel J Corsi, Curtis Cooper; Medicine, University of Ottawa, Ottawa, ON, Canada

Background: There are approximately 245,000 HCV-infected Canadians, many of whom live in under-served and remote areas without access to HCV healthcare specialists. Telemedicine (TM) can provide healthcare to these marginalized patients. We compared patient characteristics and direct-acting antiviral (DAA) treatment outcomes in HCV TM and non-TM patients (The Ottawa Hospital Viral Hepatitis Outpatient Clinic) residing in Eastern Ontario. **Methods:** A cohort database analysis was performed on 1258 patients followed at The Ottawa Hospital and Regional Viral Hepatitis Program between January 2012 and May 2016. TM (n=148) and non-TM (n=1110) patients were compared by examining baseline characteristics and clinical outcomes. **Results:** TM patients were younger (49.8 vs 52.4 years), more likely to be Indigenous (7.4% vs 2.5%), to have injection drug (69% vs 55%) and incarceration (46% vs 35%) histories, and more likely to be genotype 3 infected (27% vs 17%). Groups were comparable in gender (65% male) and cirrhotic stage (23%). 62% of TM patients underwent transient elastography assessment during regional outreach Fibroscan blitzes compared to 60% of our non-TM patients. 24 TM and 214 non-TM HCV-infected patients have completed DAA therapy. Ledipasvir-sofosbuvir+/-ribavirin was the most frequently prescribed DAA regimen (79% of TM and 57% of non-TM patients, p=0.15). The SVR rate in the TM group was 95% and 91% in the non-TM group (p=0.59). **Conclusion**: Our TM program successfully engages and retains a remote population enriched for characteristics associated with barriers to successful HCV treatment. TM patients were able to engage in HCV care, achieving high SVR rates comparable to those obtained by traditional models of care.

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The following people have nothing to disclose: Holly Hatashita, Parmvir Parmar, Daniel J Corsi

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Hepatitis C Virus Treatment Response to Ledipasvir/Sofosbuvir among patients co-infected with HIV and HCV: Real World Data in a Black Population

Jaspreet Banga[1], Sobia Nizami[1], Mario Portilla[1], Sandhya Nagarakanti[3], Jihad Slim[2], Shobha Swaminathan[1]; [1]Rutgers New Jersey Medical School, Newark, NJ; [2]Saint Michaels Medical Center, Newark, NJ; [3]Beth Israel Medical Center, Newark, NJ

Background: Treatment of Hepatitis C virus (HCV) infection with pegylated interferon and ribavirin had poor responses for patients with Human Immunodeficiency virus (HIV). This improved significantly with direct acting antivirals (DAAs) and are comparable to HCV mono-infected patients. However, it has been suggested that treatment outcomes among black persons treated with ledipasvir/sofosbuvir (LDV/SOF) may be inferior. We assessed treatment responses to LDV/SOF in a cohort of black HIV/HCV co-infected persons in Newark, New Jersey. **Methodology**: Retrospective chart reviews were conducted for black, genotype 1, HIV/HCV co-infected patients treated with LDV/SOF in the University Hospital Infectious Diseases Practice between January 2014 and February 2016. Data collected included demographics, HCV treatment history, duration of LDV/SOF regimen, and treatment response. **Results**: A total of 52 HIV/HCV co-infected black patients received treatment with LDV/SOF during the study period. Preliminary data are being presented on 46 patients. The study population was 63% male, mean age 58 years, and 37% had cirrhosis. 46% were null responders to prior HCV treatment (pegylated interferon, ribavirin, boceprevir/telaprevir) and 83% of patients had genotype 1a (GT1a). At baseline, median CD4 count was 679 cells/mm^3, median HCV viral load was 2974728 IU/mL, median Fibrosure score was 0.66, and median creatinine clearance was 78% of patients changed ART prior to beginning LDV/SOF treatment due to drug interactions. 37 and 9 patients received 12 and 24 weeks of LDV/SOF respectively, 67% on 24 week treatment had cirrhosis. Two patients were prematurely discontinued from treatment due to logistical issues. Mean FIB-4 and APRI scores at baseline were 2.99 and 0.89, respectively. Few patients (<1%) experienced side effects with no resulting discontinuations. Overall, 94% had SVR with 3 relapses (all cirrhotic). SVR rates were 92% for genotype 1a, 95% for prior null responders and 82 % among cirrhotics. **Conclusion**: In this real world cohort of black, genotype 1, HIV/HCV co-infected patients, LDV/SOF had high SVR12 rate of 94% and was extremely well tolerated. This data supports the high efficacy of LDV/SOF in a highly difficult-to-treat patient population. Additional studies should be performed to assess if ribavirin should be added to LDV/SOF in co-infected patients with cirrhosis.

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Jihad Slim - Speaking and Teaching: BMS, Merck, Abbvie, Jansen, ViiV, Gilead

Shobha Swaminathan - Advisory Committees or Review Panels: Gilead Sciences; Grant/Research Support: Gilead Sciences

The following people have nothing to disclose: Jaspreet Banga, Sobia Nizami, Mario Portilla, Sandhya Nagarakanti

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Burden of disease in patients with chronic hepatitis C in the Austrian REAL Study

Michael Gschwantler[1], Peter Ferenci[2], Bernhard J. Bauer[3], Hermann Laferl[4], Thomas Bamberger[5], Rudolf E. Stauber[6], Ivo Graziadei[7], Jan Hettinger[8], Astrid Teskey[8], Andreas Maieron[9]; [1]Department of Medicine IV, Wilhelminen Hospital, Vienna, Austria; [2]Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; [3]Department of Internal Medicine, LKH Hörgas-Enzenbach, Hörgas, Austria; [4]Department of Medicine IV, Infectious Diseases, Kaiser-Franz-Josef Hospital, Vienna, Austria; [5]Department of Internal Medicine II, Kepler University Hospital, Linz, Austria; [6]Department of Internal Medicine, Medical University of Graz, Graz, Austria; [7]Department of Internal Medicine, Academic Teaching Hospital, Hall, Austria; [8]AbbVie GmbH, Wien, Austria; [9]Department of Internal Medicine 4, Gastroenterology & Hepatology, Elisabethinen Hospital, Linz, Austria

Background: The direct-acting antiviral regimen of ombitasvir (OBV), paritaprevir (identified by AbbVie and Enanta, co-dosed with ritonavir [PTV/r]) ± dasabuvir (DSV) ± ribavirin (RBV) was approved in 2015 in Europe for treatment of patients with chronic hepatitis C genotype 1 (GT1) or 4 (GT4) infection. To this date, real-world data as well as data on patient-reported outcomes (PROs) on this regimen are limited. **Goals:** In this study, we investigated PROs in real-world for the treatment regimen of OBV/PTV/r ± DSV ± RBV. **Methods:** GT1 and GT4-infected patients, participating in the multi-center, non-interventional cohort study REAL (NCT02582658) in Austria, were included in this analysis. Patients received the regimen of OBV/PTV/r ± DSV ± RBV according to the local label. Effectiveness was assessed by SVR12. Health-related quality of life (HRQoL), health/disease awareness and work

productivity were assessed by standardized questionnaires (EQ-5D-5L; WPAI Hep C V2.0; PAM-13). **Results:** As of March 31 2016, a total of 151 patients received the regimen of OBV/PTV/r ± DSV ± RBV. Baseline characteristics are shown in the table. Assessment of HRQoL by EQ-5D-5L showed no major differences in index scores in the total population at baseline (BL; mean: 0.827; SD: 0.177; n = 117) and end of treatment (EOT; mean: 0.885; SD: 0.121; n = 48). For patients with available data at both time points (n = 42), mean change in index score was 0.006 (SD: 0.135), indicating that there was no reduction of HRQoL due to treatment. Analysis of total activity impairment scores by WPAI revealed no significant differences between BL (mean 24.4; SD: 26.7; n = 115) and EOT (mean 24.5; SD: 28.6; n = 44) as well, suggesting that treatment did not adversely affect total activity of patients. Upcoming results (including SVR12 data) will be presented at the meeting. **Conclusions:** In this study, the treatment with OBV/PTV/r ± DSV ± RBV did not adversely impact HRQoL and total activity of patients in a real-world setting in Austria, confirming previous results on the tolerability of this regimen.

Baseline Characteristics

Baseline Characteristics	OBV/PTV/r ± DSV ± RBV (N = 151)
Male, n (%)	106 (70%)
Age > 65 Years, n (%)	22 (15%)
HCV Genotype	
GT1a	62 (41%)
GT1b	80 (53%)
Other GT1	2 (1.3%)
GT4	7 (4.6%)
Liver Cirrhosis, n (%)	21 (14%)
Prior HCV-Treatment, n (%)	58 (39%) (n =149)
HCV Treatment	
OBV/PTV/r + RBV (12 Weeks)	6 (4%)
OBV/PTV/r + DSV (12 Weeks)	97 (64%)
OBV/PTV/r + DSV + RBV (12 Weeks)	48 (32%)
Suspected Transmission	
Drug Use (i. v.)	46 (30%)
Blood Transfusion or Transplantation	23 (15%)
Unknown	70 (46%)
Other or Data not available	12 (8%)

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Michael Gschwantler - Advisory Committees or Review Panels: Janssen, BMS, Gilead, AbbVie; Grant/Research Support: AbbVie, Gilead; Speaking and Teaching: Janssen, BMS, Gilead, AbbVie

Peter Ferenci - Advisory Committees or Review Panels: Idenix, Gilead, MSD, Janssen, Salix, AbbVie, BMS, Wilson Therapeutics; Patent Held/Filed: Madaus Rottapharm; Speaking and Teaching: Gilead, Roche

Bernhard J. Bauer - Advisory Committees or Review Panels: Abbvie, BMS; Speaking and Teaching: Abbvie, MSD, Gilead, BMS

Hermann Laferl - Advisory Committees or Review Panels: Janssen; Grant/Research Support: Gilead, AbbVie, Roche; Speaking and Teaching: Gilead

Thomas Bamberger - Advisory Committees or Review Panels: Abbvie, MSD, BMS; Grant/Research Support: Gilead; Speaking and Teaching: Abbvie, BMS, Gilead

Rudolf E. Stauber - Advisory Committees or Review Panels: Gilead, MSD, BMS; Grant/Research Support: AbbVie

Ivo Graziadei - Advisory Committees or Review Panels: Gilead, AbbVie, MSD, Janssen, BMS; Speaking and Teaching: Gilead, AbbVie, MSD, BMS

Jan Hettinger - Employment: AbbVie GmbH, Austria

Astrid Teskey - Employment: AbbVie GmbH

Andreas Maieron - Advisory Committees or Review Panels: MSD, Jannsen, BMS, Bv∂hringer Ingelheim, Gilead, Abbvie ; Grant/Research Support: Roche; Speaking and Teaching: Roche, MSD, Jannsen, Gilead, Abbvie

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Community-Based Real World Outcomes of Sofosbuvir/Ledipasvir Without Ribavirin in the Treatment of Asians with Chronic Hepatitis C Virus Genotype 6 in the United States

Robert J. Wong[1], My T. Nguyen[2], Huy N. Trinh[3], Andrew Huynh[2], Mytop Ly[2], Huy A. Nguyen[3], Khanh K. Nguyen[3], Jenny C. Yang[3], Ruel T. Garcia[3], Brian S. Levitt[3], Eduardo DaSilvera[3], Robert Gish[4]; [1]Gastroenterology and Hepatology, Alameda Health System - Highland Hospital, Oakland, CA; [2]Silicon Valley Research Institute, San Jose, CA; [3]San Jose Gastroenterology, San Jose, CA; [4]Gastroenterology and Hepatology, Stanford University Medical Center, Stanford, CA

Background: The highest prevalence of chronic hepatitis C virus (HCV) genotype 6 (GT6) is seen among Southeast Asian populations. While previous interferon-based therapies offered high cure rates, sofosbuvir/ledipasvir (SOF/LDV) is the first all-oral ribavirin-free treatment approved for HCV GT6, offering a safe and highly efficacious treatment option. However, large studies evaluating real world outcomes of this regimen are lacking for GT6. **Aim:** To evaluate real world treatment outcomes for GT6 in a large community-based gastroenterology practice in the United States. **Methods:** A retrospective cohort study evaluated 65 adults (age ≥18) with chronic HCV GT6 treated with SOF/LDV without ribavirin at a community gastroenterology clinic in the U.S. from November 2014 to May 2016. Rates of undetectable virus at week 4 on treatment, at end of treatment (EOT), and SVR12 were stratified by presence of cirrhosis and prior treatment (treatment naïve vs. treatment experienced). Multivariate logistic regression models evaluated for predictors of treatment failure or relapse. **Results:** Among 65 patients with chronic HCV GT6 treated with SOF/LDV without ribavirin, 52.3% were male and the mean age at start of treatment was 66.3 years (SD 9.7). 41.5% (n=27) had cirrhosis and 15.4% (n=10) were treatment experienced, having relapsed after prior treatment with pegylated interferon and ribavirin. Overall, 97.3% had undetectable virus at week 4 on treatment, 96.9% had undetectable virus at EOT, and 95.3% achieved SVR12 (Table). One patient had detectable virus at EOT and two patients had viral relapse at week 12 post-treatment despite achieving undetectable virus at EOT. Resistance testing of these treatment failure patients was attempted but unsuccessful due to lack of conforming primers to define the possible resistance mutations. SVR12 was achieved in 100% in females vs. 91.2% in males, p=0.096. SVR12 in cirrhotics was 92.3% vs. 97.4% in patients without cirrhosis, p=0.347. No significant predictors of treatment failure or relapse were identified on regression modeling. **Conclusions:** Among a large community-based real world cohort of Asian chronic HCV GT6 patients in the United States, all oral SOF/LDV without ribavirin is a safe and effective treatment. SVR12 in the real world setting was similar to SVR12 reported in clinical trials.

Treatment Outcomes Among Asian HCV Genotype 6 Patients Treated with Sofosbuvir/Ledipasvir

	Overall	Non-Cirrhotic	Cirrhotic	Treatment-Naive	Treatment-Experienced
Undetectable Virus at End of Treatment	96.9%	97.3%	96.3%	98.2%	90.0%
SVR12	95.3%	97.4%	92.3%	94.4%	100.0%

Disclosures:

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Huy N. Trinh - Grant/Research Support: Gilead, Intercept, Abbvie, merk; Speaking and Teaching: Gilead; Stock Shareholder: Gilead

Huy A. Nguyen - Advisory Committees or Review Panels: Gilead, BMS; Speaking and Teaching: Gilead

Jenny C. Yang - Employment: Gilead Sciences, Inc

Robert Gish - Advisory Committees or Review Panels: Gilead, AbbVie, Arrowhead, Ionis, MERCK; Consulting: Eiger, Genentech, MERCK; Speaking and Teaching: Gilead, AbbVie, MERCk; Stock Shareholder: Arrowhead

The following people have nothing to disclose: My T. Nguyen, Andrew Huynh, Mytop Ly, Khanh K. Nguyen, Ruel T. Garcia, Brian S. Levitt, Eduardo DaSilvera

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Real-world SVR Rates for Paretaprevir/ritonavir, Ombitasvir, Dasabuvir vs. Sofosbuvir/ledipasvir Regimens With and Without Ribavirin

Adeel A. Butt[1], Peng Yan[2], Kristen M. Marks[1], Obaid S. Shaikh[2], Kenneth E. Sherman[3]; [1]Division of Infectious Diseases, Weill Cornell Medical College, Mars, PA; [2]VA Pittsburgh Healtcare System, Pittsburgh, PA; [3]University of Cincinnati, Cincinnatti, OH

Background: Addition of ribavirin to newer DAA regimens is of unclear benefit. We determined the SVR rates for persons treated with Paritaprevir/ritonavir, Ombitasvir, Dasabuvir (PrOD) regimen with and without ribavirin and compared this with sofosbuvir/ledipasvir (SOF/LDV) regimens in real-world settings. **Methods:** In the ERCHIVES database, a well-established national cohort of HCV-infected Veterans, we identified HCV genotype 1 infected persons initiated on the above regimens. We excluded those with HIV coinfection, positive HBsAg and missing HCV RNA. **Results:** We identified 1,235 persons on PrOD (75.5% ribavirin) and 4,247 on SOF/LDV (23.3% ribavirin). Among HCV genotype 1a infected persons, ribavirin was prescribed to 99.2% on PrOD, and 23.3% on SOF/LDV. The SVR rates ranged from 92.6% to 100% regardless of the treatment regimen, presence of cirrhosis or HCV subtype, except in HCV genotype 1a without cirrhosis on PrOD without ribavirin, (SVR 83%, N=5/6). There were minor, clinically insignificant differences in SVR rates in those treated with or without ribavirin in each of the treatment groups, regardless of presence of cirrhosis at baseline. In multivariable logistic regression analysis, and with the exception of GT1a cirrhotics treated with PrOD, with too small numbers to evaluate, ribavirin use was not associated with achieving SVR in any group. **Conclusion:** PrOD and SOF/LDV regimens are associated with high rates of SVR in actual clinical settings, which are comparable to clinical trials results. No meaningful difference in SVR rates was observed in those prescribed or not prescribed ribavirin with SOF/LDV or PrOD (for genotype 1b).

Table. Sustained virologic response in various treatment groups, by presence of cirrhosis at baseline and HCV subtype.

Regimen	HCV genotype*	N	SVR12	Cirrhosis	N	SVR12
Sofosbuvir + ledipasvir	1a	2408	95.14%	Yes	519	93.26%
				No	1889	95.66%
	1b	771	95.46%	Yes	149	92.62%
				No	622	96.14%
Sofosbuvir + ledipasvir + ribavirin	1a	758	94.59%	Yes	375	93.33%
				No	383	95.82%
	1b	194	96.39%	Yes	91	94.51%
				No	103	98.06%
PrOD	1a	6	83.33%	Yes	1	100.00%
				No	5	80.00%
	1b	297	98.99%	Yes	23	100.00%
				No	274	98.91%
PrOD + ribavirin	1a	725	95.03%	Yes	146	93.84%
				No	579	95.34%
	1b	177	97.18%	Yes	76	97.37%
				No	101	97.03%

PrOD, paritaprevir, ritonavir, ombitasvir, dasabuvir.

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The following people have nothing to disclose: Peng Yan

931
Hepatitis C (HCV) Virologic Outcomes in Veterans taking Ledipasvir/Sofosbuvir with Concomitant Acid Suppressing Medication

Austin W. Chan[1,2], William E. Bryan[2], Mohamed A. Hashem[2], Mary L. Townsend[2], Laura Ann Wang[4,2], Steve S. Choi[3,2], Susanna Naggie[1,2]; [1]Infectious Diseases, Duke University, Durham, NC; [2]Durham Veterans Affairs Medical Center, Durham, NC; [3]Gastroenterology, Duke University, Durham, NC; [4]School of Medicine, Duke University, Durham, NC

Background: Ledipasvir/Sofosbuvir (LDV/SOF) is a directly acting anti-viral combination therapy that has been approved for treatment of Hepatitis C infection. However, ledipasvir has been noted to have a drug interaction with acid suppressing medications, most notably with the proton pump inhibitor (PPI) drug class, resulting in potential for decreased serum concentrations of ledipasvir. Due to the exclusion of acid suppressing medications from registration trials, it is unclear if co-administration of LDV/SOF with PPI impacts sustained virologic response at 12 weeks (SVR12). **Methods:** Using the Veterans Affairs (VA) Informatics and Computing Infrastructure (VINCI), we were able to query the pharmacy database for all prescriptions of LDV/SOF that were dispensed through the VA system from October 10, 2014 – December 31, 2015. In addition, we queried the pharmacy database for PPI co-administration the identified LDV/SOF cohort. PPI usage was defined as any active PPI prescription that overlapped with the treatment period for LDV/SOF including refills. The primary outcome was SVR12, defined as any HCV RNA drawn >12weeks after completion of therapy. **Results:** Of an initial 30,231 prescriptions of LDV/SOF, SVR12 data was available for 10,501 veterans. Of the 10,501 veterans who completed a course of LDV/SOF during the study period, 2,004 received co-administration of a PPI. The cohort was predominantly male (96%), average age 62 (26 – 92) years and 52% Caucasian, 36% African American, and <1% were Alaskan Native/Pacific Islander, Asian, and Native American. There was no difference in demographics based on PPI exposure. For those patients who received LDV/SOF alone, the rate of SVR12 was 94.9% (8066/8497). For those patients who received LDV/SOF concomitant with PPI, the rate of SVR12 was 94% (1885/2004), p = 0.118. Further stratified analysis by stage of liver disease, duration of LDV/SOF therapy, dose of PPI, only active PPI refill, and genotype will be presented. **Conclusion:** In this large real-world cohort of veterans completing a course of LDV/SOF for the treatment of chronic HCV infection, a concomitant prescription for PPI acid suppressing medications did not result in lower SVR12. Further investigations into dosing per the package insert are needed to confirm that these medications do not result in higher relapse rates.

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Effectiveness of DACLATASVIR plus SOFOSBUVIR in HCV-GT3 patients – Results from the German Hepatitis C Registry (DHC-R)

Stefan Mauss[1], Klaus H. Boeker[2], Markus Cornberg[3], Rainer Günther[4], Hartwig H. Klinker[5], Andreas Schober[6], Kilian Weigand[7], Tim Zimmermann[10], Tina Nakonz[8], Conrad Fischer[9], Peter Buggisch[11]; [1]Center for HIV and Hepatogastroenterology, Duesseldorf, Germany; [2]Leberpraxis, Hannover, Germany; [3]Hannover Medical School, Hannover, Germany; [4]University Hospital Kiel, Kiel, Germany; [5]University Hospital Wuerzburg, Wuerzburg, Germany; [6]Hepatologische Praxis, Goettingen, Germany; [7]University Hospital Regensburg, Regensburg, Germany; [8]Bristol-Myers Squibb GmbH & Co. KGaA, Munich, Germany; [9]Consultant in Medical Affairs and HEOR, Munich, Germany; [10]University Hospital Mainz, Mainz, Germany; [11]IFI Institute for Interdisciplinary Medicine, Hamburg, Germany

Background and Aims: Approximately 350,000 adults in Germany are chronically infected with HCV, with an HCV genotype (GT) 3 proportion of approx. 28%. Effectiveness and safety of the direct-acting antiviral (DAA) regimen containing daclatasvir (DCV) in patients with GT3 is reported from the German Hepatitis C-Registry (DHC-R). **Methods**: The DHC-R is a non-interventional prospective cohort study that enrolled approx. 9,300 HCV patients receiving DAA-containing regimens between Feb. 1, 2014 and Feb. 15, 2016. Amongst these 1,074 patients with GT3 were enrolled. Effectiveness was assessed by sustained virologic response at post-treatment week 12 or 24 (SVR12/24). **Results**: As of Feb. 15, 2016, 1,017 patients were treated with DCV+SOF ± RBV, of these 383 (38%) patients had GT3 with 137 (36%) being treatment experienced and 127 (33%) cirrhotic. 168 patients have reached at least 12 W of post treatment follow up. Treatment duration was 12 or 24 weeks in 98 and 50 patients respectively. 20 patients received divergent treatment durations. Ribavirin was prescribed in 19% of the patients receiving 12 weeks of treatment and in 74% receiving 24 weeks of treatment. SVR rates in subgroups are reported in table 1. To date, from 168 HCV-GT3 patients with available ≥12 week follow-up data (mITT-population), 154 patients finished treatment as planned, of these 152 achieved SVR12/24, resulting in a mITT-SVR rate of 90.5%. In non-cirrhotic patients (n=66), treatment according to EU- or US-label with 12 weeks of DCV+SOF resulted in 95.5% SVR12/24 (mITT). SVR12/24 in decompensated cirrhosis was close to 80% (n=15/19). Discontinuation of therapy occurred in 14 patients: 1 virologic breakthrough, 4 due to adverse events, 3 unplanned events, 3 LTFU, 1 lack of adherence and 2 patients died (DCV+SOF+RBV: 1 gastro-intestinal bleeding, 1 cause unknown). **Conclusions**: In this large, real-world cohort of HCV GT3-infected patients, treatment with DCV+SOF ± RBV achieved high rates of sustained virologic response.

Table 1: mITT SVR12/24 Rates in Subpopulations

Subpopulations (n)	DCV+SOF 12W	DCV+SOF+RBV 12W	DCV+SOF 24W	DCV+SOF+RBV 24W	DCV+SOF±RBV All treatment durations*
	SVR12/24 (n/N; %)	SVR12/24 (n/N; %)	SVR12/24 (n/N; %)	SVR12/24 (n/N; %)	SVR12/24 (n/N; %)
Treatment-naïve (n=95)	46/51; 90.2%	13/13; 100%	3/4	14/14; 100%	83/95 87.4%
Treatment-experienced (n=73)	22/22; 100%	12/12; 100%	10/10; 100%	20/22; 90.9%	69/73 94.5%
Non-cirrhotic (n=100)	63/66; 95.5%	17/17; 100%	1/1	7/8	92/100 92%
Cirrhotic (n=68)	5/7	8/8	12/13; 92.3%	27/28; 96.4%	45/68 91.8%
Decompensated cirrhosis (n=19)	4/5	1/1	4/4	4/5	15/19 78.9%

No percentage presented if subgroup <10 patients;

*including 7 pts. <12W, 8 pts. >12W;<24W, 5 pts. >24W of treatment

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Stefan Mauss - Advisory Committees or Review Panels: BMS, AbbVie, ViiV, Gilead; Speaking and Teaching: BMS, AbbVie, Janssen, Gilead, MSD

Klaus H. Boeker - Consulting: Janssen; Speaking and Teaching: MSD, Roche, Gilead, BMS, Falk Foundation, Novartis, AbbVie

Markus Cornberg - Advisory Committees or Review Panels: Merck (MSD Germamny), Roche, Gilead, Novartis, Abbvie, Janssen Cilag, BMS; Grant/Research Support: Merck (MSD Germamny), Roche; Speaking and Teaching: Merck (MSD Germamny), Roche, Gilead, BMS, Novartis, Falk, Abbvie

Rainer Günther - Speaking and Teaching: Roche Pharma AG, Gilead, AbbVie

Hartwig H. Klinker - Advisory Committees or Review Panels: AbbVie, BMS, Gilead, Hexal, Janssen, MSD; Grant/Research Support: AbbVie, BMS, Gilead, Janssen, MSD, Arrowhead, Novartis; Speaking and Teaching: AbbVIe, BMS, Gilead, Janssen, MSD

Tim Zimmermann - Advisory Committees or Review Panels: Abbvie; Speaking and Teaching: BMS

Tina Nakonz - Employment: Bristol-Myers Squibb

Conrad Fischer - Independent Contractor: BMS, Germany, Intercept Pharma, Germany

Peter Buggisch - Advisory Committees or Review Panels: Janssen, AbbVie, BMS; Speaking and Teaching: Falk, MSD, Gilead, Merz Pharma

The following people have nothing to disclose: Andreas Schober, Kilian Weigand

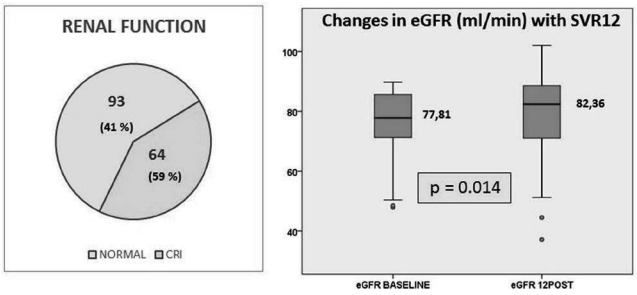
933

Improvement of renal function associated to sustained viral response in patients with chronic infection by hepatitis C virus (HCV) and renal insufficiency

Rafael Granados[1], Miriam Serrano[1], José María Martín[1], Antoni Adrover[1], Miriam Moreno[1], Melisa Hernández[2], María José Pena[2]; [1]Internal Medicine, Dr Negrín Hospital, Las Palmas34, Spain; [2]Microbiology, Dr Negrín Hospital, Las Palmas, Spain

Background and aim Chronic infection by hepatitis C virus (CIHCV) is known to cause some forms of kidney disease. Eradication of HCV may improve the renal disfunction in these patients. **The aim** of our study was to determine the prevalence of renal insufficiency and the effect of treatment with direct acting antivirals (DAA) on the renal dysfunction when it was present, in a cohort of patients with CIHCV. **Method** *Design*: Prospective study. *Patients*: All patients with CIHCV who initiated therapy with DAA between April and Dec/15 were included. Prospectively were collected demographic, clinical and laboratory variables. Fibrosis was measured by biopsy or Fibroscan (F2: 7,5-9,4 KPa, F3: 9,5-12,4 Kpa and cirrhosis ≥12,5 KPa). *Treatment*: DAA were given according the EASL guidelines. *Sustained virologic response (SVR12)*: undetectable viral load by COBAS Taqman 12 weeks after ending the treatment. *Renal function*. We calculated the estimated glomerular filtration rate (eGFR) with the CKD-EPI equation before and 12 weeks after the end of treatment. The function was defined according to the KDIGO classification. *Primary endpoints*. Proportion of patients with chronic renal insufficiency (CRI), defined

as a GFR < 90 ml/min and changes in the GFR 12 weeks after the end of treatment in those patients with CRI baseline. **Results** 157 individuals were included, with mean age 54 years and 66 % male. 68% were pre-treated with PR ± IP first generation**.** 132 (84%) had genotype 1 (1a: 32 %, 1b:64 % and others: 4 %), 15 (10%) genotype 3 and 10 (6%) genotype 4. The baseline viral load was > 800.000 UI/mL in 72% and 17 % were diabetics. Fibrosis stage: 16 (10%) were F0-F1;37 (24%) F2; 40 (25%) F3 and 64 (41%) had cirrhosis. 154/157(98,1%) had SVR12. 64/157 (41%) had a CRI baseline. Of these, 63 finished the treatment and 12 weeks of follow-up with 100% SVR12. In this subgroup, the eGFR improved significantly after obtaining SVR12 (Median: 77,81 ml/min vs 82,36 ml/min; p= 0.014). **Conclusions** 1) The prevalence of CRI in patients with CIHCV is high (41%). 2) In patients with CIHCV and CRI, the eGFR improves significantly after SVR12.



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Exposure-Response Analyses to Demonstrate Similar Efficacy and Better Tolerability for Low Dose Ribavirin Compared to Weight based Ribavirin with the 3D Regimen (Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir) in HCV GT1 Infection

Akshanth R. Polepally[2], Balakrishna S. Hosmane[1], Chih-Wei Lin[2], Mukul Minocha[2], Haoyu Wang[1], Amit Khatri[2], Rajeev M. Menon[2]; [1]Biometrics, AbbVie Inc.,, North Chicago, IL; [2]Clinical Pharmacokinetics and Pharmacodynamics, AbbVie Inc.,, North Chicago, IL

Background & Aims: The 3D regimen (ombitasvir/paritaprevir/ritonavir and dasabuvir) ± weight based ribavirin (RBV) is approved for the treatment of hepatitis C virus (HCV) genotype 1 (GT1) infection. With the potent 3D regimen, RBV dose reduction is expected to improve tolerability with minimal impact on efficacy. The objectives of the analyses were to predict the efficacy (percent 12-week sustained virologic response [$\%SVR_{12}$]) and the safety event incidence rates (total bilirubin [TBIL] elevation and hemoglobin [Hgb] reduction) for the 3D regimen + low dose (600 mg) RBV (3D + LDR) compared to the 3D regimen + weight based (1000 or 1200 mg daily) RBV (3D + WBR). **Methods:** Efficacy and safety data were available from six phase 3 and two phase 2 studies (3D ± WBR). Multiple linear logistic regression (MLR) model was developed (SAS 9.2) to establish the relationship between SVR_{12} and trough concentration (C_{trough}) values of DAAs and RBV for the GT1a infected subjects only (N = 1253). GT1b subjects were not included as they achieved > 99% SVR_{12}. Separate MLR models for the relationship between safety incidence rates (by severity) and area under the plasma concentration-time curve (AUC) values were developed (R 3.0.1) using the data of GT1 infected subjects from six phase 3 studies and one phase 2 study (N = 2346). Relevant covariates were included in the models based on statistical and clinical significance. The final models were used to predict the $\%SVR_{12}$, grade 3 TBIL elevation and grade 2 Hgb reduction for 3D + LDR compared to 3D + WBR. **Results:** C_{trough} values of DAAs, RBV along with age, sex, cirrhosis (presence *vs* absence), baseline viral load, and interleukin-28B (IL28B) genotype (non-CC *vs* CC) were associated with SVR_{12}. The expected change in SVR_{12} for 3D + LDR compared to 3D + WBR was < 1% across easy-to-treat (non-cirrhotic, female, IL28B CC) to hard-to-treat (cirrhotic, male, IL28B non-CC) GT1a subpopulations. In safety analyses, paritaprevir and RBV AUC values and baseline TBIL were associated with TBIL elevation; RBV AUC, baseline Hgb, sex, and cirrhosis were associated with Hgb reduction. The predicted probability of grade 3 TBIL elevation and grade 2 Hgb reduction with 3D + LDR were 2.3% and 0.7% which were significantly lower than observed 5.1% and 6.9% with 3D + WBR, respectively. **Conclusion:** Exposure-response analyses demonstrated that lowering the RBV dose (to 600 mg) from weight based dosing with 3D regimen would improve tolerability with minimal or no effect on SVR_{12} (< 1% change) in HCV GT1 infection.

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Balakrishna S. Hosmane - Consulting: AbbVie

Chih-Wei Lin - Employment: AbbVie

Mukul Minocha - Employment: AbbVie; Stock Shareholder: AbbVie

Haoyu Wang - Employment: AbbVie; Stock Shareholder: AbbVie

Amit Khatri - Employment: AbbVie, Inc; Patent Held/Filed: AbbVie, Inc; Stock Shareholder: AbbVie, Inc

Rajeev M. Menon - Employment: AbbVie; Patent Held/Filed: AbbVie; Stock Shareholder: AbbVie

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RUBY-II: Efficacy and Safety of a Ribavirin-free Ombitasvir/Paritaprevir/Ritonavir ± Dasabuvir Regimen in Patients with Severe Renal Impairment or End-Stage Renal Disease and HCV Genotypes 1a or 4 Infection

Edward J. Gane[1], Ricard Solà[2], Eric Cohen[3], Stuart K. Roberts[4], Jacob George[5], Richard Skoien[6], Stephen Riordan[7], Niloufar Mobashery[3], Manal Abunimeh[3], Daniel E. Cohen[3], Kosh Agarwal[8]; [1]Auckland City Hospital, Auckland, New Zealand; [2]Hospital del Mar. IMIM, Universitat Autónoma de Barcelona, Barcelona, Spain; [3]AbbVie, Inc, North Chicago, IL; [4]Alfred Hospital, Melbourne, VIC, Australia; [5]Westmead Institute for Medical Research and University of Sydney, Westmead, NSW, Australia; [6]Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia; [7]University of New South Wales, Randwick, NSW, Australia; [8]Institute of Liver Studies, Kings College Hospital NHS Foundation Trust, London, United Kingdom

BACKGROUND: Chronic hepatitis C virus (HCV) infection is of particular significance for those with end-stage renal disease (ESRD). In a clinical trial in patients with severe or ESRD, 12 weeks of treatment with ombitasvir (OBV)/paritaprevir (PTV; discovered by AbbVie and Enanta)/ritonavir (r) with dasabuvir (DSV) ± ribavirin (RBV) for HCV genotype (GT) 1 infection led to sustained viral response at post-treatment week 12 (SVR12) in 90% of patients, with no study drug discontinuation due to adverse events (AEs). However, RBV was commonly associated with hemoglobin declines and dose interruption. Here, we assessed the safety and efficacy of RBV-free treatment with OBV/PTV/r ± DSV in patients with ESRD and chronic HCV GT1 or 4 infection. **METHODS:** RUBY-II is a phase 3b, open-label, multi-center study that enrolled treatment-naïve patients with either GT 1 or GT4 infection without cirrhosis and end-stage renal disease (eGFR <30 ml/min), including

those on hemodialysis. Patients in Arm 1 (GT1a) received OBV/PTV/r (25/150/100 mg) once daily and DSV (250 mg) twice daily for 12 weeks. Arm 2 (GT4) received OBV/PTV/r (25/150/100 mg) once daily for 12 weeks. The primary endpoint is the percentage of patients with SVR12 (HCV RNA <15 IU/mL). All patients who received ≥1 dose of study drug are included in the safety and efficacy analyses. **RESULTS:** A total of 18 patients were enrolled; 12 (67%) of patients were male, 13 (72%) had GT1a infection, and 5 (28%) had GT4 infection; all 18 patients were on dialysis. Of the 13 patients with available data post-treatment, SVR4 was achieved in 12/13 (92%) patients. The patient who did not achieve SVR4 elected to undergo renal transplantation and withdrew consent at treatment week 2. One other patient discontinued study drug but achieved SVR12. Safety is summarized in Table 1. **CONCLUSIONS:** The RBV-free, direct-acting antiviral regimen of OBV/PTV/r ± DSV for 12 weeks in treatment naïve patients with severe or end-stage renal disease and HCV GT1a or 4 infection appears both safe and effective in patients with ESRD including those on hemodialysis. Complete SVR12 data will be available for presentation.

Event, n (%)	HCV GT1a OBV/PTV/r + DSV 12 Weeks (n = 13)	HCV GT4 OBV/PTV/r 12 Weeks (n = 5)
Any AE	13 (100)	5 (100)
Serious AE	3 (23)	1 (20)
AE leading to study drug discontinuation	1 (8)*	1 (20)†
Hemoglobin, Grade ≥2 (<10 g/dL)	4 (31)	2 (40)
ALT, Grade ≥3 (>5 x ULN)	1 (8)*	1 (20)‡
Total Bilirubin, Grade ≥3 (>3 x ULN)	0	0

*Discontinued study drug, still achieved SVR12

†Discontinued study drug due to renal failure and transplant

‡Patients' ALT returned to normal range within 10 days without dose interruption

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Edward J. Gane - Advisory Committees or Review Panels: AbbVie, Janssen, Gilead Sciences, Achillion, Merck; Speaking and Teaching: AbbVie, Gilead Sciences, Merck, Alnylam

Ricard Solà - Consulting: Abbvie; Speaking and Teaching: Gilead, Abbvie, Bristol-Myers Squibb, Merck Sharp & Dohme, Janssen

Stuart K. Roberts - Board Membership: AbbVie, Gilead

Jacob George - Advisory Committees or Review Panels: Pharmaxis, BMS, MSD, Gilead, Janssen, Abbvie; Grant/Research Support: MSD

Niloufar Mobashery - Employment: Abbvie; Stock Shareholder: abbvie

Manal Abunimeh - Employment: AbbVie

Daniel E. Cohen - Employment: AbbVie; Stock Shareholder: AbbVie

Kosh Agarwal - Advisory Committees or Review Panels: Gilead, BMS, Novartis, Janssen, AbbVie; Consulting: MSD, Janssen, Achillion, Intercept; Grant/Research Support: Roche, Gilead, BMS, Arbutus; Speaking and Teaching: Astellas, Gilead, BMS, GSK

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936

Serum concentration of asunaprevir affects alanine aminotransferase elevation for patients with chronic hepatitis C and the protective effects of ursodeoxycholic acid

Shuhei Hige, Itaru Ozeki, Ryoji Tatsumi, Masakatsu Yamaguchi, Mutsuumi Kimura, Tomohiro Arakawa, Tomoaki Nakajima, Yasuaki Kuwata, Takahiro Sato, Takumi Ohmura, Joji Toyota, Yoshiyasu Karino; Hepatology, Sapporo-Kosei General Hospital, Sapporo, Japan

Background/Aims: Asunaprevir (ASV) is administrated with daclatasvir (DCV) for genotype 1chronic hepatitis C patients in Japan. Alanine aminotransferase (ALT) elevation is the most frequent adverse event. However, the precise mechanism has not been elucidated. Ursodeoxycholic acid (UDCA) is used as a hepatoprotective medicine in case of liver dysfunction. In this study, we investigated the significance of serum ASV concentration and the relationship with ALT elevation. **Patients and Methods:** 132 patients with genotype 1 chronic hepatitis C were treated with 100mg of ASV twice and 60mg of DCV once daily. Pharmacokinetics (PK) of ASV was investigated in 25 cases. Trough concentrations of ASV (C-ASV $_{trough}$) at week 2, 4, 6, 8 and 12 were measured. Intensive PK study was performed in 10 cases and C-ASV of 0, 0.5, 1, 2, 4, 6, 8 and 12 hours after ASV administration were measured at day 14. C-ASV $_{trough}$ at week 1 or 2 was measured for other 117 cases. C-ASV was measured by HPLC. 55 cases were administrated UDCA continuously before the start of the combination therapy and 51 cases were not. Those who improved ALT<30 IU/L and maintained during the treatment period were classified as a stable [Rel(-)] group and those who did not as a relapser [Rel(+)] group. **Results:** In the intensive PK study, median C max was 951 ng/mL (283-4500) and t max was 1.97 hours (0.9-2.1). Mean C-ASVs $_{trough}$ between week 2 and 12 were widely distributed from 16.2 to 195.8 ng/mL by individuals, but the differences in the same case was small: mean SD was 41.5% of the mean value. Median C-ASV $_{trough}$ of cirrhotic cases with Child-Pugh (CP) score 6, CP score 5 and non-cirrhotic cases was 168, 77 and 52 ng/mL (p=0.06). Median C-ASV $_{trough}$ was significantly correlated with type 4 collagen-7S, FIB-4 index, WFA$^+$-M2BP, liver stiffness measurement by Fibroscan ^{TM} (r=0.50, 0.40, 0.40, 0.39; p<0.001). The maximum value and the period of ALT elevation was 97.4 IU/L and 13.7 weeks in UDCA(-) group and 65.4 IU/L and 15.2 weeks in UDCA(+) group. Median C-ASV $_{trough}$ (ng/mL) in Rel(-) and Rel(+) group was 48.7 and 92.5 in UDCA(-) cases (p=0.03), 112.5 and 71.1 in UDCA(+) cases (n.s.). In UDCA(-) cases, the probability of ALT elevation during the treatment was 25.0% for C-ASV $_{trough}$ <50 ng/mL cases and 58.6% for C-ASV $_{trough}$ ≥50 ng/mL cases. C-ASV $_{trough}$ did not affect SVR (72 ng/mL in SVR cases and 62 ng/mL in non-SVR cases: n.s.). **Conclusions:** ASV concentration correlated with hepatic reserve and the degree of fibrosis. ALT elevation during the combination therapy with ASV and DCV for patients with genotype 1 HCV infection was associated with serum ASV concentration and UDCA reduced ALT elevation.

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In patients with chronic HCV infection, antiviral treatment with DAAs can be managed by specialized nurses. Results of a large real-life cohort

Giovanna Scoazec, Murielle François, Anne Varaut, Françoise Roudot-Thoraval, Daniel Dhumeaux, Ariane Mallat, Christophe Hezode; Hepatologie, Hospital Henri Mondor, Creteil, France

Background: The availability of effective DAAs for the treatment of chronic HCV infection has resulted in a major increase of the number of patients susceptible to benefit from these new therapeutic approaches. Many of these patients have advanced liver disease and require rapid access to antiviral treatment. Therefore, innovative strategies are needed to optimize patient management, cope with large cohorts of patients and accelerate treatment initiation. The objective of this study was to compare the management of selected HCV patients treated with DAAs between hepatologist physicians and specialized nurses

in a tertiary care center. **Methods:** 548 patients, candidates for all-oral DAA regimens, were prospectively allocated to treatment supervised either by a hepatologist physician (n=261, group P) or a specialized nurse (n=287, group N). Key exclusion criteria were Child C cirrhosis, hepatocellular carcinoma, or severe comorbidities. Cirrhosis was defined by FibroScan score>12.5 kPa, or FibroTest score>0.75. Patients received all-oral regimens according to international guidelines, including mainly SOF+DCV±RBV (56.6%), SOF+LDV±RBV (25%) or SOF+SIM±RBV (11.9%). **Results:** 60.6% of patients were male with median age of 59.4 years at DAA treatment initiation. Cirrhosis was present in 47.1%; 30 patients were Child B; median MELD score was 6. 10.8% of patients were organ-transplanted. 13.9% had renal failure, 17.9% diabetes and 37.8% hypertension; 1.1% had HCV-HIV co-infection. HCV genotype 1 was predominant (61.2%), followed by genotypes 4 (17.7%), 3 (13.3%), 2 (5.9%), 5 (1.1%) and 6 (0.7%). 53.6% were treatment-experienced patients. 86.1% were treated for 12 weeks and 13.9% for 24 weeks. There were no significant differences in baseline characteristics and treatment duration between both groups (P and N). Overall, SVR12 rate was 92.7% (91.2%, group P vs 94.1%, group N). Premature treatment discontinuations occurred in 1.8% (1.9 %, group P vs 1.7%, group N). Severe adverse events were observed in 3.5% (4.3%, group P vs 2.8%, group N). Death during treatment period was reported in 0.9% (1.5%, group P vs 0.3%, group N). Loss to follow up (1.8% in the overall population) was significantly more frequent in group P (3.4%) than in group N (0.3%) (p=0.008). **Conclusions:** This study in a large real-life cohort strongly shows that all-oral DAA regimens can be safely and successfully managed by specialized nurses. This strategy may accelerate DAA treatment access for all HCV patients.

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938

Hepatitis C Treatment with Direct Acting Antiviral Therapy: Report of a Global Survey

Maen Masadeh, Huafeng Shen, Yazan Hasan, Andrew Johannes, Antonio J. Sanchez; Division of Gastroenterology and Hepatology, University of Iowa Hospitals and Clinics, Iowa City, IA

Aim: Direct-acting antiviral (DAA) therapies have been developed for Hepatitis C (HCV) treatment with increasing efficacy. Our aim was to describe patterns of HCV management in liver and infectious diseases (ID) specialists.**Methods:** An Institutional Review Board approved survey was emailed to members of the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA).All responses were anonymous. **Results:**801 responses out of 4224 mailings were received; 295 treat HCV patients. More AASLD respondents treat HCV than IDSA respondents (94%vs.66% P< 0.001).Therapy of choice in treatment naïve patients with genotypes 1, 2, 3 and 4 were Ledipasvir/Sofosbuvir (93%),Sofosbuvir/Ribavirin (75%),Daclatasvir/Sofosbuvir (80%) and Ledipasvir/Sofosbuvir (78%) respectively.HCV treatment failure was encountered by 61% of participants; more frequently by liver than ID specialists (83% vs.44% p<0.001).Liver specialists treat more HCV in decompensated cirrhosis than ID specialists (86% vs 34% p<0.001) and HCV recurrence after liver transplant (LT) (74% vs.11.3% p<0.0001).Years of experience treating HCV did not affect approach to HCV treatment failure or hepatic fibrosis assessment methods before HCV treatment, liver biopsy was obtained by <10 % of respondents. Insurance coverage was a major limiting factor preventing initiation of DAAs in 86% of practitioners.**Discussion:**To our knowledge, this is the largest survey on the patterns of HCV management in liver and ID specialists.The majority of respondents adhere to the AASLD/IDSA HCV treatment guidelines, liver specialists treat more decompensated cirrhotic and post LT patients. Liver biopsy has been largely replaced by non-invasive methods for assessment of hepatic fibrosis. ID specialists have been identified as a group that could expand the HCV treatment workforce, but less than 66% of IDSA respondents treat HCV. It is essential to identify barriers for ID specialists to treat HCV and augment HCV care capacity. This survey raises important issues on the need for a consensus amongst insurance programs to improve HCV treatment access on a global scale.

HCV Practice Patterns By Specialty

	Hepatology (n = 132)	Infectious disease (n= 153)	P-value £
Assessment of hepatic fibrosis			0.004
Liver biopsy	13 (9.9%)	10 (6.5%)	
Fibrosure/Fibrospect	36 (27.3%)	74 (48.4%)	
Fibroscan/Elastography	71 (53.8%)	60 (39.2%)	
Other	12 (9.1%)	9 (5.9%)	
Approach to DAA failure			0.537
Wait for new DAA's to be approved	56 (53.3%)	30 (48.4%)	
Treat with a different DAA	49 (46.7%)	32 (51.6%)	

Values are numbers (%). £ Fisher's exact test.

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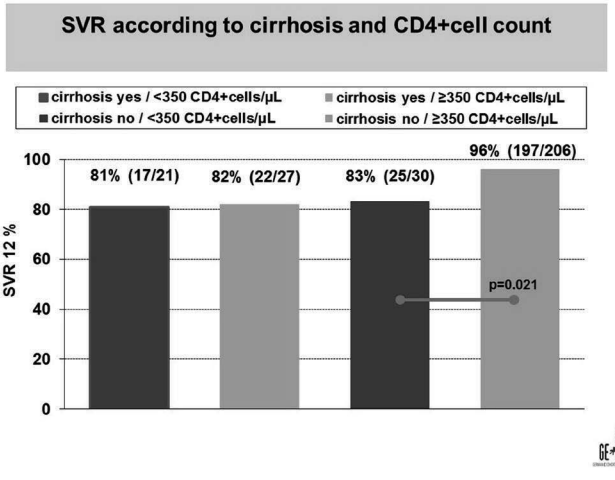
Are risk factors still relevant for HCV treatment with directly-acting agents against HCV in HIV-HCV-coinfection? Results from the German hepatitis C cohort (GECCO)

Stefan Mauss[1], Patrick Ingiliz[2], Thomas Lutz[3], Knud Schewe[4], Jürgen K. Rockstroh[5], Florian Berger[1], Julian Schulze zur Wiesch[6], Christoph Boesecke[5], Heiner W. Busch[7], Guenther Schmutz[1], Axel Baumgarten[2], Stefan Christensen[7]; [1]Center for HIV and Hepatogastroenterology, Duesseldorf, Germany; [2]2.) Medizinisches Infektiologie Zentrum Berlin, Berlin, Germany; [3]Infektiologikum, Frankfurt, Germany; [4]ICH, Hamburg, Germany; [5]Department of Internal Medicine 1, University Hospital Bonn, Bonn, Germany; [6]1. Department of Internal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [7]CIM, Muenster, Germany

Introduction Directly-acting agents (DAA) against HCV have improved treatment of chronic hepatitis C due to higher efficacy, better tolerability and substantial reduction of contraindications. Despite this major progress relapses still occur and we assessed the influence of traditional risk factors on treatment outcome in HIV-HCV-Coinfection. **Methods** The GECCO cohort is a multicenter cohort from 9 sites in Germany. All patients (n=1643) started on the following DAA regimen were included in the analysis: pegylated interferon (PegIFN) +ribavirin (RBV) +sofosbuvir (SOF); SOF +RBV; SOF +simeprevir (SMV); SOF +daclatasvir (DCV) +/- RBV; SOF/ledipasvir (LDV); paritaprevir/ritonavir (PRT/r)/ombitasvir (OBV) +/- RBV and +/- dasabuvir (DSV). Treatment outcome was measured as sustained virologic response at week 12 after end of therapy (SVR12, ITT). A proportion of patients in GECCO are also part of the German Hepatitis C Registry. **Results** The analysis is based on the 345 HIV/HCV-coinfected patients in the GECCO

cohort. Risk factors associated with lower SVR12 rates were the presence of liver cirrhosis (95% vs. 84%) (p=0.02) and having <350 CD4 cells/μl (94% vs. 83%) (p=0.02). Although the presence of liver cirrhosis strongly correlated with a CD4 cell count <350/μl (p<0.001), having <350/μl CD4 without cirrhosis was also associated with lower SVR rates (Figure). Age, sex, HCV-RNA >6 Mio IU/mL, ALT level, CDC stage, specific antiretroviral therapy and HCV treatment regimen were not associated with statistically lower SVR 12 rates. **Conclusions** Despite considerably improved efficacy of treatment of chronic hepatitis C with DAA in HIV/HCV-coinfection low CD4 cells <350/μl and liver cirrhosis remain risk factors for treatment failure. The association between the presence of liver cirrhosis and low CD4+ cell counts may be explained by portal hypertension with splenomegaly and consecutive lymphopenia.



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Stefan Mauss - Advisory Committees or Review Panels: BMS, AbbVie, ViiV, Gilead; Speaking and Teaching: BMS, AbbVie, Janssen, Gilead, MSD

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Knud Schewe - Advisory Committees or Review Panels: abbvie, gilead, msd, bms, janssen cilag, hexal; Speaking and Teaching: msd, hexal, gilead

Jürgen K. Rockstroh - Advisory Committees or Review Panels: Abbvie, Cipla, BMS, Merck, Roche, Tibotec, Abbvie, Bionor, Tobira, ViiV, Abbott, Gilead, Janssen; Consulting: Novartis; Grant/Research Support: Gilead, Merck; Speaking and Teaching: BMS, Merck, Siemens, Tibotec, Gilead, Janssen, ViiV

Christoph Boesecke - Consulting: Abbvie, ViiV; Speaking and Teaching: MSD, Gilead, BMS

Heiner W. Busch - Speaking and Teaching: Tibotec, MSD, Janssen, BMS, Gilead, Abbott

Stefan Christensen - Advisory Committees or Review Panels: BMS, Abbvie, Janssen, ViiV, Gilead, MSD; Speaking and Teaching: Gilead, MSD, Abbvie, BMS, Janssen

The following people have nothing to disclose: Florian Berger, Julian Schulze zur Wiesch, Guenther Schmutz, Axel Baumgarten

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Impact of SVR to interferon-free antiviral regimens on liver stiffness measurement and liver functionality in HCV infected patients with severe liver disease: a real life study

Marcello Persico[1], Mario Masarone[1], Andrea Aglitti[1], Rosa Caruso[1], Alessandro Federico[2], Marcello Dallio[2], Silvia Camera[3], Nicola Caporaso[3], Filomena Morisco[3]; [1]Internal Medicine and Hepatology Unit, Department of Medicine, University of Salerno, Salerno, Italy; [2]Gastroenterology Unit, Department of Clinical and Experimental Medicine, Second University of Naples, Naples, Italy; [3]Gastroenterology Unit,, Department of Clinical Medicine and Surgery, University of Naples "Federico II", Naples, Italy

Background: New interferon-free regimens with 2nd generation Direct Antiviral Agents(DAA) demonstrated high efficacy among HCV-infected patients in registered trials. Nevertheless, little is known about the impact of these therapies on liver stiffness measurement(LSM) and liver functionality in "real-life" settings. **Aims**: to evaluate the impact of SVR on LSM and clinical and liver parameters indexes of 2nd generation interferon-free DAA therapy on a real-life population of HCV infected patients with Metavir F3 and F4 liver fibrosis. **Patients and methods**: 282 HCV patients(M/F: 55.6/44.4%, Age:62.84±10.49, BMI: 25.97±3.69) with F3 or F4 liver fibrosis undergoing antiviral therapy with DAA, were consecutively enrolled from April to December 2015 in three tertiary centers of Hepatology of Southern Italy, decompensated cirrhosis were excluded. Genotypes were: 1b:62.9%; 1a:4,0%; 2:23,7%; 3:6,8%; 4:2,5%. Patients were treated on the basis of EASL/AISF guidelines with: Sofosbuvir(SOF)+Ribavirin(RBV)(26.0%), SOF+Simeprevir±RBV(28.8%), SOF+Ledipasvir±RBV(14.0%), Ombitasvir+Paritaprevir+Ritonavir+Dasabuvir±RBV(24.8%), Ombitasvir+Paritaprevir+Ritonavir ±RBV (1.4%), SOF+Daclatasvir±RBV(5.0%). Of every patient clinical, biochemical and imaging data(LSM and Ultrasonography), Child-Pugh and MELD scores were collected at the baseline before therapy starting(T0), at the End of Therapy (EoT) and after 12 weeks, at the Sustained Virological Response (SVR12). **Results**: of the 282 patients 68.6% were Metavir F4(LSM>=12.5 kPascal) and 31.4% F3. SVR12 was reached in 97,5% of patients. In F3 and F4 patients LSM, and (in F4 patients) Child and MELD score significantly decreased from T0 to EoT(p<0,00001 each). Interestingly, no significant differences between these variables were found between EoT and SVR12 (p=ns). At an univariate analysis of the clinical and liver functionality parameters, baseline Glucose(p<0.005),Type 2 Diabetes(p<0.001), ALT(p<0.001), PLTs (p<0.005), were found associated with a significant EoT LSM (>=2kPascal) improvement. At a multiple regression with Age, Sex, BMI, Glucose, Diabetes, ALT,MELD, Child and Platelets levels(PLT) as independent variables, only ALT and PLTs were directly, and Diabetes inversely, associated with significant LSM reduction. **Conclusions**: Virological response to Interferon-free regimens is associated to fibrosis regression and recovery of liver functionality and this can be detected as early as EoT response is achieved, whereas no differences between EoT and 12 weeks post-treatment can be found in SVR patients. Diabetes seem to negatively influence LSM improvement. Further investigations are advised to assess long term effects of SVR.

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Massive Disparity in Insurance Approval; A Comparison Between Ledipasvir/sofosbuvir Based Hepatitis C Therapy and Adalimumab Based IBD Therapy

Mohammad Arsalan Siddiqui[1], Hany Eraqi[2], Sadiq Omar[1], SyedMohammed Jafri[3]; [1]Internal Medicine, Henry Ford Hospital, Detroit, MI; [2]School of Medicine, Wayne State University, Detroit, MI; [3]Gastroenterology, Henry Ford Hospital, Detroit, MI

Purpose: We evaluated the success rate for insurance approval for a single center setting for hepatitis C therapy involving ledipasvir/sofosbuvir and compared it to IBD therapy involving Adalimumab. Methods: Pharmaceutical records were reviewed for all patients prescribed ledipasvir/sofosbuvir and Adalimumab between July 2014 and November 2015. Data was extracted including type of insurance, insurance approval, fibrosis staging based on fibroscan for the patients who were prescribed ledipasvir/sofosbuvir and data for type of IBD, severity of anemia, location, extraintestinal manifestations and perianal complications was collected for the patients who were prescribed Adalimumab. Results: 783 patients were prescribed therapy with ledipasvir/sofosbuvir based therapy and the over-all approval rate was 77.8%. In comparison ammong the 55 patients who were prescribed Adalimumab 52 (94.5%) were approved, 2 patients were denied and 1 was still pending approval. Among the patients who were prescribed ledipasvir/sofosbuvir by insurance companies 296 patients (37.8%) had Medicare, 424 (54.1%) private insurance and (8.2%) had Medicaid. The approval rates were 93% for Medicare patients, 79% for private insurances and 32% for Medicaid patients. Amongst private insurances, Private A had approval rate of 87%, Private B had approval rate of 73% and other private insurances had approval of 71%. In the Adalimumab group, 7.3% patients had Medicare and Medicaid each, 14.6% patients had Private A, 69.1% had Private B and 1.8% had other private insurance. All the patients who had Medicaid or Medicare were approved. Of the 2 patients who were denied one had Private B, Crohn's disease as the diagnoses and absence of anemia or extraintestinal manifestations. Whereas the second patient had insurance other than Private A or B, Ulcerative colitis as the diagnoses, presence of moderate anemia and no extra-intestinal manifestations. Conclusion: We evaluated insurance approval rates of ledipasvir/sofosbuvir based hepatitis C therapy and Adalimumab based IBD therapy. The over-all approval rate of therapy based on ledipasvir/sofosbuvir was 77.8% and Medicaid patients had a very low approval rate of 32%. The overall approval rate for Adalimumab based therapy was 94.5% and all the Medicare and Medicaid patients were approved. The only patients who were denied had private insurance.

Table showing approval rates in percentage of ledipasvir/sofosbuvir based on insurance type (p-value < 0.001)

Medicaid	32.1
Medicare	92.9
Private	78.9

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942

Treatment of elderly HCV patients with severe fibrosis: safety and efficacy data from RESIST-HCV, a large regional database

Vincenza Calvaruso[1], Irene Cacciola[2], Maurizio Russello[11], Antonio Davi[3], Gaetano Scifo[4], Riccardo Volpes[5], Arturo Montineri[6], Tullio Prestileo[7], Salvatore Madonia[8], Giuseppe Malizia[17], Antonio Digiacomo[9], Gaetano Bertino[18], Antonio Magro[19], Anna Licata[10], Bruno Cacopardo[11], Antonino Salvo[12], Luigi Guarneri[20], Ignazio Scalisi[13], Giovanni Mannino[14], Pietro Colletti[21], Fabio Cartabellotta[15], Vincenzo Portelli[16], Giovanni Raimondo[2], Antonio Craxì[1], Vito Di Marco[1]; [1]Gastroenterologia & Epatologia, DIBIMIS,, University of Palermo, Palermo, Italy; [2]University of Messina, Messina, Italy; [3]Infectious Diseases Department, Modica Hospital, Italy, Italy; [4]PO Umberto I, Siracusa, Italy; [5]ISMETT, Palermo, Italy; [6]Azienda Ospedaliera Universitaria Policlinico-Vittorio Emanuele, Catania, Italy; [7]Infectious disease, Ospedale Civico, Palermo, Italy; [8]Internal Medicine I, AO V. Cervello, Palermo, Italy; [9]Ospedale Regina Margherita, Comiso, Italy; [10]DIBIMIS, University of Palermo, Palermo, Italy; [11]Ospedale Garibaldi Nesima, Catania, Italy; [12]ASP di Caltanissetta Presidio Ospedaliero S. Elia,, Caltanissetta, Italy; [13]Ospedale Vittorio Emanuele II, Castelvetrano, Italy; [14]Infectious disease, Ospedale Cannizzaro, Palermo, Italy; [15]Ospedale Buccheri La Ferla, Palermo, Italy; [16]infectious disease, ASL DI TRAPANI, Trapani, Italy; [17]Gastroenterology unit,, AO V. Cervello, Palermo, Italy; [18]U.O.C. di Medicina Interna e Urgenza, A.O.U.P. "Vittorio Emanuele" di Catania -, Catania, Italy; [19]U.O.C. Medicina Interna, ASP di Agrigento, Presidio Ospedaliero S. Giovanni di Dio, Agrigento -, Agrigento, Italy; [20]U.O.C. Malattie Infettive, ASP di Enna, Presidio Ospedaliero "Umberto I", Enna -, Enna, Italy; [21]U.O.C. di Malattie Infettive, A.O.U.P. "P. Giaccone" Palermo, Palermo, Italy

Background and Aim: Phase 3 studies of DAAs in patients with chronic hepatitis C or cirrhosis have included few patients over 70 years. In Italy, restricted prescription of IFN-free regimens to patients with severe fibrosis or cirrhosis has skewed the usage of DAA toward the more advanced age fascia, which contains patients with frequent co-morbidities and co-medications, not candidates to OLT. To evaluate the safety and efficacy of DAA regimens we used the ongoing dataset from our regional database, RESIST-HCV, which includes all HCV patients presenting for treatment to Liver centres throughout Sicily in order to evaluate appropriateness and priority. **Patients and methods:** Between March 2015 and May 2016, 9,154 patients were registered in RESIST-HCV, 4,798 (52.4%) met the AIFA criteria for treatment and 4,039 (44,1%) started DAA regimens. Of these 4,039 patients, 1,566 (38.7%) were elderly (age 70 years). Regimen choice and use of ribavirin were based on viral genotype and stage of disease, according to guidelines. **Results:** The cohort of 1,566 elderly patients had a higher prevalence of women (50% vs 35%,p<0.001), P/R naïve patients (54% vs 44%,p<0.001), genotype 1b (82% vs 63%,p<0.001), F4 fibrosis (70% vs 59%,p<0.001), HCC previous treated (6% vs 3%,p<0.001), diabetes (29% vs 23%,p<0.001), arterial hypertension (53% vs 30%,p<0.001), hearth disease (6% vs 3%,p<0.001), stage-3 kidney disease (4% vs 2%,p<0.001) and co-medications (81% vs 68%,p<0.001) as compared to 2,473 patients under 70 years. HIV co-infection (0.06 vs 5%,p<0.001) and a previous OLT (4.5% vs 6.8%,p<0.03) were less frequent in the elderly. In May 2016, 1,568 patients (38%) concluded treatment and 732 patients (18%) concluded the 12 weeks of follow-up. By ITT, the rate of ETR was 99.5% (556/558) in the elderly and 99.3% (1,007/1.010) in the under 70 and the rate of SVR was 94.6% (264/279) in the elderly and 90.6% (395/436) in the under 70. Two patients died (1 elder, liver failure; 1 non-elder, variceal bleeding).

Conclusions: Use of IFN-free DAAs regimens in practice is as safe and effective in elderly patients with cirrhosis or severe fibrosis due to HCV as in a younger population. The lifetime utility of HCV eradication in the elder in terms of reduction of events and overall survival needs evaluation in long-term observational cohorts.

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Telemedicine-based Hepatitis C Virus (HCV) Management for Individuals on Opioid Agonist Treatment (OAT)

Andrew H. Talal[1], Phyllis Andrews[2], Anthony McLeod[2], Yang Chen[3,1], Marianthi Markatou[3,1], Clewert Sylvester[2], Lawrence Brown[2]; [1]Center for Clinical Care and Research in Liver Disease, SUNY, University at Buffalo, Buffalo, NY; [2]START Treatment & Recovery Centers, Brooklyn, NY; [3]Biostatistics, University at Buffalo, Buffalo, NY

Background and aims: Despite high HCV prevalence, persons on OAT rarely engage in HCV care as most programs refer patients offsite. Telemedicine (two-way videoconferencing) permits direct interaction between patients and specialists in distinct locations and might be useful for HCV treatment of OAT patients. Methods: HCV RNA positive patients undergo an HCV evaluation via telemedicine with an onsite physician assistant and a hepatologist. All pretreatment labs and visits are performed onsite. Direct acting antivirals (DAA) are procured by a specialty pharmacy and are co-administered with methadone using directly observed therapy. Charges are submitted electronically to third party payers. Patient satisfaction is assessed by the telemedicine satisfaction questionnaire (TSQ). Results: Over 14-months, 54 HCV RNA-positive patients (63% male, 70% black/African-American, 29% Hispanic, 24% HIV-infected) received an HCV evaluation via telemedicine. All patients were well stabilized on methadone and all except 3 have HCV genotype 1. Fibrosis assessment in 44 patients who underwent Fibrosure revealed: mild (stage 0-1) in 14/44 (32%), moderate (stage 1-2) in 15/44 (34%), and severe (stage ≥ 3) in 15/44 (34%) patients. DAAs have begun in 28 and have been completed in 21 patients. HCV RNA is undetectable in all 21 patients at treatment completion (2 pts) or post-treatment weeks 4 (4 pts) or 12 (15 pts). Sixteen patients are undergoing evaluation or awaiting DAAs, and 10 remain untreated. To date, insurance mandated fibrosis or drug use restrictions have not prevented patients from ultimately receiving therapy. No auditory or visual communication issues were identified and selected TSQ results are illustrated (Table). Medication adherence has been excellent. Conclusion: Telemedicine-based HCV care is a feasible, reimbursable model for HCV treatment delivery in an OAT program with excellent initial patient acceptance that strengthens over time. Patient adherence and antiviral efficacy have been excellent. Telemedicine can virtually integrate specialty-based care into the OAT clinic.

Selected TSQ Results

Question	Option	First TSQ	Later TSQ
Q1: I prefer to see the doctor through a computer rather than to go to an off-site clinic.	Disagree	7.7	11.1
	Undecided	28.9	0.0
	Agree	38.5	55.6
	Strongly agree	25.0	33.3
Q5: I would recommend medical treatment via computer to a friend.	Undecided	21.1	0.0
	Agree	48.1	55.6
	Strongly agree	30.8	44.4
Q10: The computer consultation met my medical needs.	Undecided	2.0	0.0
	Agree	65.4	22.2
	Strongly agree	32.7	77.8

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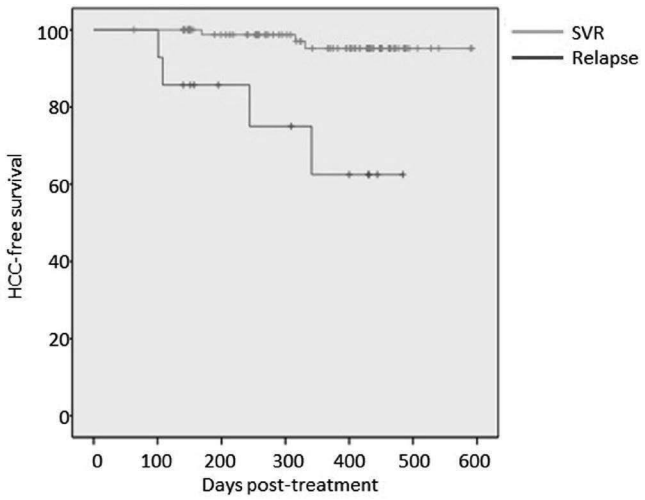
944
Successful hepatitis C treatment in advanced cirrhosis with DAA reduces HCC incidence

Andrea Affronti[1], Meena Ju[2], Janet Catt[2], William M. Rosenberg[1], Douglas Macdonald[1]; [1]Institute for Liver and Digestive Health, University College London, London, United Kingdom; [2]Hepatology, Royal Free Hospital, London, United Kingdom

Background: Directly-acting antivirals are safe and effective in advanced hepatitis C cirrhosis but the impact of SVR on morbidity and mortality in advanced disease is unknown. We examined 1-year outcomes and UKELD and ALBI score in 105 HCV patients with advanced cirrhosis treated in the UK HCV Early Access Program with either Sofosbuvir/Ledipasvir or Sofosbuvir/Daclatasvir. **Results**: 80% of patients had a Childpugh score >7 at baseline and the average follow-up time was 63 weeks post-treatment. SVR was achieved in 90 patients (86%) whilst 15 relapsed. SVR did not predict death at 1 year (6/105 overall) nor progression to transplantation (4/105 overall) but was associated with significant improvements in UKELD (49.3 pre- versus 47.5 1 year post-SVR, p=0.005) ALBI score (2.17 pre- versus 1.63 1 year post-SVR) which were not seen in patients who relapsed. Strikingly, the cumulative probability of HCC incidence 1 year post-treatment was signifcantly higher in the relapse group (33.3%) versus the SVR group (4.4%) (p=0.002, Fisher's Exact Test). Further, SVR was the only significant predictor of a post-treatment diagnosis of HCC independently of MELD, UKELD and ALBI on multivariate analysis. **Conclusion**: These data suggest rapid benefits from DAA treatment in advanced HCV cirrhosis. Reduction in transplantation rates may only become evident with longer follow-up but are strongly predicted by falls in UKELD in this group. It is unclear whether the lower incidence of HCC in the SVR group represents an inhibition of tumour initiation or reduced growth of radiologically undetectable lesions pre-treatment. In either scenario, improvement in liver function with SVR should widen treatment options at the time of HCC diagnosis.

Fig 1. Cumulative HCC survival from end of DAA treatment of HCV cirrhosis.



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945
Community-based, Individualized, Hepatitis C Therapy in Nepal

Holly A. Murphy[1], Sameer M. Dixit[2], Andrew Trotter[2], Apurva Rai[3], Ujjwal Karmacharya[1], Patricia Kramarz[1], Philippe A. Creac'h[4]; [1]Deutsche Gesellschaft fur Internationale Zusammenarbeit (GIZ) GmbH, Kathmandu, Nepal; [2]Center for Molecular Dynamics-Nepal, Kathmandu, Nepal; [3]SPARSHA-Nepal, Kathmandu, Nepal; [4]The Global Fund, Geneva, Switzerland

Purpose: With direct acting antiviral therapy (DAA) expansion to resource-limited settings there is an urgency to validate best practices for population-based screening and treatment of hepatitis C (HCV). The Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ) GmbH (German Development Cooperation) implemented a community-based screening and treatment model for mono-infected and HIV/HCV co-infected persons in Nepal where over 150,000 individuals are living with HCV genotype 3 (GT3: 60%) and genotype 1 (GT1: 40%) (Kinkel, H). **Methods:** We "pivoted" HCV screening and treatment within 3 existing opioid substitution treatment (OST) sites screening 600 patients with HCV viral load and GT, AST/Platelet Ratio Index (APRI) and fibroscan; enrolling 150 HCV mono-infected and 150 HIV-HCV co-infected for individualized treatment in an ongoing study. Patients with GT3 disease with optimal predictors (baseline HCV viral load <3,000,000 IU/ml, HIV-negative, no cirrhosis, age <50, body mass index < 30 kg/m2, favorable IL28B SNP) received 12-weeks sofosbuvir/peg-IFN-RBV (SIR) vs S/daclatasvir (SD) +/- R (cirrhotics). GT1-regimens included: S/ledipasvir (SL) or SD +/- R (cirrhotics). **Results:** We demonstrated optimal 4-week complete rapid virologic response (RVR_c) (94%) without significant toxicity among the first 105 patients treated (n=69 HIV+; 50% with tenofovir disoproxil fumarate (TDF)-containing antiretroviral regimens). Treatment regimens were: 50% SD and 35% SL (with R for 17 patients with compensated cirrhosis), 15% SIR. An APRI cut-off of 2 (compared to fibroscan 10) had 51% sensitivity, 95% specificity (89% negative predictive value) for advanced fibrosis. **Conclusions:** Both optimal outcomes and drug tolerability demonstrated the effectiveness of community, OST-based HCV screening and treatment in a resource-limited setting with simple individualized DAA-based therapy. Excellent early outcomes across GT 1 and 3 in this "real-life" setting encompassing HIV-infected and injecting drug users supports simple HCV diagnostic/treatment models implemented through OST sites. These results will be valuable for extending population-based HCV treatment to resource-limited settings. **Reference:** Kinkel H et al. Prevalence of Hepatitis B and C infection and assessment of HCV-genotype among people who inject drugs in three regions of Nepal (PloS One, 2015)

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946
Investigation of the prevalence and characteristics of RAVs in DAA-naive and –experienced European patients

Julia Dietz[1], Simone Susser[1], Johannes Vermehren[1], Kai-Henrik Peiffer[1], Georgios Grammatikos[1], Sandra Passmann[1], Dany Perner[1], Caterina Berkowski[1], Peter Ferenci[2], Maria Buti[3], Beat Mullhaupt[4], Bela Hunyady[5], Holger Hinrichsen[6], Stefan Mauss[7], Joerg Petersen[8], Peter Buggisch[8], Andreas Schober[9], Gisela Felten[10], Dietrich Hueppe[10], Andreas Zipf[11], Ulrich Spengler[12], Thomas von Hahn[13], Gaby Knecht[14], Thomas Lutz[14], Thomas Berg[15], Stefan Zeuzem[1], Christoph Sarrazin[1]; [1]Medizinische Klinik 1, Goethe-University Hospital, Frankfurt am Main, Germany; [2]Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria; [3]Hospital Universitario Valle Hebron and Ciberehd, Barcelona, Spain; [4]Swiss Hepato-Pancreato-Biliary Center and Department of Gastroenterology and Hepatology, University Hospital Zürich, Zürich, Switzerland; [5]Somogy County Kaposi Mór Teaching Hospital, Kaposvár, Hungary; [6]Practice of Gastroenterology, Kiel, Germany; [7]Practice of Gastroenterology, Düsseldorf, Germany; [8]Institute for Interdisciplinary Medicine IFI, Hamburg, Germany; [9]Practice of Hepatology, Göttingen, Germany; [10]Practice of Hepatology, Herne, Germany; [11]Practice of Gastroenterology, Mannheim, Germany; [12]Department of Internal Medicine, University of Bonn, Bonn, Germany; [13]Department of Gastroenterology, Hepatology and Endocrinology, Medizinische Hochschule Hannover, Hannnover, Germany; [14]Infektiologikum, Frankfurt am Main, Germany; [15]Department of Gastroenterology and Rheumatology, University Hospital Leipzig, Leipzig, Germany

Background: Treatment of chronic hepatitis C virus (HCV) infection with interferon-free direct acting antiviral (DAA)-based combination therapies leads to high sustained virologic response rates. However, resistance-associated variants (RAVs) are frequently associated with treatment failure. This study analyzed the prevalence and characteristics of RAVs in DAA-naïve and –experienced patients in a large European resistance database. **Methods:** We collected serum samples of 3990 European patients who were infected with HCV genotypes (GT) 1a (n=1632), 1b (n=1501), 1c/e (n=7), 2 (n=125), 3 (n=558), 4 (n=158), 5 (n=7) and 6 (n=2). RAVs which were shown to be associated with treatment failure or confer a >2 fold changed drug susceptibility were analyzed within NS3, NS5A and NS5B. Overall, 2214 patients were DAA-naïve while 538 individuals displayed a virologic failure to sofosbuvir (SOF)/RBV±PEG, SOF/simeprevir (SMV), SOF/daclatasvir (DCV), SOF/ledipasvir (LDV) or 3D (paritaprevir

(PTV)/ombitasvir (OMV)/dasabuvir (DSV)). **Results:** In DAA-naïve patients the rate of RAVs in GT1 was 20% in NS3, 16% in NS5A and 27% in NS5B. In individuals with GT2 and 4 the prevalence of pre-existing RAVs was variable due to the frequent natural occurrence of NS5A RAVs. For GT3 the dominant Y93H NS5A RAV was observed in only 2% at baseline. Failure to treatment with SOF/RBV±PEG led to a significant selection of L159F in GT1b and GT3 infected patients. However, currently it is unclear whether this variant has an impact on the efficacy of salvage therapies. After DCV, LDV or OMV containing regimens in GT1, NS5A RAVs occurred frequently (70-90%). In GT1a dependent on the NS5A inhibitor different pattern of L28, Q30, L31 and Y93 variants were observed while in GT1b Y93 variants were characteristic. Typical RAVs pattern with partial overlap have been observed after failure to NS3 protease inhibitors SMV (Q80K, R155K, D168E/N/V) and PTV (Y56H, R155K, D168E/N/V). In patients with GT3, Y93H increased from 2% in DAA-naïve to 73% in individuals with DCV/SOF failure while LDV/SOF selected no RAVs in GT3. Interestingly, we identified 10 patients with virologic failure to at least 2 subsequent DAA-based antiviral therapies. **Conclusions:** Virologic failure is associated with the appearance of characteristic RAVs in the DAA target regions of all genotypes. Typical RAVs pattern exist for the different DAAs, drug classes and HCV genotypes/subtypes which may enable selection of effective salvage regimens. However, few patients showed failure to at least 2 interferon-free DAA-based antiviral drug regimens.

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Beat Mullhaupt - Advisory Committees or Review Panels: Norgine; Consulting: MSD, Intercept; Grant/Research Support: Gillead; Speaking and Teaching: Bayer, BMS, MSD, Gilead

Bela Hunyady - Advisory Committees or Review Panels: AbbVie, Bristol-Myers Squibb, Accelsiors, Bohringer-Ingelhein, Fresenius-Kabi, Gilead Sciences, MSD/Merck, Roche Hungary; Board Membership: AbbVie, Bristol-Myers Squibb, Accelsiors, Bohringer-Ingelhein, Fresenius-Kabi, Gilead Sciences, MSD/Merck, Roche Hungary; Consulting: AbbVie, Bristol-Myers Squibb, Accelsiors, Bohringer-Ingelhein, Fresenius-Kabi, Gilead Sciences, MSD/Merck, Roche Hungary; Grant/Research Support: AbbVie, Bristol-Myers Squibb, Accelsiors, Bohringer-Ingelhein, Fresenius-Kabi, Gilead Sciences, MSD/Merck, Roche Hungary; Speaking and Teaching: AbbVie, Bristol-Myers Squibb, Accelsiors, Bohringer-Ingelhein, Fresenius-Kabi, Gilead Sciences, MSD/Merck, Roche Hungary

Holger Hinrichsen - Advisory Committees or Review Panels: BMS, Janssen, Gilead, Abbvie; Speaking and Teaching: MSD

Stefan Mauss - Advisory Committees or Review Panels: BMS, AbbVie, ViiV, Gilead; Speaking and Teaching: BMS, AbbVie, Janssen, Gilead, MSD

Joerg Petersen - Advisory Committees or Review Panels: Bristol-Myers Squibb, Gilead, Novartis, Merck, Bristol-Myers Squibb, Gilead, Novartis, Merck; Grant/Research Support: Roche, GlaxoSmithKline, Roche, GlaxoSmithKline; Speaking and Teaching: Abbott, Tibotec, Merck, Abbott, Tibotec, Merck

Peter Buggisch - Advisory Committees or Review Panels: Janssen, AbbVie, BMS; Speaking and Teaching: Falk, MSD, Gilead, Merz Pharma

Dietrich Hueppe - Advisory Committees or Review Panels: Roche, MSD, Novatis, Gilead, BMS, Janssen, AbbVie

Thomas von Hahn - Speaking and Teaching: Abbvie, Janssen

Thomas Lutz - Advisory Committees or Review Panels: Gilead, MSD, AbbVie, BMS, Janssen Cilag; Grant/Research Support: Gilead, GlaxoSmithKline, MSD, AbbVie, Janssen Cilag; Speaking and Teaching: ViiV, BMS

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Stefan Zeuzem - Consulting: Abbvie, Bristol-Myers Squibb Co., Gilead, Merck & Co., Janssen

Christoph Sarrazin - Advisory Committees or Review Panels: Bristol-Myers Squibb, Janssen, Merck/MSD, Gilead, Roche, Abbvie, Janssen, Merck/MSD; Consulting: Merck/MSD, Merck/MSD; Grant/Research Support: Abbott, Roche, Merck/MSD, Gilead, Janssen, Abbott, Roche, Merck/MSD, Qiagen; Speaking and Teaching: Gilead, Novartis, Abbott, Roche, Merck/MSD, Janssen, Siemens, Falk, Abbvie, Bristol-Myers Squibb, Achillion, Abbott, Roche, Merck/MSD, Janssen

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947

The Impact of Concomitant Acid Reducing Therapy (ART) on Sustained Virologic Response (SVR-12) Among Genotype 1 Infected Chronic Hepatitis C (CHC) Patients Treated with Ledipasvir/Sofosbuvir (LDV/SOF) With or Without Ribavirin

Patrick Spoutz[1], Monica Schaefer[1], Prashant K. Pandya[2,3], Mark Patterson[4]; [1]Pharmacy Benefits Management, VA Heartland Network (VISN-15), Kansas City, MO; [2]Gastroenterology, Kansas City VA Medical Center, Kansas City, MO; [3]Gastroenterology and Hepatology, Kansas University Medical Center, Kansas City, KS; [4]Pharmacy Practice and Administration, UMKC School of Pharmacy, Kansas City, MO

Background: Pharmacokinetic studies have shown that the solubility of the ledipasvir component of the LDV/SOF combination is decreased as intra-gastric pH increases and hence the prescribing information cautions against the concomitant use of acid reducing therapy (ART). A recent retrospective analysis of a real-world cohort revealed reduction in SVR-12 among patients receiving concomitant LDV/SOF therapy and ART. However this study was limited as to the dose, duration and frequency of ART use. Aim: Our aim was to evaluate the impact of ART on SVR among patients receiving LDV/SOF with or without ribavirin for genotype 1 CHC. Methods: This retrospective data analysis used data from the VA Corporate Data Warehouse, on a large cohort of Veterans Affairs patients in VISN-15, with manual chart reviews for data validation. Only patients who had completed antiviral therapy and had post treatment week 12 viral load available were included for this analysis. Descriptive statistics and a student's t-test were conducted for continuous variables and a chi-square was utilized for categorical variables. Multivariate logistic and linear regressions were used to assess SVR12 rates between groups, controlling for covariates of interest. Results: Of 766 patients undergoing LDV/SOF antiviral therapy for CHC, 219 patients were excluded due to missing baseline laboratory variable. SVR12 was achieved in 92.3% (144/156) of the patients receiving ART and 94.1% (368/391) in those without, p=0.435. Only 10 (6.4%) of 156 patients receiving ART during their treatment were prescribed doses higher than recommended by the package insert (all of whom achieved SVR-12). The group receiving ART were more likely to have advanced liver disease than the comparator group as defined by FIB4 score of 3.65 vs. 3.06, p=0.033., ICD-9 codes for cirrhosis 37.2% vs. 27.9%, p=0.033, and ICD-9 codes for decompensated liver disease, 12.8% vs. 6.6%, p=0.019. A subgroup analysis of patients (n=93) receiving at least 8 weeks of overlap between of PPIs/H2RAs and LDV/SOF had a reduced SVR12 of 87.1% (81/93), p=0.019 on univariate analysis. Controlling for differences in baseline and treatment characteristics, no statistical difference was found between the groups for SVR-12, OR: 0.593 (95% CI 0.254-1.384) and no statistical difference in SVR12 rates remained between the subgroup receiving 8 weeks or more of acid suppressive medications and the con-

trol group, OR: 0.618 (95% CI 0.257-1.484). Conclusions: The use of ART within the guideline provided by the prescribing information for LDV/SOF does not impact SVR-12 among patient chronically infected with genotype 1 HCV.

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948
Real-World Retreatment of Sofosbuvir/Ledipasvir (SOF/LDV) Failures In Hepatitis C Virus Genotype 1 infection

Brian Pearlman[1,2], Andrew Hinds[1], Michael Perrys[2]; [1]Center for Hepatitis C, Atlanta Medical Center, Atlanta, GA; [2]internal medicine, medical college of georgia, Augusta, GA

Background: Direct-acting antiviral (DAA) therapy virologic failure for hepatitis C virus occurs in fewer than 10% of cases. There is a paucity of data guiding therapeutic decisions for second-line DAA therapy utilized for first-line failures. The AASLD and the European Association for the Study of the Liver (EASL) have made recommendations that include switching to a different DAA class based on resistance testing/baseline resistance-associated failures (RAVs). The current study analyzed a real-world population of HCV therapy non-responders and the outcome of their second-line regimens chosen based upon genotypic resistance testing after first-line regimen failure (SOF/LDV). **Methods:** Data derived from two referral sites, one academic and one community-based teaching. All patients had GT-1 and 90% adherence to SOF/LDV to which they had virologic failure (cannot have stopped therapy from an adverse event or failed for other reasons). All patients had NS5a, NS3 and NS5b genotypic population-based sequencing analyses within 30 days of virologic failure. Patients were given second-line regimens based on RAV-directed provider choice. Population-based resistance testing utilized. **Results:** Results including RAVs detected at failure and salvage regimens (see TABLE). 62% had been treatment-naïve prior to failing SOF/LDV, and 38% were prior PEG/RBV virologic failures [no PI failures]. 54% were Black. 62% were cirrhotic and 31% bridging fibrosis (F3). 85% were GT1a. 69% had used PPIs at least once during therapy (all denied using twice-daily dosing). At SOF/LDV failure, 77% had detectable NS5a RAVs, 15% had detectable NS5a with NS3 RAVs. At interim analysis, 92% (n=12/13) had achieved SVR-12 (intention-to-treat), with one patient lost to follow-up after achieving end-of-treatment response (as treated efficacy, 100%). **Conclusions:** Salvage regimens chosen based on population-based resistance testing performed after LDV/SOF failures (GT-1) were successful with a 92% efficacy at interim analysis.

Patient Age (years)	Prior Therapy	SOF/LDV Duration (weeks)	Stage (Metavir)	PPI use	Virus Genotype	Post-Failure NS5a RAVS	Post-Failure NS3 RAVS	Salvage Therapy Used	Salvage Therapy Duration (weeks)	Outcome
56	N	8	3	Y	1a	Q30R	N	SS	12	SVR-12
69	N	8	2	Y	1a	Q30Y, Y93H	N	SS	12	SVR-12
46	N	8	3	N	1a	Q30R, L31M	N	SS	12	SVR-12
68	PEG/RBV	24	4	Y	1b	Y93H	N	SS	12	SVR-12
54	N	12	4	Y	1a	L31M	Q80K	3D+RBV	12	SVR-12
67	PEG/RBV	24	4	N	1a	N	N	3D+RBV	24	SVR-12
58	N	12	4	Y	1a	Y93H, L31V	N	SS	24	SVR-12
62	PEG/RBV	12+RBV	4	Y	1b	Y93H	N	SS	24	SVR-12
66	N	12	3	Y	1a	Y93N	Q80K, Y56H	3D+RBV	12	SVR-12
58	PEG/RBV	12	3	Y	1a	N	N	3D+RBV	12	SVR-12
42	N	12	4	Y	1a	M28T	N	SS	12	Lost to follow-up
70	PEG/RBV	12+RBV	4	N	1a	L31M, H58D	N	SS	24	SVR-12
56	N	12	4	Y	1a	N	N	SS	12	SVR-12

Abbreviations: SOF, sofosbuvir; LDV, ledipasvir; PPI, proton-pump inhibitor; RAV, resistant-associated variant; N, no or none; Y, yes; SS, simeprevir+sofosbuvir; SVR-12, sustained virologic response; PEG, peginterferon; RBV, ribavirin; 3D, ombitasvir, paritaprevir-ritonavir, dasabuvir.

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949
High Efficacy of Ledipasvir/Sofosbuvir Combination With or Without Ribavirin in the Treatment of Chronic Hepatitis C Genotype 4–infected Compensated and Decompensated Cirrhosis Patients: Real Life Data From Saudi Arabia

Faisal M. Sanai[1], Adnan AlZanbagi[2], Mohamed A. Babatin[3], Abdullah S. Alghamdi[3], Hamdan AlGhamdi[4], Kahlid Alswat[5], Abdulrahman A. Aljumah[4], Abduljaleel M. Al Alwan[4], Ayman Abdo[5], Waleed K. Al-Hamoudi[5], Abdullah Alaseeri[6], Yaser Dahlan[1], Ashwaq Alsahafi[3], Hammad S. Alothmani[3], Haziz Albiladi[3], Ibrahim H. Altraif[4]; [1]Gastroenterology Unit, Dept. of Medicine, King Abdulaziz Medical City, Jeddah, Saudi Arabia; [2]Gastroenterology Unit, Department of Medicine, King Abdallah Medical City, Makkah, Saudi Arabia; [3]Gastroenterology Unit, Dept. of Medicine, King Fahad Hospital, Jeddah, Saudi Arabia; [4]Hepatobiliary Sciences & Liver Transplantation, King Abdulaziz Medical City, Riyadh, Saudi Arabia; [5]Gastroenterology Unit, Dept. of Medicine, Liver Disease Research Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia; [6]Infectious Disease Dept, King Fahd Medical City, Riyadh, Saudi Arabia

Limited clinical trial data has shown high efficacy of co-formulated ledipasvir/sofosbuvir (LDV/SOF) in the treatment of patients infected with hepatitis C virus (HCV) genotype (GT)-4 infected patients, although the data is limited in cirrhotic patients. This study assessed real-world safety and efficacy of co-formulated ledipasvir/sofosbuvir (LDV/SOF) with or without ribavirin (RBV) in GT4 infected patients with compensated and decompensated cirrhosis. Methods: In this ongoing, observational cohort, we included HCV GT4 treatment naïve and -experienced patients with (n=40) and without (n=118) decompensated cirrhosis for a 12-24 week treatment regimen with LDV/SOF. RBV (55.7% of patients) was dosed by physician discretion between 600 – 1200 mg daily. Patients with prior DAA failure were excluded from the analysis. Compensated cirrhosis (F4, Metavir) was ascertained by Fibroscan. Decompensated cirrhosis (Child's - Pugh score ≥7) was ascertained by established clinical, biochemical and radiological criteria. The primary efficacy endpoint was SVR_{12} and drug discontinuation and/or occurrence of grade 3/4 adverse events. Results: A total of 158 adult patients with a mean age of 59.0±29.7 years, and HCV RNA 5.8±0.8 IU/mL were enrolled, 94 (59.5%) were female, and 73 (46.2%) were treatment-experienced to pegylated interferon ± RBV. All patients have completed ≥4 weeks on therapy, with HCV RNA undetectable (<15 IU/mL) in 84/158 (53.1%) patients, and all 129 had reached end-of-therapy with undetectable/below range HCV RNA. No virologic breakthroughs were observed in any of the patients. Overall 81/87 (93.1%) patients who had completed 12 weeks of post treatment follow up achieved SVR_{12} (compensated cirrhosis, n=57 [SVR_{12} 91.9%], decompensated cirrhosis, n=24 [SVR_{12} 96.0%]). Of the 6 patients who failed therapy (all relapsed), one had decompensated cirrhosis while the other 5 had compensated cirrhosis, including 5 who were treatment naïve and 1 being treatment experienced. Four of the 6 patients who failed therapy received concomitant RBV. Adverse events were grade 1 or 2 and there were no drug discontinuations related to side effects. Two patients with decompensated (1 Child's B and 1 Child's C) cirrhosis died from underlying disease progression while on therapy. Conclusion: The interim analysis of this cohort shows that LDV/SOF with or

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without RBV is highly effective with a favorable safety profile in HCV GT4 patients with underlying cirrhosis. SVR_{12} rates were high in all patient categories regardless of the presence of decompensated cirrhosis or prior treatment experience. Treatment was generally well-tolerated with few side effects.

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The following people have nothing to disclose: Adnan AlZanbagi, Mohamed A. Babatin, Abdullah S. Alghamdi, Hamdan AlGhamdi, Kahlid Alswat, Abdulrahman A. Aljumah, Abduljaleel M. Al Alwan, Ayman Abdo, Waleed K. Al-Hamoudi, Abdullah Alaseeri, Yaser Dahlan, Ashwaq Alsahafi, Hammad S. Alothmani, Haziz Albiladi

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Safety and efficacy of daclatasvir plus asunaprevir combination therapy in hemodialysis patients infected with hepatitis C virus genotype 1b

Shiho Miyase, Keiko Mizobe, Natsumi Tsukano, Hirohumi Iwashita, Shigetoshi Fujiyama; Department of Gastroenterology and Hepatology, Kumamoto Shinto General Hospital, Kumamoto, Japan

Background: The rate of hepatitis C virus (HCV) positivity is higher in patients on hemodialysis than in the general population. Several studies have reported that HCV infection is associated with poor prognosis in hemodialysis patients, with interferon-based therapy showing a lower sustained virologic response rate (SVR) in hemodialysis patients than in patients not requiring dialysis. The combination of orally administered daclatasvir (DCV) plus asunaprevir (ASV), which is effective in patients infected with HCV genotype 1b, is expected to be safe in chronic hemodialysis patients because both drugs are mainly metabolized by the liver. This study evaluated the safety and efficacy of DCV plus ASV combination therapy in hemodialysis patients infected with HCV. Methods: Nineteen hemodialysis patients infected with HCV genotype 1b infection were treated with DCV plus ASV combination therapy from December 2014 to January 2016. Sixteen patients (nine men and seven women) were followed for more than 12 weeks after the end of treatment. SVR after 12 weeks (SVR12) and discontinuation of therapy or dose reductions owing to adverse events were evaluated. Results: Of the 16 patients, 13 were treatment-naïve, and three had been treated with interferon-based regimens. Median patient age was 65 years (range, 51–81 years), with 11 patients (68.7%) older than age 60 years. Seven patients (43.8%) had compensated liver cirrhosis. Despite two patients having resistance-associated variants (RAVs) in the HCV NS3 region at baseline, all 16 patients (100%) achieved SVR12. One patient with cirrhosis discontinued treatment at 6 weeks owing to onset of acute pneumonia, and another patient required ASV dose reduction owing to a mild hepatic disorder. Both patients recovered after discontinuation or dose reduction, later achieving SVR12. Conclusion: DCV plus ASV combination therapy in hemodialysis patients infected with HCV has high antiviral activity and is tolerated, even in older patients and patients with liver cirrhosis and RAVs.

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Real-World Effectiveness and Safety of DAA Combination Therapies in Elderly Patients > 70 Years of Age in the German Hepatitis C-Registry (DHC-R)

Tania M. Welzel[1], Eckart Schott[2], Albrecht Stoehr[3], Stefan Mauss[4], Klaus H. Boeker[5], Tim Zimmermann[6], Karl-Georg Simon[7], Holger Hinrichsen[8], Thomas Berg[9], Heike Pfeiffer-Vornkahl[10], Stefan Zeuzem[1], Dietrich Hueppe[11], Heiner Wedemeyer[12], German Hepatitis C-Registry[13]; [1]Department of Medicine I, JW Goethe University Hospital, Frankfurt, Germany; [2]Charité Campus Virchow-Klinikum (CVK), Berlin, Germany; [3]ifi-institute for interdisciplinary medicine, Hamburg, Germany; [4]Center for HIV and Hepatogastroenterology, Duesseldorf, Germany; [5]Center of Hepatology, Hannover, Germany; [6]I. Dept. of Medicine, University of Mainz, Mainz, Germany; [7]MVZ Dr.Eisenbach Dr.Simon Dr.Schwarz GbR, Leverkusen, Germany; [8]Leberstudienzentrum Kiel GbR, Kiel, Germany; [9]Department of Hepatology, University Hospital Leipzig, Leipzig, Germany; [10]e.factum GmbH, Butzbach, Germany; [11]Center of Gastroenterology, Herne, Germany; [12]Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [13]Leberstiftungs-GmbH Deutschland, Hannover, Germany

Introduction: Few pivotal trials reported outcomes of novel direct-acting antiviral (DAA) therapies in elderly patients. We investigated effectiveness and safety of all-oral DAA regimen in patients >70 yrs. of age vs. younger patients (≤70 yrs.) in the DHC-R. **Methods:** The DHC-R (Deutsches Hepatitis C-Register) is a multicenter real-world cohort including approximately 9,300 patients. Patients are treated at the discretion of the physician. Data are collected by a web-based system. Data quality is analyzed by plausibility checks and on site monitoring. The analysis includes patients who initiated treatment between 02/01/2014 and 05/15/2015 (N=5,228) and who were observed for at least 40 weeks after initiation of antiviral treatment. Primary effectiveness endpoint was SVR12. **Results:** Of 5,228 patients who initiated treatment, 506 (9.7%) were > 70 yrs. of age (Table 1). Intent-to-treat (IIT) and per-protocol (PP) SVR12 was 91.7% (3,111/3,392) and 95.9% (3,100/3,231) in patients ≤70 yrs., and 91.6% (340/371) and 95.8% (338/353) in patients >70 yrs., respectively. In cirrhotic patients ≤70 yrs., ITT and PP SVR12 was 88.7% (885/998) and 92.3% (880/953), compared to 89.7% (157/175) and 94.0% (157/167) in elderly patients >70 yrs. of age. Frequency of adverse events (AEs) was 54.3% (275/506) and 52.7% (2488/4722) in patients >70 yrs. and ≤70 yrs. of age, respectively. Proportion of serious AEs was higher in patients >70 yrs (6.1%; 31/506), compared to patients ≤70 yrs. (3.2%; 153/4722). Overall, 18 of 5,228 patients died, of whom 4 were >70 years of age. **Conclusions:** Despite a higher proportion of SAEs, all-oral DAA therapies were generally safe and effective in elderly patients >70 yrs. Overall treatment outcomes were similar to those observed in younger patients.

Table 1: Characteristics of N=5,228 patients who initiated DAA therapy

Characteristics	Age ≤70 years (N=4,722)	Age >70 years (N=506)
Female (n, %)	1,863 (39.5%)	329 (65.0%)
Prior treatment (n, %)	2,454 (52.0%)	267 (52.8%)
Cirrhosis (n, %)	1,404 (29.7%)	233 (46.0%)
Genotype		
GT1a	1,690 (35.8%)	59 (11.7%)
GT1b	1,827 (38.7%)	393 (77.7%)
GT1 – other subtype	24 (0.5%)	2 (0.4%)
GT1 – subtype unknown	177 (3.7%)	19 (3.8%)
GT2	203 (4.3%)	22 (4.3%)
GT3	561 (11.9%)	4 (0.8%)
GT4	234 (5.0%)	6 (1.2%)
GT5/6	6 (0.2%)	1 (0.2%)
Treatments		
SOF+RBV	478 (10.1%)	29 (5.7%)
SIM+SOF±RBV	290 (6.1%)	64 (12.7%)
DCV+SOF±RBV	775 (16.4%)	58 (11.5%)
DCV+SIM±SOF	2 (0.04)	1 (0.2%)
LDV+SOF±RBV	2,566 (54.3%)	270 (53.4%)
OBV/PTV/r±DSV±RBV	611 (12.9%)	84(16.6%)

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Tania M. Welzel - Advisory Committees or Review Panels: Novartis, Janssen, Gilead, Abbvie, Boehringer-Ingelheim+, BMS

Eckart Schott - Advisory Committees or Review Panels: Gilead, Roche, Bayer, BMS, Abbvie, Janssen, MSD; Speaking and Teaching: Gilead, Novartis, Roche, MSD, Bayer, Falk, BMS, Janssen, Abbvie

Albrecht Stoehr - Advisory Committees or Review Panels: Abbvie, VIIV; Board Membership: MSD; Speaking and Teaching: Janssen, MSD, Gilead, Abbvie, BMS, VIIV

Stefan Mauss - Advisory Committees or Review Panels: BMS, AbbVie, ViiV, Gilead; Speaking and Teaching: BMS, AbbVie, Janssen, Gilead, MSD

Klaus H. Boeker - Consulting: Janssen; Speaking and Teaching: MSD, Roche, Gilead, BMS, Falk Foundation, Novartis, AbbVie

Tim Zimmermann - Advisory Committees or Review Panels: Abbvie; Speaking and Teaching: BMS

Karl-Georg Simon - Advisory Committees or Review Panels: AbbVie, BMS, JANSSEN, MSD; Speaking and Teaching: AbbVie, BMS, FALK, GILEAD, JANSSEN, NORGINE, MERZ, MSD

Holger Hinrichsen - Advisory Committees or Review Panels: BMS, Janssen, Gilead, Abbvie; Speaking and Teaching: MSD

Thomas Berg - Advisory Committees or Review Panels: Gilead, BMS, Roche, Tibotec, Vertex, Jannsen, Novartis, Abbott, Merck, Abbvie; Consulting: Gilead, BMS, Roche, Tibotec; Vertex, Janssen; Grant/Research Support: Gilead, BMS, Roche, Tibotec; Vertex, Jannssen, Merck/MSD, Boehringer Ingelheim, Novartis, Abbvie; Speaking and Teaching: Gilead, BMS, Roche, Tibotec; Vertex, Janssen, Merck/MSD, Novartis, Merck, Bayer, Abbvie

Heike Pfeiffer-Vornkahl - Employment: efactum GmbH

Stefan Zeuzem - Consulting: Abbvie, Bristol-Myers Squibb Co., Gilead, Merck & Co., Janssen

Dietrich Hueppe - Advisory Committees or Review Panels: Roche, MSD, Novatis, Gilead, BMS, Janssen, AbbVie

Heiner Wedemeyer - Advisory Committees or Review Panels: Transgene, MSD, Roche, Gilead, Abbott, BMS, Falk, Abbvie, Novartis, GSK, Roche Diagnostics, Eiger; Consulting: MyrGmbH; Grant/Research Support: MSD, Novartis, Gilead, Roche, Abbott, Roche Diagnostics; Speaking and Teaching: BMS, MSD, Novartis, ITF, Abbvie, Gilead

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Frequency and predictive value of detectable HCV RNA at the end of treatment with ledipasvir/sofosbuvir ± ribavirin in a large real world cohort: Results from the German Hepatitis C-Registry (DHC-R)

Benjamin Maasoumy[1], Stefan Mauss[2], Peter Buggisch[3], Klaus H. Boeker[4], Rainer Günther[5], Michael P. Manns[1], Heike Pfeiffer-Vornkahl[6], Hartwig H. Klinker[7], Eckart Schott[8], Christoph Sarrazin[9], Heiner Wedemeyer[1], Dietrich Hueppe[10], Johannes Vermehren[9], German Hepatitis C-Registry[11]; [1]Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [2]Center for HIV and Hepatogastroenterology, Duesseldorf, Germany; [3]ifi-institute for interdisciplinary medicine, Hamburg, Germany; [4]Center of Hepatology, Hannover, Germany; [5]Universitätsklinikum Schleswig-Holstein (UKSH), Campus Kiel, Kiel, Germany; [6]e.factum GmbH, Butzbach, Germany; [7]Dept. of Internal Medicine II, University of Würzburg, Würzburg, Germany; [8]Charité Campus Virchow-Klinikum (CVK), Berlin, Germany; [9]J. W. Goethe-University Hospital, Frankfurt, Germany; [10]Center of Gastroenterology, Herne, Germany; [11]Leberstiftungs-GmbH Deutschland, Hannover, Germany

Introduction: AASLD/IDSA guidelines for hepatitis C virus (HCV) infection state that testing for HCV RNA can be considered at the end of antiviral treatment (EOT) with interferon-free regimens. However, it remains rather unclear how the respective results have to be interpreted. The aim of this study was to analyze the frequency and predictive value of detectable HCV RNA results at the EOT with ledipasvir(SOF)/sofosbuvir(SOF)±ribavrin(RBV) in a large real world cohort of HCV genotype 1 infected patients. **Methods:** The DHC-R (Deutsches Hepatitis C-Register, German Hepatitis C-Registry) is a national multicenter real-world cohort including approx. 9,300 patients. Patients are treated at the discretion of a physician. Data are collected by a web-based system. Data quality is analyzed by plausibility checks and on site monitoring. This data analysis is based on a subset of patients fulfilling the following inclusion criteria: a) chronic HCV genotype 1 infection; b) completion of a full course of antiviral treatment with LDV/SOF±RBV of either 8, 12 or 24 weeks; c) available SVR12 data; d) HCV RNA measurement with either the Roche COBAS AmpliPrep/COBAS TaqMan (CAP/CTM) or the Abbott RealTime HCV assay (ART). **Results:** A number of 471 patients fulfilled the inclusion criteria and had a valid HCV RNA result at the respective EOT with LDV/SOF±RBV. Overall, SVR rate among these patients was 99% (n=464/471), 97% (n=66/68) in patients treated with and 99% (n=398/403) among those treated without RBV. HCV RNA was detectable in 34 patients (7%) at the EOT. Almost half of these patients (44%; n=15) even had a viral load above the limit of quantification. However, only two patients with a detectable EOT result failed to achieve SVR12 (SVR rate 94%; n=32/34). One of these patients had a detectable/not quantifiable HCV RNA result, the other a quantifiable viral load at the EOT. Detectable HCV RNA at the EOT was far more frequent if the ART was used. While the CAP/CTM detected HCV RNA in only 2% (n=9/384) of patients, HCV RNA was detectable in 29% of patients (n=25/87) in whom the ART was used at the EOT. **Conclusions:** Almost one out of three HCV genotype 1 patients has a detectable or even a quantifiable HCV RNA result at the end of LDV/SOF±RBV therapy if the ART is used. However, SVR rates remain very high in these patients. Therefore, treatment should not be extended.

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Stefan Mauss - Advisory Committees or Review Panels: BMS, AbbVie, ViiV, Gilead; Speaking and Teaching: BMS, AbbVie, Janssen, Gilead, MSD

Peter Buggisch - Advisory Committees or Review Panels: Janssen, AbbVie, BMS; Speaking and Teaching: Falk, MSD, Gilead, Merz Pharma

Klaus H. Boeker - Consulting: Janssen; Speaking and Teaching: MSD, Roche, Gilead, BMS, Falk Foundation, Novartis, AbbVie

Rainer Günther - Speaking and Teaching: Roche Pharma AG, Gilead, AbbVie

Michael P. Manns - Consulting: Roche, BMS, Gilead, Boehringer Ingelheim, Novartis, Enyo Pharma, Eiger, GSK, Merck/MSD, Janssen, Medgenics, Biotest, AbbVie; Grant/Research Support: Merck/MSD, Roche, Gilead, Novartis, Boehringer Ingelheim, BMS, AbbVie, Janssen; Speaking and Teaching: Merck/MSD, Roche, BMS, Gilead, Janssen, GSK, Novartis, AbbVie

Heike Pfeiffer-Vornkahl - Employment: efactum GmbH

Hartwig H. Klinker - Advisory Committees or Review Panels: AbbVie, BMS, Gilead, Hexal, Janssen, MSD; Grant/Research Support: AbbVie, BMS, Gilead, Janssen, MSD, Arrowhead, Novartis; Speaking and Teaching: AbbVIe, BMS, Gilead, Janssen, MSD

Eckart Schott - Advisory Committees or Review Panels: Gilead, Roche, Bayer, BMS, Abbvie, Janssen, MSD; Speaking and Teaching: Gilead, Novartis, Roche, MSD, Bayer, Falk, BMS, Janssen, Abbvie

Christoph Sarrazin - Advisory Committees or Review Panels: Bristol-Myers Squibb, Janssen, Merck/MSD, Gilead, Roche, Abbvie, Janssen, Merck/MSD; Consulting: Merck/MSD, Merck/MSD; Grant/Research Support: Abbott, Roche, Merck/MSD, Gilead, Janssen, Abbott, Roche, Merck/MSD, Qiagen; Speaking and Teaching: Gilead, Novartis, Abbott, Roche, Merck/MSD, Janssen, Siemens, Falk, Abbvie, Bristol-Myers Squibb, Achillion, Abbott, Roche, Merck/MSD, Janssen

Heiner Wedemeyer - Advisory Committees or Review Panels: Transgene, MSD, Roche, Gilead, Abbott, BMS, Falk, Abbvie, Novartis, GSK, Roche Diagnostics, Eiger; Consulting: MyrGmbH; Grant/Research Support: MSD, Novartis, Gilead, Roche, Abbott, Roche Diagnostics; Speaking and Teaching: BMS, MSD, Novartis, ITF, Abbvie, Gilead

Dietrich Hueppe - Advisory Committees or Review Panels: Roche, MSD, Novatis, Gilead, BMS, Janssen, AbbVie

Johannes Vermehren - Advisory Committees or Review Panels: AbbVie, Abbott; Speaking and Teaching: AbbVie, Bristol-Myers Squibb, Gilead, Medtronic

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The effect of interferon-free DAAs combination therapy on innate immune responses (NK cell activity and frequency of CD56^{dim} and CD56^{bright} NK cell subset in peripheral blood) in chronic hepatitis C patients

Ikuo Nakamura, Yoshihiro Furuichi, Katsutoshi Sugimoto, Yoshiyuki Kobayashi; Department of Gastoenterology and Hepatology, Tokyo Medical University, Tokyo, Japan

Aim : Hepatitis C virus (HCV) is one of the most important agents of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. So far, the interferon-free DAAs combination therapy is one of the most effective treatment for chronic hepatitis C patients. The effect of these therapies might be involved to the immune responses, that are composed of innate immune responses and adaptive immune responses. The aim of this study was to examine the effect of DAAs combination therapy on innate immune responses (NK cell activity and frequency of CD56 ^{dim} and CD56 ^{bright} NK cell subset in peripheral blood) in chronic hepatitis C patients. Patients and Methods : In twenty-three chronic hepatitis C patients with HCV of genotype 1b , the combination therapy of DAAs was performed (Asunaprevir + Daclatasvir : fifteen, HARVONI® (Sofosbuvir + Ledipasvir) : five, VIEKIRAX® (Ombitasvir + Paritaprevir / ritonavir) : three). Ten patients were male and thirteen patients were female. Just before and at the end of the therapy (EOT), NK cell activity and the frequency of CD56^{dim} NK cell and CD56^{bright} NK cell in peripheral blood were estimated by Cr release assay (E/T=20) and three-color flowcytometry. Statistical analysis was performer by one-way ANOVA. This study was approved by the ethics committee of the institute and written informed consent was obtained from each patient. All procedures in this study were conducted in accordance with Declaration of Helsinki. Results : The analysis by ANOVA showed that NK cell activity significantly improved at EOT compared with just before therapy (p □ 0.001). It also showed that frequency of CD56 ^{dim} NK cell in peripheral blood was significantly increased at EOT compared with just before therapy (p □ 0.05). Conclusion : The combination therapy of DAAs in chronic hepatitis C patients has improved NK cell activity by increasing the frequency of CD56^{dim} NK cell in peripheral blood. It was revealed that reduction of HCV load in chronic hepatitis C patients could restore NK cell activity that was reduced by HCV. Therefore, the results of our study implied that DAAs combination therapy might be able to reduce the risk of HCC in chronic hepatitis C patients by restoring the activity of innate immune responses.

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The following people have nothing to disclose: Ikuo Nakamura, Yoshihiro Furuichi, Katsutoshi Sugimoto, Yoshiyuki Kobayashi

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Improved Hepatic Profile in Hepatitis C Virus (HCV) Genotype (GT) 4-Infected Egyptian Patients with Compensated Cirrhosis Receiving Ombitasvir/Paritaprevir/Ritonavir with Ribavirin (AGATE-II)

Imam Waked[1], Gamal E. Esmat[2], Rabab F. Omar[2], Naglaa A. Allam[1], Mohamed Hassany[3], Mohamed Mohey[2], Ayman Yosry[2], Gamal Shiha[4,5], Reham Soliman[5], Marisol Martinez[6], Roula B. Qaqish[6], Coleen Hall[6], Niloufar Mobashery[6]; [1]National Liver Institute, Menoufiya, Egypt; [2]Cairo University, Cairo, Egypt; [3]National Hepatology & Tropical Medicine Research Institute, Cairo, Egypt; [4]Mansoura University, Mansoura, Egypt; [5]Egyptian Liver Research Institute and Hospital (ELRIAH), Mansoura, Egypt; [6]AbbVie Inc., North Chicago, IL

Background: In Egypt, HCV GT4 infection accounts for over 90% of all HCV infections. AGATE-II is a large Egyptian phase 3 trial that enrolled treatment-naive or previously treated (pegIFN + RBV) patients infected with HCV GT4, without cirrhosis (Arm A) or with compensated cirrhosis (Arms B/C). Patients received the 2 direct-acting antiviral agent regimen of ombitasvir (OBV), an NS5A inhibitor, paritaprevir (PTV), an NS3/4A protease inhibitor, and ritonavir (r), a pharmacokinetic enhancer, plus ribavirin (RBV). **Methods:** All patients received OBV/PTV/r (25/150/100 mg) once daily plus weight-based RBV. Overall, 100 patients without cirrhosis were allocated to 12-week treatment (Arm A) and 60 patients with compensated cirrhosis were randomized 1:1 to 12-week treatment (Arm B) or 24-week treatment (Arm C). All patients were followed for 48 weeks post-treatment. The primary objectives of AGATE-II were to assess safety and sustained virologic response 12 weeks post treatment (SVR12). Here, we assess changes in liver biomarkers in cirrhotic patients between baseline (BL) and post-treatment week (PTW) 24 in Arm B and PTW12 in Arm C. **Results:** Among patients with compensated cirrhosis, SVR12 rates were 97% (30/31) in the 12-week arm in both the ITT and mITT populations (excluding non-virologic failures), while in the 24-week arm, SVR12 rates were 93% (27/29) and 96% (27/28) in the ITT and mITT populations, respectively. Adverse events were mainly mild/moderate in severity with no patient discontinuing due to an adverse event. Most liver biomarkers, including those of fibrosis and liver function, showed improvements from BL to PTW24 (Arm B) and PTW12 (Arm C) (Table). Final data on liver biomarker changes at PTW48 will be presented. **Conclusions:** In HCV GT4-infected Egyptian patients with compensated cirrhosis, treatment with OBV/PTV/r + RBV for 12 or 24 weeks was well tolerated and resulted in high SVR rates at PTW12 and in an improvement from BL in most liver

biomarkers to PTW 12 and 24. Further follow-up of patients through PTW48 will determine the magnitude and durability of these changes.

Parameter	Arm B: OBV/PTV/r + RBV for 12 weeks				Arm C: OBV/PTV/r + RBV for 24 weeks			
	N	BL Mean	PTW24 Mean	Mean Δ from BL to PTW24	N	BL Mean	PTW12 Mean	Mean Δ from BL to PTW12
INR	29	1.115	1.158	0.043	28	1.149	1.218	0.069
Platelet count (x109/L)	30	156.7	166.0	9.4	28	139.0	139.2	0.2
Albumin (g/dL)	30	4.16	4.47	0.31	28	4.05	4.24	0.19
ALT (U/L)	30	80.5	24.0	-56.5	28	75.6	24.8	-50.8
AST (U/L)	30	61.2	27.2	-34.0	28	65.6	28.4	-37.3
Total bilirubin (mg/dL)	30	0.85	0.63	-0.22	28	0.96	0.79	-0.17
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; INR = International Normalized Ratio; PTW = post-treatment week.								

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Marisol Martinez - Employment: Abbvie; Stock Shareholder: Abbvie

Roula B. Qaqish - Stock Shareholder: AbbVie

Coleen Hall - Employment: AbbVie; Stock Shareholder: AbbVie

Niloufar Mobashery - Employment: Abbvie; Stock Shareholder: abbvie

The following people have nothing to disclose: Rabab F. Omar, Naglaa A. Allam, Mohamed Mohey, Ayman Yosry, Gamal Shiha, Reham Soliman

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Hepatitis C could now be cured for under US $100 per person: analysis of mass generic production of Direct Acting Antivirals

Andrew M. Hill[2], Dzintars Gotham[1], Melissa Barber[3], Anton Pozniak[2], Joseph M. Fortunak[4]; [1]Faculty of Medicine, Imperial College London, London, United Kingdom; [2]St Stephens AIDS Trust, Chelsea and Westminster Hospital, London, United Kingdom; [3]Centre of Development Studies, Cambridge University, Cambridge, United Kingdom; [4]Chemistry and Pharmaceutical Sciences, Howard University, Washington, DC

Background: Although novel direct-acting antivirals (DAAs) achieve high sustained virological response (SVR) rates of >90% in chronic hepatitis C (HCV), global access to DAAs is limited, due to high prices. Reduced prices offered through voluntary licensing are available in countries that represent only 50% of the worldwide epidemic. The per-kilogram price of active pharmaceutical ingredient (API) and steady, high demand volumes are key determinants of the total production cost of any medicine. The aim of the study was to calculate currently feasible prices for DAAs, assuming large volume of demand and competitive manufacture. **Methods:** Data on per-kilogram prices and volumes of API exported from India were analysed from an online database (www.infodriveindia.com) for Jan-Jun 2016. Linear regression models were calculated, weighted by shipment size. Given the lack of export data on velpatasvir, the API cost was calculated by analysis of chemical synthesis and costs of raw materials. Costs of per-pill API requirements were combined with estimated costs for formulation and excipients ($0.04/ pill), packaging ($0.35/month), and a profit margin of 50% was added. **Results:** Export volumes from India in Jan-Jun 2016 were, sofosbuvir: 10,200 kg, (equivalent to 303,000 12-week treatment courses), daclatasvir: 5,443 kg (1,080,000 courses), ledipasvir: 240 kg (32,000 courses). API prices decreased throughout the time frame. Mean API prices on June 1st 2016 were: sofosbuvir $1,094/kg, daclatasvir $998/kg, ledipasvir $2,441/kg. API cost for velpatasvir was estimated at $8,900-11,700/kg. US price was up to 1,355 times higher than the target price for sofosbuvir, 4500 times for daclatasvir, and 984 times higher for sofosbuvir+ledipasvir. **Conclusions:** HCV DAAs production costs are falling rapidly. 12-week treatments of sofosbuvir can be manufactured for an estimated $62, daclatasvir $14, sofosbuvir+ledipasvir $96, velpatasvir $119-154. These target prices all include a 50% profit margin for generic suppliers. These prices show the potential for mass treatment of Hepatitis C in access programs similar to those used for people with HIV/AIDS.

Calculated target prices and current prices for 12-week DAA treatment courses

Drug	June 2016 API cost/kg	Target price per 12-week treatment	Current global lowest price per 12-week treatment	Current US price per 12-week treatment
Sofosbuvir (SOF)	$1,094	$62	$324	$49,860-84,000
Daclatasvir	$998	$14	$153	$50,653-63,000
Ledipasvir (LDV)	$2,441	$34	unknown	unknown
SOF+LDV	N/A	$96	$507	$56,700-94,500
Velpatasvir	$8,900-11,700	$119-154	unknown	unknown

all prices USD

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The following people have nothing to disclose: Andrew M. Hill, Dzintars Gotham, Melissa Barber, Joseph M. Fortunak

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High Rates of Medical and Psychiatric Comorbidities in HIV/HCV Coinfected Patients Treated With Sofosbuvir-Containing Regimens in Registrational Clinical Trials.

Mark S. Sulkowski[2], Curtis Cooper[1], Jean-Michel Molina[3], Susanna Naggie[4], K.C Huang[5], Anu O. Osinusi[5], Luisa M. Stamm[5], Benedetta Massetto[5], John McNally[5], Diana M. Brainard[5], John G. McHutchison[5], David L. Wyles[8], Jürgen K. Rockstroh[7], Douglas T. Dieterich[6]; [1]University of Ottawa, Ottawa, ON, Canada; [2]Johns Hopkins Hospital, Baltimore, MD; [3]Hopital Saint-Louis, AP-HP and University of Paris Sorbonne Cité, Paris, France; [4]Duke University Medical Center, Durham, NC; [5]Gilead Sciences Inc, Foster City, CA; [6]Mount Sinai School of Medicine, New York, NY; [7]University of Bonn, Bonn, Germany; [8]UCSD School of Medicine, San Diego, CA

BACKGROUND: HIV/HCV coinfected patients have a high prevalence of medical and psychiatric diseases which may limit access to HCV therapy. Recent trials of DAA therapy in HIV/HCV coinfected patients have demonstrated high SVR rates similar to that observed in HCV monoinfection; however the generalizability of these results have been questioned due to the clinical trial setting and the exclusion of certain antiretrovirals. The goal of this analysis was to describe the prevalence of medical and psychiatric disease and DDI interactions in HIV/HCV coinfected subjects enrolled in Gilead trials. **METHODS:** An integrated analysis of data from HIV/HCV coinfected patients enrolled in 4 phase 3 registrational trials (PHOTON-1 and -2 [sofosbuvir [SOF] + ribavirin [RBV] for 12 or 24 weeks], ION-4 [ledipasvir (LDV)/SOF ± RBV for 12 weeks] and ASTRAL-5 [SOF/velpatasvir (VEL) for 12 weeks] was performed. Patients with severe medical or psychiatric conditions were excluded from these trials. An assessment of demographics, medical history, concomitant medications, safety and efficacy will be presented. **RESULTS:** A total of 940 patients were included in this analysis; a majority (71%) were enrolled in the United States. Across all studies, there was a high preva-

lence of hypertension (28%), gastro-esophageal reflux disease (GERD) 16% and hyperlipidemia (14%). A high proportion had psychiatric comorbidities including depression (37%) and anxiety (20%). Prior or ongoing substance abuse was reported in 17% of patients. These rates were similar to that described in a recent analysis of over 18,000 HIV/HCV coinfected patients in the US (Meyer N et al, ICAAC 2015). In the PHOTON-2 study which was conducted in Europe, a smaller proportion reported both medical and psychiatric comorbidities. Overall SVR rates ranged from 79% to 96% based on the treatment regimen, similar to that observed in HCV monoinfected patients. **CONCLUSIONS:** The use of interferon-free DAA regimens has resulted in the ability to successfully treat HIV/HCV coinfected patients with complex comorbidities in clinical trials which can be generalizable to real world practice.

Study Regimen N (%)	PHOTON-1 SOF+RBV 12 or 24 weeks N=224	PHOTON-2 SOF+RBV 12 or 24 weeks N=275	ION-4 LDV/SOF 12 weeks N=335	ASTRAL-5 SOF/VEL 12 weeks N=106	Total N=941
Hypertension	67 (30)	25 (9)	130 (39)	44 (41)	266 (28)
Diabetes	15 (7)	5 (2)	33 (10)	10 (9)	63 (7)
Hyperlipidemia	40 (18)	14 (5)	54 (16)	28 (26)	136 (14)
GERD	43 (19)	19 (7)	72 (21)	21 (20)	155 (16)
Pulmonary disease	23 (10)	31 (11)	43 (13)	12 (11)	109 (12)
Substance Abuse (prior or current)	56 (25)	41 (15)	44 (13)	36 (34)	177 (19)
Depressive disorders	117 (52)	61 (22)	125 (37)	49 (46)	352 (37)
Bipolar Disease	16 (7)	1 (<1)	18 (5)	8 (7)	43 (5)
Anxiety disorders	49 (22)	19 (7)	73 (22)	36 (34)	177 (19)
SVR rates	79%	86%	96%	95%	N/A

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Mark S. Sulkowski - Advisory Committees or Review Panels: Merck, AbbVie, Janssen, Gilead, Trek, Cocrystal; Grant/Research Support: Merck, AbbVie, Janssen, Gilead

Curtis Cooper - Advisory Committees or Review Panels: Gilead, Abbvie, MERCK; Grant/Research Support: MERCK, Gilead, Abbvie; Speaking and Teaching: MERCK, Abbvie, Gilead

Jean-Michel Molina - Board Membership: Gilead, BMS, Janssen, merck, Abbott, boehringer; Grant/Research Support: merck; Speaking and Teaching: merck, gilead, BMS

Susanna Naggie - Advisory Committees or Review Panels: Merck; Grant/Research Support: Tacere, Gilead, AbbVie, BMS, Jenssen, Merck

Anu O. Osinusi - Employment: Gilead Sciences Inc; Stock Shareholder: Gilead Sciences Inc

Luisa M. Stamm - Employment: Gilead Sciences

Benedetta Massetto - Employment: Gilead Sciences, Inc.; Stock Shareholder: Gilead Sciences, Inc

John McNally - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

Diana M. Brainard - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

John G. McHutchison - Employment: gilead; Stock Shareholder: gilead

David L. Wyles - Advisory Committees or Review Panels: Bristol Myers Squibb, Gilead, Merck, AbbVie; Grant/Research Support: Gilead, Merck, Bristol Myers Squibb, AbbVie, Tacere

Jürgen K. Rockstroh - Advisory Committees or Review Panels: Abbvie, Cipla, BMS, Merck, Roche, Tibotec, Abbvie, Bionor, Tobira, ViiV, Abbott, Gilead, Janssen; Consulting: Novartis; Grant/Research Support: Gilead, Merck; Speaking and Teaching: BMS, Merck, Siemens, Tibotec, Gilead, Janssen, ViiV

Douglas T. Dieterich - Advisory Committees or Review Panels: Gilead, BMS, Abbvie, Janssen, Merck, Achillion

The following people have nothing to disclose: K.C Huang

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Excellent SVR12 rates with Viekira Pak in a real-world cohort of HCV Genotype 1 patients predominantly with cirrhosis – the Australian *REV1TAL* Study

John Lubel[1,2], Joanne Mitchell[3], Stephen Pianko[4], Alex J. Thompson[5,6], David M. Iser[5], Alessia Gazzola[3], Sarah Chivers[2], Gauri Mishra[4], John Gough[5], Simone I. Strasser[7], Gregory Dore[8], Katherine A. Stuart[9], Jacob George[10,11], Edmund Tse[12], Amany Zekry[13], Miriam Levy[14], Gerry C. MacQuillan[15], Vince Fragomeli[16], Paul Gow[17], Brenda Morales[17], Joe Sasadeusz[18], Saroj Nazareth[19], Steven J. Bollipo[20], Tracey L. Jones[20], Amanda J. Wade[21], Stuart K. Roberts[3]; [1]Gastroenterology and Hepatology, Eastern Health, Melbourne, VIC, Australia; [2]Eastern Health Clinical School, Monash University, Melbourne, VIC, Australia; [3]Gastroenterology, Alfred Health, Melbourne, VIC, Australia; [4]Gastroenterology, Monash Health, Melbourne, VIC, Australia; [5]Gastroenterology, St Vincent's Hospital, Melbourne, VIC, Australia; [6]Gastroenterology, University of Melbourne, Melbourne, VIC, Australia; [7]AW Morrow Gastroenterology and Liver Centre, Royal Prince Alfred Hospital, Sydney, NSW, Australia; [8]HIV, Immunology, Infectious Diseases Department, St Vincent's Hospital, Sydney, NSW, Australia; [9]Gastroenterology, Princess Alexandra Hospital, Brisbane, QLD, Australia; [10]Storr Liver Centre, Westmead Institute for Medical Research, Sydney, NSW, Australia; [11]University of Sydney, Sydney, NSW, Australia; [12]Gastroenterology, Royal Adelaide Hospital, Adelaide, SA, Australia; [13]Gastroenterology, St Georges Hospital, Sydney, NSW, Australia; [14]Gastroenterology, Liverpool Hospital, Sydney, NSW, Australia; [15]Gastroenterology, Sir Charles Gairdner Hospital, Perth, WA, Australia; [16]Gastroenterology, Nepean Hospital, Sydney, NSW, Australia; [17]Victorian Liver Transplant Unit, Austin Health, Melbourne, VIC, Australia; [18]VIDS and Peter Doherty Institute, Royal Melbourne Hospital, Melbourne, VIC, Australia; [19]Gastroenterology, Royal Perth Hospital, Perth, WA, Australia; [20]Gastroenterology, John Hunter Hospital, Newcastle, NSW, Australia; [21]Infectious Diseases, Barwon Health, Geelong, VIC, Australia

Background In phase III registration trials, ritonavir boosted paritaprevir, with ombitasvir and dasabuvir (PrOD) +/- ribavirin was safe, well tolerated and had excellent efficacy with SVR12 rates >95%. However, real-world data on the safety and efficacy of PrOD therapy in cirrhotic patients is limited. **Methods** Between October 2014 and July 2015, a compassionate access program supported by AbbVie Pty Ltd was conducted in Australia across 47 treatment centers. Patients were included if they received at least one dose of PrOD. Primary end-points were SVR12 (HCV viral load < LLOQ at least 12 weeks post treatment) and drug discontinuation rates due to adverse events. The frequency and nature of serious adverse events with particular focus on death, hepatic decompensation and grade 4 biochemical abnormalities were collected. **Results** In this current analysis of 461 patients (74% cirrhosis, 9.8% CPB) complete treatment outcome data was available in 86% (n=395), with an overall SVR of 95.5%. SVR12 rates were similar for cirrhotic and non-cirrhotic patients (95.5% and 97.8%, respectively). Most patients were infected with Genotype 1a (64%) and most received ribavirin (90%). Baseline features of the fully characterized patients are shown in Table 1. Similar to previous reports, baseline viral load, MELD score and liver stiffness did not influence SVR. Early cessation of therapy occurred in 6.1% of patients and in these patients SVR12 was lower at 53%. Hyperbilirubinaemia on therapy was common with 4.3% of patients developing hyperbilirubinaemia ≥ 100μmol/L. To date no deaths have been reported, 34 patients (7.4%) required hospital admission, 9 patients (2.0%) developed hepatic decompensation, Grade 4 laboratory abnormalities occurred in 10 patients (2.2%). **Conclusion** In

a real-world setting, treatment with PrOD in Genotype 1 HCV infection achieves excellent SVR12 rates including in those with cirrhosis. Hepatic decompensation occurred infrequently.

Baseline parameters and SVR12

Age, median (range) years	56.1 (25.7 -79.7)
Male : Female (%)	66.7 : 33.3
BMI (Kg/m2)	28.2 ± 5.5
Genotype 1a/1b/1ab (%)	64.4 / 28.1 / 7.2
Treatment naïve, %	54.2 %
Cirrhosis (%)	74%
Child-Pugh Class A/B/C, %	90.2 / 9.8 / 0.0
MELD in cirrhotic patients (median, range)	8,(6-22)
Ribavirin included in regimen (%)	90.2%
Overall SVR12	95.5%
SVR 12 - Cirrhotic	95.5%
SVR 12 - Non-cirrhotic	97.8%
SVR 12 - Genotype 1a	93.8%
SVR 12 - Genotype 1b	100%

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John Lubel - Advisory Committees or Review Panels: Gilead, Abbvie, Bayer; Grant/Research Support: BMS, MSD, Abbvie; Speaking and Teaching: Gilead, Abbvie, BMS, Jansen, Roche

Stephen Pianko - Advisory Committees or Review Panels: Roche, Novartis, GILEAD, Roche, Novartis; Consulting: GILEAD; Speaking and Teaching: JANSSEN, BMS

Alex J. Thompson - Advisory Committees or Review Panels: Gilead, Abbvie, BMS, Merck, Spring Bank Pharmaceuticals, Arrowhead, Roche; Grant/Research Support: Gilead, Abbvie, BMS, Merck; Speaking and Teaching: Roche, Gilead, Abbvie, BMS

David M. Iser - Speaking and Teaching: AbbVie, Bristol Myers Squibb, Gilead, Janssen, Merck, Roche

Simone I. Strasser - Advisory Committees or Review Panels: AbbVie, MSD, Bristol-Myers Squibb, Gilead, Norgine, Bayer Healthcare; Speaking and Teaching: Roche Products Australia, Bayer Healthcare, Bristol-Myers Squibb, MSD, Gilead, Abbvie

Gregory Dore - Board Membership: Gilead, Merck, Abbvie, Bristol-Myers Squibb; Grant/Research Support: Gilead, Merck, Abbvie, Bristol-Myers Squibb; Speaking and Teaching: Gilead, Merck, Abbvie, Bristol-Myers Squibb

Katherine A. Stuart - Advisory Committees or Review Panels: Gilead, Bayer, AbbVie; Grant/Research Support: Roche

Jacob George - Advisory Committees or Review Panels: Pharmaxis, BMS, MSD, Gilead, Janssen, Abbvie; Grant/Research Support: MSD

Amany Zekry - Advisory Committees or Review Panels: GILEAD, BMS, MSD, Abbvie

Miriam Levy - Advisory Committees or Review Panels: Bayer; Grant/Research Support: Gilead

Vince Fragomeli - Advisory Committees or Review Panels: Roche, MSD, Jansen

Brenda Morales - Advisory Committees or Review Panels: MSD, Jansen, Roche, Abbvie, BMS

Joe Sasadeusz - Advisory Committees or Review Panels: Merck, Gilead, BMS; Grant/Research Support: Roche, Gilead, Avvbie; Speaking and Teaching: Gilaed, Merck, BMS, Merck

Amanda J. Wade - Grant/Research Support: AbbVie

Stuart K. Roberts - Board Membership: AbbVie, Gilead

The following people have nothing to disclose: Joanne Mitchell, Alessia Gazzola, Sarah Chivers, Gauri Mishra, John Gough, Edmund Tse, Gerry C. MacQuillan, Paul Gow, Saroj Nazareth, Steven J. Bollipo, Tracey L. Jones

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Regression of fibrosis in HCV patients treated with direct acting antivirals (DAAs)

Stephanie Hametner, Remy Schwarzer, Alexander Ziachehabi, Rainer Schöfl, Andreas Maieron; Gastroenterology and Hepatology, Elisabeth Hospital, Linz, Austria

Introduction: sustained virological response (SVR) due to antiviral therapy is associated with changes in biochemical markers of liver function. So far little is known about the effects of SVR on liver fibrosis. Therefore we investigated the effects of DAA based HCV therapy on fibrosis measured by transient elastography (TE). Methods: over a period of 12 months (03/2014-03/2015) we treated a total of 154 patients with a DAA based therapy; 121 patients had baseline evaluation including TE and SVR 12; of those, a total of 108 patients were followed up at least 24 weeks post treatment including TE. TE results were classified as very reliable (IQR/M≤10%), reliable (IQR/M ≤30% or ≥30% and <7,5kPa) and not reliable (IQR/M>30%). Patients were devided into two groups (cirrhosis and non cirrhosis) according to TE results (cut off F4>13kPa). Only patients with correct TE results were included.Results: 108 patients in total, 43 (39.8%) female, median age 60, (female: 63 (IQR 55-73), male: 58 (IQR 54-63)); distribution of genotypes was as follows: 1a: 27.8%, 1b: 57.4%, 1: 3.7%, 3: 7.4%, 4: 1.9%. 55.6% were considdered cirrhotics.69.4% had previous treatment including PI based regimes. All patients included in this evaluation achieved SVR 12. Baseline (BL) and follow-up TE results are shown in table 1. In a subgroup of 47 cirrhotic patients with correct TE>13 kPa, 48.9% showed a regression of fibrosis to F3 according TE evaluation. In those with proven regression BL TE measured 17.1kPa (IQR: 14.3- 20.9), FUP TE results showed 8.9kPa (IQR: 8.3-10.8). Conclusion: SVR in HCV patients due to DAA therapy appears to induce regression of fibrosis in our patients. Moreover in a significant proportion of patients with TE proven cirrhosis we noticed stage migration from F4 to F3. This work underlines that downstaging of fibrosis even in cirrhotic patients could happen, however histological verification is lacking. One might wonder whether in subgroups of cirrhotics with fibrosis regression TE decline can be translated in less liver related endpoints; therefore a longer observation of our patients is planned.

TE results in different patient populations

	BL TE (M & IQR)	FUP TE (M & IQR)	p-value
all patients (n=108)	18.2 (9.9-21)	11.8 (5.4-12)	<0.0001
no cirrhosis (n=48)	9.3 (6.3-11.4)	6.2 (4.6-7.7)	<0.0001
cirrhosis (n=60)	25.3 (14-33.3)	16.3 (8.8-20.9)	<0.0001

BL (baseline), TE (transient elastography), FUP (follow up)

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Stephanie Hametner - Speaking and Teaching: MSD, BMS, Gilead science, AbbVie

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Andreas Maieron - Advisory Committees or Review Panels: MSD, Jannsen, BMS, Bv∂hringer Ingelheim, Gilead, Abbvie ; Grant/Research Support: Roche; Speaking and Teaching: Roche, MSD, Jannsen, Gilead, Abbvie

The following people have nothing to disclose: Remy Schwarzer, Rainer Schöfl

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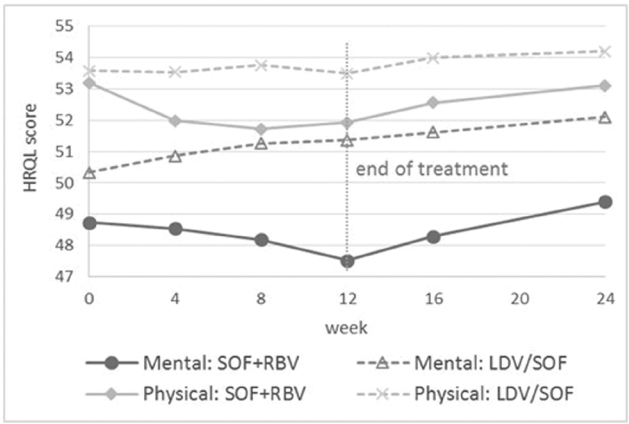
Comparison of Health-Related Quality of Life (HRQL) in Asian Patients with Chronic Hepatitis C Treated with Interferon (IFN)-free Ribavirin (RBV)-Containing Regimens vs Interferon-free and Ribavirin-free Regimens

Zobair M. Younossi[1], Maria Stepanova[16,2], Kwang-Hyub Han[3], Wan-Long Chuang[4], Henry Lik-Yuen Chan[5], Young-Suk Lim[6], Rong-Nan Chien[7], Sang Hoon Ahn[3], Sook-Hyang Jeong[8], Ting-Tsung Chang[9], Seung Woon Paik[10], Cheng-Yuan Peng[11], Chi-Jen Chu[12], Youn-Jae Lee[13], Ching-Lung Lai[14], Jia-Horng Kao[15], Sharon Hunt[16]; [1]Center for Liver Disease, Department of Medicine, Inova Fairfax Hospital, Falls Church, VA; [2]Beatty Liver and Obesity Research Program, Department of Medicine, Inova Fairfax Hospital, Falls Church, VA; [3]Yonsei University College of Medicine, Seoul, Korea (the Republic of); [4]Kaohsiung Medical University, Kaohslung, Taiwan; [5]Chinese University of Hong Kong, Hong King, China; [6]University of Ulsan College of Medicine, Seoul, Korea (the Republic of); [7]Chang Gung University, Keelung, Taiwan; [8]Seoul National University College of Medicine, Seongnam, Korea (the Republic of); [9]National Cheng Kung University, Tainan, Taiwan; [10]Sungkyunkwan University School of Medicine, Seoul, Korea (the Republic of); [11]China Medical University, Taichung, Taiwan; [12]Taipei Veterans General Hospital, Taipei, Taiwan; [13]Inje University, Busan, Korea (the Republic of); [14]Queen Mary Hospital, Hong Kong, China; [15]National Taiwan University, Taipei, Taiwan; [16]Center for Outcomes Research in Liver Diseases, Washington, DC

BACKGROUND: Given the potential side effect of RBV, we assessed its impact on HRQL of Asian patients with HCV. **METHODS**: Short Form-36v2 was administered before, during, and after treatment in 2 clinical trials of sofosbuvir (SOF)-based regimens: Ledipasvir (LDV)/SOF and SOF+RBV (2014-2015, South Korea, Hong Kong, and Taiwan). HRQL scores were compared between patients receiving LDV/SOF and SOF+RBV. **RESULTS**: 425 patients were enrolled [247: SOF+RBV (87% HCV genotype 2) and 178: LDV/SOF (all genotype 1)]. Patients were 13% cirrhotic, 63% treatment-naïve, and 8% reported overt fatigue. The SVR-12 rates were 98.0% (SOF+RBV) and 98.3% (LDV/SOF). Baseline scores were similar between the two groups. However, soon after treatment, a number of HRQL declined in those receiving SOF+RBV (up to -2.6 points by wk2, up to -4.2 by wk4, up to -5.8 by wk8, up to -6.1 by the end of treatment) ($p<0.05$). In contrast, improvements in HRQL scores in those receiving LDV/SOF were observed starting at wk2 (up to +2.3); these improvements continued throughout treatment (up to +3.3 by wk4, up to +3.8 by wk8, up to +3,5 by the end of treatment) ($p<0.05$). Notably, no HRQL decrements were observed in the LDV/SOF. After treatment cessation, in those who received RBV, some decrements (up to -3.3) were observed at post-treatment wk4. These HRQL impairments resolved by post-treatment wk12 (up to +2.7) ($p<0.05$). In contrast, in those who completed LDV/SOF, HRQL improvements were up to +5.0 by post-treatment wk4, up to +5.2 by post-treatment wk12 ($p<0.05$). In multivariate analysis, use of RBV was independently associated with mild impairment in HRQL (betas range from -1.3 to -5.0 points to Physical and Mental Summary scores and SF-6D utility; all $p<0.05$). **CONCLUSION**: The use of RBV is associated with mild impairment in HRQL in Asian patients with HCV. LDV/SOF leads to improvement of HRQL during treatment and after acheiving SVR.

Figure. The average HRQL scores in Asian patients.



Disclosures:

Wan-Long Chuang - Advisory Committees or Review Panels: Gilead, Abbvie, Roche, PharmaEssentia; Speaking and Teaching: Gilead, Roche, BMS, MSD, PharmaEssentia

Henry Lik-Yuen Chan - Advisory Committees or Review Panels: Gilead, Janssen, Bristol-Myers Squibb, Roche, Novartis Pharmaceutical, Abbvie; Speaking and Teaching: Echosens

Young-Suk Lim - Advisory Committees or Review Panels: Bayer Healthcare, Gilead Sciences; Grant/Research Support: Bayer Healthcare, BMS, Gilead Sciences, Novartis

Cheng-Yuan Peng - Advisory Committees or Review Panels: AbbVie, BMS, Gilead, MSD, Roche

Chi-Jen Chu - Advisory Committees or Review Panels: Gilead; Speaking and Teaching: BMS, Merck, Abbvie, Roche

Ching-Lung Lai - Advisory Committees or Review Panels: Bristol-Myers Squibb, Gilead Sciences Inc; Consulting: Bristol-Myers Squibb, Gilead Sciences, Inc; Speaking and Teaching: Bristol-Myers Squibb, Gilead Sciences, Inc; Stock Shareholder: Gilead Sciences

The following people have nothing to disclose: Zobair M. Younossi, Maria Stepanova, Kwang-Hyub Han, Rong-Nan Chien, Sang Hoon Ahn, Sook-Hyang Jeong, Ting-Tsung Chang, Seung Woon Paik, Youn-Jae Lee, Jia-Horng Kao, Sharon Hunt

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Efficacy and safety of DAA-based oral therapy in a large cohort of HCV patients treated in clinical practice in Italy and monitored by the NAVIGATORE web-platform

Marta Milan[1], PierGirogio Scotton[3], Lucas G. Cavallaro[2], Monica Basso[1], Sandro Panese[4], Diego Tempesta[4], Sara Piovesan[1], Anna Maria Cattelan[6], Davide Campagnolo[1], Patrizia Burra[5], Francesco P. Russo[5], Antonio Carlotto[11], Paolo Angeli[7], Alessandro Vario[8], Paolo Fabris[9], Tosca Bertin[9], Maurizio Carrara[10], Liliana Chemello[7], Pierangelo Rovere[12], Franco Capra[13], Giada Carolo[13], Salvatore Lobello[14], Silvia Adami[15], Giovanna Scroccaro[15], Alfredo Alberti[1]; [1]DMM, University of Padova, Padova, Italy; [2]Ospedale Belluno, Belluno, Italy; [3]Ospedale Treviso, Treviso, Italy; [4]Ospedale Venezia-Mestre, Venezia, Italy; [5]Gastroenterology, University of Padova, Padova, Italy; [6]Azienda Ospedaliera di Padova, Padova, Italy; [7]Clinica Medica 5, University of Padova, Padova, Italy; [8]Ospedale Schiavonia, Schiavonia, Italy; [9]Ospedale Vicenza, Vicenza, Italy; [10]Ospedale Bussolengo, Bussolengo, Italy; [11]Ospedale Santorso, Santorso, Italy; [12]Ospedale Legnago, Legnago, Italy; [13]University of Verona, Verona, Italy; [14]Ospedale S Antonio, Padova, Italy; [15]Regione Veneto, Venezia, Italy

To assess efficacy, safety and clinical outcomes of DAA-based therapy in advanced liver disease, we are currently monitoring with a web-based platform (NAVIGATORE) all HCV patients treated with oral DAAs in a vast geographic area of the North-East of Italy. At the time of this analysis, 2595 treated patients have been included (64.8% Males, mean age 57.9+10.8-

range 21-90yrs, 41.6% HCV-1b, 20% HCV-1a, 12.4% HCV-2, 17,2% HCV-3,7.7% HCV-4. 75% had cirrhosis (1741 CHILD A and 197 CHILD B, 7 CHILD C), 3,6% extrahepatic disease, 14,3% F3 fibrosis. Diabetes was present in 11.4%, CVD in 14,8% Obesity in 5% Nephropathy in 1,5%.Patients were treated according to guidelines and monitored monthly during therapy and every 3 months thereafter. Efficacy and safety analysis is described in the table Efficacy was excellent in most groups, not being significantly affected by comorbidities. However, it was reduced by around 10% in patients with Child B cirrhosis. Tolerability and safety were excellent in patients with F3 and with Child A cirrhosis, while were reduced in Child B patients, particularly when treated with Ribavirin. Conclusions : these results confirm the excellent efficacy and safety of DAA-based oral HCV treatments in compensated disease, while results in Child B cirrhosis appear somehow compromised by lower tolerability of RBV containing regimens.

EFFICACY ANALYSIS (SVR12)	SOF/RBV	SOF/SMV +/- RBV	SOF/LDV +/. RBV	SOF/DCV +/- RBV	OBT/PTV/r + DSV +/- RBV	OBT/PTV/r +/- RBV
F3						
HCV-1a/1b	--	100%	100%	--	100%	--
HCV-2	91.7%	--	--	--	--	--
HCV-3	100%	--	--	100%	--	--
HCV-4	--	100%	--		--	100%
EXTRAHEPATIC DISEASE						
HCV-1a/1b	--	100%	100%	--	100%	--
HCV-2	92.3%	--	--	--	--	--
HCV-4	--	100%	--	--	..	100%
CIRRHOSIS						
HCV-1a	--	86.1%	96%	95%	95%	--
HCV-1b	--	91%	94%	95%	95%	--
HCV-2	91%	--	--	--	--	--
HCV-3	71%	--	--	93.4%	--	--
HCV-4	--	86.5%	83.4%	--	--	100%
CHILD B	66.6%	--	75%	86%	--	..
SAFETY ANALYSIS	F3		Child A		Child B	
	RBV yes	RBV no	RBV yes	RBV no	RBV yes	RBV no
Early Discontinuation	0	0.7%	1.2%	1.1%	2.7%	3.3%
Clinically Significant Side Effects	3.6%	0	3.9%	1.8%	7.6%	0.9%
Ascites	0	0	1.3%	1.8%	10.9%	4.9%
Encephalopathy	0	0	0.1%	0	3.4%	0
Death	0	0	0	0	5.9%	2.4%

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Anna Maria Cattelan - Advisory Committees or Review Panels: Abbot; Consulting: BMS, Viiv

Patrizia Burra - Grant/Research Support: Novartis, Astellas, Kedrion, Grifols, Biotest, Gilead, Alfawassermann

Antonio Carlotto - Advisory Committees or Review Panels: Abbvie

Paolo Angeli - Advisory Committees or Review Panels: Sequana Medical, Nano-Antibiotics

Franco Capra - Independent Contractor: MSD; Speaking and Teaching: Gilead Sciences

Giada Carolo - Board Membership: Abbvie; Speaking and Teaching: BMS

Alfredo Alberti - Advisory Committees or Review Panels: Merck, roche, Gilead, Merck, roche, Gilead, Merck, roche, Gilead, Merck, roche, Gilead, Abbvie, Janssen; Grant/Research Support: Merck, gilead, Merck, gilead, Merck, gilead, Merck, gilead, Abbvie, Janssen; Speaking and Teaching: novartis, BMS, novartis, BMS, novartis, BMS, novartis, BMS

The following people have nothing to disclose: Marta Milan, PierGirogio Scotton, Lucas G. Cavallaro, Monica Basso, Sandro Panese, Diego Tempesta, Sara Piovesan, Davide Campagnolo, Francesco P. Russo, Alessandro Vario, Paolo Fabris, Tosca Bertin, Maurizio Carrara, Liliana Chemello, Pierangelo Rovere, Salvatore Lobello, Silvia Adami, Giovanna Scroccaro

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Effectiveness And Safety Of Ombitasvir, Paritaprevir/ Ritonavir And Sofosfuvir/Ledipasvir In Patients With Genotype 4 Chronic Hepatitis C Virus Infection: Results From The Spanish Real World Cohort

Javier Crespo[3], Jose L. Calleja[1,2], Sacristran Begoña[5], Belen Ruiz-Antoran[7], Javier Ampuero[6,2], Javier García-Samaniego[8,2], Francisco Gea[9,2], Maria Buti[10,2], Sabela Lens[11,2], Joaquin Cabezas[3], Rosa María Morillas[12], Jose Ramon Salcines[13], Juan Manuel Pascasio[14], Juan Turnes[15], Federico Saez-Royuela[16], Juan Arenas[17], Diego Rincón[18], Martin Prieto[19], Francisco Jorquera[20], Juan José Sánchez Ruano[21], Carmen Navascues[22], Esther Molina[23], Xavier Torras[24,2], Silvia Montoliu[25], Jose M. Moreno[26], Miguel Angel Serra[27], Raul J. Andrade[28,2], Conrado M. Fernández-Rodríguez[29], Miguel Fernandez-Bermejo[30], Miguel A. Simon[31], Lucía Bonet[32], Juan de la Vega[33], Moises Diago[34], Jose Ramon Fernandez[35], Gloria Sanchez-Antolin[36], Inmaculada Fernandez[4]; [1]Department of Gastroenterology, Hospital Universitario Puerta de Hierro, Madrid, Spain; [2]CIBEREHD, Madrid, Spain; [3]Department of Gastroenterology, Hospital Universitario Marques de Valdecilla, Santander, Spain; [4]Department of Gastroenterology, Hospital Universitario 12 de Octubre, Madrid, Spain; [5]Department of Gastroenterology, Hospital San Pedro, Logroño, Spain; [6]Department of Gastroenterology, Hospital Universitario de Valme, Sevilla, Spain; [7]Clinical Pharmacology, Hospital Universitario Puerta de Hierro, Madrid, Spain; [8]Department of Gastroenterology, Hospital Universitario La Paz, Madrid, Spain; [9]Department of Gastroenterology, Hospital Universitario Ramon y Cajal, Madrid, Spain; [10]Department of Gastroenterology, Hospital Universitario Vall D Hebrón, Barcelona, Spain; [11]Liver Unit, Hospital Clinic, Barcelona, Spain; [12]Department of Gastroenterology, Hospital Germans Trias I Pujol, Barcelona, Spain; [13]Department of Gastroenterology, Hospital de Laredo, Laredo, Spain; [14]Department of Gastroenterology, Hospital Universitario Virgen del Rocio, Sevilla, Spain; [15]Department of Gastroenterology, Hospital de Montecelo, Pontevedra, Spain; [16]Department of Gastroenterology, Hospital Universitario de Burgos, Burgos, Spain; [17]Department of Gastroenterology, Hospital Universitario de Donostia, San Sebastian, Spain; [18]Department of Gastroenterology, Hospital Universitario Gregorio Marañon, Madrid, Spain; [19]Department of Gastroenterology, Hospital Universitario La Fe, Valencia, Spain; [20]Department of Gastroenterology, Complejo Asistencial Universitario León, Leon, Spain; [21]Department of Gastroenterology, Hospital Universitario de Toledo, Toledo, Spain; [22]Department of Gastroenterology, Hospital Universitario Central de Asturias, Oviedo, Spain; [23]Department of Gastroenterology, Hospital Clínico Universitario Santiago, Santiago de Compostela, Spain; [24]Department of Gastroenterology, Hospital Santa Creu i Sant Pau, Barcelona, Spain; [25]Department of Gastroenterology, Hospital Universitario Tarragona, Tarragona, Spain; [26]Department of Gastroenterology, Complejo Hospitalario Universitario de Albacete, Albacete, Spain; [27]Department of Gastroenterology, Hospital Clinico de Valencia, Valencia, Spain; [28]Department of Gastroenterology, Hospital Universitario Virgen de la Victoria, Malaga, Spain; [29]Department of Gastroenterology, Hospital Universitario Fundación Alcorcón, Madrid, Spain; [30]Department of Gastroenterology, Hospital San Pedro de Alcantara, Caceres, Spain; [31]Department of Gastroenterology, Hospital Clinico Universitario Lozano Blesa, Zaragoza, Spain; [32]Department of Gastroenterology, Hospital Universitario Son Espases, Palma de Mallorcca, Spain; [33]Department of Gastroenterology, Hospital San Agustin, Aviles, Spain; [34]Department of Gastroenterology, Hospital Universitario General de Valencia, Valencia, Spain; [35]Department of Gastroenterology, Hospital Universitario de Cruces, Bilbao, Spain; [36]Department of Gastroenterology, Hospital Universitario Rio Hortega, Valladolid, Spain

Introduction: Hepatitis C virus (HCV) genotype (GT) 4 represents

15% of total global HCV infection.Clinical trials showed an efficacy over 90% with oral antiviral therapy.This study assessed real-world effectiveness and safety of sofosfuvir/ledipasvir (SOF/LED) and paritaprevir/ritonavir/ombitasvir (2D) with or without ribavirin in patients with GT4 chronic HCV infection. **Material and Methods:**Retrospective, multicentre,non-randomized, prospective collected data,national study that included naive and treatment experienced patients with HCV GT 4 infection who were treated with 2D or SOF/LED.Patients with at least SVR 4 post-treatment were selected for analysis. The results for both cohorts are shown separately. **Results:**The total cohort includes 301 patients with SVR 4 data in 252.The global SVR4 and SVR12 were 97.2% (245/252) and 95.7% (224/234) respectively. 130 patients were treated with SOF/LED.Most of the patients (83.8%) were male,mean age of 54 years, 57% were F4 (12 patients CHILD B or C); 53.9% of patients were treatment-naive, 43.1% received ribavirin.The SVR4 and SVR12 week post-treatment were 96.2% and 95.4% (124/130) respectively.Four patients experienced virological failure (relapse).Approximately 4.6% of patients reported at least one serious adverse events (SAEs). One patient experienced hepatic decompensation (ascites).No patient discontinues therapy.No patient died during the treatment.In this subcohort SOF/LED, bilirubin ≥2 mg/dL is the only baseline factor associated with lack of response.None of the baseline factors investigated were significantly associated with SAEs on multivariate analysis. 122 patients were treated with 2D with or without RIBA.Most of the patients (75%) were male,mean age of 53 years.35.2% were F4 (5 CHILD B),36.1% of patients were treatment-naive,94.3% received ribavirin.The SVR4 and SVR12 week post-treatment were 98.4% and 96.2% (100/104) respectively. One patient experienced virological failure (relapse). SAEs were reported for 7 patients (5.7%),one patient with hepatic decompensation (encephalopathy).No patient died during the treatment.Baseline factors significantly associated with failure to achieve SVR12 after 2D treatment on multivariate analysis were bilirubin ≥2 mg/dL and albumin <3 g/dL (p<0.05).Baseline albumin <3g/dL (p<0.05),and platelets ≤70,000/ mm3 were significantly associated with development of SAEs. **Conclusion:** The two regimen evaluated sofosfuvir/ledipasvir or ombitasvir/paritaprevir/ritonavir with or without RBV achieved a high rate of efficacy (SVR 95.4% and 96.2% respectively) in clinical practice with a good safety profile and was associated with minimum rates of treatment discontinuation.

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Jose L. Calleja - Advisory Committees or Review Panels: Gilead, Abbvie ; Speaking and Teaching: Abbvie, Gilead, Janssen, BMS

Javier García-Samaniego - Consulting: Bristol-Myers-Squibb, Gilead, Janssen, Abbvie

Maria Buti - Advisory Committees or Review Panels: Gilead, Janssen, MSD; Grant/Research Support: Gilead, Janssen; Speaking and Teaching: Gilead, Janssen, BMS

Rosa María Morillas - Advisory Committees or Review Panels: BRISTOL, GILEAD, AbbVie; Speaking and Teaching: ROCHE, JANSSEN, MSD

Juan Turnes - Advisory Committees or Review Panels: Gilead, Abbvie, Janssen, BMS; Speaking and Teaching: Gilead, Abbvie, Janssen, MSD, BMS

Federico Saez-Royuela - Speaking and Teaching: Gilead Sciences, S.L., AbbVie Spain S.L.U.

Juan Arenas - Advisory Committees or Review Panels: Abbvie; Speaking and Teaching: MSD, BMS, Gilead

Martin Prieto - Advisory Committees or Review Panels: Gilead, Abbvie, Bristol

Juan José Sánchez Ruano - Advisory Committees or Review Panels: GILEAD; Speaking and Teaching: GILEAD, ABBVIE, BMS, JANSSEN

The following people have nothing to disclose: Sacristran Begoña, Belen Ruiz-Antoran, Javier Ampuero, Francisco Gea, Sabela Lens, Joaquin Cabezas, Jose Ramon Salcines, Juan Manuel Pascasio, Diego Rincón, Francisco Jorquera, Carmen Navascues, Esther Molina, Xavier Torras, Silvia Montoliu, Jose M. Moreno, Miguel Angel Serra, Raul J. Andrade, Conrado M. Fernández-Rodríguez, Miguel Fernandez-Bermejo, Miguel A. Simon, Lucía Bonet, Juan de la Vega, Moises Diago, Jose Ramon Fernandez, Gloria Sanchez-Antolin, Inmaculada Fernandez

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Preliminary clinical outcome data among patients with hepatitis C virus infection receiving direct-acting antiviral therapy in the Chronic Hepatitis Cohort Study, 2014-2015

Philip R. Spradling[1], Jian Xing[1], Loralee B. Rupp[2], Anne C. Moorman[1], Stuart C. Gordon[2], Mei Lu[2], Eyasu H. Teshale[1], Joseph A. Boscarino[3], Yihe Daida[4], Mark A. Schmidt[5], Scott D. Holmberg[1]; [1]Division of Viral Hepatitis, CDC, Atlanta, GA; [2]Henry Ford Health System, Detroit, MI; [3]Geisinger Health System, Danville, PA; [4]Kaiser Permanente — Hawaii, Honolulu, HI; [5]Kaiser Permanente — Northwest, Portland, OR

Background: Data describing clinical outcomes of direct-acting antiviral (DAA) therapy among patients infected with hepatitis C virus (HCV) in general healthcare settings are limited. We examined DAA-associated outcomes among HCV-infected patients in the Chronic Hepatitis Cohort Study (CHeCS), an observational study conducted at 4 US healthcare organizations. Methods: Patients who began a DAA regimen from January 2014–August 2015 were included in the analysis. We examined frequency of treatment completion and of sustained viral response (SVR) 12 weeks post-treatment vs. no SVR by sociodemographic, clinical, and treatment-related factors, and conducted multivariable analysis to identify factors independently associated with SVR. Results: Of 613 patients who began an initial DAA regimen during the study period, 212 (48%) were treatment experienced, 210 (54%) had cirrhosis, 81 (18%) were of black race, and 24 (5%) were HIV-coinfected: 280 (46%) had HCV genotype 1a (G1a); 136 (22%) had G1b; 107 (17%) had G2; 68 (11%) had G3; 5 (1%) had G4-6; and 17 (3%) had mixed genotype infection. Overall, 401 (65%) patients received a sofosbuvir (SOF) regimen without ledipasvir (LDV) (i.e., SOF ± simeprevir or daclatasvir ± ribavirin [RBV]) and 211 (34%) received SOF with LDV ± RBV. No patients received an ombitasvir-containing regimen. Of 545 (89% of 613) patients with available SVR data, 463 (85%) achieved SVR. Among patients with G1a, frequencies of SVR ranged from 77% (SOF without LDV and no RBV) to 96% (SOF with LDV ± RBV); among those with G1b, 70% (SOF regimen without LDV + RBV) to 98% (SOF with LDV ± RBV). The frequency of SVR was 83%, 80% and 75% among patients with G2, G3, and G4-6 infection, respectively. In multivariable analysis controlling for all variables, the sole factor independently associated with SVR was receipt of SOF with LDV ± RBV (aOR 6.1 vs. SOF regimen without LDV and no RBV). Neither age, sex, race/ethnicity, previous treatment status, presence of cirrhosis, genotype, comorbidity score, body mass index, or HIV coinfection were associated with SVR. Of the 613 patients who initiated treatment, 68 (11%) either had completed treatment but did not yet have SVR data available (n=32), were still receiving treatment at the close of the study period (n=22), or stopped treatment early (n=14). Conclusions: Among patients who received DAAs in these general healthcare settings, half of whom had cirrhosis and previous treatment, the frequency of treatment completion and SVR was high. Receipt of a regimen other than SOF with LDV was associated with a lower likelihood of achieving SVR.

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An Open-Label, Multicenter Study of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir with or without Ribavirin in US Veterans with Genotype 1 Chronic Hepatitis C Infection: Efficacy and Safety Results of TOPAZ-VA

Michael Fuchs[1], Timothy R. Morgan[2], Mariem Charafeddine[3], Norbert Bräu[4], Warren N. Schmidt[5], Michael Kozal[6,7], Susanna Naggie[8], Ramsey Cheung[9], Tami Pilot-Matias[3], Yao Yu[3], Kristine Richards[3], Victoria Mullally[3], Daniel E. Cohen[3], Alexander Monto[10], Doris H. Toro[11]; [1]Hunter Holmes McGuire VA Medical Center, Richmond, VA; [2]VA Long Beach Healthcare System, Long Beach, CA; [3]AbbVie Inc., North Chicago, IL; [4]James J. Peters VA Medical Center, Bronx, NY; [5]Iowa City VA Healthcare System, Iowa City, IA; [6]VA Connecticut Healthcare System, New Haven, CT; [7]Yale University School of Medicine, New Haven, CT; [8]Durham VA Medical Center, Durham, NC; [9]VA Palo Alto Healthcare System, Palo Alto, CA; [10]San Francisco VA Medical Center, San Francisco, CA; [11]VA Caribbean Healthcare System, San Juan, PR

Introduction: Hepatitis C virus (HCV) infections are approximately 2-3 times more common among US veterans receiving care through Veterans Affairs (VA) Medical Centers than among the general population; 80% of infections are classified as genotype 1 (GT1). Historically, HCV therapies have been less successful in veterans than in the general population; comorbidities such as psychiatric disorders and regular alcohol/tobacco use may account for this difference. Ombitasvir/paritaprevir/ritonavir and dasabuvir (3-DAA) ± ribavirin (RBV) is approved in the US for HCV GT1-infected adults with or without cirrhosis. This study prospectively evaluated safety and efficacy of 3-DAA in HCV GT1-infected US veterans, including patients with ongoing psychiatric disorders and current or past alcohol/tobacco use. **Methods:** TOPAZ-VA was a phase 3b, open-label trial conducted in HCV GT1, treatment-naive or –experienced US veterans (N=99) with or without cirrhosis at 11 US VA Medical Centers. Participants received 3-DAA + RBV, except in non-cirrhotic GT1b-infected individuals, who received 3-DAA only. Treatment duration was 12 weeks, except for GT1a-infected patients with cirrhosis (24 weeks). Sustained virologic response (SVR4, SVR12), drug-associated resistance variants, and adverse events (AEs) were assessed. **Results:** Select baseline demographics are presented (table). Current alcohol consumption and tobacco use were reported at baseline by 21% and 48% of patients, respectively. In addition, 39% of patients reported ongoing psychiatric disorders. SVR4 was achieved in 96% of all patients and in 94% of those with ongoing psychiatric disorders (intent-to-treat population; missing data imputed as failures). A total of 78 (79%) patients experienced AEs, most commonly fatigue (28%), headache (20%), and nausea (15%). Serious AEs were observed in 7% of patients and considered 3-DAA-related in 1% of cases. 9 patients discontinued treatment, 6 due to AEs. **Conclusions:** In HCV GT1-infected US veterans, 3-DAA ± RBV was associated with high SVR4 rates and was well tolerated. The presence of psychiatric disorders and alcohol consumption did not appear to impact SVR4. All available safety, efficacy, and resistance results will be presented.

Patient characteristics	3-DAA±RBV 12 or 24 weeks (N=99)
Male, n (%)	95 (96)
Black, n (%)	37 (38)
Age, median (range), years	62 (36-73)
BMI, median (range), kg/m2	27 (17-39)
HCV GT1a/b, n (%)	67 (68)/ 32 (32)
IL28B non-CC, n (%)	73 (74)
Treatment-experienced, n (%)	28 (28)
Cirrhosis (Metavir score F4), n (%)	20 (20)

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Ramsey Cheung - Grant/Research Support: Gilead Sciences, AbbVie

Tami Pilot-Matias - Employment: AbbVie; Stock Shareholder: Abbott

Yao Yu - Employment: Abbvie

Kristine Richards - Employment: AbbVie; Stock Shareholder: AbbVie

Daniel E. Cohen - Employment: AbbVie; Stock Shareholder: AbbVie

The following people have nothing to disclose: Norbert Bräu, Warren N. Schmidt, Victoria Mullally, Alexander Monto, Doris H. Toro

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Viral response to hepatitis C direct-acting antivirals significantly improves diabetes control

Sheena B. LeClerc[1], Yngve Falck-Ytter[2,3], Corinna Falck-Ytter[1,4], Kristina Pascuzzi[1], Christopher Burant[5,3], Kelsey Rife[1]; [1]Pharmacy, Louis Stokes Cleveland Veterans Affairs Medical Center, Willoughby Hills, OH; [2]Gastroenterology, Louis Stokes Cleveland VAMC, Cleveland, OH; [3]Case Western Reserve University, Cleveland, OH; [4]Medicine, Louis Stoke Cleveland VAMC, Cleveland, OH; [5]Geriatric Research Education and Clinical Center (GRECC), Louis Stokes Cleveland VAMC, Cleveland, OH

Purpose: Hepatitis C virus (HCV) causes inflammation of hepatocytes that over time can lead to cirrhosis. In addition to the effects on the liver, it can cause extrahepatic complications and insulin resistance. Studies have demonstrated an association between HCV and the progression of insulin resistance to diabetes as well as improved glycemic control upon virologic response. However, the clinical impact of improved glycemic control in diabetic patients who achieve sustained virologic response 12 weeks post-treatment (SVR_{12}) is unknown. **Objectives:** The primary objective of this study was to determine the impact on antihyperglycemic medication needs in patients who achieved SVR_{12} from HCV direct-acting antivirals (DAAs). Secondary objectives were to determine the impact on antihyperglycemic medication needs in patients who relapse, and to determine the impact on hemoglobin A1c in patients achieving SVR_{12}. **Methodology:** Patients with a diagnosis of diabetes who completed a course of HCV DAAs from February 1, 2014 – October 1, 2015 were identified using ICD-9/10 codes and medication dispense history. Retrospective patient data was collected from the electronic medical record. The co-primary endpoints were the change of antihyperglycemic medications categorized as de-escalation, no change, or escalation from baseline to the end of HCV treatment, and from baseline to 3 months post-treatment in patients achieving SVR_{12}. Secondary endpoints included the change in antihyperglycemic medica-

tions in relapsers, and the change in A1c from baseline to 4 months post-treatment in those achieving SVR_{12}. Descriptive statistics were used for all endpoints and a paired t-test was used for A1c data. **Results:** Of the 209 patients identified,131 patients met inclusion criteria. The majority of patients were male (98%), mean age of 63, and were primarily black (59%). Advanced fibrotic liver disease was present in 53% of patients. Of the 122 patients who achieved $SVR_{12,}$ 27% (33/122) had a de-escalation of their antihyperglycemics from baseline to 3 months post-treatment compared to 11% (1/9) of the HCV DAA relapsers. There was available A1c data for 49% of patients who achieved SVR_{12}, which showed a statistically significant decrease in A1c of 0.63 percentage points (95% CI 0.31% - 0.93%). **Conclusions:** This study found a clinically meaningful de-escalation of antihyperglycemics as well as a significant decrease in A1c for diabetic patients who were able to achieve SVR_{12} from HCV DAAs, demonstrating an additional potential benefit of SVR_{12}. Close diabetes follow-up during and post-HCV treatment is warranted. Prospective and larger studies are needed to validate these results.

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The potential impact of drug-drug interactions (DDIs) in the selection of direct acting antivirals (DDAs) in the current treatment of chronic hepatitis C (CHC) in routine clinical practice

George V. Papatheodoridis[1], John Goulis[2], Spilios Manolakopoulos[3], Christos K. Triantos[4], Kalliopi Zachou[5], Margarita Papatheodoridi[1], Argyro Koukoufiki[2], Anastasia Kourikou[3], Konstantinos A. Zisimopoulos[4], Christos Tsoulas[6], George N. Dalekos[5]; [1]Department of Gastroenterology, Medical School of National and Kapodistrian University of Athens, Laiko General Hospital, Athens, Greece; [2]4th Department of Internal Medicine, Medical School of Aristotle University of Thessaloniki, Thessaloniki, Greece; [3]2nd Department of Internal Medicine, Medical School of National and Kapodistrian University of Athens, Hippokratio General Hospital, Athens, Greece; [4]Department of Gastroenterology, University Hospital of Patras, Patras, Greece; [5]Department of Medicine and Research Laboratory of Internal Medicine, Thessaly University Medical School, Larissa, Greece; [6]Gilead Sciences Hellas, Athens, Greece

Background/Aim: DDIs represent the main limitation of the current DAAs against HCV. We determined the prevalence of co-morbidities and use of co-medications with DDI potential in CHC patients (pts) in Greece. **Methods:** 500 consecutive CHC pts (age:49±14 yrs, M/F:322/178) seen in 2015 at the outpatient liver clinics of 5 tertiary Greek centers (100 pts from each center) were included. HIV coinfected pts were excluded. Demographics, habits, lab tests, HCV and liver disease characteristics, co-morbidities and co-medications were recorded. All co-medications were classified into those with no/no clear data for DDIs, potential DDIs and contraindication for each DAA according to HEP Drug Interaction Checker (Liverpool Univ.). **Results:** At least one co-morbidity was present in 243 (49%) pts, while 174 (35%) pts were on chronic co-medication(s). Contraindications due to DDIs were present in 30 (6%) pts for paritaprevir/ritonavir/ombitasvir±dasabuvir (3D/2D), 10 (2%) pts for simeprevir (SMV) and 2 pts (0.4%) for sofosbuvir (SOF) or daclatasvir (DCV) or ledipasvir/sofosbuvir (LDV/SOF) (P<0.001). Contraindications/potential DDIs were more frequently present for NS3 protease inhibitors (inh.) containing agents than NS5A inh.±SOF (P≤0.040) than SOF (P<0.001 vs NS3 inh.; P≤0.030 vs NS5A inh.) (Table). Contraindications/Potential DDIs were more frequently present in pts with age ≥50 than <50 yrs (P≤0.034), F3-4 than F0-2 or F4 than F0-3 (P≤0.019) for all DAAs and in genotype (G) 1/4 than 2/3 for all DAAs (P≤0.036) except LDV/SOF and 3D/2D (Table). In multivariate analyses, presence of contraindications/potential DDIs for all agents was independently associated with F3-4 or F4 fibrosis. **Conclusions:** Contraindications/Potential DDIs for current DAAs are frequently present (~25%) for NS3 inh., but can be also present for NS5A inh. (17%) or SOF (12%). The probability of DDIs is higher for pts with priority for DAAs therapy (eg with advanced liver disease) and therefore caution and careful selection of the appropriate DAAs regimen is warranted in clinical practice.

Table. Patients with contraindications due to DDIs or potential DDIs to HCV DAAs

	Pts, n	SMV	SOF	DCV	LDV/SOF	3D/2D
All pts	500	22.8%	11.8%	17.4%	16.8%	27.0%
Age ≥50 yrs	253	27.7%	15.0%	22.5%	22.1%	34.0%
Age <50 yrs	247	17.8%	8.5%	12.1%	11.3%	19.8%
F0-2*	226	17.7%	8.4%	12.8%	13.3%	23.0%
F3-F4*	224	30.4%	16.5%	23.7%	22.8%	35.3%
F0-3*	306	20.6%	9.2%	14.1%	14.1%	23.9%
F4*	144	31.3%	19.4%	27.1%	26.4%	40.3%
G1/4#	286	26.9%	14.7%	22.4%	18.9%	29.4%
G2/3#	210	17.1%	8.1%	11.0%	14.3%	23.8%

*Fibrosis stage was unknown in 50 pts; #Genotype (G) was unknown in 4 pts

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Spilios Manolakopoulos - Advisory Committees or Review Panels: NOVARTIS, ABBVIE, MSD, BMS, GILEAD, JANNSEN; Consulting: GILEAD, BMS, ABBVIE, JANNSEN, MSD; Grant/Research Support: BMS, GILEAD; Speaking and Teaching: ABBVIE, MSD, GILEAD, BMS, GSK, JANNSEN

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Ledipasvir/Sofosbuvir + Ribavirin (LDV/SOF+RBV) for 12 Weeks in Decompensated HCV Genotype 1 Patients: SOLAR-1 and -2 Studies Compared to a Real-World Dataset

Michael R. Charlton[1], Michelle C. Cheung[2], Michael P. Manns[3,4], Nika Sajed[5], Philip Troke[6], James G. Spellman[5], Amanda Copans[5], Sarah Arterburn[5], Diana M. Brainard[5], William Irving[7], Graham R. Foster[2]; [1]Division of Hepatology and Liver Transplantation, Intermountain Medical Center, Salt Lake City, UT; [2]Liver Unit, Blizard Institute, Queen Mary University of London, London, United Kingdom; [3]Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [4]German Center of Infection Research (DZIF), Hannover-Braunschweig, Germany; [5]Gilead Sciences, Inc., Foster City, CA; [6]Gilead Sciences Ltd, London, United Kingdom; [7]NIHR Nottingham Digestive Diseases Biomedical Research Unit, Nottingham, United Kingdom

BACKGROUND: Patients with decompensated HCV have limited treatment options and a poor prognosis. Recently, the FDA approved treatment with LDV/SOF+RBV in GT 1 decompensated patients based on the SOLAR-1 and -2 studies. Real-world datasets are important to show generalizability of clinical trial data. Here, real-world data from the UK expanded access program (EAP) are compared to clinical trial data in decom-

pensated HCV patients. **METHODS:** Data from 2 open-label phase-2 trials (SOLAR-1 and -2) are compared to real-world data from the UK EAP collected through Month 6 in CPT-B and CPT-C HCV patients treated with LDV/SOF+RBV. The UK EAP cohort was selected based on its size and availability of comparable data. SVR and relapse rates, MELD improvement, and safety are presented. **RESULTS:** High SVR rates were observed in SOLAR-1 and -2 (87.0%) and the UK EAP (89.7%). MELD improvements ≥3 at Month 6 were similar within CPT class for SOLAR-1 and -2 and the EAP among those achieving SVR (23.8% vs. 17.0% for CPT-B and 38.2% vs. 33.3% for CPT-C, respectively). LDV/SOF+RBV was generally safe and well-tolerated. Death rates were low (2.0-5.2%), not attributed to treatment, and more frequently observed in CPT-C patients. See Table 1. **CONCLUSIONS:** HCV GT 1 patients with decompensated cirrhosis achieve high cure rates and comparable MELD improvement with LDV/SOF+RBV in clinical trials and the real-world. Safety was consistent with known disease progression in this population with advanced liver disease. The impact of SVR and MELD improvement on long-term clinical outcomes is unknown.

Table 1

Study	Patient Type	N	SVR, n (%)	Relapse, n (%)	Other virologic outcome, n (%)	MELD Improvement ≥3*, n (%)	Deaths, n (%)
SOLAR-1 & -2	All	97†	80/92 (87.0)	8/88 (9.1)	4/92 (4.3)	23/76 (30.3)	5/97 (5.2)
	CPT-B	52	45/52 (86.5)	6/51 (11.8)	1/52 (1.9)	10/42 (23.8)	1/52 (1.9)
	CPT-C	45†	35/40 (87.5)	2/37 (5.4)	3/40 (7.5)	13/34 (38.2)	4/45 (8.9)
UK EAP	All	148†‡	122/136 (89.7)	7/129 (5.4)	7/136 (5.1)	21/121 (17.4)	3/148 (2.0)
	CPT-B	110†	89/101 (88.1)	7/96 (7.3)	5/101 (5.0)	15/88 (17.0)	3/110 (2.7)
	CPT-C	13†	9/10 (90.0)	0/9	1/10 (0.1)	3/9 (33.3)	0/13

*Among patients achieving SVR.
†5 patients (all CPT-C) in SOLAR-1 and -2 and 12 patients (9 CPT-B; 3 CPT-C) from the EAP transplanted prior to SVR12 excluded for all assessments except death. No patient had virologic failure.
‡25 patients were CPT-A (n=24) or had unclear baseline CPT score (n=1), but had history of decompensation.

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Philip Troke - Employment: Gilead Sciences Ltd.; Stock Shareholder: Gilead Sciences Ltd.

James G. Spellman - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

Amanda Copans - Employment: Gilead Sciences

Sarah Arterburn - Employment: Gilead Sciences Inc.; Stock Shareholder: Gilead Sciences Inc.

Diana M. Brainard - Employment: Gilead Sciences; Stock Shareholder: Gilead Sciences

William Irving - Advisory Committees or Review Panels: Novartis, MSD, Janssen Cilag, Bristol Myers Squibb; Grant/Research Support: GSK, Pfizer, Janssen Cilag, Gilead Sciences, Abbvie; Speaking and Teaching: Janssen Cilag, Roche

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The following people have nothing to disclose: Michelle C. Cheung

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Changes in cerebral hemodynamics in cirrhotic patients after liver transplantation

Ricardo Macías-Rodríguez[1,2], Astrid Ruiz-Margain[1,2], Carlos Cantu-Brito[3], Francisco Javier Cubero[2], Octavio René García-Flores[1], Elena Larrieta-Carrasco[1], Aldo Torre[1]; [1]Gastroenterology, INCMNSZ, Mexico, Mexico; [2]Medizinische Klinik III, Universitätsklinikum RWTH, Aachen, Germany; [3]Neurology, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico

Background and aims: Improvement in cognitive function after liver transplantation (LT) has been related to decreased cerebral white matter lesions induced by microvascular lesions (leukoaraiosis) secondary to low-grade cerebral edema and systemic inflammation. However most of studies have addressed these changes in the acute setting during and immediately after LT in cirrhosis as well as in acute liver failure and few have evaluated the long-term changes in cerebral hemodynamics in this population, therefore we aimed to investigate the long-term changes on cerebral hemodynamics in cirrhotic patients after LT. **Methods:** This was a prospective cohort study. We performed Transcranial Doppler Ultrasonography (TCD) measuring Pulsatility index (PI), Resistance index (RI) and breath-holding index (BHI) in the middle cerebral artery pre and post-LT. PI, RI and BHI evaluate cerebrovascular structural integrity and reactivity, respectively. Neuropsychometric tests and West-Haven criteria were used for hepatic encephalopathy (HE) characterization. To address systemic inflammation, we measured plasma levels of IL-6 and TNF-α. Descriptive statistics and Wilcoxon's test were used. **Results:** Twenty-seven patients were included (16 males); median follow up after LT was 6 months, median age pre-LT was 47(40-55) years, the main etiology was hepatitis C virus (58%), most of patients were Child-Pugh B (14/27), MELD score was 16(12-20), MELD-Na 18.5, PHES -3 and CFF 38.5Hz. Previous to the LT 17/27 patients had HE and 11/27 ascites. A decrease in PI and RI was observed in all patients except 3 after LT, and an increase in BHI in 12/27. The changes on cerebral hemodynamics paralleled those in systemic inflammation (table 1). Clinical improvement in cognition was observed in all patients with overt HE after LT. **Conclusions**: These results show an improvement in cerebral hemodynamics at long-term after LT in cirrhosis, indicating less arterial cerebral vasoconstriction (decrease in PI/RI) which seems to be influenced by systemic inflammation; this could explain the improvement in cognitive function after LT. TCD could be considered as a useful tool for the assessment of the changes in cerebral hemodynamics pre and post-LT in cirrhosis.

Table 1. Changes in cerebral hemodynamics and inflammatory markers before and after LT.

	Pre-LT(n=27)	Post-LT (n=27)	% change	P value
RI	1.49 ± 0.35	1.21 ± 0.33	-16.1 ± 27.3	0.002
PI	0.98 ± 0.16	0.84 ± 0.16	-12.6 ± 19.9	0.002
BHI	0.78 ± 0.49	0.76 ± 0.52	1.6 (-51 to 100)	0.933
IL-6 (pg/mL)	21.9 (7.8-79.1)	9.5 (5.0-19.8)	-66.5 (-91.8 to 8.4)	0.046
TNF-α (pg/mL)	16.6 (2.8-46.3)	7.9 (0-17)	-63.5 (-100 to -39.6)	p<0.001

Results are expressed as mean ± SD or median (IQR)

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Blood and Biopsy mRNA Signatures of Acute Rejection in Liver Transplant Recipients

Josh Levitsky[1], Sunil M. Kurian[2], Tom Whisenant[2], Daniel R. Salomon[2], Anthony J. Demetris[3], Michael M. Abecassis[1]; [1]Northwestern, Chicago, IL; [2]Scripps, La Jolla, CA; [3]UPMC, Pittsburg, PA

Background: Biomarker profiles diagnostic of acute rejection (AR) could enhance the diagnosis and management of liver transplant (LT) recipients. Our aim was to identify diagnostic genomic (mRNA) signatures of AR that are distinct from patients with other causes of graft dysfunction and normal function. Methods: LT recipients undergoing liver biopsies for cause had blood collected for mRNA expression (Affymetrix® Hu133 Plus Peg microarrays). Two independent pathologists and a hepatologist confirmed the following phenotypes: TX (normal function); AR; HCV-R (hepatitis C recurrence); mixed AR+HCV-R. For the blood analysis, a discovery training set generated a locked classification model for each phenotype which was then tested on a second validation set, using both 5-fold and leave-one out cross-validations (LOOCV). An additional subset that had biopsy tissue underwent a 3-way discovery comparison of AR vs. HCV-R vs. AR+HCV-R. Results: 162 LT recipients (39 TX, 44 AR, 54 HCV-R; 25 AR+HCV-R), age 54.8±8.1 years, 62% male, mean 2.9±1.1 years from LT, were analyzed. The predictive accuracies of these signatures in differentiating AR from TX, HCV-R, and AR+HCV-R, as well as HCV-R from AR+HCV-R, were high and varied based on the 5-Fold CV vs. LOOCV models (Table 1). The biopsy tissue mRNA profiling differentiated AR, HCV-R, and mixed HCV+AR with 83% accuracy. Biological function and canonical pathway mapping of the blood/graft profiles suggest several immune/inflammatory genes differentially expressed in recipients with AR vs. the other etiologies. Conclusion: We have identified blood and graft mRNA signatures that can distinguish AR from other major causes of graft injury in LT recipients with high accuracy. These biomarkers may be useful in the management of LT recipients, such as non-invasively diagnosing AR and in immune monitoring guiding immunosuppression modifications. Samples from a recently completed prospective multicenter study (NIAID CTOT14) will be used to externally validate these signatures and test their predictive value prior to AR.

Predictive Accuracy of Blood mRNA Profiles for Acute Rejection in LT Recipients

Classifier	5-Fold CV	LOO CV
AR vs. TX	76.9%	94%
AR vs. HCV-R	73.3%	90.1%
AR vs. AR+HCV-R	81.2%	98.6%
AR+HCV-R vs. HCV-R	74.7%	97.4%

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The following people have nothing to disclose: Tom Whisenant, Anthony J. Demetris

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Outcomes Following Liver Retransplantation in Primary Sclerosing Cholangitis

Shria Kumar[1], Dustin Carpenter[1], Mariana C. Chiles[1], Sumit Mohan[1], Robert S. Brown[2], Jean C. Emond[2], Elizabeth C. Verna[2]; [1]Columbia University Medical Center, New York, NY; [2]Center for Liver Disease and Transplantation, Columbia University Medical Center, New York, NY

Background: Primary sclerosing cholangitis (PSC) recurs post-liver transplant (LT) in up to 20% of patients. Given the lack of disease altering therapy, recurrent PSC is a common cause of graft loss and need for re-LT in these patients. **Methods**: Data from the Scientific Registry of Transplant Recipients database for transplants from 2002-2015 were utilized to evaluate outcomes in patients with PSC who underwent re-LT. Patients <18 years old, with multi-organ transplants, acute liver failure, or graft survival of < 30 days were excluded. Predictors of re-LT in this population as well as predictors of graft loss following re-LT were evaluated with cox proportional hazards analysis. **Results**: 58,905 patients underwent primary LT in the study period, 3,357 (5.7%) with PSC. Re-LT was significantly more common in patients with PSC compared to patients without PSC (7% v. 3%, p<0.01). Among patients with PSC, baseline characteristics were similar between patients with and without re-LT except those with re-LT were significantly younger, more likely male, more likely to receive donor after cardiac death organ (DCD) and experience acute rejection. In multivariable analyses, age (HR 0.98, p<0.01), male sex (HR 1.6 p =0.02), donor risk index (DRI, per 0.1 increase HR 3.4, p<0.01), deceased donor (HR 2.1, p=0.03), DCD (HR 2.8, p<0.01) and acute rejection (HR 2.7,p<0.01), were independent predictors of re-LT. At re-LT, mean age was 42 years, mean lab MELD 23 (27 with exception), median time since initial LT was 30 (IQR 9 -74) months, and median post-re-LT follow-up was 36 (IQR 9-73) months. The 1,3, and 5 years post-re-LT graft survival were significantly higher in patients with PSC compared to non-PSC patients (89, 79, and 74% vs. 80, 70 and 63%, respectively, p<0.01). Age (0.97, p<0.01), DRI (for 0.1 increase, HR 2.4, p=0.04), and having a deceased donor (1.68, p<0.01) independently predicted graft loss. The most common cause of death following re-LT was infection (38%), followed by malignancy (17%) and graft failure (13%). **Conclusions**: LT recipients with PSC require re-LT more commonly than patients transplanted for other diseases; donor characteristics including DRI and DCD as well as rejection may play important roles in predicting graft loss. Fortunately, graft survival following re-LT in patients with PSC is significantly higher than in patients without PSC and re-LT may provide prolonged survival in this population.

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The Braden scale, a standard tool for assessing pressure ulcer risk, predicts ambulatory status and disability after liver transplantation

Jane Lim[1], Sentia Iriana[1], Shahzad Ahmed[1], Danielle Tholey[2], Tram T. Tran[1], Nicholas Nissen[1], Irene K. Kim[1], Andrew S. Klein[1], Alagappan A. Annamalai[1], Barry Schlansky[2], Vinay Sundaram[1]; [1]Cedars-Sinai Medical Center, Los Angeles, CA; [2]Oregon Health Sciences University, Portland, OR

Aims: The Braden scale is a validated measure of pressure ulcer risk that is assessed in all hospitalized patients in the United States (US), as required by Center for Medicare and Medicaid services. Prior findings have shown the Braden scale to predict clinical outcomes in cirrhosis. Our aim was to evaluate the association of pressure ulcer risk according to the Braden scale with early disability-related outcomes and mortality after liver transplantation (LT). **Methods:** We performed a retrospective cohort study of deceased-donor LT recipients at a single center from 2011-2014. Patients were categorized by Braden score on admission as low risk for pressure ulcers (>18), mild to moderate risk (16-18), or high risk (<16). We performed logistic regression to evaluate the association of Braden scale category with post-LT in-hospital mortality, discharge to rehabilitation facility, non-ambulatory status at discharge, and 30-day rehospitalization, and linear regression to evaluate post-LT length of hospital stay (LOS). **Results:** Of 169 patients studied, mean age was 57, and most patients were male (68%), white (54%) and had hepatitis C (56%). Nearly 52% of patients received Model for End-Stage Liver Disease (MELD) exceptions for hepatocellular carcinoma (HCC). After adjusting for differences in age, gender, race, liver disease etiology, diabetes, dialysis, body mass index, HCC, MELD score, albumin, and donor risk index, the high-risk Braden score category was significantly more likely to be non-ambulatory at discharge (OR=4.56; p=0.02) and to discharge to a rehabilitation facility (OR=9.04; p<0.01) **(Table 1).** High-risk Braden score patients also had a trend for longer LOS (p=0.07). Braden score category was not associated with in-hospital mortality or 30-day readmission rate. **Conclusion:** A standardized measure of pressure ulcer risk performed on all inpatients in the US predicted early disability after LT. Consideration of the Braden scale during the LT evaluation may facilitate a prognostication of disability and early use of directed interventions to optimize functional status.

Multiple regression models evaluating the Braden Scale and post-liver transplant outcomes*

Outcome	Braden score > 18 (no risk for pressure ulcer)	Braden score 16-18 (Mild-moderate risk for pressure ulcer) (Adjusted OR, 95% CI)	Braden Score <16 (High risk for pressure ulcer) (Adjusted OR, 95% CI)
Discharge to rehabilitation facility	Reference	1.03 (0.38 - 2.83, p=0.94)	9.04 (2.59 - 31.5, p<0.01)
Non-ambulatory at discharge	Reference	1.48 (0.05 - 4.65, p=0.50)	4.56 (1.27 - 16.4, p=0.02)
Inpatient mortality	Reference	3.17 (0.49 - 20.2, p=0.22)	5.71 (0.71 - 46.2, p=0.10)
30-day readmission	Reference	1.09 (0.42 - 2.88, p=0.85)	0.76 (0.238 - 2.41, p=0.64)
Length of stay**	Reference	9.24 (-2.25 - 20.7, p=0.11)	10.2 (-.708 - 21.1, p=0.07)

*adjusted for age, gender, race, liver disease etiology, diabetes, dialysis, body mass index, HCC, MELD score, albumin, and donor risk index

**Describes adjusted b-coeffecient in linear regression

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Liver Transplant Significantly Improves Gut Microbial Dysbiosis and Microbial Diversity in Cirrhotic Patients

Jasmohan S. Bajaj[1], Masoumeh Sikaroodi[2], Melanie White[1], Andrew Fagan[1], HoChong Gilles[1], Douglas M. Heuman[1], Patrick M. Gillevet[1]; [1]VCU and McGuire VAMC, Richmond, VA; [2]George Mason University, Manassas, VA

Unfavorable microbiota changes or dysbiosis is associated with cirrhosis progression. However the impact of liver transplantation (LT) on microbiota is unclear. **Aim**: to define the impact of LT on gut microbiota composition compared to healthy controls (HC). **Methods**: Outpatient cirrhotics listed for LT were enrolled. Study visits were pre/6 mths post-LT once on stable immunosuppression. At both visits, pts underwent stool collection for microbiota using multi-tagged pyrosequencing. Analysis was performed for microbial diversity (chao1 higher=more diversity), genus-level changes (LEFSe) & cirrhosis dysbiosis ratio pre/post LT. Cirrhosis dysbiosis ratio studies relative abundance of beneficial autochthonous to potentially pathogenic bacteria (low score=worse). Pre/Post-LT patients were compared to an age-matched cohort of HC. **Results**: We enrolled 56 pts (56±7 years, 37 men, 55% HCV, MELD 29±8) who were seen before/after LT and 45 HC (age 54±8 years). 45 pts were on rifaximin, 35 on lactulose & 12 on ciprofloxacin for SBP prophylaxis. Patients received LT 8±6 months after enrollment &were seen again 7±2 mths post LT. At the time of the post-LT visit, all were on Bactrim and stable tacrolimus doses. None of the patients had recent infections, had their HCV eradicated, were actively rejecting, required re-LT or had recurrent cirrhosis. *Pre- vs. post-transplant microbiota*: There was a significant increase in diversity (Chao1 pre 137 vs post 183.1, p<0.05) after LT. There was a significant improvement in the cirrhosis dysbiosis ratio (pre 0.36 to post 1.6, p=0.009). On LEFSe, there was a significant reduction in potentially pathogenic genera (*Escherichia, Shigella, Salmonella*) with a significant increase in potentially beneficial taxa i.e. *Ruminococcaceae, Lachnospiraceae &* other Clostridial families. *Comparison with HC*: HC had the highest diversity (Chao1 218.8, p<0.05) and best dysbiosis ratio (2.1, p=0.002) compared to both pt groups. Pre-LT vs HC: As expected, greater dysbiosis was seen in pre LT pts compared to HC with pathogenic genera (*Escherichia, Shigella, Salmonella*) and lower autochthonous taxa. Post-LT vs HC: After LT pts had increased *Bacteroidaceae* compared to HC with any increase in pathogenic genera in either group. Despite increasing significantly from pre-LT levels, beneficial Clostridial families remained significantly lower post LT compared to HC. **Conclusions**: Liver transplant significantly improves gut microbial diversity and dysbiosis but not to the level of healthy controls. Significant increases in autochthonous taxa & suppression of pathogenic ones relative abundance post-LT indicate restoration of the impaired gut-liver axis.

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The following people have nothing to disclose: Masoumeh Sikaroodi, Melanie White, Andrew Fagan, HoChong Gilles

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Good glycaemic control pre-operatively protects against some adverse outcomes associated with diabetes in liver transplant recipients

Charlotte Boughton[1], Omar Mustafa[1], Abid Suddle[2], Michael A. Heneghan[2], Nigel Heaton[2], John G. O'Grady[2], Stephanie Amiel[1]; [1]Diabetes, King's College Hospital, London, United Kingdom; [2]Institute of Liver Studies, King's College Hospital, London, United Kingdom

Pre-existing diabetes is an important risk factor for poor outcomes following liver transplantation. The benefit of improved glycaemic control pre-transplant on outcomes has not been established. The aim of this study was to assess whether good glycaemic control pre-operatively protects against the deleterious effects of diabetes on liver transplantation outcomes. We retrospectively analysed data from 235 adult liver transplant recipients, including 69 individuals with pre-transplant diabetes transplanted at a single tertiary referral centre between January 2013 and September 2015. We divided recipients with diabetes into those with poor (HbA1c ≥8.5%/69.4mmol/mol) and those with acceptable glycaemic control (HbA1c <8.5%/69.4mmol/mol). Mean follow-up duration was 21.8 months. Recipients with diabetes were 5.7 ± 0.2 years older (P=0.001), and 3.2 ± 0.1 kg/m^2 more overweight (P=0.001). All-cause mortality was unaffected by the presence of diabetes. However, recipients with diabetes had increased rates of all-cause allograft failure (RR v non-diabetics (*ND*) 2.7, 95%CI 1.1-6.7, P=0.032). Presence of diabetes was associated with a reduced risk of rejection (RR vs ND 0.6, 95%CI 0.3-0.9, P=0.039). However, rejection rates were higher in diabetic recipients with HbA1c ≥8.5% compared to those with an HbA1c <6.5% (40% vs 4.3%, P=0.023). Incidence of infection was increased in recipients with diabetes (RR vs ND 1.36, 95%CI 1.1-1.7, P=0.013), with the risk of infection greatest in those with an HbA1c ≥8.5% compared to those with an HbA1c <6.5% (P=0.046). The incidence of acute kidney injury was increased in recipients with diabetes (RR vs ND 1.30 95%CI 1.1-1.5 P<0.001) and acceptable glycaemic control pre-transplant did not protect against this. Diabetic recipients with an HbA1c ≥8.5% were more likely to be re-admitted to ITU within 30 days of transplantation than those with better glycaemic control (P=0.023). Length of stay in intensive care (ITU) and in hospital were not significantly affected by the presence of diabetes. However, recipients with a pre-transplant HbA1c ≥8.5% had an increased duration of stay in hospital compared to those with an HbA1c <6.5% (29.0 vs 15.6 days, P=0.048) and a trend towards an increased length of stay in ITU compared to those with better glycaemic control (7.3 vs 3.3 days, P=0.07). In conclusion, pre-transplant diabetes is associated with increased incidence of allograft failure, infection and AKI following liver transplantation. Good glycaemic control pre-operatively may protect against the deleterious effect of diabetes on infection and is associated with a reduced risk of readmission to ITU and a reduced length of stay in hospital.

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Everolimus with low-dose calcineurin inhibitor in pediatric liver transplant recipients: 12-month results of the H2305 study

Rainer Ganschow[1], Bo-Goran Ericzon[2], Anil Dhawan[3], Khalid Sharif[4], El-Djouher Martzloff[5], Jose A. Aguilar[5], Jennifer Ng[5], Patricia M. Lopez[5]; [1]University Medical Center, Bonn, Germany; [2]Karolinska University Hospital, Stockholm, Sweden; [3]King's College Hospital, London, United Kingdom; [4]Birmingham Children's Hospital NHS Foundation Trust, Birmingham, United Kingdom; [5]Novartis Pharma AG, Basel, Switzerland

Background: Everolimus (EVR) combined with low-dose tacrolimus (LTac) provides significant improvement in renal function in adult liver transplant recipients (LTxR), compared with standard-dose tacrolimus. There are very limited studies on use of EVR in pediatric LTxR (pLTxR). **Methods:** CRAD001H2305 (NCT01598987) is a 24-month (M) multi-center, open-label, single-arm study evaluating renal function, efficacy, safety and tolerability of EVR combined with low-dose cyclosporine (LCsA) or LTac in pLTxR. At 1M to 6M post-LTx, eligible pLTxR (≥1M and <18 years [Y]; n=56) of full-size or technically-modified liver grafts received EVR (starting dose 0.8 mg/m^2 BID, thereafter adjusted to maintain trough level 3–8 ng/mL) + LTac (C0h M1–3: 3–6 ng/mL, after M3: 2–5 ng/mL) or LCsA (C0h M1–3: 50–150 ng/mL, after M3: 25–100 ng/mL) ± steroids. Primary objective was renal function assessment by eGFR (by Schwartz formula) from baseline (BL) to M12. Analysis of the safety data by the Data Monitoring Committee in February 2015 resulted in stopping of study enrollment and discontinuation of the study medication in <7Y. **Results:** Baseline mean (SD) age and eGFR were 4.9Y (4.6) and 90.5 mL/min/1.73m^2 (22.2), respectively. At M12, eGFR had increased compared with BL (90.5 vs. 96.7 mL/min/1.73m^2, respectively). Mean eGFR change was numerically greater in pLTxR <2Y (7.3 mL/min/1.73m^2) vs. those 2–18Y (5.3 mL/min/1.73m^2). Urinary protein/creatinine ratio and urinary protein excretion had decreased from BL to M12. Incidence of composite efficacy failure (treated biopsy proven acute rejection [tBPAR], graft loss or death) was low at 1.9% and due to occurrence of a single tBPAR; no graft loss or death occurred in the study period. Serious infections had occurred in 76.0% of pLTxR <2Y and 48.4%% of 2–18Y at M12. Further, 32.0% of pLTxR <2Y and 12.9% of 2–18Y had serious AEs/infections leading to discontinuation of study drug. An increased rate of post-transplant lymphoproliferative disease was observed in subjects <2Y (12.0%, n=3) vs. those 2–18Y (6.5%, n=2). No negative effect on growth and development was observed. **Conclusions:** Although the H2305 study demonstrates good efficacy and renal function at M12 with EVR + LTac/LCsA in pLTxR, the safety findings in this population, particularly those <2Y, remain to be better established.

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El-Djouher Martzloff - Employment: Novartis Pharma AG

Jose A. Aguilar - Employment: Novartis Pharma AG

Jennifer Ng - Employment: Novartis Pharma AG

Patricia M. Lopez - Management Position: Novartis

The following people have nothing to disclose: Khalid Sharif

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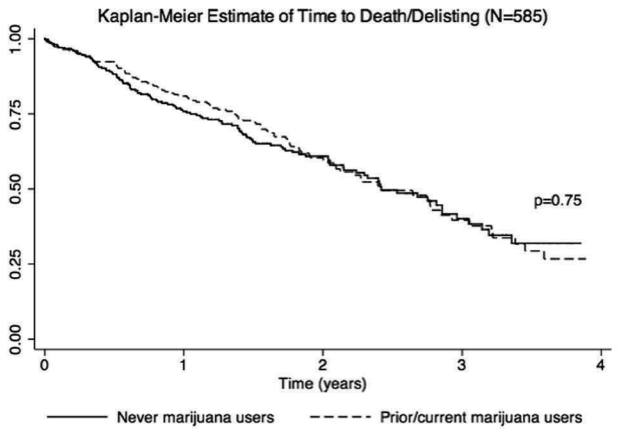
Marijuana use does not affect outcomes on the liver transplant waitlist

Prashant Kotwani, Varun Saxena, John P. Roberts, Bilal Hameed; UCSF, San Francisco, CA

Background: There is conflicting data on marijuana (MJ) use and progression of liver disease. Liver transplant outcomes research among MJ users is limited. Aims: Determine the prevalence and factors associated with MJ use. Assess the impact of MJ use on time to waitlist death/delisting and time to transplant. Methods: Retrospective cohort of adults evaluated for transplant from 1/1/2012 to 12/31/2013 at UCSF. MJ use was defined as self-report in psychosocial assessment and/or urine toxicology. Statistics included Poisson regression, Kaplan-Meier and Cox regression models. Results: 884 adults were evaluated and 585 (66%) were listed with a median follow up of 1.4 years. Prevalence of MJ use was 48%, with 7% being current users and 41% prior users. In multivariate analysis, statistically significant predictors of MJ use included age 18-29 years (IRR=2.2), white race (IRR=1.2), tobacco use (IRR=1.4), alcohol use (IRR=9.0), illicit drug use (IRR=2.6), and MELD<20 (IRR=1.2). Among listed patients, MJ use was not associated with death/delisting in unadjusted survival analysis (Figure). In adjusted analysis among listed patients, MJ use was not a significant predictor of death/delisting whereas age 18-29 years (HR=5.7, 95% CI 2.1-15.6), HBV/HCV cirrhosis (HR=1.5, 95% CI 1.1-2.0), MELD>20 (HR=3.3, 95% CI 2.4-4.4), and HCC (HR=1.4, 95% CI 1.1-2.0) were. Similarly, among listed patients, MJ use was not a predictor of receiving a transplant whereas alcohol use (HR=0.6, 95% CI 0.4-0.8), prescription opiate/benzodiazepine use (HR=0.7, 95% CI=0.5-0.9), MELD>20 (HR=2.9, 95% CI 2.2-3.8), and HCC (HR=1.6, 95% CI 1.2-2.1) were. Conclusions: Almost half of evaluated candidates were current or prior users of MJ. However, MJ use was not associated with worse outcomes on the waitlist. MJ use should not be penalized by transplant centers and UCSF no longer considers MJ use to be a contraindication for liver transplant.



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The following people have nothing to disclose: Prashant Kotwani, Varun Saxena, Bilal Hameed

975

Antiphospholipid antibodies associated vascular events are an underrecognized cause of morbidity and mortality after liver transplantation: Benefit of plasmapheresis and anticoagulation in transplanted patients with high thrombotic risk

Alejandra Villamil, Juan C. Bandi, Felix Nunez, Eduardo G. Mullen, Leticia Yamamoto, Eduardo De Santibanes, Adrian Gadano; Hospital Italiano de Buenos Aires, Los Polvorines, Argentina

Antiphospholipid antibodies (aPL-ab) are frequently present in patients with end-stage liver disease and associated with morbidity and graft loss post-transplant as a result of vascular thrombosis. Risk is increased in patients with pre-OLT aPL-related thrombotic events or high titer circulating aPL-ab. Plasmapheresis and immunosuppression have been proposed as adequate therapy post-development of vascular complications. Aim: To evaluate the impact of pre-OLT plasmapheresis with post-OLT anticoagulation in patients transplanted for end-stage liver disease with high risk for aPL-ab vascular complications. Patients and Methods: Between 2005 and 2015 321 patients transplanted for end-stage liver disease were screened for aPL-ab and lupus anticoagulant activity. 86/321 patients (27%) had increased levels of aPL-ab (anticardiolipin IgM and/or IgG isotypes, anti Beta-2 glycoprotein) and/or lupus anticoagulant activity. 29/86 fulfilled high thrombotic risk criteria and were randomly divided in 2 groups: Group A (n=12): patients with standard low dose aspirin ± low weight heparin post-OLT. Group B (n=17): patients with 1-2 hours pre-OLT plasmapheresis with fresh frozen plasma followed by post OLT anticoagulation for at least 3 months. Clinical and Doppler US evaluations were performed immediately post OLT and at different time-points for the first 6 months. Etiology, severity of cirrhosis and immunosuppression did not differ between groups. Immunosuppressive regimen included steroids + CyA (n=10) or tacrolimus (n=19) ± mycophenolate. Results: 11/12 patients in group A developed aPL-ab related complications (cerebrovascular ischemia n=3, humeral thrombosis n=2, hepatic artery thrombosis n=1, intestinal ischemia n=1, retinal artery thrombosis n=1, portal vein thrombosis, catastrophic antiphospholipid syndrome(CAPS) n=4) resulting in grafts loss (n=1), irreversible neurologic damage (n=1) and death (n=5). In Group B 3/17 patients developed an aPL-associated complication: 2 CAPS and 1 hepatic artery thrombosis resulting in 2 deaths. Thrombotic complication rate was 37.9 % vs 10.3 %, $p<.0001$. No differences were observed in the development of CAPS and renal microangiopathy. There was a tendency to higher aPL related deaths among patients with only standard therapy (17.2 % vs 6.9 %, $p.06$) Conclusion: aPL-ab are a significant under-recognized cause of thrombotic complications and mortality post-OLT. Pre-OLT plasmapheresis with post-OLT anticoagulation post-OLT may be an effective strategy to prevent aPL-ab associated vascular complications in high risk patients.

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Risk factor analysis of disease recurrence after liver transplantation for primary biliary chonlangitis

Noriyo Yamashiki[1], Akira Mori[2], Yoshihide Ueda[1,3], Atsushi Yoshizawa[2], Hironori Haga[4], Toshimi Kaido[2], Hideaki Okajima[2], Shinji Uemoto[2,1]; [1]Organ Transplantation Unit, Kyoto University Hospital, Kyoto, Japan; [2]Department of Hepato-Biliary-Pancreatic Surgery and Transplantation, Graduate School of Medicine, Kyoto University, Kyoto, Japan; [3]Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan; [4]Department of Pathology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Background: Recurrence of primary biliary cholangitis (PBC) is reported in approximately 10% to 30% of recipients after liver transplantation (LT), and can cause late graft dysfunction resulting in re-transplantation or death. Although several factors such as immunosuppressant or the use of ursodeoxycholic acid (UDCA) were reported to be associated with recurrence of PBC (rPBC), confirmatory data are still scarce. Methods: Retrospective review of 106 liver transplant recipients (male 6, female 100, age 51±8.4 years) with PBC was conducted. Episodic and protocol liver biopsies were performed an average number of 0.5 per year in each recipient. The first appearance of histological rPBC by Scheuer's classification was regarded the date of rPBC. Risk factors for survival was analyzed using Cox regression hazard model. Subhazard for rPBC was calculated using Fine and Gray model and death without rPBC was regarded as a competing risk. Results: There were 3 deceased donor LT and 103 living-donor LT (left lobe 44, right lobe 57, posterior lobe 2). Mean age of donors was 40 (19–66) years, and 67 (63.2%) were blood relatives. Initial immunosuppressant was tacrolimus in 92 and cyclosporine A in 14. Median follow-up after LT was 7.1 (0.02 – 18.7) years, and 75 were followed at least 1 year; at 1-year follow-up, UDCA was continued in 65(86%), corticosteroid in 47 (62%), and antimetabolite in 55 (73%). Overall patient survival at 1, 5, 10 years were 72.5%, 70.4%, and 64.6%, respectively. rPBC was diagnosed in 33 at the median interval from LT of 4.0 (0.5 – 14.5) years. By univariate analysis, donor age>40years (HR 2.45 p=0.01) and 4 or more HLA (HLA A, B, DR) mismatch (HR 3.77, p<0.01) were risk factors for patient survival. Multivariate analysis showed 4 or more HLA mismatch was the only independent factor for patient death (HR 3.36, p=0.02). For rPBC, 4 or more HLA mismatch (HR 0.38, p=0.06), IgM>500mg/dl (HR 1.93, p=0.06), AMA-M2 >180mg/dl (HR 2.04, p=0.07), and use of cyclosporine A (HR 2.74, p=0.02) were considered for risk factors, but the use of cyclosporine A was the only independent factor for rPBC by multivariate analysis (HR 2.75, p=0.02). The use of UDCA, antimetabolite, or continuous corticosteroid were not found to be associated with rPBC. Conclusions: HLA mismatch was associated with poor patient survival and the use of cyclosporine A was associated with rPBC. Preemptive use of UDCA was not associated with occurrence of rPBC. Further investigation is needed to evaluate the factors associated with disease progression of rPBC.

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Simultaneous kidney transplantation at time of liver re-transplantation improves survival

Sonali Paul[1], Joel T. Adler[2], James F. Markmann[2], Heidi Yeh[2]; [1]GI / Hepatology, MGH, Cambridge, MA; [2]Surgery, MGH, Boston, MA

Background: Since the development of the Model for End-Stage Liver Disease (MELD) score, there has been an increase in the number of simultaneous liver-kidney transplants (SLK). Previous research has suggested that patients with cirrhosis and kidney dysfunction who undergo their first liver transplantation alone (LTA) have decreased patient survival than those receiving SLK transplants. However, it is uncertain if this benefit is seen in those requiring a second liver transplant. Methods: Scientific Registry of Transplant Recipients who underwent a second liver transplant between 2000 and 2013 were analyzed. Survival was estimated using Kaplan-Meier analysis by log rank testing. Cox proportional hazards regression analysis was performed to determine the relationship between recipient and donor variables and patient survival. Results: 3436 patients had a median follow-up of 28.6 months (range 0-120). Median age was 52.2 years (18-75) and the majority were men (n=2311, 67%,) and white (n=2426, 70%). 87% (n=2994) underwent LTA alone and 13% (n=442) received SLK. A total of 1451 (42%) patients died during the study period; 173 (40%) in those receiving SLK and 1278 (43%) with LTA. Patients undergoing SLK were significantly older, more likely to be black, and have higher MELD scores, serum creatinine, and bilirubin, but less likely to be in the ICU and had lower INR. In univariate analysis, post-liver transplant survival was greater in those who underwent SLK (median 36 months; 3 months, 1 year, 3 year, and 5 year survival probability's were 85%, 77%, 71%, 64%) compared to those who underwent LTA (median 26 months; 83%, 74%, 66%, 60%). This was not statistically significant (p=0.07). After adjusting for confounders, SLK patients were 21% less likely to die after liver transplant than those who underwent LTA (HR= 0.7985, p = 0.02). Of the 2994 patients that underwent LTA, 888 had a serum creatinine greater than 2.0 mg/dL. In these patients, post-liver transplant survival was significantly greater in SLK patients compared to LTA at 3 months, 1 year, 3 years, and 5 years (85%, 77%, 71%, 64% versus 80%, 70%, 59%, 52% respectively; p<0.001). Conclusions: Outcomes following liver re-transplantation have improved over time, although they continue to be worse than for primary liver transplantation. After adjusting for confounders, among all patients who require a second liver transplant, SLK outcomes are better than for LTA. This effect is most pronounced in post-liver transplant patients with impaired renal function. Given the implications for organ allocation, future research is needed to determine the factors related to this discrepancy.

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The following people have nothing to disclose: Sonali Paul, Joel T. Adler, James F. Markmann, Heidi Yeh

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Expression of cholesterol regulatory enzymes SREBP-2 and HMG-CoA R predicts the outcome of human liver transplantation

Anna Baulies[1,2], Juan C. Valdecasas[3,2], Jose Fuster[3,2], Antoni Rimola[3,2], Jose Fernandez-Checa[1,2], Carmen Garcia-Ruiz[1,2]; [1]Instituto Investigaciones Biomedicas Barcelona, CSIC, Barcelona, Spain; [2]IDIBAPS and CIBEREHD, Barcelona, Spain; [3]Liver Unit, Hospital Clinic, Barcelona, Spain

Liver transplantation (LT) is an effective therapy for the treatment of chronic liver diseases and hepatic liver failure. However, the unbalance between organ availability and the increasing number of potential candidates undergoing LT seriously limits this therapeutic approach. This fact has prompted the need to expand the inclusion criteria of grafts for LT, and some grafts accepted for transplantation present steatosis. Liver steatosis is considered a primary factor of graft failure after LT but the mechanisms involved in this process are not fully characterized. Although, macrovesicular steatosis has been considered a key factor determining the outcome of LT, recent findings have shown that cholesterol accumulation controls hepatic ischemia/reperfusion injury through sensitization to inflammatory cytokines and oxidative stress. Hence, our aim was to characterize the levels of cholesterol and expression of regulatory enzymes in order to optimize selection criteria of liver grafts and to predict the outcome of LT. METHODS: Graft biopsies were collected before (donor) and after (recipient) liver transplantation. A total of 182 donor biopsies were analyzed for StARD1, SREBP2, CHOP, PDK and HMG-CoA R mRNA expression by RT-PCR. Free cholesterol was analyzed by HPLC. Graft rejection and clinical outcome after LT was followed during the first year in all patients. RESULTS: MELD score of the recipient and StARD1 mRNA level of the donor biopsy correlated at 3 and 6 months after LT, while MELD score and SREBP2 and HMG-CoA R mRNA levels in the donor biopsy correlated at 6 months after LT. StARD1 mRNA levels in the donor biopsy correlated with total cholesterol and triglycerides levels in the graft. When clinical data and mRNA profile were statistically related to patient survival following LT, MELD score significantly increased in patients with bad prognosis and those exhibiting higher SREBP2 and HMG-CoA R mRNA levels in donor liver biopsies. StARD1 mRNA levels and free cholesterol content of the donor biopsy showed a trend to increase in patients that died during the first year of LT. Moreover, the percentage of patients with enhanced SREBP2 and HMG-CoA R mRNA levels significantly increased in the third tertile, indicating bad prognosis for patients with SREBP2 and HMG-CoA R expression beyond a specific threshold. Finally, a multivariant analysis confirmed elevated hazard risk for patients with elevated mRNA levels of SREBP2 and HMG-CoA R in the donor biopsy, while the levels of PDK1 and CHOP had less impact. CONCLUSION: Determination of cholesterol regulatory enzymes SREBP2 and HMGCoA mRNA levels could be a good predictor for the outcome of LT

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979

High MELD score does not affect outcome of Living Donor Liver Transplantation: Experience in 1000 recipients

Neeraj Saraf, Sanjay K. Yadav, Narendra S. Choudhary, Sanjiv Saigal, Prashant Bhangui, Sanjay Goja, Amit Rastogi, Arvinder Soin; Medanta Liver Institute, Medanta Medicity, Gurgaon, India

Background : In countries where deceased organ donation is scarce, there is big gap between demand and supply of organs and living donor liver transplantation (LDLT) plays an important role in meeting this unmet need. There are few studies analyzing outcomes of LDLT in patients with high Model for End-stage Liver Disease (MELD) score. This study was conducted to analyse the effect of pre-transplant MELD score on outcomes following LDLT. **Methods:** Outcome of 1000 patients who underwent LDLT from July 2010 to March 2015 was analysed retrospectively. Recipients of ABO blood group incompatible transplant, acute liver failure and paediatric age group were excluded from the study. For HCC patients, the actual disease MELD was considered for analysis. The worst MELD score within a month before LDLT was considered. Patients were grouped into low MELD <25 and high MELD ≥25 scores to compare outcomes at one year. Continuous variables were analysed using independent student t test. Categorical variables were compared using the Chi square test. Cumulative overall survival rates were calculated using Kaplan–Meier methods, A two tailed p value <0.05 was considered significant. All statistical data were generated using SPSS 20 (Chicago, Inc USA). **Results:** Out of 1000 LDLT recipients, 849 were in low MELD group (Mean MELD = 16.90±9.2) and 151 were in high MELD group (Mean MELD = 28.77±7.2).There was higher prevalence of hepatitis C virus (HCV) (31.1% vs 19.9%, p=0.00) and hepatocellular carcinoma (HCC) (26% vs 6%, p=0.00) in low MELD group and alcoholic liver disease (29% vs 40.4%, p=0.00) in high MELD group.There was no significant difference in the mean length of intensive care unit (6.83±5.02 vs 7.21±5.30, p=0.25) and hospital stay (17.28±7.69 vs 17.53±9.26, P=0.52) between low and high MELD groups. no significant difference was observed between the operative time, graft weight, GRWR and type of graft harvested between the groups. However, patients with high MELD score required significantly more transfusion of fresh frozen plasma (3.19±3.42 vs 4.32±3.82, p= 0.04). Similarly, there were no significant difference in rates of sepsis (11.1% vs 11.3%, p=0.51), hepatic artery thrombosis (4.2% vs 2.6%, p=0.25) or biliary complications (12.4% vs 9.9%, p=0.24) and acute cellular rejection (8.1% vs 10.6%, p=0.19) No significant difference was observed in survival (87.2% vs 84.1%, p=0.18) between the two groups at one year. **Conclusion:**Pre-transplant high MELD score does not adversely affect outcomes after LDLT. In view of shortage of deceased organs, LDLT can be justified in high MELD recipients.

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Cardiac risk stratification in patients undergoing liver transplantation – results of a three-tiered assessment approach based on traditional cardiac risk-factors

Marcus Robertson[1], William W. Chung[1], Tessa V. O'Halloran[1], Omar Farouque[2], Mark Horrigan[2], Paul Gow[1], Peter W. Angus[1]; [1]Liver Transplant Unit, Austin Hospital, Heidelberg, VIC, Australia; [2]Department of Cardiology, Austin Hospital, Heidelberg, VIC, Australia

Background: Although screening of liver transplantation (OLT) candidates for coronary artery disease (CAD) is recommended, there is a lack of data on the effectiveness of screening strategies. In 2010, our centre adopted a 3-tiered cardiac risk assessment protocol which stratifies patients into risk groups based on age and cardiac risk-factors. **Objectives:** To assess the safety and efficacy of a 3-tiered cardiac risk stratification protocol in patients undergoing OLT assessment. **Methods:** Consecutive patients ≥18 years undergoing OLT assessment over a 40-month period from 2010 to 2014 were prospectively included. Patients were stratified into one of 3 cardiac risk groups and received standardised investigations (Table). Primary outcomes were peri- or post-operative cardiac events. **Results:** 240 patients were included. Median age was 55 (IQR 48 - 59), 75% were male and median MELD score was 17 (IQR 13 – 22). The most common indications for OLT were hepatitis C, alcohol, hepatocellular carcinoma and NAFLD. Documented cardiac risk factors included: diabetes (25%), smoking (47%), hypertension (17%), hypercholesterolemia (9%), family (26%) or personal (10%) history of ischemic heart disease (IHD), and obesity (21%). 61% (147) patients had ≥2 risk factors. 38 patients were identified as low risk (LR), 123 intermediate risk (IR) and 79 high risk (HR). 1 LR patient with severe pulmonary hypertension (PHT) on ECHO and coronary angiogram (CA) was rejected. 9 patients (4 IR and 5 HR) had inducible ischemia at DSE and proceeded to CA, with 2 rejected due to severe CAD. 61 HR patients with a normal DSE progressed to CT coronary angiogram (CTCA). 12 patients had significant CAD detected by CTCA of whom 2 were rejected, 4 were listed when no critical stenosis were detected by CA, 4 were listed without CA and 2 were rejected for non-cardiac indications. Overall 7 patients were not listed for OLT due to abnormal cardiac investigations. Two cardiac events were recorded (event rate 0.8%), both in the IR group: 1 non-fatal intra-operative cardiac arrest and 1 death post-OLT from cirrhotic cardiomyopathy; neither patient had CAD identified prior to OLT. **Conclusions:** Cardiac risk stratification based on traditional cardiac risk factors with the selective use of DSE, CA and CTCA is a safe and feasible approach that results in a very low peri-operative cardiac event rate.

Risk group	Investigations	Results and follow-up
Low risk - Age <45 OR Diabetic patient <35 AND no cardiac RF	Trans-thoracic ECHO	Normal: No further investigation Abnormal: referral to high-risk Cardiology clinic
Intermediate risk - Age >45 OR Diabetic patients age 35-50 OR history of heart disease OR Males >35 with 1 additional cardiac RF*	Dobutamine stress ECHO (DSE)	Normal: No further investigation Evidence of ischemia: Coronary angiogram (CA)
High risk - Age >60 OR Diabetic patient >50	DSE	Normal: CT coronary angiogram (CTCA) Evidence of ischemia: CA

*additional risk-factors (RF) include hypertension, smoking, first-degree relative with CAD, hypercholesterolemia

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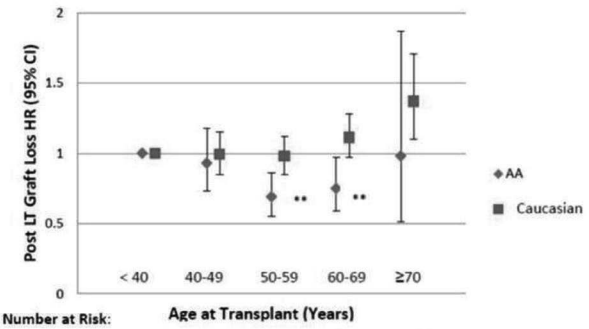
981

Increased Graft Loss Among Younger African American Women After Liver Transplantation

Shravan Dave, Jennifer L. Dodge, Norah Terrault, Monika Sarkar; UCSF, San Francisco, CA

Background: The number of women undergoing liver transplant (LT) is increasing and gender-specific models of care are needed. Racial/ethnic disparities in post-LT outcomes have been identified in predominantly male cohorts, but racial/ethnic influences on graft outcomes in women are unknown. Methods: Using the United States Scientific Registry of Transplant Recipients (SRTR) database, we examined the association of race/ethnicity and graft loss in women (death or retransplant) from 2002-2012. Covariates included recipient and donor characteristics, socio-economic factors, and medical co-morbidities. Results: The eligible cohort included 11,051 Caucasians, 2,171 Hispanics, 1,876 African Americans (AA), and 762 Asian women with a median follow-up of 3.1 years. Graft survival at 5 years was lower among AA women (60%) as compared to Caucasians (71%), Hispanics (70%) and Asians 73% (p< 0.001). Risk of graft loss was higher in AA women aged < 40 at LT compared to AA women ages 50-69, while risk increased with increasing age after age 60 years among Caucasian women (Figure). Risk of graft loss from chronic rejection was higher in younger as compared to older AA women (HR 3.3, 95% CI 2.1-5.1, p<0.001), with no significant risk differences between older AA and Caucasian women (p=0.31). However, non-compliance causing graft loss was not significantly different between younger and older AA women, or between younger AA and younger Caucasian women (p values ≥ 0.15). Conclusions: AA women, especially those age <40 years, are at higher risk for graft loss compared to older AA women and women of other racial/ethnic groups. Graft loss from chronic rejection is more frequent in these young AA women, which is not explained by medication non-compliance. Studies of racial differences in drug metabolism are therefore needed to better understand the mechanisms underlying differential rates of rejection and graft loss.

Lower Risk of Graft Loss Among AA Women Aged 50-69 Years Compared to AA Women < 40 Years of Age at LT*



Number at Risk:	< 40	40-49	50-59	60-69	≥70
AA, n=	379	379	730	366	22
Caucasians, n=	1251	2062	4318	3049	371

* Reference group is age < 40 years for respective races

** p < 0.01 for age/race interaction among AA women, with AA women < 40 as the reference

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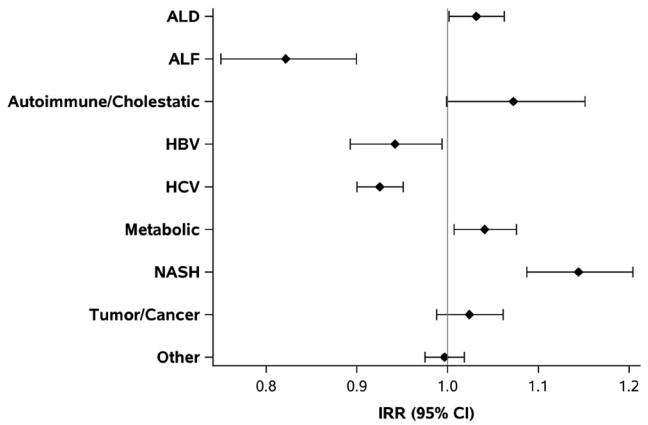
The following people have nothing to disclose: Shravan Dave, Jennifer L. Dodge, Monika Sarkar

982

Nonalcoholic Steatohepatitis is the Most Rapidly Increasing Indication for Liver Transplantation in Young Adults in the United States

Danny Issa[3], Kymberly Watt[2], Ghassoub Rifai[1], Rocio Lopez[1], Naim Alkhouri[1], Iliana Doycheva[2]; [1]Digestive Disease Institute, Cleveland Clinic, Cleveland, OH; [2]Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN; [3]Virginia Commonwealth University, Richmond, VA

Background: Although NASH can progress to cirrhosis during early adulthood, it is thought that NASH is a rare indication for liver transplantation (LT) in young adults. The aims of this study were to estimate the frequency of LT performed for NASH in young adults (18-40 years) compared to other indications, to assess the changes of frequency over 10 years, and to evaluate post-LT outcomes. **Methods:** We performed a retrospective cohort analysis of all young adults who received their first LT in the US between 2002 and 2012, using the United Network for Organ Sharing database. Incidence rate ratios (IRR) were calculated for each indication. Kaplan-Meier analysis was used to assess survival. Outcomes of LT for NASH were compared to those transplants done for other metabolic diseases. **Results:** A total of 5,157 young adults underwent LT between 2002 and 2012. Mean age at time of LT was 32 ± 7 years and 54% were male. The most common indication for LT was autoimmune/cholestatic disease (25%) followed by acute liver failure (ALF) (18%). The incidence of LT performed for NASH increased from 0.53% in 2002 to 4.46% in 2012. Indication IRR were significantly higher in NASH compared to all other indications for LT in young adults; demonstrating NASH as the most rapidly increasing indication for LTs with a 14% increase per year [IRR (95% CI) = 1.14 (1.09, 1.20)] (figure). The 5-year graft survival rates were lower and the re-transplantation rates were higher in NASH compared to other metabolic liver diseases (69% vs 79%, respectively; P=0.003 for graft survival and 11% vs 8%, respectively; P=0.046 for re-transplantation). **Conclusions:** NASH is the most rapidly growing indication for LT among young adults in the US and now accounts for approximately 5% of all transplants. LT for NASH in young adults was associated with lower graft survival and higher rates of re-transplantation compared to other metabolic diseases.



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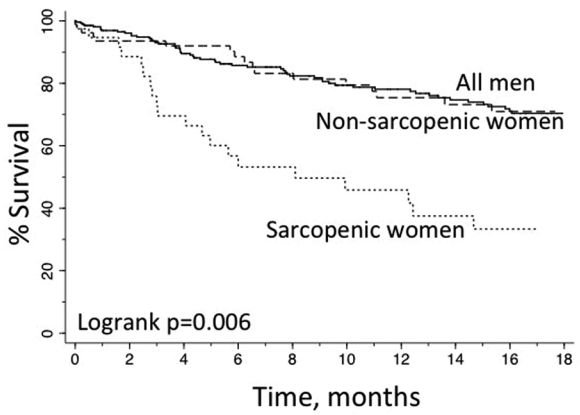
Sarcopenia accounts for the gender disparity in waitlist mortality in liver transplantation: From the Fitness, Life Enhancement, and Exercise in Liver Transplantation (FLEXIT) Consortium

Jennifer C. Lai[2], Elizabeth J. Carey[1], Aldo J. Montano-Loza[3], Connie W. Wang[2], Srinivasan Dasarathy[4], Michael A. Dunn[5]; [1]Mayo Clinic Arizona, Phoenix, AZ; [2]UCSF, San Francisco, CA; [3]University of Alberta, Alberta, AB, Canada; [4]Cleveland Clinic, Cleveland, OH; [5]University of Pittsburgh, Pittsburgh, PA

Background. Women awaiting liver transplant (LT) experience higher rates of waitlist mortality (WLM) than men. We hypothesized that sarcopenia contributes to this gender disparity. **Methods**. Included were all adults newly listed for LT in 2012 at 5 LT centers with an abdominal CT scan within 3 months of listing. Skeletal muscle index (SMI, cm^2/m^2) was defined as total abdominal skeletal muscle area at L3 (cm^2) normalized for height (m^2). Competing risks regression, with deceased donor LT as the competing risk, evaluated the association between female sex and WLM. We used an SMI cut-off of 39 cm^2/m^2 to define sarcopenia in women. **Results.** Of 396 LT candidates, 119 (30%) were women. Women vs. men were similar by age and race, but more likely to have NASH (15v.11%) or cholestatic disease (24v.5%) and less likely to have HCC (30v.43%); they were shorter (162v.175cm), lighter (71v.85kg), but had similar BMI (27v.27kg/m^2) [p<0.05 for each]. Compared to men, women had similar median MELD (15 v.15; p=0.42), but lower creatinine (0.8v.0.9 mg/dL; p<0.01). Median (IQR) SMI was 42 (36-47) cm^2/m^2 in women and 50 (44-55) cm^2/m^2 in men. By median 9 mo followup, 43(36%) women and 69(25%) men had WLM (p=0.02). In univariable competing risks regression, female, vs. male, sex was associated with 55% increased risk of WLM (HR 1.55; 95%CI 1.06-2.27; p=0.02). Adjustment for SMI completely mitigated this gender disparity (female sex HR 1.11, 95%CI 0.74-1.67; p=0.60), with no change after adjustment for MELD and Black race. Rates of WLM were significantly higher among sarcopenic women (56%) compared to non-sarcopenic women (26%). **Conclusion.** Our multi-center data suggest that the presence of sarcopenia accounts for the gender disparity in LT waitlist mortality. Sarcopenic women are especially at risk for death on the waitlist and should receive targeted interventions to prevent or reverse sarcopenia while awaiting LT.

Figure. Unadjusted survival among men, non-sarcopenic, and sarcopenic women awaiting LT.



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984

Complications of ERCP in Post-Orthotopic Liver Transplant Patients In the Setting of Rectal Indomethacin Usage

Nikhil R. Thiruvengadam[1], Michael L. Kochman[2,3], Vandana Khungar[2], Christine C. Hsu[2], Ranjeeta Bahirwani[2], Kimberly A. Forde[2,4]; [1]Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA; [2]Gastroenterology Division, Perelman School of Medicine, Philadelphia, PA; [3]Center for Endoscopic Innovation, Research and Training, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA; [4]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, Philadelphia, PA

Background Biliary tract complications (anastomotic strictures and leaks) are known to occur after orthotopic liver transplantation (OLT). ERCP is first line therapy for management of these complications. Post-ERCP pancreatitis (PEP) is the most common complication after ERCP and post-OLT patients have previously been shown to be at low risk for PEP. Thus, they have been excluded from most trials studying PEP prophylaxis. Rectal indomethacin has been demonstrated to have benefit for PEP reduction in other low-risk populations. The objective of this study was to determine the incidence of PEP and other procedural complications in post-OLT patients and examine the effect of rectal indomethacin. Methods We conducted a single-center retrospective cohort study in 882 post-transplant patients undergoing ERCP at the Hospital of the University of Pennsylvania between January 1, 2008 and December 31, 2015. After June 2012, 100 mg rectal indomethacin was routinely administered following ERCP. We examined procedural complications including post-sphincterotomy bleeding, cholangitis and PEP and moderate to severe PEP, as determined by Cotton et al. criteria. All patients were contacted within 48-72 hours of their procedure for outcome assessment. After comparison of baseline characteristics, multivariable logistic regression modeling, with adjustment for confounders, was used to determine the association between indomethacin and PEP and moderate to severe PEP. Results 19 cases of PEP, 7 cases of bleeding, 2 cases of cholangitis and no cases of perforation were identified following these procedures. The 284 patients who received indomethacin were compared to 598 who were unexposed. There were significant differences in the groups with respect to PD cannulation, endotracheal intubation and the type of anesthesia received. PEP occurred in 0.35% of indomethacin patients compared to 3.01% in the unexposed group. After adjustment for PD cannulation and biliary sphincterotomy, rectal indomethacin was associated with a 90% decrease in PEP (OR 0.10, 95% CI 0.01 – 0.76, p<0.001). 1.83 % of the unexposed group developed moderate to severe PEP compared to no patients in the indomethacin group (p=0.01). No differences in the other complications were seen between two cohorts. Conclusion In conclusion, we demonstrated: 1. Post-OLT patients have a low risk of post-ERCP complications including pancreatitis, bleeding and cholangitis. 2. Rectal indomethacin significantly decreased rates of post-ERCP pancreatitis and rates of moderate to severe pancreatitis with no adverse effect on bleeding. Post-OLT patients may benefit from routine usage of rectal indomethacin following ERCP.

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985

Achieving Sustained Virological Response with Anti-Viral Therapy to Hepatitis C Decreases Risk of End Stage Renal Disease in Liver Transplant Recipients: A Single Center Retrospective Cohort Study

Sanjaya K. Satapathy[1,2], Kiran Joglekar[3], Manish Talwar[1,2], Jason M. Vanatta[1,2], James D. Eason[1,2], Satheesh Nair[1,2]; [1]Surgery, Methodist Unversity Hospital Transplant Institute, Memphis, TN; [2]Surgery, University of Tennessee Health Sciences Center, Memphis, TN; [3]Internal Medicine, Unversity of Tennessee Health Sciences Center, Memphis, TN

AIM: Patients with chronic hepatitis C virus (HCV) infection remain at increased risk for developing chronic kidney disease (CKD). We assessed the effect of Sustained Virological Response (SVR) with anti-viral therapy (AVT) for Hepatitis C both pre and post liver transplantation (LT) on long-term renal outcomes. **METHODS:** Medical records of 1126 consecutive liver transplant (LT) recipients (01/2006- 08/2015) were reviewed. 446 patients with HCV cirrhosis were identified, and after excluding patients with graft loss < 180 days, prior renal transplantation, simultaneous liver kidney transplant, hepatitis B co-infection, no prior AVT, or those who had missing data for AVT or documentation of SVR, 257 patients were included for final analysis. Serial estimated glomerular filtration rate (eGFR) was calculated using the MDRD study equation post LT. Incidence of ESRD was compared over 5 years from LT in patients who received AVT and achieved SVR to patients who failed anti-viral treatment. LT recipients with hepatitis C were categorized based on timing of AVT; treatment pre-LT, within 1 year of LT and beyond 1 year from LT. **RESULTS:** Hepatitis C treated group with SVR (173) and treatment failure group (84) were similar in baseline demographics and clinical characteristics except SVR group had lower viral load and were less likely to be treated with m-TOR inhibitors. Frequency of ESRD among patients with SVR was significantly lower compared to those who did not achieve SVR [4 of 173(2.3%) versus 19 of 84(22.6%), P< 0.0005]. Among the patients with SVR, the incidence of ESRD in patients treated prior to LT, within 1 year of LT and beyond 1 year from LT was 0 %(n=34), 2.1% (n=48), and 3.3% (n=91) respectively. Achieving SVR was the only variable strongly associated with preventing decline in eGFR < 30ml/min/1.73 m^2 at end of follow up (HR 0.127; P= 0.000002, Figure 1). Achieving SVR prior to LT led to least frequency of decline of eGFR < 30ml/min/1.73 m^2 compared to those treated after LT (Figure 2) over 5 years of follow up. **CONCLUSION: Achieving SVR in LT recipients with HCV significantly decreases the risk of developing ESRD. AVT prior to LT should be strongly considered while awaiting liver transplant to preserve renal function.**

Figure 1

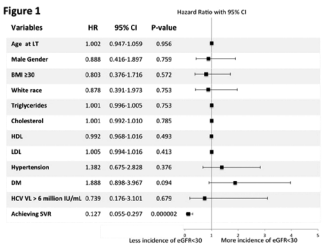
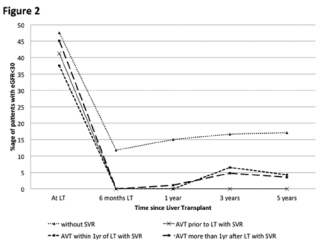


Figure 2



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Satheesh Nair - Advisory Committees or Review Panels: Jansen; Grant/Research Support: Gilead; Speaking and Teaching: Abbvie, Valeant, BMS, Intercept

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The Impact of HLA Serotyping and HLA Matching for PSC, PSC/AIH, AIH, PBC/AIH, and PBC Patients on Post-Liver Transplant Graft Failure: an Analysis of the UNOS Database

Yuval A. Patel[1], Jacqueline B. Henson[1], Julius M. Wilder[1], Jiayin Zheng[2], Shein-Chung Chow[2], Carl L. Berg[1], Andrew J. Muir[1]; [1]Division of Gastroenterology and Hepatology, Duke University Medical Center, Durham, NC; [2]Department of Biostatistics, Duke University School of Medicine, Durham, NC

Purpose: To investigate the differences and relative influence of HLA recipient/donor characteristics on post-liver transplant graft failure (GF) for this immune-related liver disease spectrum. **Methods:** We performed a retrospective analysis of the UNOS database for adult liver transplant recipients (age≥18 years) from 4/1/1994 to 6/30/2015 for PSC, PSC/AIH, AIH, PBC/AIH, and PBC with complete recipient/donor HLA serotyping. We excluded multiorgan transplants and retransplants. Cox proportional hazards regression was used to investigate the influence of HLA recipient/donor serotyping and matching on GF while controlling for age, sex, race/ethnicity, medical condition at transplant (ICU, hospital, neither), total bilirubin, creatinine, albumin, donor age<60 vs >60, deceased vs living donor, donor after cardiac death status, and graft type (split/whole). Univariate analyses were adjusted for multiple comparisons, and a p<0.05 in the multivariate model was considered significant. **Results:** During this time period, 2548 PSC, 39 PSC/AIH, 1292 AIH, 75 PBC/AIH, and 1825 PBC patients with complete HLA recipient/donor data were transplanted. GF was noted in 38.3% (2212/5779). 5-year graft survival was lower in AIH compared to PBC (71.1% vs 75.6%, p=0.028), but the other groups were similar. HLA serotyping and matching characteristics that were significant in the multivariable model (adjusted, p<0.05) are listed in the Table. No significant findings were noted for PSC/AIH and PBC. **Conclusions:** Certain recipient/donor HLA serotypes and matching status for patients transplanted for immune-related liver diseases are significantly associated with GF using the large UNOS dataset. Further investigation is needed to elucidate the impact and potential role of HLA serotyping in liver transplantation to further optimize outcomes in recipients with immune-related liver disease.

Adjusted Hazard Ratios for Graft Failure by HLA Characteristics

	PSC	AIH	PBC/AIH
Recipient HLA-B7	1.21 (1.04-1.40), P=0.012		
Recipient HLA-B57	1.48 (1.12-1.95), P=0.006		
Recipient HLA-B58			13.60 (2.66-69.66), P=0.002
Recipient HLA-B75	2.79 (1.04-7.49), P=0.042		
Recipient HLA-DR1		0.61 (0.44-0.85), P=0.004	
Recipient HLA-DR3		0.76 (0.63-0.92) P=0.005	
Recipient HLA-DR13	1.18 (1.03-1.34), P=0.014		
Donor HLA-B41			27.50 (2.88-262.50), P=0.004
Donor HLA-B55	1.56 (1.12-2.18), P=0.009		
Donor HLA-B58	1.59 (1.13-2.25), P=0.008		
Donor HLA-DR7		1.28 (1.05-1.57), P=0.017	
Donor HLA-DR8	1.28 (1.02-1.60), P=0.031		
Donor HLA-DR13			3.93 (1.44-10.71), P=0.008
Donor and Recipient HLA DR-13			9.83 (2.44-39.67), P=0.001

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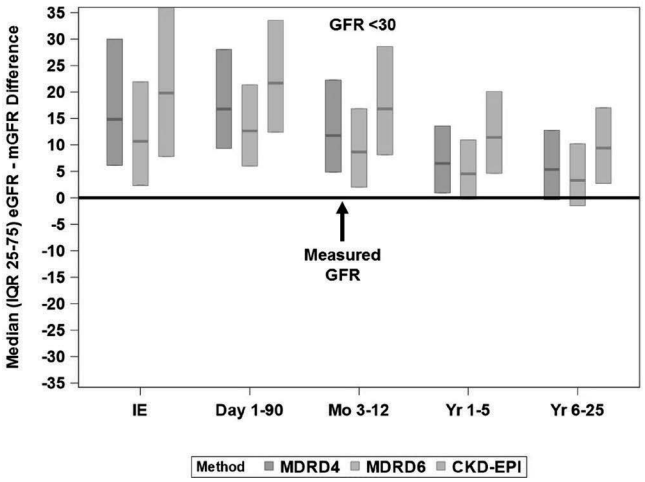
Estimation of renal function is poor with creatinine based equations before or after liver transplantation

Sumeet K. Asrani[1], Linda W. Jennings[1], Stevan A. Gonzalez[1], James F. Trotter[1], Michael Emmett[1], Josh Levitsky[2], Mitra K. Nadim[3], Goran Klintmalm[1]; [1]Baylor University Medical Center, Dallas, TX; [2]Northwestern University, Chicago, IL; [3]University of Southern California, Los Angeles, CA

Introduction: In patients undergoing liver transplantation (LT), decisions concerning renal function usually rely on calculated GFR (eGFR) using creatinine based equations. We hypothesized that current equations are suboptimal to make clinical decisions. **Methods:** We compared calculated to protocol measured GFR (using iothalamate clearance) over 30 years. We compared MDRD-4, MDRD-6, CKD-EPI and examined the difference in calculated and protocol measured GFR (**pre LT:** initial evaluation and **post LT:** d1-90, mo 6-12, year 2-5 and year 6-25). We further examined performance in stage III CKD (30-59 ml/min/1.73m^2), stage IV CKD (<30 ml/min/1.73m^2) and among patients at risk for intrinsic renal disease (age>60, DM, HTN). **Results:** Between 1985 and 2016, there were 13,418 paired measurements in 3,254 patients. The correlation between eGFR and mGFR overall was moderate (MDRD4 r= 0.69; MDRD6 r=0.71; CKD-EPI r=0.66) but poor in stage III (MDRD4 r= 0.26; MDRD6 r= 0.27;CKD-EPI r=0.30) or stage IV CKD (MDRD4 r= 0.23; MDRD6 r= 0.22;CKD-EPI r=0.26) and amongst patients at risk for intrinsic renal disease (MDRD4 r= 0.42; MDRD6 r=0.43; CKD-EPI r= 0.40). There was >10% difference in eGFR and mGFR in >70% of patients at any given time point. In stage IV CKD (n=1,377), all equations **overestimated** renal function: the overall median difference was (MDRD4 9.4 ml/min; MDRD6 7.1 ml/min; CKD-EPI 14.1ml/min). In stage IV CKD, the difference was highest at time of initial evaluation **prior to LT** (MDRD4 14.8 ml/min; MDRD6 10.7 ml/min; CKD-EPI 19.8 ml/min and within the first **90 days after LT** (MDRD4 16.8 ml/min; MDRD6 12.7 ml/min; CKD-EPI 21.7 ml/min); median differences decreased 6-25 years after LT.(Figure) **Conclusion:** Calculated GFR using creatinine based equations substantially overestimate renal function at times when clinically meaningful decisions matter most, either pre LT (e.g. SLKT vs. LT) and immediately after LT (e.g. CNI minimization).Correlation improves after 6 years post LT; however impactful interventions are less helpful at that time.

Median (IQR 25-75) difference between calculated GFR and measured GFR.



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Josh Levitsky - Consulting: Transplant Genomics Incorporated

Goran Klintmalm - Grant/Research Support: Astellas, Novartis, Opsona

The following people have nothing to disclose: Sumeet K. Asrani, Linda W. Jennings, James F. Trotter, Michael Emmett, Mitra K. Nadim

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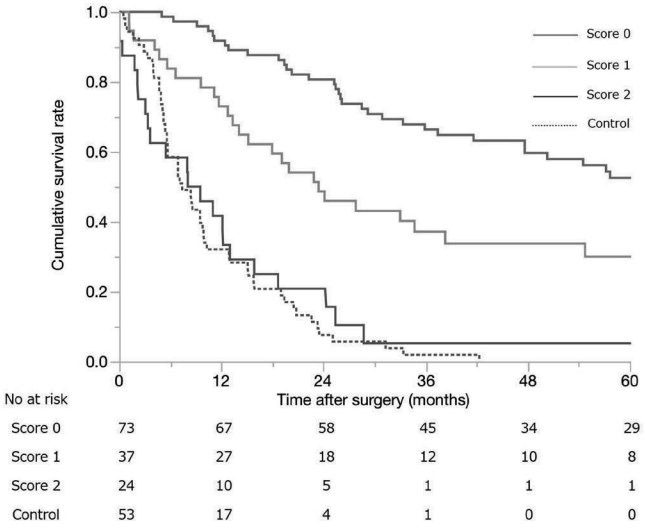
Preoperative prognostic score predicting survival of intrahepatic cholangiocarcinoma after surgery

Tomoaki Yoh, Satoru Seo, Kojiro Taura, Kentaro Yasuchika, Toshimi Kaido, Shinji Uemoto; Surgery, Kyoto Univercity, Kyoto, Japan

Background Although surgery is the potentially curative treatment for intrahepatic cholangiocarcinoma (IHCC), the outcomes were still unsatisfactory. We aim to establish the preoperative prognostic score identifying patients who need further therapeutic option. Methods: A total of 187 patients were collected from a prospectively maintained institutional database. Among them, 134 patients who underwent hepatectomy were enrolled. As preoperatively available predictors, inflammation parameters and tumor markers were evaluated. Remaining 53 inoperable patients were used as a control when performing survival analysis. Results: The overall median survival time (MST) and 3/5-year survival was 33.3 months and 48/38%. Multivariate analyses using preoperative predictors identified NLR (≥ 5), CRP (≥ 5mg/dl), and CA19-9 (≥ 500 IU/ml) were independently associated with poorer overall survival. Given these results, preoperative prognostic score was defined as follows: 0 = none of these factors; 1 = presence of each one factor, and 2 = presence of more than 2 factors. MST and 3/5-year survival of those scoring 0 was 70.3 months and 66 /53% compared with 23.4 months and 37/ 30% for those scoring 1 and 8.8 months and 5/5% for those scoring 2 (0 and 1, P < 0.004; 1 and 2, P< 0.001, respectively). Moreover, survival between patients scoring 2 and 53 inoperable control patients was almost the same (MST: 7.4 months and 3/5 year survival: 2/0%, respectively, P=0.53). Conclusions: This preoperative prognostic score of ICC is simple and useful, identifying patients who need further therapeutic option.



No at risk						
Score 0	73	67	58	45	34	29
Score 1	37	27	18	12	10	8
Score 2	24	10	5	1	1	1
Control	53	17	4	1	0	0

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989
Von Willebrand Factor antigen predicts retransplantation-free survival after first liver transplantation

Andreas Wannhoff[1], Conrad Rauber[1], Kilian Friedrich[1], Christian Rupp[1], Karl Heinz Weiss[1], Wolfgang Stremmel[1], Schemmer Peter[2], Daniel Gotthardt[1]; [1]Internal Medicine IV, University Hospital Heidelberg, Heidelberg, Germany; [2]Department of Surgery, University Hospital Heidelberg, Heidelberg, Germany

Background: Liver transplantation (LT) is a successful treatment option for end-stage liver. After LT, liver-related, infectious and cardiovascular complications contribute to reduced graft and patient survival. These conditions are associated with an increase in von Willebrand factor antigen (VWF-Ag), which was previously also correlated with survival in cirrhotic patients. We evaluated VWF-Ag as predictive marker after LT. **Methods:** We conducted a prospective study in patients after first LT treated at the University Hospital Heidelberg. Patients that were seen for follow-up after LT in the outpatient clinic of our department between November 2012 and August 2013 were screened. To be included, patients had to be at least 18 years of age at time of inclusion, and only patients after first LT were eligible. We measured VWF-Ag in these patients and followed them prospectively with regard to the primary endpoint, namely retransplantation-free survival. **Summary:** Six of the 80 patients died or received re-LT during follow-up. Median VWF-Ag was 510.6% in these patients and significantly higher (*P*=0.001) than in the patients alive at the end of follow-up (median: 186.8%). ROC analysis (AUC: 0.914) revealed an optimal cut-off of 286.8% for prediction of the primary endpoint (sensitivity: 100%, specificity: 81.1%). Survival was longer in patients with a VWF-Ag below this cut-off compared to those with a higher VWF-Ag (*P*<0.001 according to log-rank test**).** VWF-Ag was associated with retransplantation-free survival in multivariate analysis as was alkaline phosphatase (ALP), but not MELD score, donor age, or cold ischemia time. A score combining VWF-Ag and ALP showed impressive capability in ROC analysis (AUC: 0.958) to distinguish between patients with regard to the primary endpoint. **Conclusions:** VWF-Ag is a non-invasive marker to predict outcome in patients after LT. Its diagnostic performance increased when combined with ALP in a newly developed score.

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Daniel Gotthardt - Advisory Committees or Review Panels: Novartis, Abbvie, BMS, Gilead, Intercept; Consulting: Pfizer, Roche; Grant/Research Support: Novartis; Speaking and Teaching: Gilead, MSD/Merck

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990

The use of calcineurin inhibitors post-liver transplantation and the donor *SOD2* C47T polymorphism influence recurrent NAFLD after liver transplantation

Nhu (Josephine) Q. Tran[1], Alexander J. Kovalic[5], David E. Kleiner[6], Dave Bridges[2], Sanjaya K. Satapathy[3,4]; [1]Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN; [2]Physiology, University of Tennessee Health Science Center, Memphis, TN; [3]Surgery, University of Tennessee Health Science Center, Memphis, TN; [4]Transplant Institute, Methodist University Hospital, Memphis, TN; [5]Medicine, University of Tennessee Health Science Center, Memphis, TN; [6]National Institute of Health, Baltimore, MD

The purpose of our study is to identify the clinical risk factors and the genetic variants associated with recurrent non-alcoholic fatty liver disease (NAFLD) post-liver transplantation (LT). The prevalence of recurrent NAFLD is high after liver transplantation and can occur up to 70%, making it an important clinical issue. We had a cohort of 155 patients who underwent a liver transplant between April 2006 and August 2015 at the Methodist University Hospital Transplant Institute. They were middle age patients (mean 57.5 +/- 9.35 years old) and mostly non-Hispanic Whites. Among the 155 patients, 70 patients had liver biopsies within 1 year after the transplantation. Histology slides were blindly rescored and 44 patients had recurrent NAFLD. We performed a candidate gene approach using the DNA extracted from donors' and recipients' liver tissues that were fixed with formalin and embedded in paraffin using the TaqMan SNP Genotyping Assays. We focused on 43 polymorphisms of 39 genes that were known to associate with pre-LT NAFLD pathogenesis and combined with the public health information extracted from the patients' medical records to investigate their association with NAFLD recurrence. In the univariable analysis, we found that higher triglycerides post-LT (p=0.025), lower creatinine level pre-LT (p=0.0398), diabetes development post-LT (p=0.046), and calcineurin inhibitors use post-LT (p=0.045) were associated with NAFLD recurrence. Multivariable logistic analysis (Table 1) showed that patients were strongly susceptible to the recurrent disease if they received a liver from a donor with *SOD2* (C47T; rs4880) (OR 10.38, 95% CI 2.11-64.18, p=0.006), had high triglyceride levels (OR 1.01, 95% CI 1.002 – 1.021, p=0.025), and were prescribed with calcineurin inhibitors after transplantation (OR 19.59, 95% CI 1.06 – 1577.22, p=0.093). In conclusion, recurrent NAFLD post-liver transplantation is more likely to develop in a recipient who receives a liver from a donor with *SOD2* C47T polymorphism and uses immunosuppressants such as ca calcineurin inhibitors.

Predictors that are associated with the recurrent NAFLD post-liver transplantation

Predictors	Odds ratio	95% CI	p-value
Intercept	0.003	(0.00001 - 0.160)	0.015
Triglyceride	1.01	(1.002 - 1.021)	0.025
Calcineurin Inhibitor (ref: None)	19.587	(1.058 - 1577.222)	0.093
Transplant Status (ref: After)	53.615	(2.288 - 6186.767)	0.038
SOD2_rs4880 (T/T, ref: C/C)	10.378	(2.110 - 64.176)	0.006
SOD2_rs4880 (T/C, ref: C/C)	3.039	(0.734 - 14.466)	0.137

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Hospital Resource Utilization with Donation after Cardiac Death in Liver Transplantation: A Single Center Experience.

Jiten P. Kothadia[1], Hrishikesh Samant[1], Fang Qiu[2], Rajani Rangray[1], Timothy M. McCashland[1], Marco A. Olivera[1]; [1]Gastroenterology and Hepatology, University Of Nebraska Medical Center, Omaha, NE; [2]Biostatistics, University of Nebraska Medical Center, Omaha, NE

Background: Donation after cardiac death (DCD) liver allografts have been used to increase the available donor pool and to bridge the gap between the number of donors and recipients. Concerns exist regarding primary non-function and ischemic biliary complications. **Aim:** To compare the direct cost and hospital resource utilization of DCD versus donation after brain death (DBD) liver transplant (LT) recipients. **Study Design:** Retrospective observational study comparing the clinical outcome of patients with DCD-LT as compared to DBD-LT. We report 38 recipients of DCD grafts and 38 age, sex and MELD score matched recipients of DBD grafts in our institution from January 2005 to October 2015. The Wilcoxon rank-sum test and chi-square test were used for comparing continuous and categorical variables respectively. Continuous outcomes were compared using Wilcoxon signed-rank tests, binary outcomes were compared using McNemar's test. The patient and graft survival were compared using the clustered log-rank test. **Results:** Donor characteristics: 33 (86.84%) DCD and 13 (34.21%) DBD were younger than 40 years of age (p <0.0001). After LT, no significant differences were observed in the total length of stay, ICU length of stay and number of re-admissions. While comparing the direct cost (LT to discharge), there was no significant difference observed between the two groups ($202,774 vs. $245,594; p = 0.08). There was no significant difference found in 1 and 5-year patient and graft survival in DCD recipients when compared to the DBD recipients (p = 0.92 and 0.08 respectively). **Conclusions:** Unlike the previous reports of increased financial and resource use in the immediate post-transplant period and decreased patient and graft survival associated with DCD allografts, there is no significant difference with DCD allografts in our matched recipient cohort. Our report supports the use of DCD allografts, as they could help to expand the donor pool for liver transplantation.

Clinical Outcomes among Use of DBD and DCD Donors in Liver Transplantation

Characteristic		DBD (n=38)	DCD (n=38)	p-value
LOS in days (LT to discharge), median (range)		12.5 (5, 41)	13 (6, 68)	0.61
ICU LOS in days, median (range)		2 (1, 6)	2 (1, 73)	0.62
No. of re-admission, median (range)		0 (0, 6)	1 (0, 12)	0.14
Direct cost, LT to discharge in USD, median (range)		202774.58 (146614.23, 560922.23)	245594.39 (149989.5, 1042627.05)	0.08
Patient Survival (%)	1 year	86.84%	84.05%	0.92
	5 year	76.30%	77.67%	
Graft Survival (%)	1 year	97.40%	87.50%	0.08
	5 year	97.40%	83.30%	

DBD, donation after brain death; DCD, donation after cardiac death; LT, liver transplantation; ICU, intensive care unit; LOS: length of stay.

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A Quality Improvement Program Improves Skin Cancer Screening Referral Rates in Liver Transplant Recipients

Carmi S. Punzalan[1], Dawn A. Melanson[1], Amanda A. Keough[1], Fredric D. Gordon[1,2], Amir A. Qamar[1,2]; [1]Hepatobiliary Diseases & Transplantation, Lahey Clinic, Burlington, MA; [2]Tufts University School of Medicine, Boston, MA

Background: Liver transplant (LT) recipients have an increased incidence of non melanoma skin cancer (NMSC). The American Association of the Study of Liver Diseases (AASLD) recommends that all LT recipients be seen by a dermatologist annually for skin exams. Aim: Determine if a quality improvement (QI) program improves adherence to the AASLD recommendation for skin cancer screening in LT recipients. Methods: A systematic method of provider education, face to face interactions, and a Patient-Provider Communication tool was used. All LT recipients seen in the clinic filled out a questionnaire to determine if they had been seen by a dermatologist within the past year. LT coordinators reviewed the questionnaire at the visit. For patients not seen by dermatology within 1 year, a referral was placed in the electronic health record. Patients who did not live locally were advised to contact their primary care providers to setup a local dermatology referral. This was documented in the chart. Referral rates were reviewed at the monthly QI Meeting. Rates were compared before and after the implementation of the program in January 2016. Only patients transplanted before January 2015 were included. Charts were retrospectively reviewed for data collection. Data analysis was conducted using SPSS version 24.0. The study was approved by the institutional review board. Results: One hundred and forty-eight patients were reviewed. The mean age was 59 years old, and 72% of patients were male. Half of the patients had been transplanted for hepatitis C. Twenty three percent of the patients had a history of NMSC. The referral rates after implementation of the QI program increased significantly (table). Of the 18 patients referred to dermatology before initiation of the program, 72% had documented dermatology visits. Three (23%) of those with visits were found to have a new NMSC. All three had a prior history of NMSC. Of the 34 referred to dermatology after the program was started, 71% had a documented dermatology visit. Three (13%) were diagnosed with a new NMSC at their exam, but 67% of those patients did not have a prior history of NMSC. On multivariate analysis, the QI program was the only factor associated with increased skin cancer screening referrals. Conclusion: NMSC is common after LT. A patient centered QI program leads to a significant increase in dermatology referral rates in LT recipients, however further efforts are required to improve rates.

Skin exam referrals improved after QI program implementation

	n=	Referral(%)
Pre-QI	74	18(24)
Post-QI	74	34(46)

pvalue=0.006

Disclosures:

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Severe Hypoalbuminemia and Presence of Ascites Are Associated with Significantly Higher Liver Transplant Waitlist Mortality Independent of MELD-Sodium Score

Joseph Ahn[2], Taft Bhuket[1], Benny Liu[1], Catherine T. Frenette[3], Walid S. Ayoub[4], Robert J. Wong[1]; [1]Gastroenterology and Hepatology, Alameda Health System - Highland Hospital, Oakland, CA; [2]Medicine, Cedars Sinai Medical Center, Los Angeles, CA; [3]Organ Transplantation, Scripps Green Hospital, San Diego, CA; [4]Liver Transplant Program, Cedars Sinai Medical Center, Los Angeles, CA

Background: The impact of severe hypoalbuminemia and concurrent ascites on survival among patients awaiting liver transplantation (LT) may not be accurately captured by Model for End-Stage Liver Disease (MELD) score. Accurate assessment of prognosis is important for prioritizing need for LT. Aim: To evaluate the additional predictive value of severe hypoalbuminemia and concurrent ascites on LT waitlist survival among U.S. adults. Methods: We retrospectively evaluated adults (age ≥18) listed for LT from 2003-2014 using United Network for Organ Sharing registry data. The effect of severe hypoalbuminemia (<2.5g/dL) and presence of ascites on LT waitlist survival was stratified by liver disease etiology and presence of hepatocellular carcinoma (HCC) and evaluated with Kaplan Meier and multivariate Cox proportional hazards models. Results: Among 128,450 patients listed for LT, 19.2% had severe hypoalbuminemia, 69.9% had ascites at time of LT listing. Significantly higher rates of severe hypoalbuminemia were seen in men, HCV patients, and patients with diabetes. Overall 6-month waitlist survival was significantly lower among patients with severe hypoalbuminemia compared to those with normal albumin (94.9% vs. 88.2%, p<0.01) and lower among those with ascites compared with no ascites (97.0% vs. 76.8%, p<0.001). When stratified by etiology, the negative impact of severe hypoalbuminemia was most significant among patients with nonalcoholic steatohepatitis (NASH) (6-month waitlist survival: NASH, 77.9% vs. HCV, 93.1%, p<0.01). The lower waitlist survival associated with severe hypoalbuminemia and ascites was seen among patients with and without HCC. On multivariate regression, severe hypoalbuminemia was associated with significantly higher waitlist mortality compared to patients with normal albumin even after correcting for MELD-Na score and presence of HCC (HR, 3.65; 95% CI, 3.25-4.09; p<0.001). Compared to patients without ascites, those with ascites at time of LT listing had significantly higher waitlist mortality (HR, 2.02; 95% CI, 1..87-2.18; p<0.001). Conclusion: Among U.S. adults awaiting LT, severe hypoalbuminemia and presence of ascites at time of LT listing was associated with significantly higher waitlist mortality independent of MELD-Na score. Higher waitlist mortality was seen with worsening hypoalbuminemia.

Predictors of Liver Transplant Waitlist Mortality

Variable	Hazard Ratio	95% CI	P-Value
Albumin ≥ 4.0 g/dL	1.00	Reference	-
Albumin 2.5 - 3.9 g/dL	2.24	2.02 - 2.49	< 0.001
Albumin < 2.5 g/dL	3.65	3.25 - 4.09	< 0.001
No Ascites	1.00	Reference	-
Ascites	2.02	1.87 - 2.18	< 0.001

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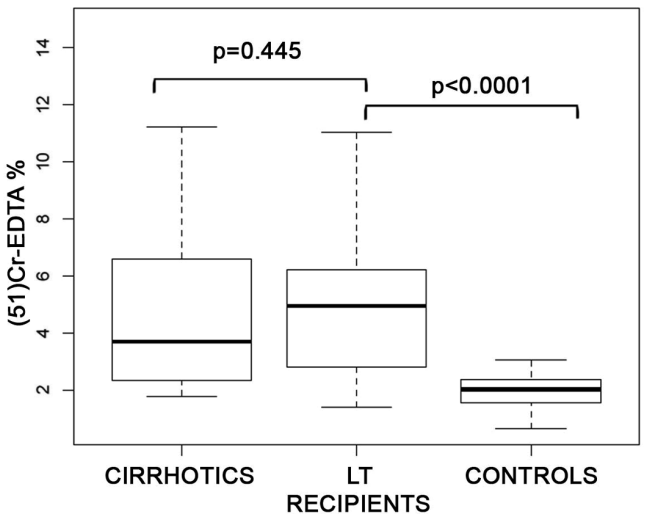
The gut liver axis after liver transplantation: modification of intestinal permeability and correlation with infectious complications and patients prognosis

Francesca R. Ponziani[1], Venanzio Valenza[2], Margherita Lorusso[2], Myrtò Elisa Carvelli[3], Rosalba Paone[3], Massimo Siciliano[1], Alfonso W. Avolio[3], Antonio Grieco[1], Salvatore Agnes[3], Maurizio Pompili[1], Antonio Gasbarrini[1], Gabriele Sganga[3]; [1]Internal Medicine and Gastroenterology, Agostino Gemelli Hospital, Rome, Italy; [2]Nuclear Medicine, Agostino Gemelli Hospital, Rome, Italy; [3]Liver transplant surgery, Agostino Gemelli Hospital, Rome, Italy

INTRODUCTION Intestinal permeability (IP) is increased in advanced stages of liver disease and is associated with the development of systemic inflammation and complications. However, little is known about the modifications of the gut liver axis after liver transplant (LT). AIM To quantify and compare IP of LT recipients to that of cirrhotic patients and of healthy controls. PATIENTS AND METHODS LT recipients, age-matched cirrhotics and healthy subjects underwent IP quantification by (51)Cr-EDTA test. Subjects with diseases potentially altering IP and with evidence of active alcohol consumption were excluded from the study. RESULTS 35 non-cirrhotic LT recipients, 35 cirrhotics (CHILD: A=13/B=11/C=11) and 35 healthy controls were enrolled. Median time from LT was 6.6 (0.3-127) months. Median (51)Cr-EDTA excretion was 4.95% (1.39-11.6), compared to 3.69% (1.78-14.83) of cirrhotics and to 2.02% of controls (overall p=<0.0001; LT recipients vs. cirrhotics p=0.445; LT vs. controls p=<0.0001; Figure 1). IP increased during time in LT recipients but the median values at ≤ 3 months, 3-12 months, and ≥ 12 months after LT did not differ significantly (p=0.550) No association between laboratory parameters, immunosuppressive medications (type/level) and IP was found except for the etiology of the previous liver disease (higher IP in case of non-viral etiology; p=0.018). The median follow-up was 72.2 months (95%CI 60.7-77.3); among the 35 LT recipients 5 developed infectious complications and 10 died. No correlation was found with IP values (p>0.05). CONCLUSIONS LT recipients have an increased IP, probably due to a multifactorial chronic alteration of the gut-liver axis. Further studies are needed to assess the clinical impact of increased IP in these patients.

Figure 1: (51)Cr-EDTA excretion in liver transplanted patients compared to cirrhotics and healthy controls.



♦ Denotes AASLD Presidential Poster of Distinction

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Prognostic Significance of Hepatic Arterial Collaterals in Liver Transplant Recipients with Biliary Strictures

André Viveiros, Rafael Rehwald, Armin Finkenstedt, Maria Effenberger, Benedikt Schaefer, Livia Dorn, Stefan Schneeberger, Herbert Tilg, Bernhard Glodny, Heinz M. Zoller, Martin Freund; Medical University and University Hospital Innsbruck, Innsbruck, Austria

Background: Biliary complications after liver transplantation can be caused by impaired hepatic arterial perfusion and are frequently associated with poor outcome and. The aim of the present study was to determine the prevalence of hepatic artery stenosis and the prognostic implications of hepatic arterial collaterals in liver transplant recipients with biliary strictures. **Patients and Methods:** Of all 732 liver graft recipients transplanted between 2004 and 2015 at our center, 105 had radiologically documented biliary strictures. High quality imaging of the hepatic artery by contrast enhanced arterial phase computed tomography or catheter angiography was available from 66 recipients. Cholangiograms were classified according to the localization of biliary strictures as anastomotic or non-anastomotic. Hepatic artery stenosis with or without collaterals was assessed in hepatic arteriograms. Clinical, demographic and biochemical recipient and donor data were retrospectively analyzed and correlated with radiological findings. **Results:** The prevalence of hepatic arterial stenosis was 68% in liver transplant recipients with biliary strictures. Non-anastomotic biliary strictures were associated with hepatic artery stenosis in 76 % (37/49) of patients. This was significantly higher than in patients with anastomotic stricture, where 47 % (8/17) of patients had a pathological hepatic arteriogram (p = 0.039). Neither location of bile duct strictures nor the presence of hepatic arterial stenosis was predictive for outcome. In contrast, arterial collaterals were associated with significantly better overall and graft survival in transplant recipients with biliary complications. **Conclusion**: Impaired hepatic arterial perfusion is frequently associated with non-anastomotic strictures, but may also be implicated in the pathogenesis of anastomotic strictures. Despite the negative prognostic impact of biliary strictures and hepatic arterial stenosis on post-transplant outcomes, hepatic arterial collaterals appear to have a protective effect.

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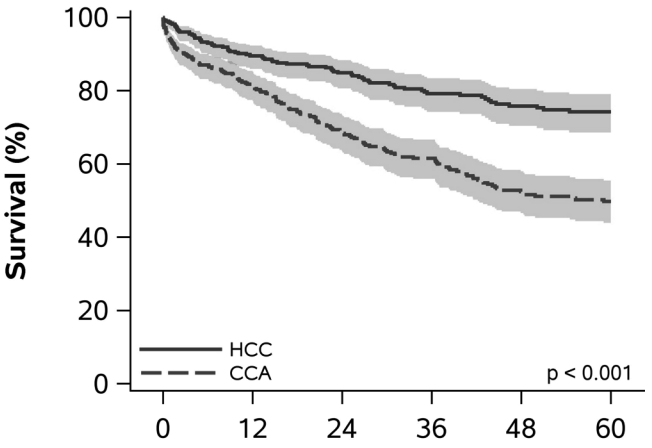
Outcomes of Liver Transplantation for Hilar Cholangiocarcinoma - An Analysis of the UNOS database

K. V. Narayanan Menon, Rocio Lopez, Carlos J. Romero-Marrero, Mangesh Pagadala; Cleveland Clinic, Cleveland, OH

Background: Liver transplantation (LT) is an accepted indication for selected patients with hilar cholangiocarcinoma (CCA). Long term outcomes are thought to comparable to patients undergoing LT for hepatocellular carcinoma (HCC). The aims of our study were to i) compare post-LT survival between subjects with CCA and those with HCC within Milan Criteria and

ii) evaluate factors associated with post-LT mortality in CCA. **Methods**: Data was extracted from the UNOS database. Adults transplanted between 2000 and 2014 with CCA or HCC were identified. Propensity score matching was used to match CCA and HCC patients on a 1:1 basis. Univariate analysis was performed to assess differences between CCA and HCC. Multivariate analysis was performed to assess factors associated with post-LT mortality in patients with CCA. **Results:** 14710 patients with HCC within Milan criteria and 394 patients with CCA underwent LT from 2000 to 2014. Mean age was 55 ± 10 years (71% male). Post-LT median follow-up was 27 months (0, 156) and was significantly shorter in the CCA group (24 vs. 32 months; p=0.028). After adjusting for age, gender, race, previous LT, MELD and propensity score, CCA patients had a higher risk of dying as those with HCC (HR=2.4; p<0.001). 5 year survival was shorter in patiets with CCA compared to HCC (50% vs 74%, p < 0.001). On multivariable analysis dialysis, ICU stay, higher MELD, region, longer post-LT hospital stay and lack of mycofenolate mofetil upon discharge were found to significantly increase the risk of post-LT mortality in CCA. **Conclusion:** CCA patient survival post-LT was lower than HCC. Further studies are needed to optimise CCA selection for LT.

Post Liver Transplant Survival



N at risk						
HCC	393	297	236	180	148	123
CCA	393	279	198	162	129	104
Survival(se)						
HCC	99.5(0.4)	89.6(1.6)	84.9(1.9)	79.2(2.3)	75.8(2.6)	74.2(2.7)
CCA	98.5(0.6)	81.8(2.0)	68.7(2.5)	61.5(2.7)	52.4(2.9)	49.8(3.0)

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The Renal Safety of MRI with Gadolinium in Patients Following Liver Transplantation

Mary Flynn, Mehul Parikh, Sebastian Perez, Sonali S. Sakaria, Ram M. Subramanian; Emory University School of Medicine, Atlanta, GA

Introduction: Intravenous contrast enhanced imaging is invaluable in diagnosing pathology following liver transplantation, including vascular and infectious complications. Given the potential risk of contrast nephropathy associated with intravenous iodinated CT contrast, alternate contrast modalities for abdominal imaging need to be examined, especially in the setting of renal insufficiency. We have recently documented the renal safety of gadolinium enhanced MRI imaging in a pre-liver transplant cohort, even in the presence of renal insufficiency. **Aims:** The purpose of this study was to examine the renal safety of MRI with gadolinium during abdominal imaging in patients following liver transplantation. **Methods**: The study involved a retrospective analysis of 549 post liver transplant patients who underwent an abdominal MRI with gadolinium in the absence of renal replacement therapy at a single academic center during 2007 to 2013. For each case, a serum creatinine was noted prior to, and within a week after the MRI. Serum creatinine values before and after the MRI were compared using a paired t-test. In addition, the cases were analyzed for the development of nephrogenic systemic fibrosis (NSF), a reported complication of gadolinium in the setting of renal insufficiency. **Results:** The mean age was 53 years (SD 11.6) with 62% males. The pre-MRI serum creatinine values ranged from 0.32 to 6.57 mg/dl (median 1.28, IQR 0.64), with 191 cases (35%) having values ≥ 1.5 mg/dl (median 1.86, IQR 0.58). The median time of the MRI following transplant was 108 days. A comparison of the pre and post MRI serum creatinine values did not demonstrate a clinically significant difference, with a mean change of -0.039 (95% CI = -0.065 to -0.013) post MRI. Subgroup analysis in those with renal insufficiency, defined as a serum creatinine ≥ 1.5 mg/dl, also did not show a clinically significant difference, with a mean change -0.168mg/dl (95% CI = -0.225 to -0.111) post MRI. In addition, no cases of NSF were noted. **Conclusion:** These observations suggest that MRI with gadolinium is a non-nephrotoxic imaging modality in patients following liver transplantation. Importantly, the renal safety of this modality extends to cases with baseline renal insufficiency (defined as Cr ≥ 1.5 mg/dl), in which contrast enhanced CT may be contraindicated due to the risk of contrast nephropathy. Therefore, gadolinium enhanced IV contrast imaging provides an invaluable imaging modality for the diagnosis of pathology following liver transplantation, especially in the setting of renal insufficiency.

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Hyperdynamic Cirrhotic Cardiomyopathy and Outcomes after Orthotopic Liver Transplant

Nikhilesh R. Mazumder, Stuart D. Russell, Aliaksei Pustavoitau, Andrew M. Cameron, Benjamin Philosophe, Behnam Saberi, Ahmet Gurakar; Medicine, Johns Hopkins Hospital, Nottingham, MD

A hyperdynamic cardiovascular state is often present in advanced cirrhosis and is thought to be reversed after liver transplant. We wished to examine the extent to which pre-transplant physiology influenced long term outcomes in patients undergoing this major operation. We retrospectively collected data on patients who underwent liver transplant for any indication and who had their operation during the period of 5/20/2008 to 12/31/2015. We excluded patients under the age of 18, those who received grafts from live donors, patients receiving other organs simultaneously, and patients who had previously undergone liver transplant. The primary outcome was time to either death or re-transplant. We advanced univariate models to multivariate models using ANOVA testing to compare Cox proportional hazards models in a stepwise fashion. Our survival analysis treated "time at risk" as time from date of transplant to date of outcome with censorship after last known follow up. Covariates included demographic data and pre-operative echocardiogram. We analyzed data from 270 liver transplant patients. They were 69.5% white, 68% male,

had an average age of 53.8 years (SD 11.2), with an average MELD at transplant of 21.8 (SD 10). Prior to transplant, the average left ventricular ejection fraction (LVEF) was 62% (SD 5.9%) with a median calculated right ventricular systolic pressure by echo of 25 mmHg. Patients had an average of 759 day of follow up with an unadjusted 13% of patients reaching the composite outcome. On univariate analysis, the greatest predictors of death or graft failure were presence of LVEF >60% (HR 3.08 95% CI [1.49, 6.38], p<0.005) and predicted RVSP in the 30-34mmHg range (HR 3.23 95% CI [1.30, 7.98], p<0.05; reference group: no tricuspid regurgitation jet by echo). These two factors remained highly significant in the full model (LVEF HR 3.14, p<0.005 ; RVSP 30-34 mmHg HR 3.09, p<0.05). Age, race, sex, BMI, presence of HCC, and MELD at transplant did not confer elevated hazard of death or re-transplant even in univariate models. Elevated estimates of LVEF and RVSP on pre-transplant screening echocardiogram predicted worse outcomes post transplant in this retrospective cohort study of patients who have received organs. This result seems to suggest that using current screening methods, there may be a group of patients who could be identified prior to transplant who may be at higher risk. Further study in this area is needed to unravel the physiologic or epidemiologic underpinnings of this finding

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Cardiac CT angiography identifies a high prevalence of significant coronary artery disease in high-risk liver transplant patients with normal dobutamine stress echography.

Marcus Robertson[1], William W. Chung[1], Omar Farouque[2], Mark Horrigan[2], Paul Gow[1], Peter W. Angus[1]; [1]Liver Transplant Unit, Austin Hospital, Heidelberg, VIC, Australia; [2]Cardiology Department, Austin Hospital, Heidelberg, VIC, Australia

Background: In patients undergoing liver transplantation (OLT), coronary artery disease (CAD) is associated with a high mortality risk and is a relative contraindication to the procedure. Evaluation for CAD is most commonly accomplished by dobutamine stress echocardiography (DSE) followed by coronary angiography (CA) if ischemia is detected. Cardiac CT angiography (CTCA) allows non-invasive detection of significant coronary artery stenoses, however its effectiveness as a screening tool is uncertain in the transplant setting. **Aims:** To assess the feasibility and outcome of CTCA in OLT candidates at high risk of CAD. **Methods:** All patients undergoing OLT assessment and considered high-risk for CAD (age >60 or diabetic patients >50) were prospectively included over a 72-month period from 2010. All patients had DSE followed by CTCA. Patients received beta-blockers for heart rate control and nitroglycerin as per a standard CTCA protocol. Primary outcomes were peri- or post-operative cardiac events. **Results:** 107 patients were included. Median age was 61 years (IQR 58 - 64) and 84% were male. The most common indications for OLT assessment were hepatocellular carcinoma (52%), hepatitis C (41%), alcohol (30%) and NAFLD (16%). Documented cardiac risk factors included diabetes (50%), smoking (56%), hypertension (21%), hypercholesterolemia (8%), family (30%) or personal (8%) history of ischaemic heart disease (IHD), and obesity (26%). 66% patients had ≥2 risk factors. CTCA was completed in 94% of patients and abandoned in 6 patients due to tachycardia. 79 (73%) were normal or showed non-obstructive (<50% stenosis) plaque. 23 (23%) showed at least one obstructive lesion (>50% stenosis). All patients with abnormal CTCA results were referred to a high-risk cardiology clinic: 2 patients were rejected for transplant due to severe CAD; 10 proceeded to CA (9 patients had non-flow limiting disease and were listed and 1 proceeded to PCI and was listed for combined coronary artery bypass graft surgery and OLT); and 11 patients were listed without further investigation. Mean coronary artery calcium score was 499 HU and not significantly different between NAFLD and non-NAFLD patients. 57 patients underwent OLT. The only cardiac event was a non-fatal cardiac arrest at reperfusion in a patient with normal DSE and CTCA. **Conclusion:** CTCA is feasible in most patients undergoing assessment for OLT and identifies CAD in a significant proportion of high cardiac risk patients with normal DSE, which in a small number of cases impacts on selection for transplantation. These findings suggest that CTCA may play a useful role in the screening of OLT candidates for occult coronary artery disease.

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Obesity is not associated with worse early outcomes in patients undergoing liver transplantation

Paul T. Kroner[1], Carolina R. Hurtado[1], Michael L. Schilsky[2], Robert S. Brown[3], Raffi Karagozian[2]; [1]Internal Medicine, Mt. Sinai St. Luke's / Mt. Sinai West Hospitals, New York, NY; [2]Yale-New Haven Liver Transplantation Center, New Haven, CT; [3]New York Presbyterian-Weill Cornell Medical College, New York, NY

Background The prevalence of obesity in the US has increased over the past decade. NASH is a well-recognized complication of obesity, and since 2004 the number of adults awaiting liver transplantation (LT) with NASH has almost tripled. Criteria to list obese patients for LT has been variable across LT centers due to concerns of obesity related complications post-transplant. The aim of this study is to evaluate early post-transplant outcomes in obese patients undergoing liver transplant using a national database. **Methods** This retrospective cohort study used the 2013 National Inpatient Sample, the largest publically available inpatient database in the US. All patients with a principal procedural ICD 9-CM codes for LT were included (50.5, 50.51, 50.59). There were no exclusion criteria. The primary outcome was in-hospital mortality. Secondary outcomes were morbidity measured by intensive care unit (ICU) admission, shock and multi-organ failure; resource utilization measured by length of hospital stay (LOS) and total hospitalization charges. Patients were classified as obese and non-obese using ICD 9-CM codes. On multivariate logistic regression, odds ratios and means were adjusted for age, sex, race, median income in the patient's zip code, Charlson Comorbidity Index, hospital region, urban location, size and teaching status. **Results** A total of 6,164 patients underwent liver transplant for the studied time frame, of which 755 were obese. Mean age was 52 years and 34% were female. The overall in-hospital mortality was 4%. (2% obese vs. 4.4% non-obese). Table 1 shows adjusted odds ratios, adjusted means and p values. On multivariate analysis, in-hospital mortality of obese and non-obese patients undergoing liver transplant did not differ. In terms morbidity, there was no difference in odds of shock, ICU admission or multi-organ dysfunction when comparing obese and non-obese. For resource utilization, obese patients displayed total decreased

LOS and total hospitalization charges when compared to the non-obese. These differences were not significant on multivariate analysis. **Conclusion** Obesity in general is not associated with increased risk of mortality, ICU admission, shock, multi-organ failure or resource utilization in patients undergoing liver transplant.

	Obese Means (95% CI)	Non-Obese Means(95% CI)
Length of Stay (days)	18.19 (15.31 - 21.06)	22.52 (19.68 - 25.36)
Total Charges	$428,256 ($353,698 - $502,814)	$512,122 ($451,009 - $573,235)
	Adjusted Odds ratio (95% confidence interval)	p-value
Overall Mortality	0.53 (0.15 - 1.85)	0.32
ICU Admission	1.41 (0.88 - 2.28)	0.15
Shock	1.01 (0.59 - 1.73)	0.97
Multi-Organ Dysfunction	1.38 (0.89 - 2.16)	0.15

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Early immunosuppression (IS) is NOT associated with outcome measures post-liver transplantation (LT)

Tommaso Di Maira[2], Gonzalo Sapisochin[1], Max Marquez[1], Francia Diaz[2], Eberhard L. Renner[1], Les Lilly[1], Eva Montalva[3], Rafae Lopez-Andujar[3], Martin Prieto[2], Marina Berenguer[2]; [1]Hepatology Transplant Unit, University Health Network, Toronto, ON, Canada; [2]Hepatology and Liver Transplantation, La Fe Hospital, Valencia, Spain; [3]Hepatobiliary Surgery and Transplantation, La Fe Hospital, Valencia, Spain

Background: a recent study described a strong association between early IS postLT and outcome. We aimed to confirm these findings in a multicenter (La Fe Hospital and Toronto General Hospital) retrospective cohort with long-term follow up. **Methods**: Tac and CsA trough levels obtained during the first 15 postLT days were collected. High IS was defined by median Tac or CsAC0 or CsAC2>10 ng/ml, 250 ng/ml or 1200 ng/ml, respectively and/or peak of Tac>20 ng/ml. Optimal IS was defined by median Tac or CsAC0/C2 levels between 7-10 ng/ml,150-250 ng/ml or 800-1200 ng/ml, respectively. Low IS was defined as below the thresholds of optimal IS. Exclusion criteria were lack of available data, < 3 IS determinations or early switch to other IS agents. Endpoints included survival, severe HCV recurrence, de novo diabetes mellitus(DM), de novo arterial hypertension(AHT), de novo malignancy(DNM), cardiovascular events(CVE), chronic renal impairment(CRI, defined as established eGFR ≤60 ml/min/1.73m^2), recurrence of hepatocellular carcinoma(HCC) and moderate/severe acute rejection(ACR) within 60 days postLT. **Results**: 565 patients (70.6% male) with a median age at LT of 55(18-70) years and median follow up of 7.73 (0-9.95) yrs were analyzed. Tac and CsA were used in 333 (58.9%) and 232 (41.1%) patients, respectively. 15-days Tac, and CsAC0 and CsAC2 median levels were 8 (1-21.2) ng/ml, 280.5 (43-573) ng/ml and 620 (103-1483) ng/ml, respectively. At baseline, renal impairment(RI) was more frequent in Low-IS than in the other groups(32%, 17% and 6%, respectively, p<.001). Patient survival at 1, 5 and 9 yrs was 93%, 80% and 69%, respectively. Severe HCV recurrence, de novo DM, AHT, DNM, CVE, CRI post-LT, HCC recurrence and ACR occurred in 25%, 38%, 29%, 9%, 7% 32%, 5% and 7%, respectively. 160 patients died due to: recurrence of primary disease(28%), DNM(18%), HCC recurrence(13%), infections(12%), CVE(6%) and others(24%). IS levels were NOT associated with survival at any time point. Adjusting for baseline features, no association were found either between IS levels and outcome-variables(HCV recurrence, p=.283; DNM p=.871, CVE p=.900, CRI p=.908, HCC recurrence p=.704). The same analysis was also performed according to the calcineurin inhibitor (FK, CsAC1 and CsAC2) and there were no significant differences. **Conclusions**: In our series, and in contrast to what has previously been described in one study, no association was found between early post-operative over-IS, defined by CNI trough levels during the first 15 postoperative days, and LT outcomes measures (survival and IS-related LT outcomes). Strategies aimed at reducing these events should likely focus in additional variables.

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Martin Prieto - Advisory Committees or Review Panels: Gilead, Bristol, Abbvie

Marina Berenguer - Advisory Committees or Review Panels: Novartis, Astellas, Gilead, BMS, MSD; Grant/Research Support: Gilead

The following people have nothing to disclose: Tommaso Di Maira, Max Marquez, Francia Diaz, Les Lilly, Eva Montalva, Rafae Lopez-Andujar

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Joint modeling of longitudinal tacrolimus exposure in the first year post-LT and risk of renal failure: a new way to optimize target tacrolimus concentrations in the future

Paul Carrier[1,2], Annick Rousseau[2], Maryline Debette-Gratien[1,2], Marie ESSIG[3,2], Pierre Marquet[2], Veronique Loustaud-Ratti[1,2], Aurélie Premaud[2]; [1]Hépato-gastroentérologie, Fédration Hépatites, Limoges, France; [2]U850 INSERM, Université de Limoges, Limoges, France; [3]Néphrologie, CHU de Limoges, LIMOGES, France

Introduction: Renal failure during the first year post liver transplantation (LT) is predictive of long-term kidney disease with an excess risk of mortality. The nephrotoxic effects of the administered calcineurin inhibitors are a major concern. The goal of this proof of concept study was to develop a joint model to investigate the relationships between longitudinal exposure to tacrolimus and the risk of renal failure in the first year post LT. **Methods:** 66 patients transplanted between 2004 and 2015 were retrospectively studied. K-means for longitudinal data was used to investigate the inter-individual variability of time-profiles of trough tacrolimus concentrations (C0) during the first month after LT and to identify longitudinal clusters (using 'kml' R package). A joint mixed effects model for longitudinal exposure to tacrolimus (i.e. through concentrations time-course) over the first year post-transplant and interval-censored event was developed in the NONMEM® software. The event targeted which defined acute renal failure was an increase in serum creatinine over 50 % during the first year post-transplantation according to the first RIFLE criteria, taking as reference the serum creatinine value at M1 (month 1) post-transplantation. **Results:** A survival without renal failure of 62 % (CI95%= 52-74%) was observed three months after LT. The longitudinal cluster analysis performed from C0 values measured from transplantation to M1 revealed two patient sub-groups: patients classified in the lowest cluster corresponding to C0 values lower 10 ng/ml tended to have less events of renal impairment (p=0.12). Additionally, joint modelling approach found that beyond M1, each 1-ng/ml increase of tacrolimus residual concentration was associated with a 4% higher risk of serum creatinine increase

of 50% compared to M1 (HR= 1.04; CI90%: 1,01-1,08). The visual predictive check (VPC) applied to Kaplan-Meier curve showed that the time-to-event model developped, appropriately described the survival without renal failure over time beyond M1. **Conclusion:** These results obtained with a new modeling approach, provide new arguments to reconsider target tacrolimus concentrations in LT. This joint model will be tested in a larger cohort and be improved by taking into account both renal failure and rejection in order to optimize tacrolimus C0 targets. These targets could be time-dependent.

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Disease Recurrence and Fibrosis Progression in Patients Transplanted for Nonalcoholic Steatohepatitis

Chandra Bhati[1], Maria Rivera[1], Michael O. Idowu[1], Carloyn Driscoll[1], Divyanshoo R. Kohli[1], R. Todd Stravitz[1], Arun J. Sanyal[1], HoChong Gilles[2], Scott C. Matherly[1], Puneet Puri[1], Velimir A. Luketic[1], Hannah Lee[1], Richard K. Sterling[1], Mohammad Siddiqui[1]; [1]Virginia Commonwealth University, Richmond, VA; [2]VA McGuire Medical Center, Richmond, VA

Nonalcoholic fatty liver disease (NAFLD) exists in two predominant histological subtypes: nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). NAFL is characterized by benign steatosis while NASH is diagnosed when steatosis is accompanied by necroinflammatory activity and fibrosis. NASH is an important cause of cirrhosis and the leading listing diagnosis among new liver transplantation (LT) waitlist registrants. However, little is known regarding disease recurrence and progression after LT in patients transplanted for NAFLD. Thus, the aim of the current study was to systematically evaluate disease recurrence and fibrosis progression in patients who had a LT for NASH **Method:** Patients who had a LT for NASH or suspected NASH between 1995 and 2013 at the authors' institution were included. Disease recurrence was evaluated with either histology or FibroScan®. All alive patients had FibroScan® performed to evaluate hepatic steatosis (controlled attenuation parameter or CAP) and fibrosis (liver stiffness measurements or LSM). The previously described cutoffs for CAP and LSM were used (de Ledinghen et al. J Gastroenterol Hepatol 2016, Wong et al. Am J. Gastro 2012). Those who failed FibroScan® were offered a liver biopsy. Charts of deceased patients were reviewed and those having a liver biopsy done >1 year post-LT were included. **Results:** Of the 103 patients who met entry criteria, 56 had a FibroScan and 34 had a liver biopsy. Steatosis was detected 42 (75%) of patients who had a FibroScan® and were defined to have recurrent NAFLD. Most patients had LSM measurement consistent with either no fibrosis (42.9%) or F1-F2 fibrosis (30.4). Advanced fibrosis (≥F3) was noted in 26.8% of the cohort while 5.4% of patients had graft cirrhosis but were clinically compensated. In patients with a liver biopsy, 88.2% had recurrent NAFLD, while 46.7% had recurrent NASH. Bridging fibrosis was noted in 23.3% of patients but no patients had cirrhosis on liver biopsy. Interestingly, serum ALT and AST levels did not correlate with disease recurrence, NASH or fibrosis stage in LT recipients transplanted for NAFLD. Three patients (2.9%) developed clinically significant graft cirrhosis and died of complications related to end-stage liver disease. **Conclusion:** Recurrent NAFLD is common post-LT and cannot be diagnosed based on serum aminotransferases. Although, advanced fibrosis can occur in nearly a quarter of patients, mortality related to graft cirrhosis is rare.

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Predicting Mortality in Patients after Liver Transplantation: An Analysis of Pre- and Post-Transplant Risk Factors

Christina C. Lindenmeyer[1], Ahyoung Kim[2], Fadi Niyazi[2], Rocio Lopez[3], Neal A. Mehta[2], Vedha Sanghi[4], Aanchal Kapoor[4], Carlos J. Romero-Marrero[1]; [1]Gastroenterology and Hepatology, Cleveland Clinic Foundation, Cleveland, OH; [2]Internal Medicine, Cleveland Clinic Foundation, Cleveland, OH; [3]Quantitative Health Sciences, Cleveland Clinic Foundation, Cleveland, OH; [4]Critical Care Medicine, Cleveland Clinic Foundation, Cleveland, OH

Background: The study of intensive care unit (ICU) outcomes in patients who undergo liver transplantation (LT) is important in order to develop systems by which patients at high risk for post-LT mortality can be more readily identified. The identification of pre- and post-LT predictors of in-hospital mortality will further help to guide the focus of critical care resources. The aim of this study was to identify modifiable factors predictive of mortality and to create a new model by which post-LT patients can be risk-stratified. **Patient and Methods:** Consecutive patients admitted to a United States tertiary care center surgical ICU after LT between 2008-2014 were followed from admission to LT and then to hospital discharge or death. Predictors of mortality were defined. Receiver Operating Characteristics (ROC) analysis was performed to assess the prediction of in-hospital mortality. Logistic regression analysis was done to develop a novel model using post-LT characteristics. **Results:** A total of 697 patients underwent LT, of which 640 patients had complete data sets and were included, aged 55.8+/-10.3 years, 69.9% males, mostly with Hepatitis C Virus (38.2%), alcohol (20.9%), and Non-alcoholic steatohepatitis- (17.2%) related cirrhosis, of which 19 (3%) died in the hospital. Higher serum creatinine (Cr) and pre-LT acute renal failure (ARF) were significantly more common in patients who died after LT (p=0.010 and 0.041, respectively). However, in multi-variate analysis, neither serum Cr nor ARF performed independently as a reliable predictor of mortality, with AUCs of 0.66 and 0.60, respectively. Pre-transplant Body Mass Index, need for renal replacement therapy, encephalopathy, ascites were not significantly associated with post-LT mortality. Occurrence of post-LT infection and ARF were significantly more common in subjects who died (p=0.019 and 0.001, respectively). There was a trend toward significance for higher estimated intra-operative blood loss; however, this variable was not readily identifiable in 14% of subjects, and

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was excluded from the multivariable model. After adjusting for post-LT infection, subjects with ARF were 3.8 times more likely to die (95% CI: 1.4, 10.8; p=0.012). The multivariable logistic regression model (z) for prediction of mortality was defined as follows: z=-4.3908+(0.6697×Infection)+(1.3285 ×ARF), with excellent performance (AUC 0.71). **Conclusion:** Post-LT ARF and presence of infection are excellent predictors of in-hospital mortality following LT. Early identification of these factors should guide targeted critical care resources in hopes of improving immediate post-LT outcomes.

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Utility of post-liver transplantation MELD and delta MELD in predicting early and late mortality

Talaat Zakareya[1], Mohammed Abbasy[1], Wael Abdel-Razek[1], Hussein A. Elsiesy[2], Faisal Abal Khail[2], Mohammed Al Sebayel[2], Imam Waked[1]; [1]Hepatology, National Liver Institute, Shebeen El-Kom, Egypt; [2]King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia

Background: The performance of early post liver transplant (LT) MELD or even its dynamic changes over time (△MELD) in predicting the mortality after LT is still controversial. **Aim**: to assess the ability of absolute and △MELD calculated at day 7 and 30 after LT to predict 1- and 5-year mortality. **Methods**: Data of 209 consecutive patients who underwent LT in two centers were reviewed. Patients who received LT for HCC were excluded as well as those who did not survive for at least one month. MELD and △MELD were calculated for each patient at 7 and 30 days after LT. **Results**: One hundred fifty-six patients were included, mostly males (n=104, 66.7%) with mean age of 51.9±8.8 years. The main indications for transplantation were decompensated HCV-related liver cirrhosis (n=138, 88.5%) and HCV-HBV co-infection (n=10, 6.4%). Donors were living in 104 and deceased in 52 patients. Survival at 1 and 5 years was 89.7 and 71.4 % respectively with a mean survival of 52.3±1.5 months. In univariate analysis, both absolute and △MELD at post-operative days 7 and 30 significantly predicted 1- and 5-year post-LT mortality. In multivariate analysis, MELD at post-operative day 30 was significantly associated with 1- (OR: 1.24, 95% CI: 1.14-1.35, P<0.0001) and 5- year mortality (OR: 1.23, 95% CI: 1.14-1.33, P<0.0001). The area under the curve for MELD at 30 days post-LT in the prediction of mortality was 0.823 (P=0.01) at 1 year, and 0.812 (P<0.001) at 5 years. A cutoff of post-LT day 30 MELD <10 could predict mortality with a sensitivity and specificity of 90% and 68.1% at 1 year, and 81.3% and 69.7% at 5 years, respectively. **Conclusion**: Failure of the MELD score to decline over the first postoperative month to less than 10 is a significant predictor of both early and late post-LT mortality.

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Hispanic Patients Have Excellent Post-Liver Transplant (LT) Outcomes

Esteban Figueroa[1], John P. Roberts[2], Danielle Brandman[1]; [1]Medicine, University of California San Francisco, San Francisco, CA; [2]Surgery, University of California San Francisco, San Francisco, CA

BACKGROUND & AIMS: Nonalcoholic steatohepatitis (NASH) is currently the second leading indication for LT and is projected to be the leading indication in the next 10 to 20 years. Given that Hispanic patients are disproportionately affected by NASH, thereby potentially comprising a greater proportion of LT recipients, it is important that further investigation be performed on this population. We aimed to evaluate the relationship of Hispanic ethnicity on post-LT mortality. **METHODS**: We performed a retrospective cohort study of adult LT recipients between 3/1/02-12/31/11. Hispanic patients were compared to White and Black patients. NASH was defined using diagnostic codes, free text, or cryptogenic cirrhosis plus BMI≥40, pre-LT diabetes (DM), or pre-LT hypertension. The association between race/ethnicity and post-LT survival was evaluated using Cox regression. **RESULTS**: 39,124 LT recipients were included (median follow-up time 4 years, IQR 2-7 years). 73% were White, 13% Hispanic, 9% Black, 4% Asian and 1% other. Comparisons were made amongst White, Hispanic and Black LT recipients. HCV was the most common indication for LT across all three groups (45% for Whites, 54% for Hispanics, and 60% for Blacks). NASH was the third leading indication for all three groups with Whites (17%) and Hispanics (16%) having a higher proportion compared to Blacks (7%). Hispanic LT recipients were more likely to have government provided health insurance (Medicare and Medicaid), have higher prevalence of BMI>30, DM, and HCC, and had longer median wait list times (109 vs 84 days for Whites and 66 for Blacks; p=0.0001). In univariable Cox regression, Hispanic ethnicity was not a significant predictor of post-LT mortality (HR 0.98) while Black race was associated with increased mortality (HR 1.36). However, when adjusting for other factors known to affect post-LT mortality, Hispanic ethnicity was associated with decreased post-LT mortality (HR 0.85, CI 0.80-0.91) while Black race remained a predictor of post-LT death (HR 1.25). In the sub-group of NASH LT recipients, the association between Hispanic ethnicity and post-LT mortality persisted (HR 0.79, CI 0.65-0.97); Black race was not associated with any difference in post-LT mortality in the NASH subgroup (HR 0.99, CI 0.70-1.43). **CONCLUSIONS**: Hispanic patients have 15% better post-LT survival than White patients despite having a higher incidence of DM, government funded insurance and longer wait list times. Despite having higher risk of NASH than other ethnicities, the proportion of Hispanic LT recipients with NASH is similar to that of White patients, which may indicate decreased access to transplant.

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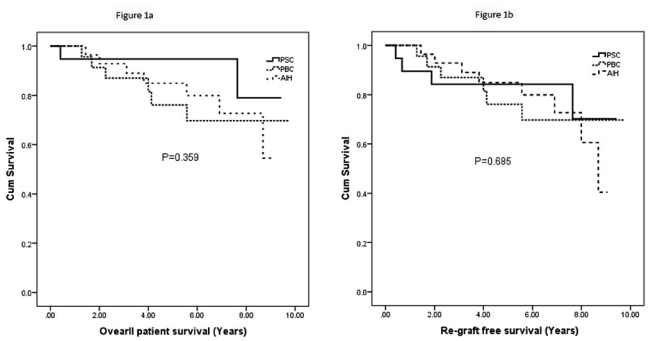
Outcomes of liver transplant recipients with autoimmune liver diseases using a dual immunosuppression regimen in a steroid free transplant protocol: A single center experience.

Sanjaya K. Satapathy[1,2], Ollie D. Jones[3], Faisal Kamal[4], Jason M. Vanatta[1,2], Satheesh Nair[1,2], James D. Eason[1,2]; [1]Surgery, University of Tennessee Health Science Center, Memphis, TN; [2]Surgery, Methodist University Hospital Transplant Institute, Memphis, TN; [3]Gastroenterology, University of Tennessee Health Sciences Center, Memphis, TN; [4]Medicine, University of Tennessee Health Sciences, Memphis, TN

Background: Liver transplant (LT) recipients with autoimmune liver disease (PSC, PBC, AIH) are at increased risk of acute cellular rejection (ACR), and in many cases graft failure due to recurrent disease. We describe our experience with dual immunosuppression in a steroid free transplant protocol and analyze its effect on disease recurrence, ACR, patient and graft survival, and complications such as sepsis and *de novo* malignancy. **Methods:** We conducted a retrospective chart review of all patients who underwent LT for AIH, PSC, or PBC between April 2006 and April 2013 at a single transplant center. We included 70 patients (AIH=28, PSC=19, and PBC=23). Immunosuppression protocol included Rabbit anti-Thymocyte Globulin 1.5 mg/kg on day of LT and on post-op day 2, 1 dose of Solumedrol 500 mg IV on day of LT, followed by mycophenolate mofetil 1000 mg bid with tacrolimus or sirolimus/everolimus indefinitely. **Results:** Overall 1-, 3- and 5-year survival was 98.6%, 91.4% and 84.6%, respectively (Median follow-up, 5.5 years). Overall patient (p=0.359, Figure 1A) and re-graft free survival (p=0.685, Figure 1B) were comparable among the disease categories. In a multivariate forward conditional stratified Cox Regression model, only steroid use for ACR predicted overall patient and graft survival. Thirty-three biopsy-proven ACR (PBC =9, PSC =5, AIH=19) was noted in 21 LT recipients (30%), 16 of 33 episodes required IV Solumderol, 3 episodes required IV thymoglobulin, and the rest were managed with optimization of their immunosuppression. Overall recurrent autoimmune liver disease was noted in 13(18.6%) of the LT recipients [PSC=3(15.8%), PBC=5(21.7%), AIH=5(17.9%)]. Thirty-two episodes of sepsis occurred in 17 patients [24.3%, PSC=9 (47.4%), PBC=4 (17.4%), AIH=4 (14.3%)]. Risk of malignancy was low with only 5 patients developing a *de novo* cancer. **Conclusion: Steroid-free dual immunosuppression protocol use in LT recipients with autoimmune liver disease had acceptable rates of survival and ACR without predisposing patients to the adverse effects of long-term steroid therapy.**

Patient (Fig. 1) and graft survival (Fig. 2) in PSC, PBC and AIH compared.



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Diastolic Dysfunction is Not Associated with Increased Morbidity and Mortality after Liver Transplantation (LT)

Sean Rudnick[1], Atif Qasim[2], John P. Roberts[3], Danielle Brandman[1]; [1]Gastroenterology, University of California, San Francisco, San Francisco, CA; [2]Cardiology, University of California, San Francisco, San Francisco, CA; [3]Transplant Surgery, University of California, San Francisco, San Francisco, CA

Background: Cardiovascular (CV) events are a major cause of early post-LT mortality. Despite the prevalence of cirrhotic cardiomyopathy in liver transplant recipients, current screening emphasizes evaluation for ischemic heart disease, systolic function, and pulmonary hypertension. Mounting evidence suggests that diastolic dysfunction is common in this patient population, and that pre-LT echocardiographic parameters may be predictive of post-LT outcomes. **Aims:** We evaluated the impact of pre-LT diastolic dysfunction on post-LT CV events, mortality, and length of stay (LOS) in the immediate post-LT period (index hospitalization). **Methods**: Adult LT recipients at UCSF from 1/1/2012-12/31/2015 were included if they had transthoracic echocardiogram (TTE) and electrocardiogram (EKG) performed within 12 months prior to LT. Patients with acute liver failure, HIV infection, and those undergoing re-LT were excluded. Covariables included liver-related (diagnosis, MELD), metabolic (diabetes/DM, hypertension/HTN), and cardiac (QT interval, TTE parameters). CV event was defined as arrhythmia, myocardial infarction, stroke, or death. Logistic regression was used to assess relationship between diastolic dysfunction and post-LT CV events. **Results**: 100 patients were included (median age 59, 61% male, 51% white). Chronic viral hepatitis was the most common etiology of liver disease (65%), with NASH/cryptogenic cirrhosis accounting for 17%. Thirty-five percent of recipients underwent LT for HCC. The median calculated MELD was 28 (IQR 15-37), and the prevalence of diastolic dysfunction was 41%. Median pre-LT QTc was 457 (IQR 438-480). Patients with or without diastolic dysfunction were similar with regard to age, gender, race, etiology of liver disease, MELD, or DM, HTN, or history of smoking (all p>0.05). Thirty-one percent of patients had an in-hospital post-LT CV event, 3% died, and median LOS was 10 days (IQR 7-16). Diastolic dysfunction was not associated with post-LT CV event (OR 1.06, 95% CI 0.45-2.50), mortality, or LOS. **Conclusions**: In this retrospective study of LT recipients at a single high-volume center, the prevalence of diastolic dysfunction on pre-transplant TTE was similar to other studies at 41%. Pre-LT diastolic dysfunction was not associated with post-LT CV events, mortality, or LOS. As existing data is in conflict with our results, it is possible that we were underpowered to detect an effect.

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The Utility of Endogenous Plasma Peptides as Biomarkers for Monitoring Liver Regeneration after Partial Hepatectomy in Pigs

Kohta Iguchi[1], Etsuro Hatano[1], Takashi Nirasawa[2], Noriyuki Iwasaki[2], Motohiko Sato[1], Gen Yamamoto[1], Yosuke Kasai[1], Satoru Seo[1], Kojiro Taura[1], Masaya Ikegawa[3], Shinji Uemoto[1]; [1]Department of Surgery, Kyoto University, Kyoto, Japan; [2]Bruker Daltonics K.K., Yokohama, Japan; [3]Department of Life and Medical Systems, Doshisha University, Kyotanabe, Japan

Background: Endogenous peptides in plasma include low-abundance messengers, hormones, or cytokines involved in physiological and disease processes in the liver. A detailed analysis of the plasma peptidome holds promise as a source of biomarkers that can be used for the diagnosis and staging of diseases, as well as for monitoring postoperative complications, such as liver failure after partial hepatectomy (PHx). Here, we hypothesized that alterations in the plasma peptide profile may reflect liver regeneration following PHx. **Methods:** To test this hypothesis, we performed comprehensive plasma peptidomic analyses on partially hepatectomized microminipigs, which are the smallest pigs in the world and were recently established as a model for biomedical research. Five microminipigs underwent 70% PHx under general anesthesia, and plasma samples were collected before, at 0 minutes and at 1, 3, 6, 24, 48, 72, 96, 120, 144, and 168 hours after PHx. Using magnetic bead purification and successive mass-spectrometry (MS) based analysis of plasma samples, as well as liquid chromatography followed by tandem MS, we identified endogenous circulating peptides specific to each phase of the postoperative course after PHx. **Results:** Some of the identified peptides might have biological relevance. Notably, peptide fragments of nucleosome components including histones were detected soon after PHx; the presence of these fragments may trigger liver regeneration in the very acute phase after PHx. An endogenous peptide derived from vasodilator-stimulated phosphoprotein was detected as an acute-phase-specific peptide, which was validated at the protein level in both plasma and liver. In addition, different epitopes of the proteins including albumin and hemoglobin subunit α showed different patterns of change after PHx. Many biomarker discovery efforts have searched for variations in the total abundance of particular proteins. However, considering our data, different epitopes of the proteins could be sensitive biomarkers for various processes in healthy and/or diseased liver, including liver regeneration after PHx. **Conclusions:** Endogenous plasma peptides clearly reflected postoperative course after PHx in pigs. Such molecules could become sensitive biomarkers for monitoring postoperative complications. Future studies are needed to validate these findings in the clinical settings.

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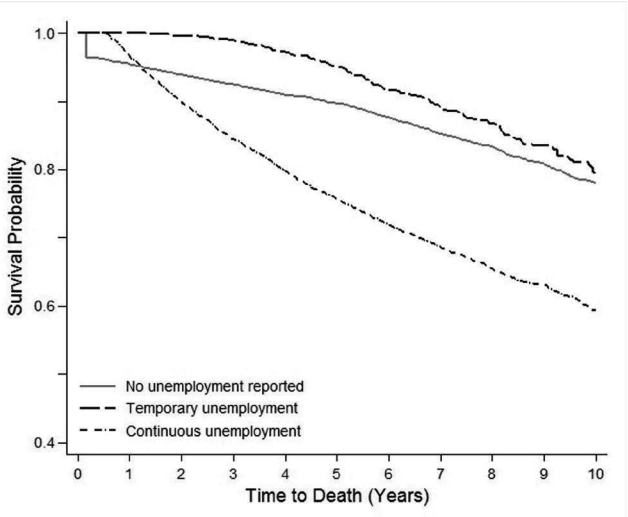
1010

Employment trajectories and outcomes of liver transplantation

Eliza W. Beal[1], Dmitry Tumin[2], Michael Nau[3], Joseph Tobias[2], Don Hayes Jr.[4], Khalid Mumtaz[5], Sylvester Black[1]; [1]The Department of General Surgery, Division of Transplantation, The Ohio State University Wexner Medical Center, Columbus, OH; [2]The Department of Anesthesiology and Pain Medicine, Nationwide Children's Hospital, The Ohio State University Wexner Medical Center, Columbus, OH; [3]The Department of Sociology, The Ohio State University, Columbus, OH; [4]The Department of Internal Medicine, Division of Pulmonary, Allergy and Critical Care, The Ohio State University Wexner Medical Center, Columbus, OH; [5]The Department of Internal Medicine, Division of Gastroenterology, Hepatology and Nutrition, The Ohio State University Wexner Medical Center, Columbu, OH

Background: The employment trajectories of liver transplant recipients who return to work may influence long-term outcomes, especially when patients experience job loss. We test the association between new unemployment and survival. **Methods:** First-time liver transplant recipients' ages 18-60 years who were transplanted May 2002-December 2014 and subsequently returned to work were identified in the United Network for Organ Sharing registry. Survival from the time of work resumption was analyzed using Kaplan-Meier curves and multivariate Cox proportional hazards models. Unemployment after work resumption was classified as temporary, if a patient later returned to work, or continuous, if a patient remained unemployed until death or censoring. **Results:** Of 44,713 liver recipients identified during the study period, 14,395 (32%) had returned to work after a median of 334 days, and were included in the analysis. Further employment trajectories included continuous employment (no unemployment reported after returning to work, 61%); temporary unemployment (9%); and continuous unemployment (30%). A Kaplan-Meier plot demonstrated worse survival in the continuous unemployment group relative to temporarily unemployed or continuously employed patients (p<0.001) **(FIGURE)**. Multivariate analysis of unemployment as a time-varying covariate found that becoming unemployed was associated with greater mortality hazard (HR=1.92; 95% CI: 1.69, 2.17; p<0.001) after adjustment for patient demographics and clinical characteristics at the time of the transplant and initial return to work. **Conclusion:** Although liver transplant recipients who return to work have better post-transplant outcomes, our study demonstrates that employment discontinuity poses a risk to long-term survival in this population.



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1011
An Evaluation of Resting and Exercise Energy Metabolism Following Liver Transplantation for Non-Alcoholic Steatohepatitis

Ajay Singhvi[1], H. Steven Sadowsky[2], Ayelet Cohen[1], Alysen Demzik[1], Mary E. Rinella[1], Lisa B. VanWagner[1], Josh Levitsky[1]; [1]Division of Gastroenterology & Hepatology, Northwestern Memorial Hospital, Chicago, IL; [2]Physical Therapy and Human Movement Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL

Background: Weight gain and metabolic syndrome occur after liver transplantation (LT), though the mechanism is poorly understood. We hypothesized this may be related to reduced metabolic rates following LT, particularly during exercise. The purpose of this study was to compare energy expenditure at rest and with exercise between LT recipients and controls. **Methods**: Fourteen post-LT subjects for non-alcoholic steatohepatitis (>1-year post) and thirteen non-LT subjects with non-alcoholic fatty liver disease (NAFLD) performed exercise testing. All subjects underwent analysis of body composition, resting energy expenditure (REE), and exercise energy expenditure ($VO_{2\ max}$). $VO_{2\ max}$ testing was conducted using a ramped-Bruce protocol and assessed by respiratory exchange ratio and peak heart rate. Subjects were stratified by sex and transplant status, and matched for BMI and age. Males and females were analyzed separately due to inherent sex-related differences in metabolic rates. **Results**: Baseline demographics were not significantly different between groups (Table 1). Post-LT females had significantly lower mean REE (Kcal/day/kg) than NAFLD females when adjusted for total body mass (14.2 vs.18.9, p=0.002) and lean body mass (19.3 vs. 26.5, p=0.001). $VO_{2\ max}$ (mL/kg/min) was also lower in post-LT females compared to NAFLD females (14.4 vs. 20.6, p<0.001). Among males, mean REE was lower in post-LT patients compared to NAFLD, but these differences were not statistically significant when adjusted for either total body mass (17.7 vs. 18.8, p=0.5) or lean body mass (23.5 vs. 26.9, p=0.09). $VO_{2\ max}$ was lower in post-LT males than in NAFLD males, though not statistically significant (20.1 vs. 23.9, p=0.2). **Discussion:** LT recipients, particularly females, have lower REE and exercise energy expenditure compared to NAFLD controls, despite similar metabolic risk factors. This may be related to hormonal factors as well as loss of hepatic innervation following LT. Individualized, more aggressive diet and exercise programs accounting for lower calorie expenditure both with rest and exercise should be instituted post-LT to optimize weight management.

Table 1: Comparison of Groups

	Male			Female		
	NAFLD (n=7) (Mean±SD)	Post-LT (n=6) (Mean±SD)	p-value	NAFLD (n=6) (Mean±SD)	Post-LT (n=8) (Mean±SD)	p-value
Age (years)	58.34±7.45	60.41±3.50	0.55	58.77±6.75	67.05±9.65	0.10
BMI (kg/m2)	33.91±4.53	33.20±5.39	0.80	30.80±2.98	29.53±1.82	0.34
% body fat	29.69±7.28	24.68±9.06	0.29	28.75±1.48	26.48±4.54	0.26
Triglycerides (mg/dL)	140.50±62.02	111.50±79.05	0.58	175.50±85.73	132.75±78.49	0.35
Low Density Lipoprotein (mg/dL)	79.75±6.24	74.25±22.47	0.65	103.50±57.94	90.75±29.99	0.60
Fasting Blood Sugar (mg/dL)	115.25±8.30	142.67±49.36	0.31	124.50±20.29	107.50±14.10	0.09
Resting Energy Expenditure for total body mass (kcal/day/kg)	18.77±1.98	17.70±3.44	0.50	18.86±1.25	14.20±2.71	0.002
Resting Energy Expenditure for lean body mass (kcal/day/kg)	26.85±3.09	23.45±3.57	0.09	26.47±1.71	19.34±3.87	0.001
VO2 max for total body mass (ml/kg/min)	23.85±4.41	20.10±4.93	0.20	20.59±2.39	14.36±2.10	<0.001

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1012
Percutaneous Transhepatic Portal Vein Angioplasty for Portal Vein Stenosis after Pediatric Liver Transplantation: A Single Center Experience

Kushal B. Naik[1,2], Clifford M. Hawkins[4,5], Anne E. Gill[4,5], Nitika A. Gupta[1,3]; [1]Transplant Services, Children's Healthcare of Atlanta, Atlanta, GA; [2]Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA; [3]Pediatrics, Emory University School of Medicine, Atlanta, GA; [4]Pediatric Interventional Radiology, Children's Healthcare of Atlanta, Atlanta, GA; [5]Radiology and Imaging Sciences, Emory University School of Medicine, Atlanta, GA

Background: Stenosis of the portal vein (PV) is a rare complication after liver transplantation (LT) in pediatric patients but it has been shown to adversely affect graft outcomes. With increased lifespan of the pediatric patient after transplant, it is important to take proactive measures to ensure long-term graft survival. In this study we reviewed the safety and efficacy of percutaneous transhepatic balloon angioplasty (PTBA) as a treatment for portal vein stenosis (PVS) post liver transplant. **Methods:** Between January 2001 and April 2016, 318 pediatric patients received a liver transplant at this tertiary referral transplant center. We reviewed their records and found that 18 children were evaluated for PVS after LT using percutaneous transhepatic portal venography (PTPV). **Results:** Of the 18, 16 patients (6F: 10M) with median age 10.5 years (IQR: 7-15) were diagnosed with PVS using PTPV and were treated with PTBA. Two patients were excluded from the analysis: one did not have PVS and the other received surgical shunt surgery instead of PTBA. 5/16 patients (31.3%) also underwent intravascular ultrasonography (IVUS). The median time between LT and PTBA was 74 months (IQR: 21-129). Half the patients were transplanted due to biliary atresia. Transhepatic approach was used in all patients. The mean pre-procedural PV pressure gradient was 6.4 mm of Hg (SD: 3.9) for the veins that did not have complete occlusion (n=9); the mean post-procedural PV pressure gradient was 0.9 mm of Hg (SD: 1.2). The mean percentage improvement in the pressure gradient across the stenotic region of the PV was 82.7% (SD: 16%; p=0.003). The average fluoroscopy time was 22.3 minutes (SD: 18.9). Median platelet, AST, ALT and GGT levels at the time of PTBA were 107 $x10^9$/L (IQR:

75-173), 46U/L (IQR: 27-152), 50U/L (IQR: 35-213) and 44U/L (IQR: 24-178) and those after PTBA at the time of 12 month follow-up visit were 181 x10^9/L (IQR: 168-255), 24U/L (IQR: 21-27), 25U/L (IQR: 20-27) and 35U/L (IQR: 17-88). At 12 months after PTBA, the mean percentage increase in platelet levels was 73% (SD: 70) and the mean percentage decreases in AST, ALT, GGT and Bilirubin were 18% (SD: 48), 23% (SD: 4), 4% (SD: 72) and 28% (SD: 30) . All the patients have required no further intervention or stenting, with portal venous patency being maintained for a median 21.6 months (IQR: 8-36). **Conclusion:** Percutaneous transhepatic angioplasty of portal vein stenosis after pediatric liver transplantation is a safe and effective treatment with long-term patency and improved clinical outcomes. This leads to increased longevity of the graft and improved quality of life.

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1013
Care Fragmentation in the 90 Day Post-Operative Period after Liver Transplantation (OLT) Increases One Year Mortalitiy Risk

Veronica Loy[2], Anai Kothari[1], Emily Weng[2], Yoshiki Ezure[1], Paul Kuo[1], Amy Lu[1], Scott Cotler[2]; [1]Surgery, Loyola University Medical Center, Maywood, IL; [2]Hepatology, Loyola University Medical Center, Maywood, IL

Background: Postoperative care fragmentation is defined as a readmission to a hospital other than the hospital where a patient underwent their initial surgical procedure. In several surgical populations, postoperative fragmentation is associated with increased risk of short and long-term adverse outcomes. The objective of this study was to evaluate whether care fragmentation was associated with reduced survival after OLT. **Methods:** A retrospective cohort review was performed using the Healthcare Cost and Utilization Project (HCUP) State Inpatient Databases for Florida and California. Patients who underwent OLT from 2006 to 2010 were included and followed for 1 year. The primary exposure was postoperative care fragmentation, defined by readmission to a non-index hospital within 90 days of discharge. Patients transferred back to the index hospital within 24 hours were considered the non-fragmented group. The primary outcome was 1-year survival. Gamma shared frailty models were used for risk adjustment, with adjustment for patient demographic, clinical, and transplant encounter variables. **Results:** A total of 2,257 patients received OLT and were readmitted in the cohort. Of these, 269 (13.5%) had fragmented postoperative care. The 1-year mortality for patients with care fragmentation was 10.8% vs. 6.4% (P=0.008). The fragmented care group had more women than the non-fragmented group (41.6% vs. 33% p = 0.009). There were no differences in Charlson comorbidity index, age, race, or etiology of liver disease between the groups. Significant differences were noted in the characteristics of the index inpatient stay between groups. At the time of liver transplant, patients who ultimately had fragmented care had longer preoperative length of stay (LOS) (7.4 vs. 4.6 days P < 0.001), longer postoperative LOS (19.7 vs. 14.9 days, P < 0.001), and higher cost of index hospitalization ($144,312.60 vs. $117,140.50, P < 0.001). After adjusting for these factors as well as age, gender, Charlson comorbidity index, and reason for transplant, patients with care fragmentation remained at heightened risk for 1-year mortality compared to those without fragmented care (HR 1.68, 95% C.I. 1.10 – 2.56). **Conclusion:** Postoperative care fragmentation following OLT is associated with a significantly increased risk of 1-year mortality. Given the complexities of post-discharge care in this patient population, efforts should be made to ensure inpatient care in the first 90 days following transplant occurs at the index transplant center.

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1014
Ultrasound and MRI Have Limited Accuracy in Diagnosing Biliary Strictures in Liver Transplant Recipients

Divyanshoo R. Kohli[1,2], Ravi Vachhani[1], Doumit BouHaidar[1], Tilak Shah[2], Andrew Mowery[1], Mohammad Siddiqui[1]; [1]Virginia Commonwealth University, Richmond, VA; [2]Hunter Holmes McGuire VA Medical Center, Richmond, VA

Introduction: Biliary strictures are an expected complication after liver transplantation (LT) occurring in 17-50% of liver transplant recipients (LTR). They are suspected when abnormalities are noted in liver enzymes and additional work up usually entails additional imaging followed by confirmatory endoscopic retrograde cholangiopancreatography (ERCP). The diagnostic accuracy of liver enzymes and imaging modalities (US and MRI) in detecting biliary strictures in LTR is unknown. The aim of the current study was to evaluate the diagnostic accuracy of liver enzymes and imaging modalities in predicting post-transplant biliary strictures. Methods: This was a retrospective study evaluating all adult patients who had a LT and subsequent ERCP for suspected biliary strictures from 2008-2015. Presence of biliary stricture was confirmed via a blinded review by three expert interventional endoscopists who had to unanimously agree on presence of a biliary stricture as defined previously [Tabibian et al, Ann Hepatol; 2015]. The optimal cut-off for liver enzymes in predicting biliary strictures was determined using the Youden Index. Finally, the diagnostic accuracy for US and MRI in predicting biliary strictures post-LT was evaluated. Results: A total of 82 subjects (58 males, age 56.35± 7.4 years) met inclusion criteria. Mean time to ERCP was 2.4±3.8 years after transplant and 48 subjects (58.5%) had a biliary stricture on blinded review. The warm ischemia time was associated with presence of biliary stricture (R=0.23, P<.05). There was an inverse relationship between biliary strictures and duration between LT and ERCP (R=-0.24, P<0.05). No relationship between biliary stricture and type of donation (living donor vs. deceased donor) was observed. The optimal cut-off for determining biliary strictures for rise in liver enzymes compared to baseline was as follows: alkaline phosphatase(AP), AST, and ALT was 75 U/L,174 U/L, 225U/L, respectively. Using these cut-offs, ALT elevations were highly sensitive (Se=100%, negative predictive value 100%) but limited by a specificity of only 43%. In contrast, increase in AP > 225 IU/L had the highest specificity of 76% but had a much lower sensitivity (Se=34%). Imaging modalities demonstrated even lower accuracy for predicting presence of biliary strictures post-LT, as MRI had a Se=43% and Sp=32% while US had Se=59% and Sp=39%. Conclusion: Imaging modalities (US, MRI) do not reliably predict presence of biliary strictures in LTR. Although, imaging modalities and rise in liver enzymes have modest accuracy in predicting biliary strictures, a rise in serum ALT without an alternative explanation offers a high negative predictive value.

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1015

Sex-Specific and Race/Ethnicity-Specific Disparities in Hepatitis B Virus-Related Liver Transplantation Outcomes in the United States

Kellie Young[2], Benny Liu[1], Taft Bhuket[1], Michele M. Tana[3], Ramsey Cheung[4], Robert J. Wong[1]; [1]Gastroenterology and Hepatology, Alameda Health System - Highland Hospital, Oakland, CA; [2]Medicine, Santa Clara Valley Medical Center, San Jose, CA; [3]Gastroenterology and Hepatology, University of California, San Francisco, San Francisco, CA; [4]Gastroenterology and Hepatology, Stanford University Medical Center, Stanford, CA

Background: Since the availability of entecavir in 2005 and tenofovir in 2008, the number of chronic hepatitis B virus (HBV) patients with progressive disease leading to liver transplantation (LT) has plateaued, but the proportion of HBV-related hepatocellular carcinoma (HCC) continues to rise. It is unclear if this trend affects both men and women or all race/ethnic groups equally. Aim: To evaluate sex-specific and race/ethnicity-specific trends in HBV-related LT listing, waitlist survival, probability of receiving LT among adults with chronic HBV in the U.S. Methods: Using the 2005-2015 United Network for Organ Sharing registry data, we retrospectively evaluated U.S. adults (age ≥18) with chronic HBV (with and without HCC) listed for LT to compare sex-specific and race/ethnicity-specific trends in LT listing. Year of LT listing was stratified into 3 time periods: 2005-2007 (era 1) vs. 2008-2011 (era 2) vs. 2012-2015 (era 3). Overall waitlist survival and odds of receiving LT were evaluated with multivariate logistic regression models stratified by presence of HCC and adjusted for sex, race/ethnicity, age, MELD scores, body mass index, and UNOS region. Results: Overall, 3046 adults with chronic HBV were listed for LT, the majority of which were Asians and men, and in the most recent era (2012-2015), men accounted 80.1% and Asians accounted for 53.0% of all HBV-related LT waitlist registrations. Although the total number of HBV patients listed for LT remained stable, the proportion of HBV patients with HCC increased from 33.3% in era 1 to 43.9% in era 3. Compared to era 1, HBV patients in era 3 were less likely to die while waiting for LT (without HCC: OR 0.60, p=0.01; with HCC: OR 0.28, p=0.005). Asians with HBV also had lower odds of waitlist death compared to non-Hispanic whites without HCC (OR 0.52, p<0.001) or with HCC (OR 0.20, p<0.001). Compared to women with HBV, men with HBV had lower odds of waitlist death, but this was only seen in the non-HCC cohort (OR 0.68, p=0.03). When evaluating odds of receiving LT, HBV patients in the latter time periods were less likely to receive LT. Compared to non-Hispanic whites with HBV, there was a trend towards higher odds of receiving LT among Asians, but only among the non-HCC cohort. (OR 1.24, p=0.07). Compared to women with HBV, a trend towards higher odds of LT was seen among men only in the HCC cohort (OR 1.33, p=0.09). Conclusion: In the most recent era, the majority of HBV-related LT listings were attributed to Asians and men, accounting for 53% and 80% of all HBV-related LT listings in the U.S., respectively. Nearly half of all HBV patients listed for LT had concurrent HCC.

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Key Predictors of 9783 De Novo Malignancies following Liver Transplantation

Mamatha Bhat[1], Kristin Mara[2], Ross A. Dierkhising[2], Kymberly Watt[3]; [1]Multiorgan Transplant Program, University Health Network, Toronto, ON, Canada; [2]Health Sciences Research, Mayo Clinic, Rochester, MN; [3]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN

Malignancy after liver transplant (LT) is a leading cause of mortality, but data is limited by small sample sizes in predominantly single-center studies. **Aim:** to determine the incidence of and risk factors for all de novo malignancies after LT in a large multi-centered database. **Methods**: The Scientific Registry of Transplant Recipients (SRTR) database comprising all adult liver transplant recipients across the United States between 2000 and 2011 was analyzed with a median of 4.43 years of follow-up. **Results**: 108,412 liver transplant recipients were included: mean age 51.9 ± 10.8 years, 64.6% male, 74.5% Caucasian, mean body mass index (BMI) 27.7±5.6kg/m2, 22.1% with pre-LT diabetes and 15.8% with previous malignancy. 15 year cancer –free survival was 77.2%. Of the malignancies, 3,795 (38.8%) were skin cancers, 1,512 (15.5%) hematologic malignancies, and 4,936 (50.5%) solid malignancies (of which 306 were hepatocellular carcinoma or cholangiocarcinoma recurrence, and further excluded from analysis). On univariate analysis, age, male gender, previous malignancy, multi-organ transplant, alcoholic liver disease and NASH, obesity, diabetes, donor BMI, donor age and mTOR exposure in year 1 were associated with increased risk. However, on multivariate analysis, age (by decade, HR 1.53; CI 1.49-1.57, p<0.001),male gender (HR 1.34; CI 1.27-1.42, p<0.001), Caucasian race (HR 1.40; CI 1.07-1.82, p=0.014), multiorgan transplant (HR 1.19; CI 1.06-1.34, p=0.005), previous malignancy (HR 1.42; CI 1.33-1.52, p<0.001) and PSC pre-LT (HR 1.14; CI 1.02-1.27, p=0.02) were independent predictors of post-LT malignancy. African-American (HR 0.54; CI 0.48-0.60, p<0.001), Hispanic (HR 0.47; CI 0.42-0.52, p<0.001), and Asian (HR 0.42; CI 0.35-0.49, p<0.001) race were associated with fewer malignancies, compared to Caucasians. Pre-LT BMI>30kg/m2 (HR 0.93, CI 0.88-0.98, p=0.0096) and diabetes (HR 0.94; CI 0.88-0.996;p=0.04) were also associated with fewer malignancies. Donor factors (age, gender, ethnicity and BMI) and recipient creatinine were not predictive of malignancy. Neither calcineurin inhibitor nor mTOR inhibitor exposure within the first year post transplant were associated with malignancy after transplant on MV analysis. **Conclusion**: Liver transplant recipients have a 10 and 15-year probability of de novo malignancy of 15.3 and 22.8% respectively. Increasing age, male gender, Caucasian race, multi-organ transplant, and PSC were predictive of a higher risk of malignancy after LT. Patients with these high-risk characteristics should be screened more vigilantly for malignancies.

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The following people have nothing to disclose: Mamatha Bhat, Kristin Mara, Ross A. Dierkhising, Kymberly Watt

1017

Shear wave elastography is a useful tool for assessment of preoperative liver function and predictor of postoperative hepatic failure in patients with hepatocellular carcinoma

Seikan Hai, Etsuro Hatano, Tadamichi Hirano, Yuichi Kondo, Nobuhiro Aizawa, Hiroko Iijima, Jiro Fujimoto; Department of Surgery,, Hyogo College of Medicine, Nishinomiya, Japan

Purpose Shear wave elastography (VTQ: Virtual Touch Quantification) is a novel noninvasive tool for assessing liver fibrosis by measuring liver stiffness. VTQ also has a possibility of evaluation of liver function at hepatectomy. This present study demonstrates the association between shear wave velocity (SWV) and liver function tests, and investigates whether SWV would be available for a predictive factor for postoperative complications. ***Patients and methods*** Clinical courses of 165 patients, who underwent hepatectomy for hepatocellular carcinoma at our department between January 2009 and March 2014, were reviewed. All patients underwent VTQ until undergoing hepatectomy. VTQ was performed five times at a different area of the right hepatic lobe and mean SWV was calculated for each patient. Postoperative hepatic failure was defined according to the International Study Group of Liver Surgery. ***Results*** Based on the hepatic fibrosis stages, SWV in F0-F4 were 1.42±0.18 m/s, 1.21±0.16 m/s, 1.44±0.49 m/s, 1.48±0.49 m/s, and 2.13±0.58 m/s, respectively. SWV in F4 (cirrhosis) was significantly faster than that in F0-F3 ($p<0.05$). SWV showed a correlation with Albumin ($r=-0.364$, $p<0.001$), Prothrombin time ($r=-0.311$, $p<0.001$), AST/PLT ratio index (APRI; $r=0.336$, $p<0.001$) and indocyanine green retention15 (ICGR15; $r=0.361$, $p<0.001$). Postoperative hepatic failure was developed in 10 patients (6.1%) and six patients (3.6%) were in-hospital death. By univariate analysis, SWV, ALT, platelet count, ICGR15, APRI, operation time and intraoperative blood loss were shown significantly as risks for postoperative hepatic failure. Multivariate analysis using a logistic regression model involving these seven significant factors determined by univariate analysis confirmed two significant independent variables: APRI and intraoperative blood loss. P value of SWV was 0.084, and SWV had a tendency to be a risk for postoperative hepatic failure. ***Conclusion*** Shear wave elastography may be a useful tool for evaluating liver function before hepatectomy and predict the possibility of postoperative hepatic failure.

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1018 ♦

Secreted Ectodomain of Sialic Acid-Binding Ig-Like Lectin-9 and Monocyte Chemoattractant Protein-1 identified from Dental Pulp Stem Cells Synergistically Resolve Acute Liver Failure in Rats by Altering Macrophage Polarity

Takanori Ito[1], Akihito Yamamoto[2], Yoji Ishizu[1], Teiji Kuzuya[1], Takashi Honda[1], Tetsuya Ishikawa[1], Masatoshi Ishigami[1], Yoshiki Hirooka[1], Hidemi Goto[1]; [1]Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [2]Oral and Maxillofacial Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

Background and AIM: We recently reported that a single injection of stem cells derived from human exfoliated deciduous teeth (SHEDs), a population of self-renewing MSCs, or serum-free conditioned medium from SHEDs (SHED-CM) markedly improves the condition of the injured liver in rat model of acute liver failure (ALF) induced by D-galactosamine (D-Gal). In another study, we identified a set of M2 macrophage inducers, monocyte chemoattractant protein-1 (MCP-1) and the secreted ectodomain of sialic acid-binding Ig-like lectin-9 (sSiglec-9) in SHED-CM, and showed that they promote functional recovery after rat spinal cord injury. In this study, we investigated the roles and therapeutic potential of MCP-1/sSiglec-9 for treating ALF. **Methods:** Rat ALF was induced by intraperitoneal injection of D-gal. 24-hours after D-Gal injection, MCP-1, Siglec-9, MCP-1/sSiglec-9 mixture, or an equivalent volume of PBS, was injected into the tail vein. We assessed survival rates, serum transaminase levels, liver histopathology, and gene expression with real time-PCR. In addition, bone marrow cells of rat were isolated, and differentiated into bone marrow macrophage with macrophage colony-stimulating factor. They were incubated in DMEM with MCP-1/sSiglec-9, IL-4, or DMEM. After a 48-hours incubation, the cells' morphologies and mRNA expression patterns were examined, and the supernatant was used as macrophage CMs. Subsequently, apoptosis model of primary hepatocytes was made using D-Gal and LPS. We evaluated the ability of anti-apoptosis in hepatocytes with macrophage CMs. **Results:** We found that a single intravenous injection of MCP-1/sSiglec-9, but not separate MCP-1 or sSiglec-9 injections, administered 24 h after D-Gal injection, markedly decreased the AST and ALT levels and improved survival rates compared with those of the other groups ($p < 0.01$). MCP-1/sSiglec-9-treated rats also exhibited significantly lower numbers of TUNEL$^+$ apoptotic cells and higher numbers of Ki-67$^+$/Albumin$^+$ proliferating hepatocytes than the PBS-treated rats. mRNA level of anti-inflammatory M2 markers, IL-10,Arginase-1,Ym-1 and TGF-β, was significantly elevated in MCP-1/sSiglec-9 group compared with control. In addition, MCP-1/sSiglec-9 promoted the M2 differentiation of bone marrow-derived macrophages *in vitro*. The CM from MCP-1/sSiglec-9-activated M2-macrophages, but not IL-4-activated M2-macrophages, suppressed D-Gal/LPS induced primary hepatocyte apoptosis ($p < 0.05$). **Conclusion:** The unique combination of MCP-1/sSiglec-9 ameliorates rat ALF through the induction of anti-inflammatory/tissue-repairing M2 macrophages.

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1019 ♦

The AIM2 inflammasome promotes the development of hepatocellular carcinoma in mice

Claudia Martínez Cardona[2,3], Beatriz Lozano-Ruiz[1,2], Victoria Bachiller[2], Francisco Algaba[2], Isabel Gomez-Hurtado[2], Alba Moratalla[1], Paula Giménez[2], Paula Piñero Romero[1], Oriol Juanola Juárez[2,3], Jose Such[2,3], Pedro Zapater[3,2], Ruben Frances[2,3], José M. González-Navajas[1,2]; [1]Alicante Institute of Health and Biomedical Research (ISABIAL-Fundación FISABIO), Alicante, Spain; [2]Networked Biomedical Research Institute for Hepatic and Digestive Diseases (CIBERehd), Madrid, Spain; [3]Universidad Miguel Hernández de Elche (UMH), Alicante, Spain

NOD-like receptors, such as NLRP3, and the dsDNA receptor Absent in Melanoma 2 (AIM2) are involved in the assembly of inflammasomes, which trigger the activation of caspase-1 and the production of inflammatory cytokines IL-1b and IL-18. We hypothesize that inflammasome activation during chronic liver injury creates an inflammatory environment that promotes the development of hepatocellular carcinoma (HCC). **Objectives:** (1) Investigate the function of the inflammasome in HCC

initiation and promotion in mice. (2) Explore the inhibition of IL-1b as a therapeutic tool in a mouse model of HCC. (3) Evaluate the expression of inflammasome components in human HCC patients. **Methods:** We evaluated the development of DEN-induced HCC in C57Bl6 mice (WT) and mice deficient in caspase-1 (*Casp1-/-*), NLRP3 (*Nlrp3-/-*) and AIM2 (*Aim2-/-*). To study the initiation and promotion phase of HCC we used a combination of DEN and carbon tetrachloride (CCl4) administration. The inhibition of IL-1b in mice was performed using anti-IL-1b antibody. Last, we analyzed PBMCs isolated from patients with HCC (n=18) and patients with advanced liver disease but without HCC as controls (n=20). **Results:** 9 months after a single DEN injection, *Casp1-/-* and *Aim2-/-* mice showed a striking reduction in tumor incidence, number and size when compared to WT mice. Liver injury and expression of inflammatory mediators in liver tissue were also reduced in these mice. By contrast, tumor development and liver injury in *Nlrp3-/-* mice was not significantly different from WT controls. DEN administration augmented the concentration of free dsDNA in serum of both WT and *Aim2-/-* mice during HCC initiation (48h post-DEN), but acute hepatocyte damage and liver inflammation were decreased in *Aim2-/-* mice at this time. IL-1b blockade ameliorated hepatocyte damage and expression of inflammatory and proliferative markers in liver tissue of DEN-treated WT mice, highlighting the role of IL-1b in this model. *Aim2-/-* mice also had reduced hepatocyte damage and expression of inflammatory and proliferative markers in liver tissue during HCC promotion (DEN+3xCCl4). In addition, DEN+CCl4 treatment increased the protein expression of AIM2 inflammasome components in the liver of WT mice. Last, AIM2 expression was upregulated in PBMCs from patients with HCC and showed a positive association with the severity of liver damage in these patients. **Conclusions:** AIM2 promotes the development of HCC in mice by increasing the injury-inflammation-regeneration response during both tumor initiation and promotion. The expression of AIM2 in HCC patients suggests that this inflammasome may also play an important role in human HCC.

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1020 ♦
Anti-lysyl oxidase like-2 (LOXL2) treatment paves the way for macrophage-mediated collagen degradation in liver fibrosis

Mordehay Klepfish[1], Milena Vugman[2], Chen Varol[2], Irit Sagi[1]; [1]Biological Regulation, Weizmann Institute of Science, Rehovot, Israel; [2]Sackler Faculty of Medicine, Sourasky Medical Center, Tel-Aviv, Israel

Liver fibrosis is the excessive accumulation of extracellular matrix (ECM) proteins including collagen that occurs in most types of chronic liver diseases. Enzymes from the lysyl oxidase (LOX) family catalyze the covalent crosslinking of collagen fibers. Specifically, lysyl oxidase like-2 (LOXL2) has been observed to regulate ECM stiffness and stability in several liver diseases associated with collagen scar formation. Therefore, inhibition of LOXL2 in liver fibrosis was proposed as a potential target for therapeutic intervention. Here we show in a mouse model of CCl4-induced liver fibrosis that treatment with a novel anti- LOXL2 antibody (Ab) targeting the catalytic site of the LOXL2 and inhibiting its extracellular activity, significantly improved liver resolution in comparison with mice treated with an isotype control Ab. Sirius red staining revealed reduced collagen deposits and histopathological score. Monitoring, matrix protease activity by *in situ* zymography further uncovered accelerated and augmented collagen degradation in anti-LOXL2-treated mice, which began already during the fibrotic phase. This was accompanied by increased infiltration of monocyte-derived macrophages localizing specifically to areas of the fibrotic fibers. Their inducible and selective ablation negated the active collagenolytic activity observed in the anti-LOXL2 treated mice. Furthermore, we provide evidence that specific macrophage-derived MMPs (i.e., -13 and -14, most in-vivo efficient collagenases) are involved in the degradation of the collagen following treatment with the Ab. Altogether, these results demonstrate that inhibition of LOXL2-governed ECM crosslinking reduces the amount of fibrosis in the liver by breaking ground for the arrival of collagenolytic macrophages, and thus constitutes a promising therapeutic strategy.

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Interaction between maternal obesity and Hedgehog signalling influences immune cell development in the foetal liver

Jiawei Li[2,1], Anisha Solanki[1], Paul Cordero[2], Vi Nguyen[2], Cansev Katar[2], Manlio Vinciguerra[2], Tessa Crompton[1], Jude A. Oben[2]; [1]Institute of Child Health, University College London, London, United Kingdom; [2]Institute for Liver and Digestive Health, University College London, London, United Kingdom

Accumulating evidence suggests that offspring of obese mothers have worse obesity and Non-Alcoholic Fatty Liver Disease (NAFLD). The mechanism of Developmental Programming of NAFLD appears to involve the innate immune system. Studies have shown that Hedgehog (Hh), a morphogen involved in embryogenesis, regulates immune cell development. Additionally, Hh signalling has been shown to play an important role in fat distribution, obesity and NAFLD. Here, we investigate the interaction of the Hh signalling pathway with maternal obesity in regulating immune development in offspring with programmed NAFLD. **Methods:** Adult wild-type and Gli3+/- female mice (shown to have increased Hh signalling *in vivo*) were subjected to either control or high-fat/high-sugar diet for 8 weeks, before being time-mated with Gli3+/- mice. At Embryonic Day 17.5, the foetal livers were analysed. **Results:** Interestingly, the foetal livers from embryos of obese mothers (Ob_Em) had a consistent upregulation of the inflammatory marker - Tumour necrosis factor-α (TNF-α), and markers of liver injury - Transforming growth factor-β (TGFβ), α-Smooth Muscle Actin (ASMA) and Collagen type 1-α (Col1-α). Flow cytometry results showed an increased percentage of neutrophils and natural killer (NK) cells in foetal livers of Ob_Em compared to wild-type embryos from lean mothers (Con_Em). Gli3+/- Con_Em also had an increased percentage of neutrophils and NK cells compared to wild-type Con_Em; however, Gli3+/- Ob_Em showed no statistical difference comparing to wild-type Con_Em in neutrophil and NK cell population. **In conclusion**, maternal obesity increases liver inflammation and injury, accompanied by an altered hepatic immunity as early as the inter-uterine stage, and the Hh signalling pathway interacts with the maternal diet in altering foetal liver development.

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1022
CEACAM1 prevents exacerbation of ConA hepatitis by promoting Treg expansion

Andrea K. Horst, Claudia Wegscheid, Christoph Schaefers, Gisa Tiegs; Institute of Experimental Immunology and Hepatology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Introduction The cellular adhesion molecule Carcinoembryonic Antigen-Related Cell Adhesion Molecule 1 (CEACAM1, CD66a) is a member of the immunoglobulin superfamily expressed on epithelia, endothelia and especially leukocytes. CEACAM1 is an immune-inhibitory receptor with a long cytoplasmic domain contains an immune receptor tyrosine-based inhibition motif (ITIM) that is pivotal for negative regulation of leukocyte activation. More specifically, CEACAM1-long suppresses the activity of NK cells, T cells and myeloid cells and controls inflammation. The role of CEACAM1 in immune-mediated liver damage and models resembling autoimmune hepatitis is unknown, therefore, we study the role of CEACAM1 in Concanavalin-mediated liver inflammation. **Methods** We use Concanavalin A injection to induce immune-mediated liver damage. Liver-resident immune cell populations were characterized by flow cytometry; Alanine aminotransferase activities (ALT) were measured in a COBAS analyzer; cytokine levels were determined by ELISA, in flow cytometry and qRT-PCR. **Results** Upon ConA injection, B6.*Ceacam1*$^{-/-}$ mice developed a more severe liver injury with increased plasma transaminase activities compared to B6.WT animals. This effect was T cell intrinsic and independent on CEACAM1-expression in the liver, since Rag1$^{-/-}$ mice that received CD4^{+} T cells from B6.*Ceacam1*$^{-/-}$ mice were more sensitive towards ConA challenge compared to animals receiving WT CD4^{+} T cells. Furthermore, B6.*Ceacam1*$^{-/-}$ mice showed significantly reduced IL-2 plasma cytokine levels and reduced IL-2 secretion by CD4^{+} T cells and NKT cells. Moreover, Treg accumulation was blunted in livers of B6.*Ceacam1*$^{-/-}$ mice upon ConA stimulation, although Tregs from B6.*Ceacam1*$^{-/-}$ mice were still suppressive in an *in vitro* suppression assay. However, B6.*Ceacam1*$^{-/-}$ Tregs failed to prevent ConA-induced liver injury and showed reduced proliferation upon adoptive transfer. **Conclusion** Our results disclose a previously undescribed protective role of CEACAM1 in a model of Th1-meditated liver injury resulting in reduction of liver pathology in Concanavalin A-medaited hepatitis. More specifically, Treg-mediated protection from immune-mediated injury relies on CEACAM1 expression on CD4+ cells and NKT cells and CEACAM1-dependent modulation of cytokine production that aids Treg proliferation.

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1023
Determination of the protective levels of IgG anti-HEV antibodies during hepatitis E virus reinfection in experimentally infected rhesus macaques

Youkyung Choi, Xiugen Zhang, Coleen Tran, Brianna Skinner; Center for Disease Control and Prevention, Atlanta, GA

Globally hepatitis E virus (HEV) may cause as many as 20 million infections annually resulting in 52,100 deaths mostly due to fulminant liver failure. HEV infection presents a significant public health problem in Asia and Africa where HEV can cause large waterborne epidemics of acute jaundice. In developing countries, the seroprevalence of anti-HEV antibody is about 40% and the highest clinical attack rate is among young adults. To better understand the secondary spread of HEV infection, often occurring in the endemic setting in developing countries, rhesus macaques were re-inoculated with a homologous strain of HEV genotype 1 to assess host immune responses contributing to protection against subsequent reinfection. After recovery from their initial HEV infection, 12 rhesus macaques were re-inoculated with homologous HEV genotype 1 (sar-55) and followed for 115 days. Three naive monkeys were used as controls. Initial IgG anti-HEV concentrations in the previously infected monkeys ranged from 1.5 to 90.7 WHO U/ml. Nine of the 12 rhesus macaques were re-inoculated with 100 monkey infectious doses (MID) and 3 animals with 1000 MIDs of HEV. Evidence of viral replication was assessed by detection of HEV RNA in stool and serum by real-time PCR and evidence of hepatitis by measuring serum alanine aminotransferase (ALT) activity. IgG anti-HEV antibody concentration and the IgG anti-HEV avidity index were analyzed in serum samples. Seven monkeys (IgG anti-HEV conc. 2.8 to 90.7 WHO U/ml, initial titers after primary infection) did not develop infection or shed virus in feces after re-inoculation. Five animals (IgG anti-HEV conc. from 1.5 to 42.7 WHO U/ml) had reinfection evidenced by HEV RNA in stool 8 to 22 days post-re-inoculation. Five re-inoculated animals that developed infection had a lower HEV-IgG avidity index (average of 38.1%) than 7 animals (average avidity index 66.5%) who did not become infected after re-inoculation. None of the re-inoculated monkeys showed elevation of ALT activity. Three control monkeys with primary infection had significantly lower IgG anti-HEV avidity index (average 29.1%) (P< 0.0001). Conclusion: Our study indicated that both pre-existing antibody and the HEV-IgG avidity index (>50%) were important factors for protection against reinfection in experimentally infected rhesus macaques. This study provides evidence of anti-HEV antibody-dependent protection against HEV reinfection.

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AIRE is not required for T regulatory cells to regulate the hepatic autoimmunity of FOXP3 dysfunction

Gwilym Webb[1,2], Fabrina Gaspal[2], Nicholas McCarthy[2], Gideon M. Hirschfield[1], Peter J. Lane[2]; [1]National Institute for Health Research Birmingham Liver Biomedical Research Unit, University of Birmingham, Birmingham, United Kingdom; [2]Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, United Kingdom

Background and aims: Mice lacking regulatory T cells (Treg) through mutations in the transcription factor FOXP3 display multi-system autoimmunity including lymphocytic peri-portal hepatic infiltrate, biochemical hepatitis and the development of anti-mitochondrial antibodies (AMA). Analogies have been drawn to primary biliary cholangitis. Mutations in the autoimmune regulator gene (*AIRE*) impair thymic presentation of otherwise tissue-restricted antigens to developing T cells and have been associated with hepatic autoimmunity in both humans and mice. **Methods:** Cells were prepared from the thymuses of 3 to 4-week-old FOXP3^{mutant} pups and 5×10^{6} were transferred into T cell deficient hosts. 5 days later hosts were repleted with peripherally-derived lymphocytes to provide 100,000 C57Bl/6 Treg (7 mice), or 100,000 AIRE$^{-/-}$ Treg (8) or nothing (7). Deficiency in AIRE was confirmed by commercial PCR

(Transnetyx®). Animals were sacrificed at onset of systemic disease (as assessed by technicians blinded to treatment) or at 6 weeks. At sacrifice, animals were assessed for serum alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) activity, AMA titre by ELISA, spleen weight as a proxy of generalised autoimmunity, leucocyte content of liver and spleen by flow cytometry, and histology and immunohistochemistry. **Results:** All animals that were repleted with AIRE$^{-/-}$ or C57Bl/6 Treg were alive and well at six weeks whereas all animals that did not receive Treg (controls) demonstrated overt autoimmunity. Transfer of either AIRE$^{-/-}$ or C57Bl/6 Treg prevented splenomegaly, reduced serum ALT, and reduced serum TNFα when compared to mice that received FOXP3 deficient T cells without subsequent Treg repletion. When assessed by flow cytometry, numbers of CD4$^+$, CD8$^+$, CD4$^+$IFNγ^+ and CD4$^+$CD44$^+$ T cells per gram of liver, but not spleen, were reduced by transfer of either AIRE$^{-/-}$ or C57Bl/6 Treg; numbers of B220+ B cells were unchanged. There was a non-significant trend to a reductions in serum LDH and AMA titre with AIRE$^{-/-}$ or C57Bl/6 transfer. The development of peri-portal infiltrate containing numerous CD4$^+$, CD45$^+$ and Ki67$^+$ cells was abolished by either AIRE$^{-/-}$ or C57Bl/6 Treg. There were no significant differences between AIRE$^{-/-}$ or C57Bl/6 Treg recipient groups **Conclusions:** These results suggest that Treg from AIRE deficient animals are sufficient to control the generalised and hepatic autoimmunity of FOXP3 dysfunction. These results contrast with work describing reversal of hepatic autoimmunity in older AIRE$^{-/-}$ BALB/c animals by adoptive transfer of wildtype Treg. Such differences implicate other host genetic factors including HLA type and environmental influences.

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1025
Blockade of OX40-OX40L prevents the development of hepatic autoimmunity in a regulatory T-cell deficient model

Gwilym Webb[1,2], Fabrina Gaspal[2], Gary M. Reynolds[1], Peter J. Eddowes[1], Gideon M. Hirschfield[1], Peter J. Lane[2]; [1]National Institute for Health Research Birmingham Liver Biomedical Research Unit, University of Birmingham, Birmingham, United Kingdom; [2]Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, United Kingdom

Background and aims: Mice lacking regulatory T cells (Treg) because of a mutation in the transcription factor FOXP3 display multi-system autoimmunity including lymphocytic peri-portal hepatic infiltrate, biochemical hepatitis and development of anti-mitochondrial antibodies (AMA). Analogies have been drawn to human primary biliary cholangitis (PBC). The secondary co-stimulatory receptor-ligand pair OX40-OX40L is implicated in the perpetuation of effector CD4$^+$ T cell responses and in maintaining T cell memory. We investigated whether antibody blockade of OX40L would ameliorate liver disease in a Treg deficient mouse model. We also assessed human disease for OX40 / OX40L dysregulation. **Methods:** Cells were prepared from the thymuses of 3 to 4-week-old FOXP3^{mutant} pups and 5×10^6 were transferred into T cell deficient hosts. 5 days later hosts were commenced on 0.25mg blocking anti-OX40L antibody IP twice weekly or control (n=10&10). Animals were sacrificed at the onset of systemic disease or 6 weeks and assessed for serum alanine aminotransferase (ALT) and lactate dehydrogenase (LDH), TNFα and AMA titre, lymphocytic content of liver by flow cytometry, and histology of liver sections. Human explant liver sections were stained for OX40; serum (s)OX40L was measured in PBC patients and healthy controls by capture ELISA. **Results:** All animals that received αOX40L were alive and well at six weeks whereas all animals that did not receive Treg (controls) demonstrated overt autoimmunity and were culled before the end of the experiment. Administration of αOX40L reduced spleen weight, reduced ALT, reduced LDH and TNFα when compared to controls. When assessed by flow cytometry, numbers of CD4$^+$, CD8$^+$, CD4$^+$IFNγ^+ and CD4$^+$CD44$^+$ T cells per gram of liver, but not spleen, were reduced by αOX40L; B220+ B cell numbers were not altered. The development of peri-portal infiltrate containing numerous CD4$^+$, CD45$^+$, OX40$^+$ and Ki67$^+$ cells was abolished by OX40L blockade. OX40 staining was present within CD4 positive infiltrates in all cases of human PBC and autoimmune hepatitis, several cases of non-alcoholic steatohepatitis and absent from almost all normal liver. sOX40L was not significantly different between PBC patients and controls. **Conclusions:** These data suggest that blockade of OX40L in a murine model of Treg deficiency is effective in reducing hepatic autoimmunity. OX40 expression is apparent in human autoimmune liver disease (AIH and PBC) but not normal liver; however, expression is also seen in some non-autoimmune inflammatory states. OX40-OX40L interactions warrant further exploration in other models of T-cell mediated disease.

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1026
Hepatic overexpression of oncogenic FoxM1 transcription factor promotes hepatocyte death and hepatic inflammation in mice

Tomohide Kurahashi, Yuichi Yoshida, Satoshi Ogura, Mayumi Egawa, Kunimaro Furuta, Yoshihiro Kamada, Shinichi Kiso, Hayato Hikita, Tomohide Tatsumi, Tetsuo Takehara; Department of Gastroenterology and Hepatology, Osaka University, Graduate School of Medicine, Suita, Japan

Background and Aims: The Forkhead Box M1 (FoxM1) is a transcription factor that belongs to the Fox family proteins and shares homology in the winged helix DNA binding domain. It has been shown that FoxM1 regulates cell cycle progression during liver regeneration and plays an important role in the development of hepatocellular carcinoma. However, despite numerous evidence in liver regeneration and carcinogenesis, its role in the liver injury during the development of chronic liver disease is not fully understood. In this study, to elucidate this issue, we developed a novel transgenic murine model that enables us to control hepatic FoxM1 expression. **Method:** We used the Tet-on and Cre-loxP systems to generate transgenic (TG) mice that conditionally express the FoxM1 protein in hepatocytes; we crossed TetO7-FoxM1 mice with Rosa26-LSL-rtTA mice and Albumin-Cre mice (TetO7-FoxM1/ Rosa26-LSL-rtTA/Albumin-Cre: designated TG mice). TG and control mice (TetO7-FoxM1/ Rosa26-LSL-rtTA: designated WT mice) were treated with doxycycline from the time of birth to induce FoxM1 expression in the liver. **Results:** We first demonstrated that FoxM1 protein expression was induced in the liver of C57BL/6J mice fed with high fat diet, suggesting the possible involvement of FoxM1 in the progression of chronic liver disease. We next confirmed the overexpression of FoxM1 protein in the liver of TG mice by Western blot and immunohistochem-

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ical analysis. At 8 weeks of age, TG mice had elevated serum ALT levels compared with WT mice [75.2 U/L in TG (n=8) vs. 15.9 U/L in WT (n=8), p<0.05]. TG mice also showed a 9 fold increase in the number of TUNEL positive hepatocytes compared with WT mice (p<0.05). This enhanced liver injury in TG mice was associated with increased gene expression of TNFα (p<0.01), F4/80 (p<0.01), and CCL2 (p<0.05). Consistent with the data *in vivo,* siRNA-mediated knockdown of FoxM1 in mouse hepatoma cell lines resulted in a significant reduction of CCL2 gene expression, suggesting the possible mechanisms by which FoxM1 regulates CCL2 expression in hepatocytes. **Conclusion:** In our current study, we demonstrated that transgenic expression of FoxM1 in hepatocytes causes hepatocytes death in mice. Our data further suggest that FoxM1 may play a role in the pathogenesis of hepatic inflammation during the development of chronic liver disease.

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1027 ♦
Hepatic Stellate Cells are Required for Activation of Kupffer Cells by Necrotic Hepatocytes—A Role for Eicosanoids

Katherine Roth, Ryan Albee, Bryan L. Copple; Michigan State University, Haslett, MI

When cells in the liver are damaged or killed, macrophages become activated to release cytokines and phagocytose dead cell debris, which facilitates liver repair. The mechanisms by which liver injury stimulates macrophage activation in the liver is not fully understood. We demonstrated previously that activation of the transcription factor hypoxia-inducible factor-1a (HIF-1α) in hepatic stellate cells (HSCs) is required for macrophages to clear regions of necrotic cells and to produce inflammatory cytokines after liver injury. This suggested that communication between HSCs and macrophages is critical for macrophage activation in the liver after injury. In support of this, we showed that necrotic hepatocytes do not directly activate liver macrophages in vitro, whereas treatment of hepatic macrophages with conditioned medium from HSCs treated with necrotic hepatocytes activated hepatic macrophages. What remains to be identified is the mediator(s) released from HSCs that modulate hepatic macrophage function. In the current study, we tested the hypothesis that eicosanoids are required for activation of liver macrophages by HSCs treated with necrotic hepatocytes. Treatment of liver macrophages with conditioned medium from HSCs exposed to necrotic hepatocytes activated the macrophages, as measured by an increase in inflammatory cytokines. However, pretreatment of the HSCs with the phospholipase A2 inhibitor, methyl arachidonyl fluorophosphonate, prevented HSC-mediated macrophage activation. Treatment of primary mouse HSCs and LX-2 cells, a human HSC cell line, with necrotic hepatocytes increased cyclooxygenase-2, prostaglandin E synthase, and 12-lipoxygenase mRNA levels. In addition, necrotic hepatocytes stimulated primary mouse HSCs to produce PGE2. In conclusion, our studies expand upon our previous *in vivo* studies by demonstrating that necrotic cells stimulate HSCs to produce an arachidonic acid metabolite that regulates liver macrophage activation. Further characterization of this pathway could provide the groundwork for novel therapies aimed at manipulating macrophage phenotype in order to alleviate liver injury or facilitate liver repair.

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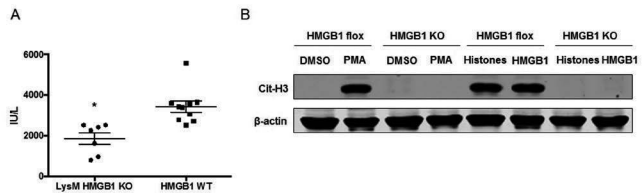
1028 ♦
Intracellular HMGB1 mediating neutrophil extracellular trap formation exacerbates liver sterile inflammation

Hai Huang[1,2], Hamza Yazdani[1], Samer Tohme[1], Patricia Loughran[1], Allan Tsung[1]; [1]Department of Suegery, University of Pittsburgh Medical Center, Pittsburgh, PA; [2]Department of Surgery, Union Hospital, Huazhong University of Science and Technology, Wuhan, China

High mobility group box-1 (HMGB1) released as damage associated molecular pattern (DAMP) during liver ischemia/reperfusion (I/R), exacerbates organ damage and inflammatory responses. Neutrophil extracellular traps (NETs) has been recently found also exacerbate sterile inflammatory injury during liver I/R. However, the role of intracellular HMGB1 in NET formation is not understood. We sought to determine the role of intracellular HMGB1 in neutrophils in NET formation during liver I/R. Myloid cells specific HMGB1 knockout (LysM-HMGB1 KO) and HMGB1-flox control mice were subjected to a non-lethal warm liver I/R. Liver damage was assessed by ALT levels and histology. Protein, cytokines, mRNA, and innate immune cell population was evaluated. LysM-HMGB1 KO mice have significantly decreased serum transaminases (sALT) (Fig A), less necrosis, inflammatory cytokines (TNF-α and IL-6) production compared to controls after I/R, suggesting a less degree of liver injury when HMGB1 in myeloid cells is absent. Significantly less NET formation was identified in the sinusoids of ischemic liver lobes in LysM-HMGB1 KO mice compared with flox control mice by confocal immunofluorescence imaging. This was associated with significantly less NET markers, serum level of myeloperoxidase (MPO)-DNA complexes, and tissue level of citrullinated histone H3 in LysM-HMGB1 KO mice compared with flox control mice. *In vitro,* no NET formation was observed in HMGB1 KO neutrophils harvested from LysM-HMGB1 KO mice under stimulation of PMA (positive control) or DAMPs (HMGB1 or histones) which was confirmed with confocal immunofluorescence imaging. Additionally, gene deletion of HMGB1 in neutrophils completely blocked citrullination of histone H3 as a key step of NET formation, compared with control neutrophils in response to various stimulations (Fig B). **Conclusion** Our study demonstrates the dominant role of intracellular HMGB1 in NET formation. Lack of HMGB1 in neutrophils leads to diminished NET formation protect the liver from organ damage and cells death after liver I/R.

(A) Serum transaminases (sALT) levels in LysM-HMGB1 KO and control Flox mice after liver I/R. Data represent the mean±SD (n=7-10 mice per group). *P<0.05. (B) citrullination of histone H3 was completed blocked in HMGB1 KO neutrophils in response to PMA and DAMPs, indicating no NET formation.



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Innate immune cell phenotype and function in different compartments of the gut-liver-axis in chronic liver diseas

Fabian J. Bolte, Ashley O'Keefe, Ohad Etzion, Rabab Ali, Elisavet Serti, T. Jake Liang, Theo Heller, Barbara Rehermann; Liver Diseases Branch, NIDDK, National Institutes of Health, DHHS, Bethesda, MD

The liver is equipped with a unique repertoire of innate and adaptive immune cells responding to viral infections and gut-derived bacterial products. The relative contribution of microbial products and virus-induced cytokines to innate immune cell activation, inflammation and severity of liver disease are currently not known. The aim of this study was to analyze innate immune cell activation and function in the three compartments of the gut-liver axis: systemic blood, portal vein blood and liver. **Methods:** Isolated lymphocytes and monocytes from liver, portal vein and systemic blood of 29 hepatitis C patients were examined by multicolor flow cytometry. In addition, plasma markers for monocyte/macrophage activation (sCD14, sCD163), intestinal barrier integrity (iFABP), and inflammation (IL-18) were studied by ELISA. **Results:** Monocytes, natural killer (NK) cells and mucosal associated invariant T (MAIT) cells were more activated in the liver than in systemic and portal vein blood as indicated by increased CD69 and HLA-DR expression. Further, NK and MAIT cells displayed a more cytotoxic phenotype in the liver than in the two other compartments as shown by *ex vivo* expression of the degranulation marker CD107a. Consistent with our findings of innate immune cell activation in the liver, sCD14 and sCD163 levels were higher in systemic than in portal plasma. sCD14 levels in both compartments correlated with activation of intrahepatic monocytes. In addition, we observed higher levels of IL-18 in HCV infected patients compared to healthy controls. IL-18 levels were similar in systemic and portal plasma and correlated with liver inflammation as assessed by the histologic activity index. Levels of iFABP, a marker of intestinal barrier loss, were increased in HCV-infected patients compared to healthy controls. Moreover, they were higher in portal than in systemic plasma. However, innate immune cell activation and degranulation were not different in systemic and portal vein blood. Likewise, the *in vitro* functional responses of monocytes to lipopolysaccharide and of MAIT cells to IL-12 and IL-18 as well as to riboflavin-synthesizing microorganisms did not differ between systemic and portal vein blood. Overall, the degree of innate immune cell activation did not correlate with the stage of liver disease as assessed by direct portal vein pressure and Ishak fibrosis score. **Conclusions:** Innate immune cell activation and inflammation are compartmentalized to the liver in patients with compensated HCV-related liver disease. Activated intrahepatic monocytes shed sCD14, resulting in higher levels of these plasma markers in systemic than in portal plasma.

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1030

Gender-specific development of experimental autoimmune cholangitis induced by double-stranded RNA

Shunin Someya, Kenichi Ikejima, Akira Uchiyama, Kumiko Arai, Kazuyoshi Kon, Tomonori Aoyama, Shunhei Yamashina, Sumio Watanabe; Department of Gastroenterology, Juntendo University Graduate School of Medicine, Tokyo, Japan

Background: Primary biliary cholangitis (PBC) is a progressive cholestatic liver disease mostly affected women. Though autoimmunity is postulated in the pathogenesis of PBC, the gender-specific mechanisms underlying the development of PBC are largely unknown. In this study, therefore, we investigated the gender difference in murine cholangitis induced by repeated injections of synthetic double-stranded RNA, which resembles human PBC. **Methods**: Male and female,8-week-old C57Bl/6 mice were given repeated intraperitoneal injections of poly I:C(5μg/g,twice/week) for 24 weeks, and liver histology was assessed. Some mice were sacrificed following a single injection of poly I:C. Serum anti-mitochondria M2 antibody (AMA-M2) was detected by ELISA. Hepatic mRNA levels for TNFα, IFNβ, and TLR3 were measured by real-time RT-PCR. Hepatic protein levels for TLR3, RIG-I, and MDA5 were measured by Western blotting. **Results**: Female mice given repeated injections of poly I:C for 16-24 weeks developed overt inflammatory infiltration surrounding bile ducts in the portal area, whereas male mice showed minimal pathological changes. Serum AMA-M2 levels were increased following chronic poly I:C treatment only in female, but not in male mice. In female mice, hepatic TNFα and IFNβ mRNA levels were swiftly elevated following a single injection of poly I:C, with peak levels at 1 hr reaching nearly 300-fold and 19-fold over basal levels, respectively. In contrast, the peak levels for TNFα and IFNβ mRNA in male mice reached only 2/3 and 1/2 of female peaks, respectively. Hepatic expression levels of TLR3, the major receptor for double-stranded RNA, were not different between male and female mice prior to injection of poly I:C. In turn, hepatic TLR3 mRNA levels were elevated transiently in 3 hr following a single poly I:C injection, the values in females reaching almost 1.5 fold higher than those in males. Moreover, hepatic protein levels for RIG-I, but not MDA5, were significantly higher in female mice as compared to those in male mice before injection of poly I:C. **Conclusions**: These findings clearly indicated that female mice exclusively develop autoimmune cholangiopathy induced by poly I:C. Further, the acute reactions against poly I:C in the liver appear to be potentiated in females, the phenomena being most likely initiated by the female-predominant expression of hepatic RIG-I levels, followed by synergistic enhancement of TLR3. It is therefore hypothesized that gender difference in innate immune responses against double-stranded RNA plays a pivotal role in the pathogenesis of autoimmune cholangiopathies including PBC.

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1031

Jagged-1/Notch1 Signaling Regulates HMGB1/TLR4-Mediated liver Inflammation by Activating PI3K/AKT/β-Catenin Pathway in Mouse Drug-Induced Damage-Associated Hepatitis

Longfeng Jiang[2], Michael Ke[1], Shi Yue[3], Youde Yan[2], Qilong Ying[3], Jun Li[2], Bibo Ke[1]; [1]Surgery, The Dumont-UCLA Transplant Center, Los Angeles, CA; [2]Department of Infectious Diseases, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [3]Department of Stem Cell Biology & Regenerative Medicine, Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC, Los Angeles, CA

Background: The Notch signaling is known to be key in the regulation of cell proliferation, differentiation, apoptosis, and immune cell function. Interactions between Notch receptors and ligands are crucial for the regulation of innate and adaptive immunity in liver inflammation. This study was designed to dissect the innate immune network regulated by Notch1 and its receptor ligand Jagged1 in acetaminophen-induced liver injury. **Methods:** Myeloid specific Notch1 knockout (Notch1$^{M\text{-}KO}$) and floxed Notch1 (Notch1$^{FL/FL}$) mice (n=6/group) were injected intraperitoneally with PBS or acetaminophen (400 ug/g, i.p.). In some experiments, Notch1$^{FL/FL}$ mice were injected with recombinant Jagged1 (rJAG-1, 40μg/kg, i.p.) or PBS and sacrificed at the indicated time. For the in vitro study, bone marrow-derived macrophages (BMMs) were isolated from Notch1$^{M\text{-}KO}$ and Notch1$^{FL/FL}$ mice and treated with treated with rJAG-1 (1 ug/ml) or PBS, and then incubated with LPS (100 ng/ml). **Results:** Notch1$^{FL/FL}$ mice received rJAG-1 were resistant to acetaminophen-induced liver injury, with increased Notch1 and its targeting gene Hes-1 expression, Akt and β-catenin phosphorylation, and significantly decreased serum ALT levels compared to the PBS-treated controls. Disruption of Notch1 in Notch1$^{M\text{-}KO}$ mice diminished Hes-1, phosphorylated Akt and β-catenin, and CyclinD1 but enhanced HMGB1, TLR4, and pro-apoptotic caspase-3 activity, with significantly increased ALT levels and liver damage in acetaminophen challenged mice. Unlike in rJAG-1 treated mice, Notch1$^{M\text{-}KO}$ significantly increased macrophage and neutrophil accumulation and hepatocellular apoptosis. Furthermore, rJAG-1 treatment in LPS-stimulated BMMs activated Notch1, Hes-1, phosphorylated Akt and β-catenin, whereas Notch1 knockdown in BMMs resulted in reduced Akt/β-catenin phosphorylation, augmented HMGB1 release, TLR4 and TNFα/IL-17A expression, as well as caspase-3 activity following LPS stimulation. **Conclusion:** This study demonstrates that Jagged1/Notch1 signaling regulates innate immune response in acetaminophen-induced liver injury. Notch1 activation inhibits HMGB1 release and TLR4 activity through activation of PI3K/Akt/β-catenin pathway. Our novel findings underscore the critical role of Jagged-1-mediated Notch1 signaling cascade in the regulation of innate immune response in acetaminophen-induced liver injury. This might imply a novel therapeutic potential for the drug-induced damage-associated lethal hepatitis.

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1032

Batf3 Dependent Dendritic Cells are Crucial for Development of Primary Biliary Cholangitis

Debby Reuveni[1], Patrick S. Leung[2], Oren Shibolet[1], M. Eric Gershwin[2], Ehud Zigmond[1]; [1]Liver Unit, Tel-Aviv Medical Center, Tel-Aviv, Israel; [2]Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis, Davis, CA

Background: Primary biliary cholangitis (PBC) is a progressive autoimmune cholestatic liver disease considered to be a cell-mediated immune reaction. Previous studies exhibited major contribution for CD8+ T cells and for the cytokine IL-12 in the pathogenesis of PBC. Dendritic cells (DC) are professional antigen presenting cells composed of distinct subsets with unique functions and phenotypic characteristics that play different roles in eliciting key immune responses. DC were identified in liver sections of PBC patients embedded in the damaged bile ducts. Batf3 is a transcription factor necessary for the development of CD8α+ dendritic cells. Previous studies have suggested important role for CD8α+ DC in defense against intracellular pathogens via cross-presentation to CD8+ T cells and secretion of IL-12. Our aim was to assess the role of Batf3 dependent DC in PBC development. Methods: We utilized an inducible murine model of PBC by immunization of mice with the xenobiotic 2-octynoic acid conjugated to bovine serum albumin (2-OA BSA). We took advantage of Batf3 KO transgenic mice that lack the transcription factor Batf3 and as a result lack the CD103+ CD11b- DC subset. Analysis included histology assessment, AMA serum titers, flow cytometry and immunohistochemistry of immune cells in the liver as well as hepatic cytokine profile by RT-PCR. Results: Histopathology assessment demonstrated peri-portal infiltration of lymphocytes and mononuclear cells in WT mice, whereas, in Batf3 KO mice only minor abnormalities were observed; These histological findings where associated with increased levels of alkaline phosphatase and total bile acid in the serum of WT mice as compared to Batf3 KO mice. Flow cytometry analysis revealed significantly decreased ratio of hepatic CD8/CD4 T cells in Batf3 mice. Furthermore, quantitative PCR studies revealed a higher expression level of pro-inflammatory cytokines in WT mice as compared to Batf3 KO mice indicating tissue inflammation process in the liver after induction of autoimmune cholangitis. Conclusion: Our results indicate a critical role for DC and specifically the CD103+CD11b- DC subset in the pathogenesis and in particularly the break of immune tolerance mechanisms in PBC, and may pave the road to new immune based cell specific targeted therapeutic endeavors.

Disclosures:

The following people have nothing to disclose: Debby Reuveni, Patrick S. Leung, Oren Shibolet, M. Eric Gershwin, Ehud Zigmond

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15-deoxy-$\triangle^{12,14}$-Prostaglandin J_2/PPARγ Axis Inhibits M1 Type Macrophage Polarization via miR326/miR27b/miR181a-1 in Mouse Liver Injury

Weiyang Li, Lei Tian, Na Chang, Jieshi Xie, Lin Yang, Liying Li; Department of Cell Biology, Capital Medical University, Beijing, China

Macrophages are central players in inflammation, which leads to liver injury. It has been reported that this process is initiated when macrophages polarize toward a pro-inflammatory M1 phenotype. Our previous data had shown that bone marrow (BM)-derived macrophages (BMMs) are recruited to injured liver and participate in inflammation. 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2), a natural peroxisome proliferator-acti-

vated receptor gamma (PPARγ) ligand, has been implicated as an anti-inflammatory compound. We have found that 15d-PGJ_2 inhibited BMMs migration and inflammatory cytokine production. But it is still unclear whether 15d-PGJ_2 involves in inflammation by regulating BMMs polarization. Here we evaluate the role of 15d-PGJ_2/PPARγ axis in M1 polarization of BMMs. We also explore whether miRNAs involve in the process, since miRNAs are reported as key regulators of immune cell functions. Mice were lethally irradiated and received BM transplants from enhanced green fluorescent protein transgenic mice, then followed by a four weeks' carbon tetrachloride (CCl_4) administration after BM reconstruction. Flow-cytometric analysis was performed to detect the amount of M1 type of BMMs. Expressions of M1 markers (NOS2, MIP-1β, TNFα) and miRNAs were measured by RT-qPCR, Western blot and cytometric beads array. High content analysis and PPARγ transcription factor assay kit were used to test the activation of PPARγ. *In vivo*, 15d-PGJ_2 suppressed M1 polarization of BMMs, as 15d-PGJ_2 reduced both population of M1 type of BMMs and NOS2, MIP-1β, TNFα expressions in injured livers. *In vitro*, BMMs were challenged upon LPS and polarized to M1 phenotype. 15d-PGJ_2 inhibited this process via PPARγ, since agonist of PPARγ caused a suppression of M1 polarization of BMMs, whereas its specific antagonist or siRNA attenuated the 15d-PGJ_2-induced down-regulations of NOS2, MIP-1β and TNFα. Indeed, 15d-PGJ_2 increased PPARγ activation in M1 type of BMMs. Bioinformatics analysis (http://www.targetscan.org, http://www.microrna.org) showed that miR-326-5p, miR-27b-3p and miR-181a-1-3p target NOS2, MIP-1β and TNFα, respectively. Using mimics and inhibitors of the three miRNAs, we confirmed that the three miRNAs regulated corresponding predicted target genes, respectively. Meanwhile, the three miRNAs expressions were decreased in damaged livers and in M1 type of BMMs, which were renewed by 15d-PGJ_2. Furthermore, the results of specific agonist, antagonist or siRNA of PPARγ indicated that 15d-PGJ_2-induced up-regulations of miRNAs were depended on PPARγ. In conclusion, these data suggest that 15d-PGJ_2/PPARγ axis inhibits polarization of BMMs toward M1 phenotype in a miRNA dependent manner.

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Augmented shedding of the leukocyte migration inhibitor soluble CD18 combined with increased plasma levels in human alcoholic hepatitis

Sidsel Stoey[1], Thomas D. Sandahl[1], AnneLouise Hansen[2], Bent Deleuran[2], Thomas Vorup-Jensen[2], Hendrik Vilstrup[1], Tue W. Kragstrup[2]; [1]Hepatology and gastroenterology, Aarhus University Hospital, Aarhus, Denmark; [2]Biomedicine, Aarhus University, Aarhus, Denmark

Introduction and aims: During human alcoholic hepatitis (AH) monocytes are activated directly by ethanol and indirectly via inflammatory factors such as LPS and TNFα, and hence numbers in the liver increase. Monocytes, especially the intermediate 'inflammatory' type, express the β2 (CD18) family of integrins, which in its active form elicit binding of monocytes to the endothelial adhesion receptors and bring about extravasation into tissue. TNFα is known to induce shedding of CD18 forming the recently discovered soluble CD18 (sCD18), which is thought to inhibit extravasation of leukocytes by concealing endothelial adhesion receptors. It is not known whether this tissue inflammation moderating mechanism is intact or what mediates it in AH. We, therefore, measured the monocyte expression of active and inactive CD18, the plasma levels of sCD18 and the monocyte's ability to shed CD18 in these patients. *Materials and methods:* By flow cytometry, we detected the surface expression of active and inactive CD18 on monocyte subsets from 15 patients with severe AH and 8 healthy controls. We quantified plasma sCD18 and macrophage activation marker sCD163 in 50 patients with severe AH at diagnosis, at day 14 and at day 30 and 20 healthy controls by in-house immunosorbant assays. Likewise, the *in vitro* shedding of CD18 from PBMC's in response to ethanol, LPS and TNFα was measured. *Results:* In patients with AH, all monocyte subsets had higher surface expression of activated CD18 than controls ($p<0.01$, all), whereas there was no difference in expression of inactive CD18. The increase in activated CD18 expression was highest in the subset of intermediate 'inflammatory' monocytes (median±IQR; AH 12101±3716 vs. controls 7504±2012, $p=0.0006$). The plasma concentration of sCD18 was increased by 30% in the patients compared with controls (1907.3±1032 vs. 1472.5±646.2, $p=0.01$) and correlated with monocyte activity as measured by plasma sCD163 ($r=0.53$ $p=0.0001$). Plasma sCD18 did not change during the follow-up period. The spontaneous production of sCD18 *in vitro* was elevated more than two fold in AH compared with controls (145±123 vs. 66±35, $p=0.001$). Stimulation with either LPS or TNFα, but not ethanol increased the shedding of CD18 and more so in patients with AH than in controls ($p<0.04$, all). *Conclusion:* In severe AH, shedding of CD18 is likely the result of monocyte activation. This suggests an anti-inflammatory mechanism that is operative within the picture of florid hepatic inflammation.

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Digoxin protects from sterile inflammation in the liver by targeting pyruvate kinase M2 (PKM2) promoted HIF-1a transactivation

Xinshou Ouyang[1], Sheng-Na Han[1], George Lau[1], Dechun Feng[2], Rebecca Cardone[1], Shi-Ying Cai[1], Rafaz Hoque[1], Yonglin Chen[1], Wei-hong Yang[1], Irma Garcia-Martinez[1], Fu-Sheng Wang[3], Bin Gao[2], Natalie J. Torok[4], Richard Kibbey[1], Wajahat Z. Mehal[1]; [1]Yale University, New Haven, CT; [2]NIAAA, NIH, Bethesda, MD; [3]Institute of Translational Hepatology, Beijing 302 Hospital, Beijing, China; [4]department of Medicine, UC Davis, Sacramento, CA

Background: Sterile inflammation after tissue damage is a ubiquitous immune response, and occurs with highest amplitude in the liver. This has major clinical consequences for alcoholic and non-alcoholic steatohepatitis (ASH and NASH) with both lacking effective therapies. Key requirements for sustained sterile inflammation are high degree of cellular oxidative stress and the activation of HIF-1a pathway. The cardiac glycoside digoxin was identified as potent suppressor of HIF-1a, but the mechanism for this, and for hepatic protection is not well defined. **Aim:** To assess whether digoxin has therapeutic effects in NASH and ASH in mice, and investigate the molecular mechanisms in both mouse and human cells. **Methods:** C57BL/6J male mice were placed on a 45% high fat diet (HFD) for 11weeks with and without digoxin (ip 1, 0.2 and 0.05 mg/kg twice a week). Digoxin 1mg/kg ip daily in mice results in the therapeutic serum levels achieved in humans (0.5-2 ng/ml). Plasma ALT, liver histology, leukocytes profiling, mitochondrial ROS, and gene transcriptome microarrays were analyzed. The chronic plus binge model of ASH was performed. The identi-

fication of digoxin interacting protein(s) in maintaining cellular redox homeostasis and suppressing HIF1a activation were investigated by proteomics, RT-PCR, reporter luciferase and ChIP-PCR assay. **Results:** Digoxin dose-dependently reduced histological injury, neutrophilic infiltrate, inflammasome activation and serum ALT values in both co-treatment (starting digoxin same time with HFD, ALT, 417 +/- 398 U/L in HFD vs 91 +/- 73 U/L in HFD+DIG, P< 0.001), and post-treatment (starting digoxin after 4 weeks HFD, neutrophil 24.6% in HFD vs 14.3% in HFD+DIG; monocytes 31.6% in HFD vs 19.1% in HFD+DIG; ALT, 400 +/- 130 U/L in HFD vs 80 +/- 17 U/L in HFD+DIG, P< 0.001) without a reduction in food intake. A low dose of digoxin (0.05 mg/kg) also shows significant protective effects again injury oxidative stress and sterile inflammation in both NASH and ALD models. The microarray transcriptome analysis revealed that digoxin treatment resulted in the significant down-regulation of ROS metabolism, antioxidant and HIF1a signaling pathway gene expression from HFD liver tissues. A broad mass spectrometry-based proteomic screening revealed that digoxin binds pyruvate kinase M2 (PKM2), and independent of PKM2 kinase activity results in chromatin remodeling and down-regulation of HIF-1a transactivation. **Conclusions:** Our data identify PKM2 as a novel mediator and therapeutic target for regulating liver sterile inflammation, and demonstrate the protective role of digoxin from ASH and NASH.

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Glycogen synthase kinase-3b (GSK3b) sensing metabolism controls NLRP3 inflammasome activation and liver injury through direct binding to ASC protein

Sheng-Na Han[1], Ziwen Liang[2], Wajahat Z. Mehal[1], Xinshou Ouyang[1]; [1]Yale University, New Haven, CT; [2]Endocrinology, Southwest Hospital of Third Military Medical University, Chongqing, China

Background: The metabolic syndrome results in sterile inflammation in the liver, and this is dependent on the activation of NLRP3 inflammasome, that is a cytosolic protein complex comprising NLRP3 protein, an adaptor protein ASC (apoptosis-associated speck-like protein), and caspase-1 to activate proIL-1b into inflammatory IL-1b. Glycogen synthase kinase-3 (GSK3) is an important metabolic regulator and is composed of the two isoforms of GSK3a and GSK3b. **Aim:** To identify the role of GSK3 isoform inhibition on inflammasome activation and metabolic liver injury. **Methods:** The NLRP3 inflammasome was activated by LPS/ATP and glucose in primary mouse macrophages. The effect of specific inhibition of GSK3 isoforms on inflammasome activation was assayed by quantifying IL-1β in the supernatant, and activated caspase-1 in cell lysates. Molecular mechanisms were investigated by protein pull-down assay, confocal imaging using forced gene expression system and endogenous protein tagged mouse macrophages. The *in vivo* role of GSK3b inhibition on metabolic liver injury was demonstrated using high fat diet (HFD) induced NASH, and diabetic models in ApoE-deficient mice. **Results:** Pharmacological inhibition of total GSK3 and GSK3b, but not GSK3a, suppressed NLRP3 inflammasome activation in response to ATP, urate crystal and the microbial alkaloid toxin staurosporine. GSK3b inhibition did not inhibit AIM2 inflammasome activation in response to double-stranded DNA and did not affect non-canonical caspase-11 inflammasome activation. GSK3b inhibition suppressed high glucose mediated NLRP3 inflammasome activation. GSK3b inhibition blocked NLRP3 inflammasome by reducing caspase-1 activation and ASC speck formation. GSK3b inhibition blocked NLRP3 inflammasome activation without affecting the level of reactive oxygen species (ROS). Pull down of endogenous GSK3b showed that it directly binds to ASC. GSK3b inhibition reduced the O-GlcNAcylation of ASC protein, and O-GlcNAc transferase-deficient macrophages also resulted in significant reduction of mature IL-1b secretion in response to NLRP3 inflammasome activation. As predicted GSK3b inhibition attenuated urate crystal-induced peritonitis, and suppressed IL-1b secretion serum and ALT, AST levels from both HFD-NASH and HFD-diabetes in ApoE-deficient mice. **Conclusions:** Our results demonstrate a critical role of metabolism-sensing GSK3b in mediating NLRP3 inflammasome activation and liver injury, thus defining a new therapeutic target for sterile inflammation in the liver.

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Macrophages are the gateway to damaging viral replication in Coronavirus infection

Agata Bartczak, Max Xuezhong M. Ma, Yujia Li, Kim Tsoi, Oyedele Adeyi, Ian McGilvray; Multi-Organ Transplant Department, University Health Network, Toronto, ON, Canada

Severe Coronavirus (CoV) infection has led to global epidemics of respiratory failure and is one cause of fulminant liver failure. In all cases, severe clinical illness is caused by the strong host inflammatory response against the virus; this is particularly true of mouse liver damage following infection by Murine Hepatitis Virus Strain 3 (MHV-3). Having previously shown that macrophage activation drives much of MHV-3 host inflammation and that the Ubiquitin Specific Peptidase 18 (USP18) pathway is linked to the type of inflammatory response generated by MHV-3, we asked whether USP18 modulates liver macrophage (Kupffer cell, KC) inflammatory responses. We found that *usp18*$^{-/-}$ mice have increased numbers of KCs and that their KCs have an M2-like ("regulatory") phenotype as characterized by increased phagocytic activity, arginase-1 expression, and anti-inflammatory cytokine (IL-10) responses to LPS. The response of *usp18*$^{-/-}$ KCs to LPS did not induce M1-like pro-inflammatory cytokines (TNF-α, IFN-γ). This pattern of cytokine expression was replicated *in vivo* following MHV-3 infection of susceptible C57BL/6 mice: *usp18*$^{-/-}$ mice had decreased levels of pro-inflammatory cytokines (TNF-α, IL-12 and MIP1-α) but increased anti-inflammatory cytokine (IL-4, IL-10) expression in the liver compared to *usp18*$^{+/+}$ mice. By contrast, *usp18*$^{+/+}$ mice had KCs that were "M1" (pro-inflammatory) based on the same criteria, with much more expression of TNF-α and IL-12 in their livers following MHV-3 infection. Based on these data, we hypothesized that *usp18*$^{+/+}$ M1-like KCs are deleterious to the inflammation-driven pathogenesis of MHV-3, but that *usp18*$^{-/-}$, M2-like KCs might be protective, such that eliminating KCs would be beneficial for *usp18*$^{+/+}$ mice but detrimental to *usp18*$^{-/-}$ mice. Surprisingly, the depletion of KCs with clodronate treatment led to improved survival of both *usp18*$^{+/+}$ and *usp18*$^{-/-}$ mice until 12 days p.i.. As expected, KC depletion eliminated the cytokine storm in *usp18*$^{+/+}$ mice; however, in the *usp18*$^{-/-}$ we did not see evidence of increased inflammation or liver damage. In both groups of animals, KC-depletion decreased early viral replication in the liver by 2 logs, which was not dependent on macrophage number since macrophages constitute a minority of the cells in the liver homogenate and the replication of MHV-3 in macrophages and hepatocytes

was similar. These studies, for the first time, illustrate the macrophage-permissive effect of MHV-3 infection of the liver and outline a potential new target for the treatment of severe CoV infection that is independent of the host inflammatory response.

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Cenicriviroc, a dual-CCR2/5 antagonist, prevents and reverses liver damage, steatosis and inflammation in alcoholic liver disease in mice

Aditya Ambade[1], Karen Kodys[1], Patrick P. Lowe[1], Donna Catalano[1], Benedek Gyongyosi[1], Eric Lefebvre[2], Pamela Vig[2], Gyongyi Szabo[1]; [1]Medicine, UMass Medical School, Worcester, MA; [2]Tobira Therapeutics, Inc, South San Francisco, CA

Purpose: Chronic alcohol abuse leads to liver inflammation, fibrosis and cirrhosis. Inflammation contributes to alcoholic liver disease (ALD), particularly to alcoholic steatohepatitis (ASH). Monocyte chemoattractant protein-1 (MCP-1/CCL2) and Chemokine (C-C motif) ligand 5 (RANTES /CCL5), through interaction with their respective receptors, CCR2 and CCR5, drive the inflammatory response in ASH. **Aim:** Here we hypothesized that dual inhibition of CCR2/5 with cenicriviroc (CVC) will attenuate the features of ALD. **Methods:** We used the Lieber-DeCarli diet model of chronic alcohol feeding (5% v/v alcohol for 6 weeks). In the "prevention" cohort, CVC (15mg/kg) or vehicle (10% Hydroxypropyl-β-Cyclodextrin / 5% Solutol HS15 / 85% Sterile Water) were injected s.c. daily for the entire length of alcohol feeding (6 weeks). In the "treatment" cohort, CVC or vehicle were injected for the last 3 weeks of alcohol feeding (weeks 4-6). Liver injury (Serum ALT and H&E), steatosis (Oil-Red-O staining and triglycerides), were assessed. Cytokine expression was analyzed by qPCR, ELISA and liver immune cell infiltration by FACS. **Results:** Mice receiving alcohol+CVC in the "prevention" cohort had significantly lower serum ALT levels compared to alcohol+vehicle controls during the entire course of alcohol feeding. At sacrifice, the alcohol+CVC group had significantly reduced inflammatory cytokine levels (TNFα, IL-1β) and steatosis compared to the alcohol+vehicle group. Mice on alcohol diet showed significant induction in serum ALT up to week 4 after which, introduction of CVC "treatment" rapidly normalized ALT levels to baseline. Liver inflammatory cytokines TNFα, IL-1β and IL-6 were significantly reduced after CVC "treatment" compared to alcohol+vehicle mice. Mice in the CVC "treatment" group showed lower liver triglycerides and lipid accumulation upon alcohol administration. Finally, CVC both in the "prevention" and "treatment" cohorts significantly lowered serum CD14 levels compared to those in the alcohol+-vehicle groups. CVC administration in both, the "prevention" and "treatment" cohorts, significantly prevented macrophage infiltration to the liver and restored alcohol-related reduction in hepatic NK and B cell counts. **Conclusions:** Blocking CCR2/5 with CVC attenuates chronic alcohol-induced macrophage infiltration to the liver thereby lowering inflammation and alcoholic hepatitis. Inhibition of CCR2/5 prevents liver damage, improves histology, and attenuates steatosis and serum CD14 in a mouse model of ALD. Our data indicates the therapeutic potential of CVC for human ALD/ASH.

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Pamela Vig - Employment: Tobira; Stock Shareholder: Tobira

Gyongyi Szabo - Advisory Committees or Review Panels: Alcohol Research and Health (NIAAA), Bile Acid Council, GALAXY Project, Nature Reviews in Gastro & Hepatology, NIH ExRNA Program, Prevent Cancer Foundation, Yale University Liver Center, Trek Therapeutics, University of Colorado Alcohol Center, University of Southern California Liver Center, University of Pittsburgh, MSTP EAB, Cytatx, Glympse Bio, Janssen Research & Development; Board Membership: ACER, Hepatology; Consulting: Novartis, Orbimed, Roviant, Salix, Tobira, Verlyx; Grant/Research Support: NIH-NIAAA, BMS, Gilead, Genfit, Genentech, University of Florida, Intercept, Tobira, Takeda, Vertex

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The Chemokine Receptor CCR2 and Interleukin 23 derived from Antigen Presenting Cells are Essential for Primary Biliary Cholangitis Progression

Debby Reuveni[1], Patrick S. Leung[2], Oren Shibolet[1], M. Eric Gershwin[2], Ehud Zigmond[1]; [1]Liver Unit, Tel-Aviv Medical Center, Tel-Aviv, Israel; [2]Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis, Davis, CA

Background: Primary Biliary Cholangitis (PBC) is a chronic autoimmune liver disease characterized by the presence of anti-mitochondrial antibodies (AMA) and hepatic antigen specific T cells, resulting in progressive cholestasis eventually leading to cirrhosis. Monocytes are plastic cells, massively recruited to inflamed tissues and differentiate into antigen presenting cells (APC). CCR2, expressed by monocytes, is crucial for the emigration of these cells from the bone marrow to the circulation. Monocyte isolated from PBC patients were found to be more sensitive to TLR signaling resulting in secretion of pro-inflammatory cytokines. Interleukin 23 (IL-23) is a pro-inflammatory cytokine belongs to the IL-12 family. IL-23 positive cells were detected in portal areas of liver tissues in advanced stages of PBC. Thus, previous studies suggest involvement of monocyte-derived cells and IL-23 in PBC pathogenesis; however, solid data evaluating their importance and function in the in-vivo context is still missing. Methods: We utilized an inducible murine model of PBC by immunization of mice with the xenobiotic 2-octynoic acid conjugated to bovine serum albumin (2-OA BSA). CCR2 knockout (KO) mice and mice with APC restricted deficiency of IL-23 ($CD11c^{cre}P19^{flox}$) were compared to wild type (WT) and $P19^{flox}$ control mice, respectively. Analysis included histology assessment, AMA serum titers, flow cytometry and immunohistochemistry of immune cells in the liver, fibrosis evaluation and hepatic cytokine profile by RT-PCR. Results: Histopathology evaluation revealed hepatic infiltration of lymphocytes and mononuclear cells in WT mice as compared to CCR2KO mice that exhibited no liver abnormalities. Immunofluorecent microscopy and flow cytometry analyses showed a massive accumulation of monocyte-derived macrophages around the portal triads in WT mice but not in CCR2KO. Flow cytometry analysis revealed significantly increased ratio of hepatic CD8/CD4 T cells in WT mice. Hepatic expression level of pro-inflammatory cytokines including TNFα and IFNγ and AMA titers in the serum were elevated in WT mice. Sirius red staining of liver sections exhibit peri-portal collagen deposition only in WT mice, a finding that was supported by a pro-fibrotic gene-expression signature in the liver. $CD11c^{cre}P19^{flox}$ mice exhibited significantly milder disease phenotype as assessed by histology, flow cytometry and hepatic cytokine profile, compared to their Cre-negative littermates. Conclusions: Our results indicate a major role for CCR2 and for APC derived IL-23 in the pathogenesis and progression of PBC and may pave the road for the development of new immune-based therapeutic modalities.

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High Mobility Group Box 1 (HMGB1) and Neutrophils in NAFLD: inhibition of T cell activation and proliferation.

Laura Antonucci[1], Cristiana Porcu[1], Barbara Barbaro[2], Stefania Straino[1], Caterina Mucciante[1], Eugenio Gaudio[3], Clara Balsano[2,1]; [1]Francesco Balsano Foundation, Rome, Italy; [2]Institute of Molecular Biology and Pathology, National Research Council, Rome, Italy; [3]Department of Anatomical, Histological, Forensic Medicine and Orthopedics Sciences, Sapienza University of Rome, Rome, Italy

Background and aims Injured cells release endogenous molecules called alarmins, which can activate immune response. The most studied alarmin, HMGB1,can translocate from the nucleus to the cytoplasm, activating the innate immune system. In liver failure elevated plasma HMGB1 levels were observed, pointing out HMGB1 as a sensitive marker of hepatotoxicity in Non-Alcoholic Fatty Liver Disease (NAFLD) which is the most common chronic liver disease which goes from steatosis up to hepatocellular carcinoma. In the early phases of NAFLD the effect of neutrophil cells in the suppression of T cell-mediated liver damage remains elusive, hence we aimed to investigate this relationship and the involvement of HMGB1. **Methods** We analyzed the HMGB1 serum levels in 40 early NAFLD patients and 20 healthy donors (HD) by ELISA, and then laboratory and clinical data collected. Immunohistochemistry (IHC) was used to show HMGB1 localization in paraffin-embedded liver biopsies. Flow cytometry analysis (FACS) was used to study Neutrophils proliferation by CFSE dilution and phenotype of mitogenically activated T cells. We performed co-culture of Neutrophils with PBMCs stained with CFSE and activated with plate-bound anti-CD3/CD28 antibodies, from both HD and patients. **Results and Conclusion** Interestingly NAFLD patients HMGB1 levels were three-fold higher than HD; in addition serum concentrations of HMGB1 positively correlated with absolute and relative number of circulating neutrophils.By IHC, we found that HMGB1 resides in the nuclei of healthy hepatocytes, whereas the cytoplasmic localization in the steatotic hepatocytes suggests a forthcoming release from the damaged tissue. We demonstrated that Neutrophils are able to suppress proliferation of T helper (CD4+) and Cytotoxic T cells (CD8+) and to inhibit the expression of their activation markers (CD25, CD39) both in HD and NAFLD patients. Moreover, we found that in HD, but not in NAFLD patients, the pre-stimulation of the neutrophils with HMGB1 enhance immune-suppression in particular of CD4+. Results in HD demonstrate that HMGB1 potentiates the suppressive activity of neutrophils on T cells, maybe to establish a protection against inflammatory response. In early NAFLD patients, whose HMGB1 levels are three-fold higher than HD,neutrophils show the same profile of HD's neutrophils stimulated *in vitro* with HMGB1.Instead neutrophils of NAFLD patients, stimulated with HMGB1,doesn't increase their suppressive activity on T cells, allowing the progression of the liver disease. Our preliminary data lead us to consider HMGB1 as one of the main actor in the suppression of T cells proliferation, already on the early phase of NAFLD.

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Plasmin is Critical for Macrophage-dependent Removal of Necrotic Cells from the Liver after Acetaminophen Overdose in Mice

Nikita Joshi[1], Ryan Albee[1], James P. Luyendyk[2], Bryan L. Copple[1]; [1]Pharmacology and Toxicology, Michigan State University, East Lansing, MI; [2]Pathobiology and Diagnostic Investigation, Michigan State University, East Lansing, MI

Acetaminophen (APAP)-induced liver injury is the number one cause of acute liver failure in the United States. Although a great deal of research has focused on developing therapies that limit liver injury after APAP overdose, many patients will not benefit from this type of therapy as liver injury is often extensive by the time they reach the clinic. These patients would most likely benefit from therapies aimed at stimulating liver repair. The mechanisms that regulate liver repair after APAP overdose, however, are not fully understood. In particular, the mechanism(s) that regulate macrophage-dependent clearance of necrotic cells from the liver are not known. A greater understanding of these mechanism(s) could lead to new therapies to stimulate liver repair in patients suffering from acute liver failure. In the present study, we tested the hypothesis that plasmin is critical for macrophage-dependent clearance of necrotic cells from the liver. To test this hypothesis, mice were treated with 300 mg/kg APAP and tranexamic acid, which inhibits conversion of plasminogen to plasmin, or vehicle (sterile saline). Tranexamic acid had no effect on APAP-induced increases in ALT at 24, 48, and 72 hours after treatment. Similarly, the area of necrosis at 48 hours after treatment was not different between tranexamic acid-treated and vehicle-treated mice. In striking contrast, whereas necrosis was largely absent in vehicle-treated mice given APAP (2.7%), the area of necrosis in mice treated with APAP and tranexamic acid was 31.7%. This indicated that plasmin inhibition prevented macrophage-dependent removal of necrotic cells from the livers of APAP-treated mice. Macrophage numbers were not different between the two groups indicating that the defect was not the result of improper recruitment of macrophages. Similarly, opsonization of the necrotic cells was not affected as the necrotic cells were similarly coated with complement factor, C3b, between the two groups. To determine whether plasmin has direct effects on macrophage function, bone marrow-derived macrophages were treated with plasmin. Plasmin increased phagocytosis and upregulated matrix metalloproteinases 8 and 13 mRNAs. Collectively, these studies demonstrate that plasmin is critical for removal of necrotic cells from the liver after APAP treatment and that plasmin may promote clearance of necrotic cells by directly stimulating macrophage phagocytosis. A greater understanding of the mechanism by which plasmin promotes macrophage phagocytosis could lead to new treatments that stimulate removal of dead cells from the liver, a process that is essential for liver repair.

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1042

Reduction of portal pressure by transjugular porto-systemic shunt (TIPS) modifies cytokine expression in LPS-stimulated blood monocytes (BM)

Benedetta Piombanti, Elisa Vivoli, Valentina L. Cacciato, Francesco Vizzutti, Roberto G. Romanelli, Andrea Cappon, Giacomo Laffi, Fabio Marra; University of Florence, Florence, Italy

Background/aims: Altered immunity is a common finding in patients with cirrhosis. The presence of subclinical systemic inflammation may contribute to portal hypertension and the development of acute-on-chronic liver failure, and cirrhotic patients are more susceptible to bacterial infections. Aim of this study was to compare the response of peripheral blood monocytes (BM) to LPS stimulation, in patients undergoing placement of a TIPS. Methods: 10 patients (6 males, age 53-81 years) with cirrhosis and portal hypertension and an indication to TIPS placement (bleeding and/or refractory ascites) were enrolled. Etiology was HCV (n=4), HBV (n=3), alcohol (n=1) or multifactorial (N=2), with a MELD score between 9 and 13. At the time of the TIPS procedure blood was drawn from a peripheral vein and from the portal vein before deployment of prosthesis. At 3 weeks after TIPS placement a sample from a peripheral vein was repeated. 12 healthy subjects (HS) served as controls (peripheral blood only). Blood MC were isolated by Ficoll and allowed to adhere on plastic dishes. After transfer to new dishes, cells were incubated with or without LPS. Cytokine expression was measured by quantitative real time PCR. Results: In unstimulated conditions, expression levels of IL-1beta, IL-6 were comparable in cirrhotic patients and in HS. In portal BM, expression of IL-10 was significantly higher than in peripheral BM from cirrhotic patients and from HS. Upon LPS stimulation, a marked increase in all three cytokines was observed, in BM isolated from all the different sites. However, LPS-stimulated mRNA levels for IL-1 beta were higher in samples collected before TIPS (both peripheral and portal) than in those collected from a peripheral vein after TIPS placement. These latter were also significantly lower than those observed in HS. Before TIPS, IL-10 levels after LPS stimulation were significantly higher in cirrhotic patients than in HS. After TIPS, IL-10 mRNA was reduced, and reached values similar to those of peripheral BM from HS. In contrast, expression of IL-6 was significantly lower in all samples from cirrhotic patients, regardless of TIPS placement or size of collection, than in HS. Expression of TLR4 was slightly, but significantly higher in all samples from cirrhotic patients. Conclusions: Cirrhosis and portal hypertension differentially affect cytokine expression in LPS-stimulated BM. Reduction of portal pressure by TIPS results induce a BM phenotype more similar the one observed in peripheral BM from HS. These data suggest that effective management of portal hypertension may have an impact on the immune responses in patients with cirrhosis.

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1043

Accumulation of monocytic myeloid-derived suppressor cells in the liver of a murine model of non-alcoholic fatty liver disease

Masanori Abe, Liying Yao, Yoshiko Nakamura, Teruki Miyake, Yusuke Imai, Takao Watanabe, Yohei Koizumi, Osamu Yoshida, Yoshio Tokumoto, Masashi Hirooka, Teru Kumagi, Yoichi Hiasa; Department of Gastroenterology and Metabology, Ehime Universiy Graduate School of Medicine, Ehime, Japan

Background/Aim: Myeloid-derived suppressor cells (MDSCs), which comprise a heterogeneous population of myeloid cells, are recognized as suppressors of T cell functions. In mice, these cells are identified by co-expression of the surface markers CD11b and Gr-1. However, an MDSC-specific marker has not been described because MDSCs and other myeloid cells display same markers. We have recently reported that $SSC^{low}CD11b^{+}Gr1^{dim}$ cells, but not $SSC^{low}CD11b^{+}Gr1^{hi}$ cells, represent authentic monocytic MDSCs in the liver. In addition, increased number of monocytic MDSCs was observed in the liver of a murine model of non-alcoholic liver disease (NAFLD). This study was aimed to understand the biology of MDSC accumulation in the NAFLD liver. **Methods:** C57BL/6 mice were fed a normal diet or a high-fat diet (NAFLD model) for 3 months. Different subtypes of $CD11b^{+}Gr\text{-}1^{+}$ cells were sorted from liver non-parenchymal cells by FACS, and cell surface markers were analyzed by flowcytometry. To observe the effect of steatosis in hepatocytes, Hepa1-6 cells were exposed to 0.1mM oleic acid or palmitic acid. RNA was extracted from the livers and Hepa1-6 cells, and gene expression of CCL2 and M-CSF was examined by real-time RT-PCR analysis. The protein levels of CCL2 and M-CSF were analyzed by immunohistochemistry and ELISA. Migratory capacity of monocytic MDSCs was examined by an *in vitro* migration assay. Finally, bone marrow cells from C57BL/6 mice were cultured with M-CSF for 3 days, and induction of monocytic MDSCs was analyzed by flowcytometry. **Results:** Among the $CD11b^{+}Gr\text{-}1^{+}$ cells in the liver, monocytic MDSCs, but not other subsets of cells, express CCR2 and CD115 (CSF-1-R) on their surface. The mRNA and protein levels of CCL2 and M-CSF were higher in the livers of NAFLD mice than in those of control mice. These results were confirmed by using Hepa1-6 cells supplemented with fatty acid. The *in vitro* migration assay showed that monocytic MDSCs migrated in response to CCL2 in a dose-dependent manner. In addition, increasing number of monocytic MDSCs were observed in cultures grown in the presence of M-CSF in a dose-dependent manner. **Conclusion:** The CCL2-CCR2 pathway might contribute to migration of monocytic MDSCs in the steatotic liver. In addition, increased M-CSF levels in the steatotic liver might contribute to the induction of monocytic MDSCs. These results suggest that targeting of these key molecules is a rational strategy for regulating the immune environment in NAFLD.

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1044

IFNλ3 enhances poly(I:C)-induced type-I IFN induction and DC maturation

Yuika Innami, Masao Honda, Kazuhisa Murai, Tetsuro Shimakami, Takayoshi Shirasaki, Seishi Murakami, Shuichi Kaneko; Kanazawa University, Ishikawa, Japan

Objective: Single nucleotide polymorphisms of the interleukin 28B (IL28B; interferon [IFN] λ3) gene are strongly associated

with sustained virological response rates when treating patients with chronic hepatitis C with PEGylated interferon and ribavirin combination therapy. Moreover, the IL28B genotype is potentially associated with the outcome of direct antiviral agent treatment in patients with decompensated cirrhosis and liver transplantation. Although IFNλ3 is expressed in BDCA3+ dendritic cells (DCs), its functional relevance in the innate immune response has not been clarified fully. **Methods:** IFNλ3 knockout (KO) mice were generated, and wild-type (WT) and IFNλ3 KO mice were injected with polyinosinic-polycytidylic acid (poly[I:C]) via the tail vein. At 48 h after injection, immune cells such as DCs, natural killer (NK) cells, and T cells in the liver were evaluated by fluorescence-activated cell sorting (FACS) analysis. For bone marrow-derived dendritic cell (BMDC) generation, bone marrow cells were cultured in media containing GM-CSF for 7 days. BMDCs were pretreated with IFNλ3 recombinant protein (r-IFNλ3) or an IFNλ3 neutralizing antibody (Ab-IFNλ3), and these cells were then stimulated with poly(I:C). **Results:** To determine whether IFNλ3 is associated with immune cell activation *in vivo,* WT and IFNλ3 KO mice were stimulated with poly(I:C) and then the number of immune cells in the liver was analyzed. In IFNλ3 KO mice, the number of DCs, NK, and T cells was significantly decreased under stimulation with poly(I:C) compared with WT mice. To investigate the effects of IFNλ3 on type-I IFN induction, BMDCs derived from WT mice were stimulated by poly(I:C) in the presence or absence of pretreatment with r-IFNλ3 or Ab-IFNλ3. Pretreatment with r-IFNλ3 significantly enhanced poly(I:C)-induced IFNβ induction. Inversely, pretreatment with Ab-IFNλ3 significantly suppressed IFNβ induction. In addition, IFNβ induction by poly(I:C) was significantly reduced in primary mouse hepatocytes derived from IFNλ3 KO mice compared with WT mice. Next, we evaluated the effects of IFNλ3 on DC maturation. Upon stimulation with poly(I:C), BMDCs derived from IFNλ3 KO mice exhibited lower expression levels of activation markers of DCs such as CD86 and MHC class II when compared with WT mice. **Conclusion:** These results suggest that IFNλ3 plays an important role in the DC-mediated immune response. We expect that IFNλ3 has therapeutic potential not only for hepatitis B/C virus infections but also for cancer immunotherapy in hepatocellular carcinoma.

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1045
IL10 associated downstream signalling pathways play a central role in severe monocyte dysfunction during acute-on-chronic liver failure.

Hannelie Korf[2], Johannie du Plessis[2], Johannes van Pelt[2], Frederik Nevens[1,2], Schalk Van Der Merwe[1], Elien De Smidt[3]; [1]Hepatology, University of Leuven, Leuven, Belgium; [2]Laboratory of Hepatology, University of Leuven, Leuven, Belgium; [3]Laboratory of Endocrinology, University of Leuven, Leuven, Belgium

Objective: Acute-on-chronic liver failure (ACLF) is characterized by rapid deterioration of liver function in cirrhosis which often precipitates organ failure. ACLF is associated with severe immunodysfunction where immune activation and paresis often co-exist. This dysregulated immune state leads to severe monocyte dysfunction that may precipitate bacterial infections. Although ACLF as disease entity has attracted much attention, little is known about the molecular mechanisms responsible for altered monocyte function in this condition. **Design:** We studied 64 patients with biopsy proven alcoholic liver disease (n=19 decompensated cirrhosis, n=23 alcoholic hepatitis, n=22 ACLF) and 7 controls. Blood was obtained at admission for biochemical tests, gene expression of PBMC's, flow cytometry and functional monocyte assays and plasma was used to determine cytokine/chemokine levels. In addition we isolated $CD14^{pos}$ monocytes from 4 donors and 5 well-characterized ACLF patients and determined gene expression by NextGen sequencing to characterize key molecular factors associated with monocyte dysfunction using pathway analysis. Additionally functional assays were performed with healthy or ACLF monocytes in the presence or absence of normal or ACLF serum. **Results:** We observed decreased expression of HLA-DR, TLR2 and TLR4 within the classical monocyte subset and elevated numbers of IL10 producing intermediate monocytes in ACLF. Functional analysis of total PBMC and isolated $CD14^{pos}$ monocytes showed severely impaired phagocytosis and oxidative burst in ACLF. Increased IL10 gene expression by PBMC's and elevated IL10 plasma levels in ACLF were associated with decreased survival at 3 and 6 months. Pathway analysis revealed significant downregulation of genes associated with immunological processes such as monocyte phagocytosis, cytokine-cytokine interactions and response to bacterial infection. Importantly, culturing healthy monocytes in ACLF serum induced an ACLF dysfunctional phenotype. Conversely, culturing ACLF-monocytes in healthy plasma reversed the ACLF phenotype and restored phagocytosis. Finally, our data indicated a central role for IL10 in the molecular pathways associated with ACLF. **Conclusion:** ACLF is associated with severe immune dysfunction. Inducing an ACLF signature in healthy monocytes using ACLF serum-containing media and reversing monocyte dysfunction of ACLF monocytes using normal serum containing medium suggests a circulating factor promotes this syndrome. IL10 associates with more severe immune dysfunction and poor survival in ACLF while expression analysis suggests a crucial role for IL10 as driver of this condition.

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1046
Neutrophil-specific production of interferon-λ1 is deficient in advanced alcohol-related liver cirrhosis

Jennifer M. Ryan[1,2], Antonio Riva[2,3], Gavin Wright[4], Alex Evans[5], Debbie L. Shawcross[1], Roger Williams[2,3], Shilpa Chokshi[2,3]; [1]Institute of Liver Studies, King's College London at King's College Hospital, London, London, United Kingdom; [2]Institute of Hepatology, Foundation for Liver Research, London, London, United Kingdom; [3]Faculty of Life Sciences and Medicine, King's College London,, London, United Kingdom; [4]Basildon and Thurrock University Hospitals, Basildon,, Basildon, United Kingdom; [5]Department of Gastroenterology, Royal Berkshire Hospital, Reading, United Kingdom

Introduction Neutrophil dysfunction is closely correlated to the susceptibility to bacterial infection observed in alcohol-related cirrhosis (ARC). This has primarily thought to be consequent to their defective phagocytosis and reactive oxygen species (ROS) production. Emerging evidence suggests that type III interferons, IFN-λ1, -λ2 and -λ3, possess anti-pathogen, anti-cancer and immuno-modulatory properties. The interplay between IFN-λ and neutrophils both in health and ARC has not been examined. **Aims** To explore whether neutrophils produce

or respond to IFN-λ in health and in ARC. **Methods** Whole blood from healthy controls (HCs)(n=8) and patients with ARC(n=11), median Child Pugh score 10, were cultured with/without *E. coli*. 2 patients had superimposed alcoholic hepatitis (DF>32). RNA was then extracted from both isolated neutrophils and total leukocyte fractions and quantitative PCR for IFN-λ1, -λ2/3, IFN-λ receptor and RPLP0 (endogenous control) performed. Patient whole blood was incubated with IFN-λ1, -λ2, or -λ3 and examined for expression of neutrophil CD182, PSGL-1, CD11b, TLR4, TLR2, CD16, CD14, CD62L. Phagocytosis and ROS production were also assessed by FACS. **Results** The most notable findings were seen in the neutrophil mRNA expression of IFN-λ1. Amongst the patients 2 groups emerged; those who did not have *E. coli*-stimulated induction of IFN-λ1 (Group 1) and those who did (Group 2), although at a lower level than the HCs. *E. coli*-stimulated neutrophil expression of IFN-λ1 in Group 1 was significantly less than in HC and Group 2 ($p<0.0001$). We observed that *E. coli*-challenged production of IFN-λ1 in the leukocyte fraction was also compromised in Group 1. Group 1 had significantly higher Child-Pugh scores and AST compared to Group 2 ($p=0.022$ and $p=0.015$, respectively). The profound difference we observed with IFN-λ1 between the groups was not seen in the neutrophil or leucocyte expression of IFN-λ2/3 and IFN-λ receptor expression. The addition of IFN-λ did not significantly alter neutrophil phagocytosis, burst or cell surface receptor expression. **Conclusion** For the first time we identify neutrophils as producers of innate type III interferons, reveal a previously unknown deficient IFN-λ production in ARC and confirm an IFN-λ response in bacterial infection. Further elucidation of these mechanisms may have important implications for therapeutic developments in an era of multi-drug resistance.

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1047
HBV and DNA Triggers a Rapid Intrinsic Innate Cytokine Response in Hepatocytes through NF-κB

Masato Yoneda[3,2], Satoru Saito[2], Eugene R. Schiff[3], Emmanuel Thomas[1]; [1]Schiff Center for Liver Diseases, Syllvester Comprehensive Cancer Center, Department of Cell Biology, University of Miami Miller School of Medicine, Miami, FL; [2]Department of Hepatology, Yokohama City University, Yokohama, Japan; [3]Schiff Center for Liver Diseases, University of Miami Miller School of Medicine, Miami, FL

Background: Cell intrinsic innate immunity provides a rapid first line of defense to thwart invading viral pathogens through the production of antiviral cytokines and inflammatory chemokines. However, the presence of many of these signaling pathways in the liver and their role in HBV pathogenesis is unknown. Recent identification of intracellular DNA sensing pathways and involvement in numerous diverse disease processes including viral pathogenesis and carcinogenesis suggests a role for these processes in HBV infection that has a DNA genome. **Methods:** In order to characterize HBV intrinsic innate immune responses and the role of DNA and RNA sensing pathways in the liver during recognition of HBV, we utilized *in vivo* and *in vitro* models including analysis of gene expression in liver biopsies from HBV infected patients. In addition, mRNA and protein expression was measured in HBV stimulated and DNA treated hepatoma cell lines (HepG2, HepG2.2.15, HepG2-NTCP and HepaRG) and primary human hepatocytes (PHHs). Specific RNA and DNA dependent innate and inflammatory pathways, such as RIG-I/MDA5 and IFI16/cGAS signaling, were studied as well as additional pathways involving the production of interferon and chemokines such as IP-10 and CCL5 that may drive subsequent liver disease. siRNA experiments were utilized to determine the signaling pathways involved in HBV recognition. Microarray analyses was used to characterize global transcriptome changes in HBV infected primary human hepatocytes. UV inactivation of HBV was utilized to determine effects observed from viral replication. **Results:** HBV and foreign DNA results in a rapid innate immune responses in hepatocytes characterized by the production of inflammatory chemokines at the mRNA and protein levels. Analysis of liver biopsies from HBV-infected patients supported a correlation among hepatic expression of specific antiviral genes including IP-10 and CCL5. In addition, HBV elicits a much broader range of gene expression alterations as demonstrated by microarray analysis. The induction of chemokines, including IP-10, was mediated predominantly by MDA5 and NF-kB-dependent pathways following HBV stimulation. **Conclusion:** HBV stimulated pathways predominantly activate an inflammatory response that would promote the development of hepatitis where as HCV stimulates a much stronger Interferon antiviral response. Understanding the mechanism underlying these inflammatory and antiviral responses may provide new strategies to trigger non-cytopathic clearance of cccDNA to ultimately cure patients with HBV infection. In addition, these data offer additional insight into HBV driven hepatocarcinogenesis.

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1048
HIF-1α activation induces autophagy in macrophages and protects from pro-inflammatory cytokine activation induced by free fatty acids

Xiaojing Wang, Ambika Pandita, Abhishek Satishchandran, Karen Kodys, Aditya Ambade, Gyongyi Szabo; Medicine, University of Massachusetts Medical School, Worcester, MA

Background and aims Hypoxia-inducible factors (HIFs) have recently been identified as important regulators of immunity and inflammation. HIF-1α plays a role in the pathogenesis of non-alcoholic steatohepatitis (NASH) where macrophage activation is a determining event in disease progression. HIF-1α is upregulated in NASH in hepatocytes where it induces steatosis; HIF-1α was also found to induce autophagy in fibroblasts. However, the role of HIF-1α in macrophages under metabolic stress has not been explored. In this study, we hypothesized that HIF-1α modulates macrophage autophagy in response to free fatty acids. Methods THP-1 macrophages were treated with free fatty acids (FFAs: 400mM oleic acid plus 200mM palmitic acid) for different time periods. RNA levels of HIF-1α and its target genes were examined by qPCR. Protein levels of HIF-1α and autophagy related molecules (LC3, Beclin-1, P62, mTOR, Bnip3) were examined by western-blot and HIF-1α DNA-binding tested by EMSA. HIF-1α silencing and overexpression were achieved using HIF-1α siRNA and pcDNA3.0-HA-HIF1α P402A, respectively. Cell supernatants were collected and tested by ELISA for pro-inflammatory (TNF-α, IL-1β, IL-6) and anti-inflammatory cytokines (TGF-β, IL-10)

and chemokines (MCP-1). Results After FFAs treatment of THP-1 cells, HIF-1α mRNA levels showed a rapid increase followed by upregulation of HIF-1α target genes, Bnip3, PAI-1 and Glut-1. HIF-1α protein levels and DNA-binding activity were also increased upon FFA treatment. FFAs-induced macrophage autophagy was indicated by increased protein levels of Bnip3, Beclin-1 and LC3-II and decrease in P62 and mTOR levels. These events paralleled induction of both pro- and anti-inflammatory cytokines in FFA-treated THP-1 cells. Silencing of HIF-1α by siRNA resulted in downregulation of Bnip3, Beclin-1 and LC3-II expression and increased production of pro-inflammatory cytokines, TNF-α, IL-1β and MCP-1, with a decrease in anti-inflammatory TGF-β suggesting that HIF-1α regulates FFAs-induced autophagy as well as inflammation in macrophages. Conversely, overexpression of HIF-1α augmented the expressions of Bnip3, Beclin-1 and LC3-II, reduced TNF-α and MCP-1 and increased TGF-β levels in macrophages providing additional evidence for HIF-1α-mediated regulation of autophagy and inflammation in macrophages. Conclusions Our results indicate that HIF-1α upregulation plays a protective role in macrophage-induced inflammation in NASH by regulating autophagy through HIF-1α-Bnip3-Beclin-1 pathway in response to free fatty acid stimulation. Our findings highlight the complex role of HIF-1α in macrophage regulation in metabolic stress and NASH.

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1049
Differential Response of Hepatic Monocyte-derived Macrophages and Kupffer Cells to Bacterial Lipopolysaccharide

Bryan L. Copple, Ryan Albee, Carly Gerhardt, Cheryl Rockwell; Pharmacology and Toxicology, Michigan State University, East Lansing, MI

The liver contains two distinct populations of macrophages, monocyte-derived macrophages (MDMs), which are F4/80^{low}, CD11b^{hi} and Kupffer cells which are F4/80^{hi}, CD11b^{low}. MDMs primarily reside within and around pre- and post-sinusoidal vessels, whereas Kupffer cells reside within the sinusoids. MDMs are replenished from myeloid progenitors in the bone marrow, whereas Kupffer cells are replenished through local proliferation of mature Kupffer cells. Beyond these observations, there is little information about whether there are functional differences between these macrophage cell types. In the present study, we determined whether these two macrophage populations produce different levels of cytokines when activated with bacterial lipopolysaccharide (LPS). MDMs and Kupffer cells were purified from the livers of mice by using antibody-labeled magnetic beads. After digestion of the liver with collagenase, dendritic cells were removed by negative selection with CD11c-labeled magnetic beads. Next, MDMs were purified from the liver digest by using magnetic beads labeled with Cx3cr1 antibody. Finally, Kupffer cells were purified from the remaining digest by using F4/80-labeled magnetic beads. Analysis of F4/80 and CD11b content by flow cytometry indicated that the MDMs and Kupffer cells were greater than 90% pure. Basal levels of tumor necrosis factor-1α (TNF-α) mRNA were 8.6-fold higher in MDMs when compared to Kupffer cells. After treatment of Kupffer cells with LPS, TNF-α, Cxcl1, and Cxcl2 were increased 15.9, 1.6, and 2.3-fold respectively. Treatment of MDMs with LPS increased TNF-α, Cxcl1, and Cxcl2 by 102.9, 3.2, and 8.2-fold respectively, indicating that LPS upregulates cytokines to a greater extent in MDMs. Lastly, basal levels of inducible nitric oxide synthase were 6-fold higher in MDMs when compared to Kupffer cells suggesting that MDMs are skewed towards an M1 macrophage phenotype. Collectively, these results indicate that MDMs are more pro-inflammatory than Kupffer cells, and that MDMs may be the main source of cytokines *in vivo* in the liver after exposure to bacterial products, such as LPS.

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1050 ♦
Long Term Mortality of Patients with Non-alcoholic Fatty Liver Disease (NAFLD)

Pegah Golabi[1], Munkhzul Otgonsuren[1], Aimal Arsalla[2], Madeline Erario[1], Manirath Srishord[1], Zobair M. Younossi[1,2]; [1]Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA; [2]Department of Medicine, Center for Liver Diseases, Inova Fairfax Hospital, Falls Church, VA

BACKGROUND: NAFLD is one of the most common causes of chronic liver disease. The long term outcomes of NAFLD in the general population setting is not well studied. **OBJECTIVES:** To compare risk of death from all causes as well as from cardiovascular and liver-specific causes in NAFLD subject according to presence or absence of metabolic syndrome (MS) conditions. **METHODS:** We used population-based survey, National Health and Nutrition Examination Survey-III (NHANES III) and its linkage to the National Death Index (NDI) death certificate records followed through 31 December 2011. We examined the association of components of MS with mortality in adults (aged 20-74) with NAFLD. MS were defined by NCEP-ATP-III guideline and NAFLD was identified by hepatic ultrasound presence of mild, moderate, or severe grade of steatosis in the absence of other causes of liver disease and excessive alcohol use. Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). **RESULTS:** The study included 3,613 participants with a median follow up of 19 years (INQ=17-20 years) from 1988 through 2011. During the follow-up period, 1,039 subjects died (370 from cardiovascular diseases and 22 from liver diseases). The prevalence of NAFLD without any MS was 13%, while prevalence of NAFLD with one MS was 28%, with two MS was 33%, with three MS was 20%, and with all four MS was 6%. In comparison to the absence of any MS conditions, HRs for all-cause mortality were 1.63 (95% CI: 0.96-2.79) for having one MS condition, 3.57 (2.32-5.49) for two MS conditions, 5.87 (3.53-9.75) for three MS conditions, 13.09 (7.49-22.87) for all four MS conditions. When age and history of cardiovascular diseases were mutually adjusted in a model, DM was independently associated with increased risk of death from all cause and cardiovascular causes (for all-cause mortality, 1.78 (1.51-2.09) and for cardiovascular diseases cause mortality, 1.83 (1.35-2.47)). In addition, NAFLD with all four MS 2 folds increased risk of death from liver-specific cause as compared NAFLD without any MS (1.96: 1.22-3.14). **CONCLUSIONS:** Increasing numbers of metabolic conditions are associated with increased risk of mortality in NAFLD. DM is the most important predictor of NAFLD.

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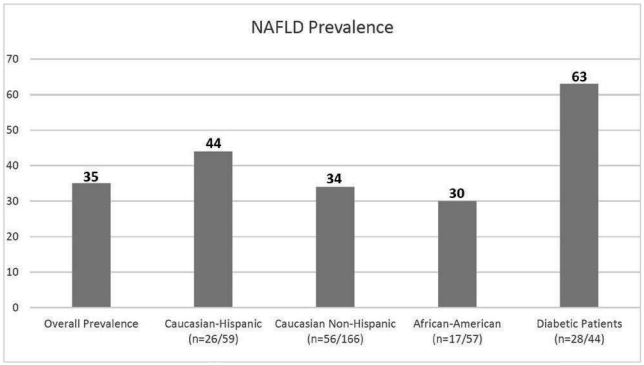
1051 ♦
Prospective Prevalence of Non-alcoholic Fatty Liver Disease (NAFLD) and Non-alcoholic Steatohepatitis (NASH) Among a Largely Middle-Aged Population Utilizing FibroScan®, Liver MultiScan (LMS), Magnetic Resonance Elastography (MRE), and Liver Biopsy: Interim Analysis

Angelo H. Paredes[1], Katharine K. Roberts[1], Induruwa N. Pathirana[1], Allyson E. Cochet[1], Pedro A. Manibusan[1], Christopher J. Lisanti[2], Ryan Schwope[2], Alan A. George[3], Katherine M. Cebe[3], James K. Aden[4], Jennifer M. Aldridge-Whitehead[2], Dustin M. Thomas[5], Stephen A. Harrison[1]; [1]Gastroenterology, Brooke Army Medical Center, Fort Sam Houston, TX; [2]Radiology, Brooke Army Medical Center, Fort Sam Houston, TX; [3]Pathology, Brooke Army Medical Center, Fort Sam Houston, TX; [4]Biomedical Statistics, Institute for Surgical Research, Fort Sam Houston, TX; [5]Cardiology, Brooke Army Medical Center, Fort Sam Houston, TX

Background: NAFLD prevalence is estimated to be as high as 30-46% in the USA. Large prospective studies are lacking correlating demographic, clinical and novel radiographic data to histopathology. Methods: Adult patients were prospectively enrolled predominantly at the time of referral for routine colon cancer screening. They were screened for evidence of NAFLD with FibroScan ®, LiverMultiScan (LMS), and MR elastography (MRE). A prior history of liver disease or alcohol ingestion greater than the accepted range for NAFLD was considered exclusionary. Patients exceeding pre-specified cutoff values on any imaging test were offered liver biopsy. Liver biopsies were read by an expert pathologist using the Brunt criteria. Results: To date, 430 participants have been enrolled, of which 284 had results available for interim analysis. Mean age: 56±6 years; mean BMI: 30±5 kg/m2; 57% male; 14% diabetic. The prevalence of NAFLD (defined by a proton density fat fraction (PDFF) of >5%) among those who completed all radiographic studies was 35% (N=284) (Fig. 1). PDFF values for NAFLD patients distributed as follows: 5-10%: 49%; 10.1-20%: 40%; >20%: 11%. One-hundred-seven biopsies have been performed to date: 29 normal, 62 Non-NASHNAFLD and 16 NASH. Among the NASH patients: 3 stage-0 (0% diabetic), 5 stage-1 (40% diabetic), 6 stage-2 (67% diabetic), and 2 stage-3 (100% diabetic). Patients with diabetes and NAFLD compared to non-NAFLD had higher FibroScan™ LSM (p=0.03), FibroScan™ CAP (p=0.0003), steatosis grade (p<0.0001), and fibrosis stage (p=0.0045). Among those with NASH vs. non-NASH NAFLD mean: FibroScan™ LSM 10.3±1.4 vs. 5.8±.24 kPa(p=0.005); LIF 2.6±0.16 vs. 2.15±0.08 (p=0.02); MRE 2.98±0.28 vs. 2.2±0.5 kPa (p=0.02), MRI cT1 889±7 vs. 924±16 (p=0.03). Conclusion: In adult patients without known liver disease interim results from novel radiographic studies and liver biopsy confirm the high prevalence of NAFLD in the USA.



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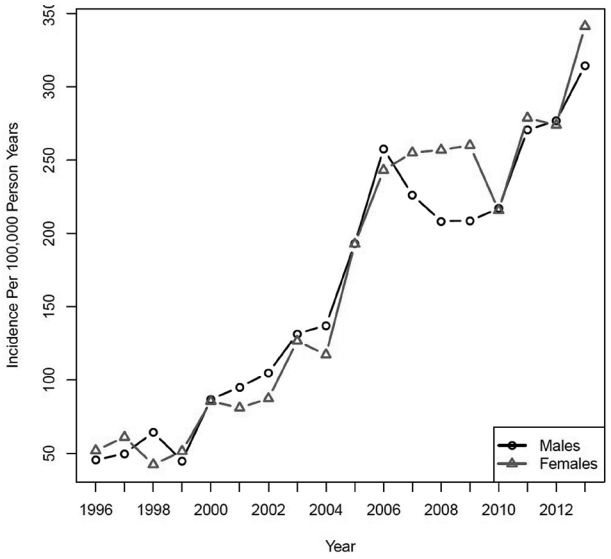
1052 ♦
The epidemiology of nonalcoholic fatty liver disease (NAFLD) in a US community

Alina M. Allen[1], Joseph J. Larson[2], Terry M. Therneau[2], Gregory J. Gores[1], Patrick S. Kamath[1]; [1]Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN; [2]Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN

Background & Aims: There is a paucity of data regarding the incidence of nonalcoholic fatty liver disease (NAFLD) in the population. We aim to determine time-trends in NAFLD incidence, mortality and cardiovascular (CV) events in a US community. Methods: Using the Rochester Epidemiology Project database, we constructed a community cohort of subjects diagnosed with NAFLD in Olmsted County, MN from 1996 to 2013. NAFLD was defined using a diagnostic code algorithm. Subjects were followed until April 2016. Mortality and CV outcomes (myocardial infarction, angina, atrial fibrillation and cerebrovascular disease) were compared to an age- and sex-matched control group (1:4) identified from the general population. Multivariable Cox regression analysis was performed to determine the impact NAFLD on mortality and CV events. Results: A total of 4,124 subjects with NAFLD (median age 52, 52% female) were identified. Between 1996 and 2013, the incidence rate has increased 6.7-fold, from 48.6 to 328.1 per 100,000 person-years without considerable sex-differences (Figure). Compared to 16,067 age- and sex-matched controls, NAFLD subjects were more likely to have diabetes (40% vs 14%, p<0.001), hypertension (67% vs 36%, p<0.001) and hyperlipidemia (78% vs 48%, p<0.001). NAFLD subjects had higher mortality (8.7% vs 5.0%) and CV events (21.1% vs 10.3%). After adjusting for presence of diabetes, hypertension, hyperlipidemia in addition to age and sex, NAFLD was independently associated with mortality (HR= 2.45, 95% CI 2.22-2.71 p<0.001) and CV events (HR= 1.73, 95% CI 1.60- 1.86 p<0.001). Conclusion: In this mostly white population, NAFLD incidence is increasing considerably. NAFLD is an independent predictor of overall mortality and CV events.



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1053
Fibrosis progression and mortality in non-alcoholic fatty liver disease

Olof Elfwén[2], Per Stål[1], Rolf W. Hultcrantz[1], Hannes Hagström[1]; [1]Center for Digestive Diseases, Unit of Hepatology, Karolinska University Hospital. Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden, Stockholm, Sweden; [2]Karolinska Institutet, Stockholm, Sweden

Introduction: Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease globally. Some patients with NAFLD have inflammation in the liver (non-alcoholic steatohepatitis; NASH) whereas some only has fatty liver without inflammation (non-alcoholic fatty liver; NAFL). Only NASH and not NAFL have previously been considered to have potential for progression of fibrosis and development of cirrhosis. *Aims*: To investigate risk factors for progression of fibrosis in patients with NAFLD, and the impact of these on subsequent mortality. *Material and Methods*: We identified all patients who had undergone a liver biopsy with the finding of NAFLD between 1971-2015 at the Karolinska University Hospital, Stockholm, Sweden. Patients who had performed two liver biopsies more than a year a part with a complete data on possible risk factors, including age, sex, presence of co-morbid diseases, BMI and biochemical parameters were identified. The cohort was divided into two groups, one with fibrosis progression and one without fibrosis progression, and then followed until death or the end of the study period. All biopsies were centrally read by one expert liver pathologist and were defined as NASH or not based on the FLIP algorithm, and scored for fibrosis using the NASH CRN system. Differences between parameters in the two cohorts were analyzed using the Mann-Whitney u-test for continuous variables and with Fischer's exact test for categorical variables. *Results*: 60 patients had serial biopsies (median interval 8.4 years, range 1-33 years), with 26 patients (43%) having fibrosis progression. Median age at baseline was 46 years, 62% were male, median BMI was 26.4 kg/m^2 and 17% had diabetes mellitus type 2. We found no significant risk factors for progression of fibrosis. Among patients with fibrosis progression, 54% had NAFL and 46% had NASH at baseline. There was no difference in fibrosis progression rate between patients with NAFL and NASH at baseline (0.11 vs. 0.15 stages per year, p=0.91). After the second biopsy, patients were followed for a median of 6.7 years (range 0-34). Of patients with fibrosis progression, 13 (50%) died during follow up versus 8 (24%) of patients without fibrosis progression (p=0.045). *Conclusions*: Both patients with NAFL and NASH can have progressive fibrosis and patients with progressive fibrosis are at a higher risk for future mortality.

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1054
Risk factors for type 2 diabetes mellitus development in non-alcoholic fatty liver disease after up to 41 years follow-up

Niklas K. Björkström[2], Per Stål[2], Rolf W. Hultcrantz[1], Hannes Hagström[1]; [1]Center for Digestive Diseases, Unit of Hepatology, Karolinska University Hospital. Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden, Stockholm, Sweden; [2]Karolinska Institutet, Stockholm, Sweden

Introduction: Non-alcoholic fatty liver disease (NAFLD) affects around 25% of the global population and is highly associated with the metabolic syndrome. Many of these patients develop type 2 diabetes mellitus (T2DM), and NAFLD patients that do develop T2DM are more likely to progress to non-alcoholic steatohepatitis (NASH) and liver fibrosis. There is a need for diagnostic tools to identify NAFLD patients who are at the highest risk of developing T2DM. The aim of this study was to find predictive factors for the risk of developing T2DM in NAFLD patients. Material and methods: A cohort of 510 patients with biopsy-proven NAFLD diagnosed between 1971 and 2009 was analyzed. Data on development of T2DM were collected from electronic and paper patient charts. Biomarkers and clinical parameters at baseline were compared for patients that developed T2DM and patients that did not. Hazard ratios (HR) for T2DM development for a number of baseline variables were calculated using multivariate Cox regression. The final model was adjusted for sex, age, hypertension, BMI, triglycerides and glucose as well as histological scoring for fat (0-3), lobular inflammation (0-3), ballooning (0-2), fibrosis (0-4) and portal inflammation (0-1). Results: We excluded 81 patients with T2DM at baseline and 90 patients with no outcome data, leaving 339 patients for final analysis. At baseline, patients had a mean age of 43.1 years. There were 121 women (35.7%), and patients were in general overweight with a mean BMI of 27.4. During a mean follow-up of 17-5 years (range 0-41), 121 individuals developed T2DM. Age at time of biopsy (aHR 1.04, 95% CI 1.01-1.06, p<0.01), serum triglycerides (aHR 1.29, 95% CI 1.11-1.49, p<0.01) and higher stages of fibrosis (aHR 1.44, 95% CI 1.01-2.05, p=0.045) were associated with increased risk for T2DM development. Conclusions: Age, fibrosis stage and triglycerides are predictive parameters for development of T2DM in NAFLD.

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The following people have nothing to disclose: Niklas K. Björkström, Per Stål, Rolf W. Hultcrantz, Hannes Hagström

1055

Race and Ethnicity in Patients with Nonalcoholic Fatty Liver Disease

Niharika Samala[2], Erin K. Hallinan[3], David E. Kleiner[4], Jay H. Hoofnagle[1], Rohit Loomba[5]; [1]Liver Diseases Branch, National Institutes of Health/ NIDDK, Bethesda, MD; [2]Medicine, Indiana University School of Medicine, Indianapolis, IN; [3]Statistics, John Hopkins University Bloomberg School of Public Health, Indianapolis, IN; [4]Pathology, National Institutes of Health/National Cancer Institute, Indianapolis, IN; [5]Medicine, University of California, San Diego, Indianapolis, IN

Background: Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in the US, affecting up to a third of adults. The prevalence of NAFLD appears to vary by race and ethnicity, but the variation may merely reflect differences in risk factors, such as obesity, dyslipidemia, diabetes and hypertension (i.e. the "metabolic syndrome"). Using data from the NASH CRN cohort study, we assessed variation in common risk factors, clinical features and severity of NAFLD by race and ethnicity. **Methods:** The NIDDK NASH CRN multicenter cohort study is aimed at helping to elucidate the pathogenesis, natural history and therapy of NAFLD. For this analysis, 1931 adult subjects were selected who were enrolled in NASH CRN and had a liver biopsy, clinical assessment and laboratory results within 6 months. Based upon self-reporting, patients were categorized as Non-Hispanic White (NHW), Hispanic White (HW), Asian, Black, or Other and compared in regards to clinical, laboratory and histological features. **Results:** Of the 1931 subjects, 74% were NHW, 7.3% HW, 5.5% Asian, 3.4% Black and 10% Other. Patients were more frequently women, ranging from 63% to 75% in all groups except Asians where men slightly outnumbered women (52%). The prevalence of diabetes, hypertension and coronary artery disease (CAD), was the highest in Blacks and lowest in HW. Mean weights (in kilograms) by group was lowest in Asians (80), intermediate in HW (89) and Other (92) and highest in NHW (100) and Blacks (102) ($p<0.0001$). A normal body mass index (BMI) was most frequent in Asians (15%) and least frequent in Blacks (0%). The NAFLD activity score (NAS) increased with increasing BMI category in NHW, Asians and Blacks while not changing with BMI in HW and Other. The frequency of the PNPLA3 GG genotype was highest in Blacks (36%), followed by Asians (31%), NHW (27%) and others (27%) and lowest in Hispanics (6%) ($p=0.04$). Proportion of patients with definite NASH vs borderline and NAFLD without NASH was not significantly different among the groups. **Conclusion:** There were significant differences in clinical features associated with NAFLD based on race and ethnicity. There was a female predominance in all groups except Asians. Mean weight of patients with NAFLD was the lowest for Asians and Hispanic Whites, intermediate for Other and Non-Hispanic Whites and highest for Blacks. Although Blacks represented a small percentage in the cohort, they had a high percentages of diabetes, hypertension, CAD and PNPLA3 GG genotype, suggesting a presence of cumulative risk factor burden for development of NAFLD in this group.

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1056

Burden of Nonalcoholic Fatty Liver Disease (NAFLD) in the United States

Arun J. Sanyal[2], Chris Estes[1], Homie Razavi[1]; [1]Center for Disease Analysis, Louisville, CO; [2]Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, Virginia Commonwealth University School of Medicine, Richmond, VA

Background: There is an urgent need to develop a comprehensive and rigorous model of the current and future burden of disease due to NAFLD and its impact on health care resource utilization to guide policy decisions for health care and drug development. **Aim:** To develop a comprehensive model of the burden of disease and its financial impact through 2030. **Methods:** The prevalence of NAFLD and its histological subtypes (NAFL and NASH) were computed from the robust national data on trends for obesity and T2DM separately and then applying the prevalence rates of NAFL and NASH from published literature to these data. The two data sets were integrated to develop a comprehensive model of NAFLD in the US population. Transition rates towards cirrhosis, end stage liver disease and cancer corrected were computed from a comprehensive literature search. Competing mortality from other background causes were estimated to assess the impact of NAFLD on excess all cause, liver-related and cardiovascular deaths. Model results were validated based upon national surveillance data for annual HCC incidence attributable to NASH. The analytical approach was similar to a previously published study on population health burden (JAMA 2013; 310:591-606). **Results:** If current trends continue, total NAFLD cases will increase from 83 million in 2015 to 101 million in 2030, a 20% increase, while total NASH cases will increase from 16.5 million in 2015 to 27.0 million in 2030, a 65% increase. The prevalence of NAFLD in the population aged ≥15 years will increase from 30% in 2015 to >33% over the next 15 years. Among total NASH cases, approximately 20% were classified as F3/F4 in 2015, increasing to >29% by 2030. The number of incident NASH-related HCC cases is projected at 12 220 in 2030, an increase of nearly 140% as compared to 2015 (5150 cases). The prevalent number of compensated and decompensated cirrhosis cases are projected to increase 180% and 200% from 2015 to 2030 (3 046 200 and 375 600 cases in 2030), respectively. Projected direct healthcare costs for NAFLD-related end stage liver disease will increase 165% from 9 570 M to 25 380 M USD during 2015-2030. By 2030, liver related mortality is estimated at 78 200 deaths, an increase of 200% from 2015 (26 280 deaths). **Conclusions:** With the projected increase in T2DM and a flattening of obesity prevalence, there will be a disproportionate increase in NASH over the next 15 years. This will translate in to a substantial increase in the burden of cirrhosis, end stage liver disease and HCC resulting in a commensurate increase in health care costs.

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Homie Razavi - Grant/Research Support: Gilead, Abbvie; Management Position: Center for Disease Analysis

The following people have nothing to disclose: Chris Estes

1057

Expression of MMP-1 in hepatic progenitor cells is a significant biomarker of human early nonalcoholic steatohepatitis

Hiroaki Yokomori[1], Yutaka Inagaki[2,5], Wataru Ando[3], Masaya Oda[4], Isao Okazaki[6]; [1]Internal Medicine, Kitasato University Medical Center, Saitama, Japan; [2]Center for Matrix Biology and Medicine, Tokai University Graduate School of Medicine, Isehara, Japan; [3]Department of Pharmaceutical Science, Kitasato University, Tokyo, Japan; [4]Organized Center of Clinical Medicine, Sanno Medical Center, International University of Health and Welfare, Tokyo, Japan; [5]Department of Regenerative Medicine, Tokai University Graduate School of Medicine, Kanagawa, Japan; [6]Internal Medicine, Sanno Hostital, International University of Health and Welfare Hospital, Tokyo, Japan

BACKGROUND & AIMS: Nonalcoholic fatty liver diseases (NAFLD) include nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). The latter is characterized by the presence of hepatic steatosis and inflammation accompanied by hepatocyte injury with or without fibrosis. Human matrix metalloproteinase-1 (MMP-1) has been shown to contribute to the regression of experimental liver fibrosis when ectopically expressed in rodents. Actually, MMP-1 accelerates tissue fibrosis in human NASH study as we have recently shown significant upregulation of MMP-1 expression in advanced stages of NASH (J Mod Hum Pathol 2016). This study was conducted to evaluate the significance of MMP-1 expression as a diagnostic marker of early NASH. **METHODS:** Eleven samples from histologically proven early NASH and NAFL specimens were examined along with five normal liver specimens. To discriminate the cell types expressing MMP-1, dual immunohistochemical staining was performed using antibodies recognizing MMP-1 and a specific marker for either Kupffer cells (KCs), capillary endothelial cells, hepatic stellate cells, and hepatic progenitor cells (HPCs). Precise localization of MMP-1 was examined by immunoelectron microscopy (IEM). Serum MMP-1 levels were measured by fluorescent beads-based immunoassay. MMP-1 expression was also examined using Western blot analyses. **RESULTS:** MMP-1 expression in normal and NAFL liver specimens was observed in a few number of KCs, sinusoidal endothelial cells and blood vessels with extremely weak immunoreactivity. In the early stage of NASH, MMP-1 was localized predominantly in KCs and monocytes, and was partially localized in HPCs. MMP-1 immunoreactive products were visualized by IEM on the abluminal portion of cell membranes of Kupffer cells, monocytes, and HPCs. Serum MMP-1 concentrations in patients with early stages of NASH (1.57±0.50 ng/ml) showed a higher tendency compared with those in healthy persons (0.84±0.16 ng/ml). **CONCLUSIONS**: Increased MMP-1 expression is associated with disease progression in early stages of NASH. Our results show that HPCs with MMP-1 expression might contribute to the repair and regeneration of early NASH liver. Serum levels of MMP-1 are useful as a marker to detect HPCs response in the early stage of NASH. MMP-1 is a promising biomarker and a therapeutic target for NASH.

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1058

Prospective Comparison between Transient Elastography, Supersonic Shear Imaging, and ARFI Imaging for Predicting Fibrosis in Subjects with NAFLD

Won Kim[1], Myoung Seok Lee[2], Young Ho So[2], Jung Ho Kim[3], Sae Kyung Joo[1], Yong Jin Jung[1]; [1]Department of Internal Medicine and Liver Research Institute, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Korea (the Republic of); [2]Radiology, Boramae Medical Center, Seoul, Korea (the Republic of); [3]Pathology, Boramae Medical Center, Seoul, Korea (the Republic of)

Background and Aims: To compare the diagnostic performance of transient elastography (TE), supersonic shear-wave imaging (SSI), and acoustic radiation force impulse imaging (ARFI) for staging fibrosis and to identify clinical factors which affect liver stiffness measurement (LSM) in a prospective NAFLD cohort. **Methods:** Ninety-four subjects with biopsy-proven NAFLD were included. For each subject, liver stiffness was measured using TE, SSI, and ARFI within 1 month of liver biopsy. The diagnostic performance for staging liver fibrosis was evaluated using receiver operating characteristic (ROC) analysis. Anthropometric data using fat-amount CT and bioelectrical impedance analysis were evaluated as covariates influencing LSM by regression analyses. **Results:** All LSM modalities were correlated with fibrosis stages ($p<0.001$) and exhibited similar performance for staging fibrosis ($p>0.05$); the areas under the ROC curves for TE (kPa), SSI (m/s, kPa), and ARFI (m/s) were 0.757, 0.761, 0.759, and 0.657 for significant fibrosis (≥F2), 0.870, 0.816, 0.809, and 0.873 for advanced fibrosis (≥F3), and 0.882, 0.900, 0.906, and 0.920 for cirrhosis (F4). ARFI tended to be more specific and SSI tended to be more sensitive in differentiating each fibrosis stage with their best diagnostic performance. Anthropometric data were correlated with failure or unreliability of LSM, especially in SSI. In regression analysis, anthropometric data might be confounders in LSM using SSI, while serum liver injury-related markers might be confounders in LSM using TE and ARFI. **Conclusions:** Diagnostic performances of individual LSM modalities for staging fibrosis in NAFLD were not significantly different. TE or ARFI might fit better for suspicion of advanced fibrosis, while TE or SSI might be more advantageous for suspicion of mild fibrosis. Pre-LSM anthropometric evaluation may help predicting LSM reliability, especially in SSI. **Keywords :** Steatosis, Fibrosis, Shear-wave velocity, Elastometry, Non-alcoholic fatty liver

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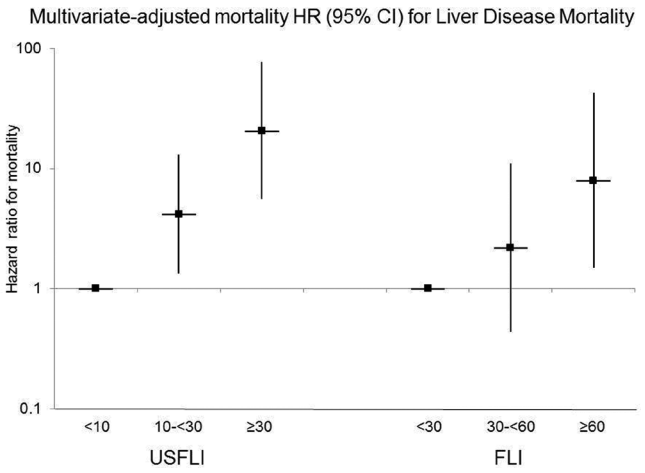
1059

The U.S. Fatty Liver Index and Fatty Liver Index as Potential Steatosis Markers Predict Liver Disease Mortality in the U.S. Population

Aynur Unalp-Arida[1], Constance E. Ruhl[2]; [1]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; [2]Social & Scientific Systems, Inc., Silver Spring, MD

Fatty liver disease is common and contributes to premature death. We examined whether the U.S. fatty liver index (USFLI) (Ruhl, Aliment Pharmacol Ther, 2015;41:65) and fatty liver index (FLI), serum markers of steatosis, were associated with increased overall and cause-specific mortality in a U.S. population-based prospective survey with up to 23 years of linked-mortality data. **Methods:** We studied 6,876 fasted viral hepatitis negative adult participants in the third U.S. National Health and Nutrition Examination Survey (NHANES), 1988-1994.

Intermediate and high steatosis probabilities were defined based on published cut-offs. Participants were passively followed for mortality, as identified by death certificate underlying or contributing cause diagnoses, by linkage to National Death Index records through 2011. Hazard rate ratios (HR) for mortality were calculated using Cox proportional hazards regression to adjust for common mortality risk factors. **Results:** The prevalence of intermediate and high steatosis probability using the USFLI as a marker was 36.8% and 20.4%, respectively. During follow-up, there were 1,939 deaths from all causes and 59 with liver disease, including primary liver cancer. A high USFLI was associated with increased liver disease mortality in age-adjusted analysis (HR, 9.3; 95% CI, 2.9-30.2). With multivariate adjustment, the risk was further increased (Figure). A high FLI was also associated with increased liver disease mortality (Figure). There was no association of a higher USFLI or FLI with all-cause, cardiovascular disease, cancer, or diabetes mortality in multivariate-adjusted analyses (Figure). **Conclusions:** In the U.S. population, a higher steatosis probability using the USFLI or FLI was independently associated with increased liver disease mortality, but not with other mortality outcomes. Liver health management with steatosis risk stratification merits further study.



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1060
Upregulated palmitic acid absorption with altered intestinal transporters in non-alcoholic steatohepatitis (NASH)

Hiroki Utsunomiya, Yasunori Yamamoto, Eiji Takeshita, Yoshio Tokumoto, Fujimasa Tada, Teruki Miyake, Masashi Hirooka, Masanori Abe, Teru Kumagi, Bunzo Matsuura, Yoshio Ikeda, Yoichi Hiasa; Departments of Gastroenterology and Metabology,, Ehime University Hospital, Toon, Japan

Background & Aims: Saturated fatty acids (SFA) are important risk factors for the development of NASH via endoplasmic reticulum stress and oxidative stress. Major sources of hepatic SFA are adipose tissue, hepatic lipogenesis *de novo*, and diet. Reports indicate that amounts of SFA derived from adipose tissue and *de novo* lipogenesis increase in NASH, but changes in dietary SFA absorption are unclear. Thus, we aimed to clarify changes in the absorption of dietary palmitic acid, a common dietary SFA that induces hepatic inflammation. We also assessed their association with the pathogenesis of NASH. **Patients and Methods:** This study included 33 controls as well as 32 and 41 patients with Brunt stages 1-2 and 3-4 defined as early (e-NASH) and advanced (a-NASH) NASH, respectively. Palmitate labeled with ^{13}C was administered directly into the duodenum using gastrointestinal endoscopy to avoid delays resulting from delivery via the stomach. Breath levels of $^{13}CO_2$ were then measured to quantify metabolized SFA before and every 30 min after administration for the next 360 min. The expression and locations of SFA transporters were assessed in jejunal biopsy samples by Western blotting and immunohistochemical staining. Associations between breath $^{13}CO_2$ levels and hepatic steatosis, fibrosis, and insulin resistance were evaluated from laboratory tests, elastography, and liver histology. **Results:** Significantly more $^{13}CO_2$ was excreted over the 360 minutes in patients with e-NASH than in controls (P<0.01) and only during the early phase (0-120 min) of patients with a-NASH compared with controls (P<0.01). Western blotting revealed higher levels of glycosylated CD36 and microsomal triglyceride transfer protein (MTTP) in patients with e-NASH and a-NASH than in controls. Immunohistochemical staining revealed strong glycosylated CD36 expression in blood vessels. The excretion of $^{13}CO_2$ by patients with e-NASH during the early phase (AUC 0-120 min‰) positively correlated with laboratory values such as type IV collagen 7s (r=0.626) and correlated with the controlled attenuation parameter (CAP) (r=0.505) and liver stiffness measurements (LSM) (r=0.697) determined by elastography. Additionally, AUC 0-120 min‰ was significantly increased in Brunt stage 2 than in stage 1 (P=0.002). The amount of excreted $^{13}CO_2$ during the late phase (AUC 120-360 min‰) positively correlated with insulin (r=0.556) and HOMA-IR (r=0.436). **Conclusion:** Dietary palmitic acid absorption was upregulated in the jejunum and apparently associated with the clinicopathological features of patients with e-NASH.

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1061
Serum Nitrotyrosine is Independently Associated with the Presence of Coronary Artery Disease in Patients with Nonalcoholic Fatty Liver Disease (NAFLD)

Elzafir Elsheikh[1,2], Azza Karrar[1,2], Sean C. Felix[2], Hussain Allawi[2], Mehmet Sayiner[2], Thomas Jeffers[2], Zahra Younoszai[2], Munkhzul Otgonsuren[2], Andrei Racila[2], Brian P. Lam[2], Jason Poff[2], Bryan Raybuck[3], Lynn Gerber[3], Zobair M. Younossi[1,2]; [1]Center For Liver Disease, Department of Medicine, Inova Fairfax Hospital, Falls Church, VA; [2]Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA; [3]Department of Medicine, Inova Fairfax Hospital, Falls Church, VA

Background and Aim: Nonalcoholic fatty liver disease (NAFLD) is associated with an increased risk of coronary artery disease (CAD). The underlying mechanism linking NAFLD to CAD is not entirely clear. Nitrotyrosine has been identified as a marker of inflammation and Nitric Oxide (NO) production. Our aim was to assess the role of nitrotyrosine as a potential link between hepatic steatosis and atherosclerosis. **Methods:** We prospectively enrolled 155 patients undergoing elective coronary angiography for suspicion of CAD. After informed consent, each patient underwent hepatic ultrasound (US). Additionally, clinical data and fasting serum was obtained. Coronary angiography (CA) results were obtained and US images were read by a central radiologist. NAFLD was defined as presence of hepatic steatosis by US in the absence of other causes of liver disease and excessive alcohol use. According to CA findings, patients

were divided into NAFLD with CAD (n=59), NAFLD with minimal luminal irregularity (MLI) with <10% stenosis of coronary arteries (n=50), and NAFLD without CAD (n=46). Concentrations of the nitrotyrosine (nM) endothelial nitric oxide synthase (eNOS) (pg/mL) were determined in the serum using ELISA assays. **Results:** Nitrotyrosine levels were highly expressed in NAFLD patients with CAD (90%) and those with NAFLD with MLI (92%) as compared to patients with NAFLD without CAD (72%) (p=0.02 and p<0.01). Multivariate analysis showed that, nitrotyrosine [OR: 6.03 (95% CI: 1.69-21.60)], age [OR: 1.1 (95% CI: 1.04-1.17)],and history of hyperlipidemia [OR: 9.48 (95% CI: 2.78-32.30)] were independently associated with increased risk of CAD in NAFLD patients. Furthermore, nitrotyrosine negatively associated with high density lipoprotein (r=-0.26; p<0.01) but positively associated with Triglyceride level (r=0.22; p=0.01). The levels of eNOS were not significantly associated with CAD in NAFLD. **Conclusions:** Increased levels of serum nitrotyrosine in NAFLD may be associated with risk of CAD. Since eNOS levels did not increase, the source of nitrotyrosine is potentially from pathological production of NO by the inducible nitric oxide synthase (iNOS).

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1062
Predictors of Nonalcoholic Fatty Liver Disease (NAFLD) and Advanced Fibrosis Stage 3-4 in Patients with NAFLD in the United States: Results of a Population Based Sample of 6,000 Patients

Michael H. Le[2], Pardha Devaki[3], Nghiem B. Ha[4], Dae Won Jun[5], Helen S. Te[6], Ramsey Cheung[1,7], Mindie H. Nguyen[1]; [1]Division of Gastroenterology and Hepatology, Stanford University Medical Center, Palo Alto, CA; [2]Stanford University School of Medicine, Stanford, CA; [3]Digestive Diseases Institute, Cleveland Clinic, Cleveland, OH; [4]School of Medicine, University of California Davis, Sacramento, CA; [5]Department of Gastroenterology, Hanyang University Medical Center, Seoul, Korea (the Republic of); [6]Section of Gastroenterology, Hepatology and Nutrition, Department of Medicine, University of Chicago Medicine, Chicago, IL; [7]Division of Gastroenterology and Hepatology, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA

Background: Overall mortality in patients with NAFLD is not increased except for NAFLD patients with significant fibrosis. However, predictors of significant fibrosis in NAFLD have not been widely examined. We conducted a study to determine the predictors of NAFLD and high risk of fibrosis stage 3-4 in NAFLD patients in the general United States population using the National Health and Nutrition Examination Survey (NHANES) conducted from 1999-2012. **Methods:** NAFLD was defined by the United States Fatty Liver Index (U.S. FLI; inclusive of age, ethnicity, GGT, waist circumference, fasting insulin and glucose). Included were those age ≥18 years who attended a medical examination after fasting. Participants were excluded if they tested positive for viral hepatitis, had significant alcohol use, or had missing data on either of the above or U.S. FLI data. We used the NAFLD fibrosis score (NFS) to determine risk of fibrosis stage 3-4. **Results:** Of the 16,644 fasted persons age ≥18 years who attended a medical examination, 6000 persons met our inclusion and exclusion criteria; of which, 30% had NAFLD. Subjects with NAFLD were older (53±17 vs 47±17; p<0.001), more likely male (59.2% vs 45.5%; p<0.001), Mexican American (9.0% vs 4.9%; p<0.001), and had lower income (37.0% vs 30.9%; p<0.001). Significant independent predictors of NAFLD were age ≥60 years, male sex, Mexican American ethnicity, high BMI, diabetes mellitus (DM; both controlled and uncontrolled), and metabolic syndrome (Table 1). Among the NAFLD population, 10.3% had a high probability of fibrosis stage 3-4 (NFS>0.676). Significant independent predictors of high risk of stage 3-4 fibrosis in subjects with NAFLD were age ≥40 years, high BMI, and DM (both controlled and uncontrolled) (Table 1). **Conclusions:** Older, obese, and diabetic patients with NAFLD are at higher risk of having stage 3-4 fibrosis and should be targeted for additional intervention.

	Adjusted Odds Ratio for NAFLD in General Population (N=6000)			Adjusted Odds Ratio for Significant Fibrosis in NAFLD Population (N=1936)		
	OR	95% CI	*p*	OR	95% CI	*p*
Age						
18-39	Referent			Referent		
40-59	1.35	0.98-1.87	0.068	6.79	1.58-29.2	0.010
≥60	2.55	1.91-3.41	<0.001	77.4	21.03-284.6	<0.001
Male	4.01	3.06-5.24	<0.001	1.18	0.70-2.00	0.52
Ethnicity						
Non-Hispanic White	Referent			Referent		
Non-Hispanic Black	0.14	0.10-0.21	<0.001	1.09	0.54-2.20	0.82
Mexican American	2.67	2.00-3.57	<0.001	0.86	0.56-1.33	0.49
Education						
>High School	Referent			Referent		
≤High School	1.07	0.87-1.31	0.52	1.45	0.94-2.22	0.088
Smoking						
Never	Referent			Referent		
Former/Current	1.15	0.91-1.46	0.24	0.92	0.61-1.38	0.67
BMI (kg/m^2)	1.34	1.30-1.38	<0.001	1.18	1.13-1.23	<0.001
Diabetes						
None	Referent			Referent		
Controlled (HbA1c<6.5)	2.74	1.70-4.42	<0.001	3.60	2.17-5.97	<0.001
Uncontrolled (HbA1c≥6.5)	3.56	2.38-5.31	<0.001	3.30	1.72-6.35	<0.001
Metabolic Syndrome	3.25	2.53-4.18	<0.001	0.95	0.61-1.51	0.84

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The following people have nothing to disclose: Michael H. Le, Pardha Devaki, Nghiem B. Ha, Dae Won Jun

1063
Circulating microRNAs as markers for liver histological lesions in patients with nonalcoholic steatohepatitis

Nandita Sarkar[1], Annapoorna Gururajan[1], Biao Li[1], Zhaoshi Jiang[1], Ren Xu[1], Constantine S. Djedjos[1], Scott Patterson[1], Robert P. Myers[1], Zachary D. Goodman[2], Michael R. Charlton[3], Nezam H. Afdhal[4], Rohit Loomba[5]; [1]Gilead Sciences, Inc., Foster City, CA; [2]Inova Fairfax Hospital, Falls Church, VA; [3]Intermountain Medical Center, Salt Lake City, UT; [4]Harvard Medical School, Boston, MA; [5]University of California San Diego, San Diego, CA

Background: MicroRNAs (miRs) are small, non-coding RNA molecules that are involved in post-transcriptional regulation of gene expression and have been implicated in the pathogenesis of nonalcoholic steatohepatitis (NASH). Our objective was to determine their utility as noninvasive markers of NASH-related liver histological lesions. **Methods:** Differential miR analysis was performed on plasma samples from 72 subjects with suspected NASH (sNASH) who failed screening for a phase 2 trial evaluating GS-4997, an inhibitor of apoptosis signal-regulating kinase 1 (ASK1) (mean age 52 years, 36% male, mean BMI 36 kg/m^2), and 50 age-/sex-matched controls (mean BMI 26 kg/m^2). miRs were isolated with a spike-in control using a total RNA isolation kit (Norgen Corp, Canada). Complementary DNA was generated using the QuantiMir kit and 380 miRs were measured by qPCR using miRnome Profiler

(System Biosciences, Mountain View). Calculations of differential miR expression were performed using the -△△Ct method with either U1 spliceosomal RNA or spike-in *C. elegans* control. Statistical analyses were performed using the Significance Analysis of Microarray (SAM) method. miRs with a minimum 2-fold difference in expression and $P \leq 0.01$ between subjects and controls were selected and correlations between miR expression with fibrosis stage and NAFLD Activity Score (NAS) were determined. Using a random decision forest method, the performance of a miR panel for distinguishing sNASH subjects from controls was determined. **Results:** Samples from 56 sNASH and 39 controls passed quality-control standards. Among 30 biopsied sNASH subjects, 57% had NAS ≥5 and 73% had stage 2-3 fibrosis. Using SAM, 96 miRs were differentially expressed between sNASH subjects and controls; 25 miRs were significantly up-regulated and 10 were down-regulated using a minimum 2-fold change and $P \leq 0.01$ as selection criteria (highest fold-change, 4.99). More than 60% of these miRs have been associated with NASH pathogenesis and several novel miRs were identified. One of the most up-regulated miRs distinguished sNASH subjects from controls with an area under the ROC curve (AUROC) of 0.891 and was strongly correlated with fibrosis (Spearman $\rho=0.66$, $P=7.9\times10^{-10}$) and NAS ($\rho=0.67$, $P=3.5\times10^{-10}$). A panel of 5 up-regulated and 5 down-regulated miRs had an AUROC of 0.925 for differentiating sNASH subjects from controls (sensitivity 80%, specificity 100%). **Conclusions:** In this exploratory study, a panel of miRs differentiated sNASH subjects from healthy controls and correlated with fibrosis stage and the NAS. Although validation of these findings is necessary, miRs have potential utility for the noninvasive diagnosis of NASH.

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Biao Li - Employment: Gilead Sciences, Inc.

Zhaoshi Jiang - Employment: Gilead Sciences, Inc.; Stock Shareholder: Gilead Scieces, Inc.

Ren Xu - Employment: Gilead Sciences Inc.; Stock Shareholder: Gilead Sciences Inc.

Constantine S. Djedjos - Employment: Gilead Sciences

Scott Patterson - Employment: Gilead Sciences, Inc.; Stock Shareholder: Gilead Sciences, Inc.

Robert P. Myers - Employment: Gilead Sciences, Inc.; Stock Shareholder: Gilead Sciences, Inc.

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Michael R. Charlton - Consulting: Gilead Sciences; Grant/Research Support: GIlead Sciences, Merck, Janssen, AbbVie, Novartis, Intercept

Nezam H. Afdhal - Advisory Committees or Review Panels: Trio Helath Care; Board Membership: Journal Viral hepatitis, LIGAND; Consulting: Merck, EchoSens, BMS, Achillion, GlaxoSmithKline, Gilead, AbbVie, ROIVANT, SHIONOGI, Co-Crystal; Employment: Springbank; Grant/Research Support: Gilead; Stock Shareholder: Springbank, GILEAD

Rohit Loomba - Advisory Committees or Review Panels: Galmed Inc, Tobira Inc, Arrowhead Research Inc; Consulting: Gilead Inc, Corgenix Inc, Janssen and Janssen Inc, Zafgen Inc, Celgene Inc, Alnylam Inc, Inanta Inc, Deutrx Inc; Grant/Research Support: Daiichi Sankyo Inc, AGA, Merck Inc, Promedior Inc, Kinemed Inc, Immuron Inc, Adheron Inc

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1064

Efficacy and safety of the non-steroidal farnesoid X receptor agonist PX-104 in patients with non-alcoholic fatty liver disease (NAFLD)

Stefan Traussnigg[1], Christian Kienbacher[1], Emina Halilbasic[1], Christian Rechling[1], Harald Hofer[1], Petra E. Steindl-Munda[1], Ghazaleh Gouya[2], Michael Wolzt[2], Martin Hornberger[3], Manfred Birkel[3], Claus Kremoser[3], Michael H. Trauner[1]; [1]Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Medical University Vienna, Vienna, Austria; [2]Department of Clinical Pharmacology, Medical University Vienna, Vienna, Austria; [3]Phenex Pharmaceuticals AG, Heidelberg, Germany

Background: Px-104 is an orally available and non-steroidal agonist of the farnesoid X receptor (FXR) as key regulator of bile acid, glucose and lipid homeostasis. This was the first clinical study with Px-104 administered to NAFLD patients. **Aims and Methods:** We performed a single center, proof of concept phase IIa study to evaluate efficacy, safety and tolerability of Px-104 in non-diabetic NAFLD patients. 21 patients were enrolled with a diagnosis of NAFLD based on liver biopsy or hepatic steatosis on ultrasound, magnetic resonance spectroscopy (MRS) and continuous attenuation parameter (CAP). Patients were treated with 5 mg of PX-104 orally once daily for 4 weeks. Serum liver enzymes, insulin sensitivity by clamp-like index (CLIX) and hepatic fat by proton (^{1}H) MRS, MRI-estimated proton density fat fraction (MRI-PDFF) and CAP were assessed. To evaluate changes in hepatic energy metabolism and Kupffer cell function we performed phosphorus (^{31}P) MRS and superparamagnetic iron oxide (SPIO) magnetic resonance imaging (SPIO-MRI), respectively. Other readouts included serum lipids and markers of bile acid (BA) metabolism/signaling. **Results:** 12 patients were allocated to treatment. A significant decrease in ALT (22%, p=0.027; 1-tailed) and GGT (50%, p=0.019; 1-tailed) was observed after 4 weeks of treatment (Table). No changes in serum alkaline phosphatase or HDL/LDL cholesterol and triglycerides were seen. Insulin sensitivity assessed by CLIX improved in 92% of patients (3.99±1.62 vs 4.59±1.79; p=0.02). However, hepatic steatosis measured by PDFF-MRI, ^{1}H-MRS and CAP as well as extended serum lipid and BA profiles including C4 and FGF-19 did not change. NADPH/γATP ratios at ^{31}P-MRS significantly decreased in 83% of patients (p=0.022) indicating reduced hepatic inflammatory stress, but SPIO-MRI showed no differences. No serious adverse events occurred but short intervals of cardiac arrhythmia recorded in 2 patients led to termination of the study. **Conclusion:** The non-steroidal FXR agonist PX-104 improved insulin sensitivity and decreased serum GGT and ALT levels after 4 weeks of treatment in non-diabetic NAFLD patients. Follow-up compounds show improved FXR efficacy and safety profile appears justified.

Clinical parameters, liver enzymes and metabolic markers

	Day 0 (Mean ± SD)	Day 28 (Mean ± SD)	P-Values
BMI	29.4±4.4	29.3±4.4	0.680
AST (mg/dl)	34.6±9.1	32.6±4.8	0.480
ALT (mg/dl)	63.6±25.7	49.8±26	0.027*
GGT (mg/dl)	140.4±139.7	70.3±87.2	0.019*
LDL (mg/dl)	119.6±43.4	107±31	0.483
HDL (mg/dl)	42.2±11.7	40±13.3	0.195
CLIX	3.99±1.62	4.59±1.79	0.020

*1-tailed

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Manfred Birkel - Employment: Phenex Pharmaceuticals AG

Claus Kremoser - Consulting: Gilead Sciences; Management Position: Phenex Pharmaceuticals AG; Stock Shareholder: Phenex Pharmaceuticals AG

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The following people have nothing to disclose: Christian Kienbacher, Emina Halilbasic, Christian Rechling, Petra E. Steindl-Munda, Ghazaleh Gouya, Michael Wolzt

1065
Nonalcoholic Fatty Liver Disease in the Non-obese: Insights from the PIVENS and FLINT Trials

Donghee Kim, Ajitha Mannalithara, Prowpanga Udompap, W. Ray Kim; Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA

Backgrounds and Aims: It is increasingly recognized that nonalcoholic fatty liver disease (NAFLD) may be present in non-obese individuals. Using individual patient level data from two randomized trials, we compare non-obese and obese patients with nonalcoholic steatohepatitis (NASH) with regard to (1) clinical and histological characteristics at baseline, (2) determinants of advanced fibrosis and (3) response to therapy. **Methods:** The two trials combined, there were 523 biopsy-proven NASH patients who received placebo or active treatment including vitamin E, pioglitazone or obeticholic acid. Subjects were divided by their body mass index (BMI) into obese (BMI≥30) and non-obese (BMI<30). **Results:** Compared to obese patients, non-obese patients were more likely to be older (mean age: 51.6 versus 48.1, p=0.003) and non-white (21.9% versus 11.9%, p=0.005) and have less diabetes (20.1% versus 31.2%, p=0.012) and higher level of HDL-cholesterol (46.4 versus 42.7, p=0.002) and lower level of HOMA-IR (4.9 versus 7.6, p<0.001). There was no difference in baseline histology between non-obese and obese NASH patients except ballooning was less common in non-obese patients (74% versus 85%, p=0.02). In logistic regression analyses, determinants of advanced fibrosis in non-obese patients included aspartate aminotransferase (AST) (odds ratio [OR]: 1.02, 95% confidence interval [CI]: 1.01-1.03), diabetes (OR: 4.14, 95%CI: 1.42-12.03), platelet count (OR: 0.98, 95%CI: 0.97-0.99), which were similar to those in obese NASH. Among treated patients with paired biopsies (n=249), the change in severity of lobular inflammation, steatosis, ballooning, and fibrosis did not significantly differ between non-obese and obese NASH patients (Table). NAFLD activity score (OR: 1.91, 95%CI: 1.23-2.97) and platelet count (OR: 0.99, 95%CI: 0.98-1.00) at baseline was associated with response in non-obese NASH patients. **Conclusion:** While there were a few phenotype differences from obese patients, NASH in non-obese patients display a similar degree of histological severity and response to therapy. A high index of suspicion for NASH is needed to recognize it in non-obese patients.

Change in Histological Features of Patients with Nonalcoholic Steatohepatitis Comparing Non-obese to Obese Patients

	Non-obese	Obese	P value
Steatosis (grade)	-0.7 ± 1.0	-0.8 ± 0.9	0.609
Lobular Inflammation (score)	-0.5 ± 0.9	-0.6 ± 0.8	0.409
Ballooning (score)	-0.5 ± 1.0	-0.5 ± 0.9	0.633
NAFLD activity score	-1.8 ± 2.0	-1.9 ± 1.9	0.743
Fibrosis (stage)	-0.3 ± 1.1	-0.3 ± 1.0	0.765

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The following people have nothing to disclose: Donghee Kim, Ajitha Mannalithara, Prowpanga Udompap

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Temporal Trends, Clinical Patterns And Outcomes Of Nafld-Related HCC In Patients Undergoing Liver Resection Over A 20 Year Period

Raluca Pais[2], Laetitia Fartoux[2], Claire Goumard[3], Olivier Scatton[3], Dominique Wendum[1], Olivier Rosmorduc[2], Vlad Ratziu[2]; [1]Service Anatomopathologie, Assistance Publique Hôpitaux de Paris, Hôpital Saint Antoine – Université Pierre et Marie Curie,UMR_S 938, INSERM – CDR Saint Antoine, Paris, France; [2]Service Hépatogastroentérologie, Assistance Publique Hôpitaux de Paris, Hôpital Pitié-Salpétrière – Université Pierre et Marie Curie,UMR_S 938, INSERM – CDR Saint Antoine, Paris, France; [3]Service Chirurgie Hepatobiliaire et Transplantation Hépatique, Assistance Publique Hôpitaux de Paris, Hôpital Pitié-Salpétrière – Université Pierre et Marie Curie, Paris, France

Background and aims: NAFLD is increasingly reported as a cause of HCC worldwide. This study determined temporal trends for prevalence of NAFLD in patients (pts) with HCC undergoing liver resection (LR) over the past 20 years and their clinical characteristics and outcomes. **Patients and methods**: Retrospective analysis of pts undergoing LR between 1995 and 2015 for HCC, by the same surgical team. HCC was confirmed by histology. NAFLD was diagnosed based on past or present exposure to obesity or diabetes without other causes of chronic liver disease. Peri-tumoral liver was assessed histologically for fibrosis stage (F0-4 by METAVIR). **Results**: 323 patients were included. Mean age was 60±14 yrs, 79% were males, 60% had cirrhosis. Liver disease etiologies were: HCV 31%, HBV 27%, NAFLD 12%, alcoholic liver disease (ALD) 11%, mixed NAFLD+ALD 7%, and other causes 12%. Pts with NAFLD were older (70±9 yrs vs. 64+10 ALD, 61±11 HCV, 51±14 HBV, p<0.001) and mainly males (87%). The prevalence of NAFLD steadily increased from 2.6% in 1995–2000 to 19.5% in 2010-2015, that of HBV increased from 18% to 32%, while HCV decreased (44% to 19.5%) and ALD remained stable (13% vs 16.5%). HCC developed in the absence of bridging fibrosis/cirrhosis in 63% of pts (F0-2) with NAFLD vs only 28% in HBV, 16% in ALD, and 7% in HCV (p<0.001). NAFLD tumors were less well differentiated and larger than ALD and HCV (87±55 mm vs 54±44 mm and 48±31 mm, respectively, p<0.001) but similar to HBV (99±44 mm). Within the NAFLD group, tumor characteristics were not different between F0-2 and F3-4 pts, except for a much higher proportion of single nodules (95% vs 54%, respectively, p<0.01). 49% of pts with NAFLD underwent major hepatectomy vs. 25% for ALD, 31% for HCV and 48% for HBV (p=0.02). In the whole cohort, 53% patients had tumor recurrence (50% NAFLD, 50% alcohol, 45% HCV and 60% HBV, p=0.29) and 40% died (36% in NAFLD and HBV, 45 and 48% in HCV and ALD). Mean time to recurrence was 1.2±1.3 yrs without significant difference according to etiology. Factors associated with HCC recurrence were: tumor size (p=0.02), number of nodules (p=0.03), satellite nodules (p<0.001), and micro and macrovascular invasion (p<0.03 and p=0.03, respectively). Satellite nodules, microvascular invasion and male sex but not the etiology of liver disease were independently associated with recurrence. **Conclusion**: Over the past 20 years there was a strong increase in NAFLD among resectable HCCs. NAFLD pts are older, overwhelmingly male, with larger tumors, developed mostly on no/early fibrosis. Survival and recurrence rates are similar to other etiologies, which justifies curative therapeutic approaches such as LR.

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The following people have nothing to disclose: Raluca Pais, Laetitia Fartoux, Claire Goumard, Olivier Scatton, Dominique Wendum

1067
Long-term disease progression and prevalence of metabolic syndrome in chronic hepatitis B patients with comorbid nonalcoholic fatty liver disease

Jiangao Fan[1], Guofeng Chen[2], Dong Ji[2,3], Dewei Ye[4], Lei Lu[5], April Wong[5], Yudong Wang[5], Jing Chen[5], Cheng Wang[5,6], Qing Shao[2], Bing Li[2], Vanessa Wu[5], Arun J. Sanyal[7], George Lau[5,2]; [1]Department of Gastroenterology, Xinhua Hospital, Shanghai, China; [2]Second Liver Cirrhosis Diagnosis and Treatment Center, 302 Hospital, Beijing, China; [3]Liver Failure Treatment and Research Center, 302 Hospital, Beijing, China; [4]State Key Laboratory of Pharmaceutical Biotechnology, The University of Hong Kong, Hong Kong, Hong Kong; [5]Division of Gastroenterology & Hepatology, Humanity & Health Medical Centre, Hong Kong, Hong Kong; [6]State Key Laboratory of Organ Failure Research, Guangdong Provincial Key Laboratory of Viral Hepatitis Research, Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, China; [7]Physiology and Molecular Pathology, Virginia Commonwealth University School of Medicine, Richmond, VA

Background & Aims: Chronic hepatitis B with comorbid nonalcoholic fatty liver disease (CHB/NAFLD) is common and increasing rapidly in Greater China region. However, the clinical significance of comorbidities in these patients remains elusive. We aimed to investigate the prevalence of metabolic syndrome components and disease progression in CHB/NAFLD compared with CHB and NAFLD. **Methods:** Total 1,015 patients with liver biopsy proved CHB (n=553), NAFLD (n=130) and CHB/NAFLD (n=332) were included in this study. Patients with baseline liver cirrhosis, hepatocellular carcinoma (HCC), history of alcohol abuse or other liver diseases were excluded. Seven hundreds and thirty-five patients (72.4%) were followed for a mean of 14.2± 2.9 years. The demographic data, baseline components of metabolic syndrome, liver cirrhosis related complications, HCC and death were noted. Cox proportional hazards model was used to evaluate the risk to development to HCC and all-cause mortality. Kaplan-Meier survival curve was produced and the differences among three groups were compared by log-rank test. **Results:** Prevalence of hypertension (8.7%, 29/332), obesity (8.7%, 29/332), diabetes mellitus (10.2%, 34/332), and hyperlipidaemia (7.8%, 26/332) in CHB/NAFLD group at baseline were significantly higher than those in CHB group, respectively [hypertension: 3.1% (17/553); obesity: 0.9% (5/553); diabetes mellitus: 4.2% (23/553); hyperlipidaemia: 2.5% (14/553). P<0.001 for all comparisons], but significantly lower than those in NAFLD group, respectively [hypertension: 20.0% (26/130); obesity: 4.6% (6/130); diabetes mellitus: 26.9% (35/130); hyperlipidaemia: 11.5% (15/130). P<0.001 for all comparisons]. During the long-term follow-up, thirty-four (9.5%) patients in CHB group, 3 (2.3%) in NAFLD group, and in 40 (16.1%) CHB/NAFLD group developed liver cirrhosis at the end of follow-up. The percentage of patients with progression to liver cirrhosis in CHB/NAFLD group is significantly higher than that in CHB group (P = 0.015) and NAFLD group (P < 0.001). Thirteen (3.6%) patients in CHB group, 2 (1.5%) in NAFLD group, and 28 (11.3%) in CHB/NAFLD group progressed to HCC. The patients with CHB/NAFLD had significantly higher cumulative hazard of progression to HCC than those in CHB group (hazard ratio=3.99, P = 0.001) and NAFLD group (hazard ratio=16.5, P = 0.007). The overall survivals among the CHB group, NAFLD group, and CHB/NAFLD group were equivalent (P >0.05). **Conclusion:** Prevalence of metabolic syndrome in CHB/NAFLD was significantly lower than that in NAFLD. CHB Patients with comorbid NAFLD had higher risk of progression to liver cirrhosis and HCC than patients with CHB or NAFLD.

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Serum endotrophin, a fragment of procollagen VI with endocrine activity, identifies optimal responders to glitazones in NASH/type 2 diabetes

Morten A. Karsdal[1], Kim Henriksen[1], Federica Genovese[1], Diana J. Leeming[1], Mette J. Nielsen[1], Bente Riis[1], Claus Christiansen[1,2], Detlef Schuppan[3]; [1]Nordic Bioscience A/S, Herlev, Denmark; [2]Center for Clinical and Basic Research (CCBR), Ballerup, Denmark; [3]Institute of Translational Immunology and Research Center for Immune Therapy, University Medical Center, Johannes Gutenberg University, Mainz, Germany

Background: Treatment of diabetic patients with full agonists of peroxisome proliferator-activated receptor gamma (PPARγ) improves insulin sensitivity, but is associated with weight gain, heart failure, peripheral oedema, and bone loss. Endotrophin, the C-terminal fragment of the α3 chain of procollagen type VI (Pro-C6), is involved in both adipose tissue extracellular matrix (ECM) remodeling and metabolic control. We established a serum assay for endotrophin to assess if this novel ECM marker adipokine could identify type 2 diabetes (DM2)/NASH patients who respond optimally to PPARγ agonists, improving the risk to benefit ratio. **Methods:** The BALLET trial (NCT00515632) aimed to compare the glucose-lowering effects and safety of the partial PPARγ agonist balaglitazone with those of pioglitazone in DM2 patients on stable insulin therapy over 6 months. Per protocol patients (n=297) were stratified into tertiles of baseline Pro-C6 levels and for follow-up on therapy and correlated with achieved glucose control in each tertile at the end of the six-month treatment period. **Results:** Endotrophin was significantly associated with therapeutic response to balaglitazone and pioglitazone. At study end, only subjects in the two highest tertiles showed significant reductions in HbA1c and fasting serum glucose compared with baseline. The Odds ratios for a 1% and a 0.5% reduction of HbA1c in the two upper tertiles were 3.83 [1.62;9.04] p<0.001, and 3.85 [1.94;7.61] p<0.0001, respectively. Endotrophin levels correlated only with adipose tissue mass, insulin resistance, and fatty liver index (composed of triglycerides, BMI, GGT, and waist circumference). Notably, PPARγ-associated adverse events such as moderate to severe lower extremity oedema only occurred in the lower tertile for Pro-C6. **Conclusion:** Elevated serum levels of endotrophin predict response to two insulin sensitizers and lower side-effects, identifying those patients with DM2/NASH that profit from PPARγ agonist treatment.

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Bente Riis - Board Membership: Nordic Bioscience A; Employment: Nordic Bioscience; Management Position: Nordic Bioscience; Stock Shareholder: Nordic Bioscience.

Claus Christiansen - Board Membership: Nordic Biosicence A/S; Stock Shareholder: Bente Christiansen

The following people have nothing to disclose: Detlef Schuppan

1069
The impact of controlled attenuation parameter on liver stiffness measurement using transient elastography in patients with non-alcoholic fatty liver disease

Dong Hyeon Lee, Won Kim, Yong Jin Jung; Internal medicine, SMG-SNU Boramae Medical Center, Seoul, Korea (the Republic of)

Background: According to a recent report, severe steatosis is likely to affect liver elasticity (E) as measured by transient elastography (TE) in subjects with non-alcoholic fatty liver disease (NAFLD). However, little is known about the impact of controlled attenuation parameter (CAP) as assessed by TE on the measurement of liver E in subjects with NAFLD. **Methods:** Two hundred eleven subjects with biopsy-proven NAFLD were included in this prospective analysis. All patients underwent acoustic radiation force impulse elastography (ARFI) and TE with CAP measurement. Logistic regression analysis and discriminant function analysis were used for calculating two kinds of CAP-adjusted E. Area under ROC curves (AUROC) were used to determine the optimal cut-offs, sensitivity, and specificity of CAP-adjusted E values for detecting advanced fibrosis (≥F3) and cirrhosis. **Results:** For diagnosing advanced fibrosis, the AUROCs for TE (CAP-adjusted E) were 0.889 (optimal cut-off, -7.739; sensitivity [se], 85.37%; and specificity [sp], 87.06%) by log odds and 0.883 (optimal cut-off, 0.263; se, 82.93%; sp, 91.76%) by formula calculated using discriminant function analysis, while, for diagnosing cirrhosis, those for TE (CAP-adjusted E) were 0.903 (optimal cut-off, -5.177; se, 90.91%; sp, 88.36%) by log odds and 0.904 (optimal cut-off, 0.381; se, 90.91%; sp, 88.36%) by formula calculated using discriminant function analysis. The AUROCs (for ≥F3, 0.893 and for F4, 0.915) for TE (E) were not significantly different from those for TE (CAP-adjusted E). However, specificity (for ≥F3, 52.94%; for F4, 84.66% in TE) was markedly improved after adjustment for CAP without diminishment of sensitivity (for ≥F3, 85.37%; for F4, 90.91% in TE) at the optimal cut-off values. **Conclusions:** There was a significant positive correlation between CAP-adjusted E and fibrosis stages in subjects with NAFLD. Although CAP-adjusted E was not superior to E in diagnosing advanced fibrosis and cirrhosis, measurement of CAP-adjusted E might obviate the need for liver biopsy in those with NAFLD.

Acoustic radiation force impulse (ARFI) sonographic, transient sonoelastographic (TE), and controlled attenuation parameter

	Stage 0-1 vs. 2-4				Stage 0-2 vs. 3-4				Stage 0-3 vs. 4			
	ARFI	TE	CAP-TE (L)	CAP-TE (D)	ARFI	TE	CAP-TE (L)	CAP-TE (D)	ARFI	TE	CAP-TE (L)	CAP-TE (D)
Cutoff value	1.2	7.1	-0.689	-0.226	1.46	7.9	-1.027	0.263	1.46	10.4	-2.107	0.381
Sensitivity (%)	64.94	66.23	66.23	71.43	63.41	85.37	60.98	82.93	81.82	90.91	68.18	90.91
Specificity (%)	74.63	82.84	81.34	69.4	95.29	52.94	88.82	91.76	91.53	84.66	82.01	88.36
AUROC	0.735	0.789	0.777	0.75	0.854	0.893	0.801	0.883	0.885	0.915	0.791	0.904
95% CI	0.670-0.794	0.727-0.842	0.715-0.831	0.686-0.807	0.799-0.899	0.843-0.931	0.741-0.853	0.832-0.923	0.834-0.925	0.869-0.949	0.730-0.844	0.856-0.940
p value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

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1070
Hepatic macrophage activation is associated with adipose tissue insulin resistance in non-diabetic patients with Non-Alcoholic Fatty Liver Disease

Chiara Rosso[1], Konstantin Kazankov[2], Milena Marietti[1], Melania Gaggini[3], Emma Buzzigoli[3], Holger J. Møller[4], Gian Paolo Caviglia[1], Maria Lorena Abate[1], Antonina Smedile[1], Giorgio Maria Saracco[5], Hendrik Vilstrup[2], Amalia Gastaldelli[3], Jacob George[6], Henning Grønbæk[2], Elisabetta Bugianesi[1]; [1]Department of Medical Sciences, University of Turin, Torino, Italy; [2]Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark; [3]Cardiometabolic Risk Unit, Institute of Clinical Physiology, CNR, Pisa, Italy; [4]Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark; [5]Department of Oncology, University of Turin, Turin, Italy; [6]The Storr Liver Centre, University of Sydney and Westmead Hospital, Sidney, WA, Australia

Background and Aim. The onset and progression of liver damage in Non-Alcoholic Fatty Liver Disease (NAFLD) is tightly associated with insulin resistance (IR) in a dysfunctional adipose tissue (AT). Macrophage activation is a key step for both the chronic low inflammatory state of IR and for hepatic damage. The aim of this study is to elucidate the pathways linking IR in the AT, circulating and hepatic macrophage activation and liver damage in 40 non-diabetic patients with biopsy-proven NAFLD. Material and Methods. [2H5]glycerol was infused in all study subjects to evaluate Glycerol-Ra and lipolysis. Adipose tissue-IR (AT-IR) was calculated as FFAs*insulin(INS) (AT-IR1) and as Glycerol-Ra*INS (AT-IR2). Soluble CD163 (sCD163), a marker of hepatic macrophage activation, was measured by an enzyme-linked immunosorbent assay (ELISA). CD163 mRNA expression in the liver was evaluated by qPCR using the CFX96 (Bio-Rad), SSoFast™ EvaGreen® Supermix (BioRad). Histology was scored according to Kleiner. Hepatic fat was assessed by liver biopsy. Visceral fat (VF) and subcutaneous fat (SF) were measured with standard nuclear magnetic resonance (NMR). **Results**. AT-IR showed significant associations with features of liver damage at liver biopsy, including hepatic fat (AT-IR1: r=0.50, p=0.001; AT-IR2: r=0.44, p=0.004), NAS score (r=0.43, p=0.006 and r=0.31, p=0.05 respectively) and fibrosis (AT-IR1: r=0.51 and AT-IR2: r=0.34, p=0.001 for both). Plasma levels of sCD163 were significantly associated with fasting plasma levels of FFAs (r=0.35, p=0.026), with lipolysis (r =0.35, p=0.028) and with AT-IR (AT-IR1 r=0.38, p=0.016 and AT-IR2 r=0.31, p=0.005). Circulating sCD163 increased proportionally to liver fat (r=0.53; p=0.005) but not to visceral or subcutaneous fat (p=NS for both). The hepatic expression of CD163 (n=20) had a linear correlation with plasma levels of sCD163 (r=0.44, p=0.05). NAFLD subjects with more than two-fold hepatic expression of CD163 had significantly higher hepatic fat content (p=0.028). The hepatic expression of CD163 was higher than two-fold in 75% of NAFLD patients with moderate (F2) and in 100% of those with severe fibrosis (F3). **Conclusions**. We speculate that in NAFLD patients hepatic macrophages activation can be directly stimulated by an increased flux of FFA due to AT-IR, thus directly linking IR, dysfunctional adipose tissue and liver damage.

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1071
Novel Fibroscan-Based Score to Diagnose NASH and its severity in A Multi-centre UK Cohort of Patients with Suspected NAFLD

Peter J. Eddowes[2], Quentin Anstee[3], Indra Neil Guha[4], David A. Sheridan[6], Emmanouil Tsochatzis[5], Jeremy Cobbold[6], Michael E. Allison[7], Victor de Ledinghen[8], Magali Sasso[1], Celine Fournier[9], Véronique Miette[1], Valerie Paradis[10], Pierre Bedossa[10], Philip N. Newsome[2]; [1]R&D, Echosens, Paris, France; [2]NIHR Birmingham Liver Biomedical Research Unit and Centre for Liver Research, University of Birmingham, Birmimgham, United Kingdom; [3]Institute of cellular medicine - Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom; [4]NIHR Nottingham Digestive Diseases Biomedical Research Unit, NHS Trust and University of Nottingham, Nottingham, United Kingdom; [5]UCL Institute for Liver and Digestive Health, Royal Free Hospital, London, United Kingdom; [6]Department of Gastroenterology, Oxford University Hospitals NHS Trust, John Radcliffe Hospital, Oxford, United Kingdom; [7]Department of Hepatology, Addenbrookes Hospital, Cambridge, United Kingdom; [8]Centre d'Investigation de la Fibrose hépatique, Hôpital Haut-Lévêque, Centre Hospitalo-Universitaire de Bordeaux, Pessac, France; [9]Medical Affairs, Echosens, Paris, France; [10]Pathology department, Hôpital Beaujon, APHP, Clichy, France

Background & Aims: Reliable non-invasive biomarkers are needed for the diagnosis and monitoring of patients with non-alcoholic steatohepatitis (NASH). Our study set out to determine the performance of a new score developed by Echosens to differentiate NASH and simple steatosis based on a single Fibroscan examination (liver stiffness and controlled attenuation parameter (CAP)). **Methods:** Patients with suspected NAFLD prospectively underwent FibroScan examination within 2 weeks of a standard of care liver biopsy (LB) between March 2014 and January 2016 at seven UK centers. LB were read in a blinded manner by two expert pathologists. NASH was diagnosed using the FLIP algorithm. NASH severity was graded according to the NAS score. To develop a score to diagnose NASH the cohort was split randomly into training (80%) and validation (20%) sets. Sample splitting was repeated 100 times leading to the selection of the optimum model. This was tested on an external validation cohort that consisted of 47 NAFLD patients from a single liver centre in France. Patients there underwent FibroScan examination within 1 day of LB, read by the same pathologists. **Results:** 174 patients with BMI <40 kg/m^2 were studied. The following patients were excluded for the score development: LB not interpretable/diagnostic of NAFLD (n=18), FibroScan not possible (n=1), FibroScan unreliable according to Boursier's criteria (n=10). Patients had a median BMI of 32.9 [IQR=6.9] kg/m^2 and age of 54 [21] years. 58% were male, 74% had a NAS score ≥3 and 58% had NASH. The external validation cohort had a median BMI of 30.0 [8.0] kg/m^2 and age of 53 [22] years. 67% were male, 82% had a NAS score ≥3 and 71% had NASH, 91% had a reliable Fibroscan examination. Performance of the scores is shown in the table. **Conclusion:** A novel score based on measurement of liver stiffness and CAP from a single FibroScan examination was able to correctly classify 79% of patients with/without NASH as well as correctly staging severity in 86%. This has promise as a non-invasive marker for detecting/staging disease activity in patients with NASH.

NASH scores performance

		Training Set (N=117)	Validation set (N=28)	External validation set: Reliable FibroScan (N=43)
Repeated slip sample validation	NAS≥3	AUC=0.85±0.02	AUC=0.85±0.07	AUC=0.89±0.00
	NASH (FLIP)	AUC=0.85±0.02	AUC=0.83±0.08	AUC=0.85±0.01
Selected scores	NAS≥3	AUC=0.85 CC=0.83	AUC=0.87 CC=0.86	AUC=0.89 CC=0.86
	NASH (FLIP)	AUC=0.84 CC=0.76	AUC=0.88 CC=0.82	AUC=0.84 CC=0.79

AUC: area under the ROC curve. CC: correctly classified patients, cut-off maximizing negative + positive predictive values.

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Magali Sasso - Employment: Echosens

Celine Fournier - Management Position: Echosens

Véronique Miette - Employment: Echosens

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1072
Risk and predictors of fibrosis progression in patients with NAFLD

Aaron P. Thrift, Hashem B. El-Serag, Xiaoying Yu, Fasiha Kanwal; Medicine, Baylor College of Medicine, Houston, TX

Background: Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in the U.S. NAFLD can result in progressive liver fibrosis and cirrhosis. However, risk of fibrosis progression as well as the determinants of this risk in unselected or unreferred patients with NAFLD remains largely unknown. We aimed to examine the proportion of patients with NAFLD who developed advanced fibrosis (defined as FIB-4>2.67) over time and to identify predictors of progression among patients with low (defined as FIB-4<1.3) or intermediate (defined as FIB-4 1.3-2.67) fibrosis at baseline. **Methods:** We identified a cohort of patients with NAFLD in national VA databases using a previously validated algorithm based on persistent ALT elevation (≥2 values ≥40 IU/mL ≥6 months apart) in the absence of hepatitis B, hepatitis C or excessive alcohol use. We calculated annual FIB-4 using laboratory results from AST, ALT and platelet tests performed within 6 months of each other. In the event of multiple tests per year in the same patient, we used the median to define annual value. For this analysis, we included NAFLD patients with at least 2 annual FIB-4 values and excluded patients with advanced fibrosis or cirrhosis at baseline (defined on the basis of FIB-4>2.67 or cirrhosis ICD-9 codes). We used Kaplan-Meier (KM) curves and survival function estimates to compare risk of fibrosis progression (FIB-4>2.67) among patient sub-groups, and Cox proportional hazards models to examine risk factors for fibrosis progression. **Results:** The analysis included a cohort of 449,498 patients with NAFLD with mean follow up of 7.99 (SD, 2.39) years. Most patients were male (95.2%) and non-Hispanic white (68.7%). Among patients with first (baseline) FIB-4<1.3 (68.3%), 1.6% progressed to advanced fibrosis after 5 years; 9.3% progressed after 12 years. Among patients with first FIB-4 in the intermediate range (31.7%), 20.3% and 48.5% progressed to advanced fibrosis after 5 years and 12 years, respectively. In the multivariable model, patients with FIB-4

between 1.3-2.67 at baseline had 6-fold higher risk of fibrosis progression than patients with FIB-4<1.3 (Hazard Ratio, 6.01; 95% Confidence Interval, 5.88-6.13). Age, sex, race, body mass index, diabetes, hypertension, and dyslipidemia were significantly associated with fibrosis progression overall and in analyses stratified by baseline degree of fibrosis. **Conclusion:** In this large national cohort of unselected patients with NAFLD, baseline degree of fibrosis was a strong predictor of the risk of progression. Among those with intermediate fibrosis, there was a large fraction of patients who progressed to high risk for fibrosis.

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1073
Nonalcoholic Steatohepatitis (NASH) is Associated with Higher Coronary Heart Disease Risk

Mohammad Siddiqui[1], Mark L. Van Natta[2], Patricia H. Belt[2], Jeanne M. Clark[2], James Tonascia[2], Naga P. Chalasani[3], Cynthia D. Guy[4], Bilal Hameed[5], Arun J. Sanyal[1]; [1]Virginia Commonwealth University, Richmond, VA; [2]John Hopkins University, Baltimore, MD; [3]Indiana University, Indianapolis, IN; [4]Duke University, Durham, NC; [5]UCSF, San Francisco, CA

Coronary heart disease (CHD) is the leading cause of mortality in patients with nonalcoholic fatty liver disease (NAFLD). The inter-relationships between risk factors for CHD and severity of the underlying liver disease are unknown. The aim of current study was to evaluate the relationship between severity of liver histology and Framingham Risk Scores (FRS) in patients with NAFLD in the NIDDK NASH CRN cohort. **METHODS:** A cross-sectional analysis of adult patients enrolled with a liver biopsy and a Framingham Risk Score (FRS) within 18 months of enrollment was performed. Fractional logistic regression models of the FRS outcome (i.e., 10-year probability of CHD) were used to evaluate the relationship between FRS and diabetes status, coronary artery disease, body mass index, HbA1c, HOMA-IR, anti-lipidemic therapy) and histological features. **RESULTS:** A total of 1,875 patients met criteria and were included in the analysis. In unadjusted regression analysis, a strong relationship was observed between FRS and metabolic medical comorbidities including diabetes (OR 1.13, 1.01-1.28, P=.03), use of anti-lipidemic therapy (OR 1.34, 1.19-1.50, P<.001), waist circumference (OR 1.01, 1.00-1.01, per cm; P<.001) and known history of coronary artery disease (OR 2.14, 1.76-2.63, P<.001) in patients with NAFLD. Higher FRS was directly related to histological features including ballooning (OR 1.10, 1.03-1.18, per score; P=.007), fibrosis (OR 1.15, 1.11-1.20, per stage; P<.001), and portal inflammation (OR 1.20, 1.08-1.33, per score; P<.001). Lower FRS was associated with higher steatosis and FRS (OR 0.91, 0.85-0.97, per score; P=.003). Definite NASH was associated with higher FRS with OR 1.12 (1.04-1.20, per category; P=.001). In a multiple fractional regression model, independent relationships with higher FRS included circumference, use of anti-lipidemic therapy, known history of CAD, increasing severity of fibrosis, definite NASH and decreasing severity of steatosis remained significant. . **CONCLUSION:** In patients with NAFLD, increasingly higher 10-year risk of CHD is associated with metabolic co-morbidities, but also with worsening histology including presence of NASH and more severe fibrosis. However, FRS went down with increasing steatosis.

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1074
Subgroup Analysis Comparing Obeticholic Acid versus Placebo for Fibrosis Improvement: a Post-hoc Analysis of the FLINT Trial

Bilal Hameed[1], Norah Terrault[1], Rohit Loomba[2], Arthur J. McCullough[3], Manal F. Abdelmalek[4], Kris V. Kowdley[5], Brent A. Tetri[6], Arun J. Sanyal[7], Lois Lee[8], Beatrice Ferguson[8], Reshma Shringarpure[8], David Shapiro[8], Naga P. Chalasani[9]; [1]University of California San Francisco School of Medicine, San Francisco, CA; [2]University of California San Diego, La Jolla, CA; [3]Cleveland Clinic, Cleveland, OH; [4]Duke University, Durham, NC; [5]Swedish Medical Center, Seattle, WA; [6]Saint Louis University, Saint Louis, MO; [7]Virginia Commonwealth University, Richmond, VA; [8]Intercept Pharmaceuticals, Inc., San Diego, CA; [9]Indiana University, Indianapolis, IN

Background and Aims: The potent and selective FXR agonist obeticholic acid (OCA) has been shown to significantly improve fibrosis in the FLINT study; a 72 week, multicenter, double-blind trial in non-alcoholic steatohepatitis (NASH) patients. The aim of this post-hoc analysis was to explore whether there were any specific subgroups who may have responded differently to OCA treatment with respect to fibrosis improvement. **Methods**: In the FLINT study, patients with NASH were randomized to 25 mg OCA or placebo (PBO) for 72 weeks of treatment. Patients who had both baseline and end of study biopsies were included in this analysis (OCA: n=102, PBO: n=98). Fibrosis improvement was defined as ≥1 stage improvement after 72 weeks of treatment based on NASH CRN scoring criteria evaluated by central pathologists. Subgroup categories such as age, sex, body mass index (BMI) at baseline, diabetes status at baseline, and weight loss at Week 24 were evaluated. Treatment effect within each subgroup was assessed in both univariate and multivariate analyses. In order to determine whether the effect of treatment varied significantly among subgroups, the interaction between treatment and subgroup was assessed. **Results**: In all subgroups evaluated in this analysis, a higher percentage of OCA-treated patients showed an improvement in fibrosis vs. PBO-treated patients (Table). Critically, the interaction between treatment and subgroup was not significantly different within each subgroup category. Similar results were observed for NAS improvement of ≥2 points without worsening of fibrosis (data not shown). **Conclusions**: Overall, more OCA-treated patients in all subgroups evaluated in this analysis achieved fibrosis improvement. No specific subgroup responded differently to OCA treatment and no interaction between treatment and subgroups was found. Further evaluation with a larger number of patients is warranted.

Table. Fibrosis Improvement After 72 Weeks of Treatment by Subgroup

Subgroup Category	Subgroup	OCA (N=102)	PBO (N=98)	p-value† Interaction of Treatment and Subgroup
Age	<55 years old	22 / 58 (38%)*	9 / 60 (15%)	0.1437
	≥55 years old	14 / 44 (32%)	10 / 38 (26%)	
Sex	Male	12 / 31 (39%)	9 / 36 (25%)	0.6211
	Female	24 / 71 (34%)*	10 / 62 (16%)	
BMI at Baseline	<35 kg/m²	17 / 54 (31%)	16 / 66 (24%)	0.0546
	≥35 kg/m²	19 / 47 (40%)*	3 / 32 (9%)	
Diabetes Status at Baseline	Absence	14 / 48 (29%)	9 / 45 (20%)	0.3777
	Presence	22 / 54 (41%)*	10 / 53 (19%)	
Weight Loss at Week 24	<5%	24 / 81 (30%)	16 / 83 (19%)	0.4493
	≥5%	12 / 20 (60%)	3 / 10 (30%)	

*p<0.05 comparing OCA vs. placebo in both univariate analysis from Cochran-Mantel-Haenszel test stratified by diabetes status and in multivariate analysis from Wald's test with treatment, subgroup, interaction between treatment and subgroup, age, gender, BMI, diabetes status, and percent weight loss at Week 24 as covariates in a logistic regression

†Determined by Wald's test of interaction of treatment and subgroup based on a logistic regression of the odds of fibrosis improvement.

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Brent A. Tetri - Advisory Committees or Review Panels: Nimbus Therapeutics, Bristol Myers Squibb, Janssen, Conatus, Allergan, Zafgen, Pfizer, Novartis, Galmed, Receptos; Consulting: Medimmune

Arun J. Sanyal - Advisory Committees or Review Panels: Bristol Myers, Gilead, Genfit, Abbott, Ikaria, Exhalenz, Pfizer, Novartis; Consulting: Salix, Immuron, Exhalenz, Nimbus, Genentech, Echosens, Takeda, Merck, Enanta, Zafgen, JD Pharma, Islet Sciences, Hemoshear; Grant/Research Support: Salix, Genentech, Intercept, Ikaria, Takeda, GalMed, Novartis, Gilead, Tobira; Independent Contractor: UpToDate, Elsevier; Management Position: Sanyal Biotechnology

Lois Lee - Employment: Intercept Pharmaceuticals

Beatrice Ferguson - Employment: Intercept Pharmaceuticals

Reshma Shringarpure - Employment: Intercept; Stock Shareholder: Intercept

David Shapiro - Employment: Intercept Pharmaceuticals; Management Position: Intercept Pharmaceuticals; Stock Shareholder: Intercept Pharmaceuticals

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1075
Impact of Vitamin D Replacement on Liver Enzymes in Non-Alcoholic Fatty Liver Disease Patients

Suparuedee Boonyagard, Karjpong Techathuvanan; Medicine, Vajira hospital, Bangsue, Thailand

Background: Non-alcoholic fatty liver disease (NAFLD), which is related to insulin resistance and metabolic syndrome,is a disease most commonly found to progress into steatohepatitis and also evidenced as a major cause of cryptogenic cirrhosis. Several recent studies showed that vitamin D plays an important role in the pathogenesis and the treatment of chronic liver disease from many causes,including NAFLD.However,studies specifically involving a role of vitamin D replacement in NAFLD are extremely limited. **Objective:**To demonstrate the effect of vitamin D replacement on liver enzymes and Inflammatory markers in NAFLD patients **Methods:**A randomized control trial was conducted at Liver clinic at Vajira hospital from January to December 2015. Sixty eligible NAFLD participants, who have ALT elevation with vitamin D insufficiency, were randomly split into two groups (30 patients per group) and assigned to receive either a vitamin D replacement or a placebo for 20 weeks. During this study, the participants were asked to maintain the same lifestyle and medication as before the experiment, as well as to have their serum calcium level monitored every four weeks for any side effects of hypervitaminosis D. Serum ALT, inflammatory markers, and homeostasis model assessment (HOMA) including Fibroscan® were compared before and after the 20-week vitamin D replacement period to evaluate the anti-inflammatory effect of vitamin D. **Results:**At the beginning of the study,there was no statistical differences between the two groups of patients on the baseline characteristics, including gender,age,BMI,underlying disease(except T2DM),ALT,inflammatory markers,FibroScan® and Inbody®. At the end of the study, ALT (-27.43 ± 24.61 U/L, p <0.001), IL-6 (-0.45 ± 1.12 pg/mL, p =0.036) and Ferritin (-52.75 ± 96.34 ng/mL, p =0.006) decreased significantly in the vitamin D group, while CAP (-4.80 ± 26.15 dB/m), hsCRP (-0.42 ± 1.65 mg/L) and liver stiffness (0.25 ± 3.48 kPa) tended to decrease. In the placebo group, Ferritin (0.69 ± 72.45 ng/mL), hsCRP (0.06 ± 1.45 mg/L), CAP (2.67 ± 30.89 dB/m) and liver stiffness (0.01 ± 2.18 kPa) increased although statistically insignificant. In addition, the decrease of serum ALT in the vitamin D group was significantly greater than in the placebo group (-27.43 ± 24.61 U/L vs -12.70 ± 25.49 U/L, respectively, p =0.026).Furthermore, all patients in the vitamin D group did not experience any side effects from hypervitaminosis D. **Conclusion:**Vitamin D replacement could significantly reduce the liver inflammation as well as contributed to the decrease of steatosis quantification in NAFLD patients with ALT elevation,without evidence of short-term adverse effects.

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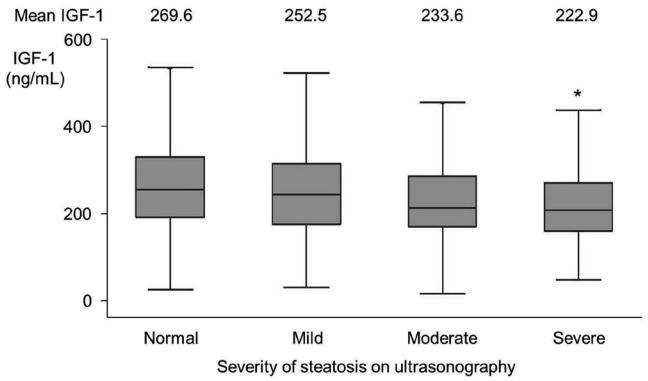
1076
The Association between Insulin-like Growth Factor-1 and Severity of Nonalcoholic Fatty Liver Disease: A Population Based Study from the National Health and Nutrition Examination Survey

Ye Eun Kwak[1], Albert Do[2], Joseph K. Lim[3]; [1]Department of Internal Medicine, Bridgeport Hospital, Yale University School of Medicine, Bridgeport, CT; [2]Department of Internal Medicine, Yale-New Haven Hospital, Yale University School of Medicine, New Haven, CT; [3]Section of Digestive Diseases, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT

Background: Growth hormone (GH) deficiency may be related to the metabolic syndrome and associated with nonalcoholic fatty liver disease (NAFLD). Insulin-like growth factor-1 (IGF-1) is produced by hepatocytes and its secretion is stimulated by GH. Our aim is to determine the association between IGF-1 level and severity of NAFLD. **Methods:** Using the Third National Health and Nutrition Examination Survey (NHANES III) data, we included 13,856 adults aged 20-74 years who had gradable ultrasonography (US) images for hepatic steatosis; of those, 1,815 were identified as having NAFLD (presence of moderate to severe hepatic steatosis on US without chronic liver disease: chronic hepatitis B, chronic hepatitis C, iron overload or excessive alcohol consumption) and 5,319 as controls. 629 in NAFLD and 2,067 in controls had available serum IGF-1 data. NAFLD and control group were stratified based on body mass index (BMI) as lean (BMI<25) and obese (BMI≥30). **Results**: Serum IGF-1 levels in NAFLD group were significantly lower (mean 230.0±99.3 ng/mL) compared with

controls (mean 266.3±106.1 ng/mL, p<0.0001). IGF-1 levels in obese NAFLD were significantly lower (mean 215.6±86.6 ng/mL) than obese controls (mean 246.7±103.0 ng/mL, p<0.0001). IGF-1 levels were inversely associated with severity of hepatic steatosis on US (Graph 1), and were significantly lower in severe steatosis compared to mild and moderate steatosis in lean NAFLD group (p=0.022 vs. mild, p=0.005 vs. moderate). In multivariate logistic regression analysis, the association of IGF-1 levels to NAFLD remained significant after adjusting for age, sex, BMI, insulin resistance, C-reactive protein, triglyceride, low-density lipoprotein and high-density lipoprotein (adjusted odds ratio=0.9988, 95% confidence interval=0.9976-0.9999, p=0.0041). **Conclusion:** Low level of serum IGF-1 is associated with NAFLD and correlates with severity of hepatic steatosis especially in lean NAFLD patients.

Graph 1. Serum levels of IGF-1 and severity of hepatic steatosis on US (*p<0.0001 vs. normal, p=0.0007 vs. mild)



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1077
Pharmacodynamic Effects of the Oral, Non-Steroidal Farnesoid X Receptor Agonist GS-9674 in Healthy Volunteers

Constantine S. Djedjos, Brian Kirby, Andrew Billin, John Gosink, Qinghua Song, Roopali Srihari, Krystyna Grycz, Jonna Weston, Mani Subramanian, William Watkins, Robert P. Myers; Gilead Sciences, Foster City, CA

C. Stephen Djedjos, Brian Kirby, Andrew Billin, John Gosink, Qinghua Song, Roopali Srihari, Krysia Grycz, Jonna Weston, G. Mani Subramanian, William J. Watkins, Robert P. Myers Gilead Sciences, Inc. Foster City, CA, USA **Background**: GS-9674 is a non-steroidal Farnesoid X Receptor (FXR) agonist in development for the treatment of nonalcoholic steatohepatitis (NASH) and cholestatic liver disorders. Oral GS-9674 increased plasma fibroblast growth factor 19 (FGF19), decreased 7-α-hydroxy-4-cholesten-3-one (C4), and improved liver histology in rodent and primate models of NASH. This first-in-human study evaluated the safety, pharmacokinetics (PK), and pharmacodynamic (PD) effects of GS-9674 in healthy volunteers. Data on PD markers (FGF19 and C4), PK/PD and PD/PD relationships, and the effects of GS-9674 on serum cholesterol are presented herein. **Methods**: In this randomized, double-blind, placebo-controlled study, subjects received single and multiple doses (QD, 14 days) of GS-9674 (10, 30, 100, or 300 mg while fasting [n=12/cohort]) or matching placebo (n=3/cohort) with a 6-day washout between the single and multiple dose periods. Plasma FGF19 (by ELISA) and serum C4 (by LC-MS/MS) were measured over 24 hours pre-dose (Day -1) and after single (Day 1) and multiple dose administration (Day 20). PD parameters for FGF19 and C4 ($AUC_{2\text{-}8hr}$ and C_{max} or C_{min}) were calculated and normalized to Day -1 values. Changes in serum cholesterol were also assessed. **Results**: PD responses to GS-9674 observed on Day 1 and Day 20 were comparable. GS-9674 doses ≥30 mg significantly increased FGF19 and reduced C4 exposure compared to placebo (Table). Changes in FGF19 and C4 $AUC_{2\text{-}8hr}$ were inversely correlated (r= -0.335 p =0.02). While FGF19 exposure did not show dose-dependent changes, changes in C4 $AUC_{2\text{-}8hr}$ were inversely associated with GS-9674 AUCtau (r= -0.45 p <0.01). Effects of GS-9674 on serum cholesterol at Day 20 were mild and not significantly different from placebo. **Conclusion**: Oral GS-9674 administration results in increased levels of FGF19 and decreased C4 confirming its biological activity. These data support the evaluation of GS-9674 in patients with NASH and cholestatic liver disorders.

Changes in PD Markers from Baseline after Multiple Dose GS-9674 Administration (Day 20)

n=12/group	Pooled Placebo	GS-9674 10mg	GS-9674 30mg	GS-9674 100mg	GS-9674 300mg
FGF19 Cmax	1.21(48.0)	2.05(94.6)*	2.39(45.9)*	2.32(44.9)*	3.08(57.0)*
FGF19 AUC2-8hr	1.35(53.9)	3.07(71.9)*	3.99(42.0)*	3.61(26.9)*	3.94(62.0)*
C4 Cmin	1.29(78.7)	0.78(59.3)	0.37(59.6)*	0.71(72.6)*	0.44(76.3)*
C4 AUC2-8hr	1.24(93.8)	0.67(86.8)*	0.39(57.1)*	0.50(101)*	0.33(97.8)*

Data presented as fold change in geometric mean (%CV) from pre-treatment (Day 20/Day -1).

*p<0.05 compared to placebo

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1078
The risk of colorectal neoplasia according to the presence and severity of non-alcoholic fatty liver disease

Joon Seong Ahn[1], Dong Hyun Sinn[1], Yang Won Min[1], Sung Noh Hong[1], Sin-Ho Jung[2], Poong-Lyul Lee[1], Seung Woon Paik[1], Hee Jung Son[1], Geum-Youn Gwak[1]; [1]Samsung medical center, Seoul, Korea (the Republic of); [2]Biostatistics and Bioinformatics Center, Samsung Cancer Research Institute, Samsung Medical Center, Seoul, Korea (the Republic of)

Background and aim We investigated whether non-alcoholic fatty liver disease (NAFLD) is associated with increased risk of colorectal neoplasia (CRN). **Methods** A cross-sectional data from a comprehensive health screening program that included 26,540 participants without malignancy, chronic liver disease or heavy drinking, who underwent first-time screening colonoscopy and abdominal ultrasonography at Samsung Medical Center between April 2003 and December 2011 was analyzed. Advanced CRN was defined as cancer or adenoma that was at least 10 mm in diameter, had high-grade dysplasia, or had villous or tubulovillous histologic characteristics, or any combination thereof. The presence of NAFLD was diagnosed with abdominal ultrasonography and exclusion of secondary causes. Severity of hepatic fibrosis in patients with NAFLD was determined by the NAFLD fibrosis score (NFS). **Results**

NAFLD patients had a higher prevalence of all CRN (38.0% vs. 28.9%, p < 0.001) and advanced CRN (2.7% vs. 1.9%, p < 0.001) than individuals without NAFLD. When adjusted for age, sex, smoking, alcohol, body mass index, first-degree family history of colon cancer, use of aspirin and metabolic factors including fasting blood glucose, use of diabetic medication, total cholesterol, triglyceride, use of dyslipidemic medication, systolic blood pressure and use of antihypertensive medication,, NAFLD patients showed higher risk for all CRN [odd ratio (OR) (95% confidence interval (CI)): 1.10 (1.03-1.17), p = 0.002] and advanced CRN [OR (95% CI): 1.21 (1.01-1.18), p = 0.049] compared to individuals without NAFLD. In addition, NAFLD patients with intermediate to high NFS (≥ -1.455) had a higher prevalence of all CRN (47.2% vs. 34.4%, p < 0.001) and advanced CRN (4.6% vs. 1.9%, p < 0.001) than patients with low NFS (< -1.455). In multivariable-adjusted models, NAFLD patients with intermediate to high NFS were at higher risk of all CRN [OR (95% CI): 1.11 (1.01-1.24), p = 0.047] and advanced CRN [OR (95% CI): 1.5 (1.14-2.10), p = 0.005] than patients with low NFS. **Conclusions** NAFLD was associated with the increased risk of CRN independent of traditional risk factors. Also, NFS was able to further stratify risk of CRN among NAFLD patients. These findings indicate that NAFLD and NFS can be useful to evaluate individual risk for CRN.

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1079
Interleukin-34 as a fibroblast-derived marker of liver fibrosis in patients with non-alcoholic fatty liver disease

Hirotaka Shoji[1,2], Sachiyo Yoshio[1], Yohei Mano[1], Erina Kumagai[1], Hiroyoshi Doi[1], Masaya Sugiyama[1], Masaaki Korenaga[1], Taeang Arai[3], Norio Itokawa[3], Masanori Atsukawa[3], Hiroshi Aikata[4], Hideyuki Hyogo[4,5], Kazuaki Chayama[4], Tomohiko Ohashi[6], Kiyoaki Ito[6], Masashi Yoneda[6], Yuichi Nozaki[7], Takumi Kawaguchi[8], Takuji Torimura[8], Masanori Abe[9], Yoichi Hiasa[9], Toshiya Kamiyama[2], Akinobu Taketomi[2], Masashi Mizokami[1], Tatsuya Kanto[1]; [1]the research center for hepatitis & immunology, national center for global health and medicine, Ichikawa, Japan; [2]Department of Gastroenterological Surgery I, Hokkaido University Graduate School of Medicine, Sapporo, Japan; [3]Division of Gastroenterology, Department of Internal Medicine, Nippon Medical School Chiba Hokusoh Hospital, Inzai, Japan; [4]Department of Gastroenterology and Metabolism, Applied Life Sciences, Institute of Biomedical & Health Sciences, Hiroshima University, Hiroshima, Japan; [5]Department of Gastroenterology and Hepatology, JA Hiroshima General Hospital, Hatsukaichi, Japan; [6]Division of Gastroenterology, Department of Internal Medicine, Aichi Medical University School of Medicine, Nagakute, Japan; [7]Department of Gastroenterology, National Center for Global Health and Medicine, Tokyo, Japan; [8]Kurume University School of Medicine, Division of Gastroenterology, Department of Medicine, Kurume, Japan; [9]Ehime University Graduate School of Medicine, Department of Gastroenterology and Metabology, Toon, Japan

Background/Aim: Non-alcoholic fatty liver disease (NAFLD) is a common cause of chronic non-viral liver disease. Activation of macrophages and hepatic stellate cells is a critical step that promotes liver fibrosis. Interleukin-34 (IL-34) shares homology with macrophage colony-stimulating factor (M-CSF) and promotes the differentiation and viability of macrophages through a common receptor, colony-stimulating factor-1 receptor (CSF-1R). We aimed to explore the feasibility of IL-34 as a fibrosis marker in patients with NAFLD. Method: We enrolled 197 liver biopsy-proven NAFLD patients with various fibrosis stages. We comprehensively evaluated the serum levels of macrophage related markers (IL-34, M-CSF, soluble CD163), 40 cytokines/chemokines, hyaluronic acid, type IV collagen 7s, and clinically-approved fibrosis scores such as APRI, FIB-4 index, NAFLD fibrosis score. We performed uni- and multivariate-analyses, receiver operating characteristic (ROC), and multivariate regression analyses for the assessment of diagnostic performance of various markers/indices. In order to clarify the source of IL-34, we performed immunohistochemical and immunofluorescence staining of frozen liver specimens obtained from NAFLD patients. Results: IL-34 significantly increased with the progression of fibrosis and was an independent marker for liver cirrhosis (odds ratio=1.233, P=0.006). For the diagnosis of liver cirrhosis, the area under the curve (AUC), sensitivity and specificity of IL-34 (0.87, 83.3%, and 80.2%, respectively) were superior to or comparable with the other serum biomarkers and fibrosis indexes. The combination of serum IL-34, type IV collagen 7s and ages, which are independent factors of liver fibrosis, [IL-34 based fibrosis score (IL-34-FS) = 0.0387*IL-34 (pg/ml) + 0.3623*type IV collagen 7s (ng/ml) + 0.0184*age (year) – 1.1850] was a practical tool for predicting the stages of fibrosis in NAFLD patients. The AUC, sensitivity, and specificity of IL-34-FS were 0.86, 75.2%, and 85.0% (significant fibrosis : fibrosis stage 2-4), 0.88, 81.7%, and 79.4% (advanced fibrosis : fibrosis stage 3-4), and 0.91, 83.3%, and 85.6% (liver cirrhosis), respectively. Immunostaining revealed that almost all of the IL-34 positive cells in the liver tissue were fibroblasts (α-SMA positive cells). Conclusion: Serum IL-34 increased with the progression of liver fibrosis mainly due to the accumulation of its source, liver fibroblasts. A novel IL-34-based fibrosis score, consisting of serum IL-34, type IV collagen 7s and age, is a feasible diagnostic marker of liver fibrosis in NAFLD patients.

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Metabolic Syndrome and Severity of Fibrosis in Non-alcoholic Fatty Liver Disease: An Age-Dependent Risk Profiling Study

Salvatore Petta[1], Mohammed Eslam[2], Luca Valenti[3], Elisabetta Bugianesi[4], Marco Barbara[1], Calogero Cammà[1], Marianna Porzio[3], Chiara Rosso[4], Silvia Fargion[3], Jacob George[2], Antonio Craxì[1]; [1]Cattedra ed U.O.C. di Gastroenterologia ed Epatologia, Palermo, Italy; [2]Storr Liver Unit, Westmead Millennium Institute and Westmead Hospital, University of Sydney, Australia, Sydney, ACT, Australia; [3]Department of Pathophysiology and Transplantation, Università degli Studi, Internal Medicine, Fondazione Ca' Granda IRCCS Ospedale Maggiore Policlinico, Milano, Italy, Milan, Italy; [4]Division of Gastro-Hepatology, Department of Medical Sciences, San Giovanni Battista Hospital, University of Torino, Torino, Italy, Turin, Italy

Background/Aims: Metabolic syndrome(MS) and its individual components are associated with nonalcoholic fatty liver disease(NAFLD) severity and progression. We sought to evaluate, in NAFLD patients discriminated by age, the effect of all components of the MS and of their combinations on the risk of severe hepatic fibrosis. **Methods:**We considered 863 consecutive biopsy-proven NAFLD patients, fully evaluated for components of MS– visceral obesity, IFG/diabetes, HDL, triglycerides and arterial hypertension. **Results:**At multivariate logistic regression analysis, F3-F4 was associated with visceral obesity(OR 20.5, 95%CI 2.29-235.9, p=0.01), IFG/diabetes(OR 2.66, 95%CI 1.76-4.04, p<0.001), and low HDL cholesterol(<40/<50 mg/dl; OR 1.73, 95%CI 1.17-2.56, p=0.006), but not triglycerides >150 or arterial hypertension. A significant interaction was found between age and visceral obesity(p=0.04). By stratifying patients for age, we confirmed the interaction between third age tertile(>54years) and visceral obesity(p=0.04). Consistently, in the lower(<41years) and middle(41-54 years) age tertiles, the risk for F3-F4 fibrosis was mostly driven by visceral obesity and IFG/diabetes, and was higher in those with all three metabolic risk factors(29% and 36% in lower and middle age tertiles, respectively). Finally, among patients in the higher age tertile(>54years), obesity did not affect fibrosis severity, and the risk of severe fibrosis was higher in those with low HDL and IFG/Diabetes with/without visceral obesity(from 52%to54%). **Conclusions:**In NAFLD, metabolic profiles at risk for severe fibrosis changed according to age, with low HDL, but mostly obesity and IFG/Diabetes being dominant in patients in lower and middle age tertiles, and HDL and IFG/Diabetes but not visceral obesity in those in the highest age tertile.

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Donor *TM6SF2* rs58542926 Genotype is an Independent Risk Factor for Development of Steatosis after Liver Transplantation

Irena Hejlova[1], Magdalena Neroldova[2], Jaroslav A. Hubacek[2], Dana Dlouha[2], Libor Kolesar[3], Milan Jirsa[2], Eva Honsova[4], Eva Sticova[4], Vera Lanska[5], Julius Spicak[1], Pavel Trunecka[1]; [1]Depatrment of Hepatogastroenterology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic, Prague, Czech Republic; [2]Center for Experimental Medicine, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; [3]Department of Clinical and Transplant Immunology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; [4]Department of Clinical and Transplant Pathology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; [5]Department of Biostatistics, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

Background & Aims: Polymorphism rs58542926 c.449 C>T v *TM6SF2* (transmembrane 6 superfamily member 2) is one of genetic factors predisposing to development of non-alcoholic fatty liver disease (NAFLD). We aimed to evaluate the influence of both recipient and donor *TM6SF2* rs58542926 genotypes on development of steatosis in liver transplant (LT) recipients. **Methods:** The study group included 272 adult LT recipients transplanted between 1995 and 2010, in whom occurrence of steatosis was evaluated by liver biopsy during first 5 post-transplant years. We analyzed *TM6SF2* rs58542926 and *PNPLA3* (patatin-like phospholipase 3) rs738409 genotypes of recipients and donors, and clinical and laboratory data. Patients with steatosis (≥5%; grade 1-3) were compared to patients without steatosis (<5%, grade 0). **Results:** Steatosis (grade 1-3) was found in 166 patients (61.0%), 106 patients (39.0%) did not develop any steatosis (grade 0). The distribution of donor *TM6SF2* rs58542926 genotypes differed significantly (p=0.036) between patients with steatosis (CC/CT/TT 80.1/19.3/0.6%) and without steatosis (CC/CT/TT 91.5/8.5/0.0%). The distribution of recipient *TM6SF2* rs58542926 genotypes was similar (p=0.91) in patients with steatosis (CC/CT/TT 77.7/19.9/2.4%) and without steatosis (CC/CT/TT 76.4/21.7/1.9%). On multivariate analysis, donor non-CC *TM6SF2* genotype (OR 3.22; 95%CI 1.42-7.99), donor non-CC *PNPLA3* genotype (OR 1.87; 95%CI 1.08-3.27) and BMI 1 year after LT (OR 1.14; 95%CI 1.06-1.24) were independent risk factors of development of post-transplant steatosis. The effect of donor *PNPLA* G allele and donor *TM6SF2* T allele was synergic, with OR 7.61 (95%CI 2.04-49.45) for presence of both donor risk alleles and OR 1.84 (95%CI 1.11-3.06) for presence of only one risk allele (*PNPLA3* G allele or *TM6SF2* T allele). **Conclusion:** Donor non-CC *TM6SF2* rs58542926 genotype is an independent risk factor of steatosis in liver transplant recipients. The effect of donor *TM6SF2* genotype is synergic to the effect of donor *PNPLA3* genotype.

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A Phase 1 Study of BMS-986036 (Pegylated FGF21) in Healthy Obese Subjects

Edgar D. Charles[1], Linda Morrow[2], Marcus Hompesch[2], Yi Luo[1], Chunyu Kate Wu[1], Rose Christian[1]; [1]Bristol-Myers Squibb, Lawrenceville, NJ; [2]Profil Institute for Clinical Research, Chula Vista, CA

Background: Fibroblast growth factor 21 (FGF21), a non-mitogenic hormone, is an important regulator of glucose and lipid metabolism. FGF21 analogs improve insulin sensitivity and lipid profiles, which contribute to nonalcoholic steatohepatitis (NASH) pathogenesis, in preclinical models as well as in obese humans with type 2 diabetes. BMS-986036 is a pegylated recombinant human FGF21 with an extended elimination half-life, enabling daily and weekly regimens to be studied. **Methods**: 96 healthy obese (BMI 30-40 kg/m^2) subjects were randomized 3:1 to subcutaneous (SC) BMS-986036 or placebo (PBO) in a 16-arm single ascending dose (SAD)/ multiple ascending dose (MAD) single-center study with primary endpoints of safety, tolerability, PK and pharmacodynamics. SAD subjects received doses of 0.3, 1, 3, 10, 30, or 60 mg of BMS-986036 or PBO. MAD subjects received BMS-986036 0.3 mg QD, 1 mg QD, 3 mg QD, 10 mg QD, 30 mg QD, 21 mg QW or PBO for 14 d. Subjects were in-house from D-2 until D15 (SAD) or D22 (MAD) and received an identical diet 48 h prior to D1 and D16. RNA expression was analyzed from D-1 and D16 (MAD) abdominal adipose tissue biopsies, and pathway analysis was conducted. Metabolomic profiling was performed on D1, D8 and D16 (MAD) serum. **Results:** Study subjects had a mean age of 41.8 y and mean BMI of 34.1 kg/m^2; 83% male, 41% Hispanic. There were no deaths, SAEs, discontinuations due to AEs or dose-related changes in AEs. Among MAD subjects who received BMS-986036, the most common AE was injection site erythema (22.2%). All treatment-related AEs were mild. BMS-986036 showed linear PK; the average elimination T1/2 was 19-24 h. Accumulation was 2-3 fold with QD dosing and negligible with QW dosing. 14 days of BMS-986036 was associated with dose-dependent improvements in body weight, insulin sensitivity, triglycerides, lipids and adiponectin (Table 1), as well as increased expression of genes involved in mitochondrial oxidative phosphorylation and metabolites associated with branched chain amino acid catabolism. **Conclusions:** Single and multiple SC doses of BMS-986036 QD or QW for up to 14 days in healthy subjects were well tolerated and associated with dose-dependent improvements in body weight, insulin resistance, triglycerides, LDL and adiponectin. Gene expression and metabolomics analyses suggest that BMS-986036 may improve mitochondrial function and amino acid homeostasis, which may be perturbed in NASH. These beneficial effects on key drivers of NASH pathogenesis support evaluation of BMS-986036 in Phase 2 studies of NASH.

D15 Adiponectin-% change from D1

PBO	0.3mg QD	1mg QD	3mg QD	21mg QW	10mg QD	30mg QD
-34.9	-22.9	-9.1	-2.7	0.3	19.4	41.7

Disclosures:

Edgar D. Charles - Employment: BMS

Linda Morrow - Stock Shareholder: Profil Institute for Clinical Research, Eli Lilly

Yi Luo - Employment: Bristaol-Myer Squibb

Rose Christian - Employment: Bristol-Myers Squibb

The following people have nothing to disclose: Marcus Hompesch, Chunyu Kate Wu

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Early detection of chronic liver disease with fibrosis among presumed healthy adults using transient elastography (TE). A population-based study

Llorenç Caballería[1], Guillem Pera[1], Ingrid Arteaga[1], Lluis Rodriguez[1], Alba Alumà[2], Carmen Expósito[1], Rosa María Morillas[5], Dolores Miranda[3], Carmen Sánchez[4], Rosa Prats[4], Marta Urquizu[1], Angels Salgado[1], Magda Alemany[1], Alba Martínez Escudé[1], Nuria Fabrellas[6], Isabel Graupera[7], Pere Toran[1], Juan Caballeria[7], Pere Gines[7]; [1]USR Metropolitana Nord, IDIAP Jordi Gol, Mataró, Spain; [2]Biochemistry, Institut Català de la Salut, Badalona, Spain; [3]Radiology, Institut Català de la Salut, Mataró, Spain; [4]Radiology, Institut Català de la Salut, Santa Coloma de Gramenet, Spain; [5]Hepatology, Hospital Germans Trias i Pujol, Badalona, Spain; [6]School of Nursing, University of Barcelona, Barcelona, Spain; [7]Liver Unit, Hospital Clínic, Barcelona, Spain

Background and aims: Cirrhosis is one of the leading causes of death worldwide. The diagnosis is usually made in late stages after acute decompensation or liver cancer has developed. Ideally, diagnosis should be made in early stages before cirrhosis occurs, but current analytical and imaging methods are inaccurate for early detection of hepatic fibrosis. Aim of the study was to investigate the usefulness of TE for early detection of silent chronic liver disease with hepatic fibrosis in presumed healthy subjects from the general population. **Methods:** Cross-sectional, descriptive, population-based study of subjects aged 18-75 yr randomly identified from people attending 18 primary care centers in Barcelona Metro Area from April 2012 to January 2016. Patients with known liver disease were excluded. Subjects were invited to participate through phone calls and 68% accepted. Medical examination, lab tests, and liver stiffness measurement (LSM) with TE were performed the same day by a single experienced operator. According to published data, LSM ≥ 6.8, 7.6, and 8.0 kPa were used as cutoffs of clinically-relevant fibrosis. A liver biopsy was suggested in subjects with abnormal LSM. **Results:** 3,076 subjects, 57% females, 94% caucasians, with mean age 54 ± 12 yr were included. Among them, 28% had metabolic syndrome (MS) and 9% excessive alcohol consumption. Less than 1% were found to be HBV and HCV+ and 24% had high aminotransferase levels. The percentages of subjects with increased LSM according to cutoffs used were 9.3%, 7.1% and 6%, respectively. In multivariate analysis, age, sex, high aminotransferases, and presence of MS were associated with increased LSM.Liver biopsy was performed in 51.5% of eligible patients. The histological diagnosis was NAFLD/NASH in 73, alcohol-related in 7, and normal liver in 4; the degree of fibrosis was F0 to F4 in 46, 13, 20, 2, and 3, respectively. There was a significant relationship between LSM and degree of fibrosis: 8.4±1.9; 7.9±1.5; 10.7±1.6; 15±1.5; and 33.9±10.8 kPa, from F0 to F4, respectively (p<0.001). The percentage of patients with significant fibrosis (≥2) was related to the LSM cutoff, being 31%, 38% and 44% for cutoffs of 6.8, 7.6 and 8 kPa, respectively. The cut-off of LSM with greatest accuracy for diagnosis of significant fibrosis (≥2) was of 9.2 kPa with 92% sensitivity and 80% specificity and AUROC of 0.87. **Conclusions:** A high percentage of presumed healthy adults from the Spanish population, 6% using cutoff of LSM of 8kPa and 2.6% extrapolating biopsy data, have liver fibrosis, in most cases related to NAFLD. TE is a good non-invasive method for screening of liver fibrosis in the general population.

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♦ Denotes AASLD Presidential Poster of Distinction

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1084

The level of the macrophage activation marker soluble CD163 is a predictor of fibrosis progression and inflammation in non-alcoholic steatohepatitis (NASH)

Miwa Kawanaka[1], Ken Nishino[1], Tomohiro Tanikawa[1], Takahito Oka[1], Noriyo Urata[1], Jun Nakamura[1], Mitsuhiko Suehiro[1], Hirofumi Kawamoto[1], Norikuni Kawanaka[2]; [1]Department of general Internal Medicine2, Kawasaki hospital, Kawasaki medical school, Okayama, Japan; [2]Department of Rheumatology, Fukui-kosei hospital, Fukui, Japan

[Background and Aim] CD163 positive (M2 phenotype) macrophage displays anti-inflammatory properties and implicated in tissue repair. This type of macrophage may contribute to the progression of fibrosis stage and nonalcoholic fatty liver disease activity score (NAS) in non-alcoholic fatty liver disease (NAFLD). We measured the levels of the macrophage activation marker, soluble CD163 (sCD163) in NASH, and investigated the relationship between sCD163 and progressive liver histology of NAFLD. To evaluate CD163 positive macrophage plays a role in the pathogenesis of NAFLD, immunohistochemical staining of CD163 were performed in tissues of repeated liver biopsies. [Target and method] Serum and liver biopsies were obtained from 247 patients with non-alcoholic fatty liver disease (NAFLD). 100 of 247 patients were undergone repeated liver biopsies. Patients were divided into five groups based on fibrosis stage and NAS (mean age: 55 years (19–82) men: 48.1%, Stage: 0/1/2/3/4:21/83/52/65/26, Grade: 0 /1/2/3:23/107/74/43). sCD163 were measured by ELISA(CD163; human ELISA kit Quantikaine). Immunohistochemical staining was done in repeated biopsies from randomly selected patients with NASH. The primary antibodies were mouse monoclonal anti human CD163(Leica, UK,10D6) diluted 1:50. [Results] sCD163 levels correlated with fibrosis stages ($P < 0.001$), and sCD163 level was significantly elevated in the advanced fibrosis of stage 4 group (1086.3 vs. 651.3; $P < 0.001$, cut-off 932; AUC, 0.85). sCD163 levels correlated with NAS ($P < 0.001$). However, in spite of low NAS, sCD163 levels were significantly elevated in burned-out NASH. Among the 100 patients who underwent repeated biopsies, 31 patients improved fibrotic degree and 37 improved NAS. sCD163 levels were significantly reduced in both patients that improved fibrotic degree and NAS. Conversely, sCD168 levels were elevated in patients whose fibrosis or NAS had worsened. CD163 positive macrophages are existed in the liver sinusoids. There was no relationship between amount of CD163 positive macrophages and progressive liver histology of NAFLD. [Conclusion] sCD163 level reflects the progression of fibrosis and inflammation in liver tissue, and sCD163 could be useful as a non-invasive biomarker in NASH or NAFLD.

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1085

Lean-non alcoholic fatty liver disease (NAFLD): liver and cardiovascular damage and its relation with visceral obesity

Anna Ludovica Fracanzani[1], Salvatore Petta[2], Rosa Lombardi[1], Giuseppina Pisano[1], Maurizio Russello[3], Laura Mensi[1], Vito Di Marco[2], Calogero Cammà[2], Paola Dongiovanni[1], Luca Valenti[1], Antonio Craxì[2], Silvia Fargion[1]; [1]Department of Pathophysiology and Transplantation Unit of Metabolic Internal Medicine, University of Milan, Ca' Granda IRCCS Foundation, Maggiore Policlinico Hospital, Milan, Italy; [2]Biomedical Department of Internal and Specialistic Medicine (DIBIMIS), Gastroenterological and Liver Unit, University of Palermo, Palermo, Italy; [3]Liver Unit, ARNAS, Garibaldi Hospital, Catania, Italy

NAFLD has been usually linked to obesity. However, recent data have shown the presence of NAFLD also in patients with normal BMI defining a new concept of lean-NAFLD. Lean-NAFLD shares many metabolic characteristics with overweight NAFLD, although a lower prevalence of Metabolic Syndrome (MetS) and liver damage has been reported. To evaluate liver and cardiovascular damage of lean-NAFLD we studied 673 consecutive patients with biopsy proven NAFLD from 3 Italian Liver Units. Methods: Biochemical parameters, carotid atherosclerotic lesions by ultrasonography, PNPLA3 and TM6SF2 genotyping and liver histology were recorded. Subjects were divided according to BMI ≤ 25 (defined as lean-NAFLD) or >25 kg/m2, and to waist circumference (WC), surrogate marker of visceral obesity (< or ≥ 88 cm (for female) and < or ≥102 cm (for male)). Results: lean-NAFLD (149 patients, 42 female, mean age 46±13) had significantly lower prevalence of hypertension (20% vs 37%, p=0.001), diabetes (11% vs 26%, p=0.0003), MetS (14% vs 39%, p=0.0002), lower total cholesterol (48±15 vs 53±14, p=0.03 and triglycerides (132±40 vs 145±45, p=0.05) than overweight/obese NAFLD (524 patients, 72 female, mean age 49±13). Carotid intima-media thickness (0.74±0.1 vs 0.84±0.3, p=0.0001), prevalence of NASH (18% vs 48%, p=0.0001) and of significant fibrosis (F2 or higher) (17% vs 42%,p=0.0001) were significantly lower in lean-NAFLD while prevalence of carotid plaques was similar. The prevalence of PNPLA3 G allele carriage did not differ in the two groups, while TM6SF2 T allele was more prevalent in lean NAFLD (4%vs 0.3%, p=0.001). Twenty-seven (18%) of lean NAFLD had steatosis of grade 3, 24 (14%), lobular inflammation ≥ 2, 10 (6%) ballooning score of 2 and 25 (17%) fibrosis ≥2. At multivariate analysis in the overall series WC higher than 88 cm (female) and 102 cm (male) was significantly associated with female gender (p=0.001), MetS (p=0.0001), NASH (p=0.05), fibrosis ≥2 (p=0.03) and diabetes (p=0.06). The logistic regression analyses of mutually adjusted BMI and WC in the overall series of NAFLD indicated that WC predicts better than BMI the presence of NASH (p<0.0001 vs p=0.001), fibrosis ≥2 (p<0.001 vs p=0.07), diabetes (p<0.0001 vs p=0.05), hypertension (p=0.0001 vs p=0.94), and plaques (p<0.000 vs p=0.9). WC was a stronger risk factor for NASH in lean subjects than in overweight subjects. In conclusion our findings indicate that 20% of NAFLD have normal BMI and of these one third have carotid atherosclerosis, and 20% severe liver damage. Evaluation of both BMI and WC allows a better definition of the severity of liver and cardiovascular damage in lean patients with NAFLD.

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1086

The impact of alcohol consumption on hepatic fibrosis in non-alcoholic fatty liver disease

Tim Mitchell[1], Gary P. Jeffrey[1,2], Gerry C. MacQuillan[1], George Garas[1], Helena Ching[1], Jeffrey M. Hamdorf[3], Leon A. Adams[1,2]; [1]Hepatology, Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [2]School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia; [3]School of Surgery, University of Western Australia, Perth, WA, Australia

Background: The impact of alcohol on liver injury in non-alcoholic fatty liver disease (NAFLD) is unclear. Alcohol may increase fibrosis progression in other chronic liver diseases such as hepatitis C, yet moderate consumption may be protective against cardiovascular disease, the leading cause of death in NAFLD patients. We aimed to determine the association between quantity and patterns of alcohol consumption and liver fibrosis in patients with NAFLD. **Methods:** Patients with NAFLD consuming ≤210 grams alcohol/week seen at a tertiary hepatology clinic or undergoing bariatric surgery, underwent a detailed evaluation including assessment of the pattern, type and duration of alcohol consumption. Liver biopsies were scored according to the NASH CRN scoring system with fibrosis staged 0-4. **Results:** 189 patients were included; mean age 51 ±12 years; 118 (62%) female, 161 (85%) obese and 76 (40%) diabetic. Mean fibrosis stage was 1.2 ±1.4 and 46 (24%) had advanced fibrosis (F3/F4). 74 (39%) patients were life-long abstainers, 22 (12%) previously drunk alcohol and 93 (49%) currently consumed alcohol with a median consumption of 20 g/week. Median (interquartile range) total lifetime alcohol consumption amongst drinkers was 21.0 (7.1-95.2) kilograms over a median duration of 21.0 (10-40) years. Thirty-one (16%) patients consumed alcohol in a binge pattern during their lifetime. Abstinence was associated with a higher mean fibrosis stage (1.6 ±1.6) compared with those who drank >0-70 g/week (0.9 ±1.1, p=0.003), and >70 to ≤210 g/week (0.5 ±0.7, p=0.003). Abstinence was also associated with a higher mean fibrosis stage (1.6 ±1.6) in comparison with non-binge drinkers (1.0 ±1.3, p=0.04), however the protective effect was lost in binge drinkers (1.1 ±1.3, p=0.2). Alcohol consumption of ≤70 g/week compared to lifelong abstinence was associated with lower odds of advanced fibrosis (OR 0.38, 95% CI 0.16-0.90, p=0.028) after adjusting for age, diabetes, BMI, sex and total lifetime consumption. Non-binge drinkers had a lower odds of advanced fibrosis compared to abstainers (adjusted OR 0.41, 95% CI 0.17-0.97, p=0.043), whereas no protective association was noted for binge drinkers (p=0.6). Neither average lifetime intake per week, cumulative life-time intake or smoking status were associated with advanced fibrosis (p>0.2 for all). **Conclusions:** Weekly alcohol intake of 70 grams or less in a non-binge pattern, is associated with lower fibrosis stage in patients with NAFLD. Given the possible protective effects of moderate alcohol consumption for cardiovascular outcomes, patients with NAFLD without cirrhosis may benefit from modest alcohol consumption.

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Leon A. Adams - Patent Held/Filed: Quest diagnostics

The following people have nothing to disclose: Tim Mitchell, Gary P. Jeffrey, Gerry C. MacQuillan, George Garas, Helena Ching, Jeffrey M. Hamdorf

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Remogliflozin Etabonate Reduces FIB-4 and NAFLD Fibrosis Scores in Type 2 Diabetic Subjects

Bill Wilkison[1], Bentley Cheatham[1], Susan Walker[2]; [1]BHV Pharma, RTP, NC; [2]apex biostatistics, Apex, NC

The etiology of non-alcoholic steatohepatitis (NASH) is due, in part, to insulin resistance and oxidative stress. Remogliflozin etabonate (Remo) is an SGLT2 inhibitor shown in previous clinical studies to reduce HbA1c and improve glycemic control. In this post hoc analysis, we examined whether these improvements in glycemic control were associated with changes in insulin sensitivity, and to what extent Remo may affect the non-invasive markers of fibrosis; FIB-4 and NAFLD Fibrosis scores. **Methods:** A 12-week, double-blind, randomized, placebo–controlled trial was conducted with 336 subjects with type 2 diabetes and an HbA1c of > 7.0% to < 9.5%. Subjects were equally randomized to each of the Remo treatments (50, 100, 250, 500, or 1000 mg bid), placebo or pioglitazone (qd). Serum alanine aminotransferases (ALT), homeostatic model assessment (HOMA) for insulin sensitivity (HOMA-IS) and beta cell function (HOMA -BCF) were assessed at Baseline, Week 4, Week 8 and Week 12. Post-prandial assessments of glucose, insulin, and C-peptide were performed at Baseline and at Week 12 using a 2-hour oral glucose tolerance test (OGTT) in a subgroup of subjects. FIB-4 and NAFLD Fibrosis Scores were determined at Baseline and Week 12. **Results:** At Week 12, Remo improved both insulin sensitivity (6-39%) and beta cell function (23-43%) in a dose-dependent manner. A statistically significant decrease from baseline in AUC (0-2 hour) weighted mean plasma glucose following the OGTT was observed for all Remo treatment groups. In subjects with elevated baseline ALT, Remo treatment resulted in a significant reduction (32-42%) in ALT at Week 12. Baseline FIB-4 scores were indicative of a broad range of fibrosis stages. Remo, at all doses, had an effect of reducing the FIB-4 scores (5-17% reduction) compared to placebo. After 12-weeks of treatment with Remo, the FIB-4 scores were consistent with a predicted improvement in fibrosis stage. Similar results were noted for NAFLD-Fibrosis scores. **Conclusions:** In previous studies using a mouse model of fatty liver disease, Remo significantly improved steatohepatitis. Compared to other SGLT2 inhibitors, Remo also displayed significant anti-oxidant activity, in *vitro* and *in vivo*. In this clinical study we show the ability of Remo to reverse insulin resistance is associated with significant lowering of ALT and improvement in both FIB-4 and NAFLD-Fibrosis scores. Remo is a safe and potent late stage clinical compound. Taken together, the pre-clinical and clinical data are highly suggestive that Remo may be a useful treatment for NASH.

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Bill Wilkison - Management Position: BHV Pharma

Bentley Cheatham - Stock Shareholder: BHV Pharma

The following people have nothing to disclose: Susan Walker

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Ectopic Fat Deposition in Skeletal Muscle was Associated with Diabetes Mellitus in Patients with Non-Alcoholic Fatty Liver Disease: A MRI-proton Density Fat-fraction Analysis

Takumi Kawaguchi[1], Tatsuyuki Tonan[2], Kiminori Fujimoto[2], Toshi Abe[2], Takuji Torimura[1]; [1]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan; [2]Department of Radiology, Kurume University School of Medicine, Kurume, Japan

Background and Aims: Diabetes mellitus (DM) is frequently seen in patients with non-alcoholic fatty liver disease (NAFLD) and is a risk factor for the development of hepatocellular carcinoma. Ectopic fat deposition in the liver, pancreas, or muscle is a causative factor for DM; however, it remains unclear which ectopic fat deposition is associated with DM in patients with NAFLD. Recently, MRI using proton density fat-fraction (MRI-PDFF) has been developed and allow us to quantify accurate fat content in various organs. The aims of this study is to investigate an association of ectopic fat deposition and DM in patients with NAFLD by using MRI-PDFF. **Material and Methods:** In this study, we enrolled 27 NAFLD patients (57.9 years, female/male 13/14) and 9 non-NAFLD patients (62.1 years, female/male 5/4; Control group). NAFLD patients were further classified into NAFLD patients with DM (NAFLD-DM group; n=11) and NAFLD patients without DM (NAFLD-non DM group; n=16). MRI-PDFF values were measured in liver (liver-FF), pancreas (pancreas-FF), and muscle (muscle-FF). Difference in MRI-PDFF value was evaluated by ANOVA followed by Scheffe's post hoc test. The usefulness of MRI-PDFF value to differentiate the NAFLD-DM group from the NAFLD-non DM group was evaluated using receiver operating characteristic (ROC) analysis. In addition, a decision-tree analysis was employed to identify the most important factor for the NAFLD-DM group. **Results:** Liver-FF, pancreas-FF, and muscle-FF values were significantly higher in the NAFD-DM and NAFLD-non DM groups compared to those in the Control group. There was no significant difference in liver-FF and pancreas-FF values between the NAFLD-DM and NAFLD-non DM group (liver-FF 8.7±2.0% vs. 10.0±1.8%, N.S.; pancreas-FF 6.4±3.0% vs. 4.8±1.2%, N.S.). However, muscle-FF value was significantly higher in the NAFLD-DM group compared to that in the NAFLD-non DM group (6.5±1.0% vs. 3.0±0.7%, P<0.01). ROC analysis revealed that muscle-FF was the most useful marker to differentiate the NAFLD-DM group from the NAFLD-non DM group (AUC=0.83, P< 0.01). With a cutoff-value of muscle-FF > 4%, sensitivity, specificity, positive and negative predictive values were 0.81, 0.74, 0.69, and 0.85, respectively. In addition, the decision-tree analysis revealed that > 5.3% of muscle-FF value was the initial divergence variable for the presence of diabetes mellitus in NAFLD patients. **Conclusions:** We first showed that ectopic fat deposition in muscle was associated with DM in patients with NAFLD by using MRI-PDFF. Thus, muscle steatosis may be an important therapeutic target for patients with NAFLD.

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Central Body Fat Distribution Is Associated with Increased Risk of Nonalcoholic Fatty Liver Disease in Lean Individuals: A Population Based Study from the National Health and Nutrition Examination Survey

Ye Eun Kwak[1], Albert Do[2], Joseph K. Lim[3]; [1]Department of Internal Medicine, Bridgeport Hospital, Yale University School of Medicine, Bridgeport, CT; [2]Department of Internal Medicine, Yale-New Haven Hospital, Yale University School of Medicine, New Haven, CT; [3]Section of Digestive Diseases, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT

Background: Although obesity is an important risk factor of nonalcoholic fatty liver disease (NAFLD), a significant number of patients with normal body mass index (BMI) also develop NAFLD (lean-NAFLD). High waist-to-hip ratio (WHR), an indicator of central fat distribution, is associated with metabolic syndrome and cardiovascular disease which in turn may be related to NAFLD. Our objective is to determine the association between central body fat distribution and lean NAFLD in the United States population using a large nationally-representative database. **Methods:** We used data from the third National Health and Nutrition Examination Survey (NHANES III) with gradable hepatic ultrasonography (US) for hepatic steatosis in adults aged 20-74 years. NAFLD was defined as presence of moderate-to-severe hepatic steatosis by US and absence of chronic liver disease (positive hepatitis B surface antigen, positive hepatitis C antibody, iron overload or excessive alcohol consumption). Control group was defined as those with normal serum aminotransferase levels and without moderate-to-severe hepatic steatosis and chronic liver disease. Lean groups in NAFLD and controls were defined as BMI less than 25. WHR, bioelectrical impedance analysis (BIA) resistance (which can predict total body fat mass), homeostatic model assessment of insulin resistance (HOMA-IR), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were recorded. **Results:** Of 13,856 adults aged 20-74 years who had gradable US images, 1,815 were identified as having NAFLD and 5,319 as controls. Of those, 295 were identified as having lean-NAFLD and 2,161 as lean-controls. There was no difference in BMI between lean-NAFLD and lean-control group (mean 22.2 ± 2.2 vs 22.1 ± 2.0, p=0.4120). WHR was significantly higher in lean-NAFLD group than lean-control group (mean 0.894 ± 0.090 vs 0.869 ± 0.078, p<0.0001) although there was no difference in BIA resistance (mean 588.8 ± 91.9 vs 590.9 ± 86.7, p=0.7113), a predictor of total body fat mass. Multivariate logistic regression showed lean NAFLD was independently associated with higher WHR (adjusted odds ratio=3587.52, confidence interval=46.3-277754, p<0.0001) after adjusting for age, sex, BMI, HOMA-IR, BIA-resistance, TG, LDL-C and HDL-C. **Conclusion:** Increased central fat distribution is associated with risk of NAFLD irrespective of total body fat mass in individuals with normal BMI.

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1090

Impact of liver histology on the post-operative morbidity and mortality of bariatric surgery

Guillaume Lassailly, robert Caiazzo, Charlotte Vanveuren, Viviane Gnemmi, Emmanuelle Leteurtre, Helene Verkindt, Gregory Baud, Florent Artru, Valerie Canva-Delcambre, Alexandre Louvet, Sebastien Dharancy, François Pattou, Philippe Mathurin; CHRU lille, Lille, France

With the epidemic problem of obesity, bariatric surgery has become an increasing treatment option. Its beneficial impact on diabetes or steatohepatitis (NASH) can increase the rate of candidates with severe comorbidities. But, post-operative morbidity and mortality of these patients with more severe liver disease is poorly known. Preliminary studies have suggested that liver injury could increase post-operative complications. However, in morbid obese patients liver injuries are frequent and varied, and the true impact of NASH is unknown. Aim: Evaluate the impact of liver histology on the post-operative morbidity and mortality of bariatric surgery. Methods: Patients operated of bariatric surgery were included and prospectively followed in the "Lille Bariatric" cohort from 1994 to 2015 in CHRU de Lille. Clinical, biological and histological data as well as post-op morbidity within 30 days were collected. The studied histological data that could impact post-op morbidity were: significant fibrosis (≥F2 METAVIR), cirrhosis, NASH and severe NAFLD (NAS≥5). If the distribution of the type of surgery was different between groups, complications were studied for each surgical procedure (gastric banding, sleeve gastrectomy, and bypass). Results : 2021 patients were included. Characteristics were: age 41.2±11.6 y, 75.6% of women, BMI 47.9±8 kg/m^2, NASH 7.9%, NAS≥5 5,2%, fibrosis≥F2 5,2%, cirrhosis 1,4%, HbA1c 5.9%, AST 25±13 IU/L, ALT 32±21IU/L and GGT 30IU/L (20-47). The main procedures were bypass (51%) and gastric banding (35%). Rate of complications was 11.5%, most frequent were: infection 21.5%, hemorrhage 10.7% and rhabdomyolysis 10.3%. In univariate analysis, histological lesions associated with morbidity were cirrhosis (25 vs 11.4% p=0.04) (whatever procedure) and fibrosis ≥ F2 (after bypass) (23.3% vs 12.5% p=0.01). NASH (13.6 vs 11.2% p=0.36) and NAS≥5 (13.2 vs 11.3% p=0.53) were not associated with morbidity. Infection was the most frequent complication and its incidence increased according to the severity of fibrosis (F0: 1.8%; F1: 3.1%; F2: 8.1; F3-F4: 11.4%). In multivariate analysis, data associated with morbidity were age 1.02 (1.003-1.3, p=0.012), BMI 1.04 (1.03-1.06, p<0.001), fibrosis ≥ F2 1.9 (1.16-3.11, p=0.010) and steatosis>30% 1.54 (1.15-2.08, p=0.04). In terms of mortality, during follow-up 19 patients died, among those, 3 died within the post-op 30 days. The overall 5 year survival was 99.06%. Conclusion: Morbidity was associated with higher age, BMI, fibrosis and steatosis. Even if morbidity was higher in patient with fibrosis and more severe liver disease, the benefit of such strategy is proved by an excellent survival at 5 years.

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1091

Next-Gen Sequencing uncovers an increased expression of fibrogenic and extracellular matrix-related genes in nonalcoholic steatohepatitis patients with iron deposition in reticuloendothelial system cells.

Priya Handa[1], Vicki Morgan-Stevenson[1], James E. Nelson[2], Laura Wilson[3], Katherine P. Yates[3], Matthew M. Yeh[4], Kris V. Kowdley[1]; [1]Organ Care Research and Liver Care Network, Swedish Medical Center, Seattle, WA; [2]Benaroya Research Institute, Seattle, WA; [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [4]University of Washington, School of Medicine, Seattle, WA

Background: We previously showed that the presence of reticuloendothelial system (RES) cell iron staining has been associated with severe histological features of disease including advanced fibrosis, increased apoptosis, increased ballooning and a definitive diagnosis of nonalcoholic steatohepatitis (NASH) in patients with nonalcoholic fatty liver disease (NAFLD). **Aim:** In this study, we aimed to map the transcriptome in the livers of NASH patients from all 4 hepatic iron phenotypes: No iron, hepatocellular (HC) iron, RES iron and mixed (HC/RES) iron(n=23-25 each, from the NASH CRN) by utilizing Next-Gen RNA sequencing, with the goal of identifying specific pathways and gene that are differentially expressed in NASH patients with RES iron. **Methods:** RNA-sequencing libraries were constructed from liver tissue. Such libraries were clustered on a flowcell using the TruSeq Paired-end Cluster Kit v.3 using a cBot clustering instrument, followed by paired-end sequencing on a HiScanSQ for 50 cycles in either direction. After the run was completed, the reads were demultiplexed and FASTQ files were generated using Casava software for each sample output. Read quality was analyzed by generating QC plots. The R Bioconductor package edgeR was used to determine differential expression between RES Iron and non RES iron samples. **Results:** Transcriptome analysis revealed that genes belonging to pathways such as extracellular matrix deposition, cellular anchoring, fibrogenesis and liver development and regeneration showed significantly increased expression in the RES livers. Gene expression levels of proteins from the aforementioned pathways such as collagen type I, IV and X, versican, lumican, laminin, fibulin, lectin, TGF- β, lysyl oxidase like 1, ADAM metallopeptidase with thrombospondin 12 (ADAMTS13), MMP2, MMP9 and WNT4, which have been previously demonstrated to be important for fibrogenesis, were significantly elevated in the RES livers relative to other groups. Additionally, we validated the findings of the next-gen RNA sequencing using quantitative RT-PCR analysis and found the expression levels of the above-mentioned genes to be significantly augmented in RES samples relative to the other groups. **Conclusions**: We have utilized Next-Gen Sequencing to establish a direct relationship between hepatic RES iron and fibrogenic and extracellular matrix deposition pathways. Detailed analysis of these pathways and specific molecular factors therein, by utilizing available or generating tissue-specific knock-out mouse models and/or specific inhibitors in mouse models and cell lines *in vitro*, will clarify if the presence of RES iron leads to fibrosis and thereby worsens NASH.

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1092

Testosterone Level in Young Women Is Independently Associated with Prevalent Non-Alcoholic Fatty Liver Disease (NAFLD) in Middle Age: Results from the Coronary Artery Risk Development in Young Adults (CARDIA) Study

Monika Sarkar[1], Lisa B. VanWagner[2], Melissa Wellons[3], Mary E. Rinella[2], John J. Carr[3], Beth Lewis[4], James Terry[3], Erica Gunderson[5], Laura Torchen[2], Marcelle I. Cedars[1], Norah Terrault[1]; [1]UCSF, San Francisco, CA; [2]Northwestern University, Chicago, IL; [3]Vanderbilt, Nashville, TN; [4]UAB, Birmingham, AL; [5]Kaiser Permanente, Oakland, CA

Background: Young hyperandrogenic women have a high risk of metabolic syndrome, including an increased risk of NAFLD. Whether testosterone (the predominant androgen) is associated with NAFLD risk independent of metabolic co-factors is not clear. It is also unknown whether normal range testosterone levels in women confer an increased risk of NAFLD. Methods: Among women followed in the prospective, multicenter Coronary Artery Risk Development in Young Adults (CARDIA) study we assessed the association of testosterone levels at Year 2 (1987-1988) with prevalent NAFLD at Year 25 (2010-2011) (n=1,056). NAFLD was defined by noncontrast CT scan with liver attenuation ≤ 40 Hounsfield units and exclusion of other causes of hepatic steatosis. The primary predictor was free testosterone and secondary predictor was total testosterone with adjustment for sex hormone binding globulin (SHBG). Logistic regression was performed and included a subgroup analysis among non-hyperandrogenic women (n=989). Results: Of the 1,056 women, 54% were black, 46% white, with mean age at entry of 26.8 years (±3.7). NAFLD was present in n=92 women (8.7%) at Year 25. Increasing quintiles of free testosterone were associated with a 25% increased odds of prevalent NAFLD on adjusted analyses (Table). Importantly, free testosterone remained strongly associated with prevalent NAFLD, even in women with normal range testosterone levels (OR 1.26, 95% CI 1.06-1.50, p=0.01). Estimates were similar using total testosterone adjusted for SHBG (AOR in entire cohort 1.18, 95% CI 1.0-1.37) including in the subgroup of non-hyperandrogenic women (AOR 1.19, 95% CI 0.99-1.37). Conclusion**:** Increasing levels of free testosterone, *even within normal range*, are independently associated with prevalent NAFLD in middle age. Androgens may have an important role in the development of NAFLD in women and provide a potential novel target for NAFLD therapeutics.

Table: Association of Free Testosterone Levels in Young Women with Prevalent NAFLD 25 Years Later (n=1,056)

	Univariate Analysis		Multivariate Analysis*	
Characteristic	**OR (95% CI)**	**p**	**AOR (95% CI)**	**p**
Age, per 5 year increase	1.02 (0.98-1.08)	0.26	0.98 (0.92-1.04)	0.49
White vs black race	1.03 (0.72-1.47)	0.87	**1.70 (1.04-2.79)**	**0.04**
Triglycerides at entry, per 20 mg/dL increase	1.13 (1.05-1.21)	< 0.01	1.07 (0.97-1.18)	0.15
BMI at entry, per 5 kg/m^2 increase	**1.45 (1.27-1.65)**	**< 0.01**	**1.07 (1.09-1.16)**	**< 0.01**
Diabetes ever during study	4.88 (3.29-7.25)	< 0.01	3.55 (2.07-6.08)	< 0.01
Free testosterone (quintiles)	**1.38 (1.14-1.68)**	**< 0.01**	**1.25 (1.06-1.47)**	**< 0.01**

*Age and race forced into multivariate model given known biological associations with NAFLD. Similar point estimates for free testosterone were obtained when using Year 25 BMI and triglyceride levels instead of study entry levels.

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1093

Role of CK18-M65 as a biomarker of acute alcoholic hepatitis and development of a modified MELD score using M65 and clinically relevant markers of severe AAH

Vatsalya Vatsalya[1,3], Matthew Cave[1,2], Heather B. Clair[2], Tom Burke[1], Keith C. Falkner[1], Craig McClain[1,3]; [1]Medicine, University of Louisville, Louisville, KY; [2]Biochemistry and Molecular Biology, University of Louisville, Louisville, KY; [3]Robley Rex Veterans Affairs Medical Center, Louisville, KY

Acute alcoholic hepatitis (AAH) has serious clinical presentation that is associated with high mortality. Thus, the acute nature of AAH necessitates reliable and predictable prognostic measures. Pathophysiologic events of AAH lead to increased hepatocytic death that may reflect the prognosis of liver injury. In this study, we aimed to identify alterations in CK18 M65 and M30 levels as markers of hepatocyte death and define clinically relevant markers of AAH. Further, we hypothesized that replacing total bilirubin with the necrotic marker (M65) in the MELD score could increase the predictability of relevant clinical and laboratory markers of AAH. Forty-one male and female patients aged 21–70 years with AAH were classified by severity as moderate or severe based on MELD score (≤ 19 or >19). Data for demographics, drinking history (AUDIT), MELD, Maddrey DF and other liver injury markers were collected. Additionally, 18 healthy volunteers were also enrolled as a comparison group. Serum CK18 protein was analyzed using ELISA and APOPTOSENSE kit. CK18 fragment levels between healthy controls and AAH patients (by severity) were compared using ANOVA. CK18 fragments, CK18-M65, and -M30 were assessed within each severity group. As expected, 25 severe AAH patients had significantly higher MELD, Maddrey DF, and AST:ALT scores compared to 16 moderate AAH patients. Both CK18-M65 and CK18-M30 fragments showed clinically relevant levels in AAH patients. The M65:M30 ratios indicated highly increased hepatocyte necrosis in both the moderate and severe AAH patients. In the severe arm patients, CK18-M65 was significantly higher, p=0.027 compared to the moderate arm patients, whereas CK18-M30 was not statistically different between the two arms, p=0.076. CK18-M65 showed a significant association with the AST:ALT ratio in both the moderate and severe arms. MELD did not show any association with the AST:ALT ratio in either the moderate or the severe arm. However, when we modified the MELD score by substituting CK18-M65 for Total Bilirubin (MELD_M65), we found a strong significant association with AST:ALT ratio in the severe arm patients. MELD_M65 also showed a trend toward a significant association with AUDIT scores, p=0.064 in the severe AAH patients, which MELD did not. A highly significant effect (adjusted R^2=0.465, p≤0.0001) was also observed between MELD-M65 and DF Maddrey in moderate and severe arm patients. Our study supports the importance of M65 in assessing liver injury in severe AAH. Further, MELD_M65 provides an alternate benchmark by incorporating mode of hepatocyte death into the assessment of severity, and provides an effective prognostic marker for severe AAH.

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Cause-specific mortality of Japanese patients with type 2 diabetes mellitus - nationwide study

Toshihide Shima[11], Hirofumi Uto[1,14], Kohjiro Ueki[2], Toshinari Takamura[3], Yutaka Kohgo[4,12], Sumio Kawata[5,13], Kohichiroh Yasui[6], Naoto Nakamura[7,15], Kazuo Notsumata[8], Tatsuaki Nakatou[9], Kyoko Sakai[10], Takeshi Okanoue[11]; [1]Digestive and Life-style Related Disease, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan; [2]Diabetes and Metabolic Diseases, Tokyo University Graduate School of Medicine, Tokyo, Japan; [3]Disease Control and Homeostasis, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan; [4]Gastroenterology and Hematology/Oncology, Asahikawa Medical College, Asahikawa, Japan; [5]Gastroenterology, Yamagata University Faculty of Medicine, Yamagata, Japan; [6]Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Kyoto, Japan; [7]Endocrinology and Metabolism, Kyoto Prefectural University of Medicine, Kyoto, Japan; [8]Gastroenterology, Fukui-ken Saiseikai Hospital, Fukui, Japan; [9]Diabetes Center, Okayama Saiseikai General Hospital, Okayama, Japan; [10]Clinical Laboratory, Saiseikai Suita Hospital, Suita, Japan; [11]Gastroenterology and Hepatology, Saiseikai Suita Hospital, Suita, Japan; [12]Gastroenterology Center, International University of Health and Welfare, Ohtawara, Japan; [13]Gastroenterology, Hyogo Prefectural Nishinomiya Hospital, Nishinomiya, Japan; [14]Gastroenterology and Hepatology Center, Miyazaki Medical Center Hospital, Miyazaki, Japan; [15]Diabetes Mellitus, Saiseikai Kyoto Hospital, Nagaokakyo, Japan

Background & Aims: In 2007 Japan Society of Diabetes mellitus (DM) reported that the leading cause of death in DM patients was hepatocellular carcinoma (HCC) among malignancies, whereas lung cancer is the leading cause of death in the general population in Japan. We previously reported the result of the cross-sectional study of causes of liver injuries in 5,642 DM patients (J Gastroenterol 2013; 48:515). Although positive rates of HBsAg (1.7%) and anti-HCV Ab (5.1%) were high in Japanese DM patients, the majority of liver injuries was considered due to NAFLD/NASH. We aimed to clarify the overall and cause-specific mortality of these patients. **Patients and Methods**: Of the 5,642 DM patients who had visited the DM clinics in 9 hospitals belonging to the Japan Study Group of NASH in the original study, 4,006 patients (2,330 males, 1,676 females, mean age: 62.9y.o and 64.6y.o.) were followed. The average duration of follow-up evaluation was 4.5 years. Mortality of Japanese aged 65 – 69 years shown in the database of the Japanese Ministry of Health, Labor and Welfare was defined as mortality of general population (controls). Cause-specific mortality calculated by person-year method was compared between DM patients and general populations. **Results**: 1) Among 4,006 DM patients, total of 248 patients (151 males:M, 97 females:F) died during the follow-up period, and mortality (/100,000 person-year) of DM patients and controls was as follows; total:1,380 vs 953 (p<0.0001), M:1,476 vs 1,371, and F:1,253 vs 565. 2) Case-specific mortality caused by malignancies of DM patients and controls was as follows; total: 810 vs 465 (p<0.0001), M: 811 vs 651, and F: 659 vs 292. Mortality by cardio-vascular disease was; total: 184 vs 189 (p=0.87), M: 186 vs 281, and F: 181 vs 103. Mortality by pneumonia was; total: 189 vs 43 (p<0.0001), M: 225 vs 69, and F: 142 vs 18. 3) Mortality caused by malignancies in DM patients and controls in males was as follows; lung cancer: 166.2 vs 161.5(p=0.90), gastric cancer: 107.6 vs 95.3(p=0.68), colon cancer: 136.9 vs 79.9(p=0.041), pancreas cancer: 58.7 vs 58.2(p=0.98), and HCC: 156.4 vs 60.7(p=0.0001). Mortality in females was as follows; lung cancer: 38.8 vs 43.6(p=0.83), gastric cancer: 116.3 vs 28.3(p<0.0001), colon cancer: 90.4 vs 40.1(p=0.027), pancreas cancer: 103.4 vs 33.9(p=0.0009), and HCC: 129.2 vs 15.8(p<0.0001). **Conclusion**: 1) Mortality of Japanese DM patients caused by malignancies or pneumonia was higher than that of controls, whereas mortality caused by cardiovascular disease of DM patients was comparable to controls. 2) HCC and colon cancer revealed significantly higher mortality in DM patients than controls in both genders.

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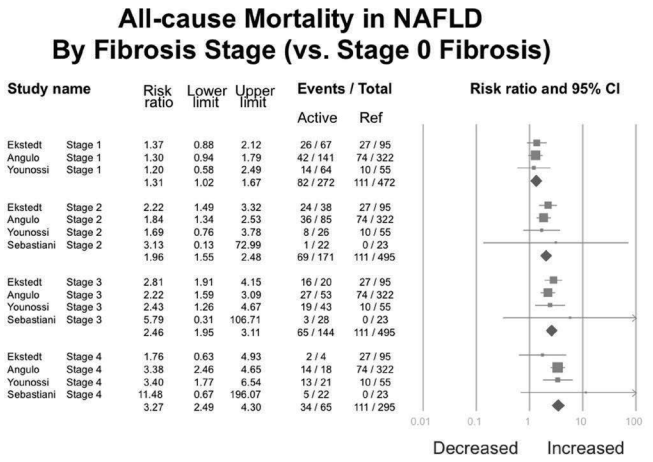
Risk of Mortality by Fibrosis Stage in NAFLD: A Systematic Review and Meta-Analysis

Janki R. Patel[1], Parambir S. Dulai[1,2], Zobair M. Younossi[3], Giada Sebastiani[4], Mattias Ekstedt[5], Hannes Hagström[6], Patrik Nasr[5], Per Stål[6], Stergios Kechagias[5], Rolf W. Hultcrantz[6], Siddharth Singh[1,2], Rohit Loomba[1,2]; [1]NAFLD Research Center, University of California at San Diego, La Jolla, CA; [2]Division of Gastroenterology, Department of Medicine, University of California at San Diego, La Jolla, CA; [3]Center for Liver Disease, Inova Fairfax Hospital, Falls Church, VA; [4]Department of Medicine, McGill University Health Centre, Montreal, QC, Canada; [5]Department of Medical and Health Sciences, Linkoping University, Linkoping, Sweden; [6]Department of Gastroenterology and Hepatology, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden

Background and Aims: Fibrosis is the most important predictor of outcomes in patients with nonalcoholic fatty liver disease (NAFLD). Quantitative risk by fibrosis stage has not been systematically assessed. Through a meta-analysis of published and unpublished data we aimed to quantify the fibrosis stage-specific risk of all-cause mortality among well-characterized NAFLD cohorts. Methods: Through a systematic search of multiple databases and author contact, up to February 2016, we identified 4 adult NAFLD cohort studies that reported all-cause mortality according to fibrosis stage (0-4). All studies used Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) histologic scoring system graded by blinded liver pathologists. Using fibrosis stage 0 as a reference population, fibrosis stage-specific risk ratios (RR) for mortality were estimated. To account for variability in follow-up among cohorts, fibrosis stage-specific mortality rate ratios (MRR) were also calculated. Results: 1200 NAFLD patients (mean age 48.6 years, 48.1% men) were included and the distribution of fibrosis stage 0, 1, 2, 3, and 4 at baseline was 41.3%, 27.0%, 14.3%, 12.0%, and 5.4%, respectively. Compared to NAFLD patients with no fibrosis (stage 0), those with fibrosis were at an increased risk for mortality and this risk was incremental according to fibrosis stage (Fig.1). A similar trend was seen with an incremental increase in the incidence of mortality: stage 1, MRR 1.60 (95% CI 1.19-2.14); stage 2, MRR 2.33 (95% CI 1.61-3.38); stage 3, MRR 3.31 (95% CI 2.43-4.52), and stage 4, MRR 5.74 (95% CI 3.01-10.95). Conclusion: NAFLD patients with fibrosis are at an increased risk for all-cause mortality and this risk is incremental according to fibrosis stage. Furthermore, NAFLD patients are at an increased risk for mortality at early stages of fibrosis and early treatment interventions may be considered in this population.



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Protein Pathway Activation Mapping of Non-alcoholic Steatohepatitis (NASH): The Role Phosphorylation of Proteins Involved in Apoptosis and Collagen Deposition

Zobair M. Younossi[2,1], Azza Karrar[2], Mariaelena Pierobon[3], Maria Stepanova[2], Kianoush Jeiran[3], Alex Hodge[3], Fanny Monge[1], Lakshmi Alaparthi[1], Dinan Abdelatif[1], Aybike Birerdinc[2], Vikas Chandhoke[2,3], Zachary D. Goodman[1], Emanuel F. Petricoin[3]; [1]Center For Liver Disease, Department of Medicine, Inova Fairfax Hospital, Falls Church, VA; [2]Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA; [3]Center for Applied Proteomics and Molecular Medicine, School of Systems Biology, George Mason University, Manasas, VA

Purpose: Hepatic fibrosis in NASH is the consequence of chronic injury potentially leading to cirrhosis. Patients with NASH and hepatic fibrosis are at increased risk for liver-related mortality. Our aim was to use Reverse Phase Protein Microarray (RPPA) based pathway activation mapping of hepatic tissue to uncover potential mechanisms that may be involved in hepatic fibrosis in NASH. **Methods**: Snap frozen hepatic tissue was used from 66 biopsy-proven Non-alcoholic fatty liver disease (NAFLD) patients [64% NASH, 36% with non-NASH NAFLD, and 61% with stage >2 fibrosis]. Proteins were extracted from hepatic tissue as previously described. Quantitative analysis of the activation/phosphorylation state of ~150 key signaling proteins was performed by RPPA. Liver biopsies (H&E and Trichrome Stains) were read by a single hepatopathologist according to NASH protocol. An Image Analysis algorithm was used to quantify the percentage of collagen deposition (% collagen) using Computer Assisted Morphometry (CAM). Phosphoproteins independently associated with fibrosis and NASH were assessed using multiple logistic regression (bi-directional stepwise selection). A p-value of ≤0.05 was considered significant. Pathway analysis was performed using KEGG Pathway mapping. **Results:** Multivariate analysis showed that phosphorylation of growth factor receptor-bound protein2 (GRb2) (p=0.032) and activation of Ephrin intracellular signaling pathway (Ephrin A3) (p=0.008) were independently associated with histologic NASH. The phosphorylated death receptor FAAD S194 (p=0.011) and pro-apoptotic protein BIM posporylation (p=0.013) were negatively associated with both histologic NASH and presence of stage>2 fibrosis. In addition, phosphorylation of Ser-3 of the actin-modulating protein, Cofilin was positively associated with stage>2 fibrosis (p=0.006), while total levels of chromatin regulator, c-Myc (p=0.026) was negatively associated. Additionally, phosphorylation of MEK 1/2 (involved in the focal adhesion, gap junction and regulation of actin cytoskeleton pathways) was negatively associated with presence of any hepatic fibrosis (p=0.0432). Focal adhesion and adherence junction pathways (ErbB2/HER2) were positively associated with collagen quantitation (p=0.01). Finally, phosphorylation of total IL-10 (p=0.0003) activating p38 mitogen activated protein kinases (p38 MAPK T180/Y182) (p<0.0001) were also independently associated with % collagen deposition by CAM. **Conclusion:** There is a strong association of signaling pathways involved in apoptosis and quantitative collagen deposition in histologic NASH. These data may suggest potential mechanistic pathways and treatment targets in NASH.

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Emanuel F. Petricoin - Advisory Committees or Review Panels: Theranostics Health, Inc; Board Membership: Ceres Nanosciences, Inc, Perthera, Inc.; Consulting: Ceres Nanosciences, Inc., Perthera, Inc.; Grant/Research Support: Ceres Nanosciences, Inc; Patent Held/Filed: Theranostics Health, Inc, Ceres Nanosciences, Inc.; Stock Shareholder: Theranostics Health, Inc, Ceres Nanosciences, Inc., Perthera, Inc.

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Identification of early transformations and biochemical changes in patients with NASH by Fourier Transform Infrared spectroscopic imaging

Christine Massie, Vishal Varma, Hari Sreedhar, Grace Guzman, Michael J. Walsh, Natalia Nieto; University of Illinois at Chicago, Chicago, IL

Background: Nonalcoholic fatty liver disease is associated with excessive fat accumulation in the liver and can progress to non-alcoholic steatohepatitis (NASH) defined by histologic hallmarks such as inflammation, cell death and fibrosis. Histologically, NASH is rather similar to alcohol-induced steatohepatitis. Liver biopsy is considered necessary to diagnose NASH and the presence of fibrosis typically predicts patient outcome. In the US, more than 12% of the population has NASH and approximately 2.7% has advanced liver fibrosis due to the disease. Thus, early diagnosis is crucial. ***Methods & Results:*** The liver microenvironment is chemically and morphologically modified during disease progression depending on disease etiology. Biochemical changes within the liver milieu and in cells due to liver injury during NASH progression are relatively poorly defined. Fourier Transform Infrared (FT-IR) spectroscopic imaging is an emerging approach to obtain detailed images that have associated biochemical information. FT-IR imaging of tissue is based on the principle that different regions of the mid-IR are absorbed by different chemical bonds (e.g., C=O, C-H, N-H) within cells or tissue that can then be related to the presence and composition of biomolecules (e.g., lipids, DNA, glycogen, proteins, collagen). In an FT-IR image, every pixel within the image comprises an entire IR spectrum that can give information on the biochemical status of the cells that can then be exploited for cell-type or disease-type classification. In this

study, we used FT-IR spectroscopic imaging to examine early transformations as well as biochemical changes in 70 patients with NASH during progression from stages I to IV. Our findings indicate that the biochemistry of stages I and II were distinctly different and could be classified perfectly based on their IR signature using multivariate analysis. Samples from patients with stages III or IV were also found to be biochemically different from patients with stages I or II. Currently, we are focusing on refining the classification to extract biochemistry from the regions of fibrosis, steatosis and inflammation to improve the classification among the four stages and determine the precise biomolecular changes that occur or could occur. ***Conclusion:*** FT-IR imaging holds exciting applications as a novel way to obtain biochemical information from cells and tissue in an entirely label-free non-perturbing route towards giving new insight into biomolecular changes that take place as part of NASH progression. This biochemical information can potentially allow for objective and automated analysis of certain aspects of NASH diagnosis and prognosis.

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Effects of dapagliflozin, a sodium-glucose co-transporter 2 inhibitor, and free omega-3 carboxylic acids on liver steatosis and hepatocyte damage biomarkers in Type 2 diabetes patients with non-alcoholic fatty liver disease

Jan Oscarsson[1], Per Lundkvist[2], Per-Anders E. Jansson[3], Lars Johansson[4], Mats Kvarnström[1], Linda Moris[5], Ulf Risérus[2], Lars Lind[2], Jan W. Eriksson[2]; [1]AstraZeneca R&D, Mölndal, Sweden; [2]Uppsala University, Uppsala, Sweden; [3]University of Gothenburg, Gothenburg, Sweden; [4]Antaros Medical AB, Gothenburg, Sweden; [5]Karolinska Trial Alliance, Stockholm, Sweden

Study purpose: The primary aim of the study was to investigate the effects of dapagliflozin (DAPA) and free omega-3 fatty acid carboxylic acids (OM-3 CA) alone and in combination on liver fat content in overweight type 2 diabetes (T2D) patients with non-alcoholic fatty liver disease (NAFLD). Methods: T2D patients with BMI >25 kg/m^2, liver fat >5.5 % on stable metformin and/or sulfonylurea treatment were randomized to placebo (n=21), 10 mg DAPA OD (n=21), 4 g OM-3 CA OD (n=20) or the combination of DAPA and OM-3 CA (n=22) in a 12 week parallel group, double blind study. 75 patients completed the study. Investigations at baseline and week 12 included abdominal MRI for liver and adipose tissue fat content assessment and a 75 g oral glucose tolerance test (OGTT). The full analysis set was used for statistics and all relative changes were calculated as geometric mean ratio. Results: The full analysis set, n=84, had a mean(SD) age of 65.5(5.9) years, BMI of 31.2(3.5) kg/m^2 and 59% were males. Mean liver fat% was 18(9.3)%. All active treatments significantly reduced liver fat% from baseline. The relative reduction in liver fat% for the combination (DAPA+OM-3 CA) was significant (-21%, adjusted p=0.046), but not significant for DAPA (-13%) or OM-3 CA (-15%) alone, as compared to placebo (-3%). Total liver fat volume (L) changed similarly to liver fat% suggesting that the change in liver fat% was not secondary to changed hepatic water volume. Both DAPA and DAPA+OM-3 CA significantly reduced body weight and abdominal subcutaneous and visceral fat volume as well as improved glucose control, including fasting glucose and 2h glucose during OGTT. Hepatocyte damage biomarkers (AST, ALT, CK-18 (M30 and M65) and gGT) were reduced by DAPA, but not by OM-3 CA or DAPA+OM-3 CA. All adverse events were mild or moderate in intensity and as expected from previous studies with these treatments. Two patients (one in the DAPA group and one in the placebo group) experienced a severe adverse event, which were assessed by the investigators as unlikely to be caused by the investigated drugs. Conclusions: The combination of DAPA and OM-3 CA resulted in a significant reduction in percentage and total liver fat, while the monotherapies resulted in numerically smaller and non-significant reductions. DAPA had unique effects on measures of hepatocyte injury, which was not evident in the combination group indicating that effects on liver fat reduction and hepatocyte damage biomarkers are not necessarily associated. This study suggests beneficial effects of SGLT2 inhibition alone or in combination with OM-3 CA on NAFLD in type 2 diabetes.

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Mats Kvarnström - Employment: AstraZeneca

Ulf Risérus - Consulting: Astra Zeneca

Lars Lind - Consulting: AstraZeneca

Jan W. Eriksson - Advisory Committees or Review Panels: NovoNordisk; Consulting: Merck Sharp and Dohme, Sanofi; Grant/Research Support: Bristol Myers Squibb, AstraZeneca; Speaking and Teaching: NovoNordisk, AstraZeneca

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Advanced fibrosis is independently associated with impaired kidney function in biopsy-proven NAFLD. Results of a multicenter cross-sectional study

Eduardo Vilar-Gomez[7,8], Rocío Aller[2], Rocío Gallego-Durán[7], Helena Pastor- Ramírez[7], Jesús Bañales[3], Maria Teresa Arias-Loste[23], Carmelo García-Monzón[1], María Luisa García-Torres[4], Víctor Aguilar-Urbano[21], Javier Salmeron[6], Jose L. Olcoz-Goñi[9], Judith Gomez-Camarero[5], Jose L. Calleja[10], Javier Abad[10], Agustin Albillos[11], Oreste Lo Iacono[12], Ruben Frances[13], Moises Diago[14], Conrado M. Fernández-Rodríguez[15], Javier García-Samaniego[16], Juan Caballeria[17], Salvador Benlloch[18], Juan Turnes[19], Raul J. Andrade[22], Luis C. Bertot[20], Javier Ampuero[7], Leon A. Adams[20], Manuel Romero-Gomez[7]; [1]Hospital Universitario Santa Cristina, Madrid, Spain; [2]Hospital Clínico Universitario de Valladolid, Vallodolid, Spain; [3]Instituto de Investigación Sanitaria Biodonostia, San Sebastián, Spain; [4]Hospital Clínico Universitario de Valencia, Valencia, Spain; [5]Hospital Universitario de Burgos, Burgos, Spain; [6]Hospital Universitario San Cecilio, Granada, Spain; [7]Instituto de Biomedicina de Sevilla (IBiS), UGC Aparato Digestivo Intercentros Hospitales Universitarios Virgen Macarena-Virgen del Rocío, CIBERehd., Seville, Spain; [8]Hepatology, National Institute of Gastroenterology, Havana, Cuba; [9]Hospital Universitario de León, Leon, Spain; [10]Hospital Puerta de Hierro, Madrid, Spain; [11]Hospital Universitario Ramón y Cajal, Madrid, Spain; [12]Hospital del Tajo, Aranjuez, Spain; [13]Hospital del Alicante, Alicante, Spain; [14]Hospital General Universitario, Valencia, Spain; [15]Hospital Universitario. Fundación Alcorcón, Madrid, Spain; [16]Hospital Universitario La Paz, Madrid, Spain; [17]Hospital Provincial Clinic de Barcelona, Barcelona, Spain; [18]Hospital La Fe, Valencia, Spain; [19]Complejo Hospitalario Universitario de Pontevedra, Pontevedra, Spain; [20]University of Western Australia, Perth, WA, Australia; [21]Hospital Costa del Sol, Málaga, Spain; [22]Hospital Universitario Virgen de la Victoria, Málaga, Spain; [23]Hospital Universitario Marqués de Valdecillas, Santander, Spain

Background: Although there is growing evidence that patients with nonalcoholic fatty liver disease (NAFLD) or steatohepatitis (NASH) have an increased prevalence/incidence of chronic

kidney disease (CKD), the relationship between reduced kidney function and histological features of patients with biopsy-proven NAFLD has not been fully elucidated. **Methods:** A total 1459 adult patients with biopsy-proven NAFLD from 33 centers in 3 countries [Spain (821 patients), Australia (245 patients) and Cuba (393 patients)] were consecutively enrolled. Biopsies were reviewed by local pathologists and scored using the NASH-CRN scoring system and fibrosis (F) stages (0-4) and subsequently classified as NAFL or NASH (combined presence of steatosis, ballooning and lobular inflammation). This study did not include patients with decompensated cirrhosis. Kidney function was assessed through CKD-EPI estimated glomerular filtration rate (eGFR) formula and CKD was defined as eGFR less than 60 ml/min/1.73 m^2. **Results:** Kidney function assessed by eGFR (ml/min/1.73 m^2) was not significantly different among patients with NAFL (n=536) (95.1 ± 17.9 ml), NASH-F0 (n=338) (95.5 ± 16.7), NASH-F1 (n=178) (95.8 ± 16.6) and NASH-F2 (n=190) (94.3 ± 16.7). However, eGFR was lower in NASH patients with advanced fibrosis (n=150 for F3, 84.5 ± 22.1; n=67 for F4, 84.9 ± 20.9), P<0.001 for ANOVA with Bonferroni adjustments. Likewise, a higher proportion of subjects with advanced fibrosis (27/217, 12%) had an eGFR of <60 ml/min/1.73 m^2 as compared with patients without advanced fibrosis (36/1242, 3%), P<0.01. After adjusting for confounding factors (BMI, diabetes, smoking, age, gender, insulin resistance, components of the metabolic syndrome and concomitant medications for comorbidities), the presence of advanced fibrosis remained as an independent predictor of decreased eGFR (β= -0.21, P<0.01) or eGFR <60 (OR: 3.6, 95% CI: 2.1-6.3, P<0.01). Non-invasive biomarkers of fibrosis including NAFLD fibrosis score (NFS, r= -0.27, P<0.01) and FIB-4 score (r= -0.22, P<0.01) were strongly related to eGFR. Patients with a NFS of >0.675 (n=229) had lower eGFR (87.2 ± 18.9 ml) as compared to those with NFS of <-1.455 (n=632) (97.9 ± 17.8 ml), P<0.01. Similarly, eGFR was decreased in patients with a FIB-4 of >2.67 (n=91) (83.1 ± 19.5 ml) as compared to those with a FIB-4 <1.30 (n=1023) (96.5 ± 18.1 ml), P<0.01. **Conclusions:** In biopsy-proven NAFLD patients, only advanced fibrosis was strongly associated with either decreasing eGFR or presence of CKD determined by an eGFR <60 ml/min/1.73 m^2, irrespective of well-known risk factors as obesity, diabetes and components of metabolic syndrome.

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Javier García-Samaniego - Consulting: Bristol-Myers-Squibb, Gilead, Janssen, Abbvie

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Transient Elastography in combination with clinical markers (BARD Score, FIB-4, NFS) can be useful in predicting the presence or absence of advanced fibrosis in patients with Non Alcoholic Fatty Liver Disease

Amreen Dinani, Rachel Jeffers, Arifa Toor, Rolland C. Dickson; Gastroenterology and Hepatology, Dartmouth Hitchcock Medical Center, Lebanon, NH

Background: Nonalcoholic fatty liver disease (NAFLD) is increasing in prevalence and may soon be the major cause of end stage liver disease. Nonivasive strategies to define fibrosis stage will be important for disease management. The aim of our study was to determine the utility of transient elastography (TE) either alone or in combination with clinical markers to assess fibrosis stage. Methods: The electronic medical records of all patients with a diagnosis of NAFLD/NASH undergoing TE from May 2014 to December 2015 at a single institution were reviewed. Patients were included if they had reliable liver stiffness measurements (LSMs) and an adequate liver biopsy sample (> 2.5cm) within 3 years of TE. LSMs were used to divide patients into two groups: advanced fibrosis (≥F3) and absence of advanced fibrosis (<F3). Clinical markers: BARD score, FIB-4 and NFS were calculated in this sub-population and combined with LSM and compared to liver biopsy to determine fibrosis stage. Results: 49 patients with the diagnosis of NASH/NAFLD had reliable LSMs and a liver biopsy were included in our study. LSMs were consistent with <F3 fibrosis in 25/49 and ≥F3 in 24/49. Fibroscan when used alone accurately predictive fibrosis stage in 86% (42/49) of patients, 20/25 with <F3 and 22/24 ≥F3. There was no difference in the predictive value of any of the individual non-invasive markers of fibrosis and no marker had increased positive predictive value or negative predictive value. LSM and all three clinical markers correlated for fibrosis stage in 33% (16/49), liver fibrosis was accurately predicted in all cases, <F3 (9/9), ≥F3 (7/7). The presence of 2/3 markers correlating with TE led to accurate predicition in those with <F3 (11/13), (1 patient lost >50lbs before liver biopsy). For ≥F3 fibrosis the addition of 1 or 2 clinical markers did not improve accurately of TE. Conclusions: TE is a valuable tool to detect or exclude the presence of advanced fibrosis in NAFLD/NASH patients. Addition of calculated clinical markers further increases the accuracy of TE. When there is discrepancy between TE and ≥2 clinical markers in <F3 fibrosis, liver biopsy should be considered. Prospective, larger studies utilizing TE, clinical markers and liver biopsy are required to confirm these results.

Transient Elastography	BARD Score/FIB-4/NFS	Accuracy of Liver Biopsy
Less than F3	Total	80% (20/25)
< F3	3 Markers correlate	100% (9/9)
< F3	2 Markers correlate	85% (11/13)
< F3	Less than 2 markers correlate	0% (0/3)
< F3	Total	92% (22/24)
≥F3	3 Markers correlate	100% (7/7)
≥F3	Less than 3 markers correlate	88% (15/17)

Disclosures:

Rolland C. Dickson - Advisory Committees or Review Panels: Gilead, BMS

The following people have nothing to disclose: Amreen Dinani, Rachel Jeffers, Arifa Toor

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Free triiodothyronine as determinant of non-alcoholic fatty liver disease in euthyroid subjects: the LifeLines Cohort Study

Eline van den Berg[1], Lynnda van Tienhoven-Wind[2], Marzyeh Amini[3], Behrooz Z. Alizadeh[3,1], Tim C.M.A. Schreuder[1], Klaas Nico Faber[1], H Blokzijl[1], Robin P.F. Dullaart[2]; [1]Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, Netherlands; [2]Endocrinology, University Medical Center Groningen, Groningen, Netherlands; [3]Epidemiology, University Medical Center Groningen, Groningen, Netherlands

Background: Non-alcoholic fatty live disease (NAFLD) is becoming the leading cause of chronic liver disease in de Western world. The liver plays a crucial role in the metabolism of cholesterol and triglycerides and thyroid hormones interact on hepatic lipid homeostasis. Given the importance of variations in thyroid function within the euthyroid range for a considerable number of health issues, including (subclinical) atherosclerosis and biochemical markers of increased cardiovascular risk, it is relevant to examine the relationship of NAFLD with thyroid function parameters in an euthyroid population. **Methods:** The study was conducted in the LifeLines Cohort Study (N=167,729), a population-based cohort study examining the health and health-related behaviors of participants living in the North of The Netherlands. Only euthyroid subjects (TSH 0.5-4.0 mU/L, FT4 11-19.5 pmol/L and FT3 4.4-6.7 pmol/L) older than 18 years were included. Exclusion criteria were participants with missing data, excessive alcohol use, known hepatitis or cirrhosis, liver functions ≥ three times the upper limit, current cancer, non-white ancestry, previous or current use of thyroid medication and current use of lipid and glucose lowering medication. A priori defined liver biochemistry, thyroid function parameters and metabolic syndrome (MetS) were studied. NAFLD was defined by using the validated Fatty Liver Index (FLI); FLI ≥60 was categorized as NAFLD. A $p<0.01$ was considered significant. **Results:** Out of 20,289 participants, a FLI ≥60 was found in 4,274 (21.1%) individuals (62.1% men, median age 46 years). Participants with FLI ≥60 had higher ALT, AST, ALP, GGT values and higher prevalence of MetS (46.7% vs. 4.2%, $p<10^{-50}$). In age- and sex-adjusted analysis FLI ≥60 was independently predicted by a higher FT3 (OR 1.34, 95% CI 1.29-1.39, per SD increment, $p<10^{-48}$) and a lower FT4 (OR 0.73, 95% CI 0.70-0.75, $p<10^{-63}$) but not by TSH. The strongest association was found for the FT3/FT4 ratio (OR 1.41, 95% CI 1.39-1.49, $p<10^{-92}$). These associations remained similar after additional adjustment for the presence of MetS (OR 17.9, 95%CI 16.2-19.8, $p<10^{-400}$). In subjects with enlarged waist circumference TSH and FT4 were lower but FT3 was higher, resulting in a higher FT3/FT4 ratio ($p<10^{-46}$). **Conclusion:** In this large cross-sectional study of 20,289 participants, we discovered that euthyroid people with suspected NAFLD are characterized by a higher FT3/FT4 ratio, probably secondary to central obesity.

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1102

Non-alcoholic fatty liver disease related cirrhosis is frequently an incidental diagnosis.

Luis C. Bertot[1], Gary P. Jeffrey[1,2], Gerry C. MacQuillan[1,2], George Garas[1,2], Michael C. Wallace[1,2], Leon A. Adams[1,2]; [1]School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia; [2]Department of Hepatology, Sir Charles Gairdner Hospital, Perth, WA, Australia

Background /Aim: Determination of the presence of cirrhosis in non-alcoholic fatty liver disease (NAFLD) is important as it alters prognosis and mandates screening for hepatocellular carcinoma (HCC). We sought to determine in a cohort of patients with NAFLD related cirrhosis, whether cirrhosis had been discovered incidentally or had been diagnosed by intent and whether patients had been screened for HCC. **Methods**: Patients with NAFLD cirrhosis seen at a tertiary academic centre had medical records reviewed to determine; mode of cirrhosis diagnosis (incidental or by intent), specialty of diagnostician, and evidence of previous clinical, imaging or laboratory features of unrecognized cirrhosis. **Results:** Of 100 NAFLD related cirrhosis patients (mean age 66 years, 62% male), the majority (n=66) were discovered incidentally and the majority of these (74%) had their NAFLD diagnosed at the same time of cirrhosis diagnosis. Incidental diagnosis was most commonly made on imaging performed for reasons unrelated to liver disease (n=21, 32%), following liver tests performed for reasons unrelated to NAFLD or liver disease (n=17, 26%), following incidental finding of varices on endoscopy (n=14, 21%), unexpected finding at surgery (n=9, 14%) or other (n=5, 8%). By intent diagnosis were predominantly made by gastroenterologists/hepatologists (27/34 patients) whereas general practitioners, surgeons and physicians were more likely to diagnose cirrhosis incidentally (p<0.001). A high proportion of patients who were diagnosed incidentally (n=48/66, 73 %) had previous evidence of cirrhosis (unexplained thrombocytopenia or splenomegaly) during previous outpatient clinic review or hospitalization, although no patient had undergone non-invasive fibrosis testing. When calculated retrospectively, the majority had high non-invasive scores prior to the diagnosis (81% had Hepascore >0.84 and NAFLD Fibrosis Score >0.676, 80% had FIB-4 >1.5.) Thirty-nine of the total cohort were diagnosed with HCC, half of whom had not received previous screening. Patients not in a HCC screening program were more likely to have a higher BCLC stage than those in a screening program (Stage C, 52% vs. 20%, p=0.01) **Conclusions:** The majority of NAFLD cirrhosis patients are diagnosed incidentally despite prior clinical and biochemical evidence. Screening with non-invasive fibrosis markers is not done outside specialty clinics but would detect 80% of these patients. Screening of HCC in NAFLD cirrhotics is associated with a lower BCLC stage at time of diagnosis. Increased awareness of screening for cirrhosis and HCC is needed in patients with NAFLD.

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♦ Denotes AASLD Presidential Poster of Distinction

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Progression of liver fibrosis in NAFLD relates to arteriosclerosis and chronic kidney disease

Yoshihito Kubotsu[1,3], Hirokazu Takahashi[1], Yoichiro Kitajima[3], Satoshi Oeda[2], Keizo Anzai[1], Yuichiro Eguchi[2]; [1]Department of Metabolism and Endocrinology, Faculty of Medicine, Saga University, Saga, Japan; [2]Liver Center, Saga University Faculty of Medicine, Saga, Japan; [3]Clinical Gastroenterology, Eguchi Hospital, Ogi, Japan

Background and aims: Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are manifestations of the metabolic syndrome, associated with arteriosclerosis (AS) and increased risk of vascular disease such as stroke, cardiovascular disease and chronic kidney disease (CKD); however, impact of liver fibrosis on AS and CKD in NAFLD/NASH is not wholly understood. We aimed to clarify the relationship between the progression of liver fibrosis, AS and CKD in NAFLD . Methods: A total of 105 NAFLD patients (male; n = 53, 23-81 years: female; n = 52, 24-73 years) diagnosed by ultrasonography were enrolled in the cross-sectional study. AS and CKD was evaluated by baPWV (brachial-ankle Pulse Wave Velocity) and eGFR (estimated Glomerular Filtration Rate). Liver fibrosis was estimated by Fib-4 index (low cut-off index = 1.30) and categolized as group L (Fib-4 ≤ 1.3; NAFL but non-NASH) or group H (1.3 < Fib-4; NASH with a possible progressed fibrosis) accordingly. Effect of liver fibrosis on baPWV and eGFR was examined by multiple logistic regression analysis. Result: Fib-4 index is positively correlated to baPWV ($r = 0.43$, $p < 0.001$) and negatively correlated to eGFR ($r = -0.43$, $p < 0.001$). baPWV of group H (n = 39) was significantly higher and eGFR was significantly lower than group L (n = 66) (baPWV; 1557 cm/sec and 1308 cm/sec, $p < 0.001$: eGFR; 67.9 ml/min/1.73m^2 and 88.5 ml/min/1.73m^2, $p < 0.001$). Multivariate analysis indicated that group H was a significant risk for increasing baPWV and decreasing eGFR independent from age, diabetes (DM) and obesity (baPWV; odds ratio = 4.07, $p < 0.05$ and eGFR; odds ratio = 8.85, $p < 0.01$). Furthermore, DM and liver fibrosis additively increased the risk for AS (group L/DM+; odds ratio = 22.8, $p < 0.01$: group H/DM-; odds ratio = 26.6, $p < 0.01$: group H/DM+; odds ratio = 33.0, $p < 0.01$). Conclusion: The progression of liver fibrosis in NAFLD is a significant risk for AS and CKD, and affects a severity of AS and CKD. AS and CKD should be carefully monitored in NAFLD regardless of comorbid diabetes.

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1104

High risk populations: Attitudes to NAFLD among Diabetologists

Thomas Marjot[1], Emilia Sbardella[1], Jonathan Hazlehurst[1], Ahmad Moolla[1], Jeremy Cobbold[2], Jeremy Tomlinson[1]; [1]Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, United Kingdom; [2]Department of Gastroenterology and Hepatology, University of Oxford, Oxford, United Kingdom

INTRODUCTION Non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2DM) are common conditions that regularly coexist and can act synergistically to drive adverse outcomes. The prevalence of NAFLD in T2DM is 70%, with 16% having evidence of advanced hepatic fibrosis. There is accumulating evidence for a role of screening for NAFLD +/- fibrosis in diabetic populations. **AIMS** Our study therefore had 3 aims: Firstly, to define the attitudes and current clinical practice of diabetes specialists towards NAFLD across the UK. Secondly, to implement an evidenced-based pathway for the assessment of NAFLD in patients attending diabetes outpatient clinics and finally, to assess the impact of a multidisciplinary approach (with combined hepatology and diabetes input) to their clinical management. **MATERIALS AND METHODS** An online survey was disseminated to diabetologists across the UK. Based on findings from this survey, all diabetic patients attending outpatient clinics at Oxford University Hospitals were screened for advanced fibrosis using a Fib-4 score. Those with elevated scores may then benefit from referral to the multidisciplinary metabolic hepatology clinic. **RESULTS** 116 diabetes specialists responded to the survey. Only 4.5% of responders correctly judged the prevalence of NAFLD in diabetic patients to be >50%. Even fewer (1.5%) correctly judged the prevalence of advanced fibrotic disease to be >15%. Whilst most diabetologists performed liver function tests, the vast majority (68%) had not used any non-invasive scoring system to assess risk of advanced disease within the last 12 months. For 20% of responders, a diagnosis of NAFLD did not affect their approach to management. In light of these findings, a local 'think NAFLD' campaign was launched to educate diabetologists on the assessment, risk and impact of NAFLD in patients with diabetes. In the subsequent 3 months 188 patients attending diabetic clinics were screened for advanced fibrosis using Fib-4. 16% of those screened had an elevated Fib-4. Data has been analyzed from >90 patients attending the multidisciplinary clinic. After 6 months follow up weight reduced by 3% (p=0.0003), ALT by 29% (p=0.0008) and HbA1c by 6.5mmol/mol (p=0.0006). **CONCLUSIONS** Amongst diabetologists, there remains limited awareness of the prevalence and severity of NAFLD in the patients they treat. Fib-4 score can easily be used in clinical practice to identify patients at risk of advanced fibrosis who are likely to benefit from a dedicated multidisciplinary approach to their management.

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Improvement in Non-Invasive Hepatic Parameters of Nonalcoholic Fatty Liver Disease in Obese Uncontrolled Type 2 Diabetes Mellitus Patients who underwent Endoscopic Duodenal–Jejunal Bypass Liner (Endobarrier) Implantation

Oranit Cohen-Ezra[1], Gabriella Segal-Lieberman[2], Alon Lang[3], Yeroham Kleinbaum[4], Yael Inbar[4], Sima Katsherginsky[4], Keren Tsaraf[1], Ziv Ben Ari[1]; [1]Liver Disease Center, Sheba Medical Center, Ramat Gan, Israel, Kadima, Israel; [2]endocrine institute, sheba medical center, Ramat Gan, Israel; [3]gastroenterology institute, sheba medical center, Ramat Gan, Israel; [4]radiology department, sheba medical center, Ramat Gan, Israel

Nonalcoholic fatty liver disease (NAFLD), the most common cause of chronic liver disease in Western countries, may progress to cirrhosis, liver failure, and complicated hepatocellular carcinoma**.** Recently, a nonsurgical bariatric technique, the Endobarrier (GI Dynamics), an endoscopically-delivered device that mimics gastric bypass surgery by shielding the duodenum and upper jejunum from contact with chyme was reported to lead to significant weight loss and to rapid improvement of type 2 diabetes, both conditions are important risk factors for NAFLD. We therefore investigated the effect of Endobarrier treatment on non-invasive hepatic parameters in obese uncontrolled T2DM patients with NAFLD. The Endobarrier device was

implanted for 12 months in the duodenum via an endoscopic procedure in 46 uncontrolled diabetic, obese, NAFLD subjects (age 52±9y, 52.17% male, BMI 37.6±9.2 m^2/kg). BMI, waist circumference, serum liver enzyme levels, glucose, HBA1c and lipid profile were performed as well as shear wave elastography (SWE) (Aixplorer SuperSonic Imagine, France) and Fibromax (FibroTest, ActiTest, SteatoTest, and NashTest) (BioPredictive, France) for the noninvasive evaluation of hepatic injury. By 3, 6 and 12 months following the Endobarrier implantation, the BMI, waist circumference, serum liver enzyme levels, glucose, HBA1c, lipid profile and the fibrosis stage (SWE and Fibromax) decreased significantly from baseline. In addition, the ActivityTest, SteatoTest (fat liver content), and NashTest (steatohepatitis score) (Fibromax) improved significantly from baseline by 6 month after the Endobarrier removal. In 10 subjects (22%) the Endobarrier was endoscopically explanted earlier due to side effects**. Conclusion:** Endobarrier, a minimally invasive bariatric technique, achieved significant improvement in hepatic fat liver content, steatohepatitis score and fibrosis stage in uncontrolled obese, diabetic, NAFLD patients. This device may be suitable for the treatment of morbid obesity and its related comorbidities including NAFLD.

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1106
Fibrosis in adipose tissue is associated with liver damage and fibrosis in NAFLD

Anna-Sophia Leven[1], Martin Schlattjan[1], Jan-Peter Sowa[1], Till Hasenberg[2], Lars Bechmann[1], Guido Gerken[1], Ali Canbay[1]; [1]Department of Gastroenterology and Hepatology, University Hospital Essen, Essen, Germany; [2]Department of General and Visceral Surgery, Alfried Krupp Krankenhaus, Essen, Germany

Background and Aims: Fibrosis occurs in different organs and is associated with damage. In non-alcoholic fatty liver disease (NAFLD), liver fibrosis is also a sign for progression. Adipose tissue seems to play an important role in the progression of NAFLD, but the contribution of adipose tissue fibrosis is unclear. The aim of our study was: (i) to check if adipose tissue in obesity exhibits fibrosis, (ii) if fibrosis in adipose tissue correlates with liver damage and fibrosis and (iii) autophagy in adipose tissue is associated with fibrosis in adipose tissue. **Methods:** Blood, visceral adipose and liver tissue samples were obtained from 62 (mean age: 43+/-10 y. w:45 / m:17) morbidly obese patients undergoing bariatric surgery. Fibrosis was assessed by Sirius Red staining in adipose and liver tissue. mRNA expression of genes related to fibrosis (collagen) and autophagy (ATG5, LC3, Beclin) were measured in adipose and liver tissue by qrt-PCR. ATG 5 staining in adipose tissue was performed by immunohistochemistry and quantitatively analyzed. Blood samples were analyzed for routine parameters and surrogate markers of apoptosis and cell death (M30, M65) by ELISA. **Results:** Increased fibrosis was observed by Sirius red and collagen expression was significantly upregulated ($p < 0.0001$) in adipose tissue of morbidly obese patients compared to controls. mRNA levels of LC3 and Beclin were significantly increased in adipose tissue of obese patients compared to controls (LC3 $p < 0.02$; Beclin $p < 0.05$). In addition the amount of ATG5-positive cells in adipose tissue was significantly correlated with fibrosis in adipose tissue. Significant correlations were also found between adipose tissue fibrosis and serum M30 as well as expression of autophagy related genes in adipose tissue. Autophagy related gene expression in liver and adipose tissue was also correlated. **Conclusions:** Morbid obesity leads to fibrosis in adipose tissue, which is associated to elevated expression of autophagy related genes. Moreover, autophagy in adipose tissue and liver tissue are correlated, implicating a possible common signalling axis leading to increased autophagic processes in different tissues. The underlying mechanisms need further characterization.

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1107
A non-bile acid intestine-selective FXR agonist reduces liver steatosis in mice

Helene Baribault, Jianhua Chao, Kenji Kozuka, I-Hsin Hsu, Limin He, Padmapriya Kumaraswamy, Matthew Siegel, Ying He, Baoming Nie, Samantha Koo-McCoy, Christopher Carreras, Qumber Jafri, Christine Dowd, Patricia Finn, Jason Lewis, Rakesh Jain, Andrew King, Jeremy S. Caldwell; Ardelyx, Inc., Fremont, CA

The Farnesoid X Receptor (FXR) is a nuclear receptor activated directly by bile acids. FXR is expressed at high levels in liver and intestine and plays a central role in the regulation of bile and lipid homeostasis. Obeticholic acid (OCA), a systemic, semi-synthetic bile acid FXR agonist, has recently been approved by the FDA for the treatment of primary biliary cirrhosis and has demonstrated beneficial effects in patients with nonalcoholic steatohepatitis (NASH); however, treatment was associated with adverse effects particularly pruritus and elevated LDL-cholesterol. Intestine-selective FXR agonists potentially offer therapeutic efficacy with improved safety profiles. To test this we recently discovered a novel, orally active, non-bile acid and intestine-selective FXR agonist, NTX023-1. Pharmacokinetic studies of NTX023-1 in peripheral circulation, portal vein, bile, gut tissue and feces supported its intestine-selective profile. NTX023-1 activated FXR target gene expression in the intestine, including FGF15, but had minimal effect on FXR target gene expression in the liver, including OSTbeta. In contrast, systemic FXR agonists OCA and Px102 globally activated FXR target genes including those in the intestine and liver. To evaluate the effects of NTX023-1 on hepatic steatosis, mice (n=10 per group) fed a western diet (WD) for 8 weeks were treated with vehicle, Px102 (30 mg/kg QD) or NTX023-1 (30 mg/kg QD or BID) for 6 weeks. WD feeding significantly increased serum and liver cholesterol (2-fold, $p<0.0001$) and liver triglycerides (4-fold, $p<0.0001$) compared with mice fed standard chow. NTX023-1 (QD or BID) and Px-102 (QD) normalized serum cholesterol, liver triglycerides and liver cholesterol content to levels comparable with those observed in mice fed standard chow. Consistent with these biochemical changes, histopathological analysis showed improvement in the macrovesicular steatosis score from 4.0 with vehicle treatment down to 1.4 ($p<0.0001$) with NTX023-1 (BID) and 2.1 ($p<0.01$) with Px-102 (QD). The efficacy of NTX023-1 appeared to be mediated primarily by the intestine as indicated by minimal increases in serum ALP, an FXR target gene product, whereas Px102 markedly increased serum ALP levels. All treatments with NTX023-1 (QD and BID) and Px-102 (QD) lowered serum bile acid levels. These results suggest that an intestine-selective FXR agonist could be useful in the treatment of hepatosteatosis in NASH patients.

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Matthew Siegel - Employment: Ardelyx

Christopher Carreras - Employment: Ardelyx; Stock Shareholder: Ardelyx

Qumber Jafri - Employment: Ardelyx Inc.

Christine Dowd - Employment: Ardelyx

Jason Lewis - Employment: Ardelyx; Management Position: Ardelyx; Stock Shareholder: Ardelyx

Andrew King - Employment: Ardelyx

Jeremy S. Caldwell - Employment: Ardelyx, Inc.

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1108
A non-invasive lipidomic test accurately discriminates NASH from steatosis and tracks evolution of the disease

Miriam Perez-Cormenzana[1], M Concepción García[3], Beatriz Antolin[3], Natalia Mora[3], Ibon Martinez-Arranz[1], De luis D. Román[2], Cristina Alonso[1], Rocío Aller[3,2]; [1]OWL, Derio, Spain; [2]Institute of Endocrinology and Nutrition, Medicine School and Department of Endocrinology and Nutrition, Hospital Clínico Universitario, University of Valladolid, Valladolid, Spain; [3]Department of Digestive Disease, Hospital Clínico Universitario, University of Valladolid, Valladolid, Spain

BACKGROUND: Nonalcoholic fatty liver disease (NAFLD) includes a spectrum of histological phenotypes including steatosis, steatohepatitis (NASH) and fibrosis. While liver biopsy is the reference for diagnosis, it is invasive and associated with procedural risks and sampling variability. Thus, there is urgent need for a noninvasive and robust diagnostic procedure. Recently, we have described a serum-based lipidomic signature associated with NAFLD able to fulfill these unmet clinical diagnostic needs by: (1) differentiating NAFLD from healthy cohort, (2) discriminating between steatosis and NASH. AIMS: To validate this non-invasive assay in NAFLD diagnosis using blind-histology as a reference standard and then apply these test in the follow-up of the patients. METHODS: Thirty patients were enrolled as a blind, biopsy-proven NAFLD cohort, collecting the serum samples at the time of liver biopsy. Metabolic syndrome was assessed based on the presence of at least three of the conditions listed by the NCEP ATPIII. Patients were prescribed a hypocaloric diet (1500kcal/day) and aerobic exercise (30-60min/day), monitored for 2 to 5 years, at which point a new serum sample was collected. The lipidomic test was established on the basis of 467 biopsy-proven patients (controls=90; steatosis=246; NASH=131) and two BMI-dependent logistic regression algorithms: 1) discriminating between NAFLD and healthy liver (assay name: OWLiver Care) and 2) between NASH and steatosis (OWLiver). The diagnostic performances of both assays were assessed by area under the ROC curve, positive and negative predictive values: 1) 0.90±0.02, 0.89 and 0.88, respectively; 2) 0.95±0.01, 0.89 and 0.90. RESULTS: Applied to the independent biopsy-proven cohort (46±12years, 33%female, weigh=86±15kg; BMI=32±5kg/m^2), the test diagnosed correctly 28 out of 30 patients, misclassifying one patient having NASH with NAS score=2, but presenting metabolic syndrome; and one patient as having steatosis with NAS score=5, although without ballooning. Once validated, the test was applied to the follow-up of the patients (weigh=84±14kg; BMI=31±4kg/m^2). 31% of the patients lose at least 5% of baseline body weight. Among those responders, 50% of them improved their diagnosis presenting positive post-interventional shifts from NASH to steatosis or steatosis to healthy liver. Interestingly, the original diagnosis remained unchanged for the 95% of the non-responder patients. CONCLUSIONS: The results obtained in the independent cohort support the feasibility of these lipidomic tests as a noninvasive tool for NAFLD diagnosis and to monitor the disease progression/regression while circumventing the need for repeat liver biopsy.

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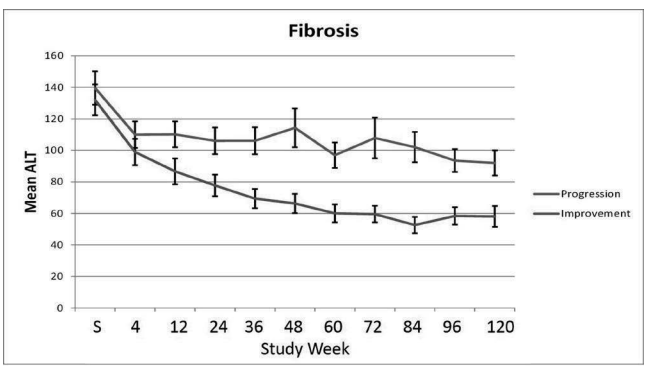
1109
Standardized Time Average of ALT is a Better Marker of Histologic Improvement in NAFLD

Damon Frezza[3], Wen Chen[3], Pinar Keskinocak[3], Turgay Ayer[3], Ran Jin[1], Sarah E. Barlow[4], Stavra Xanthakos[6], Joel E. Lavine[5], Miriam B. Vos[1,2]; [1]Emory University, Atlanta, GA; [2]Children's Healthcare of Atlanta, Atlanta, GA; [3]Georgia Institute of Technology, Atlanta, GA; [4]Baylor College of Medicine, Houston, TX; [5]Columbia University, New York, NY; [6]Cincinnati Children's, Cincinnati, OH

Background: Change in liver histology is the current standard for NAFLD treatment response, but liver histology has limitations including risk, high cost and imprecision. ALT is a commonly used surrogate marker but relationship of ALT to histologic change is not adequately defined, particularly in children. We hypothesized that combining ALT measurement *with* time duration of the ALT change would predict histologic change better than the reduction ratios currently used. **Methods**: This was a retrospective analysis of the 2-year, randomized, controlled TONIC trial published in 2011 by the NASH Clinical Research Network comparing placebo to metformin or vitamin E, along with lifestyle advice. Participants with a liver biopsy at screening (S) and 96 weeks were included in the analysis (N=147). ALT standardized time average (ALT STA), combining level of ALT and time duration at the level, was calculated using the area under the curve of the percent change in ALT plotted against time for each patient. Three methods of assessing ALT were compared (1) ALT reduction ratio (baseline compared to final), 2) mean ALT and 3) ALT STA. **Results:** Average fibrosis score was 1.25 ± 0.98 at baseline and NAS was 4.6 ± 1.4 (out of 8 possible). ALT was significantly different between improvement and progression of fibrosis with separation greatest after 36 weeks (Figure 1). Improvement in NAS was also associated with a significantly improved ALT however the separation was seen after 48 weeks. ALT STA was superior to ALT reduction ratio and mean ALT in predicting both fibrosis and NAS improvement (AUC 0.56, 0.66, 0.67 for fibrosis and 0.72, 0.65, 0.75 for NAS respectively, p<.05 for all except ALT reduction ratio for fibrosis). **Conclusions:** ALT STA was the best predictor of histologic improvement. Short term ALT (less than 36 weeks for fibrosis and 48 weeks for NAS) did not differentiate well between those who improved versus progression. ALT STA may be a useful surrogate marker of fibrosis change and NAS improvement in clinical trials for pediatric NAFLD.

ALT trend for fibrosis progression versus improvement.



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♦ Denotes AASLD Presidential Poster of Distinction

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1110
The Presence and Severity of Coronary Artery Disease in Patients with Biopsy-Proven NAFLD: A Prospective Prevalence Study

Kelvin N. Bush[2], Ryan I. Prentice[2], Emilio Fentanes[2], Richard W. Hilliard[2], Christopher J. Lisanti[3], Ryan Schwope[3], Katherine M. Cebe[4], Pedro A. Manibusan[1], Angelo H. Paredes[1], James K. Aden[5], James Watts[2], Dustin M. Thomas[2], Stephen A. Harrison[1]; [1]Gastroenterology, Brooke Army Medical Center, Fort Sam Houston, TX; [2]Cardiology, Brooke Army Medical Center, Fort Sam Houston, TX; [3]Radiology, Brooke Army Medical Center, Fort Sam Houston, TX; [4]Pathology, Brooke Army Medical Center, Fort Sam Houston, TX; [5]Biomedical Statistics, Institute for Surgical Research, Fort Sam Houston, TX

Background: Nonalcoholic fatty liver disease (NAFLD) is a global health concern that is increasing in prevalence. NAFLD has been associated with increased cardiovascular disease, but the relationship has been evaluated in limited observational studies. Prospective data on the association between NAFLD and coronary artery disease (CAD) are lacking. The purpose of this ongoing study is to define the prevalence and severity of CAD among patients with biopsy-proven nonalcoholic steatohepatitis (NASH) and non-NASH NAFLD. Methods: Adult patients were prospectively enrolled predominantly at the time of referral for routine colon cancer screening. They were screened for evidence of NAFLD with FibroScan ®, LiverMultiScan (LMS), and MR elastography (MRE). A prior history of liver disease or alcohol ingestion greater than the accepted range for NAFLD was considered exclusionary. Patients exceeding pre-specified cutoff values on any imaging test were offered liver biopsy and coronary CT angiography/coronary artery calcium (CCTA/CAC) to screen for the presence and severity of CAD. CAD was determined on a per-patient and per-vessel basis using a 16 segment model and severity was defined as obstructive (≥50% stenosis), non-obstructive (1-49% stenosis), or no CAD (vessels free of any plaque). Segment involved score (SIS) was defined as any atherosclerotic plaque in a coronary segment with diffuse CAD defined as a SIS > 3. CAC was quantified according to the Agatston method. Results: To date, 400 participants have been enrolled, of which 91 have completed biopsy and 61 patients have completed both CCTA and liver biopsy. Among all patients with evidence of NAFLD on biopsy, CAD was found in 31 (50.8%). Of these patients, diffuse CAD was present in 17 (54.8%) patients and obstructive CAD in 7 (22.6%) patients. Median coronary artery calcium (CAC) score was 111 (IQR 29, 373). In the 52 patients with non-NASH NAFLD, CAD was detected in 27 (51.9%) patients. Of these, diffuse CAD was present in 14 (51.9%) and no patients were found to have obstructive CAD. Median CAC score was 58 (28, 358). In the 9 patients with biopsy-proven NASH, CAD was present in 4 (44.4%) with diffuse CAD present in 3 (75%). Median CAC score was 338 (IQR 171, 503). There was no difference found between the rates of CAD, diffuse CAD, or median CAC scores in patients with non-NASH NAFLD compared with NASH patients. Conclusions: The prevalence of CAD, particularly diffuse CAD, is high among patients with both non-NASH NAFLD and NASH. Median CAC score > 300 observed in the biopsy-proven NASH patients may portend increased risk for cardiovascular events.

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The following people have nothing to disclose: Kelvin N. Bush, Ryan I. Prentice, Emilio Fentanes, Richard W. Hilliard, Christopher J. Lisanti, Ryan Schwope, Katherine M. Cebe, Pedro A. Manibusan, Angelo H. Paredes, James K. Aden, James Watts, Dustin M. Thomas

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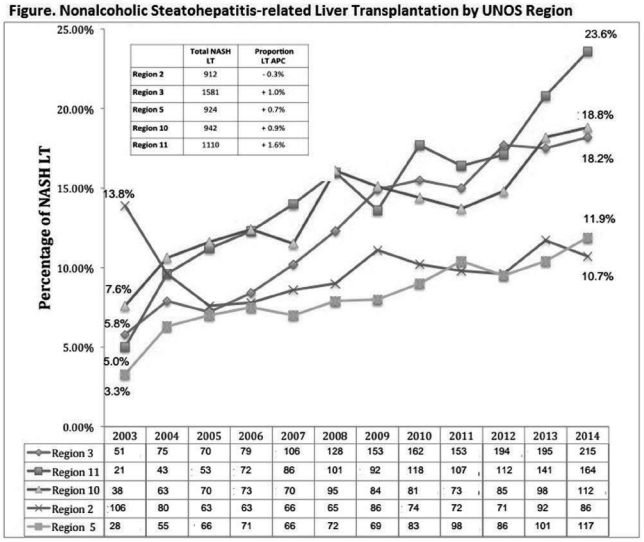
Geographic Variation in Nonalcoholic Steatohepatitis-Related Liver Transplantation

George Cholankeril[1,2], Ryan B. Perumpail[3], Menghan Hu[4], Channa R. Jayasekera[5], Edward W. Holt[5], Stevan A. Gonzalez[6], Stephen A. Harrison[7], Zobair M. Younossi[8], Robert J. Wong[9], Aijaz Ahmed[3]; [1]Roger Williams Medical Center, Providence, RI; [2]Internal Medicine, Boston University School of Medicine, Boston, MA; [3]Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA; [4]Biostatistics, Brown University School of Public Health, Providence, RI; [5]Hepatology, California Pacific Medical Center, San Francisco, CA; [6]Hepatology, Simmons Transplant Institute, Baylor All Saints Medical Center, Fort Worth, TX; [7]Gastroenterology and Hepatology, Brooke Army Medical Center, Fort Sam Houston, TX; [8]Center for Liver Disease, Department of Medicine, Inova Fairfax Hospital, Falls Church, VA; [9]Division of Gastroenterology and Hepatology, Alameda Health System - Highland Hospital, Oakland, CA

Background & Aims: With obesity becoming a widespread national epidemic, the prevalence of non-alcoholic steatohepatitis (NASH) and NASH-related liver transplantation (NASH-LT) have risen substantially. Our aim is to evaluate temporal trends in NASH-LT within the 11 United Network for Organ Sharing (UNOS) Regions. Methods: We conducted a cohort study utilizing the UNOS 2003-2014 data stratified into 11 UNOS Regions to evaluate the frequency of NASH-LT in adults within the United States (US). To determine etiology, we queried primary and secondary diagnosis codes for NASH along with alcoholic liver disease (ALD) and chronic hepatitis C (HCV). Results: There were 8,266 (10.9%) NASH-LT with an annual percentage change (APC) of +0.68%. Compared to HCV and ALD, NASH group had lower male and Hispanic ethnicity distribution. However, NASH group had a higher mean age, BMI, Caucasian distribution and co-morbid diabetes. The highest number of NASH-LT were within UNOS Region 3 (n=1581), Region 11 (n=1110), Region 10 (n=942), Region 2 (n=924) and Region 5 (n=912), and constituted over 63% of all NASH-LT. The annual number of NASH-LT in Region 3 and Region 11 increased +13.7% and +11.9%, respectively. Region 11 (15.5%), Region 10 (13.8%) and Region 3 (12.9%) had the highest percent of NASH-LT performed. Region 11 (APC=1.6%) and Region 3 (APC = 1.0%) had the highest annual rise in proportion of NASH-LT (Figure). By 2014, the percentage of NASH-LT reached 23.6% in Region 11, 18.8% in Region 10 and 18.2 % in Region 3. Conclusion: The Southeast (Region 3, Region 11) and portions of Midwest (Region 10), where obesity is prevalent, accounted for the majority of the rise in NASH-LT. Further studies are needed to clearly establish a relationship between geographic trends in the prevalence of obesity and NASH-LT.

Figure. Nonalcoholic Steatohepatitis-related Liver Transplantation by UNOS Region



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Effect of Cenicriviroc on the Pharmacokinetics and Safety of HMG-CoA Reductase Inhibitors (Atorvastatin, Simvastatin and Rosuvastatin) in Healthy Subjects

Eric Lefebvre[1], Stuart I. Harris[2], Michael S. Willett[3], Star Seyedkazemi[1], Will Chang[1], Patrick Smith[4], Mildred D. Gottwald[1]; [1]Tobira Therapeutics, Inc., South San Francisco, CA; [2]Seaview Research, Inc., Miami, FL; [3]Ready Clinical, LLC, Princeton, NJ; [4]d3 Medicine, LLC, Parsippany, NJ

Background: Cenicriviroc (CVC) is an oral, once-daily CCR2/5 antagonist currently evaluated in a Phase 2b study in 289 adults with non-alcoholic steatohepatitis (NASH) and liver fibrosis (CENTAUR; NCT02217475). CVC is a substrate for CYP3A4, CYP2C8, and P-glycoprotein (P-gp). CVC is a weak inhibitor of CYP3A4; its *in vivo* effects on breast cancer resistance protein (BCRP), P-gp and CYP1A2 substrates are unknown. Statins are widely used to treat dyslipidemia in patients with NASH, type 2 diabetes and metabolic syndrome. Atorvastatin and simvastatin are substrates for CYP3A4, rosuvastatin for BCRP, digoxin for P-gp and caffeine for CYP1A2. **Methods:** Phase 1, 3-period, fixed-sequence study in 36 healthy subjects evaluating the effect of CVC at steady-state (150 mg QD for 10 days) on the PK, safety and tolerability of test drugs: single-dose atorvastatin (20 mg), simvastatin (20 mg), rosuvastatin (20 mg; administered with caffeine 200 mg and digoxin 0.25 mg). Three groups of 12 subjects each received the test drug alone on Day 1, CVC alone for 10 days (starting on Day 2 or 3 depending on the half-life of the test drug) and CVC with the test drug on the last study day. Plasma samples were collected over 24–48 hours post-dose for atorvastatin, simvastatin, and rosuvastatin, with and without CVC administration. C_{max}, C_{min} and AUC_{0-tau} were determined using non-compartmental methods. Least square geometric means, geometric mean ratios (GMRs) and confidence intervals (CIs) were calculated. **Results:** With CVC co-administration: atorvastatin C_{max} and AUC_{0-tau} increased by 1.2-fold and 1.4-fold, respectively; simvastatin C_{max} and AUC_{0-tau} increased by 2.6-fold and 2.5-fold, respectively; rosuvastatin C_{max} and AUC_{0-tau} increased by 4.0-fold and 3.5-fold, respectively. CVC effects on caffeine and digoxin PKs were not clinically significant (≤1.2-fold increase for C_{max} and AUC_{0-tau}). Co-administration was well tolerated; all AEs were mild, with no serious AEs or AEs leading to discontinuation. **Conclusions:** Co-administration of CVC with atorvastatin resulted in a modest interaction, not considered clinically significant. The interaction of CVC with simvastatin or rosuvastatin suggests that a dose adjustment may be warranted when co-administered. No meaningful effects of CVC on P-gp and CYP1A2 substrates were observed.

	Least square geometric mean (95% CI)		GMR (90% CI)
Atorvastatin PK	**A (Atorvastatin, N=12)**	**B (Atorvastatin + CVC, N=12)**	**B/A**
C_{max} (ng/mL)	2.44 (2.09, 2.85)	2.98 (2.55, 3.48)	1.22 (1.02, 1.46)
C_{min} (ng/mL)	0.33 (0.28, 0.39)	0.51 (0.43, 0.60)	1.54 (1.27, 1.88)
AUC_{0-tau} (ng·hr/mL)	20.73 (19.43, 22.12)	28.45 (26.66, 30.36)	1.37 (1.27, 1.48)
Simvastatin PK	**A (Simvastatin, N=12)**	**B (Simvastatin + CVC, N=12)**	**B/A**
C_{max} (ng/mL)	7.43 (6.27, 8.80)	19.29 (16.28, 22.84)	2.60 (2.14, 3.16)
C_{min} (ng/mL)	0.08 (0.07, 0.08)	0.26 (0.25, 0.27)	3.31 (3.18, 3.43)
AUC_{0-tau} (ng·hr/mL)	20.95 (18.40, 23.84)	51.97 (45.66, 59.15)	2.48 (2.14, 2.88)
Rosuvastatin PK	**A (Rosuvastatin, N=12)**	**B (Rosuvastatin + CVC, N=12)**	**B/A**
C_{max} (ng/mL)	4.87 (4.01, 5.91)	19.30 (15.90, 23.41)	3.96 (3.17, 4.95)
C_{min} (ng/mL)	0.71 (0.60, 0.84)	1.33 (1.13, 1.57)	1.88 (1.55, 2.28)
AUC_{0-tau} (ng·hr/mL)	48.26 (41.13, 56.63)	170.06 (144.94, 199.54)	3.52 (2.93, 4.24)

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Michael S. Willett - Employment: Ready Clinical, LLC; Independent Contractor: Tobira Therapeutics, Inc.

Star Seyedkazemi - Employment: Tobira Therapeutics; Stock Shareholder: Tobira Therapeutics

Will Chang - Consulting: InCarda Therapeutics, Inc. ; Employment: Tobira Therapeutics, Inc.

Patrick Smith - Consulting: tobira

Mildred D. Gottwald - Employment: Tobira Therapeutics; Stock Shareholder: Tobira Therapeutics, Gilead Sciences, Tobira Therapeutics, Alexza Pharmaceuticals, Inc.

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Impact of plasma transaminase levels on the peripheral blood glutamate levels and memory functions in healthy subjects

Yoshihiro Kamada[2,1], Ryota Hashimoto[4,3], Hidenaga Yamamori[3], Yuka Yasuda[3], Tetsuo Takehara[1], Yuko Fujita[5], Kenji Hashimoto[5], Eiji Miyoshi[2]; [1]Department of Gastroenterology & Hepatology, Osaka University, Graduate School of Medicine, Suita, Japan; [2]Department of Molecular Biochemistry & Clinical Investigation, Osaka University Graduate School of Medicine, Suita, Japan; [3]Deparment of Psychiatry, Osaka University Graduate School of Medicine, Suita, Japan; [4]Molecular Research Center for Children's Mental Development, Osaka University, Suita, Japan; [5]Division of Clinical Neuroscience, Chiba University Center for Forensic Mental Health, Chiba, Japan

Background & Aims: Peripheral blood levels of aspartate aminotransferase [AST/GOT (glutamate-oxalacetate transaminase)] and alanine transaminase [ALT/GPT (glutamate-pyruvate transaminase)] are most frequently reliable biomarker of liver injury. Although AST and ALT play central roles in glutamate production as transaminases, peripheral blood levels of AST and ALT have been regarded only as liver injury biomarkers. AST and ALT catalyze transamination from aspartate

or alanine to glutamate and are important positive regulators of tissue glutamate levels. Glutamate is a principal excitatory neurotransmitter, which affects memory functions in the brain. Blood glutamate levels have been reported to be altered in many cognitive function disorders. In this study, we investigated the impact of blood transaminase levels on blood glutamate concentration and memory. ***Methods:*** Psychiatrically, medically, and neurologically healthy subjects (n=514, female/male: 268/246) were enrolled in this study through local advertisements. Plasma AST and ALT levels were measured with a conventional automated analyzer. Plasma amino acids (glutamate, glutamine, glycine, D-serine, and L-serine) were measured using a high performance liquid chromatography (HPLC) system. The five indices, verbal memory, visual memory, general memory, attention/concentration, and delayed recall of the Wechsler memory Scale-Revised (WMS-R) were used to measure memory functions. ***Results:*** Both plasma AST and ALT had a significant positive correlation with plasma glutamate levels (AST: R=0.19, P=1.1×10^{-5}; ALT: R=0.30, P=5.0×10^{-12}). Plasma AST and ALT levels were significantly negatively correlated with four of five memory functions [verbal memory: R=-0.11, P=0.014 (AST), R=-0.13, P=4.0×10^{-3} (ALT); visual memory: R=-0.11, P=0.012 (AST), R=-0.11, P=0.014 (ALT); general memory: R=-0.13, P=0.0044 (AST), R=-0.14, P=0.0013 (ALT); and delayed recall: R=-0.13, P=0.0033 (AST), R=-0.15, P=4.0×10^{-4} (ALT)], but were not correlated with attention/concentration (R=-0.022, P=0.61). Plasma glutamate was significantly negatively correlated with three of five memory functions. Multivariate analyses demonstrated that plasma AST, ALT, and glutamate levels were significantly correlated with memory functions even after adjustment for gender and education. ***Conclusions:*** As far as we know, this is the first report which could demonstrate the impact of blood transaminase levels on blood glutamate concentration and memory functions in human. These findings are important for the interpretation of obesity-induced metabolic syndrome with elevated transaminases and cognitive dysfunction.

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Genetic Basis for Nonalcoholic Fatty Liver Disease: The role of *MBOAT7* p.Gly17Glu-missense Variant

Silvia Sookoian[1], Diego M. Flichman[2], Martin Garaycoechea[6], Carla Gazzi[3], Gustavo O. Castaño[4], Carlos J. Pirola[5]; [1]Clinical and Molecular Hepatology, Institute of Medical Research Alfredo Lanari-IDIM, University of Buenos Aires and National Scientific and Technical Research Council (CONICET), Ciudad Autonoma de Buenos Aires, Argentina; [2]Department of Virology, University of Buenos Aires and National Scientific and Technical Research Council (CONICET), Ciudad Autonoma de Buenos Aires, Argentina; [3]Department of Pathology, Institute of Medical Research A Lanari-University of Buenos Aires, Ciudad Autonoma de Buenos Aires, Argentina; [4]Medicine and Surgery Department, Liver Unit, Hospital Abel Zubizarreta, Ciudad Autonoma de Buenos Aires, Argentina; [5]Molecular Genetics and Biology of Complex Diseases, Institute of Medical Research Alfredo Lanari-IDIM, University of Buenos Aires and National Scientific and Technical Research Council (CONICET), Ciudad Autonoma de Buenos Aires, Argentina; [6]Surgery Department, Hospital de Alta Complejidad en Red El Cruce "Nestor Carlos Kirchner", Fcio. Varela, Argentina

Background and Aims: Current knowledge on the genetic basis of nonalcoholic fatty liver disease (NAFLD) demonstrates that variants not just contributing to the disease susceptibility but severity are located in genes that regulate lipid metabolism. Specifically, the rs738409 in *PNPLA3* has been consistently associated with NAFLD severity and fibrosis stage across different populations in adults and children. However, associations with further discovered variants located in lipid-related loci, including the recently identified rs641738 (p.Gly17Glu) in *MBOAT7* (Membrane Bound O-Acyltransferase Domain Containing 7) were not consistently replicated across ethnic groups; MBOAT7 encodes for a member of the membrane-bound O-acyltransferases family that has specificity for arachidonoyl-CoA as an acyl donor. Notably, reported results showed genotype frequencies deviated from Hardy-Weinberg equilibrium (HWE). Here, we explored whether the *MBOAT7*-rs641738 is associated with the genetic risk of NAFLD and the disease severity in a case-control study of patients with NAFLD proven by liver biopsy. **Methods**: Our study included 634 individuals (372 patients with NAFLD and 262 healthy controls); genotyping was performed by a Taqman assay. Our sample had 96% power for the additive genetic model. To account for possible population stratification, we used a collection of 13 SNPs at different loci that were analyzed with the Structure program and which showed similar clustering for cases and controls.. **Results:** In our population, genotype frequencies in controls (n= CC: 84, CT: 137, TT: 41) and patients (CC: 134, CT: 178, TT: 60) were in HWE; minor allele frequency was 40.8 %. The rs641738 variant was neither associated with increased susceptibility to NAFLD (Cochran-Armitage test for trend chi-sq. = 0.397, P = 0.529) or the disease severity (p = 0.61). However, in univariate analysis we observed a significant association with circulating triglycerides (TG) (p=0.004). The rs641738 was not associated either with glucose metabolism, HOMA-index, total, HDL, LDL-cholesterol or other MetS components. **Conclusion:** While the role of rs641738 in NAFLD seems not to be conclusive, the variant may be associated with TG levels and so, it might indirectly regulate intermediate steps of fatty acid (polyunsaturated fatty acids-PUFA and PUFA-containing TG) biosynthesis. Still unexplored gene-diet interactions may explain disproportionately impact of variants on NAFLD among different ethnic groups. Not replicated observations among different populations indeed may result from disparities in the dietary composition.

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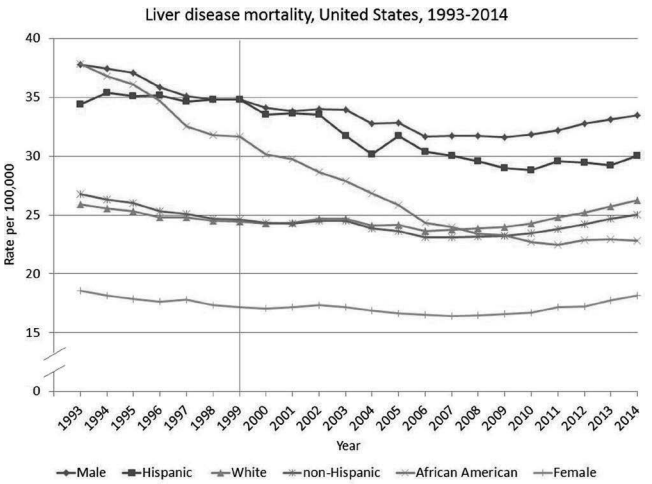
The Burden of Liver Disease in the United States Population

Aynur Unalp-Arida[1], Constance E. Ruhl[2]; [1]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; [2]Social & Scientific Systems, Inc., Silver Spring, MD

Chronic liver disease and cirrhosis was the 12th leading cause of death in the U.S. in 2014. We used national databases to update estimates of the liver disease burden in the U.S. **Methods:** The National Ambulatory and Hospital Ambulatory Medical Care Surveys, Nationwide Inpatient Sample, and Vital Statistics of the U.S. databases were used to estimate medical care and mortality with a primary or other diagnosis of liver disease, excluding viral hepatitis and hepatocellular carcinoma. Rates were age-adjusted and shown per 100,000 population for the most recent year available. **Results:** Liver disease contributed to 2.7 million ambulatory visits, 1.3 million hospital discharges, and 94,000 deaths. Ambulatory visit rates with a liver disease diagnosis were higher among women compared with men (874 vs. 724), whites compared with African Americans (772 vs. 509) and Hispanics compared with non-Hispanics (1064 vs. 766). Hospital discharge rates were also increased among Hispanics compared with non-Hispanics (438 vs. 354), but were higher among men compared with women (417 vs. 302) and similar among whites and African Americans (361 vs. 369). From 1993 to 2013, the ambulatory visit rate rose by 12-fold (65 to 804) and the hospital discharge rate doubled (183 to 357). Mortality rates were higher among men compared with women (33 vs. 18) and Hispanics compared with non-Hispanics (30 vs. 25), and slightly higher among whites compared with African Americans (26 vs. 23). The mortality rate declined slowly from 1993 through 2007 and then increased slowly through 2014. The decline was steepest among African Americans with a recent reversal among other subgroups (Figure). **Conclusions:** The burden of liver disease in the U.S. is substantial and increasing. The reversal of a declining mortality trend is concerning and deserves further population monitoring of liver-related outcomes.



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An angiotensin receptor-like 1 receptor, APJ, plays an important role in promoting fibrosis and angiogenesis in an early stage of non-alcoholic steatohepatitis

Wataru Ando[1], Hiroaki Yokomori[2], Yutaka Inagaki[3,4], Rie Kubota[1], Katsuya Otori[1], Isao Okazaki[5]; [1]Department of Clinical Pharmacy, School of Pharmacy, Kitasato University, Minato-ku, Tokyo, Japan; [2]Department of Internal Medicine, Kitasato University Medical Center, Kitamoto city, Japan; [3]Center for Matrix Biology and Medicine, Tokai University Graduate School of Medicine, Isehara city, Japan; [4]Department of Regenerative Medicine, Tokai University School of Medicine, Isehara city, Japan; [5]Department of Internal Medicine, Sanno Hospital, International University of Health and Welfare, Minato-ku, Tokyo, Japan

Background and Aims: It remains unknown how inflammation promotes liver fibrosis in the early stage of non-alcoholic steatohepatitis (NASH). We previously found using immuno-electron microscopy (IEM) that expression of APJ, an angiotensin receptor-like 1 receptor, was up-regulated in relation with angiogenesis in human liver cirrhosis. Apelin, a selective endogenous ligand of APJ receptor, has recently been reported as a liver fibrosis marker. In the present study, we examined the serum apelin levels and the hepatic expression of APJ in both early and advanced stages of NASH patients. **Materials and Methods:** This study enrolled 25 histologically proven NASH patients and 22 healthy controls. Serum apelin-36 levels were measured by ELISA and compared with the histopathological findings estimated by Brunt's fibrosis staging. Localization of APJ receptor was examined by IHC and IEM using 8 liver samples from NASH patients and 3 normal liver specimens. Expression of APJ receptor was also examined by Western blot analysis. **Results:** Serum apelin-36 levels in the early stage (1462 ± 359 pg/mL) and advanced stage of NASH (2165 ± 815 pg/mL) were significantly higher than those in controls (957 ± 190 pg/mL) ($p = 0.048$ and $p < 0.001$, respectively). Serum apelin-36 levels were increased in parallel to the fibrosis stages. Western blot analysis confirmed the increased expression of APJ receptor in early NASH livers compared with control livers ($p = 0.01$). Interestingly, the advanced stage of NASH livers exhibited lower expression of APJ receptor compared with the early NASH livers ($p = 0.01$). IHC revealed that APJ receptor was localized mainly in the arterial capillaries and, to the lesser extent, in the sinusoids of control livers. In the early stage of NASH, APJ receptor showed strong positive staining in hepatic sinusoidal lining cells and inflammatory cells in the pericentral areas, and weakly in hepatic sinusoidal lining cells in the periportal area. In the advanced NASH, APJ was observed mainly in sinusoidal lining cells in the regions of portal fibrosis and arterial capillaries in fibrotic septum. However APJ expression was weaker than in early NASH livers. IEM examination revealed aberrant expression of APJ receptor in the proliferated arterial capillaries opening into the sinusoid. APJ receptor was also found on the caveolae of proliferated capillary endothelial cells and pericytes. **Conclusions:** The localization of APJ receptor shown by IEM suggested the association with angiogenesis even in the early stage of NASH. Apelin and APJ receptor are closely related with fibrosis and angiogenesis in NASH.

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The Pharmacokinetics of GS-4997, an Inhibitor of Apoptosis Signal-Regulating Kinase 1 (ASK1), in Subjects with Mild, Moderate, and Severe Hepatic Impairment

Cara H. Nelson[1], Srini Ramanathan[1], Lu Wang[1], Thomas O'Riordan[1], Robert P. Myers[1], Constantine S. Djedjos[1], Ellen Kwan[1], Thomas Tarnowski[1], Jolene Berg[2], Eric Lawitz[3], Thomas C. Marbury[4], Kenneth Lasseter[5]; [1]Gilead Sciences, Inc., Foster City, CA; [2]DaVita Clinical Research, Minneapolis, MN; [3]Texas Liver Institute, University of Texas Health Sciences Center, San Antonio, TX; [4]Orlando Clinical Research Center, Orlando, FL; [5]Clinical Pharmacology of Miami, Miami, FL

Background GS-4997 is a selective and potent small molecule inhibitor of ASK1 in clinical development for the treatment of nonalcoholic steatohepatitis (NASH) and severe alcoholic hepatitis. This study evaluated the short-term safety and PK of GS-4997 in subjects with mild, moderate, or severe hepatic impairment (HI) and subjects with normal hepatic function to support development of GS-4997 dosing recommendations in patients with cirrhosis. **Methods** Subjects with stable mild, moderate, or severe HI (Child-Pugh-Turcotte A, B, or C, respectively [n=10 per group]) and healthy controls with normal hepatic function, matched for age (±10 years), gender, and BMI (±20%) (n=10 per HI group) received a single, 6 mg oral dose of GS-4997 followed by intensive PK sampling over 120 hours. Safety was monitored and a parametric analysis of variance using a mixed effects model was used to fit logarithmically-transformed PK parameters (AUC and C_{max}). The 90% confidence intervals (CIs) were constructed for the geometric mean ratios (GMR) of these parameters between each HI group and matched control subjects. Since HI may alter protein binding, the free fraction of GS-4997 in plasma was also determined and summarized by hepatic function. **Results** All subjects completed the study; all treatment-emergent adverse events (AEs) were mild (Grade 1) or moderate (Grade 2). Only one AE (Grade 1 headache) occurred in more than one subject (n=4). Total plasma exposures (C_{max} and AUC) were similar in subjects with mild or moderate HI compared to healthy controls (Table 1). There was a modest increase in AUC in subjects with severe HI versus control subjects. Compared with control subjects, the free fraction of GS-4997 was increased in subjects with severe HI, but not with mild or moderate HI as compared to controls (7.0% unbound vs 5.3% unbound). **Conclusions** The safety results from this study were consistent with the overall safety profile for GS-4997. GS-4997 exposures were similar in subjects with mild or moderate HI as compared to those with normal hepatic function and subjects with severe HI had modestly higher exposures. The results of this study support continued clinical development of GS-4997 in patients with liver dysfunction due to NASH or alcoholic hepatitis without dose adjustment regardless of presence of HI.

Table 1. Summary of PK results in subjects with hepatic impairment vs. normal hepatic function (control)

	GMR% (90% CI)		
GS-4997 PK Parameter	Mild HI: Control (N=10:10)	Moderate HI: Control (N=10:10)	Severe HI: Control (N=10:10)
AUCinf (ng•h/mL)	111 (87.0, 140)	105 (77.1, 143)	143 (121, 169)
AUClast (ng•h/mL)	112 (87.7, 144)	99.9 (73.4, 136)	142 (119, 170)
Cmax (ng/mL)	100 (83.7, 120)	88.7 (74.8, 105)	91.2 (78.8, 106)

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Cara H. Nelson - Employment: Gilead Sciences, Inc.; Stock Shareholder: Gilead Sciences, Inc.

Srini Ramanathan - Employment: Gilead Sciences

Lu Wang - Employment: Gilead Sciences

Thomas O'Riordan - Employment: Gilead Sciences Inc; Stock Shareholder: Gilead Sciences Inc

Robert P. Myers - Employment: Gilead Sciences, Inc.; Stock Shareholder: Gilead Sciences, Inc.

Constantine S. Djedjos - Employment: Gilead Sciences

Thomas Tarnowski - Employment: Gilead Sciences, Inc.; Stock Shareholder: Gilead Sciences, Inc.

Eric Lawitz - Advisory Committees or Review Panels: AbbVie, Achillion Pharmaceuticals, Regulus, Theravance, Enanta, Idenix Pharmaceuticals, Janssen, Merck & Co, Novartis, Gilead; Grant/Research Support: AbbVie, Achillion Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmith-Kline, Idenix Pharmaceuticals, Intercept Pharmaceuticals, Janssen, Merck & Co, Novartis, Nitto Denko, Theravance, Salix, Enanta; Speaking and Teaching: Gilead, Janssen, AbbVie, Bristol Meyers Squibb, Merck, intercept

Thomas C. Marbury - Employment: Orlando Clinical Research Center

The following people have nothing to disclose: Ellen Kwan, Jolene Berg, Kenneth Lasseter

1118

Phase 1 Study of BMS-986171 (Pegylated FGF21) in Healthy Obese Subjects

Chunyu Kate Wu, Edgar D. Charles, Anh Bui, Rose Christian, Malaz Abu Tarif; Bristol-Myers Squibb, Lawrenceville, NJ

Background: Fibroblast growth factor 21 (FGF21), a non-mitogenic hormone, is an important regulator of glucose and lipid metabolism. FGF21 analogs improve insulin sensitivity and lipid profiles, which contribute to NASH pathogenesis, in preclinical models as well as in obese humans with type 2 diabetes. BMS-986036, a first generation pegylated human FGF21 variant, has an extended elimination half-life compared to endogenous human FGF21, enabling daily and weekly regimens to be studied. BMS-986171 is a pegylated FGF21 variant that has been modified to decrease proteolysis and further extend half-life to support at least once-weekly dosing. **Methods**: A randomized, placebo-controlled single ascending dose study in obese (BMI 30-40 kg/m^2) healthy subjects was conducted. There were 5 cohorts of 8 subjects randomized 3:1 to subcutaneous (SC) BMS-986171 0.6 mg, 2 mg, 6 mg, 20 mg, or 60 mg vs placebo. Serum BMS-986171 concentration vs time data were used to derive T1/2, Cmax, Tmax, AUC(INF) and total clearance (CLT/F). A compartmental PK model was developed for the simulation of concentration vs time profiles of weekly dosing regimens. **Results:** At baseline, mean age was 39.8 y, male 68%, Hispanic 40%. There were no deaths, SAEs or discontinuations due to AEs. Most (95%) treatment-related AEs were of mild intensity. PK results are in **Table 1**. The average terminal T1/2 of BMS-986171 was 83-96 h. Cmax was observed at 72 h after dosing. Dose-normalized Cmax and AUC(INF) were consistent across doses, indicating that PK was linear and dose-proportional. Steady-state PK was projected to be achieved within 3-4 wks, with an accumulation index of 1.4-1.8-fold after weekly dosing. **Conclusions:** BMS-986171 was well-tolerated in single doses up to 60 mg. Compared to BMS-986036, BMS-986171 showed improved PK exposure due to a prolonged terminal T1/2. PK and safety data are supportive of continued clinical development of weekly dosing of BMS-986171 in NASH.

Table 1

Dose, QW (mg)	T1/2 (h)*	Tmax (h)**	Cmax (ng/mL)*	AUCinf (h*mg/mL)*	CLT/F (L/hr)*
0.6 (N=3)	--	--	--	--	--
2 (N=5)	83 (15)	72 (48-72)	87.8 (47)	18.6 (39)	0.141 (45.9)
6 (N=6)	87.4 (17)	72 (48-72)	283 (53)	67.0 (42)	0.105 (43.2)
20 (N=6)	85.4 (14)	72 (36-72)	1347 (36)	264 (37.3)	0.088 (50.3)
60 (N=4)	95.8 (23)	72 (48-168)	3530 (11)	911 (12)	0.067 (12.4)

* mean (standard deviation)

** median (range)

Disclosures:

Edgar D. Charles - Employment: BMS

Rose Christian - Employment: Bristol-Myers Squibb

Malaz Abu Tarif - Employment: Bristol-Myers Squibb; Stock Shareholder: Bristol-Myers Squibb

The following people have nothing to disclose: Chunyu Kate Wu, Anh Bui

1119

What is the optimal exercise regimen for patients with NAFLD: Aerobic or resistance exercise?

Takumi Kawaguchi[1], Ryuki Hashida[2,3], Takato Ueno[4,5], Hironori Koga[1,5], Jacob George[6], Naoto Shiba[2,3], Takuji Torimura[1,5]; [1]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan; [2]Department of Orthopedics, Kurume University School of Medicine, Kurume, Japan; [3]Division of Rehabilitation, Kurume University Hospital, Kurume, Japan; [4]Asakura Medical Association Hospital, Asakura, Japan; [5]Liver Cancer Division, Research Center for Innovative Cancer Therapy, Kurume University, Kurume, Japan; [6]Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, Sydney, NSW, Australia

Background & aims: Exercise is a first-line therapy for patients with non-alcoholic fatty liver disease (NAFLD). Both aerobic and resistance exercise improve NAFLD, however, the most effective exercise protocol remains unclear. Moreover, given the high prevalence of cardiovascular diseases in NAFLD, the choice of exercise type in relation to exercise energy consumption has not been compared. We sought to assess the required frequency, intensity, and duration of aerobic and resistance exercise required for improvement of hepatic steatosis and to compare the exercise regimens with regard to energy consumption in patients with NAFLD. **Methods:** A literature search was performed using PubMed, Web of Science, and Scopas to January 28, 2016 for articles assessing the effect of aerobic or resistance on hepatic steatosis. From a total of 95 articles, 24 studies including 25 aerobic and 7 resistance exercise protocols were selected for systematic review. **Results:** For aerobic exercise, a decrease in hepatic steatosis was seen in 92.0% (23/25) of protocols (n = 1695). The median effective protocol was 4.8 metabolic equivalents (METs) for 40 min/session, 3 times/week for 12 weeks. For resistance exercise, a reduction of hepatic steatosis was seen in 85.7% (6/7) of protocols (n = 116). The median effective protocol was 3.5 METs for 45 min/session, 3 times/week for 12 weeks. Aerobic and resistance exercise reduced 2.4% [0-21%] and 12% [2-13%] of intrahepatic lipid, respectively. No significant difference was seen in the duration, frequency, or period of exercise between the two exercise regimens. Energy consumption was significantly lower in the resistance than in the aerobic exercise group (11,064 [6,394-21,087] vs. 6,470 [4,104-12,310] kcal/total period, P = 0.0475). **Conclusions:** Resistance exercise improves NAFLD with less energy consumption. Resistance exercise may be more feasible and beneficial than aerobic regimens for NAFLD patients with poor cardiorespiratory fitness or for those who cannot tolerate or participate in aerobic exercise. These data also suggest a possible link between mode of exercise and hepatic lipid metabolism.

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1120

Effects of *Lactobacillus reuteri* associated with guar gum and inulin in the gut permeability in nonalcoholic steatohepatitis

Silvia M. Ferolla, Claudia A. Couto, Geyza N. Armiliato, Paula V. Vidigal, Gabriela S. Ataliba, Maria de Lourdes A. Ferrari, Eduardo G. Vilela, Henrique G. Torres, Aloisio S. Cunha, Teresa C. Ferrari; Hospital das Clinicas, Instituto Alfa de Gastroenterologia, Federal University of Minas Gerais, Belo Horizonte, Brazil

The probable role of the gut in nonalcoholic steatohepatitis (NASH) progression is still not elucidated, although evidence from animal and human studies suggest that increased gut permeability could allow the passage of gut-derived endotoxin to the liver enhancing inflammation. We aimed to investigate the prevalence of increased intestinal permeability in subjects with NASH, and if synbiotic supplementation containing 10^8 colony forming units (CFU) of *L.reuteri* plus 4g of partially hydrolyzed guar gum and inulin (twice daily) could improve this parameter. We included 50 biopsy-proven NASH patients in a randomized, controlled clinical trial. Twenty-seven subjects received synbiotic supplementation and healthy nutritional counseling for three months, and 23 individuals received only healthy nutritional counseling for the same period of time. Clinical appointments were scheduled every month to provide synbiotic. The gut permeability was evaluated at baseline and after the intervention by lactulose/mannitol urinary excretion. For the test, urine samples were taken after the patients have drunk 120ml of isosolar solution containing lactulose and mannitol. The measurements were performed by high performance liquid chromatography (HPLC). The results were reported as the percentage of urinary excretion of each probe in relation to the amount ingested; and the final result of the test, as the ratio between the excreted percentages of lactulose and mannitol. The results of the test were compared to the reference values established in a healthy population. At baseline the median age was 57 ys and 76% patients were female. Most patients (98%) were obese, 76% hypertensive, 76% dyslipidemic, 70% sedentary, 80% presented alterations in the glucose metabolism and 98% were classified as having metabolic syndrome. There were no diferences in clinical and histological parameters between groups. The patients with NASH presented a high prevalence (51.1%) of increased gut permeability. At baseline, there was no difference in the frequency of increased gut permeability between the groups: 55.6% in the study group and 44.4% in control group (p=0.465). After three months of synbiotic supplementation, there were no differences in the percentage of lactulose and mannitol excretion neither in the lactulose/mannitol excretion ratio in the intervention group (p=0.492; p=0.459; p=0.737, respectively) as well as in the control group (p=0.248; p=0.950; p=0.374), respectively. Patients with NASH presented a high frequency of increased gut permeability, which was not improved with *L. reuteri* plus partially hydrolyzed guar gum and inulin supplementation.

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1121

Circulating, hepatocyte-derived extracellular vesicles correlate with fibrosis stage and portal pressure in patients with nonalcoholic steatohepatitis

Davide Povero[2], Casey Johnson[2], Hirokazu Yamashita[2], Robert P. Myers[1], Constantine S. Djedjos[1], Mani Subramanian[1], Zachary D. Goodman[3], Stephen A. Harrison[4], Arun J. Sanyal[5], Jaime Bosch[6], Ariel E. Feldstein[2]; [1]Gilead Sciences, Inc., Foster City, CA; [2]University of California San Diego, San Diego, CA; [3]Inova Fairfax Hospital, Falls Church, VA; [4]San Antonio Military Medical Center, Fort Sam Houston, TX; [5]Virginia Commonwealth University, Richmond, VA; [6]University of Barcelona, Barcelona, Spain

Background: Extracellular vesicles (EVs) are membrane-bound particles released from dying or activated cells. In experimental models, EVs released by hepatocytes during lipotoxicity are internalized by neighboring cells and contribute to liver fibrosis and angiogenesis. The objectives of this study were to quantify and characterize EVs in serum of patients with nonalcoholic steatohepatitis (NASH). **Methods:** EVs were isolated using a sequential centrifugation process from serum of healthy controls and NASH patients with advanced fibrosis (Ishak 3-6). Dynamic light scattering analysis (Zetasizer; Malvern, Worcestershire, UK) and electron microscopy determined the size and morphology of EVs and flow cytometry quantified the total number of EVs (calcein-FITC+) and hepatocyte-derived EVs (asialoglycoprotein receptor 1 [ASGPR1]-Cy3+). EV number was compared between NASH patients and controls, and associations between EV number and NASH characteristics including liver biochemistry, NAFLD Activity Score and its components, fibrosis stage, hepatic collagen content and α-smooth muscle actin expression by morphometry, serum fibrosis markers, and hepatic venous pressure gradient (HVPG; in cirrhotic subjects) were determined. **Results:** 50 NASH patients (median age, 55 yrs; 68% female; 50% cirrhotic) and 11 controls (54 yrs; 73% female) were included; EVs were detected in all subjects with both exosomes and microparticles identified. Compared with controls, NASH patients had greater median (IQR) numbers of total EVs (1399 [1019-2001] vs. 1004 [510-1174] per μL serum; P=0.007) and hepatocyte-derived EVs (646 [498-855] vs. 372 [333-402] per μL; P<0.001). The number of total EVs did not correlate with demographics, liver biochemistry, histology, fibrosis markers, HVPG, or MELD. However, the number of hepatocyte-derived EVs correlated with fibrosis stage (ρ=0.28; P=0.048), Fibrotest (ρ=0.31; P=0.037), ELF test (ρ=0.28; P=0.056), NAFLD Fibrosis Score (ρ=0.29; P=0.047), bilirubin (ρ=0.26; P=0.066), platelets (ρ=-0.38; P=0.006), and HVPG (ρ=0.40; P=0.047). Moreover, patients with clinically significant portal hypertension (HVPG ≥10 mmHg) had more hepatocyte-derived EVs than patients with HVPG <10 mmHg (median, 830 vs. 568 per μL; P=0.014). **Conclusions:** In patients with NASH, the number of circulating, hepatocyte-derived EVs correlates with fibrosis stage, serum fibrosis markers, and HVPG. Characterization of the content of these EVs may help elucidate the pathogenesis or fibrosis and portal hypertension.

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Zachary D. Goodman - Grant/Research Support: Gilead Sciences, Galectin Therapeutics, Intercept, Alexion, Conatus, Cempra, Nitto Denko, Tobira, Exalenz

Stephen A. Harrison - Advisory Committees or Review Panels: Merck, Nimbus Discovery, Fibrogen, Intercept, CLDF, Zafgen, Pfizer; Consulting: NGM Biopharmaceuticals, Medivation; Grant/Research Support: Genfit; Speaking and Teaching: Gilead, Abbvie, CLDF, Merck

Arun J. Sanyal - Advisory Committees or Review Panels: Bristol Myers, Gilead, Genfit, Abbott, Ikaria, Exhalenz, Pfizer, Novartis; Consulting: Salix, Immuron, Exhalenz, Nimbus, Genentech, Echosens, Takeda, Merck, Enanta, Zafgen, JD Pharma, Islet Sciences, Hemoshear; Grant/Research Support: Salix, Genentech, Intercept, Ikaria, Takeda, GalMed, Novartis, Gilead, Tobira; Independent Contractor: UpToDate, Elsevier; Management Position: Sanyal Biotechnology

The following people have nothing to disclose: Davide Povero, Casey Johnson, Hirokazu Yamashita, Mani Subramanian, Jaime Bosch, Ariel E. Feldstein

1122

Efficacy and Safety of a Supervised Exercise Intervention in Patients with Cirrhosis due to Non-alcoholic Fatty Liver Disease

Paul Crabtree[1,4], Helena Ching[1,3], Gary P. Jeffrey[1,3], Jonathan Tibballs[2], Gerry C. MacQuillan[1,3], George Garas[1,3], Robert U. Newton[4], Leon A. Adams[1,3]; [1]School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia; [2]Radiology, Sir Charles Gairdner Hospital, Perth, WA, Australia; [3]Hepatology, Sir Charles Gairdner Hospital, Perth, WA, Australia; [4]Edith Cowan University, Exercise Medicine Research Institute, Perth, WA, Australia

BACKGROUND AND AIMS: Patients with cirrhosis due to non-alcoholic fatty liver disease (NAFLD) are at risk of liver and cardiac related morbidity and mortality. Lifestyle change, incorporating exercise, is recommended and may improve cardio-respiratory fitness (VO2 peak), which predicts mortality in cirrhosis patients. The efficacy and safety in this patient population is not well established. Our aim was to determine the impact of exercise training on aerobic fitness with secondary outcomes including hepatic steatosis, liver injury, insulin resistance, body composition, muscle strength, safety, and quality of life measures. **METHODS:** Patients with histologically confirmed NAFLD cirrhosis and low baseline physical actively levels underwent 12 weeks of progressive aerobic and resistance exercise (45 mins, thrice weekly) supervised by an exercise physiologist. Aerobic capacity was assessed using a graded cardiopulmonary exercise test, strength via 1 repetition maximum (1RM) test; liver steatosis by magnetic resonance spectroscopy, body composition by DEXA and quality of life using validated questionnaires (SF-36, CLDQ). **RESULTS:** Eight of 25 (32%) patients approached consented to the study, with lack of interest or availability the main reason for refusal. Subjects were 75% female, mean age 62±8 years, BMI 36.2±9, 87% Childs A with portal hypertension. From baseline to week 12, the exercise intervention produced a significant improvement in Peak Vo2 (16.7±0.8 ml/kg/min to 20.1±7.3 ml/kg/min respectively, p=0.043) and maximal 1RM strength (leg press; 101±52 kg to 148±53 kg p=0.012, seated row; 61±16 kg to 69±18 kg p=0.012). Functional capacity improvement occurred with improved six minute walk test distances (482±60m to 509±64m p=0.028) and timed up and go (6.8±0.9sec to 6.0±1.1sec, p=0.025). Lean muscle mass increased (53.9±9.7kg to 55±9.1kg p=0.05) and overall fat mass fell (40.4±7.1kg to 39.4±7.6kg p=0.035). Trends towards significance were seen with reductions in waist circumference (p=0.068) and total fat mass (p= 0.069). No significant effects were noted on hepatic steatosis, liver enzymes, insulin resistance or lipid profiles. Quality of Life improved with changes in the Chronic Liver Disease Questionnaire score (5.40 to 5.63 p=0.012) and the Physical Domain of the SF-36 (63.7 to 84.4 p=0.035). No adverse events were noted. **Conclusions**: Uptake of exercise is poor among NAFLD cirrhotic patients, however appropriate exercise leads to clinically significant improvements in aerobic fitness, strength and functional capacity with associated reduction in fat mass and improvement in quality of life. Strategies to increase patient participation are required.

♦ Denotes AASLD Presidential Poster of Distinction

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Leon A. Adams - Patent Held/Filed: Quest diagnostics

The following people have nothing to disclose: Paul Crabtree, Helena Ching, Gary P. Jeffrey, Jonathan Tibballs, Gerry C. MacQuillan, George Garas, Robert U. Newton

1123
Probiotics do not improve hepatic outcomes after Laparoscopic Sleeve Gastrectomy surgery: a randomized clinical trial

Shiri Sherf Dagan[1,5], Shira Zelber-Sagi[1,3], Gili Zilberman-Schapira[4], Muriel Webb[1], Assaf Buch[1,2], Andrei Keidar[5,6], Asnat Raziel[5], Nasser Sakran[5,7], David Goitein[5,8], Natalia Goldenberg[5], Jemal A. Mahdi[4,9], Meirav Pevsner-Fischer[4], Niv Zmora[4,10], Mally Dori-Bachash[4], Eran Segal[11], Eran Elinav[4], Oren Shibolet[1,2]; [1]Gastroenterology, Tel-Aviv Medical Center, Israel, Tel Aviv, Israel; [2]Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel; [3]School of Public Health, Faculty of Social Welfare and Health Sciences, University of Haifa, Haifa, Israel; [4]Immunology Department, Weizmann Institute of Science, Rehovot, Israel; [5]Assuta Medical Center, Tel Aviv, Israel; [6]Department of Surgery, Rabin Medical Center, Campus Beilinson, Petach Tiqva, Israel; [7]Department of Surgery A, Emek Medical Center, Afula, Israel; [8]Department of Surgery C, Sheba Medical Center, Tel Hashomer, Israel; [9]Department of Microbiology Immunology and Genetics, Ben-Gurion University, Beer-Sheba, Israel; [10]Research Center for Digestive Tract and Liver Diseases, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [11]Department of Computer Science and Applied Mathematics, Weizmann Institute of Science, Rehovot, Israel

Background &Aims: Probiotics are commonly used after bariatric surgery; however uncertainty remains regarding their efficacy. Our aim was to compare the effect of probiotics vs. placebo on hepatic, inflammatory and clinical outcomes post laparoscopic sleeve gastrectomy (LSG). Methods: This randomized, double-blind placebo-controlled trial of 6-months treatment with probiotics (Bio-25;Supherb) vs. placebo and 6-months of additional follow-up was conducted among 100 morbidly obese non-alcoholic fatty liver disease (NAFLD) patients who underwent LSG surgery. The primary outcome was a reduction in liver fat content, measured by abdominal-ultrasound, and secondary outcomes were improvement of fibrosis, measured by shear-wave elastography, metabolic and inflammatory parameters, anthropometrics and quality of life (QOL). Fecal samples were collected and analyzed for microbial composition. Results: One hundred patients (60% women, mean age of 41.9±9.8 years and BMI of 42.3±4.7kg/m2) were randomized, 80% attended the 6-month visit and 77% completed the 12-month follow-up. The Hepato-Renal Index (HRI) and NAFLD remission rate were similarly reduced in the probiotics and placebo groups at 6-months post-surgery (-0.9±0.5 vs. -0.7±0.4 score, P=0.059 and 52.5% vs. 40%, P=0.262, respectively) and at 12-months post-surgery. Fibrosis, ALT, C-Reactive Protein (CRP), leptin, Caspase-generated cytokeratin-18 (CK-18) levels were significantly reduced and QOL significantly improved within-groups (P≤0.014 for all), but no between-group differences were noted at 6-months post-surgery (P≥0.173 for all) and at 12-months post-surgery. The relative abundances of 4 main phyla increased (Firmicutes, Proteobacteria, Actinobacteria and Verrucomicrobia) and of one main phylum decreased (Bacteroidetes) to a similar extent in both arms at 6-months post-surgery. Conclusions: Probiotics administration does not improve hepatic, inflammatory and clinical outcomes 6 and 12-months post LSG.

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1124
Simple resistance exercise for 24 weeks decreases alanine aminotransferase levels in patients with non-alcoholic fatty liver disease

Manabu Hayashi, Atsushi Takahashi, Hiromichi Imaizumi, Masashi Fujita, Ken Okai, Kazumichi Abe, Hiromasa Ohira; Department of Gastroenterology and Rheumatology, Fukushima Medical University School of Medicine, Fukushima, Japan

Background and aim: Exercise therapy is effective and recommended for non-alcoholic fatty liver disease (NAFLD), but no reports have examined whether significant reductions in serum levels of alanine aminotransferase (ALT) are achieved with exercise therapy in patients with NAFLD. The aim of this study is to assess the effects of simple resistance exercise for 24 weeks in NAFLD. **Methods:** Fifty nine patients with NAFLD were assigned to a resistance exercise group (n = 28) or a control group (n = 31). The resistance exercise group performed 2 exercises (push-ups and squats) 3 times a week on nonconsecutive days for a trial periods of 24 weeks. Patients in the control group proceeded with regular physical activities under a restricted diet throughout the study. The effects of exercise were compared between groups after 24 weeks. Biochemical blood parameters, hepatic steatosis and body composition were assessed. Hepatic steatosis and body composition were evaluated by ultrasound and bioelectrical impedance analysis, respectively. **Results:** A significant time-by-treatment interaction was seen between ALT levels and HOMA-IR. ALT levels (76.9 ± 63.4 vs. 59.3 ± 49.2 IU/L, p = 0.003) and HOMA-IR (4.0 ± 2.9 vs. 3.1 ± 1.6, p = 0.025) were significantly decreased with exercise, but not in the control group. We also found a significant time-by-treatment interaction in hepatic steatosis grade (p = 0.021). Moreover, hepatic steatosis grade (2.00 ± 0.82 vs. 1.55 ± 0.71, p = 0.001) was significantly decreased with exercise, but not in the control group Changes in ALT levels correlated negatively with changes in muscle:body weight ratio in the exercise group. **Conclusion:** These data demonstrate that 24 weeks of simple resistance exercise comprising squats and push-ups represents an effective treatment for NAFLD.

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1125
Intra-Gastric Balloon (IGB): an endoscopic treatment option for obesity and NAFLD

Vi Nguyen, Jiawei Li, Paul Cordero, Gilberto Alejandro S. Cuevas, Mai Khatib, Jude A. Oben; The Institute for Liver and Digestive Health, UCL, London, United Kingdom

Background & Aims The incidence of NAFLD continues to parallel the rising obesity rates. While bariatric surgery provides an effective tool for weight loss, it is not a feasible option for all. Endobariatric devices, including intra-gastric balloons (IGBs), may provide an alternative option for weight control. We report on the outcomes with the IGB in the treatment of obesity and NAFLD in a single centre. **Methods** The outcomes following IGB placement in obese patients with insulin resis-

tance from 2005 till 2015 at a tertiary hospital in central London, United Kingdom were retrospectively examined. Clinical, anthropometric and biochemical data were routinely recorded and examined at baseline, and after IGB removal at 6 months. **Results** Data from 135 patients were available for analysis. Most were women (96/135, 71%) of Caucasian background (66%), with a mean age of 47 ± 12 years. Diabetes was present in 39/135 (29%) at baseline, and other features of metabolic syndrome also apparent in 45/135 (45%) of patients. Mean baseline weight was 117.9 ± 22 kg, with BMI 41.7 ± 6.6 kg/m^2, and waist circumference 124.2 ± 13.6 cm. Median baseline HOMA-IR was 3.6 (2.1-5.9). Following 6 months of IGB placement, significant changes were seen with weight (mean loss of 11.3kg), and BMI (mean reduction by 4.1 kg/m^2); p<0.01. Significant improvements were also seen with ALT, GGT, and HOMA-IR, all changes corresponding with weight loss (p <0.05 for all). Commonly reported side effects included nausea, vomiting, and abdominal discomfort, with premature IGB removal required in 14 cases (10.4%). **Conclusions** IGB provides an effective, alternative non-surgical means of inducing weight loss for the management of obesity and obesity-associated liver dysfunction over the short term. Improvements in insulin resistance and hepatic transaminases correlated with greater degrees of weight change.

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1126
Metabolomic analyses reveal a novel role for Protease Activated Receptor-2 (PAR2) in driving steatosis in Non-Alcoholic Steatohepatitis (NASH)

Rajashree Rana[1], Andrew M. Shearer[1,2], Conor Calnan[1], Nga Nguyen[1], Laura Fynn[1], Tianfang Huang[1], James Baleja[2], Lidija Covic[1,2], Athan Kuliopulos[1,3]; [1]Center for Hemostasis and Thrombosis Research, Tufts Medical Center, Boston, MA; [2]Department of Developmental, Molecular and Chemical Biology, Tufts University, Boston, MA; [3]Oasis Pharmaceuticals, Lexington, MA

Background and purpose: Protease activated receptor-2 (PAR2) is a cell surface G-protein coupled receptor (GPCR) highly expressed in multiple cell types in the liver including hepatocytes, stellate cells and inflammatory macrophages. PAR2 is activated by proteolytic cleavage of its N-terminal exodomain by serine proteases. Recently, PAR2 has been proposed to be an important regulator of obesity and metabolic syndrome, however, the connection between PAR2 signaling and metabolism in the liver is not understood. The aim of this study was to evaluate the role of PAR2 signaling in liver metabolism leading to the pathogenesis of fatty liver disease and NASH. *Methods*: We used the methionine choline deficient (MCD) diet-induced mouse model for NASH over 3-8 week time periods and analyzed both systemic and hepatic metabolites by nuclear magnetic resonance (NMR). Liver metabolites were extracted from snap-frozen liver by a chloroform-methanol extraction method and quantified by enhanced NMR metabolomics to compare individual metabolites in wild type versus PAR2-deficient mice and mice treated with the PAR2-inhibitory pepducin PZ-235. Systemic metabolites were extracted from plasma by a methanol denaturation method. The expression of the regulatory enzymes of critical metabolic pathways was also measured. *Results*: We found that PAR2 deficiency or inhibition with PZ-235 provides striking protection against diet-induced hepatic steatosis and inflammation. PAR2 deficiency as well as treatment with PZ-235 significantly decreased hepatic triglycerides (*p< 0.0001*), plasma levels of liver enzymes (ALT *p< 0.0001* and AST *p=0.0072*) and reduced NAFLD activity score (NAS) by 40-60 % in the NASH models. Metabolomics and gene expression experiments show that PAR2 inhibition enhances beta-oxidation of fatty acids and suppresses the metabolic pathways leading to reactive-oxygen species (ROS) production. *Conclusions:* PAR2 signaling plays a critical role in regulating hepatic steatosis, inflammation and ROS generation in NASH, a condition that can lead to cirrhosis and hepatocellular carcinoma, for which there is currently no approved means of pharmacological intervention. Development of novel PAR2 inhibitors as exemplified by the PAR2 pepducin PZ-235 may provide a blueprint for the development of efficacious agents to suppress NASH.

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1127
Non-alcoholic fatty liver disease in an HIV-infected cohort with abnormal liver function tests: prevalence and risk factors

Rebekah G. Judge[1], James B. Maurice[1], Mark Nelson[2], Mark R. Thursz[1]; [1]Hepatology, Imperial College London, London, United Kingdom; [2]Chelsea and Westminster Hospital, London, United Kingdom

Background: Abnormal liver function tests (LFTs) are frequently observed in Human Immunodeficiency Virus (HIV) monoinfected individuals in the absence of alcohol excess and evidence has emerged that non-alcoholic fatty liver disease (NAFLD) may be an important cause. However, the aetiology of NAFLD in HIV infection remains unclear. **Aims:** To identify the prevalence of and risk factors for NAFLD in patients with HIV and abnormal LFTs. **Methods:** A retrospective case-control study was conducted. HIV outpatients with persistently abnormal liver function (Alanine aminotransferase (ALT) ≥ 60iu/l (1.5x upper limit of normal) on ≥ 2 occasions ≥ 6 months apart) were identified. Clinical records were examined to assess demographic, clinical, biochemical and HIV characteristics. NAFLD cases were defined as patients with radiological evidence of hepatic steatosis in the absence of viral hepatitis B and C, excess alcohol intake or other causes of secondary steatosis. Controls were defined as patients who had no evidence of hepatic steatosis on ultrasound and no identifiable cause of liver disease. **Results:** Among an HIV cohort of 9500 patients, 348 patients with persistently elevated ALT were identified. Causes of elevated ALT were hepatitis C virus co-infection (24%), hepatitis B virus co-infection (2%), alcohol excess (16%), NAFLD (15%), drug induced hepatitis (9%), and other liver disease (9%). There was no identifiable cause in 26% of patients. Most cases had early stage disease; median (interquartile range) FIB-4 score of 1.35 (0.83-2.41). After exclusion criteria were applied 52 NAFLD cases were compared to 48 controls using binary logistic regression. Body mass index (BMI) [Odds ratio (OR) 1.27; 95% confidence interval (CI), 1.106-1.498; *p*=0.001], a history of hyperlipidaemia [OR, 3.434; 95% CI, 1.504-7.840; *p*=0.003], high-density lipoprotein (HDL) cholesterol [OR, 0.094; 95% CI, 0.017-0.523; *p*=0.007] and HDL: Cholesterol ratio [OR, 1.460; 95% CI 1.072-1.989; *p*=0.016] were significantly associated with NAFLD in univariate analysis. In multivariable analysis, BMI [adjusted OR, 1.236; 95% CI, 1.050-1.455; *p*=0.011] and hyperlipidaemia [adjusted OR, 4.098; 95% CI 1.284-13.083;

p=0.017] were independently associated with NAFLD. HIV-related factors were not significantly associated with NAFLD in univariate or multivariable analysis. **Conclusion:** NAFLD was an important cause of persistently raised ALT in a large cohort of HIV-infected patients and was associated with metabolic rather than HIV-related factors. Management of metabolic risk factors is a priority in this patient group.

Disclosures:

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1128
Validation of guidelines on blood-elastography combination for non-invasive fibrosis staging in NAFLD

Paul Cales[1], Alexandra Ducancelle[2], Julien Vergniol[3], Brigitte Le Bail[4], Françoise Lunel-Fabiani[2], Victor de Ledinghen[3], Jerome Boursier[1]; [1]Hepatology Department, Centre Hospitalier Universitaire d' Angers, Angers Cedex 9, France; [2]Virology, CHU, Angers, France; [3]Hepatology, CHU, Pessac, France; [4]Pathology, CHU, Pessac, France

Recent EASL international guidelines have suggested combining a blood test and liver stiffness measurement (LSM) to stage liver fibrosis in NAFLD. However, whether such a combination provides a gain in accuracy compared to its two constitutive tests has not been demonstrated statistically. Therefore, we sought firstly to compare the accuracies of these three test categories in NAFLD, and secondly to compare the accuracies of tests between NAFLD and the reference etiology, chronic hepatitis C (CHC), where most tests have been developed and validated. **Methods**. Populations included 225 patients with NAFLD and 698 with CHC (total: 923). Sixteen tests (13 blood tests, LSM with Fibroscan, and 2 combining LSM and 5 blood markers into unique scores: FibroMeters^{VCTE}) were evaluated in NAFLD and 13 in CHC. References were Metavir fibrosis staging by liver biopsy and CHC etiology. Accuracy was evaluated mainly by the Obuchowski index (OI) targeting all fibrosis stages and secondarily by AUROCs for binary diagnostic targets. **Results**. ***1/NAFLD population***: the combined FibroMeters^{VCTE} had significantly higher OIs and AUROCs for significant and severe fibrosis than their two constitutive tests. Thus, OIs were: FibroMeter^{VCTE2G}: 0.846 vs FibroMeter^{V2G}: 0.773 (p=0.002) or vs LSM: 0.808 (p=0.014). NAFLD-specific tests were less accurate than CHC-specific tests: e.g. OIs: FibroMeter^{V2G}: 0.773 vs FibroMeter^{NAFLD}: 0.716 (p=0.027) or vs NAFLD fibrosis score: 0.674 (p=0.005). ***2/ NAFLD vs CHC population***: OIs were (respectively NAFLD vs CHC in decreasing order of accuracy in NAFLD): FibroMeter^{VCTE2G}: 0.846 vs 0.812 (p=0.124), LSM: 0.808 vs 0.754 (p=0.054), FibroMeter^{ALD}: 0.802 vs 0.750 (p=0.039), Zeng score: 0.785 vs 0.734 (p=0.030), Hepascore: 0.778 vs 0.752 (p=0.300), FibroMeter^{V2G}: 0.773 vs 0.797 (p=0.422), Fib-4: 0.693 vs 0.741 (p=0.174), APRI: 0.676 vs 0.742 (p=0.081), Fibrotest: 0.670 vs 0.762 (p=0.006). ***Conclusion:*** In NAFLD, single accurate tests developed in CHC performed better than tests developed specifically for NAFLD. A test combining blood markers and LSM outperformed its constitutive tests, validating the recent EASL guidelines in NAFLD. Non-invasive fibrosis evaluation can thus be simplified in NAFLD by using a single test: LSM (or one of the best-performing blood tests developed in CHC), either alone or, preferably, combined to blood markers, i.e. a blood-elastography test, as developed in CHC.

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1129
Staging fibrosis and excluding advanced fibrosis in patients with NAFLD: comparison of non-invasive markers in an interim analysis from a prospective multicentre study

Peter J. Eddowes[1], Quentin Anstee[2], Indra Neil Guha[3], David A. Sheridan[4], Emmanouil Tsochatzis[5], Jeremy Cobbold[6], Michael E. Allison[7], Valerie Paradis[8], Pierre Bedossa[8], Philip N. Newsome[1]; [1]NIHR Liver Biomedical Research Unit and Centre for Liver Research, University of Birmingham, Birmingham, United Kingdom; [2]Institute of cellular medicine - Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom; [3]NIHR Nottingham Digestive Diseases Biomedical Research Unit, NHS Trust and University of Nottingham, Notthingham, United Kingdom; [4]Institute of Translational and Stratified Medicine, Plymouth University, Phymouth, United Kingdom; [5]UCL Institute for Liver and Digestive Health, Royal Free Hospital, London, United Kingdom; [6]Department of Gastroenterology, Oxford University Hospitals NHS Trust, John Radcliffe Hospital, Oxford, United Kingdom; [7]Department of Hepatology, Addenbrookes Hospital, Cambridge, United Kingdom; [8]Pathology department, Hôpital Beaujon, APHP, Clichy, France

Background & Aims: Hepatic fibrosis is a major determinant of clinical outcomes in non-alcoholic fatty liver disease (NAFLD) and there remains a clear need to establish the accuracy of non-invasive markers of fibrosis. This study aims to prospectively compare the diagnostic performance and ability to exclude advanced fibrosis of the following non-invasive tests in NAFLD: FibroScan, FibroMeter V, FibroMeter NAFLD, FibroMeter VCTE, NAFLD Fibrosis score (NFS), Fib4, APRI, BARD and AST/ALT ratio. **Methods:** Patients with suspected NAFLD prospectively underwent FibroScan examination and blood sampling within 2 weeks of a standard of care liver biopsy (LB) between March 2014 and January 2016 at seven UK centres. LB were staged in a blinded manner by two expert pathologists according to the NASH CRN system. Diagnostic performance was assessed in terms of area under the ROC curves (AUC). Ability to exclude advanced fibrosis was assessed using published cut-offs except for FibroMeter (FM), for which cut-offs have not yet been published. Cut-offs for FM were determined that maximized the Youden index. **Results**: 155 patients (57% male, median age 54 [IQR 20] years, median BMI 33.2 [8.1] kg/m^2) had a complete dataset for analysis. Fibrosis distribution was: F0: 23%, F1: 25%, F2: 21%, F3: 25%, F4: 6%. 43% of the patients had a NAS score ≥5. Performance summary of the tests is presented below in the table. **Conclusion:** FibroMeter VCTE, which combines biochemical parameters with liver stiffness measured by FibroScan, has the highest performance characteristics with positive and negative predictive values of 67 and 93% respectively at confirming or excluding ≥F3 fibrosis.

Performance of non-invasive fibrosis scores

	Performance to stage fibrosis (AUC)			Ability to exclude F≥3		
Fibrosis scores	F≥2	F≥3	F=4	Cutoff	PPV	NPV
FibroScan	0.79 [0.72-0.86]	0.84 [0.77-0.90]*	0.92 [0.85-0.98]	9.6†	0.65	0.87
FM VCTE	0.80 [0.73-0.87]	0.89 [0.83-0.95]	0.93 [0.87-1.00]	0.41‡	0.67	0.93
FM V	0.75 [0.67-0.82]*	0.83 [0.76-0.90]*	0.89 [0.79-0.99]	0.40‡	0.55	0.91
FM NAFLD	0.74 [0.66-0.82]*	0.81 [0.74-0.89]*	0.85 [0.74-0.96]*	0.33‡	0.59	0.89
NFS	0.70 [0.61-0.78]*	0.78 [0.70-0.85]*	0.80 [0.68-0.92]*	-1.445†	0.51	0.90
				0.676†	0.64	0.72
Fib4	0.72 [0.64-0.80]*	0.81 [0.73-0.88]*	0.87 [0.79-0.95]*	1.30†	0.61	0.87
				3.25†	0.67	0.71
APRI	0.71 [0.62-0.79]*	0.71 [0.63-0.80]*	0.82 [0.74-0.90]*	1†	0.54	0.70
AST/ALT	0.59 [0.50-0.68]*	0.69 [0.60-0.78]*	0.77 [0.61-0.93]*	0.8†	0.46	0.79
				1†	0.50	0.74
BARD	0.65 [0.57-0.74]*	0.69 [0.61-0.78]*	0.73 [0.63-0.84]*	2†	0.41	0.84

* AUC significantly inferior from FM VCTE (Delong test). Cut-offs were either as published (†) or established by maximizing Youden index (‡).

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1130
Low Socioeconomic Status Is Associated With Greater Disease Severity And Comorbidities In Those With Nonalcoholic Fatty Liver Disease

Mohammad Siddiqui[1], Patricia H. Belt[2], James Tonascia[2], Laura Wilson[2], Rohit Kohli[3], Jeanne M. Clark[2], Melissa Contos[1], Danielle Brandman[4], Arun J. Sanyal[1]; [1]Virginia Commonwealth University, Richmond, VA; [2]John Hopkins University, Baltimore, MD; [3]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [4]UCSF, San Francisco, CA

Lower socioeconomic status has been associated with worse outcomes in many chronic medical diseases like diabetes and hypertension. However, there is no data describing the impact of socioeconomic status in patients with nonalcoholic fatty liver disease (NAFLD) and associated metabolic diseases. Therefore, the aim of the current study is to evaluate disease severity and prevalence of metabolic syndrome and its component in patients with NAFLD based on combined household income. **METHODS:** This was a retrospective analysis of the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) database, which included adult patients (age>18 years) with histologically confirmed NAFLD. Baseline combined household income was collected and the cohort was divided into those with household income of <$50,000 (low household income or LHI) or ≥$50,000 (high household income or HHI). Histological parameters, disease severity and medical co-morbidities were compared across the two groups. **RESULTS:** A total of 1,691 patients (N=663 for LHI and N=1,028 for HHI) were included in the current analysis. Female gender (63% vs. 58%; P<.0001) and non-Caucasian race (23% vs. 16%, P=.0001) were over-represented in the LHI group. LHI cohort had higher BMI (35.6±6.6 vs. 33.5±6.1 kg/m^2; P<0.0001) and were more likely to have diabetes (50% vs. 33%; P<.0001) and metabolic syndrome (69% vs. 60%; P<.0001) compared to HHI group. Serum alanine aminotransferase levels of 56 U/L (IQR 36-85 U/L) in the HHI was significantly higher than 50 U/L (IQR 32-75 U/L, P=0.03) observed in LHI cohort. No differences in distribution of steatosis grade and lobular inflammation were observed between the two cohorts. However, the LHI cohort was more likely to have hepatocellular ballooning (68% vs. 61%; P<.01). A higher percentage of the LHI (31% vs. 23%; P=.002) had more than mild portal inflammation, a histological marker of disease progression in NAFLD. Finally, subjects in the LHI cohort were more likely to have NASH (59% vs. 52%, P=.01) and advanced fibrosis (36% vs. 29%, P<.01) than the HHI cohort. **CONCLUSION:** In patients with NAFLD, lower household income is associated with histologically more advanced disease and higher prevalence of metabolic syndrome.

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1131
Hepatic DNA Damage Response with Dysregulation of Ataxia Telangiectasia Mutated and Related Signaling Pathways Characterizes Liver Injury in Nonalcoholic Steatohepatitis

Preeti Viswanathan[1], Priya Gupta[2], Yogeshwar Sharma[2], Sanjeev Gupta[2]; [1]Pediatric Gastroenterology and Hepatology, Childrens Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY; [2]Medicine and Pathology, Marion Bessin Liver Centre, Albert Einstein College of Medicine, New York, NY

Factors driving progression of liver disease in NASH versus in simple hepatic steatosis are not well understood. Rapidly rising rates in NASH of serious complications, e.g., cirrhosis or HCC, require that further pathophysiological mechanisms are identified, such that at-risk people may be segregated early for suitable interventions. As DNA damage response (DDR) associated with persistent oxidative stress serves major roles in hepatotoxicity and cancer, we examined ATM and related pathway-specific perturbations in human livers with NASH. **Methods and Results:** Tissue samples from human liver explants were categorized histologically as normal (Group 1), fatty liver (Group 2) and NASH (Group 3) (n=6 ea). Total RNA was extracted from multiple samples per group and probed with an array of 84 genes for pathways in DDR. Normalized gene expression levels were compared by 2-ΔΔCt method with annotations of 2-fold up- or down-regulated genes in various groups by Ingenuity Pathway Analysis. We noted most significant differences in comparisons of Group 1 (healthy) and Group 3 (NASH) samples with over representation of DDR pathways, including ATM, BRCA and multiple other regulators of cell cycle, checkpoint controls and DNA damage/repair mechanisms. These pathways included key downstream regulators of ATM/ATR-related DDR, i.e., Chek2 and Chek1, as well as other genes. Pathways related to cancer were highly prominent in Group 3 indicating disease progression in tissue samples studied. To substantiate RNA level findings in tissues, we immunostained liver sections for γH2AX - an early marker of DNA double-strand breaks – and found 30-40% hepatocytes expressed γH2AX in Group 3 (NASH), whereas only rare hepatocytes in Groups 1 or 2 were γH2AX-positive, p<0.05. Next, to verify whether ATM-related gene expression changes were also present at protein level, we studied tissue lysates with spotted arrays for 1300 phosphoproteins representing most major signaling pathways to identify 2-fold or greater differences in expression. This analysis confirmed prevalence in Group 3 samples of numerous activated phosphoprotein members with up to 100-fold greater expression in ATM, BRCA,

and other related DNA damage/repair pathways, along with pathways of cancer, oxidative stress, inflammation, cell cycling and checkpoint controls, etc. **Conclusions**: DDR related to ATM pathways separated NASH from fatty liver or normal liver. Substantial increases in this ATM-related DDR will likely be of pathophysiological and prognostic significance for liver injury, remodeling and oncogenesis in NASH. This should be appropriate for developing markers to identify and characterize NASH at early stages.

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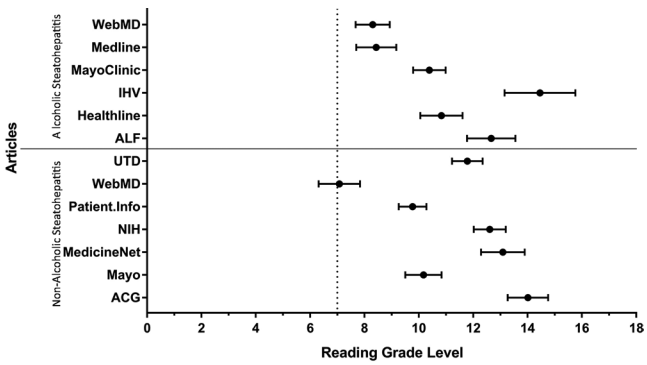
1132
Analysis of Online Patient Education Materials for Alcoholic and Non-alcoholic Steatohepatitis

Rishabh Gulati[1], Mohammad Nawaz[2], Laura Rotundo[1], Nikolaos Pyrsopoulos[2]; [1]MEDICINE, RUTGERS NEW JERSEY MEDICAL SCHOOL, Newark, NJ; [2]Gastroenterology and Hepatology, RUTGERS NEW JERSEY MEDICAL SCHOOL, Newark, NJ

Background & Aims Role of the Internet is ever increasing in the present era as the first source of medical information. Imprecise, partial comprehension of textual information limits its efficacy in communicating the disease process to the patient. Initially applied by the Military, readability tests have since been utilized in a variety of fields to adjudge comprehension level of documents. Here, we report a comparative readability analysis of online patient-centered text pertaining to Alcoholic hepatitis (AH) & Non-Alcoholic Steatohepatitis (NASH). Methods Patient-centered information from websites of ACG, American Liver Foundation (ALF), Healthline.com, Institute of Human Virology (IHV), Mayo Clinic, Medline, Medicinenet.com, National Institutes of Health (NIH), Patient.info, Uptodate & WebMD were downloaded & processed in Microsoft Word. All data were formatted & categorized into subsections. Propriety information & medical terms were expunged to limit bias. Text was then analyzed for their specific level of readability using six validated readability metrics. Results Modified documents for NASH had a mean grade 1 lower than their original counterparts & 0.24 lower for AH. The highest mean readability grade level for AH was recorded by IHV (14.15±0.6 grade levels) & for NASH by ACG (14±0.6grade levels). The least reading grade level for AH was recorded by NIH (7.89±1.1) & by WebMD (7.1±0.61) for NASH. Treatment subsection had the highest mean grade level both for AH (11.72±1.19) & NASH (11.9±0.61). ANOVA analysis showed significant differences in reading grade level depending on the source website($p<0.05$), & subsection when compared with all readability tests. The treatment section was usually the most difficult section written when compared to other subsections($p<0.05$). Conclusions Patient education material, with the exception of WebMD, is above the recommended 6th grade level. Treatment section is often the most difficult section to comprehend. Greater emphasis on clear & simple language is warranted to increase quality & comprehension of online patient education resources.



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1133
Subtle Iron Deficiency is Common During Vitamin E Treatment For NAFLD

Yaron Rotman, Shilpa Lingala, Nevitt Morris; Liver & Energy Metabolism Unit, Liver Diseases Branch, NIDDK, NIH, Bethesda, MD

Introduction & Aim: Vitamin E (VitE) is an effective treatment for non-alcoholic steatohepatitis (NASH). VitE has been associated with hemorrhagic stroke and platelet dysfunction, but similar events were not reported in studies of VitE in NASH. After encountering a patient with gastrointestinal (GI) bleeding on VitE therapy, we aimed to determine the risk of iron (Fe) deficiency in non-alcoholic fatty liver disease (NAFLD) patients treated with VitE. **Methods**: Hemoglobin (Hb), MCV, RDW and ferritin were monitored prospectively and frequently in 20 patients with biopsy-proven NAFLD in an ongoing randomized trial (NCT01792115) of different doses of natural VitE (200, 400 or 800 IU/d) with mean treatment duration of 24 weeks (4-144). Subjects with decompensated cirrhosis, coagulopathy or thrombocytopenia were excluded. To determine specificity to VitE treatment, we compared rates of Fe deficiency to historic data from a similar trial at our center with 48 weeks of metformin (Loomba, AP&T, 2009), as well as to available data from the PIVENS trial (Sanyal, NEJM, 2010) **Results**: 10 subjects (50%) exhibited new-onset (8) or worsening of preexisting (2) Fe deficiency after a median VitE treatment of 7.5 weeks (4-12). Anemia (Hb 9.1-11.2 g/dL) was seen in 5 patients (25%) after a median of 24 weeks (20-36), while 5 subjects had Fe deficiency without anemia. Of 7 patients with complete workup, a GI source was found in 6 (86%), including colonic diverticulosis, gastric ulcer, gastric hyperplastic polyp and hemorrhoids. One subject was on aspirin, and 6 (60%) had a past history of Fe deficiency. Notably, Fe deficiency spontaneously resolved without VitE cessation in 4 subjects. No bleeding or anemia occurred after a week 4 on-treatment liver biopsy. Fe deficiency occurred in all 3 diabetics (100%) compared to 7/17 (41%) non-diabetics ($p<0.01$, Mantel-Cox). Age, sex, NASH activity score, cirrhosis and VitE dose were not associated with Fe loss. In comparison, only 3/17 (18%) of metformin-treated patients developed mild Fe deficiency (without anemia), a significantly lower rate than with VitE ($p=0.02$, Mantel-Cox). In the PIVENS trial (which excluded diabetics), anemia or Hb decline did not differ between the VitE and placebo arms at weeks 24, 48 or 96, but red cell indices were not available. **Conclusion**: Occult GI bleeding and Fe deficiency

are common during VitE treatment for NAFLD, likely reflecting its effect on platelet function, which in turn may increase the risk for bleeding from preexisting GI lesions. Close monitoring of iron status is warranted during the first 3 months of treatment, especially in diabetics and subjects with past history of Fe deficiency.

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1134
Renin-angiotensin system inhibitors, type 2 diabetes and fibrosis progression in patients with NAFLD

Serena Pelusi[1], Salvatore Petta[2], Chiara Rosso[3], Vittorio Borroni[1], Anna Ludovica Fracanzani[1], Paola Dongiovanni[1], Antonio Craxi[2], Elisabetta Bugianesi[3], Silvia Fargion[1], Luca Valenti[1]; [1]Internal Medicine, University of Milano, Fondazione IRCCS Ca Granda, Milano, Italy; [2]University of Palermo, Palermo, Italy; [3]University of Torino, Torino, Italy

Background&Aims: The clinical determinants of fibrosis progression in nonalcoholic fatty liver disease (NAFLD) are still under definition. Aim of this study was to assess the clinical determinants of fibrosis progression rate (FPR) in NAFLD patients with baseline and follow-up histological evaluation, with a special focus on the impact of pharmacological therapy. ***Methods:*** In an observational cohort of 118 Italian patients from tertiary referral centers, liver histology was evaluated according to Kleiner. Independent predictors of FPR were selected by a stepwise regression approach. ***Results:*** Median follow-up was 36 months (IQR 24-77). Twenty-five patients (18%) showed some amelioration, 63 (53%) had stability, 30 (25%) had progression of fibrosis. Patients with nonalcoholic steatohepatitis (NASH) had similar demographic and anthropometric features, but a higher prevalence of type 2 diabetes (T2D; p=0.010), and use of renin-angiotensin axis system (RAS) inhibitors (p=0.005). Fibrosis progression was dependent of the length of follow-up, and was associated with, but did not require, the presence of NASH (p<0.05). Both fibrosis progression and faster FPR were independently associated with higher APRI score at follow-up, absence of treatment with RAS inhibitors, and T2D diagnosis at baseline. There was a significant interaction between use of RAS inhibitors and T2D on FPR (p=0.002). RAS inhibitors were associated with slower FPR in patients with (p=0.011), but not in those without (p=NS) T2D. ***Conclusions:*** NASH is not required for fibrosis progression in NAFLD, whereas T2D seems to drive fibrogenesis independently of hepatic inflammation. Use of RAS inhibitors may contrast fibrosis progression especially in high-risk patients affected by T2D.

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1135
The Trend of Nonalcoholic Steatohepatitis (NASH) among Adults awaiting Liver Transplantation in the United States over the Next Decade

Kaveh Hajifathalian[1], Ibrahim Hanouneh[2], Arthur J. McCullough[1]; [1]Cleveland Clinic Foundation, Cleveland, OH; [2]Minnesota Gastroenterology, Minneapolis, MN

Background Nonalcoholic Steatohepatitis (NASH) is currently the second leading indication for liver transplantation (LT) in the United States. Several studies have predicted NASH to become the leading indication for liver transplantation. However, none have focused on whether this increase trend of NASH will continue during the coming decade. The aim of the study is to predict the future trend of NASH among adults awaiting liver transplantation in the United States using data from Organ Procurement and Transplantation Network (OPTN) as well as National Health and Nutrition Examination Surveys (NHANES). Methods We extracted data from available NHANES rounds on prevalence and secular trend of metabolic risk factors from 1988 through 2014, namely BMI, fasting plasma glucose, DM, systolic blood pressure, total cholesterol, and triglyceride. We also extracted data from OPTN datasets on frequency and secular trend of primary diagnoses at the time of liver transplantation between 2001 and 2012. Using a 10-year lag time we used the prevalence of metabolic risk factors to predict the future prevalence of NASH as the main diagnosis at the time of liver transplantation. Results Between 2001 and 2012 NASH shows a significant increasing trend as the main diagnosis at the time of liver transplantation, going from less than 1% to more than 8% (p<0.001). In univariate analysis population prevalence of metabolic risk factors, namely BMI ((p<0.001), fasting plasma glucose (p=0.031), systolic blood pressure (p<0.001), and total cholesterol (p=0.010) show a statistically significant association with frequency of NASH as the main diagnosis at the time of liver transplantation. Assuming the observed trend between 2001 and 2012 will continue, a univariate model based on calendar year predicts that at 2024 NASH will be the main diagnosis for 20.4 % of the liver transplantations (95% CI 17.5-23.4). The best multivariate model including BMI and systolic blood pressure in addition to calendar year decreases this prediction to 16.0% (95% CI 6.1-25.9). Conclusions During the previous decade, prevalence of NASH as the main cause of liver disease has been increasing among transplant patients. The observed slowing in the increasing trends of obesity and hypertension predicts a subsequent slowing in the increasing trend of NASH over the next decade.

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1136
Exclusion of Clinically Significant Non-Alcoholic Fatty Liver Disease with Multi-Parametric Magnetic Resonance Imaging: A Prospective Evaluation

Peter J. Eddowes[1], Natasha McDonald[2], Nigel P. Davies[3], Scott I. Semple[4], Stefan G. Hubscher[1,5], Timothy J. Kendall[6], James Hodson[7], Philip N. Newsome[1], Catherine Kelly[8], Amy H. Herlihy[8], Matthew D. Kelly[8], Jonathan Fallowfield[2], Gideon M. Hirschfield[1]; [1]Centre for Liver Research, University of Birmingham, Birmingham, United Kingdom; [2]MRC Centre for Inflammation Research, University of Edinburgh, Edinburgh, United Kingdom; [3]Medical Physics, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; [4]Clinical Research Imaging Centre, University of Edinburgh, Edinburgh, United Kingdom; [5]Department of Cellular Pathology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; [6]Division of Pathology, University of Edinburgh, Edinburgh, United Kingdom; [7]Institute of Translational Medicine, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; [8]Perspectum Diagnostics Ltd., Oxford, United Kingdom

Aims Measurement of hepatic T1 with multi-parametric magnetic resonance imaging (MRI) has been shown to correlate with fibrosis, steatosis and inflammation. This study aims to prospectively evaluate multi-parametric MRI in patients undergoing

investigation for Non-Alcoholic Fatty Liver Disease (NAFLD) in secondary care. Methods 50 consecutive patients from 2 centres underwent non-contrast MRI, blood sampling and FibroScan in the 2 weeks prior to a standard of care liver biopsy (LB). MRI sequences generated fat fraction (PDFF), T1 and T2* maps. Hepatic iron excess shortens T1 independently of fibrosis so iron corrected T1 (cT1) was calculated from measured T1 and T2* using Liver*Multiscan* software (Perspectum Diagnostics, Oxford, UK). Histological features of NAFLD were scored according to the NASH-CRN system by pathologists blinded to the MRI findings. Results 38 patients had non-alcoholic steatohepatitis (NASH) and 12 simple steatosis (SS), with similar patient demographics in the two groups. Overall the median age was 54 (range 18-73) years. Mean (±SD) BMI was 33.6 (±5.1) Kg/m^2 with 28 (56%) males and 43 (86%) Caucasians. Multi-parametric MRI had high accuracy for assessing the severity of steatosis. Mean PDFF for grades 1, 2 and 3 steatosis were 7.6, 15.7 and 21.5% respectively (Spearman Rho(ρ)=0.77 p<0.0001). Overall disease activity as defined by the NAFLD activity score (NAS) showed significant correlation with cT1 (ρ=0.51 p<0.0001), enhanced liver fibrosis (ELF) test (ρ=0.46 p=0.001) and liver stiffness (LS) (ρ=0.42 p=0.003). To separate NASH and SS, AUROC (95% CI) for ELF, LS and cT1 were 0.87 (0.77-0.79), 0.82 (0.70-0.94) and 0.69 (0.50-0.88) respectively. cT1 was not significantly associated with Kleiner fibrosis stage (ρ=0.25 p=0.08) although LS (ρ=0.72 p<0.0001) and ELF (ρ=0.60 p<0.0001) were. To exclude those without clinically significant disease (NASH or >F1 fibrosis) cT1 showed a greater negative predictive value (NPV) than either ELF or LS. AUROC (95%) CI, positive predictive value, NPV, sensitivity and specificity for published cut-offs for the exclusion of significant disease are outlined in table 1. Conclusion In NAFLD, multi-parametric MRI can accurately assess steatosis grade and disease activity as defined by NAS. This suggests a role in disease monitoring. The high NPV of cT1 to exclude significant disease also suggests a role in the initial assessment of patients suspected of having NAFLD thus potentially avoiding liver biopsy.

Table 1

	AUROC (95%) CI	Cut-off	PPV	NPV	Sensitivity	Specificity
cT1	0.73 (0.53-0.93)	875ms	0.88	0.83	0.97	0.50
LS	0.82 (0.69-0.94)	7.0kPa	0.88	0.40	0.76	0.60
ELF	0.89 (0.80-0.99)	7.7	0.85	0.57	0.92	0.40

Disclosures:

Catherine Kelly - Employment: Perspectum Diagnostics Ltd; Stock Shareholder: Pespectum Diagnostics Ltd

Amy H. Herlihy - Employment: Perspectum Diagnostics

Matthew D. Kelly - Management Position: Perspectum Diagnostics Ltd

Gideon M. Hirschfield - Advisory Committees or Review Panels: Intercept Pharma, GSK; Consulting: Cymabay, Novartis; Grant/Research Support: Falk Pharma, BioTie, Takeda

The following people have nothing to disclose: Peter J. Eddowes, Natasha McDonald, Nigel P. Davies, Scott I. Semple, Stefan G. Hubscher, Timothy J. Kendall, James Hodson, Philip N. Newsome, Jonathan Fallowfield

1137
Acculturation and NAFLD Risk among Hispanics of Mexican-Origin: findings from the National Health and Nutrition Examination Survey.

Maya Balakrishnan[1], Fasiha Kanwal[1,2], Hashem B. El-Serag[1,2], Aaron P. Thrift[1,3]; [1]Section of Gastroenterology and Hepatology, Baylor College of Medicine, Houston, TX; [2]Department of Medicine, Houston VA HSR&D Center for Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX; [3]Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, TX

Background: Acculturation is associated with increased risk of obesity and possibly diabetes among Hispanic-Americans. Its association with non-alcoholic fatty liver disease (NAFLD) is unknown. We evaluated the association between acculturation and NAFLD risk among Mexican-Americans using cross-sectional data from the National Health and Nutrition Examination Survey (NHANES). **Methods**: We used two separate aggregated datasets: (i) NHANES III (1988-1994) and (ii) pooled data from three continuous cycles of NHANES (years 1999-2000, 2001-2002, and 2003-2004; "NHANES 1999-2004"). Two NAFLD definitions were used in NHANES III (one based on ultrasound and the second, on elevated aminotransferases) and one NAFLD definition was used in NHANES 1999-2004 (elevated aminotransferases). Acculturation was defined in three ways: by place of birth (U.S. vs. Mexico), language preference, and generational status. We calculated adjusted odds ratios (OR) and 95% confidence intervals (CI) using multivariate logistic regression. **Results**: Compared to Mexican-born, U.S.-born Mexican-Americans had a higher prevalence of obesity, hypertension, and hypercholesterolemia, had higher income, and had more high school education, health insurance, and access to medical care. In NHANES III, birthplace was not associated with risk of NAFLD defined by ultrasound (unadjusted OR=0.85, 95% CI 0.70-1.02; adjusted OR = 0.96, 95% CI 0.72-1.27) or elevated aminotransferases (unadjusted OR=1.19, 95% CI 0.92-1.54; adjusted OR = 1.04, 95% CI 0.77-1.40). Likewise, there was no association between acculturation – defined by birthplace, language preference, or generational status – and risk of NAFLD by elevated aminotransferases in NHANES 1999-2004. **Conclusions**: Despite the greater prevalence of NAFLD risk factors among highly acculturated Mexican-Americans, there was no association between acculturation and risk of NAFLD in NHANES.

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1138
Risk factors of liver steatosis or non-alcholic steatohepatitis after living liver donor transplantation

Hisamistu Miyaaki, Satoshi Miuma, Naota Taura, Hidetaka Shibata, Kazuhiko Nakao; Department of Gastroenterology and Hepatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Posttransplant liver steatosis occurs frequently and could affect patient's outcome. In this study, we aimed to clarify the risk factors of steatosis or non-alcoholic steatohepatitis (NASH) after living liver donor transplantation. We retrospectively examined 81 living liver transplant recipients and donors and identified risk factor of steatosis and NASH. Patients underwent liver biopsies 1 year after liver transplantation and yearly thereafter, or when abnormal liver enzyme levels were detected. Liver

steatosis (>10%) was found in 20 cases (25%). NASH was diagnosed in 7 patients (8.6%). The average time to steatosis after liver transplantation was 2.74±1.55 years. Patients with liver steatosis group was younger than that without liver steatosis (steatosis: no-steatosis=50.3±10.9: 58.4±8.4, p=0008). The prevalence of steatosis was significantly higher in donors with steatosis than that without steatosis (steatosis: no-steatosis=52% :16%, p<0.01). Likewise, donor steatosis was found to be significantly associated with NASH (NASH: NAFL: no steatosis=85%:35%:16%) On multivariate analysis also showed recipient age (p<0.001) and donor steatosis (p<0.001) as risk factors of liver steatosis. Forty -three of 81 recipient and donor were examined the single-nucleotide polymorphisms (SNPs) of the patatin-like phospholipase 3 gene (PNPLA3), which have been identified as predictors of severity of non-alcoholic fatty liver disease. There was no significant difference of the prevalence of liver steatosis among recipients SNPs. On the other hand, liver steatosis was seen in a significantly higher number of donors with PNPLA3 GG alleles than in those with CC and CG (CC: CG: GG=7%:26%:60%, p<0.05). All Patients (3cases) with NASH showed PNPLA3 GG alleles. In conclusions, donor factors (donor steatosis, genotype) affect the risk of liver steatosis and NASH after living liver transplantation.

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1139
Volixibat, a minimally absorbed, oral, apical sodium-dependent bile acid transporter (ASBT) inhibitor, increases bile acid excretion, reduces serum lipids, is safe and tolerable in overweight and obese subjects, a population characteristic of NASH

Melissa Palmer[1], Lee Jennings[1], Debra Silberg[2], Caleb Bliss[1], Patrick Martin[1]; [1]Shire, Lexington, MA; [2]Shire, Zug, Switzerland

Background: Abnormal cholesterol metabolism and accumulation of toxic free cholesterol in hepatocytes may result in hepatic inflammation and fibrosis, and is a potential factor contributing to the pathogenesis of NASH. Accordingly, removal of cholesterol from the liver is a treatment approach that could decrease and possibly reverse damage. Volixibat (SHP626, formerly LUM002) blocks bile acid (BA) reabsorption by inhibiting the ASBT in the terminal ileum. Consequently, BAs are excreted in the feces forcing the liver to synthesize new BA from cholesterol in the liver and serum. It is hypothesized that inhibition of BA reuptake could lead to therapeutically beneficial metabolic, anti-inflammatory, anti-steatotic, and anti-fibrotic effects in NASH. **Aim:** To assess the safety, tolerability, pharmacodynamics (PD) and pharmacokinetics (PK) of volixibat administered for 12 days. **Methods:** Double-blind, randomized, placebo (PBO)-controlled, dose-finding, Phase 1 study, of overweight or obese men and non-childbearing women (18–65 years old) randomized to 7 cohorts of varying volixibat dose (2–80mg) and regimen (once daily (QD), twice daily (BID) or titration). Evaluations included PD assessments (fecal BA and serum 7α-hydroxy-4-cholesten-3-one [C4] concentration – a marker of synthesis of BA from cholesterol), PK, stool hardness (Bristol Stool Chart [BSC]), safety and tolerability. **Results:** 84 subjects were randomized to volixibat (n=63) or PBO (n=21). Consistent with the minimal absorption of volixibat, PK could not be calculated. Mean (±SD) daily fecal BA excretion was higher in subjects receiving volixibat (930.61 ± 468.965 μmol) than in those receiving PBO (224.75 ± 195.403 μmol). Maximal inhibition of BA reabsorption occurred at volixibat doses ≥20mg QD; 10 mg QD was about two thirds of maximal effect, and 5 mg BID was about one third greater than 10 mg QD and comparable to 20 mg QD. On the final day of dosing (Day 12), mean serum C4 concentration was higher with volixibat than PBO. Median (range) reduction of 0.70 (-2.8 to 0.4) mmol/L in total cholesterol and of 0.6990 (-3.341 to 0.570) mmol/L in LDL cholesterol was observed with volixibat. While, overall, volixibat was considered to be safe and well-tolerated, frequency of bowel movements increased from an overall median of 1 daily evacuation (range: 0–4) predose to 2 evacuations (range: 0–8) during treatment, and was not dose-dependent. Proportionately more stool samples were rated Type 6 or 7 (BSC) with volixibat than PBO. There were no serious adverse events; all subjects completed the trial. **Conclusions:** This dose-finding study supports further investigation of volixibat in patients with NASH.

Disclosures:

Melissa Palmer - Employment: Shire; Management Position: Shire; Stock Shareholder: Shire

Lee Jennings - Independent Contractor: Shire

Debra Silberg - Employment: Shire

Caleb Bliss - Employment: Shire; Stock Shareholder: Shire

Patrick Martin - Employment: Shire; Management Position: Shire; Stock Shareholder: Shire

1140
Evaluation of the Safety and Pharmacokinetic Effects of the Oral, Non-Steroidal Farnesoid X Receptor Agonist GS-9674 in Healthy Volunteers

Brian Kirby, Constantine S. Djedjos, Joanne Birkebak, Qinghua Song, Krystyna Grycz, Jonna Weston, Mani Subramanian, William Watkins, Robert P. Myers, Anita Mathias; Gilead Sciences, Foster City, CA

Brian Kirby, C. Stephen Djedjos, Joanne Birkebak, Qinghua Song, Krysia Grycz, Jonna Weston, G. Mani Subramanian, William Watkins, Robert P. Myers, Anita Mathias Gilead Sciences, Inc., Foster City, CA, USA **Background**: GS-9674 is a selective, non-steroidal agonist of the Farnesoid X Receptor (FXR) in development for the treatment of nonalcoholic steatohepatitis (NASH) and cholestatic liver disorders. GS-9674 is highly selective for FXR over drug metabolism and transport regulating nuclear hormone receptors (e.g. PXR, CAR or AhR), highly protein bound, has a low potential for systemic inhibitory based drug-drug interactions, and undergoes oxidative metabolism. This first-in-human study evaluated the s afety, pharmacokinetics (PK), and pharmacodynamic (PD) effects of GS-9674 in healthy volunteers. Safety and PK data are presented herein. **Methods**: In this randomized, double-blind, placebo-controlled study, subjects received single and multiple doses (QD, 14 days) of GS-9674 (10, 30, 100, or 300 mg while fasting [n=12/cohort]) or matching placebo (n=3/cohort) with a 6-day washout between the single and multiple dose periods. Safety and PK parameters of GS-9674 and GS-716070 (major circulating metabolite of GS-9674, ~40-fold less potency against FXR compared to GS-9674) were summarized by treatment group. Data on the pharmacodynamic effects of GS-9674 are presented elsewhere. **Results**: All enrolled subjects (N=60) completed the study. The rate of adverse events was similar between placebo (33%) and actively treated subjects (33%, 25%, 33%, and 25%, in the 10, 30, 100, and 300 mg cohorts, respectively). All adverse events were non-serious, grade 1 or 2 in severity, and were considered unrelated to GS-9674. GS-9674 was rapidly absorbed with maximum plasma concentrations (C_{max}) occurring 1.25 to 3.25 hours post-dose. Across the doses tested, GS-9674 exhibited a median steady-state half-life ($T_{1/2}$) of 6

to 16 hours. In general, GS-9674 AUC and C_{max} increased less than dose-proportionally upon single and multiple dosing. As expected due to the short $T_{1/2}$ of GS-9674 and once daily dosing, minimal to no accumulation was observed for AUC, C_{max} or C_{24} from single to multiple dose administration. The $T_{1/2}$ of GS-716070 was similar to that of GS-9674. At the 100 mg dose of GS-9674, the AUC and C_{max} of GS-716070 were ~60% and ~35%, respectively of values observed for GS-9674. **Conclusion:** Single and multiple daily doses of the non-steroidal FXR agonist GS-9674 were well tolerated in healthy subjects. The safety, PK profile, and biological activity of GS-9674 support its evaluation in subjects with NASH and cholestatic liver disorders.

Disclosures:

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Constantine S. Djedjos - Employment: Gilead Sciences

Joanne Birkebak - Employment: Gilead

Krystyna Grycz - Employment: Gilead Sciences, Inc.; Stock Shareholder: Gilead Sciences, Inc.

William Watkins - Employment: Gilead Sciences

Robert P. Myers - Employment: Gilead Sciences, Inc.; Stock Shareholder: Gilead Sciences, Inc.

Anita Mathias - Employment: Gilead Sciences Inc.,

The following people have nothing to disclose: Qinghua Song, Jonna Weston, Mani Subramanian

1141
Assessment of change of intrahepatic fat amount using controlled attenuation parameter in clinical trial

Sang Bong Ahn[1], Dae Won Jun[2], Jae Yoon Jeong[2], Joo Hyun Sohn[2]; [1]Internal Medicine, Eulji General Hospital, Seoul, Korea (the Republic of); [2]Department of Internal Medicine, Hanyang University School of Medicine, Seoul, Korea (the Republic of)

Background: Multi-echo modified Dixon (mDixon) sequence (MR-PDFF) is a safe and non-invasive alternative for the quantification of hepatic fat content. And it has accepted reasonable method to assess the change of hepatic fat amount in phase II study. Recently controlled attenuation parameter (CAP) has been showed good correlation with intrahepatic fat amount compare to liver biopsy as well as MRS data in large cross sectional cohort. However there is little known whether change of CAP scores can be used in clinical trial. We investigated the correlation with CAP and MRS by serial examination in clinical trial setting. Methods: Sixty-five NAFLD patients were evaluated with MRS and transient elastography including CAP in clinical study. Both MRS and CAP were evaluated after three month probiotic clinical trial in patients with NAFLD. Results: Baseline CAP and MR-PDFF showed good correlation assessing hepatic steatosis (r=0.60, p<0.001). Also, changes of CAP value was also correlated with changes of intra-hepatic fat % using MR-PDFF (r=0.35, p=0.008) in clinical trial setting. Concordance rate of improvement or aggravation was comparable in both two methods. However, the less change amount was small in CAP value, the less concordance rate showed more weak with MR-PDFF. When the change of CAP value after treatment was less than 20, concordance rate with MR-PDFF was decreased to 15/25 (60%). Conclusion: CAP and MRS have a comparable diagnostic value for the hepatic steatosis quantification as well as assessing changes of hepatic fat amount in clinical trial. However, a careful interpretation of the steatosis change using CAP score should be given when the absolute change value was less than 20 in clinical trial setting.

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1142
Emerging Increase in the Prevalence and Severity of Nonalcoholic Fatty Liver Disease: Epidemiological Study from General Mediterranean Population

Salvatore Petta[1], Carola Buscemi[2], Silvio Buscemi[2], Davide Corleo[2], Vito Di Marco[1]; [1]Cattedra ed U.O.C. di Gastroenterologia ed Epatologia, Palermo, Italy; [2]Metabolism and Clinical Nutrition Laboratory, Di.Bi.M.I.S., University of Palermo, Palermo, Italy, Palermo, Italy

Background/Aims: The worldwide spread of obesity and diabetes is leading to a drastic increase in nonalcoholic fatty liver disease(NAFLD) and its complications. We aimed to assess prevalence of NAFLD and of its severity among a general Mediterranean population. **Methods:**We considered 886 consecutive individuals included in the ABCD study(ISRCTN15840340), a longitudinal observational single-centre study of a cohort representative of the general population of Sicily. All patients were negative for HCV, HBV and HIV infection, had alcohol intake <20 g/day for females and <30 g/day for males. Hepatic ultrasound(US) was used to diagnose steatosis and FibroScan(M and XL probe) to measure liver stiffness and controlled attenuation parameter(CAP). Liver stiffness>6.9 KPa was considered suggestive of significant liver fibrosis(Petta S et al, Hepatology 2015), and CAP≥310 dB was considered suggestive of moderate-severe steatosis(de Ledinghen V et al, JHEP 2014). **Results:**Steatosis by US was diagnosed in 396 individuals(44.6%) and was significantly associated with male gender, type 2 diabetes, low HDL, and visceral obesity. When splitting the analysis according to gender, steatosis was independently linked to visceral obesity(OR 2.63,95%CI1.62-4.27,p<0.001) and low HDL(OR 2.06,95%CI1.10-3.85,p=0.02) in males, and to visceral obesity(OR 2.75,95%CI1.80-4.19,p<0.001) and type 2 diabetes(OR 2.19,95%CI1.00-4.87,p=0.05) in females. The rate of US steatosis, stiffness > 6.9 kPa and CAP≥310 progressively increased from males without obesity and low HDL(35.1% steatosis;among theme 18.6% CAP≥310, and 13.5% stiffness >6.9), to those with one risk factor(from 57.7% to 62.1% steatosis;among them 42.8% CAP≥310, and from 21.4% to 23.2% stiffness >6.9), and further to those with both risk factors(74.2% steatosis;among them 35% CAP≥310, and 30% stiffness >6.9). Similarly, in females the rate of US steatosis, stiffness> 6.9 kPa and CAP≥310 progressively increased from patients without obesity and diabetes(23.7% steatosis;among them 6.1% CAP≥310, and 6.1% stiffness >6.9), to those with only one risk factor(from 33.3% to 50.8% steatosis;among them CAP≥310 from 30.5% to 54.5%, and stiffness >6.9 from 11.1% to 27.2%), and further to those with both risk factors(74.2% steatosis;among them 47.1% CAP≥310, and 26.4% stiffness >6.9). **Conclusions:**NAFLD is present in more than 40% of general population and its prevalence, as well as the prevalence of liver damage, increases according to the presence of obesity and low HDL in males, and obesity and diabetes in females. The impact of variants of PNPLA3 and TM6SF2 genes on steatosis and liver damage in this population is under investigation.

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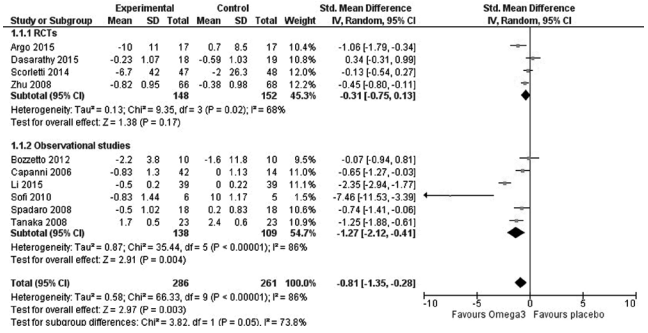
1143

Decreased Hepatic Steatosis with Omega-3-Fatty Acids: Systematic Review and Meta-Analysis

Devika Kapuria[1], Shariq Shamim[3], Kevin Kennedy[3], James H. O'Keefe[1,3], James DiNicolantonio[3], Fabrizio D'Ascenzo[4], John H. Helzberg[1,2]; [1]Department of Internal Medicine, University of Missouri-Kansas City, Kansas City, MO; [2]Department of Gastroenterology/Hepatology, Saint Luke's Hospital of Kansas City, Kansas City, MO; [3]Department of Cardiology, Saint Luke's Hospital Mid America Heart Institute, Kansas City, MO; [4]Cardiology Division, Department of Medical Sciences, University of Turin, Turin, Italy

Purpose: The prevalence of non-alcoholic fatty liver disease (NAFLD) may correlate with a deficiency of omega-3-fatty acids (ω3FA), excess of omega-6 fatty acids and refined carbohydrates in Western diets, and can be associated with coronary artery disease and metabolic syndrome. This meta-analysis collates the effect of ω3FA supplementation on hepatic steatosis. **Methods:** We searched Medline, Embase, and Ovid Databases from 1996-2016. Review of titles/abstracts, full text, and data extraction were performed. Studies were included if hepatic steatosis was present, defined by MRI, ultrasound, or histology. Data was pooled, and meta-analysis conducted using random effects model. Data was presented in standardized mean difference (SMD) and mean difference (MD). **Results:** A total of 715 studies were identified with 10 studies included for final analysis. A total of 524 patients were in the pooled cohort, with 286 (54.5%) administered ω3FA. The dose of ω3FA ranged between 2-4 grams/day and duration of treatment from 8 weeks to 18 months. A decrease in hepatic fat was observed in the ω3FA arm (SMD -0.81 95% CI -1.35 to -0.28 Chi^2 66.33%). Pooled analysis also revealed a decrease in ALT in the omega-3 arm (MD -7.64 95% CI -14.27 to -1.00 Chi^2 14.05%) and improved HOMA-IR (MD -0.55 95% CI -1.31 to 0.20 I^2 12%) and triglycerides (MD -45.97 95% CI -58.29 to –33.65 I^2 0 %). Sensitivity analysis after excluding observational studies also demonstrated reduction in liver fat (SMD -0.31 95% CI -0.75 to 0.13 Chi^2 9.35). **Discussion** ω3FA treatment is associated with a reduction in liver fat in patients with hepatic steatosis. There is conflicting data regarding reduction in hepatic fibrosis, inflammation, and ballooning degeneration, possibly because of variance in dosage levels and duration of treatment. Subgroup analyses demonstrate a reduction in ALT and decreased triglycerides and insulin resistance. With their known safety profile, ω3FA supplementation may be beneficial for reducing hepatic steatosis and ALT, improving dyslipidemia and insulin resistance, and decreasing cardiovascular risk.

Forest Plot showing association of omega-3-fatty acids with liver fat



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♦ Denotes AASLD Presidential Poster of Distinction

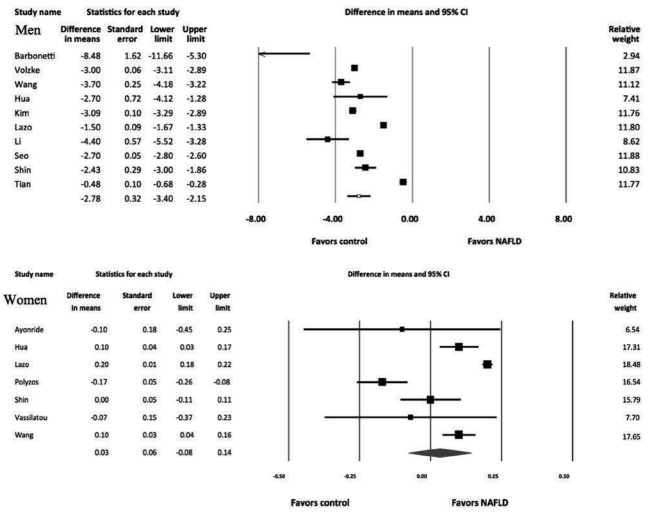
1144

Association Between Endogenous Sex Hormones and Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis

Veeravich Jaruvongvanich[2], Anawin Sanguankeo[1], Sikarin Upala[1]; [1]Bassett Medical Center, Cooperstown, NY; [2]University of Hawaii, Honolulu, HI

Background: Endogenous sex hormones are associated with the risk of diabetes and metabolic syndrome. Recent studies suggested the role of these hormones in nonalcoholic fatty liver disease (NAFLD). We conducted a systematic review and meta-analysis of observational studies investigating the association between sex hormones and NAFLD. **Methods**: A comprehensive search of the databases of the MEDLINE and EMBASE was performed from inception through April 2016. The inclusion criterion was the observational studies that assessed the association of serum total testosterone (TT) and sex-hormone binding globulin (SHBG) and NAFLD. We calculated pooled mena difference (MD) and odds ratio (OR) of TT and SHBG with 95% confidence intervals (CI) comparing between subjects with and without NAFLD by using random-effects model. **Results**: Sixteen trials comprising 13,721 men and 5,840 women met the inclusion criteria. TT levels were lower in men with NAFLD (MD = -2.78 nmol/l, 95%CI -3.40 to -2.15) than in those without. Men with higher TT levels had lower odds of NAFLD (OR=0.56, 95%CI 0.39 to 0.80), whereas higher TT levels increased the odds of NAFLD in women (OR=1.40, 95%CI 1.11 to 1.77). In both sexes, SHBG levels were lower in patients with NAFLD than controls (men: MD = -8.72 nmol/l, 95%CI -16.70 to -0.75; women: MD = -17.05, -23.58 to -10.53) and higher SHBG levels were associated with reduced odds of NAFLD (men: OR=0.35, 95%CI 0.25 to 0.45; women: OR=0.77, 95%CI 0.67 to 0.89). **Conclusion**: Our meta-analysis demonstrated a sex-dependent association between TT and NAFLD. Lower TT levels are associated with men with NAFLD and inversely associated with women with NAFLD, whereas higher SHBG levels are associated with lower NAFLD odds in both men and women.

Random effects pooled mean difference of TT in subjects with and without NAFLD in men and women



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The following people have nothing to disclose: Veeravich Jaruvongvanich, Anawin Sanguankeo, Sikarin Upala

1145

BCAT1 is Associated with Clinical Decompensation in NAFLD: A Pilot Study

Kara Wegermann[1], Ricardo Henao[2], Yiping Pan[3], Anna Mae Diehl[3], Manal F. Abdelmalek[3], Cynthia A. Moylan[3]; [1]Department of Medicine, Duke University Medical Center, Durham, NC; [2]Electrical and Computer Engineering, Duke University, Durham, NC; [3]Division of Gastroenterology, Duke University Medical Center, Durham, NC

Background Recently, a 64 gene expression (GEx) profile differentiated mild and severe nonalcoholic fatty liver disease (NAFLD) fibrosis independent of clinical factors. We evaluated whether GEx profiling was associated with clinical decompensation and death, aiming to identify molecular pathways linked to morbidity and mortality in NAFLD. **Methods** We performed a retrospective analysis of patients with biopsy-proven NAFLD whose liver tissue was previously evaluated for GEx via microarray. Patients were assessed from liver biopsy (2007-2009) until death, liver transplantation, or study end. Outcomes included decompensation (ascites, hepatic encephalopathy, hepatocellular carcinoma, or variceal bleeding) and a composite incorporating stroke, myocardial infarction, and death. Associations between the composite outcome and GEx were quantified using generalized linear models controlling for age, body mass index, diabetes mellitus and fibrosis stage. **Results** Of the 86 patients included, most (67%, n=58) were female and white (89%, n=77). Median age at study entry was 53 years (range, 27 to 81). Median follow up was1986 days (range, 0 to 2997). Four patients, all white women, experienced clinical outcomes (two with hepatic decompensation, two with strokes). Fibrosis at study entry ranged from stage 1 to 4. Forty-two genes showed significant differential expression ($p<0.05$) and a two-fold change in expression between patients with and without the composite outcome. Two probes on branched chain amino-acid transaminase 1 (*BCAT1*) were upregulated (p=0.02; fold change 2.1, 2.2). Principal Components Analysis and hierarchical clustering confirmed that GEx aided in differentiating patients with outcomes from those without. **Conclusions** *BCAT1* initiates the catabolism of essential branched chain amino acids and here we found it to be upregulated in NAFLD patients with clinical decompensation. Its upregulation has previously been associated with high liver fat content and poor prognosis in hepatocellular carcinoma. Our results suggest that perturbations in hepatic metabolism are associated with poor outcomes in NAFLD patients, and points toward the need for further investigation of such targets.

Table 1: Selected differentially expressed genes ($p < 0.05$) in patients with and without outcomes

Gene	GO Function	Fold Change
BCAT1	Branched chain amino acid metabolism	2.13, 2.20
ADAMDEC1	Metalloendopeptidase activity, Immune response	3.47
PF4V1	Chemokine activity	3.08
BCL2A1	Apoptosis signaling	2.24
ITGAM	Integrin, Cell adhesion	2.33
MTHFD2	One carbon metabolism	2.13

Disclosures:

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The following people have nothing to disclose: Kara Wegermann, Ricardo Henao, Yiping Pan, Anna Mae Diehl, Cynthia A. Moylan

1146

Vitamin D is Not Associated with Histologic Severity in NAFLD: Results of a Paired Clinical and Hepatic Gene Expression Profile Analysis

Yuval A. Patel[1], Ricardo Henao[2], Cynthia A. Moylan[1], Cynthia D. Guy[3], Dawn L. Piercy[1], Anna Mae Diehl[1], Manal F. Abdelmalek[1]; [1]Division of Gastroenterology and Hepatology, Duke University Medical Center, Durham, NC; [2]Department of Electrical and Computer Engineering, Duke University, Durham, NC; [3]Department of Pathology, Duke University Medical Center, Durham, NC

Introduction: Vitamin D (VD) deficiency has been associated with obesity and insulin resistance; however, the role of VD deficiency in NAFLD is not well understood. **Aim:** To determine the relationship of serum 25-hydroxyvitamin D levels and hepatic expression of VD metabolizing genes with clinical and histologic features of NAFLD. **Methods:** 283 adults in the Duke NAFLD Clinical database with a VD level within 3 months of liver biopsy were included. 244 had NAFLD histologic features and 39 (controls) had no pathologic diagnosis. Clinical characteristics, VD level and NAFLD histologic features were summarized and compared between groups. Generalized linear models were used to analyze the association of VD levels and metabolizing genes including VD receptor (VDR), VD binding protein encoded by group specific component (GC), cytochrome P450 complexes CYP27A1, CYP2R1, CYP3A4, CYP27B1 and CYP24A1, parathyroid hormone receptor (PTH1R), retinoic X receptor (RXR), nuclear receptor coactivator (NCOA), SMAD and peroxisome proliferator-activated receptor (PPAR) with NAFLD histologic severity while adjusting for confounders and correcting for multiple comparisons. **Results:** No differences in age, gender, BMI, hypertension (HTN), hyperlipidemia (HLD), hypercholesterolemia (HCL), hypertriglyceridemia (HTG) or VD level (27.6±11.8 ng/ml vs 27.9±12.8 ng/ml; p=0.87) were noted between groups. NAFLD patients were more likely to have higher HBA1c (6.5±1.2 vs 5.9±1.0; p=0.009) and light skin (83.6% vs 64.1%, p=0.005). VD level was not associated with severity of steatosis, lobular inflammation, ballooned hepatocyte or fibrosis. In univariate analysis, of 33 candidate genes (with 98 gene probes) in mild (n=40, stage 0-1) vs advanced (n=32, stage 3-4) fibrosis, only 5 genes (with 6 gene probes) were significant after multiple comparisons. After controlling for confounders, the association decreased (Table). **Conclusions:** In our pilot study, VD levels or hepatic expression of candidate genes involved in VD metabolism are not associated with NAFLD histologic severity. Few genes of interest (SMAD2, PTH1R, NCOA7 and SMAD9) warrant further investigation in larger studies.

Hepatic Gene Expression of VD Pathway Genes

Affymetrix Probe ID	Gene	Unadjusted P-Value	*Adjusted P-Value
202426_s_at	RXRA	0.02	0.15
203075_at	SMAD2	0.05	0.08
226563_at	SMAD2	0.03	0.08
205911_at	PTH1R	0.02	0.08
225344_at	NCOA7	0.02	0.09
227719_at	SMAD9	0.03	0.08

All P-Values adjusted for multiple comparisons. *Adjusted = Age, Gender, BMI, Race, HBA1c, Diabetes Mellitus, HTN, HLD, HCL, HTG.

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1147

Usefulness of the Controlled Attenuation Parameter (CAP) for detecting liver steatosis and metabolic syndrome in health check-up

Hiroyasu Morikawa[2], Sawako K. Uchida[1], Norifumi Kawada[1]; [1]Department of Hepatology, Osaka City University, Osaka, Japan; [2]Department of Premier Preventive Medicine, Osaka City University, Osaka, Japan

Background & Aims: Currently more than three million people undergo a comprehensive health check-up for preventive medicine, called Ningen Dock, annually in Japan. Controlled attenuation parameter (CAP) evaluated with transient elastography (FibroScan) is a recent method for non-invasive assessment of steatosis. Its usefulness in clinical practice is unknown. Especially the relationship between CAP and the metabolic syndrome is not revealed. In the health check-up, we introduced CAP for the first time and prospectively investigated the relationships between CAP and clinical or biological parameters. Patients and Methods: All CAP examinations performed in 1120 participants without suspected chronic liver disease from self-report. Liver stiffness and CAP measurements were performed by FibroScan 502 touch with 3.5 MHz standard M probe by experienced operators. The following factors were analyzed for their influence on CAP value and the relationships between CAP and clinical-biological parameters: age, gender, body mass index (BMI), waist circumference, hypertension, diabetes, metabolic syndrome, alcohol use, liver stiffness measurement, and different biological parameters. Results: Characteristics of participants were as follows: males 62.6%, median age 56 (21-87) years, mean BMI 23.1 ± 3.6 kg/m2, 25.2% of participants overweight (BMI >25 kg/m2), and waist circumference 84.6 ± 8.5 cm. CAP measurement was unreliable in 98 cases (8.8%). CAP measurement failure was independently associated with FBS. Steatosis was detected in 41.4% by US (liver/kidney contrast) and 21.5% by CT (liver/ Spleen ratio, <1.1) whereas it was detected in 49.6% by the CAP (>238 dB/m). The numbers of subjects with S0 (>238 dB/m): S1 (238 to <260 dB/m): S2 (260 to <293 dB/m): S3 (<293 dB/m) steatosis according to the CAP value were 515: 150: 174: 183, respectively. Simple regression analyses indicated that CAP values were significantly correlated with BMI (r=0.556), waist circumference (r=0.515), visceral fat area (r=0.423), L/S ratio (r=-0.395), ALT (r=0.395), Triglyceride (r=0.347), and high density lipoprotein (r=-0.336; p<0.001, 95%CI). By multivariate analysis, factors associated with CAP were BMI, ALT, and Triglyceride. Conclusion: The CAP seems to be useful for immediately detecting hepatic steatosis in the comprehensive health check-up. The association of CAP with the metabolic syndrome could be of interest for preventive medicine.

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1148

The combination of Index of NASH score and liver stiffness improves the noninvasive diagnostic accuracy for severe liver fibrosis in patients with Non-Alcoholic Fatty Liver Disease

Ramy Ibrahim Kamal Jouness[1], Chiara Rosso[1], Salvatore Petta[2], Monica Cucco[1], Milena Marietti[1], Gian Paolo Caviglia[1], Maria Lorena Abate[1], Calogero Cammà[2], Antonina Smedile[1], Antonio Craxi[2], Giorgio Maria Saracco[3], Elisabetta Bugianesi[1]; [1]Department of Medical Sciences, University of Turin, Turin, Italy; [2]Sezione di Gastroenterologia, DiBiMIS, University of Palermo, Palermo, Italy; [3]Department of Oncology, University of Turin, Turin, Italy

Background and Aim: The screening for Non-Alcoholic Steatohepatitis (NASH) in subjects with Non-Alcoholic Fatty Liver Disease (NAFLD) is hampered by uncertainties around the non-invasive tools of liver damage. This study is aimed at: 1. validating the recently developed ION (Index of NASH) and 2. assessing the diagnostic performance of single and combined noninvasive tools of liver damage in a large cohort of patients with biopsy-proven NAFLD. **Material and Methods**. We analysed data from 254 Italian patients (136 from southern Italy and 118 from northern Italy) consecutively enrolled and biopsied. The following non-invasive scores of liver fibrosis were calculated according to published algorithms: ION, NFS, FIB-4. The apoptotic fragments of CK-18 (M30) were measured by ELISA immunoassorbent assay and Liver Stiffness (LS) was evaluated by FibroScan. Liver histology was scored according to Kleiner. NASH was diagnosed by the local pathologist according to joined presence of steatosis, inflammation and ballooning (with or without fibrosis). Severe fibrosis was defined as fibrosis ≥ F3. Cut-off points to rule-in or rule-out F3-F4 fibrosis were calculated by the Youden index. **Results**: In the whole cohort, the AUCs of ION and CK-18 for the diagnosis of NASH were 0.622 (NPV 44, PPV 81) and 0.599 (NPV 41, PPV 81), respectively, confirming the poor performance of the tests for the noninvasive diagnosis of NASH. Both tests performed better for the diagnosis of severe fibrosis: the AUCs of ION and CK-18 were 0.724 (NPV 86, PPV 41) and 0.693 (NPV 84, PPV 46). In the same population the AUCs of NFS, FIB-4 and LS for the diagnosis of severe fibrosis were 0.694 (NPV 86, PPV 45), 0.677 (NPV 82, PPV 45) and 0.816 NPV 88, PPV 57), respectively. Next we tested several combinations of all noninvasive tools in order to improve their diagnostic performance for the risk of severe fibrosis. The combination of ION plus LS, NFS plus LS and FIB-4 plus LS similarly improved the performance of each single test, providing a correct classification in 80%, 81% and 79% of cases, respectively. **Conclusions**: The combination of LS with either ION, NFS or FIB-4 is better than each single noninvasive test to accurately exclude severe liver fibrosis.

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1149

The Effect of 12-Months of Intensive Lifestyle Intervention on Serum Biomarkers of Hepatic Steatosis, Inflammation and Fibrosis in Adults with Type 2 Diabetes

Mariana Lazo[2,1], Menglu Liang[1], James J. Potter[2], Jeanne M. Clark[2]; [1]Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [2]Medicine, Johns Hopkins University, Baltimore, MD

Objective: Weight loss through diet and exercise is currently recommended as the treatment for NAFLD, however the efficacy of this treatment in improving NAFLD, other than reducing steatosis, in patients with type 2 diabetes is unproven. **Methods**: We evaluated participants enrolled in the Fatty Liver Ancillary Study to the Look AHEAD (Action for Health in Diabetes) trial, a multi-center clinical trial designed to assess the long-term effects of an intensive lifestyle intervention (ILI) compared to diabetes support and education (DSE) on serious cardiovascular events in overweight or obese adults with type 2 diabetes. Participants with known chronic viral hepatitis or cirrhosis, use of systemic corticosteroids, or habitual consumption of ≥14 alcoholic drinks per week were excluded from this ancillary study. Using stored serum samples, we measured FibroMax (FibroTest, SteatoTest and NashTest) and Cytokeratin-18 (CK-18) at baseline and after 1 year of the study. We used recommended lab cutoffs for steatosis, NASH, and fibrosis in our analyses. We analyzed the outcomes by treatment arm, and by amount of weight loss across treatment arms. **Results**: 123 participants randomized to ILI (n=62) or DSE (n=61) had stored specimens and were included in the analyses. At baseline, 54% were women, mean age was 61 years, mean BMI 36 kg/m^2. Based on recommended cutoffs, 53% had significant steatosis (SteatoTest≥S2), 18% had NASH (NashTest =N2), 9% had significant fibrosis (FibroTest≥F3). The median [25th and 75th percentile] CK-18 was 211 [173.0, 309.0] (U/L). After 12 months, participants assigned to ILI, as compared to DSE, lost more weight (-8.2% vs. -0.10%; p<0.01) and had a greater decline in CK-18 (-38.0 vs. -14.00; p=0.03). At 12 months, the percentage with significant steatosis decreased more among the ILI than the DSE (-13.6 vs. -5.3; p=0.06). Similarly, the percentage of participants with NASH decreased more among the ILI as compared to the DSE (-10.1 vs -3.5; p=0.04). Compared to those with little or no weight change, those with a 5% weight loss had a significantly greater decline in CK-18 and improvement in SteatoTest. There were no significant 12-month changes in FibroTest, by intervention group, or by degree of weight loss. **Conclusions**: Intensive lifestyle intervention in patients with T2DM may be beneficial in reducing hepatic steatosis and inflammation. These serum biomarkers of NAFLD-steatosis and NASH appear to be sensitive to change and may be useful to monitor treatment responses.

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Ample Sleep May Protect Against Steatosis and Steatohepatitis

James Philip G. Esteban[1], Lisa E. Rein[2], Aniko Szabo[2], Samer Gawrieh[3], Kia Saeian[1]; [1]Division of Gastroenterology and Hepatology, Medical College of Wisconsin, Milwaukee, WI; [2]Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, WI; [3]Division of Gastroenterology and Hepatology, Indiana University, Indianapolis, IN

Introduction Studies suggest that circadian rhythm disruptions result in a liver milieu that promotes steatosis and steatohepatitis. Since the sleep-wake cycle is arguably the body's most important circadian rhythm, sleep patterns may affect the natural history of non-alcoholic fatty liver disease (NAFLD). The study aims to determine if sleep duration in particular is associated with NAFLD. **Methodology** Data was obtained from combined National Health and Nutrition Examination Surveys (NHANES) from 2005-2012. Subjects with incomplete data, hepatitis B or C infection, significant alcohol intake, and hepatotoxic medication use were excluded. Subjects were divided a priori into 3 groups based on sleep duration: <6 hours, 6-9 hours and >9 hours. Multivariate regression was used to estimate the effect of sleep duration on NAFLD fibrosis score (NFS), fatty liver index (FLI) and ALT after adjusting for age, sex, ethnicity, smoking, alcohol use and caloric intake. High ALT is defined as >29 U/L in men and >22 U/L in women based on previous NHANES analyses. **Results** A total of 10,125 adults (4,585 with fasting labs) were included. Mean sleep duration was 6.92 ± 0.02 hours. A total of 1,415 had <6 hours of sleep, 8,121 had 6-9 hours, and 588 had >9 hours. People who slept <6 hours were younger, non-Hispanic Black, obese and have higher triglycerides, while those who slept >9 hours were older, female and Mexican or non-Hispanic White. People who slept 6-9 hours smoked less and were less likely to be diabetic, hypertensive and non-alcohol drinkers. In multivariate regression, sleeping <6 hours increased the odds of high probability FLI and high ALT by 41% and 26%, respectively, while sleeping >9 hours decreased the odds of high probability FLI and high ALT by 36% and 40%, respectively. Although the difference is statistically significant (p=0.01), the mean ALT of the <6 hours group is only 2.7 U/L higher than the >9 hours group. The odds of high probability NFS was increased by sleeping >9 hours in univariate (p=0.045), but not multivariate, analysis. **Conclusion** Sleeping at least 6 hours per night may protect against steatosis and steatohepatitis. Sleep duration, however, does not appear to affect fibrosis risk. The study suggests that sleep may be a modifiable risk factor for NAFLD. Further research is warranted, using biopsies to define NAFLD phenotypes and liver-related morbidity and mortality as endpoints.

Multivariate Odds Ratios of Fatty Liver, Fibrosis and High ALT

Sleep in Hours	High Prob NFS OR (CI, p-value)	High Prob FLI OR (CI, p-value)	High ALT OR (CI, p-value)
<6 vs 6-9	0.88 (0.73-1.06, p=0.179)	1.41 (1.17-1.71, p=0.001)	1.26 (1.05-1.52, p=0.015)
>9 vs 6-9	1.04 (0.73-1.47, p=0.834)	0.91 (0.64-1.27, p=0.560)	0.76 (0.60-0.96, p=0.020)
>9 vs <6	0.92 (0.65-1.29, p=0.609)	0.64 (0.43-0.95, p=0.027)	0.60 (0.45-0.81, p=0.001)

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Baseline patient characteristics and non-invasive image analysis in a Phase 2 therapeutic trial of GR-MD-02 in NASH patients with stage 3 fibrosis

Stephen A. Harrison[1], Karol Barstow[1], Adam E. Allgood[2], Peter G. Traber[2]; [1]Gastroenterology, Brooke Army Medical Center, Fort Sam Houston, TX; [2]Galectin Therapeutics, Norcross, GA

Introduction: Non-invasive approaches to the assessment of non-alcoholic steatohepatitis (NASH) with various degrees of fibrosis in the context of clinical trials is an important goal for drug development. Three leading candidates for non-invasive monitoring include multi-parametric magnetic resonance imaging (LiverMultiScan, LMS), liver stiffness measurement using vibration controlled transient elastography (Fibroscan, FS), and liver stiffness measurement using magnetic resonance elastography (MRE). Aim: To examine the baseline patient characteristics and the relationship between LMS, FS, and MRE in an ongoing single site trial of the antifibrotic GR-MD-02 in NASH patients with stage three fibrosis. (https://clinicaltrials.gov/ct2/show/NCT02421094?term=GR-MD-02&rank=6) Methods: 30 patients, all with biopsy confirmed NASH and stage 3 fibrosis, were enrolled in a double-blind, placebo-controlled clinical trial comparing placebo (15 patients) with 8 mg/kg GR-MD-02 (15 patients). All enrolled patients had baseline non-invasive assessment within one month of randomization with LMS (Perspectum Diagnostics), MRE (Siemens), and FS (Echosens). Results: The mean age and BMI of the enrolled patients were 58.2 years and 35.6 kg/m2, respectively. The cohort included 16 men and 14 women, 29 of whom were white with 12 Hispanic and one Asian and 6 had diabetes. Median (IQR, 25th-75th percentile) values for LMS, FS, and MRE were a cT1 value of 974 (950-1009) milliseconds, 14.6 (11.2-23.9) kPa, and 4.2 (3.3-5.4) kPa, respectively. There was significant correlation between FS and MRE measures of liver stiffness ($r = 0.6$, $P<0.0005$), and when two FS outliers were removed the correlation improved ($r = 0.81$, $P<0.0005$). In contrast, there was no significant correlation between LMS cT1 and either liver stiffness measurement, FS ($p=0.11$) or MRE ($p=0.12$). Conclusion: Liver stiffness measured by FS and MRE, both of which have been shown to relate with the degree of liver fibrosis, are well correlated in this cohort of NASH patients with biopsy proven stage 3 fibrosis. LMS cT1 and LIF, which is a composite if steatosis, inflammation and fibrosis is not well correlated to either measure of liver stiffness, possibly because it evaluates a combination of fibrosis and necroinflammation.

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Adam E. Allgood - Employment: Galectin Therapeutics

Peter G. Traber - Management Position: Galectin Therapeutics

The following people have nothing to disclose: Karol Barstow

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Waist Circumference is a Stronger Anthropometric Predictor of NAFLD than Bioimpedence Analysis-Measured Body Fat

Maya Balakrishnan[1], Theresa Nguyen Wenker[2], Fasiha Kanwal[1,3], Hashem B. El-Serag[1,3], Aaron P. Thrift[1,4]; [1]Section of Gastroenterology and Hepatology, Baylor College of Medicine, Houston, TX; [2]Internal Medicine, Baylor College of Medicine, Houston, TX; [3]Department of Medicine, Houston VA HSR&D Center for Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX; [4]Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, TX

Aim: Bioelectrical impedance analysis (BIA) is a safe, inexpensive, simple, and reproducible method used in the clinical setting for assessing body composition, including total body fat. In this study we sought to determine whether there is an association between total body fat measured by BIA and the risk of nonalcoholic fatty liver disease (NAFLD), and whether there is added benefit of BIA over conventional body fat measures (body mass index [BMI] and waist circumference [WC]) in determining NAFLD risk. **Methods:** We conducted a cross sectional study among 123 subjects who underwent BIA, measurement of BMI, WC, and liver imaging. We defined NAFLD as the presence of hepatic steatosis on abdominal imaging (ultrasound, CT scan, or MRI) in the absence self-reported viral hepatitis or excessive alcohol intake. The distribution of conventional measures and BIA measures of body fat were compared between cases with NAFLD and controls without NAFLD using logistic regression models adjusted for age, sex and race/ethnicity. We additionally adjusted the models including BIA measure by conventional measures of BMI and WC to examine whether associations with BIA derived total fat and NAFLD risk was independent of BMI and WC. **Results:** There were 48 cases and 75 controls. There were no between group differences in age, sex and race/ethnicity. In the models adjusted for age, sex and race/ethnicity, BMI, higher total body fat weight and trunk fat weight, and larger weight circumference were each statistically significantly associated with increased risk of NAFLD. With each 5kg increase in total body fat and trunk fat weight there was a statistically increased risk of NAFLD (total body fat weight OR=1.27, 95% CI 1.04-1.54; fat trunk weight, OR=1.45, 95% CI 1.05-2.01). With each 5cm increase of waist circumference there was 34% increase in the risk of the risk of NAFLD (OR=1.34, 95% CI 1.11-1.62). However, in the multivariate models for total body fat weight and trunk fat weight adjusted for BMI and WC in a stepwise manner, the associations were attenuated and they were no long statistically significantly associated with risk of NAFLD. WC was the strongest predictor of NAFLD risk, even in the presence of the BIA measures (highest vs. lowest tertile, OR adjusted for total body fat percent =8.48, 95% CI 1.68-42.8, p-trend=0.02). **Conclusion:** BIA provides reliable measurements of body fat that are associated strongly with increased risk of NAFLD. However, there does not seem to be additional predictive value for BIA measures over BMI and WC in clinical practice.

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RYI-018: A Monoclonal Antibody Cannabinoid Receptor 1 Inverse Agonist For The Treatment of Metabolic Diseases

Anke Kretz-Rommel[1], Roger Ferrini[1], Derek Mann[2], Lei Shi[3], Teddy Yang[3], Alan Glicklich[1], Paul Grayson[1]; [1]Bird Rock Bio, Inc, LA Jolla, CA; [2]Faculty of Medical Sciences, Newcaste University, Newcastle, United Kingdom; [3]RuiYi, Shanghai, China

The cannabinoid (CB) 1 receptor, a G protein-coupled receptor (GPCR), is the most abundantly expressed GPCR in the central nervous system (CNS) with low expression levels in peripheral tissues. However, CB1 is upregulated in adipose tissue, liver and kidney in disease. CB1 has been implicated in human diseases including obesity, NASH, diabetes and diabetic nephropathy, and fibrosis. CB1 has been previously targeted with small molecule antagonists for the treatment of obesity as well as non-alcoholic steatohepatitis (NASH). While efficacious in clinical trials, all drugs were ultimately discontinued due to undesired central nervous system (CNS) side effects. We hypothesize that a monoclonal antibody will have similar efficacy in NASH and other metabolic diseases, but is devoid of CNS liabilities due to restricted access of antibody to the CNS. Importance of CB1 in peripheral tissues driving disease has been demonstrated, including CB1 on adipocytes, macrophages, hepatocytes and hepatic stellate cells playing an important role in lipid synthesis, fatty acid oxidation, adiponectin production, insulin sensitivity and production of pro-fibrotic factors. Conditional knock-out data in macrophages or hepatocytes in mouse models of metabolic disease demonstrated a role of peripheral CB1 further strengthened by data from a new generation of small molecule CB1 antagonists that remain potent in animal models despite limited CNS penetration. However, the CNS drug levels of the more peripherally restricted molecules might still be a concern while monoclonal antibodies might be the most suitable therapeutic modality to avoid CNS effects. We utilized our iCAPS technology that stabilizes GPCRs in their native conformation for the selection of monoclonal antibodies to the CB1 receptor. We identified a panel of highly selective CB1 binders, with RYI-018 as the lead. We demonstrated in vitro using cell lines and human hepatic stellate cells that similar to rimonabant, RYI-018 is an inverse agonist and antagonizes the receptor with comparable potency. Studies in rhesus and cynomolgus monkey showed less than 0.01% of RYI-018 is found in cerebrospinal fluid (CSF), and labeled PET imaging demonstrated lack of CNS penetration. We confirmed increased expression of CB1 with increased disease severity in NASH, and demonstrated activity in a NASH model (STAM model) using a surrogate molecule. Hence we believe RYI-018 is an exciting potential therapeutic for the treatment of NASH and other metabolic diseases with the benefits previously observed with small molecules but lacking the CNS liabilities. RYI-018 will commence clinical trials in Q4_2016.

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Roger Ferrini - Employment: Bird Rock Bio

Lei Shi - Stock Shareholder: Bird Rock Bio

Teddy Yang - Stock Shareholder: RuiYi

Alan Glicklich - Employment: Bird RockBio, Inc; Stock Shareholder: Bird Roc bio

Paul Grayson - Employment: Bird Rock Bio

The following people have nothing to disclose: Derek Mann

1154

ALT as a non-invasive biomarker of histological response to pharmacotherapy in NASH patients: insights from the elafibranor GOLDEN505 trial

Vlad Ratziu[1,2], Stephen A. Harrison[3], Sven Francque[4], Pierre Bedossa[5], Quentin M. Anstee[6], Fouad Ben Sudrik[7], Alice Roudot[7], Sophie Megnien[7], Dean W. Hum[7], Rémy Hanf[7], Bart Staels[9], Arun J. Sanyal[8]; [1]Hepatology, Hopital Pitie Salpetriere, Paris, France; [2]Institute of Cardometabolism and Nutrition, Paris, France; [3]Brooke Army Medical Center, Fort-Worth, TX; [4]Antwerp Univesrity, Antwerp, Netherlands; [5]Hopital Beaujon, Clichy, France; [6]Newcastle University, Newcastle, United Kingdom; [7]Genfit, Loos, France; [8]Virginia Commonwealth University, Richmond, VA; [9]INSERM U1011, European Genomic Institute for Diabetes (EGID), Université Lille 2, Lille, France

Background and aims: While ALT imperfectly predicts histological severity, a relation between ALT changes and histological response (HR) in treated NASH patients (pts) has been suggested. If confirmed, this will help predict treatment efficacy without the need for a control liver biopsy. We assessed ALT and histological changes in the 1-year GOLDEN505 randomized trial of elafibranor (ELA). **Methods:** Pts treated with placebo (PBO, N=77) or ELA 120mg (N=77) were included. HR was defined as resolution of NASH without fibrosis worsening. All completers (N=154) and NAS≥4 (NAFLD activity score) completers (N=129), both with high baseline ALT (N=75, ALT_{high}: ALT>1.5 ULN) and low baseline ALT (N=79, ALT_{low}: ALT≤1.5 ULN) were analyzed for effects on ALT and HR. HR was also assessed in pts with ALT decrease (N=99) or with stable or increased ALT (N=53) at end-of-treatment. **Results:** At baseline, median ALT was higher with increasing NAS: 41 IU/ml in NAS=3 to 63 IU/ml in NAS=6 (p<0.001). ALT_{high} had more severe histological lesions than ALT_{low} (NAS=5.4±1.2 vs 4.6±1.2, p<0.001). When considering baseline ALT, the HR rate was higher with ELA than with PBO in ALT_{high} pts (22% vs 11%, respectively, OR=11.6, p<0.001) while in ALT_{low} pts the difference was lower: 22% vs 18%, OR=1.54, p=0.5. This was confirmed in NAS≥4 pts (ALT_{high}: 22% ELA vs 8% PBO, OR = 16.8, p<0.001; ALT_{low}: 19% ELA vs 15% PBO, OR=1.97, p=0.4). Compared to PBO, ELA reduced ALT both in ALT_{high} and in ALT_{low} (LSmean±SE was -9.9± 10.1 % and -13.9±12.3 % respectively). When considering ALT changes on treatment, the HR rate was higher in pts with an ALT decline than in those with stable or increasing ALT (26% (26/99) vs 4% (2/53), p<0,001). Also, ALT changes were larger in HR (N=28) than in non responders (N=126):-29±23% vs +1±57%; p<0.001. In both ELA and PBO, a progressive decrease in ALT was observed in HR but not in non-responders. In ELA, ALT reduction was higher in HR (N=17) than in non-responders (N=60):-34±23% vs -3±67, p<0.05. Similarly, in PBO, ALT reduction was higher in HR than in non-responders (N=66):-20±21% vs +5±47%, p<0.05. In pts with declining ALT, ELA had higher HR rates than PBO (30% vs 22%, OR = 2.05, p<0.145) with a stronger difference for NAS≥4: 30% vs 16%, OR = 3.21, p<0.05). **Conclusion**: A decline in ALT is associated with histological improvement, particularly on active pharmacotherapy. Pts who resolve NASH have the strongest time-dependent reduction in ALT. A higher baseline ALT is associated with more active disease and better response of HR to ELA over PBO. Although ALT reduction is not an absolute predictor of HR it may provide important insight on treatment effect

Disclosures:

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Stephen A. Harrison - Advisory Committees or Review Panels: Merck, Nimbus Discovery, Fibrogen, Intercept, CLDF, Zafgen, Pfizer; Consulting: NGM Biopharmaceuticals, Medivation; Grant/Research Support: Genfit; Speaking and Teaching: Gilead, Abbvie, CLDF, Merck

Quentin M. Anstee - Grant/Research Support: Vertex Pharmaceuticals, Vertex Pharmaceuticals, Vertex Pharmaceuticals, Vertex Pharmaceuticals

Alice Roudot - Employment: GENFIT

Sophie Megnien - Employment: GENFIT

Dean W. Hum - Management Position: Genfit

Rémy Hanf - Management Position: GENFIT

Bart Staels - Advisory Committees or Review Panels: MSD; Consulting: Genfit

Arun J. Sanyal - Advisory Committees or Review Panels: Bristol Myers, Gilead, Genfit, Abbott, Ikaria, Exhalenz, Pfizer, Novartis; Consulting: Salix, Immuron, Exhalenz, Nimbus, Genentech, Echosens, Takeda, Merck, Enanta, Zafgen, JD Pharma, Islet Sciences, Hemoshear; Grant/Research Support: Salix, Genentech, Intercept, Ikaria, Takeda, GalMed, Novartis, Gilead, Tobira; Independent Contractor: UpToDate, Elsevier; Management Position: Sanyal Biotechnology

The following people have nothing to disclose: Sven Francque, Pierre Bedossa, Fouad Ben Sudrik

1155
Utility of *PNPLA3* genotype and circulating miR-122 for histological features and hepatocellular carcinoma of biopsy-proven nonalcoholic fatty liver disease

Norio Akuta, Yusuke Kawamura, Fumitaka Suzuki, Satoshi Saitoh, Yasuji Arase, Shunichiro Fujiyama, Hitomi Sezaki, Tetsuya Hosaka, Masahiro Kobayashi, Kenji Ikeda, Hiromitsu Kumada, Mariko Kobayashi, Yoshiyuki Suzuki; Toranomon Hospital, Tokyo, Japan

BACKGROUND: It is still unknown whether genetic and epigenetic factors might affect the pathogenesis of nonalcoholic fatty liver disease (NAFLD). Especially, clinical utility of *PNPLA3* genotype and circulating microRNA-122 (miR-122) for histological features of NAFLD is still unclear. **METHODS:** The rates of survival and hepatocellular carcinoma (HCC) development after up to 35 years of follow-up, were investigated in 314 Japanese patients with biopsy-proven NAFLD. 23 patients were with HCC at the time of diagnosis of NAFLD, and 4 patients developed HCC during the follow-up. The impact of *PNPLA3* rs738409 and serum miR-122 levels for histological features and HCC was evaluated. The relative expression of serum miR-122 was calculated using the comparative cycle threshold (CT) method ($2^{-\Delta\Delta CT}$) with spiked cel-miR-39 as normalized internal control. **RESULTS:** The cumulative survival rates were 92, 92, and 92% at the end of 10, 20, and 30 years, respectively. The cumulative HCC rates were 3, 3, and 20% at the end of 10, 20, and 30 years, respectively. The cumulative survival and HCC rates varied significantly according to severity of fibrosis stage, but not by *PNPLA3* genotype. Fibrosis stage of *PNPLA3* GG type was significantly more progressive than that of CG type by multiple comparisons. Multivariate analysis identified *PNPLA3* genotype as the predictors of fibrosis stage 2 or more, but the impact tended to decrease on fibrosis stage 3 or more. Serum miR-122 levels partly affected to severity of steatosis, ballooning, lobular inflammation, and fibrosis stage, but those tended to decrease on fibrosis stage 4 compared with fibrosis stage 3. Multivariate analysis identified HCC and/or histological components of NASH, as morphological factors that independently influenced serum miR-122 levels at the diagnosis of NAFLD. In cross-sectional evaluation, serum miR-122 levels of patients without HCC were significantly higher than those with HCC in patients of fibrosis stage 3 but not fibrosis stage 4. In longitudinal evaluation of one patient with the follow-up time of 25 years, from the diagnosis of NAFLD until HCC, serum miR-122 levels had already tended to decrease before the progression of fibrosis stage. **CONCLUSIONS:** *PNPLA3* genotype partly affected to histological features including fibrosis stage. HCC and/or histological components of NASH affected to serum miR-122 levels, independently. Impact of *PNPLA3* genotype, and levels of serum miR-122 tended to decrease on fibrosis stage 4. Further prospective studies are needed to investigate the impact of *PNPLA3* genotype and serum miR-122 for histological features and hepatocarcinogenesis of NAFLD.

Disclosures:

Fumitaka Suzuki - Speaking and Teaching: BMS

Kenji Ikeda - Speaking and Teaching: Eisai company, Dainippon Sumitomo Pharmaceutical company

Hiromitsu Kumada - Speaking and Teaching: Bristol-Myers Squibb,Pharma International, MSD, Abbvie, Glaxosmithkline, Gilead Sciences, Diainippon Sumitomo Pharma

Yoshiyuki Suzuki - Speaking and Teaching: Bristol-Myers Squibb

The following people have nothing to disclose: Norio Akuta, Yusuke Kawamura, Satoshi Saitoh, Yasuji Arase, Shunichiro Fujiyama, Hitomi Sezaki, Tetsuya Hosaka, Masahiro Kobayashi, Mariko Kobayashi

1156
SGLT-2 inhibitors improved liver inflammation and fibrosis of NAFLD patients with type 2 diabetes mellitus with a favorable effect of weight reduction

Takamasa Ohki[1], Isogawa Akihiro[2], Mayuko Kondo[1], Shigeyuki Kurosaki[1], Kazuyoshi Funato[1], Satoshi Kawamura[1], Shuya Maeshima[1], Yuki Karasawa[1], Kentaro Kojima[1], Michiharu Seki[1], Nobuo Toda[1], Kazumi Tagawa[1]; [1]Gastroenterology, Mitsui Memorial Hospital, Tokyo, Japan; [2]Diabetes and metabolizm, Mitsui Memorial Hospital, Tokyo, Japan

Background: Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are the newest class of oral diabetes agents available on the market. An important advantage of SGLT-2 inhibitors is their favorable effect on the reduction of body weight. **Aims:** The aim of this study is to elucidate the effectiveness of SGLT-2 inhibitors as a treatment for NAFLD patients with T2DM. **Methods:** We retrospectively enrolled consecutive 50 Japanese NAFLD patients with T2DM who were treated with SGLT-2 inhibitors. We compared the changes of liver inflammation, fibrosis, and body weight at the end of follow-up. We also assessed the factors which contributed to the normalization of ALT level. **Results:** The mean age was 52.6 years old and 40 (80.0%) patients were male gender. The mean BMI was 29.9 kg/m^2. All patients were administered 50 mg ipragliflozin once daily and the mean dosing period was 451 days. At the end of follow-up, body weight significantly decreased (85.1 kg to 81.9 kg, $P < 0.01$) with amelioration of HbA1c level (8.1% to 7.6%, $P < 0.01$). Serum ALT level also significantly decreased (70 IU/l to 53 IU/l, $P < 0.01$) with improvement of FIB-4 index (1.53 to 1.26, $P = 0.01$). Finally, 30 patients (60.0%) achieved normal ALT level. The mean reduction weight in patients who achieved normal ALT level was 3.94 kg and 1.98 kg in patients who did not achieved normal ALT level ($P = 0.01$). Univariate logistic regression analysis indicated that reduction of body weight (OR: 1.37 per 1 kg $P = 0.02$), and improvement of HbA1c level (OR: 3.369 per 1.0%, $P = 0.02$) as factors which contributed to normalization of ALT level. **Conclusions:** Administration of SGLT-2 inhibitors led not only good glycaemic control but also normalization of ALT level and alteration of FIB-4 index with a favorable effect of body weigh reduction.

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Isogawa Akihiro - Speaking and Teaching: Astellas Pharma Inc.

The following people have nothing to disclose: Takamasa Ohki, Mayuko Kondo, Shigeyuki Kurosaki, Kazuyoshi Funato, Satoshi Kawamura, Shuya Maeshima, Yuki Karasawa, Kentaro Kojima, Michiharu Seki, Nobuo Toda, Kazumi Tagawa

1157

How Healthy are "Healthy Volunteers"? Prevalence and Potential Impact of Fatty Liver Disease in Volunteers to Clinical Trials

Varun K. Takyar[1], Anand Nath[1,2], Andrea Beri[3], Yaron Rotman[1]; [1]Liver & Energy Metabolism Unit, Liver Diseases Branch, NIDDK, NIH, Bethesda, MD; [2]Department of Internal Medicine, Medstar Washington Hospital Center/Georgetown University School of Medicine, Washington, DC; [3]NIH Biomedical Translational Research Information System (BTRIS), Laboratory of Informatics Development, NIH Clinical Center, Bethesda, MD

Introduction: Healthy volunteer subjects are crucial for biomedical research; inadvertent inclusion of subjects with chronic liver disease as healthy controls can compromise study validity and subject safety. NAFLD is often overlooked as a chronic liver disease, despite its increasing prevalence. **Aim:** To identify the prevalence and potential impact of NAFLD in presumably healthy volunteers for clinical trials at the NIH Clinical Center. **Methods:** Cross-sectional study of all subjects with a diagnosis of "Healthy Volunteer" between 2011-2015. De-identified subject and study data were retrieved from electronic database. Subjects with viral hepatitis or alcohol abuse were excluded and analysis was limited to subjects with concomitant ALT and weight measurements. Subjects were divided into 3 groups: healthy non-NAFLD (ALT<20 for women or <31 for men and BMI≤25), presumed NAFLD (elevated ALT and BMI>25), and indeterminate (elevated ALT or increased BMI). Between-group comparisons were limited to the presumed NAFLD and healthy subjects. All reported comparisons are significant at $p<0.01$. Study level data included trial type, inclusion/exclusion criteria and potential impact of recruiting NAFLD subjects on study validity as assessed from protocol précis. **Results:** 3241 subjects participated as healthy volunteers in 161 clinical trials, (1-29 trials per subject). Median BMI was 26.9 kg/m^2 and median ALT - 27 u/l. Abnormal ALT was present in 1431 (44%) and 1787 (55%) had an abnormal weight. 919 subjects (28.4%) had presumed NAFLD, 942 (29.1%) were healthy and 1380 (42.6%) were indeterminate. NAFLD subjects were older (37.2 vs. 29.6 years), and had higher triglycerides (117±77 vs. 78±38 mg/dL), LDL-C (108±34 vs. 89±27 mg/dL), and HbA1c (5.6±0.9% vs. 5.2±0.4%) and lower HDL-C (52±16 vs. 63±17 mg/dL). The 161 trials included 106 non-interventional, 40 interventional and 15 vaccine studies, and 31%, 24%, and 25% of their subjects, respectively, had NAFLD. Impact of NAFLD on study validity was assessed to be high, low or none in 5, 31 and 125 studies. The proportion of NAFLD subjects was not different between impact levels. Liver enzymes or BMI were used for screening in only 38% and 25% of studies, respectively, only 16% used both and this did not differ by impact. **Conclusion:** NAFLD is common, and often overlooked in subjects enrolling as healthy volunteers for clinical trials, despite its potential impact on subject safety and validity of study findings.

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1158

Advanced Nonalcoholic Steatohepatitis (NASH) Associated with Activated, Proinflammatory Phenotypes of Circulating Neutrophils

Lucy M. Golden-Mason[1,2], Silvia Giugliano[1], Eric L. Campbell[1], Linling Cheng[1], Christine A. Collins[1,2], Hugo R. Rosen[1,2]; [1]GI/Hepatology, University of Colorado, Aurora, CO; [2]Denver Veteran's Affairs Medical Center, Denver, CO

Background: Nonalcoholic steatohepatitis (NASH) represents one of the most common causes of chronic liver disease. Associated with an increased risk of cirrhosis and hepatocellular carcinoma, NASH is now one of the leading indications for liver transplantation in the US. Several observations suggest a role for neutrophil activation and expansion in the pathogenesis of NASH. The aim of the present study was to characterize peripheral neutrophil populations in subjects with biopsy-proven NASH. Methods: Flow cytometric analysis of whole blood was used to identify and phenotype conventional and low density neutrophil populations (LDGs) in freshly isolated cells. Intracellular staining assessed the levels of Neutrophil elastase (NE) and myeloperoxidase (MPO). Neutrophils (>97% purity) were isolated from whole blood using the MACSxpress™ platform (Miltenyi Biotec). To examine the direct cross-talk between neutrophils and hepatic stellate cells (HSCs), the LX2 HSC line was cultured with supernatants from isolated neutrophils (>98% purity) cultured for 4 hours in the absence of exogenous stimulation. Serum ELISAs for neutrophil activation markers (MPO/NE) were also performed. **Results:** Thirteen NASH subjects (10 female, 3 male) were recruited the majority (85%) of whom had advanced disease (NAS>5). Non-obese subjects served as controls. LDG levels were increased in NASH subjects (0.60%, $CD45^+CD14^-CD15^+$ % of low forward and side scatter [fsc:ssc] leukocytes) compared to controls 0.18%, $p<0.05$, Wilcoxin signed rank). LDG populations displayed several phenotypic differences when compared to conventional neutrophils including, decreased CD15, CD16 and CD62L expression ($p<0.005$ in all cases). In addition, we observed differences in the expression of chemokine/cytokine receptors involved in mobilization and activation of neutrophils on LDGs. CXCR4 was increased ($p<0.0001$) and G-CSF receptor (CD114) was decreased ($p=0.0002$). A significant decrease for G-CSF receptor expression between NASH subjects and controls was also noted ($p<0.05$). An increased intensity for intracellular MPO was observed in conventional neutrophils from NASH subjects (MFI 29133) compared to controls (MFI 15029, $p<0.05$). Circulating MPO levels were increased in NASH subjects (1,601 vs 6,433pg/ml, $p<0.005$). No difference was seen for circulating NE levels. Supernatants from isolated neutrophils enhanced MMP9 and inhibited IL-8 expression in LX2 HSCs stimulated with LPS/TGF-b. **Conclusions:** Taken together, these findings support previously unidentified roles for neutrophils in the pathogenesis of NASH and suggest that neutrophils may represent a potential therapeutic target to ameliorate this disease.

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The following people have nothing to disclose: Lucy M. Golden-Mason, Silvia Giugliano, Eric L. Campbell, Linling Cheng, Christine A. Collins, Hugo R. Rosen

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Diagnosing of NASH and Assessing NASH Disease Severity by a Global Measure of Liver Function, the HepQuant® (HQ)-SHUNT Test

Steve M. Helmke[1], John D. Marr[2], Michael W. Cookson[1], Jennifer DeSanto[1], Shannon Lauriski[1], James F. Trotter[2], Gregory T. Everson[1]; [1]Gastroenterology and Hepatology, University of Colorado, Aurora, CO; [2]Baylor University Medical Center, Dallas, TX

Background and Aims: NASH is very difficult to diagnose and stage and the only accepted method is liver biopsy. The patchy nature of NASH fibrosis causes biopsy sampling error and 40% variability in staging (Ratziu, et al, 2005). The HepQuant® (HQ)-SHUNT test generates a disease severity index (DSI) which is a global measure of liver function. The goal of this pilot study was to determine if DSI could diagnose NASH and assess NASH disease severity. **Methods**: Healthy controls (N=50) included 30 of normal weight (BMI 18.5-25), 16 overweight (BMI 25-30), and 4 obese (BMI>30). Patients were from 2 centers, University of Colorado Denver (N=16) and Baylor University Medical Center Dallas (N=15), and 27 had biopsy-diagnosed NASH and 4 had cryptogenic cirrhosis, concurrent obesity, and presumed late stage NASH. There were 4 patients with Brunt-Kleiner fibrosis stage F1, 4 with F2, 5 with F3, and 18 with F4 (cirrhosis). Clinical manifestations of NASH disease severity were captured from patient histories and included medium/large varices and any decompensation events (ascites, encephalopathy, variceal bleed, or jaundice). The HQ-SHUNT test involves serum sampling prior to, and at 5, 20, 45, 60, and 90 minutes after simultaneous administration of IV ^{13}C-cholic acid (CA) and oral 4D-CA. Clearances of ^{13}C-CA and 4D-CA were measured and DSI calculated from the clearances. The ability of DSI to diagnose NASH and to assess NASH disease severity was evaluated by AUROC analyses (c-statistic) and by the diagnostic performance (sensitivity, specificity, PPV, NPV) at the optimum cutoffs which were defined by the maximum Youden Index (J). **Results:** The HQ-SHUNT DSI could differentiate NASH patients from healthy control subjects, even overweight and obese controls, with high c-statistic, specificity, PPV, and Youden Index (J) (Table section A). A biopsy diagnosis of cirrhosis could identify NASH patients at risk of medium/large varices or those at risk of decompensation, but HQ-SHUNT DSI could identify both groups with a higher c-statistic, and much better specificity, PPV, and Youden Index (J) (Table sections B & C). **Conclusions**: The HQ-SHUNT test could be a minimally-invasive alternative to biopsy for the diagnosis of NASH. The HQ-SHUNT test DSI could outperform fibrosis stage in assessing NASH disease severity.

Diagnostic Performance of HQ-SHUNT and Biopsy

	AUROC c-statistic	Optimum Cutoff	Sensitivity	Specificity	PPV	NPV	Youden Index (J)
A. Ability to Diagnose NASH in a cohort of Healthy Controls (N=50) and NASH Patients (N=31)							
HQ-SHUNT	0.94	DSI > 16.5	84%	98%	96%	91%	0.82
B. Ability to Identify Patients who had Medium/Large Varices (N=9) in the NASH cohort (N=31)							
HQ-SHUNT	0.92	DSI > 28	89%	91%	80%	95%	0.80
Biopsy	0.80	Cirrhosis	100%	59%	50%	100%	0.59
C. Ability to Identify Patients who had Decompensation (N=9) in the NASH cohort (N=31)							
HQ-SHUNT	0.99	DSI > 28	100%	95%	90%	100%	0.95
Biopsy	0.80	Cirrhosis	100%	59%	50%	100%	0.59

Disclosures:

Steve M. Helmke - Patent Held/Filed: University of Colorado

Gregory T. Everson - Advisory Committees or Review Panels: Roche/Genentech, Abbvie, Galectin, Bristol-Myers Squibb, HepC Connection, BioTest, Gilead, Merck; Board Membership: HepQuant LLC, PSC Partners, HepQuant LLC; Consulting: Abbvie, BMS, Gilead, Bristol-Myers Squibb; Grant/Research Support: Roche/Genentech, Abbvie, Bristol-Myers Squibb, Merck, PSC Partners, Gilead; Management Position: HepQuant LLC, HepQuant LLC; Patent Held/Filed: Univ of Colorado; Speaking and Teaching: Abbvie

The following people have nothing to disclose: John D. Marr, Michael W. Cookson, Jennifer DeSanto, Shannon Lauriski, James F. Trotter

1160

Natural killer T cells and mucosal associated invariant T cells share phenotypic and functional alterations in patients with non-alcoholic fatty liver disease

Elisavet Serti, Jens M. Werner, Meghan Keane, Fabian J. Bolte, Shilpa Lingala, Nevitt Morris, T. Jake Liang, Yaron Rotman, Barbara Rehermann; Liver Diseases Branch, NIDDK, National Institutes of Health, DHHS, Bethesda, MD

Natural killer T (NKT) cells and mucosal-associated invariant T (MAIT) cells are innate-like T cells with evolutionarily conserved semi-invariant T cell receptors. They are enriched in the liver, and respond not just to inflammatory cytokines but NKT cells also recognize lipid antigens and MAIT cells also recognize riboflavin metabolites that are produced by bacteria. We aimed to examine the role of NKT and MAIT cells in nonalcolholic fatty liver disease (NAFLD). **Methods:** Multicolor flow cytometry was performed on paired blood and liver samples of 20 clinically well characterized NAFLD patients. For comparison, we used blood samples from healthy volunteers and paired blood and liver biopsies from patients with chronic hepatitis C before and after viral clearance. Results were correlated to BMI, liver fat by MRI spectroscopy, and ALT. **Results:** NAFLD patients had a lower frequency of MAIT cells in the blood than in healthy controls (p=0.0049). Both NKT and MAIT cells were more activated than those of healthy controls and HCV patients, as evidenced by increased expression of CD38, Tim-1 and FasL on NKT cells, and increased CD38 and HLA-DR expression for MAIT cells. NKT and MAIT cells of NAFLD patients expressed increased levels of the degranulation/ cytotoxicity marker CD107a, but IFNγ and TNFα production by NKT cells was impaired upon in vitro stimulation with cytokines (IL-12/IL-18) or T cell receptor ligand (aGalCer). In NAFLD patients, NKT and MAIT cells were more frequent and more activated (CD38+) in the liver than in peripheral blood. NKT cell CD38 expression correlated with ALT levels and liver fat content (r=0.557, p=0.013 and r=0.572, p=0.085 respectively). Similarly, liver MAIT cell frequency correlated with liver fat (r=0.767, p=0.002), and the expression of the co-stimulatory molecule Tim-1 on MAIT cells correlated with ALT levels and BMI (r=0.605, p=0.016 and r=0.486, p=0.033 respectively). Pro-inflammatory cytokines were within normal limits in the plasma of NAFLD patients, except for increased levels of IL-8 and IL-18. Both cytokines are produced by activated monocytes/macrophages and IL-18 is known to activate both NKT and MAIT cells. Increased monocyte activation was confirmed by HLA-DR expression, and increased macrophage activation by sCD163 levels in the plasma. **Conclusions:** NKT and MAIT cells share an activated and cytotoxic phenotype in NAFLD patients, which may be driven by IL-18 from activated monocytes/macrophages. Frequency and activation status of liver NKT and MAIT cells correlate with clinical disease parameters of NASH, suggesting a role of these cells in disease pathogenesis.

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The following people have nothing to disclose: Elisavet Serti, Jens M. Werner, Meghan Keane, Fabian J. Bolte, Shilpa Lingala, Nevitt Morris, T. Jake Liang, Yaron Rotman, Barbara Rehermann

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Improved Noninvasive prediction of Liver Fibrosis by Liver Stiffness Measurement in Patients with Nonalcoholic Fatty Liver Disease Accounting for Controlled Attenuation Parameter Values

Salvatore Petta[1], Vincent W. Wong[2], Calogero Cammà[1], Jean-Baptiste Hiriart[3], Grace L.H. Wong[2], Fabio Marra[4], Julien Vergniol[3], Anthony W. Chan[5], Vito Di Marco[1], Wassil Merrouche[3], Henry Lik-Yuen Chan[2], Marco Barbara[1], Brigitte Le Bail[6], Umberto Arena[4], Antonio Craxì[1], Victor de Ledinghen[3]; [1]Cattedra ed U.O.C. di Gastroenterologia ed Epatologia, Palermo, Italy; [2]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, HONG KONG, Hong Kong; [3]Centre d'Investigation de la Fibrose hépatique, Hôpital Haut-Lévêque, Bordeaux University Hospital, Pessac, France, PRESSAC, France; [4]Dipartimento di Medicina Sperimentale e Clinica, Università degli Studi di Firenze, Florence, Italy; [5]Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong, Hong Kong, HONG KONG, Hong Kong; [6]Service de Pathologie, Hôpital Pellegrin, Bordeaux University Hospital, Bordeaux, France, BORDEAUX, France

Background and aims: Liver stiffness measurement (LSM) frequently overestimates the severity of liver fibrosis In Nonalcoholic Fatty Liver Disease (NAFLD). Controlled Attenuation Parameter (CAP) is a new parameter provided by the same machine used for LSM, and associated with both steatosis and BMI, the two factors mostly affecting LSM peformance in NAFLD. We aimed to determine wheter prediction of liver fibrosis by LSM in NAFLD patients is affected by CAP values. **Methods:** Patients (n=324) were assessed by clinical and histological (Kleiner score) features. LSM and CAP were performed using the M probe. CAP values were grouped by tertiles (lower from 132 to 298, middle from 299 to 338, higher form 339 to 400 dB/m). **Results:** Among patients with F0-F2 fibrosis, mean LSM values- expressed in kPa- increased according to CAP tertiles (6.8 vs. 8.6 vs. 9.4; p=0.001), and along this line the AUC of LSM for the diagnosis of F3-F4 fibrosis was progressively reduced from lower to middle and further to higher CAP tertiles (0.915, 0.848-0.982; 0.830, 0.753-0.908; 0.806, 0.723-0.890). As a consequence, in subjects with F0-F2 fibrosis, the rates of false-positive LSM results for F3-F4 fibrosis increased according to CAP tertiles (7.2% in lower vs. 16.6% in middle vs. 18.1% in higher). Consistent with this, a decisional flow-chart for prediciting fibrosis was suggested by combining both LSM and CAP values. **Conclusions:** In patients with NAFLD, CAP values should always be taken into account in order to avoid overestimations of liver fibrosis assessed by TE.

Disclosures:

Vincent W. Wong - Advisory Committees or Review Panels: AbbVie, Gilead, Janssen, Tobira; Consulting: Merck, NovaMedica; Speaking and Teaching: Gilead, Echosens

Grace L.H. Wong - Speaking and Teaching: Echosens, Echosens, Echosens, Echosens

Fabio Marra - Consulting: Bayer Healthcare, Abbvie, AstraZeneca; Grant/Research Support: ViiV; Speaking and Teaching: Gilead

Henry Lik-Yuen Chan - Advisory Committees or Review Panels: Gilead, Janssen, Bristol-Myers Squibb, Roche, Novartis Pharmaceutical, Abbvie; Speaking and Teaching: Echosens

Victor de Ledinghen - Board Membership: Janssen, Gilead, BMS, Abbvie, Intercept Pharma, Supersonic Imagine; Grant/Research Support: Supersonic Imagine; Speaking and Teaching: AbbVie, Merck, BMS, Gilead

The following people have nothing to disclose: Salvatore Petta, Calogero Cammà, Jean-Baptiste Hiriart, Julien Vergniol, Anthony W. Chan, Vito Di Marco, Wassil Merrouche, Marco Barbara, Brigitte Le Bail, Umberto Arena, Antonio Craxì

1162

Diagnostic performance of FibroTest, SteatoTest, and ActiTest in patients with NAFLD using the SAF-score as histological reference

Mona Munteanu[1], Dina Tiniakos[2], Quentin Anstee[2], Frederic Charlotte[3], Giulio Marchesini[5], Elisabetta Bugianesi[4], Michael H. Trauner[6], Claudia P. Oliveira[7], Christofer Day[2], Jean-Francois Dufour[8], Stefano Bellentani[9], Yen Ngo[1], Stefan Traussnigg[6], Pierre Bedossa[10], Vlad Ratziu[3], Thierry Poynard[3]; [1]BioPredictive, Paris, France; [2]Newcastle University, Newcastle, United Kingdom; [3]APHP UPMC Liver Center, Paris, France; [4]Universita degli studi di torino, Torino, Italy; [5]Universita di Bologna, Bologna, Italy; [6]Medizinischen Universitaet Wien, Wienna, Austria; [7]University of São Paulo, Sao Paulo, Brazil; [8]Berne University, Berne, Switzerland; [9]Universita di Modena, Modena, Italy; [10]Beaujon Hospital, Clichy, France

Background: Blood tests of liver injury are less well validated in NAFLD than in patients with chronic viral hepatitis. We aimed to improve the validation of three blood tests used in NAFLD patients, FibroTest for fibrosis staging, SteatoTest for steatosis grading and ActiTest for inflammation activity grading. **Methods:** We pre-included new NAFLD patients with biopsy and blood tests from a single-center cohort (FibroFrance) and from the multicenter FLIP consortium. Contemporaneous biopsies were blindly assessed using the new SAF score, which provides a reliable and reproducible diagnosis and grading/staging of the three elementary features of NAFLD (steatosis, inflammatory activity) and fibrosis with reduced interobserver variability. We used non-binary-ROC (NonBinROC) as the main endpoint to prevent spectrum effect and multiple testing. **Results:** A total of 600 patients with reliable tests and biopsies were included, 27% with steatosis >67%, 43.2% with severe or very severe activity and 27.5% with bridging or cirrhosis. The median NonBinROCs (95% CI) of tests were all significant (P<0.0001): 0.572 (0.542-0.602) for FibroTest and fibrosis stages, 0.551 (0.521-0.581) for ActiTest and activity grades, and 0.556 (0.512-0.600) for SteatoTest and steatosis grades. These significant results persisted in sensitivity analyses stratified by cohort population, gender, biopsy length, time interval biopsy-tests, diabetes and severe obesity. The median FibroTest values increased (P<0001) steadily with fibrosis stages after F1, ranging from 0.18 in F0, 0.21 in F1, 0.28 in F2, 0.41 in F3 and 0.71 in cirrhosis; none of the other fibrosis tests (NAFLD Fibrosis Score, BARD score and FIB4 score) had such significant increase between each fibrosis stages.The ActiTest median values increased (P<0001) for the two features of the SAF activity score, ballooning and lobular inflammation. For ballooning, the value was 0.22 if absence (n=116), 0.36 if moderate (n=253) and 0.39 if severe (n=231), with a significant difference between grades 0 and 1. For lobular inflammation, the value was 0.23 if absence (n=118), 0.35 if moderate (n=331), and 0.43 if severe (n=151), all with significant differences between adjacent stages (P<0.05). **Conclusion:** In patients with NAFLD, SteatoTest, ActiTest and FibroTest are non-invasive tests that, with some limitations, may offer an alternative to biopsy and correlate with the simple grading/staging of the SAF scoring system across the three elementary features of NAFLD: steatosis, inflammatory activity, and fibrosis.

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Mona Munteanu - Employment: BioPredictive

Quentin Anstee - Advisory Committees or Review Panels: Intercept; Consulting: Genfit, Eli Lilly, Pfizer, Inventiva, Imperial Innovations; Grant/Research Support: Abbvie, GSK

Giulio Marchesini - Advisory Committees or Review Panels: Sanofi-Synthelabo; Board Membership: GENFIT, Gilead, Glaxo, Novartis; Grant/Research Support: Merck Sharp & Dome; Speaking and Teaching: Novo Nordisk, Merck Sharp & Dome, Boerhinger Ingelheim, Eli Lilly, Astra-Zeneca

Michael H. Trauner - Consulting: Albireo, Falk, Phenex, Gilead, Novartis, MSD; Grant/Research Support: Falk, Albireo, Intercept

Jean-Francois Dufour - Advisory Committees or Review Panels: Bayer, BMS, Gilead, AbbVie, Novartis, Sillagen, Genfit, Intercept

Yen Ngo - Employment: BioPredictive

Stefan Traussnigg - Grant/Research Support: Phenex Pharmaceuticals

Vlad Ratziu - Advisory Committees or Review Panels: GalMed, Abbott, Genfit, Enterome, Gilead; Consulting: Tobira, Intercept, Exalenz, Boehringer-Ingelheim

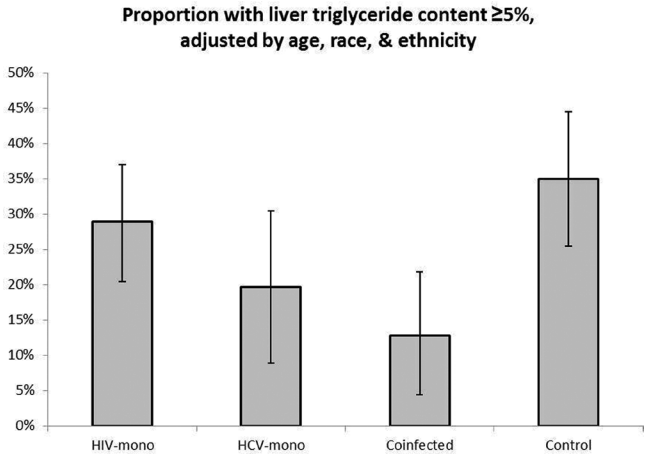
Thierry Poynard - Advisory Committees or Review Panels: Merk; Grant/Research Support: Gilead; Stock Shareholder: BioPredictive

The following people have nothing to disclose: Dina Tiniakos, Frederic Charlotte, Elisabetta Bugianesi, Claudia P. Oliveira, Christofer Day, Stefano Bellentani, Pierre Bedossa

1163
HIV-infected and Uninfected Adults with Non-Genotype 3 Hepatitis C Virus Have Less Hepatic Steatosis than Adults with Neither Infection

Jennifer C. Price[1], Yifei Ma[1], Rebecca Scherzer[1], Natalie Korn[1], Kyle Tillinghast[1], Marion G. Peters[1], Susan Noworolski[1], Phyllis Tien[1,2]; [1]University of California, San Francisco, San Francisco, CA; [2]Department of Veteran Affairs Medical Center, San Francisco, CA

Background: Hepatic steatosis (HS) is common in persons with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections, but the independent contributions of HCV and HIV to HS is unclear. Methods: Magnetic resonance imaging and spectroscopy were used to measure visceral adipose tissue (VAT) and HS in 356 adults: 57 HCV-monoinfected, 70 HIV/HCV-coinfected,122 HIV-monoinfected, and 107 uninfected controls. Subjects with genotype 3 HCV were excluded due to the genotype's reported steatogenic effects. For prevalence estimates, HS was defined as MRS triglyceride content [total lipids/(total lipids + water)]≥ 0.05. Multivariable linear regression models were used to determine the association of HIV and HCV status with HS levels. Results: The prevalence of HS was highest in the controls (33%) and HIV-monoinfected (28%), followed by the HCV-monoinfected (19%) and HIV/HCV-coinfected (11%) (p=0.003 across groups). Compared to controls, after adjusting for demographic, lifestyle, and metabolic factors, HCV monoinfection and HIV/HCV coinfection were associated with 38% (95%CI:-55%,-12%) and 42% (95%CI:-59%,-18%) less HS, respectively, while HIV monoinfection was not significantly different. Further adjusting for APRI, HCV monoinfection and HIV/HCV coinfection remained associated with 48% (95%CI:-64%,-26%) and 54% (95%CI:-69%,-32%) less HS, respectively. Excluding subjects with suspected cirrhosis did not change results. Hispanic ethnicity, male sex, VAT, and HOMA-IR were independently associated with greater HS. Conclusions: Contrary to expectations, HIV/HCV-coinfected and HCV-monoinfected adults had less HS than controls even after adjusting for demographic, lifestyle, metabolic factors, and fibrosis and excluding cirrhotics. Our findings suggest that non-genotype 3 HCV infection may be protective against HS. The mechanisms by which this occurs and impact of HCV treatment on HS need investigation.



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The following people have nothing to disclose: Yifei Ma, Rebecca Scherzer, Natalie Korn, Kyle Tillinghast, Susan Noworolski, Phyllis Tien

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Noninvasive Fibrosis Markers are Associated with Coronary Artery Calcification in Nonalcoholic Fatty Liver Disease

Do Seon Song, U Im Chang, JinMo Yang, Jeong Won Jang, Si Hyun Bae, Seung Kew Yoon, Se Hyun Cho; Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea (the Republic of)

Background/Aim Nonalcoholic fatty liver disease (NAFLD) is associated with increased risk of coronary artery disease. In addition, the advanced fibrosis in NAFLD patients is associated with cardiovascular disease and overall mortality. Therefore, we investigated the association between coronary atherosclerosis and noninvasive fibrosis markers to detect the high risk population for coronary artery disease. **Methods** Between January 2011 and December 2015, a total 665 subjects with NAFLD were analyzed. NAFLD was diagnosed by ultrasonography in St. Vincent's Hospital Heath Promotion Center. Coronary atherosclerosis, represented as coronary artery calcification score (CACS), was assessed by cardiac computed tomography. NAFLD fibrosis score (NFS), Fibrosis-4 (FIB-4) score, aspartate aminotransferase (AST) to Platelet Ratio Index (APRI) score, and Forns index were used as noninvasive fibrosis markers. **Results** The mean age of the study population was 51.5±9.3 years, and 486 subjects (73.5%) were male. On univariate analysis, high CACS (≥ 100) was significantly associated with old age (≥ 55 years), diabetes mellitus, serum glucose (≥100mg/dL), and estimated glomerular filtration rate (GFR) (all *P*s < 0.05), and seemed to be associated with hypertension and body mass index (≥ 25kg/m^2) (all *P*s < 0.10). On multivariate analysis, old age and male gender were only significant risk factors (*P* < 0.001 and *P* = 0.024). NFS, FIB-4 and Forns index were significantly associated with high CACS (all *P*s < 0.001) and NFS and FIB-4 score were significantly factors even after adjustment for traditional risk factors (*P* = 0.043 and *P* = 0.009). AUROCs of NFS and FIB-4 were 0.689 and 0.683 for predicting the high CACS, and the cut-off values were -1.774 and 0.85, respectively. **Conclusion** Hepatic fibrosis assessed by noninvasive fibrosis markers, such as NFS and FIB-4, was independently associated with high CACS. Therefore, noninvasive

fibrosis markers are helpful to detect the high risk population of coronary artery disease.

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JinMo Yang - Employment: catholic university

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1165

A possible contribution of occult hepatitis B virus infection to hepatocarcinogenesis in Japanese patients with nonalcoholic fatty liver disease

Yoshihiro Ikura[1], Kenichi Harada[2], Tatsuya Osuga[3]; [1]Department of Pathology, Takatsuki General Hospital, Takatsuki, Japan; [2]Human Pathology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan; [3]Department of Gastroenterology, Takatsuki General Hospital, Takatsuki, Japan

Background and Aims: Augmentation of patients with nonalcoholic fatty liver disease (NAFLD) has become a big public-health problem in most industrialized countries. At present hepatocarcinogenesis related to NAFLD is an additional critical issue that should be solved urgently. Despite many energetic investigations, detailed pathologic mechanisms of hepatocarcinogenesis in patients with NAFLD are obscure. Of course hepatocellular carcinomas (HCCs) developed in livers (even though steatotic) of patients positive for serum hepatitis viruses are not recognized to be NAFLD-related ones. On the other hand, occult hepatitis B virus (HBV) infection is considered one of potential factors in hepatocarcinogenesis, especially in HBV-endemic areas. We hypothesized that occult HBV may be contributing to NAFLD-related hepatocarcinogenesis, and carried out the following molecular pathologic study. **Methods:** Nine NAFLD patients (7 men and 2 women; 61-81yr) diagnosed pathologically as having HCC were subjects of this study. Besides their clinical and laboratory data, we analyzed their liver tissue specimens (non-tumorous portions) histologically and with polymerase chain reaction (PCR)-based HBV genomic study. DNA was extracted from five 10-μm-thick sections of each formalin-fixed paraffin-embedded tissue. The PCR was performed using HBV X gene-specific primers, and samples having shown a positive result were further examined by direct sequencing. **Results:** Most of the patients (8 of 9 cases) had 2 or more metabolic factors (diabetes, dyslipidemia, obesity, hypertension), but 1 had no such factors. No one was positive for hepatitis B surface antigen, but 3 patients were positive for hepatitis B core antibody (anti-HBc). Collectively every patient had either diabetes or anti-HBc positivity. Histologically, non-tumorous portions showed cirrhosis in 5 cases, and no or only mild (perivenular) fibrosis in 4 cases. From the DNA samples of 2 of 3 anti-HBc-positive cases, PCR amplicons of an expected size (161-bp) were generated, and one of them was proved as the targeted HBV X gene segment by direct sequencing. This case was of simple steatosis without fibrosis and had no metabolic factors. **Conclusions:** The present study revealed that in Japan NAFLD-related hepatocarcinogenesis was at least in part associated with occult HBV infection. In addition, the results suggested that diabetes and anti-HBc, not liver histology, might be useful predictors of NAFLD-related hepatocarcinogenesis.

Disclosures:

The following people have nothing to disclose: Yoshihiro Ikura, Kenichi Harada, Tatsuya Osuga

1166

Validation of non-invasive scoring systems for the prediction of overall mortality and liver related events in non-alcoholic fatty liver disease

Luis C. Bertot[1], Gary P. Jeffrey[1,2], Gerry C. MacQuillan[1,2], George Garas[1,2], Yi Huang[1], Leon A. Adams[1,2]; [1]School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia; [2]Department of Hepatology, Sir Charles Gairdner Hospital, Perth, WA, Australia

Background/Aims: Predictors of mortality and liver decompensation help determine prognosis and thus influence management of patients with non-alcoholic fatty liver disease (NAFLD). We examined the accuracy of four clinical models in the prediction of mortality and liver related events in NAFLD. **Methods:** Hepascore, NAFLD fibrosis score (NFS), APRI and FIB 4 scores were calculated at time of biopsy in 249 patients with NAFLD between 2006 to 2014 from a tertiary centre. Patients were followed for outcomes of overall mortality/liver transplantation and occurrence of first event of hepatic decompensation. Analysis included multivariate Cox proportional hazards modelling, C statistics and Homer-Lemershow test (H-L) for model calibration. **Results:** A total of 249 patients (mean age 54 ±13 years, 56% women, BMI, 37 ±9.0 kg/m^2, 52% with type 2 diabetes) were followed for a mean of 3.2 years, (range 1-9). 9.6 % of patients died or underwent liver transplant and 14.5 % developed a liver related event. Hepascore [hazard ratio (HR) 4.6, 95 % confidence intervals (CI) 2.27-9.34], NFS (HR 3.1, CI: 1.82-5.27), APRI (HR 2.3, CI: 1.33-4.0) and FIB4 (HR 2.8, CI: 1.63-5.13) were associated with overall mortality. The HRs for liver related events were 5.0 (95 % CI: 2.78-9.0), 4.0 (95% CI: 2.53 -6.43), 2.87 (95% CI: 1.8-4.5) and 4.1 (95 % CI: 2.4-7.2) for Hepascore, NFS, APRI and FIB 4 respectively. NFS, Hepascore and FIB-4 had similar predictive accuracy, for both overall mortality/liver transplant and liver related events outcomes (Table 1). Each model calibrated well with no differences between observed and predicted risk for overall mortality/liver transplantation. **Conclusions:** Non-invasive scoring systems are useful tools to predict overall mortality and liver related events in NAFLD patients according to predefined risk groups.

C index of four non-invasive scoring systems to predict outcomes

Score	Overall mortality/liver transplant	Liver related events
NAFLD fibrosis score	0.79 ±0.04 (0.71-0.87)	0.84 ±0.03 (0.78-0.91)
Hepascore	0.79 ±0.05 (0.70-0.89)	0.83±0.03 (0.76-0.91)
FIB-4	0.79 ±0.04 (0.70-0.88)	0.85 ±0.04 (0.79-0.92)
APRI	0.70 ±0.05 (0.60-0.80)	0.77±0.04 (0.69-0.86)

Values represents C statistics ± Standard Error (95% CI)

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The following people have nothing to disclose: Luis C. Bertot, Gary P. Jeffrey, Gerry C. MacQuillan, George Garas, Yi Huang

1167

Hepatic steatosis in Crohn's disease – Non-invasive comparison between NASH and Crohn's -

Katharina Willuweit[1], Malte Brandenburg[1], Svenja Sydor[1], Sophia Assmuth[1], Annemarie Wegehaupt[1], Sonja Kinner[2,3], Alisan Kahraman[1], Guido Gerken[1], Ali Canbay[1], Lars Bechmann[1]; [1]Department of Gastroenterology and Hepatology, University Hospital Essen, Essen, Germany; [2]Department of Radiology, School of Medicine and Public Health, Madison, WI; [3]Department of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen, Essen, Germany

Recent studies indicate an increasing prevalence of hepatic steatosis and non-alcoholic steatohepatitis (NASH) in several alimentary tract diseases, including inflammatory bowel diseases (IBD). We and others have shown that NASH in IBD patients is associated with an increased susceptibility for acute-on-chronic liver failure. To date, little is known about the mechanisms leading to hepatic steatosis in IBD. With this study, we aimed to analyze and compare non-invasive predictors of liver injury in patients with NASH and individuals with Crohn's disease (CD). Therefore we included patients with established NASH and patients with established CD without a history of liver disease and analyzed serum markers of liver injury, a breath test for small intestinal bacterial overgrowth (SIBO) and transient elastography as well as controlled attenuation parameter (CAP) to assess hepatic steatosis. As expected, patients with NASH had a significantly higher BMI compared to CD. Accordingly ALT and AST levels were significantly higher in NASH vs. CD. SIBO occurred in only two individuals and was not associated with steatosis. Interestingly, while transient elastography revealed increased liver stiffness in NASH vs. CD, there was no significant difference in CAP as a measure for hepatic steatosis between the groups. In fact, 43.8% of CD patients had a CAP >283dB/m, a previously established cutoff value for significant hepatic steatosis with a maximum CAP of 400dB/m in one patient. Although most patients remained within normal limits, AST and ALT were significantly higher in CD patients with CAP >283dB/m compared to CD patients with lower CAP results. In order to identify conditions associated with higher CAP results, we reviewed the patients' drug regimens. To our surprise steroid therapy was not associated with CAP in this cohort. However, individuals with CAP below 283dB/m were more likely to be treated with biologicals. In fact, CAP was significantly lower in patients on biologicals as compared to other treatment strategies (237.3 ± 11.7 vs. 306.2 ± 20.6 dB/m; p<0.05). Thus, in this cohort, NASH was associated with higher BMI, transaminase levels and liver stiffness, while hepatic steatosis as assessed by CAP was not pronounced compared to CD. In CD patients with significant steatosis, higher transaminase levels indicate subliminal hepatic inflammation, despite being within normal levels. Treatment with biologicals seems to protect CD patients from hepatic steatosis. In conlusion, we identified a high rate of hepatic steatosis in CD with alterations in transaminase levels and a potential association with biologicals.

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1168

A prospective study to evaluate the efficacy of a standardized low calorie diet according to PNPLA3 genotype in patients with Non Alcoholic Fatty Liver Disease (NAFLD) – week 2 data interim analysis

Manuela Teufelhart[1], Harald Hofer[2], Helmuth Haslacher[3], Robert Winker[1], Bernhard Meyer[1], Peter Ferenci[2], Benedikt Mehl[1], Christian Rabitsch[1], Sonja Nistler[1], Michael H. Trauner[2], Thomas-Matthias Scherzer[1]; [1]Health Care Center, Sanatorium Hera, Vienna, Austria; [2]Internal Medicine III, Dept. of Gastroenterology and Hepatology, Medical University of Vienna, Vienna, Austria; [3]Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria

Background. Approximately 30% of the Western population suffers from NAFLD, rising up to 90% in obese people. Complications of NAFLD include Non Alcoholic Steatohepatitis (NASH), liver cirrhosis, hepatocellular carcinoma as well as aggravation of diabetes and cardiovascular diseases. PNPLA3 is an important genetic factor associated with NAFLD. Aim of the study is to analyze the efficacy of a standardized low calorie liver diet (HEPAFAST, Bodymed, Kirkel, Germany) especially compounded for NAFLD patients (pts) and the influence of PNPLA3 genotypes on treatment outcome. **Methods.** In this study 81 non cirrhotic patients are stratified according to PNPLA3 genotypes (27 patients per group; CC,CG,GG). All patients receive a protein shake therapy (HEPAFAST) for 2 weeks and instructions to follow a low glycemic and insulinemic (LOGI) diet for another 6 weeks (EOT). All patients are seen longitudinally for four time points (baseline, week 2, 2 months and 6 months-follow up). At each time point liver fat content is assessed by an independent/blinded investigator with Fibroscan CAP. Additionally Fatty Liver Index (FLI), waist circumference (WC), BMI, HbA1c, triglycerides (TG) and GGT are analyzed. **Results.** To date 31 patients were included in this study, 26 pts [age 43±9.6 (mean±SD; m:19, f:7; PNPLA3 genotypes: CC:15, CG:8, GG:3] finished the HEPAFAST Shake therapy from baseline to week 2. All outcome variables decreased till week 2 (second time point): (1) Fibroscan CAP 322.9±31.6 dB/m2 to 270.7±36.0 (Δ52.2±32.0; p<0.001), (2) FLI 79.4±16.1 to 60.0±22.0 (p<0.001), (3) WC 109.7±8.5cm to 106.2±9.0 (p<0.001), (4) BMI 32.4±3.7 to 30.8±3.0 (p<0.001), (5) HbA1c 5.4±0.3% to 5.3±0.0 (p=0.092), (6) TG 128.7±77.6mg/dl to 86.7±73.0 (p<0.001) and (7) GGT 44.7±31.1U/l to 30.8±18.0 (p<0.001). Evaluation according to PNPLA3 genotype revealed a higher Fibroscan CAP drop for PNPLA3 G-allele carriers [CC: 316.4±35.1 to 271.5±43.6 (Δ44.9±35.5) vs G-allele carriers 331.7±25.0 to 269.6±23.8 (Δ62.2±31.0); p=0.12]. 16 patients finished 2 month treatment period including LOGI diet. Fibroscan CAP further decreased from baseline to 2 months [328.9±27.8 to 248.6±31.9 (Δ80.3±28.0); p<0.001]. **Conclusion.** A low calorie diet with HEPAFAST shakes is a very effective strategy to significantly lower liver fat in NAFLD patients. This effect seems to be more pronounced in patients carrying the PNPLA3 G-allele.

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Comparison of Fibrosis Scoring Tools in predicting Liver Fibrosis in Nonalcoholic Fatty Liver Disease

Sumant Arora[1], Steven Young[1], Ashwani Singal[2]; [1]Internal Medicine, University of Alabama at Birmingham, Montgomery, AL; [2]Gastroenterology and Hepatology, University of Alabama at Birmingham, Birmingham, AL

Background: Liver biopsy (LB) is the gold standard tool to evaluate fibrosis in NAFLD patients. Five simple noninvasive serum tests using routine evaluation and laboratory values have been used to evaluate fibrosis in NAFLD: Fibrosis-4 score (FIB-4), NAFLD fibrosis score (NFS), aspartate aminotransferase (AST) to platelet ratio index (APRI), AST to alanine transaminase (AST/ALT) ratio and BARD (BMI, AST/ALT ratio, diabetes) score. Data on comparing the accuracy of these scores are scanty. We aimed to compare the diagnostic utility of these scores among NAFLD patients seen at a tertiary university-based academic center. **Methods**: Medical charts of well defined NAFLD patients on LB were reviewed to collect data on demographics, laboratory values needed to compute the five scores to be compared, and fibrosis stage on LB. Patients with concomitant hepatitis C, alcohol use >20 g/d, and any other liver disease were excluded. Fibrosis stage on liver biopsy was staged F0-F4 and stratified to F0-2 (no to minimal fibrosis) and F3-F4 (advanced fibrosis to cirrhosis). Accuracy of each score for F0-2 or F3-4 and area under the receiver operating characteristic (AUROC) curve was derived for each scoring system. **Results**: Of 141 (83 F3-F4)NAFLD patients (mean age 56 years; 65% male; 81% white; 48% diabetic; 58% hypertension; 37% dyslipidemia; 16% gastric bypass). Cut off values used to predict F0-2 were: <1.45 for FIB (n=46), <-1.455 (n=59) for NFS, <0.5 (n=56) for APRI, <1 (n=66) for AST/ALT ratio, and <2 for BARD score. Respectively, cut-off values for predicting F3-4 were >3.25 (n=47), >0.675 (n=33), >1.5 (n=46), >1 (n=75), and 2-4 (n=117). The accuracy and AUROC for each score are depicted in Table1. Overall, combined use of all the five simple scores (in order of their AUROC) accurately predicted fibrosis stage, with potentially avoiding LB in 74% (104 of 141) NAFLD patients. **Conclusion**: Of all the available non-invasive fibrosis scores in NAFLD patients, FIB-4 was the most accurate. Combined use of these fibrosis scores is a simple, noninvasive tool to accurately predict fibrosis and reduce the need for LBs. Well-designed prospective studies are needed to incorporate liver stiffness measurements into the serum fibrosis scores to further improve the accuracy of non-invasive assessment of fibrosis in NAFLD patients.

Table1 Predictive Accuracy of Fibrosis scores in NAFLD

Fibrosis score	% Accuracy for F0-F2	% Accuracy for F3-F4	AUROC
FIB-4	80	81	0.82
NAFLD FS	66	82	0.79
NAFLD FS	68	80	0.78
AST/ALT ratio	59	75	0.72
BARD	67	64	0.66

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1170

Is Lysosomal Acid Lipase (LAL) deficiency a cause of atypical nonalcoholic fatty liver disease ?

Khalid Abdullah[1], Robinder Abrol[1], Herman Ortiz[1], Maria Welsh[1], Scott A. Zela[1], Chukwuma I. Egwim[1,2], Victor Ankoma-Sey[1,2]; [1]Liver Associates of Texas, Houston, TX; [2]GI/Hepatology, Houston Methodist Hospital, Houston, TX

Background Nonalcoholic fatty liver (NAFLD) is usually diagnosed in the context of the metabolic syndrome. However, there are other uncommon causes of NAFLD such as Lysosomal Acid lipase (LAL) deficiency. LAL is a rare, autosomal recessive disorder caused by a decrease or absence of the LAL enzyme, which is responsible for breaking down fats in the lysosomes. Two major phenotypes of LAL deficiency identified are:i) Early onset (also known as Wolman disease) which occurs in infants. ii)Late onset (also known as Cholesteryl Ester Storage Disease [CESD]) which occurs in children and adults. The aim of this study is to evaluate the possibility of CESD as a cause of NAFLD in adult patients who lack the typical predisposing features of NAFLD in a Hepatology practice. Methods: 200 Consecutive patients diagnosed with NAFLD at the Liver Associates of Texas hepatology clinics from June 2015- March 2016 were screened for risk factors of NAFLD. Screening criteria that favored the possibility of LAL deficiency in "atypical NAFLD patients" used in patient selection for LDL deficiency testing was: dyslipidemia with low HDL-cholesterol levels (<40mg/dL in males; <50mg/dL in females and/or low triglyceride levels (<150mg/dL) and/or persistent elevation of LDL-c > 160mg/dL despite statin therapy. Eleven patients NAFLD who met these criteria were identified in our study. These patients were offered and consented to participate in LAL deficiency diagnostic testing which is based on LAL enzyme activity testing -Lysosomal acid lipase blood spot. Statistical analysis: all analyses were performed using SPSS v19 . Results: The study group included six males and five females, mean age of patients was 48.7 years (SD 13.6), mean body mass index (BMI) 29 kg/m2 (SD 7.11). Mean ALT 56 U/L (SD 32.5), mean AST 39 U/L (SD 19.5) and mean of NAFLD fibrosis score 0.817 (SD 1.199). 27.2 % of patients had liver cirrhosis. Mean LAL blood spot for the patients was 356.8 pmole/hr/spt (SD 120.8), this mean is within normal reference range of LAL enzyme (40-600 pmole/hr/spt). Conclusion: Our study suggests that LAL deficiency is not a common cause of "atypical NAFLD". This subset of NAFLD patients will need further studies to clarify risk factors and better define this phenotype.

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1171

Longer Lactation Duration is Associated with Decreased Non-Alcoholic Fatty Liver Disease in the CARDIA Cohort Study

Veeral H. Ajmera[1], Norah Terrault[1], Lisa B. VanWagner[2], Monika Sarkar[1], Cora E. Lewis[3], John J. Carr[5], Erica Gunderson[4]; [1]Gastroenterology, UCSF, San Francisco, CA; [2]Gastroenterology, Northwestern University, Chicago, IL; [3]Preventive Medicine, University of Alabama, Birmingham, Birmingham, AL; [4]Division of Research, Kaiser Permanente, Oakland, CA; [5]Radiology, Vanderbilt University, Nashville, TN

Insulin resistance is associated with nonalcoholic fatty liver disease (NAFLD) and lactation lowers blood glucose and triglycerides and increases insulin sensitivity. We hypothesized that longer duration of lactation would be associated with lower prevalence of NAFLD. Participants from the multicenter Coronary Artery Risk Development in Young Adults (CARDIA) prospective cohort study who delivered ≥ 1 post-baseline (Y0: 1985-1986) birth(s), and underwent CT quantification of hepatic steatosis 25 years following cohort entry (Y25: 2010-2011) were included (n = 844). Duration of lactation was defined by self-report for post-baseline births, and NAFLD at Y25 was assessed by central review of CT images and defined by liver attenuation ≤ 40 Hounsfield Units after exclusion of other causes of hepatic steatosis. Unadjusted and multivariable logistic regression analyses were performed using an *a priori* set of confounding variables; age, race, education, body mass index (BMI), and post-baseline births (1 vs. 2+). Confounding variables with P-value < 0.05 during backward stepwise elimination were included in the final multivariable model. Of 844 parous women (48% black, 52% white, mean age 49 years at Y25 exam), 203 (24%) reported no lactation, 282 (33%) reported up to 6 months, 197 (23%) reported > 6 to < 12 months, and 162 (19%) reported ≥ 12 months and 54 (6%) had NAFLD. Longer lactation duration was associated with white race and lower BMI, at the baseline visit (P<0.05). Longer lactation duration was inversely associated with NAFLD in unadjusted logistic regression (OR per 3-month increase: 0.87, 95% CI: 0.75-1.00, p=0.056), and this association was strengthened (aOR per 3-month increase: 0.85, 95% CI: 0.72-0.99, p=0.04) after adjustment for potential confounders (Table). **Conclusion:** Longer duration of lactation is associated with lower odds of NAFLD in mid-life after adjustment for confounders. Lactation is a modifiable risk factor that may reduce NAFLD in parous women.

Association between Characteristics of Women and NAFLD at 25 Years

	Unadjusted		Multivariable Adjusted*	
Characteristic	OR (95% CI)	P	aOR (95% CI)	P
Lactation duration (per 3 month increase)	0.87 (0.75 - 1.00)	0.056	0.85 (0.72 - 0.99)	0.04
Age (per 5 years)	1.38 (0.94 - 2.02)	0.10		
White race (vs Black)	1.29 (0.74 - 2.25)	0.37	2.25 (1.19 - 4.24)	0.01
Births from Y0-Y25 ≥ 2 (vs 1)	0.57 (0.33 - 0.99)	0.05		
Baseline BMI (per 5 kg/m^2 increase)	1.45 (1.17 - 1.81)	< 0.01	1.54 (1.21 - 1.95)	< 0.01
Education > High School vs ≤ High School	0.76 (0.39 - 1.49)	0.43		

*Multivariable model determined by backward stepwise elimination with race, BMI and lactation duration in final model

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1172

Atrial fibrillation is highly prevalent, associated with significant morbidity, and undertreated in patients with biopsy-proven NASH

Maureen P. Whitsett[1], Amy Yang[2], Lisa B. VanWagner[2,3], Mary E. Rinella[2,3]; [1]Internal Medicine, Northwestern Memorial Hospital, Chicago, IL; [2]Northwestern Memorial Hospital, Chicago, IL; [3]Gastroenterology & Hepatology, Northwestern Memorial Hospital, Chicago, IL

Background: Elevated liver chemistries and ultrasound diagnosed fatty liver are associated with atrial fibrillation (AF) independent of traditional AF risk factors. AF is a potent risk factor for stroke and is associated with poor outcomes in after transplantation for nonalcoholic steatohepatitis (NASH) cirrhosis. The prevalence of AF in patients with NASH or NASH cirrhosis is unknown. **Purpose:** To assess the prevalence and impact of AF on healthcare utilization in patients with NASH or NASH cirrhosis. **Methods:** Patients with biopsy-proven NASH or NASH cirrhosis were identified using ICD9 billing codes from a tertiary care center Electronic Database from 2002-2015. NASH/cirrhosis was confirmed through independent review of liver biopsy reports at our center. ICD9 codes identified the presence of comorbidities and AF prevalence. T-test, Chi-square or Fisher exact tests were used to compare medication usage and comorbidities, as well as hospitalization and length of stay between patients with NASH and AF versus patients with NASH without AF. **Results:** Of 9108 patients with an ICD9 diagnosis of NASH/cirrhosis, 514 (5.6%) patients had a coexisting diagnosis of AF and 220 (2.4%) had biopsy-proven NASH/cirrhosis. Mean age of biopsy-proven NASH/cirrhosis patients was 53.7 ± 12.8 years and 38.1% were male. The prevalence of AF was 3.6% in biopsy-proven NASH and 3.2% in NASH cirrhosis patients. Patients with NASH/cirrhosis and AF were older (62.7 vs. 53.1 years) and had a higher prevalence of hypertension (80% vs. 46%m p=0.015), heart failure (40% vs. 9%, p=0.002) and cerebrovascular (20% vs. 2%, p=0.002), or vascular disease (47% vs. 13%, p=0.003), compared to those without AF. Among biopsy-proven NASH/cirrhosis patients, 12 (80%) had a CHA2DS2VASc score 2 indicating high stroke risk and need for anticoagulation. No patients were on anticoagulation and only 1 patient was on an anti-platelet agent. No patients received cardioversion or ablation. Patients with NASH and AF had more hospital visits (4.3 vs. 2.0, p=0.006) and longer hospital stays compared to those without AF (11.1 vs. 4.5 days, p=0.002). **Conclusion:** AF prevalence is higher in patients with NASH and NASH cirrhosis compared to general population estimates of 1.7%. Patients with concurrent NASH/cirrhosis and AF have a high burden of stroke, heart failure and healthcare utilization. However, NASH/AF patients do not receive anticoagulation despite it's indication based on the CHA2DS2VASc score. Future studies are needed to identify at risk NASH patients with AF and encourage guideline-based management. This may improve AF outcomes and impact cardiovascular outcomes in the burgeoning NASH population.

Disclosures:

Mary E. Rinella - Advisory Committees or Review Panels: Abbvie, Intercept; Consulting: Fibrogen, NGM, Shire

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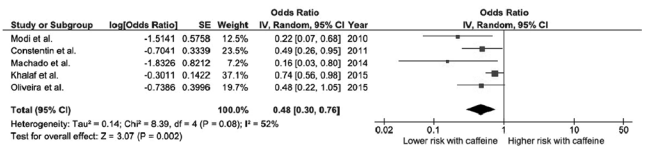
1173

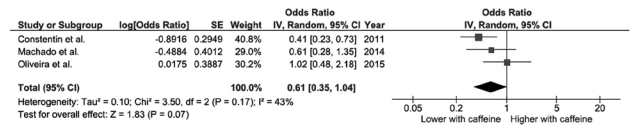
Coffee Consumption and Risk of Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis

Karn Wijarnpreecha[1], Charat Thongprayoon[1], Patompong Ungprasert[2,3]; [1]Internal Medicine, Bassett Medical Center and Columbia University College of Physicians and Surgeons, Cooperstown, NY; [2]Internal Medicine, Division of Rheumatology, Mayo Clinic, Rochester, MN; [3]Medicine, Division of Rheumatology, Faculty of Medicine Siriraj hospital, Mahidol University, Bangkok, Thailand

Background/Objectives: Nonalcoholic fatty liver disease (NAFLD) is a worldwide public health concern. Coffee might have protective effect against NAFLD. However, results of previous reports are conflicting. Therefore, we conducted this meta-analysis to summarize all available data. **Methods**: This study consisted of two meta-analyses. The first meta-analysis included observational studies comparing risk of NAFLD who did and did not drink coffee. The second analysis included studies comparing the risk of liver fibrosis between NAFLD patients who did and did not drink coffee. Pooled odds ratios (OR) and 95% confidence interval (CI) were calculated. **Results**: Out of 355 articles, five studies met our eligibility criteria and were included in the analysis. The risk of NAFLD in subjects who drank coffee was significantly lower than subjects who did not (pooled OR 0.71; 95% CI, 0.60-0.85). We also found a significantly decreased risk of liver fibrosis among NAFLD patients who drank coffee compared to those who did not with the pooled OR of 0.70 (95% CI, 0.60-0.82). **Conclusions**: Our study demonstrated a significantly decreased risk of NAFLD among coffee drinkers and significantly decreased risk of liver fibrosis among patients with NAFLD who drank coffee on a regular basis. Whether consumption of coffee could be considered as a preventative measure against NAFLD needs further investigations.

Forest plot of the included studies the impact of coffee and presence of NAFLD and liver fibrosis in NAFLD





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1174

Global Trends in the Management of Nonalcoholic Steatohepatitis (NASH): Treatment Patterns and Outcomes

Arun J. Sanyal[2], Amber L. Martin[1], Sarah M. Cadarette[1], Karin Henriksson[3,4], Bernt Kartman[3], Mark Berner Hansen[5,6]; [1]Evidera, Lexington, MA; [2]Virginia Commonwealth University, Richmond, VA; [3]AstraZeneca Gothenburg, Mölndal, Sweden; [4]Uppsala University, Uppsala, Sweden; [5]The Digestive Disease Center Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark; [6]Zealand Pharma, Glostrup, Denmark

PURPOSE: NASH is a liver inflammation and ballooning degeneration condition caused by accumulation of fat deposits in the liver that lead to fibrosis. Symptoms typically do not emerge until later in the disease and no approved therapies exist. Current guidelines recommend lifestyle changes and treating associated conditions; advanced stages may require liver transplantation. A systematic literature review was performed to define the knowledge base related to treatment of NASH. METHODS: Literature databases were searched from 2000–2015 and supplemented with conference abstracts from 2013–2015 to identify studies reporting treatment patterns, guidelines, or outcomes in NASH. RESULTS: In the last 15 years, 74 articles examined treatments in NASH. The majority (63%) were trials assessing pharmacological treatments or supplements, and most observational studies evaluated surgical interventions (18/28), mainly liver transplants (13/18). NASH therapy options differ around the world. Diet and lifestyle changes have been studied worldwide and have shown improvements in both liver enzyme and histological measures. Alternative therapies have demonstrated benefits, but these are not widely studied. Pioglitazone, studied in Europe, the US, and India, consistently reduced liver enzymes. It also significantly improved histological measures for steatosis, and lobular inflammation. The effect on ballooning and fibrosis varied between the US and India. Rosiglitazone significantly improved liver enzymes compared with baseline levels, as well as scores for all evaluated histological measures in a US-based study. However, when compared with placebo in a European trial, it showed no effect on histological measures. Vitamin E has demonstrated benefits in both US and European studies. Vitamin E statistically improved NAS scores and liver enzyme levels relative to baseline values or placebo, but did not significantly improve fibrosis score. When combined with ursodeoxycholic acid, it significantly decreased hepatic steatosis. Evidence on treatment patterns for NASH is limited. Vitamin E and pioglitazone are prescribed to NASH patients by 70% of gastroenterologists surveyed and 14% of hepatologists. CONCLUSIONS: Pharmacological treatments with glitazones and vitamin E demonstrated variable performance in trials but commonly led to histologic improvement and reductions in liver enzymes in NASH patients. Whether these treatments have an effect on halting disease progression to cirrhosis is unknown. More real-world studies with larger sample sizes are needed to document treatment use and outcomes in clinical practice. Approved treatments remain an unmet need in managing NASH.

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Amber L. Martin - Consulting: AstraZeneca

Karin Henriksson - Employment: AstraZeneca R&D

Bernt Kartman - Employment: AstraZeneca; Stock Shareholder: AstraZeneca

The following people have nothing to disclose: Sarah M. Cadarette, Mark Berner Hansen

1175

Ethnic diversity at presentation in patients with NASH: Data from a tertiary referral center

Parvez S. Mantry[1], Ashwini P. Mehta[2], Paul Hess[1], Anup Kumar[1], Jeffrey S. Weinstein[1], Hector E. Nazario[1], Maisha Barnes[1], Mangesh Pagadala[1], Adil Habib[1]; [1]The Liver Institute, Methodist Dallas Medical Center, Dallas, TX; [2]Gastroenterology, Plaza Medical Center, Fortworth, TX

Background: Non alcoholic Steatohepatitis (NASH) presentation shows significant ethnic diversity in the US population. Our aim was to understand these differences in an area of high

endemicity of obesity and metabolic syndrome using the database at a tertiary referral center. **Methods:** We conducted a retrospective analysis of patients who were seen and followed at the Liver Institute or one of our satellite clinics with a diagnosis of NASH based on ICD-10(K75.81) and ICD -9(571.8) codes from January 2011 to Jan 2016. We excluded patients with incomplete data and those lost of follow up. Data from liver biopsy, imaging, labs, demographics and comorbidities linked to metabolic syndrome were collected. An IRB exemption was obtained for retrospective analysis of de-identified data.. **Results:** We analyzed the charts of 650 patients with complete information. 451 patients presented with abnormal LFTs (ALT>ULN) and 437 patients presented with fatty liver on imaging. 62% of the entire cohort was female. The self reported race distribution was: Caucasian - 51%, Hispanic-29.5% African-American 11.25%, Asian- 4.9%, Others 1%, Unknown-2.8%. The median age at presentation in the cohort was 57.6 years and varied in different ethnic groups with hispanics and Asians presenting at a younger age than others. Differences in BMI at presentation were minor in most racial groups except in Asians. 185 of the 650 patients had cirrhosis on presentation either on biopsy or imaging characteristics or signs of portal hypertension on imaging or endoscopy. In terms of metabolic syndrome comorbidities,291 patients had Diabetes, 296 patients had hypertension and 326 patients had hyperlipidemia - all 3 were present in 151(23%) patients. The ethnic distribution of bridging fibrosis or cirrhosis at presentation was Caucasian -46% Hispanic -31%, AA- 22%, Asians-9%. The differences in characteristics and disease severity are presented in Table1. **Conclusions:** We present our analysis of a large single center tertiary referral center database of patients with NASH.This is a very representative cohort in the Southwest region of the US in terms of ethnic mix. Both Asians and Hispanic Americans tend to present at a younger age. 29% of patients at presentation had cirrhosis highlighting the need for early referral and fibrosis assessment in these patients.

Ethnic Diversity in NASH at presentation

Race	Caucasian	Hispanic	African Am	Asian	Others/unk
N of patients(%) total 650	329 (51%)	192(30%)	72(11%)	32(5%)	22(3%)
median Age at presentation (M,F)	M58, F59	M55,F56	M60,F60	M51,F60	
median BMI at presentation	35.1	35.0	34.2	28.3	34.7
Cirrhosis at presentation	119(36%)	46(24%)	10(14%)	3(9%)	7(31%)
Diabetes at presentation	151(46%)	89(46%)	29(40%)	16(50%)	7(32%)

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Jeffrey S. Weinstein - Speaking and Teaching: Merck

Hector E. Nazario - Speaking and Teaching: Merck, Gilead, Abbvie, Janssen

The following people have nothing to disclose: Ashwini P. Mehta, Paul Hess, Anup Kumar, Maisha Barnes, Mangesh Pagadala, Adil Habib

1176

Nonalcoholic steatohepatitis (NASH) or high probability of fibrosis based on noninvasive marker panels (APRI, FIB-4, NFS) at disease presentation is associated with increased all-cause mortality in patients with nonalcoholic fatty liver disease (NAFLD)

Nghiem B. Ha[2,1], Richard H. Le[1], Sam Trinh[1], Michael D. Nguyen[1], Benjamin Yip[3,1], Joseph K. Hoang[1], Mindie H. Nguyen[1]; [1]Division of Gastroenterology and Hepatology, Stanford University Medical Center, Palo Alto, CA; [2]School of Medicine, University of California, Davis, Sacramento, CA; [3]Department of Internal Medicine, University of California, Irvine, Irvine, CA

Purpose: NAFLD is associated with higher risk of liver-related complications and mortality, but ethnicity-related natural history data remains limited. We aim to examine disease presentation and natural history of NAFLD in an ethnically diverse cohort. **Methods**: We analysed a retrospective cohort of 872 consecutive NAFLD patients (246 Asians, 436 Caucasians, and 190 Hispanics) seen at a medical center from 1999-2009 by ethnicity. NAFLD was diagnosed by imaging/histological evaluation. Exclusion criteria: viral/drug-induced hepatitis, heavy alcohol use, or inflammatory/genetic liver disease. Study endpoints: development of NASH, cirrhosis, decompensation, liver cancer, and death. **Results**: Asians were more likely male with a lower mean BMI (28.2±5.2 vs 33.6±8.2,p<0.001). Majority of Hispanics were female (69%) and presented at a younger age (42±14 vs. 48±14 years,p<0.001). More Asians had hyperlipidemia (55% vs 40-51%,p=0.01) and hypercholesterolemia (29% vs 18-25%,p=0.03); however, all three groups had similar rates of hypertension (54-60%), diabetes (30-40%), and coronary artery disease (11-14%). All three groups had similar low/intermediate/high probability of fibrosis per AST to Platelet Ratio and Fibrosis-4 score. Asians were less likely to have high probability of fibrosis per NAFLD Fibrosis Score (5% vs 12-19%,p<0.001). Multivariate analysis demonstrated that older age (OR=1.04,95%CI=1.02-1.05), higher BMI (OR=1.06,95%CI=0.53-1.60), diabetes (OR=2.73,95%CI=1.81-4.14) and Hispanic ethnicity (OR=1.75,95%CI=1.05-2.91) were significantly associated with NASH/high probability of fibrosis at baseline. Median follow-up was 85(6-274) months. All three groups had similar 12-year cumulative incidence rates of NASH (5-8%,p=0.11), cirrhosis (3-8%,p=0.99), decompensation (3-7%,p=0.41), and all-cause mortality (4-9%,p=0.39). In multivariate Cox proportional hazard models also inclusive of age, sex, BMI, diabetes, and ethnicity, NASH/high probability of fibrosis at baseline was significantly associated with development of cirrhosis (HR=4.27,95%CI=1.35-13.51,p=0.01) and all-cause mortality (HR=2.72,95%CI=1.19-6.22,p=0.02). All-cause mortality among patients with NASH/high probability of fibrosis was estimated to be 13.7/1000 person-years compared to patients with NAFLD/low probability of fibrosis (4.5/1000 person-years,p=0.004). **Conclusion**: Despite differences in disease presentation, disease sequelae from NAFLD to NASH, cirrhosis, decompensation, and all-cause mortality was similar among Asians, Caucasians, and Hispanics. Patients with NASH/high probability of fibrosis at disease presentation may benefit from closer disease monitoring to reduce mortality.

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1177

Evaluation of non-invasive markers for the diagnosis of nonalcoholic steatohepatitis

Natsuko Kobayashi, Takashi Kumada, Hidenori Toyoda, Toshifumi Tada; Ogaki Municipal Hospital, Oogaki, Japan

Background and aim Nonalcoholic fatty liver disease (NAFLD) is one of the common liver diseases in both Western and Asian countries. Liver biopsy is the gold standard for definitive diagnosis of non-alcoholic steatohepatitis (NASH). However liver biopsy is painful, costly, and has a risk of bleeding. Several laboratory markers including C-reactive protein (CRP), adiponectin, cytokeratin 18 (CK18), and hyaluronic acid (HA) are reportedly useful for differentiating NASH from non-alcoholic fatty liver (NAFL). However, few reports compared these markers in the identical patients. We investigated the utility of non-invasive markers for the diagnosis of NASH. Methods A total of 229 NAFLD patients who underwent liver biopsy were investigated. The NASH or NAFL was diagnosed by the Matteoni classification (type 1 and 2 were classified as NAFL and type 3 and 4 were classified as NASH). We measured following markers in addition to routine laboratory examination in these patients; HA, type IV collagen7s, total CK 18 and fragmented CK18 (fCK18), adiponectin, human tissue inhibitor of metalloproteinase-1 (hTIMP-1), matrix metallopeptidase 2 (MMP2), branched chain amino acid/tyrosine molar ratio (BTR), AST/ALT, APRI, FIB-4index, Forns index, and NAFLD fibrosis score. We investigated the ability of these markers to predict NASH from NAFLD. Results 140 patients were diagnosed as NASH histologically. 72 NASH patients had degree 0-2 fibrosis (F0-2), and 68 patients had degree 3-4 fibrosis (F3-4) according to Brunt classification. Multiple logistic regression analysis identified HA (Odds ratio [OR]: 1.014 95%CI: 1.002-1.026 P=0.024), FIB-4index (OR: 2.097 95%CI: 1.177-3.735 P=0.012), and fCK18 (OR: 1.002 95%CI: 1.001-1.002 P<0.001) as factors independently associated with diagnosis of NASH. AUROCs of HA, FIB-4index, and fCK18 for the diagnosis of NASH were 0.77 (95%CI: 0.71-0.83), 0.76 (95%CI: 0.69-0.82), and 0.72 (95%CI: 0.65-0.78), respectively. FIB-4index (OR: 1.907 95%CI: 1.063-3.419 P=0.03) and fCK18 (OR: 1.002 95%CI: 1.001-1.002 P<0.001) could differentiate NASH and NAFL even excluding patients with NASH with advanced fibrosis (F3-4). AUROCs of FIB-4index and fCK18 for diagnosis of NASH with mild fibrosis (F0-2) from NAFLD were 0.703 (95%CI: 0.63-0.77) and 0.704 (95%CI: 0.63-0.77), respectively. Conclusions Several laboratory markers are useful to predict NASH from patients with NAFLD. FIB-4index and fCK18 have an ability to predict the NASH even focusing on NASH with mild fibrosis.

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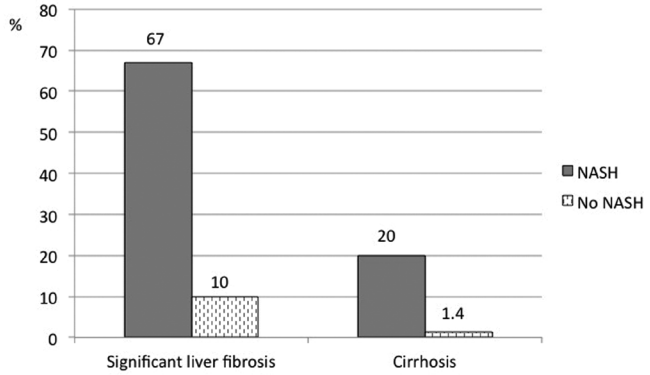
1178

Cytokeratin 18 and Transient Elastography with Controlled Attenuation Parameter as Screening Tools for Nonalcoholic Steatohepatitis in HIV Mono-Infected Patients

Amine Benmassaoud, Marc Deschenes, Peter Ghali, Lynda Lennox, Philip Wong, Marina B. Klein, Giada Sebastiani; Medicine, McGill University Health Centre, Montreal, QC, Canada

Background: Persons living with HIV are at high risk of nonalcoholic steatohepatitis (NASH). However, data on NASH in HIV mono-infection are scarce. **Methods**: We conducted a prospective screening study of prevalence and predictors of NASH in unselected HIV mono-infected patients by the serum biomarker cytokeratin 18 (CK-18) and transient elastography (TE) with associated controlled attenuation parameter (CAP). Patients with significant alcohol intake or coinfection with hepatitis B or C were excluded. NASH was defined as presence of fatty liver (CAP ≥238 dB/m) and CK-18 >246 U/L. Those cases defined as NASH were offered a liver biopsy. Significant liver fibrosis and cirrhosis (stage 2 and 4 out of 4, respectively) were defined as TE measurement ≥7.1 and ≥13 kPa, respectively. Predictors of NASH were determined using multivariable logistic regression analysis. **Results**: 159 consecutive HIV mono-infected patients (median age 52.7, IQR 46-58.8 years; 81.5% men; median CD4 count 605, IQR 451-798 cell/uL; 90% on antiretrovirals) were included. Fatty liver and NASH were diagnosed in 49.7% and 9.4% of cases, respectively. Significant liver fibrosis and cirrhosis were more frequent in patients with NASH than those without NASH (see Figure; p<0.001). After adjusting for age and BMI, elevated ALT (OR=12.4, 95% CI 2.9-54.1; p=0.001) and TE measurement ≥7.1 (OR=7.8, 95% CI 1.9-31.8; p=0.004) were independent predictors of NASH. 13 out of 15 patients with a non-invasive diagnosis of NASH agreed to undergo a liver biopsy and histology confirmed NASH in all cases. **Conclusion**: NASH diagnosed by CK-18 and TE with CAP is very frequent in HIV mono-infected persons, particularly in case of elevated ALT and TE measurement. A non-invasive diagnostic strategy employing these non-invasive tools can help early identification of NASH and initiation of interventions by reducing the need for liver biopsy in persons living with HIV.



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Marc Deschenes - Advisory Committees or Review Panels: Merk, Gilead, Abbvie, Lupin, Intercept

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The following people have nothing to disclose: Amine Benmassaoud, Peter Ghali, Lynda Lennox

1179

Controlling HIV using cART contributes to metabolic disorder and hepatic steatosis

Raphael Mohr, Christoph Boesecke, Robert Schierwagen, Carolynne Schwarze-Zander, Jan-Christian Wasmuth, Jürgen K. Rockstroh, Jonel Trebicka; Internal Med 1, University Hospital Bonn, Bonn, Germany

Objectives: Available data on the prevalence of hepatic steatosis (HS) in a real-life HIV-infected population are scarce and discrepant. Controlled attenuation parameter (CAP) determi-

nation is accurate in identifying significant hepatic steatosis (fat accumulation in >10% of hepatocytes). The aim of this study was to assess the prevalence and factors associated with significant hepatic steatosis in HIV-infected patients. **Methods:** 364 HIV-infected patients were included in this prospective, cross-sectional study. All patients underwent controlled attenuation parameter (CAP) determination. Steatosis was classified as S1,(significant steatosis) in CAP>238 dB/m, S2 in CAP>260 dB/m, S3 in CAP>292 dB/m. Logistic regression and cox-regression uni- and multivariate analyses were performed to analyze the associations between HS and demographics, metabolic data, virologic factors and antiretroviral therapy. **Results:** 287 (79%) were HIV mono-infected, 20 (6%) were HBsAg-positive, 57 (16%) were anti-HCV-positive, of which 31 (54%) had achieved sustained virologic response (SVR). Significant hepatic steatosis was detected in 149 (41%) patients (S1:29%, S2:34%, S3:37%). Interestingly, less severe steatosis was observed in patients with a longer duration of known HIV-infection [10 (0-29) vs. 12 (0-29) yrs; p = 0.031] and longer cART naïve periods [2 (0-20) vs. 3 (0-21) yrs; p = 0.037]. As expected, patients with significant steatosis showed higher mean HbA1c levels [5.3 (2.7-8.1) vs. 5.5 (3.6-11.4) %; p = 0.015], higher mean BMI [23 (15-41) vs. 26 (19-38) kg/m2; p < 0.001], higher triglycerides [153 (28-1549) vs. 228 (43-1193) mg/dl; p < 0.001] and lower HDL cholesterol [50 (8-127) vs. 45 (18-100) mg/dl; p = 0.002] compared to patients without steatosis. Interestingly, multivariate analysis revealed that while BMI was independently associated with steatosis [OR, 1.24; 95% CI, 1.12-1.37; p < 0.001], longer cART-naïve periods [HR, 0.90; 95% CI, 0.83-0.94; p < 0.001] were associated with less hepatic steatosis development. No impact on severity of steatosis was identified for any antiretroviral drug class. **Conclusions:** Hepatic steatosis is highly prevalent among HIV-infected patients. Obesity is an independent predictor of steatosis development, while suppression of viral replication might contribute to hepatic steatosis, which however was not related to antiretroviral drugs known to cause metabolic changes.

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Utility of the NAFLD Fibrosis Score in Predicting Advanced Fibrosis in a Predominantly Latino Population

Aradhna Seth[2], Maya Balakrishnan[2,4], Shilpa Jain[3], Gagan K. Sood[1,4]; [1]Department of Surgery, Division of Abdominal Transplantation/ Transplant Hepatology, Baylor College of Medicine, Houston, TX; [2]Department of Medicine, Baylor College Of Medicine, Houston, TX; [3]Department of Pathology, Baylor College of Medicine, Houston, TX; [4]Division of Gastroenterology and Hepatology, Baylor College of Medicine, Houston, TX

Background: Among ethnic groups in the United States, the highest estimated prevalence of non-alcoholic fatty liver disease (20-25%) is observed among Latinos. The NAFLD fibrosis score (NFS) is a widely used tool for prediction of fibrosis among patients with NAFLD. However the NFS was validated in predominantly Caucasian study populations and its accuracy for prediction of advanced fibrosis among Latinos is uncertain. Therefore we undertook this study to determine the diagnostic accuracy of NFS for advanced fibrosis among a population comprised predominantly of Latino adults with NAFLD. **Methods:** This was a retrospective cross-sectional study among 137 adults with NAFLD who underwent liver biopsies between 2010-2014 in Ben Taub General Hospital (Houston, TX). Exclusion criteria were: evidence of heavy alcohol use (>30 g/day in men; >20 g/day in women), secondary liver disease, drug induced liver injury, or HIV infection. The NFS was calculated from labs obtained within three months of liver biopsy and compared to histologic stage of fibrosis. Statistical Analysis Software (SAS®) and Microsoft Excel used to calculate descriptive statistics, area under the receiver-operating curve (AUROC), sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV). **Results:** The overall mean age and BMI were 47± 11.9 years and 32 ± 6.7kg/m2 respectively; 77% (n=105) were Latino and 78% (n=107) women; 50% were diabetic (n=69). Forty percent had advanced fibrosis (n=55). Patients with advanced fibrosis were older (p=0.026), had lower platelets (p< 0.001) and albumin (p< 0.001) and higher NFS (p<0.001) compared to patients with mild fibrosis. Using a low NFS cutoff of -1.455, the NPV and PPV were 69 % and 77 % in Latinos vs 85% and 60% in overall group. Using a high NFS cutoff of 0.676, the NPV and PPV were 85 and 59 % in Latinos vs 70% and 81% in overall group. The diagnostic accuracy of the NFS for advanced fibrosis was AUROC=. 0.77 [95% CI =0.6819,0.8757] in Latinos vs AUROC 0.80 [95% CI=0.7278, 0.8788] in overall group. Using the NFS, liver biopsy could have been avoided in 63% of patients overall and 64% in the Latino subgroup.**Conclusion:** NAFLD fibrosis score can reliably exclude advanced fibrosis in high proportion of Latino patients with NAFLD, allowing liver biopsy to be used in more directed manner.

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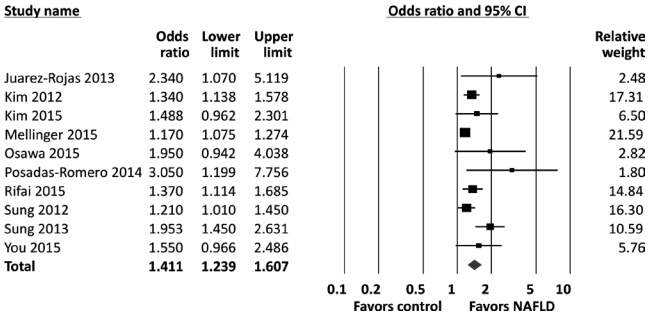
1181
Nonalcoholic Fatty Liver Disease is Associated with Coronary Artery Calcification: a Systematic Review and Meta-Analysis

Veeravich Jaruvongvanich[2], Anawin Sanguankeo[1], Kamonkiat Wirunsawanya[2], Sikarin Upala[1]; [1]Bassett Medical Center, Cooperstown, NY; [2]University of Hawaii, Honolulu, HI

Background: Whether nonalcoholic fatty liver disease (NAFLD) is related to subclinical artherosclerosis is unclear. Coronary artery calcium scanning (CAC) is the robust predictor of coronary events in the asymptomatic individuals. Several recent studies have investigated the association between NAFLD and this surrogate marker. Thus, we conducted a systematic review and meta-analysis to better characterize the association between NAFLD and CAC. **Methods:** A comprehensive search of the databases of the MEDLINE and EMBASE was performed from inception through May 2016. The inclusion criterion was the observational studies' assessment of the association between NAFLD and CAC in adult subjects. Pooled odds ratio (OR) and 95% confidence interval (CI) from multivariate model with confounder adjustment were calculated using a random-effect, generic inverse variance method. The between-study heterogeneity of effect-size was quantified using the Q statistic and I^2. **Results:** Data were extracted from 15 studies (all cross-sectional studies) involving 35,409 subjects. NAFLD is significantly associated with CAC > 0 (Figure 1) and CAC > 100 with pooled OR of 1.41 (95% CI 1.24-1.61, $P_{heterogeneity}$ = 0.01, I^2=57%) and 1.24 (95% CI 1.02-1.52, $P_{heterogeneity}$ = 0.09, I^2=42%). The association between NAFLD and CAC > 0

was stronger in women than men ($P_{between\ sex}$ = 0.017). **Conclusions:** NAFLD is also associated with coronary calcification independent of traditional risk factors, obesity and metabolic syndrome in asymptomatic individuals and this association was appeared to be stronger in women.

Meta-analysis of NAFLD and coronary artery calcium >0



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Exercise training mediates lipid infiltration of skeletal muscle and contributes to improve pathogenesis of NAFLD

Hirokazu Takahashi[1], Yoichiro Kitajima[2,1], Yoshihito Kubotsu[1,2], Satoshi Oeda[3], Keizo Anzai[1], Yuichiro Eguchi[3]; [1]Department of Metabolism and Endocrinology, Faculty of Medicine, Saga University, Saga, Japan; [2]Clinical Gastroenterology, Eguchi Hospital, Ogi, Japan; [3]Liver Center, Faculty of Medicine, Saga University, Saga, Japan

Background and aim Physical exercise has beneficial effects on metabolic homeostasis. Exercise training increases the skeletal muscle mass, decreases lipid infiltration in skeletal muscle and contributes to improve insulin resistance and NAFLD. We aimed to analyze the actual impact of changes of the skeletal muscle after exercise training on NAFLD. **Method** Longitudinal study was performed in 60 patients (30 males) who were diagnosed as fatty liver disease by abdominal ultrasound at Saga University Hospital and affiliate facilities. Patients with a drinking history (≥ 20 g/day of alcohol), viral hepatitis, autoimmune liver diseases or malignant disease were excluded. Patients performed exercise as 27 metabolic equivalent tasks (METs)/ week for 6 months. Food intake was adjusted as 25 kcal/kg bodyweight. We evaluated the abdominal lumbar muscle area by CT imaging and obtained skeletal muscle area index (SAI; lumbar muscle area (cm^2)/ height $(cm)^2$). Lipid infiltration of the skeletal muscle (intramuscular adipose tissue content, IMAC) and of liver (liver-spleen ratio, L/S ratio) was also measured by CT imaging-based technique. Factors which contributed to improve L/S ratio and ALT were identified by multiple regression model. **Result** Exercise training decreased IMAC in 46 patients (76.7%) with decreased BMI, decreased fasting plasma glucose, decreased ALT and improved L/S ratio ($p < 0.001$, respectively) while 14 patients without decrease of IMAC failed to improve these parameters. Exercise training increased SAI in 16 patients with decreased BMI, decreased ALT and improved L/S ratio; however, interestingly, 46 non-responders of SAI also showed significant improvement of these parameters. Decrease of IMAC (t value: 3.92, $p < 0.001$) and increase of SAI (t value: 2.52, $p = 0.014$) significantly correlated to improvement of ALT level. Decrease of IMAC was independent factor to improve L/S ratio (t value: 4.83, $p < 0.001$) while there was no significant correlation between increase of SAI and improvement of L/S ratio. **Conclusion** Although increased skeletal muscle mass was not a factor to improve liver steatosis in NAFLD, decreased lipid infiltration in skeletal muscle contributes to improve liver steatosis as well as ALT level in our exercise training program for NAFLD. Lipid infiltration of skeletal muscle could be an indicator of the exercise training effect on NAFLD and possible therapeutic target of NAFLD.

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Elevated hepatic SPARC levels are associated with increased risk of hepatocellular injury in severely obese patients with non-alcoholic fatty liver disease.

Guillermo Mazzolini[2], Catalina Atorrasagasti[2], Agostina M. Onorato[2], Estanislao Peixoto[2], Martin Schlattjan[1], Svenja Sydor[1], Jan-Peter Sowa[1], Guido Gerken[1], Ali Canbay[1]; [1]Department of Gastroenterology and Hepatology, University Hospital Essen, Essen, Germany; [2]Gene Therapy Laboratory, Instituto de Investigaciones Medicas Aplicadas, Universidad Austral-CONICET, Buenos Aires, Argentina

Background and aims: Mechanisms that control progression from simple steatosis to steato-hepatitis and fibrosis in patients with non-alcoholic fatty liver disease (NAFLD) are still matter of investigation. SPARC, a secreted matricellular protein, is over-expressed in the liver under chronic injury. Contribution of SPARC accumulation to disease severity, and mechanisms involved, are largely unknown in NAFLD. We assessed the hypothesis that SPARC is increased in livers with more necrosis and inflammation and therefore at high risk of fibrosis. *Methods*: qrt-PCR, immunohistochemistry, and ELISA were employed to localize and quantify changes in SPARC in 62 morbidly obese patients with NAFLD and in a mouse model of diet-induced-NASH. Results were correlated with the severity of liver disease and progression from simple steatosis to NASH. *Results*: In obese patients 2 subgroups were identified with either high SPARC expression (n=20) or low SPARC expression (n=42) in liver tissue. High expression of SPARC paralleled more extensive hepatocellular necrosis, necroptosis, and increased pro-fibrogenic factors. In line with these findings, in the NASH animal model SPARC knockout mice were protected from inflammatory injury, and showed less inflammation and fibrosis. *Conclusions*: SPARC accumulation is associated with more severe liver injury and fibrogenic processes in NAFLD. SPARC may be a promising diagnostic and therapeutic target to monitor progression in NAFLD patients.

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The Role Of Genetic Variability Of PNPLA3 (rs738409) On Predispotion To Non-Alcoholic Fatty Liver Disease In Lean Patients

Ramazan Idilman[1], Senem C. Karatayli[2], Fatih Karakaya[1], Onur Keskin[1], Bilge Gozukara[1], Berna Savas[3], Mithat Bozdayi[2], Atilla Halil Elhan[1], Cihan Yurdaydin[1]; [1]Gastroenterology, Ankara University School of Medicine, Ankara, Turkey; [2]Ankara University Hepatology Institue, Ankara, Turkey; [3]Pathology, Ankara University School of Medicine, Ankara, Turkey

Background/Aims: Patients with normal body mass index (BMI) present non-alcoholic fatty liver disease (NAFLD) and designated as lean NAFLD. The aims of the present study were to investigate the role of genetic variability of the patatin-like phospholipase domain-containing 3 (PNPLA3) on predisposition to NAFLD and disease severity in lean NAFLD patients. **Material and Methods:** A total of 219 consecutive NAFLD patients and 151 healthy controls were assessed. DNA was extracted from peripheral blood, and a single nucleotide polymorphism was assessed by PCR-DNA sequencing. **Results:** At the time of the diagnosis, the median BMI was 29.3 kg/m^2 (36% were obese, 11% were lean). The median NAS of the available 174 liver biopsies was 5.0, and a histological diagnosis of NASH was obtained in 60%. The frequency distribution of the GG genotype of the PNPLA3 was significantly higher in NAFLD patients than in healthy controls (p=0.01). In patients with NAFLD, the GG genotype was associated with lower platelets counts (p<0.05), the presence of steatohepatitis (p<0.05) and hepatic fibrosis (p<0.05) compared to the CC and CG genotypes. In subgroup analysis of NAFLD patients, 23 patients (11%) were lean-NAFLD. The presence of diabetes mellitus, insulin resistance, hypertension and hyperlipidemia were slightly higher in obese patients compare to lean patients (p>0.05). However, serum aminotransferases levels were slightly higher in lean patients. Median serum AST and GGT levels were 32.5 U/L (range: 19-102 U/L) vs 30.0 U/L (range: 4-133 U/L) (p=0.575), and 38 U/L (range: 13-111 U/L) vs 35 U/L (range: 10-442 U/L) (p=0.51), respectively. The presence of liver fibrosis was slightly more common in lean NAFLD than that of in obese NAFLD patients (59% vs 49%, p=0.441). The GG genotype was slightly more prevalent in lean NAFLD patients compared to obese NAFLD patients (57.0% vs 46.0%, p=0.610). When compare to lean (n=13) and obese NAFLD patients (n=89) with GG genotype, serum aminotransferases levels were slightly higher in lean patients with GG genotype compared to obese patients with GG genotype. Median serum AST and GGT levels were 37.0 U/L (range: 21-102 U/L) vs 30.0 U/L (range: 13-111 U/L) (p=0.543), and 44 U/L (range: 15-111 U/L) vs 34 U/L (range: 10-442 U/L) (p=0.216), respectively. Lean NAFLD patients with GG genotype had slightly more fibrotic liver than that of obese NAFLD patients (67% vs 54%, p=0.723). **Conclusion:** Patients with GG genotype of rs738409 polymorphism in PNPLA3 are more likely to develop NAFLD in lean patients as well as in obese patients. The GG genotype was associated with more severe liver disease both in obese and also in lean NAFLD patients.

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Probiotic VSL#3 improves liver histology in patients with nonalcoholic fatty liver disease – A proof of concept study.

Ajay K. Duseja[1], Subrat K. Acharya[2], Manu Mehta[1], Shruti Chhabra[2], . Shalimar[2], Satyavati Rana[3], Ashim Das[5], Siddhartha Datta Gupta[4], Radha K. Dhiman[1], Yogesh K. Chawla[1]; [1]Hepatology, Post Graduate Institute of Medical Education & Research, Chandigarh, India; [2]Department of Gastroenterology and Human Nutrition, All India Institute of Medical Sciences, New Delhi, India, New Delhi, India; [3]Department of Gastroenterology, Post Graduate Institute of Medical Education & Research, Chandigarh, India; [4]Department of Pathology, All India Institute of Medical Sciences, New Delhi, India, New Delhi, India; [5]Department of Histopathology, Post Graduate Institute of Medical Education & Research, Chandigarh, India

Introduction – Pharmacological treatment of nonalcoholic fatty liver disease (NAFLD) is still evolving. There is no randomised human study with histological end point in adults with the use of probiotic VSL#3 (De Simone Formulation; Mix of Lactic acid bacteria and Bifidobacteria) in patients with NAFLD. Aim of the present study was to evaluate the efficacy of probiotic VSL#3 in adult patients with NAFLD. **Methodology** – In a two-centre, prospective, double blind, placebo controlled, randomised, proof of concept study, 39 patients with liver biopsy proven NAFLD were randomized into two groups (Clinical Trials Registry India - CTRI/2008/091/000074). All patients gave a written informed consent and study had the approval of the respective institutes' ethics committee. Group 1 (n=19, M=13, mean age=38 ±10 yrs) received standard medical treatment (SMT) with life style modifications and oral probiotic VSL#3 (2 caps t.i.d; 675 Billion CFU/day) for one year; group 2 (n=20, M=15, mean age-33±6 yrs) received SMT + identical placebo (2 caps t.i.d) for one year. Primary objective of the study was the histological improvement in NAFLD activity score (NAS), its components or hepatic fibrosis and secondary objectives were improvement in serum ALT and cytokine profile. **Results** – Ten out of 19 patients (52.6%) in VSL#3 group and 5 out of 20 (25%) in placebo group underwent a repeat liver biopsy at one year. In comparison to baseline, even though there was no significant improvement in hepatic steatosis; hepatocyte ballooning (p=0.036), lobular inflammation (p=0.003) and NAS score (p=0.007) improved significantly at 1 year in VSL#3 group. When compared to placebo, the improvement in NAS score was significantly higher in the VSL#3 group (4.3±1.6 to 2.7±0.9 vs 4.2±1.9 to 3.2±2.1, p=0.004) with significant difference in improvements in individual components of hepatocye ballooning (p=0.05) and hepatic fibrosis (p=0.018). In addition to histological improvement, there was significant improvement in serum ALT (45.0±29.6 vs 68.0±40.6 IU/L; p=0.046), leptin (3.9±1.3 vs 5.7±2.3ng/ml, p=0.006) and TNF-α (107.7±94.3 vs 243.1±167.1pg/ml, p=0.016) in VSL#3 group in comparison to placebo at 1 year. **Conclusions** - In this proof of concept study, patients with NAFLD managed with lifestyle modifications + probiotic VSL#3 showed significant improvement in liver histology. VSL#3 also improved serum ALT and cytokine profile in patients with NAFLD.

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Comparison of non-invasive markers for assessing fibrosis in Asian patients with non-alcoholic fatty liver disease

Hye Won Lee, Beom Kyung Kim, Seung Up Kim, Do Young Kim, Sang Hoon Ahn, Kwang-Hyub Han, Jun Yong Park; Yonsei University College of Medicine, Seoul, Korea (the Republic of)

Background/aims: The prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing worldwide. We investigated whether liver stiffness (LS) and controlled attenuation parameter (CAP), assessed using transient elastography (TE), could assess liver steatosis and fibrosis accurately. **Methods:** A total of 214 patients who underwent liver biopsy and concomitant TE were recruited from a tertiary hospital in Korea and analyzed between November 2011 and December 2014. Liver fibrosis was assessed using AST to Platelet Ratio Index (APRI), NAFLD fibrosis score, and Fibrosis-4 (FIB-4). **Results:** The study population were separated into a control group (n = 103) and a NAFLD group (n = 111) based on liver biopsy results. Patients with NAFLD had a mean age of 39.7 years and there was a male predominance (n = 85, 76.6%). The accuracy of CAP for detecting steatosis grade, assessed by the area under the receiver operating curve (AUROC), was 0.882, 0.906, and 0.870 for ≥S1, ≥S2, and ≥S3, respectively. The optimal cut-off values for steatosis were 248 dB/m for S1, 281 dB/m for S2, and 315 dB/m for S3. Moreover, the AUROC for LS for detecting fibrosis grade were 0.887, 0.958, and 0.986 for ≥F2, ≥F3, and ≥F4, respectively. The optimal cut-off values for fibrosis in patients with NAFLD were 7.65 dB/m for F2, 8.75 dB/m for F3, and 14.45 dB/m for F4. The sensitivity and specificity of the optimal cut-off values for detecting ≥ F3 and ≥ F4 were good (F3: 100% and 72%, respectively, and F4: 80.0 and 98.0%, respectively), and were better than other noninvasive markers, including APRI, NAFLD fibrosis score, and FIB-4. Approximately 24 (21.6%) patients with NAFLD showed discordance between TE and histology. The predictive factors for discordance were age, body mass index (BMI), and the grade of steatosis. **Conclusion:** TE resulted in the accurate detection of not only steatosis but also fibrosis in patients with NAFLD. In addition, TE had better sensitivity and specificity for detecting advanced fibrosis and cirrhosis than other noninvasive markers.

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Reconstruction of the biliary tree using primary in vitro propagated extra-hepatic cholangiocytes and biodegradable scaffolds

Fotios Sampaziotis[1,2], Miguel Cardoso de Brito[2], Steve Sawiak[3], Maria J. Gómez-Vázquez[4], Natalie L. Berntsen[12], Olivia C. Tysoe[2], Daniel Ortmann[2], Alessandro Bertero[2], Johannes Bargehr[5], Mariëlle C. Zonneveld[2], Marianne T. Pedersen[6], Matthias Pawlowski[5], Nikitas Georgakopoulos[2], Loukia Yiangou[2], Edmund M. Godfrey[7], Sara S. Upponi[7], Richard Gieseck[8], Casey Rimland[2], Ingrid Simonic[9], Susan Davies[10], Kim B. Jensen[6], Sanjay Sinha[5], William Gelson[11], Graeme J. Alexander[5], Espen Melum[12], Nicholas R. Hannan[13], Kourosh Saeb-Parsy[2], Ludovic Vallier[2]; [1]Hepatology, Cambridge University Hospitals NHS Foundation Trust, Hitchin, United Kingdom; [2]Surgery, Cambridge University, Cambridge, United Kingdom; [3]Clinical Neurosciences, University of Cambridge, Cambridge, United Kingdom; [4]Pathology, University of Cambridge, Cambridge, United Kingdom; [5]Medicine, University of Cambridge, Cambridge, United Kingdom; [6]Biotech Research and Innovation Centre, University of Copenhagen, Copenhagen, Denmark; [7]Radiology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; [8]Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, MD; [9]Medical Genetics Laboratories, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; [10]Histopathology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; [11]Hepatology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; [12]Norwegian PSC research center, Clinic for Specialized Medicine and Surgery, Oslo University Hospital, Rikshospitalet, Oslo, Norway; [13]Center for Biomolecular Sciences, University of Nottingham, Nottingham, United Kingdom

Background: The treatment of extra-hepatic bile duct disorders such as biliary atresia, primary sclerosing cholangitis and biliary strictures is limited to liver transplantation or hepatojejunostomy due to the lack of healthy tissue suitable for biliary reconstruction. **Objectives:** 1. Development of a platform for large-scale in vitro expansion of native cholangiocytes 2. Use of these cells for the generation of bioengineered biliary tissue and performance of a biliary reconstruction in vivo **Methods:** Primary human cholangiocytes were isolated from deceased organ donors (n=8). 3D culture of the cells was based on our established protocol for the maturation and maintenance of stem cell derived cholangiocytes. Extrahepatic Cholangiocyte Organoids (ECOs) were seeded on bioengineered Polyglycolic Acid (PGA) scaffolds to generate a bio-artificial biliary tissue. A model of extrahepatic biliary injury (EHBI) was generated by compromising the integrity of the biliary tree in immunodeficient NSG mice through a longitudinal incision in the gallbladder wall. ECO-populated PGA scaffolds (n=8) were sutured in place to repair the wall defect. Acellular scaffolds (n=2) and fibroblast populated scaffolds (n=5) were used as negative controls. **Results:** ECOs express key biliary markers such as CK7, CK19, GGT, CFTR and maintain their functional properties in vitro, including ALP, GGT, CFTR activity. Transcriptomic analyses revealed close correlation between ECOs and primary cholangiocytes (r:0.92). ECOs seeded on PGA scaffolds formed structures resembling biliary tissue maintaining their functional properties and marker expression. All animals undergoing biliary reconstruction with ECO-populated scaffolds (n=8) survived for up to 3 months, with integration of the cells in the biliary epithelium, while all animals transplanted with acellular PGA scaffolds (n=2) died within 24 h (P=0.0027, log-rank test). 3 of 5 animals receiving fibroblast-populated scaffolds survived but none of the transplanted gallbladders were successfully reconstructed and the biliary epithelium was replaced by fibrotic

tissue. The patency of the reconstructed biliary tree was confirmed using magnetic resonance cholangiopancreatography (MRCP). **Conclusion:** Biliary epithelial cells derived from the extrahepatic biliary tree can be effectively propagated in vitro, while maintaining their transcriptional and functional identity. The regenerative potential of ECOs is further illustrated by their capacity to organize into a bioengineered functional biliary epithelium and rescue an EHBI murine model. To our knowledge, this is the first report of an organ reconstruction using human primary cells expanded in vitro.

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Contribution of Jagged1/Notch Signaling to Murine Fibrotic Liver Regeneration through Possible Dedifferentiation of Mature Hepatocytes

Yasuhiro Nakano[1,2], Sachie Nakao[1,2], Hideaki Sumiyoshi[1,2], Kenichiro Mikami[2,6], Yuri Tanno[2], Daigo Kasahara[1,3], Hiroshi Kimura[3], Tadashi Moro[1,7], Akihide Kamiya[1,5], Katsuto Hozumi[1,4], Yutaka Inagaki[1,2]; [1]Center for Matrix Biology and Medicine, Tokai University Graduate School of Medicine, Isehara, Japan; [2]Department of Regenerative Medicine, Tokai University School of Medicine, Isehara, Japan; [3]Department of Mechanical Engineering, Tokai University School of Engineering, Hiratsuka, Japan; [4]Department of Immunology, Tokai University School of Medicine, Isehara, Japan; [5]Department of Molecular Life Sciences, Tokai University School of Medicine, Isehara, Japan; [6]Department of Gastroenterology and Hematology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan; [7]Research Laboratory, Minophagen Pharmaceutical Co., Ltd., Zama, Japan

Background & Aims. The liver is well known to possess high regenerative capacity. However, its regeneration is often impaired in patients with liver cirrhosis. Although progenitor cell recruitment has been implicated in the regeneration of fibrotic liver, the origin and nature of such hepatic progenitor cells (HPC) are not fully understood. On the other hand, recent studies using genetic lineage tracing analysis indicate that dedifferentiation of mature hepatocyte plays an important role in injured/fibrotic liver regeneration. In the present study, we show that Jagged1/Notch signaling accelerates this dedifferentiation process and contributes to the regeneration of fibrotic liver. ***Materials & Methods.*** Liver fibrosis was induced in wild type and Jagged1 conditional knockout (Jag1 cKO) mice by repeated carbon tetrachloride (CCl_4) injections. Excised liver specimens were subjected to immunohistochemical staining and quantitative gene expression analyses of fibrosis-related molecules and HPC markers. The survival rates and the extent of cell proliferation were compared between the wild type and Jag1 cKO mice during the regenerative process alter partial hepatectomy of fibrotic liver. Primary mature hepatocytes were co-cultured with quiescent or activated hepatic stellate cells (HSC), and their dedifferentiation to alpha-fetoprotein (AFP)-expressing HPC were evaluated using a Notch inhibitor or HSC obtained from Jag1 cKO mice. ***Results.*** A significant number of AFP-positive cells with features of HPC and high proliferative ability were detected along the fibrous septa after repeated CCl_4 injections to wild type mice. The septal myofibroblasts highly expressed a Notch ligand, Jagged1, and the Notch signal was activated in adjacent AFP-expressing HPC. Studies with Jag1 cKO mice demonstrated that Jagged1 deletion suppressed the mobilization and proliferation of AFP-positive HPC in fibrotic liver tissue and decreased the survival rate of CCl_4-treated fibrotic mice, but not untreated normal animals, after partial hepatectomy. Consistent with these *in vivo* results, cell culture experiments indicated that increased Jagged1 expression in activated HSC up-regulated AFP expression in the co-cultured hepatocytes. This dedifferentiation of hepatocytes was suppressed by adding a Notch inhibitor to the culture media or using HSC obtained from Jag1 cKO mice. ***Conclusion.*** These results indicate that Jagged1/Notch signaling contributes to the regeneration of fibrotic liver through possible dedifferentiation of mature hepatocytes. They provide insight into a novel important role of Jagged1/Notch signaling in liver pathophysiology.

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Functional maintenance of direct converted hepatocyte–like cells with 3D printing technique

JinHyouk Lim[1], Kyo Jin Kang[1], Dongho Choi[1], Su A Park[2], Heung Mo Yang[3], Dongwook Han[4], Jaemin Jeong[1], Hyeryeon Jeon[1]; [1]Hanyang university, Seoul, Korea (the Republic of); [2]Korea Institute of Machinery and Materials, Seoul, Korea (the Republic of); [3]Sungkunkwan University College of Medicine, Seoul, Korea (the Republic of); [4]Kunkuk University, Seoul, Korea (the Republic of)

Aims: To deal with the liver failure at the end stage, liver transplantation is ultimately the only treatment at the terminal stages of disease. However, the demand for liver transplantation is more than number of provision cadaveric livers or liver tissues from living donors. Hence, developing the way of acquiring hepatocytes has been considered as an important researching issue for decades. In recent, direct conversion technology has been developed for generating induced hepatocyte-like cells (iHeps) through ectopically expressing liver-specific transcription factors. On the other hands, tissue-engineering including '3-dimensional (3D) bioprinting technology' has been advanced for organ-like structures and thereby capturing the complexity of *in vivo* environments. Therefore, we herein report the reconstruction of 3D bioprinted hepatic architecture for recapitulating the microenvironment in liver by using the iHeps as a source of hepatocytes. **Methods:** To generate iHeps, mouse embryonic fibroblasts (5×10^4 cells) were transduced with pMX retroviruses expressing individual hepatic transcription factors, *Hnf4a* and *Foxa3*. After 48 h, the cells were further cultured in hepatocyte culture medium (HCM) on Type I collagen-coated dish for inducing lineage transition toward iHeps. For 3D bioprinting, the iHeps encapsulated with 3% alginate hydrogel, and then extruded through nozzle pressure. After crosslinking with calcium chloride, hepatic structure was formed with 25 mm x25 mm. **Results:** After 8 ~ 10 days of transduction, we observed epithelial iHep colonies with high proliferation rate. Upon several passaging, the number of the fibroblasts was reduced, while the iHeps grew dominant on the dish. Both qPCR and immunofluorescence analyses revealed that iHeps shared typical hepatic gene and protein expression profiles with liver tissue. Moreover, iHeps also had functional characteristics as hepatocytes such as glycogen storages and xenobiotic activity. Through 3D bioprinting method, we can efficiently construct multiple layered-3D hepatic structures. Interestingly, we found that mimicking the 3D hepatic structure not only assists the iHeps to stably repopulate, but also enhanced

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hepatic gene expression profiles of iHeps. **Conclusions:** Combining 3D bioprinting technology with iHep generation protocol may be a realistic option for overcoming the problems including donor shortage and surgical complications of liver transplantation, and thereby offers a new paradigm in the field of liver regenerative medicine.

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Mechanisms of the beneficial effects of MSC on human hepatocytes for use in the treatment of acute liver failure: Tunneling nanotube-based transfer of MSC mitochondria to hepatocytes.

Raquel Fernandez-Dacosta[1], Anil Dhawan[2], Charlotte A. Lee[1], Valeria Iansante[1], Simon Walker[2], Sharon Lehec[1,2], Emer Fitzpatrick[2], Celine Filippi[2]; [1]Dhawan Lab, Institute of Liver Studies, King's College London, London, United Kingdom; [2]King's College Hospital NHS Foundation Trust, London, United Kingdom

Introduction: Intraperitoneal transplantation of encapsulated primary human hepatocytes is an emerging therapy for children with acute liver failure. However, sustaining the function of cryopreserved hepatocytes isolated from marginal grafts remains a challenge. Mesenchymal stromal cells (MSC) enhance hepatocyte viability and metabolism, through mechanisms not yet fully understood. MSC have been reported to rescue different types of injured cells by transfer of functional mitochondria through actin-based nanostructures called tunneling nanotubes (TNT).Therefore, we hypothesized that MSC rescue hepatocyte function via TNT-based mitochondria transfer. Objectives: to (i) assess if a TNT-based transfer of mitochondria occurs between MSC and hepatocytes; (ii) to study TNT composition, and (iii) to determine if TNT inhibition stops mitochondria transfer and affects MSC trophic effects on hepatocytes. Materials and Methods: Mitochondrial transfer from MSC to hepatocytes was followed over 24h of co-culture using FACS as well as live- and fixed-cell microscopy, after staining of MSC mitochondria with a mitochondria-targeted red fluorescent die (MitoTracker Red). TNT presence in the co-cultures was studied by fluorescent microscopy. Characterization of TNT was performed by immunofluorescence to detect actin and tubulin expression. TNT-disruption was tested by dosing actin polymerization inhibitors: Latrunculin A (LatA) and Cytochalasin D (CytD). MTT and Annexin V/PI assays were used to assess LatA/CytD cytotoxicity. Mitochondrial transfer after TNT inhibition was quantified by FACS. Results: Hepatocytes containing red fluorescent mitochondria were detected as early as 2h after co-culture onset, using live microscopy (n=3) and confirmed by FACS (n=3), with statistical significance at 4 and 6h of co-culture (21±6 and 27.6±10%, $p<0.05$ vs monocultures). TNT containing MSC mitochondria were observed between co-cultured MSC and hepatocytes (Fig.1). Actin was identified as the main TNT structural component. 0.5μM LatA achieved TNT inhibition without cytotoxic effect on the cells, leading to a decrease in the number of hepatocytes with MSC mitochondria. Conclusion: Our preliminary studies show that MSC are able to transfer mitochondria to primary hepatocytes through actin-based TNT, which might be the responsible mechanism for the beneficial effects of MSC on hepatocyte function. This data is helpful to further advance our knowledge to use co-transplantation of MSC and hepatocytes in the treatment of liver disease. Transfection of MSC with a mitochondria-targeted red fluorescent protein (DsRed) is currently being performed to further confirm/infirm these results.

Disclosures:

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1191
Platelet rich plasma enhances adipose-derived *mesenchymal* stem cell therapeutic effects for liver cirrhosis in mice

Nhung H. Truong[1,2], Nam H. Nguyen[1], Trinh V. Le[1], Huy M. Le[3], Nghia Huynh[3], Dat Q. Ngo[3], Thanh V. Nguyen[4], Aixuan Holterman[5], Ngoc K. Phan[1,2], Phuc V. Pham[1,2]; [1]Laboratory of stem cell research and application, University of Science, Vietnam National University, Ho Chi Minh city, Ho Chi Minh, Viet Nam; [2]Faculty of Biology and Biotechnology, University of Science, VNU-HCM, Ho Chi Minh, Viet Nam; [3]University of Medicine and Pharmacy, HCM city, Vietnam, Ho Chi Minh, Viet Nam; [4]Nguyen Tat Thanh University, Ho Chi Minh city, Vietnam, Ho Chi Minh, Viet Nam; [5]Department of Surgery/Pediatric Surgery, Peoria, IL, USA, University of Illinois College of Medicine, Peoria, IL

Background: Mesenchymal stem cells (MSC) can proliferate and differentiate into hepatocytes as potential cell sources for cirrhosis treatment. Studies showed that platelet rich plasma (PRP) may enhance liver regeneration. We test the hypothesis that PRP co-administration enhances MSC treatment for mouse cirrhosis. **Method:** Male Swiss mice were treated orally with olive oil or CCl4 for 11 weeks. PRP were obtained from healthy mice. Mouse adipose-derived stem cells (mADSCs) from 3 weeks CCl4 mice were cultured for 3 passages (P3-mADSCs) prior to transfer by tail vein injection with or without PRP into 11 weeks CCl4 mice. Liver and serum were harvested at 7 and 21 days after transplantation. Hepatocyte-enriched markers and ECM gene expression were characterized using q-RT-PCR. MSC markers, hepatocyte-enriched proteins and fibrosis were evaluated by flow cytometry and/or immunohistochemistry. Mice were divided into 6 groups (n=10 each group). 1) normal, 2) cirrhotic, 3) cirrhotic /PBS; 4) cirrhotic/PRP (0.2 ml/mice with PRP from healthy mice), 5) cirrhotic/mADSCs (5 x 10^5 cells/mice), and 6) cirrhotic/mADSC-PRP. **Result:** mADSCs were highly positive with CD44, CD90 and CD105. Relative to normal liver cells, P3-mADSCs highly expressed *Alb, Ck18, Ck19, Tnf, c-met, Cyp1a1, Afp, Muc1, Ldl receptor;* and are strongly positive for Cyp1a1 (98.21±1.57%) and Hgf (95.55±3.11%); moderately positive for alfa-fetoprotein, Aat and Alb. After transplantation, transplanted cells into CCl4-treated mice were found in the 21 days liver. Compared to mADSCs, mADSCs and PRP cotreatment most effectively improved serum AST/ALT/bilirubin and albumin levels in day 7 cirrhotic mice ($p<0.05$); and significantly down-regulated *procollagen* (104-fold less) and *TGF-beta 1* (10-fold less) in day 21 cirrhotic liver. Histology index and collagen deposition were improved in 100% of mADSC/PRP- and mADSCs- cirrhotic mice compared to 33.3% of PBS- or PRP- cirrhotic liver ($p<0.05$). **Conclusion:** Cultured mADSCs express hepatocyte markers. Injected mADSCs home to the cirrhotic liver. PRP coadministration enhances mADSC effects to further improve liver function, and further reduce fibrosis.

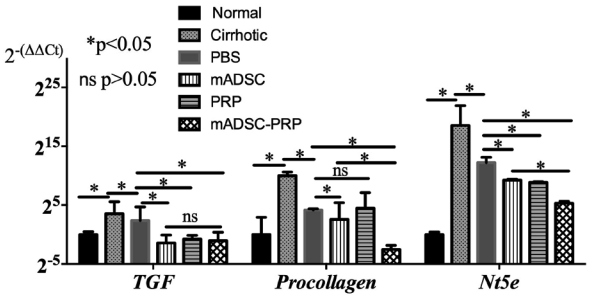

Chart of gene expression level in the 21 days liver after mADSCs transplantation

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Identification of pre-adult hepatic stem cell niche by label retaining cell assay during fetal development

Reiichiro Kuwahara[1], Tatsuya Ide[1], Hironori Koga[1], Neil D. Theise[2], Takuji Torimura[1]; [1]Medicine, Kurume University School of Medicine, Kurume, Japan; [2]Pathology and Medicine, Mount Sinai Beth Israel, New York, NY

Background and Aim: By label retaining cell assay in an acetaminophen injury model, we previously identified the most proximal portions of the biliary tree (canals of Hering: CoH) and, in addition, peribiliary hepatocytes (PbH) which were neighboring to CoH as locations of potential functional stem cell niche (Kuwahara et al, Hepatology 2008). The aim of this study is to investigate the possible role of CoH and PbH in normal liver development, in the absence of injury. Methods: For the labeling of dividing cells in the fetal liver, BrdU was injected intraperitoneally to pregnant mice at 3 time points (E12, E15, and E19). Postnatal mice received intraperitoneal injection of BrdU at the age of 6, 13, 20, 27, 34, 41, 48 and 55 days. To confirm the BrdU labeling in the fetal and postnatal liver, some mice were sacrificed 24 hours after each labeling. The other pregnant mice were allowed to give birth, and newborn mice were raised to 8 weeks old, growth and maturation of the liver providing the "chase" for BrdU label washout following the BrdU labeling and then sacrificed. Likewise, the other postnatally labeled mice were sacrificed at the age of 8 weeks. PbH and biliary cell in CoH were analyzed by double immunohistochemistry (IHC) of biliary keratins (PanK)/BrdU (cell division), PanK/Ki-67 (proliferation). The ratio of liver weight to body weight (LW/BW-R) was analyzed at every week old of mice. Results: The stability of BrdU labeling in the liver was confirmed by IHC of BrdU. The Ki67 index of postnatal mice liver showed that frequencies of cell proliferation of hepatocytes and biliary cells in CoH were highest at the age of 7 days and then diminished steadily. The peaks of LW/BW-R were 5.88% and 5.64% at the age of 5 weeks in both male and female mice, respectively. At 8 weeks post "chase", distributions of BrdU-retaining PbH and biliary cells in CoH to total BrdU positive cells (lobular and peribiliary hepatocytes + biliary cells in CoH) were significantly higher in prenatally labeled liver than those in postnatally labeled liver. In postnatally labeled liver, these distributions were significantly higher in the liver with labeling at the age of 13 days than those in the liver with labeling at the age of 6, 20 and 27 days, respectively. Conclusion: These data support that PbH and CoH cells serve resident stem cell functions including contributing to parenchymal mass during organogenesis and early postnatal development and also suggest that while these stem cell niches in adults may be quiescent, only activated in some kinds of injury, they are continually activated and contributing to cell lineages in the developing fetal and postnatal periods.

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Enhancement of hepatocyte differentiation from human embryonic stem cells by Salvianolic acid B through activation of Wnt signaling and inhibition of Notch signaling

Jiamei Chen[1,2], Mark Zern[2], Ping Liu[1], Yuyou Duan[2]; [1]Shuguang hospital affiliated to Shanghai University of Tranditional Chinese Medicine, Insitute of liver disease, Shanghai University of Tranditional Chinese Medicine, Shanghai, China; [2]Department of Internal Medicine, Institute for Regenerative Cures, University of California Davis Medical Center, Sacramento, CA

Human embryonic stem cells-derived hepatocytes (hEH) could provide a powerful tool for enabling cell-based therapies in the clinic, and studying the mechanisms underlying human liver development and disease, testing the efficacy and safety of pharmaceuticals. However, current in vitro protocols yield hEH with low levels of liver functions relative to adult primary human hepatocytes. Here, we investigated the potential of Salvianolic acid B (Sal B), an active pharmaceutical compound present in Salvia miltiorrhiza, exerting an antifibrotic effect in previous researchs, to enhance hepatocyte differentiation from human embryonic stem cells (hESCs). hESCs line, H9 was used in our standard differentiate protocol. After treatment with Sal B, albumin expression was consistently increased, as determined by qPCR, ELISA and Westen-blot, indicating that Sal B might promote hepatocyte differentiation process. Expression of a large number of important phase I and II metabolizing enzymes and phase III transporters, were also increased in treated cells, indicating that biotransformation function would likely be increased. In addition, we found that expression of cholangiocyte marker, CK7 was significantly reduced by treatment with Sal B. This suggests that one possible mechanism by which Sal B may promote hepatocyte differentiation is through inhibiting the formation of cholangiocytes. Our investigations further revealed the activation of Wnt pathway in Sal B-treated cells, as determined by up-regulation of Wnts which resulted in the increase of the amount of nuclear β-catenin, leading to the increase of TCF1, and its downstream targets, cyclin D1 and c-myc. Notch receptors (Notch1, Notch4), Notch ligands (Jagged1and Jagged2), Notch receptor targets (Hes1, 5), were down-regulated in treated cells, suggesting that Notch pathway was inhibited. Numb, a direct transcriptional target of the Wnt signalling pathway and a negative regulator of Notch pathway, was up-regulated, indicating that its up-regulation is consistent with activation of Wnt signaling and suppression of Notch signaling. Thus, our study demonstrated that the enhancement of hepatocyte differentiation is mediated through activation of Wnt signaling pathway and inhibition of Notch pathway by Sal B. In conclusion, Sal B can promote hepatocyte differentiation from hESCs. This demonstrates that Sal B treatment appears to enhance our efforts to generate mature hepatocytes for cell-based therapeutics and for pharmacological and toxicological studies.

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The following people have nothing to disclose: Jiamei Chen, Mark Zern, Ping Liu, Yuyou Duan

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Clinical study of liver regenerative therapy of cirrhosis using autologous adipose tissue-derived stromal cells and the characterization of the obtained stromal cells.

Yoshio Sakai[1], Akihiro Seki[1], Hajime Sunagozaka[1], Takeshi Terashima[1], Kazunori Kawaguchi[1], Hatsune Mochida[2], Alessandro Nasti[2], Geraldine B. Buffa[1], Masatoshi Yamato[2], Kosuke Ishida[4], Masaaki Takamura[2], Soichiro Usui[2], Takashi Wada[3], Masao Honda[1], Shuichi Kaneko[4,1]; [1]Department of Gastroenterology, Kanazawa University, Kanazawa, Japan; [2]Disease Control and Homeostasis, Kanazawa University, Kanazawa, Japan; [3]Department of Nephrology, Kanazawa University, Kanazawa, Japan; [4]System Biology, Kanazawa University, Kanazawa, Japan

Adipose tissue is enriched with mesenchymal stromal/stem cells. We conducted the clinical study for liver regenerative therapy of cirrhosis by intrahepatic arterial administration of freshly isolated autologous adipose tissue derived stromal/stem (regenerative) cells (ADRCs) (UMIN000009122, NCT01062750). We also characterized the obtained fresh cells (ADRCs) as well as the cultured expanded stromal cells (ADSCs). **[Methods]** The objectives were cirrhosis patients who provided the written informed consent. The patients underwent liposuction of their subcutaneous adipose tissues in their abdomen or buttock. The obtained adipose tissues were immediately processed using the adipose-tissue dissociation equipment (Celution®, Cytori Therapeutics Inc.) to obtain autologous ADRCs. The designated number of cells (3.3x10^5/Kg (n=2), 6.6x10^5/Kg (n=2)) were infused through the catheter positioned at the hepatic artery. Safety evaluation was assessed 1 month after the treatment. Surface antigen of ADRCs and cultured cells (ADSCs) were assessed by FACS. Serum cytokine/chemokine concentration was measured by Bio-Plex®. We also analyzed gene expression of the freshly isolated ADRCs compared to the cultured ADSCs by DNA microarray. **[Result]** Four liver cirrhosis patients were enrolled, (HI-01(type C), HI-03 (type C), HI-04 (NASH), HI-05(type B)). The number of infused ADRCs were 2.2x10^7 ~ 4.4x10^7. Among ADRCs and ADSCs, 10.3 ~45.8 % and 80.998.9% of cells, respectively, expressed the mesenchymal stem cell surface marker CD44. No severe adverse events occurred. Three among 4 treated patients improved serum albumin concentration during 36 months after treatment. Serum HGF, M-CSF, MIF, IL18, and IL-6 were elevated in all 4 patients one day after treatment. The surplus ADRCs after treatment were successfully expanded and the spindle-like shape of mesenchymal stem cell was observed. Gene expression profile analysis using clusters analysis showed the two distinct clusters discerning ADRCs from ADSCs, completely, regardless of the patient's etiologies of cirrhosis. The freshly isolated ADRCs were shown to involve inflammatory features, suggesting that they were related to immunomodulatory biological effects. **[Conclusion]** Intrahepatic arterial administration of autologous freshly isolated ADRCs with immunomodulatory biological effects were confirmed to be safely conducted without serious adverse events.

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Therapeutic targeting of Hsp90 alleviates liver macrophage-specific NLRP3 inflammasome activation in alcoholic liver injury

Daniel Bullock, Asmita Choudhury, Pranoti Mandrekar; Medicine, University of Massachusetts Medical Center, Worcester, MA

Background/Aims: Inflammasomes are multimeric protein complexes that respond to PAMPs or DAMPs that serve as a scaffold to promote cleavage of pro-caspase-1 and subsequent active IL-1β and IL-18 production. Previous studies show activation of NLRP3 inflammasome in alcoholic liver disease (ALD). Further the role of stress-mediated protein heat shock protein 90 (hsp90) as a chaperone for NLRP3 inflammasome scaffold was identified. Studies in our laboratory have demonstrated that chronic alcohol induces hsp90 and its inhibition alleviates alcoholic liver injury. Here we hypothesize that hsp90 is required for alcohol mediated NLRP3 inflammasome activity in the liver, specifically in macrophages/Kupffer cells and its therapeutic targeting reduces active IL-1β in the alcoholic liver. Methods: C57/BL/6J mice were subjected to 2 weeks and 6 weeks of chronic-single binge or chronic-multiple binge alcohol feeding respectively. Specific hsp90 inhibitor, 17-DMAG was injected intraperitoneally either every alternate day (5mg/kg) or at the end of the alcohol feeding (50mg/kg). Whole livers were harvested and subjected to inflammasome qPCR and IL-1β ELISA. Hepatocytes and liver macrophages were isolated at the end of the feeding and NLRP3 and IL-1β analyzed. For mechanistic studies, bone marrow derived macrophages (BMDM) were differentiated in vitro and stimulated with LPS ± ATP and DMAG (0.5μM-2.0μM) or directly heat shocked and stimulated with ATP, and analyzed for inflammasome mRNA and protein. Results: Chronic alcohol mediated induction of NLRP3 expression ($p<0.002$) was observed in alcohol exposed whole livers and restricted to isolated liver macrophages/Kupffer cells, but not hepatocytes. Inhibition of hsp90, using 17-DMAG significantly inhibited NLRP3 ($p<0.01$), ASC ($p<0.01$) and pro-caspase-1 ($p<0.002$) in liver macrophages exposed to chronic alcohol in vivo. Bioactivity of 17-DMAG in the liver was confirmed by induction of hsp70 expression. Further 17-DMAG decreased chronic alcohol-binge induced IL-1β protein in whole livers ($p<0.001$). In vitro studies reveal that 17-DMAG and heat shock (induction of hsp70 independent of hsp90 inhibition) reduced active IL-1β ($p<0.0002$) and caspase-1 cleavage in BMDM, demonstrating that both inhibition of hsp90 and induction of hsp70 can prevent robust NLRP3 inflammasome signaling. Conclusion: Our results support our hypothesis that hsp90 is crucial in alcohol mediated NLRP3 inflammasome activation which is restricted to liver macrophages. Overall we demonstrate clinical relevance of hsp90 inhibition in preventing NLRP3 inflammasome and active IL-1β production, and predict protective function of hsp70/hspA1A in ALD.

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