UEG Week 2018 Oral Presentations

MONDAY, OCTOBER 22, 2018   08:00–10:00
Opening Session: Part 1 – Room A_____

OP001   EARLY ENDOSCOPIC RETROGRADE CHOLANGIOGRAPHY WITH BILIARY SPHINCTEROTOMY OR CONSERVATIVE TREATMENT IN PREDICTED SEVERE ACUTE BILIARY PANCREATITIS (APEC): A MULTICENTER RANDOMIZED CONTROLLED TRIAL

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Introduction: Patients with acute biliary pancreatitis may develop cholangitis, organ failure and other life-threatening complications. Early biliary decompression by endoscopic retrograde cholangiography (ERC) and biliary sphincterotomy may ameliorate the disease course, but previous randomized trials have shown conflicting results. Recent guidelines advise ERC in biliary pancreatitis only in case of cholangitis, and to consider ERC in case of (persistent) cholestasis. Whether early ERC and biliary sphincterotomy is beneficial in patients with predicted severe acute biliary pancreatitis with or without cholestasis, but without cholangitis, remains debated.

Aims and Methods: We randomized 230 patients in 25 Dutch hospitals with predicted severe acute biliary pancreatitis (based on an Acute Physiology and Chronic Health Evaluation [APACHE II] score of ≥ 8, a modified Imrie score of ≥ 3 or a C-reactive protein level of > 150 mg/L within 24 hours of admission) and without cholangitis, to early ERC with biliary sphincterotomy within 24 hours after presentation at the emergency department or conservative treatment with on-demand ERC in case of cholangitis or persistent cholestasis. The primary end point was a composite of death or major complications (i.e. new-onset persistent organ failure, cholangitis, bacteremia, pneumonia, pancreatic necrosis and pancreatic insufficiency) during 6 months of follow-up. Patients were stratified for the presence of cholestasis (based on a bilirubin level of $> 40\mu$mol/L or a dilated common bile duct (defined as > 8mm in patients ≤ 75 years or > 10mm in patients > 75 years)).

Results: The primary end point occurred in 45 of 117 patients (39%) in the early ERC group compared with 50 of 113 patients (44%) in the conservative group (risk ratio 0.89; 95% confidence interval 0.68-1.15; p = 0.37). 112 patients (96%) in the early ERC group underwent ERC at a median of 20 hours after presentation at the emergency department (interquartile range [IQR] 14-23 hours), and after a median of 29 hours after onset of symptoms (IQR 22-44 hours). Biliary sphincterotomy was performed in 90 patients (78%). In 35 of the 113 patients (31%) allocated to conservative treatment, ERC was performed later in the disease course for cholangitis or persisting cholestasis after a median of 8 days (IQR 3-34 days) after randomization. In the early ERC group, cholangitis occurred less often compared with conservative treatment (2% versus 10%; p = 0.01) without significant differences in patient outcome including new-onset organ failure (19% versus 15%; p = 0.45), death (7% versus 9%; p = 0.57) or other components of the primary end point. In the conservative group with on-demand ERC, the total number of ERCs decreased with 66% (128 versus 44 ERCs) without negatively impacting overall outcome. In the subgroup of patients with cholestasis at randomization, no statistically significant difference in the primary end point was found (32% versus 43%; risk ratio 0.79; 95% confidence interval 0.57-1.10; p = 0.18).

Conclusion: In patients with predicted severe acute biliary pancreatitis without cholangitis, early ERC with endoscopic biliary sphincteromy within 24 hours after presentation at the emergency department did not reduce the primary end point of death or major complications.

Disclosure: NJS reports grants from Dutch Organization for Health Research and Development (ZonMw, Grant no. 837002008) and from Fonds NutsOhra (Grant no. 1203-052). The sponsors had no involvement in any stage of the study design or analysis and interpretation of the study results.

Reference

1. Schepers NJ, Bakker OJ, Besselink MG, et al. Early biliary decompression versus conservative treatment in acute biliary pancreatitis (APEC trial): study protocol for a randomized controlled trial. *Trials* 2016; 17: 5.

OP002   A COMPREHENSIVE MOLECULAR CLASSIFICATION OF CROHN'S DISEASE USING GENE EXPRESSION DATA

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Introduction: There is an important heterogeneity among Crohn's disease patients including clinical presentation and severity, disease location, disease behavior, presence of extra-intestinal manifestations or not, disease course or individual response to therapies. There is also a huge number of genetic combinations and exposition to environmental factors. At the molecular level, transcriptome performed on mucosal samples exhibit a striking heterogeneity. A molecular classification could prove more relevant to predict disease course, response to treatment and to identify new drug targets.

Aims and Methods: Our aims are to identify shared and unique molecular features, clinically significant subtypes, and potential therapeutic targets. We conducted an integrated analysis of several cohorts from the IBD Over Time (IBDOT) consortium, including surgical samples of ileal disease and endoscopic samples of both ileal and colonic disease. We also searched for data available in the public domain. We performed molecular clustering (ConsensusClusteringPlus) using mRNA from microarray and RNA-seq, after correcting for batch effect. Cibersort was used to impute immune cells fractions from bulk transcriptome. Finally, KEGG pathway analysis was performed to characterize identified clusters.

Results: We included in the analysis 580 samples of the IBDOT consortium (all by microarray) and 971 samples available in the public domain (508 by RNA-Seq and 736 by microarray). We saw a clear batch effect between the different platforms and cohorts. Colonic and ileal samples were well clustered together in each cohort. After correction for batch effect using biopsy location as a covariate, we identified 4 robust clusters of Crohn's disease samples. Colonic samples clustered together (C3). Ileal samples clustered mainly in 2 groups, 1 APOA1-low highly inflammatory (C1), the other APOA1-high less inflammatory (C2). The fourth group (C4) was smaller and contained ileal samples only. Immune cells fractions showed a neutrophilic infiltration in C1, and a higher proportion of CD8 T cells and Gamma-Delta T cells in C2. Pathway analysis confirmed a typical IBD-like inflammation in C1, and a more subdued inflammation in C2.

Conclusion: We performed the first molecular classification of Crohn's disease using more than 1500 gut samples from 6 different cohorts. 4 robust disease groups were identified, representing both disease location and levels of inflammation. Some limitations were the high heterogeneity of disease stage and limited data on disease characteristics for the data collected in the public domain. Future work could look at the disease course of these 4 clusters and determine their persistence over time.

Disclosure: Nothing to disclose

MONDAY, OCTOBER 22, 2018   10:30–12:00
Opening Session: Part 2 – Room A_____

OP003   NLRP6 SUPPORTS SURVIVAL OF T HELPER 1 CELLS BY REGULATING APOPTOSIS

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Introduction: NOD-like family pyrin domain containing 6 (NLRP6) protects from DSS colitis, and NLRP6-deficient animals have a dysbiotic microbiota (1,2). In other animal facilities variants in the composition of the microbiota between wt and NLRP6-deficient animals are explained by cage effects and mother variates but not by the genotype (3,4). Although intestinal epithelial cells highly express NLRP6, the reconstitution of wt animals with Nlrp6-deficient bone marrow leads to similar colitis-associated tumor formation as in Nlrp6-deficient animals (5).

Aims and Methods: NLRP6 is highly expressed by epithelial and goblet cells, but its function in hematopoietic cells is rather unknown. Here, we determined the expression of NLPR6 in *in vitro* differentiated T cells, and in T cells after co-transfer of wt and NLPR6-deficient T cells in RAG hosts to minimize the influence of different microbiotas on NLPR6 expression by T cells.

Results: NLPR6 is not expressed by naïve CD4 and CD8 T cells, B cells and bone marrow-derived macrophages in contrast to epithelial cells. When naïve T cells are differentiated to Th1 cells, Th1 cells express NLPR6, whereas only a minority of differentiated Th2 cells and Th17 have NLPR6. Promoter analysis of the human and mouse NLPR6 starting site revealed binding regions for STAT1, STAT5a and Tbx21 (T-bet). T-bet induced NLPR6 expression in differentiated Th1 cells because NLPR6 was not detected in Tbx21-deficient T cells. The production of IFNg by NLPR6-deficient Th1 cells is reduced compared to wt T cells, which is independent of inflammasome assembly, because in ASC-deficient T cells differences in IFNg production was not observed. Moreover, differences in IL-13 and IL-17 production by in vitro differentiated Th2 and Th17 cells and differences in Foxp3 Treg cells between wt and NLPR6-deficient T cells was not observed. Similar frequencies of wt and NLPR6-deficient T cells entered the active phase of the cell cycle as indicated by Ki67 staining and had similar proliferative capacities as determined by CFSE washout. T cell developmental defects were not observed in wt and NLPR6-deficient littermates in thymus, spleen lymph nodes and colonic lamina propria. However, reduced numbers of NLPR6-deficient T cells with reduced IFNg production were noted after co-transfer of wt and NLPR6-deficient T cells in RAG hosts. Principle component analysis of RNA-seq from wt and NLPR6-deficient T cells obtained from reconstituted RAG hosts revealed a two-cluster structure, which was confirmed by hierarchical clustering of all differentiated genes with no influence of the host on T cells. The 628 down- and the 923 up-regulated genes were compared to hallmark signatures, which revealed enrichment of apoptosis, interferon gamma response, inflammatory response, IL-6 JAK STAT3 signaling and TNFα signaling signatures in NLPR6-deficient T cells. Annexin V/viability staining confirmed increased apoptosis of NLPR6-deficient T cells compared to wt T cells after co-transfer in RAG hosts. Transfer of wt CD45RBhigh T cells into RAG hosts resulted in somewhat increased body weight loss and increased disease scores compared to RAG hosts receiving NLPR6-deficient T cells two weeks after transfer.

Conclusion: The expression of NLPR6 by differentiated Th1 cells is rather intrinsic induced and independent of different microbiotas because NLPR6 expression was observed by *in vitro* differentiated T cells. As consequence increased apoptosis was observed after transfer of NLPR6-deficient T cells in RAG hosts. NLRP6 facilitates the survival of CD4 T cells.

Disclosure: Nothing to disclose

References

1. Levy M et al, *Cell*. 2015 Dec 3; 163(6): 1428–43.
2. Elinav E et al., *Cell*. 2011 May 27; 145(5): 745–57.
3. Mamantopoulos M et al. *Immunity*. 2017 Aug 15; 47(2): 339–348.
4. Lemire P et al. *Cell Rep*. 2017 Dec 26; 21(13): 3653–3661.
5. Chen GY et al. *J Immunol*. 2011 Jun 15; 186(12): 7187–94.

OP004   EARLY SURGERY VERSUS STEP-UP PRACTICE INCLUDING ENDOSCOPY FOR CHRONIC PANCREATITIS: A MULTICENTER RANDOMIZED CONTROLLED TRIAL [ESCAPE TRIAL]

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Introduction: Surgery for chronic pancreatitis is currently used as last resort treatment when the first steps of the step-up approach, medical and endoscopic treatment, have failed. It has been suggested that early surgery may lead to better pain relief and preservation of pancreatic function, as compared to the current step-up approach of medical and endoscopic treatment, and surgical therapy if all else fails. We conducted a multicenter randomized controlled trial to compare early surgery with the current step-up approach.

Aims and Methods: We included patients with chronic pancreatitis according to the MANNHEIM criteria with a dilated pancreatic duct ($\geq$ 5 mm) and severe continuous or intermittent pain attacks, who had only recently started treatment with opioids. Patients who used strong opioids for more than 2 months or weak opioids for more than 6 months in the last 2 years were excluded. Patients were randomly assigned to early surgery (6 weeks after randomization; if pancreatic head < 4cm: lateral pancreatojejunostomy, if $\geq$4cm: Frey procedure) or to the step-up approach (step 1: pain medication, step 2: endoscopic intervention, if step 1 failed, step 3: surgical intervention, if step 2 failed). Failure criteria were strictly defined. The primary endpoint was the mean Izbicki pain score during 18 months of follow-up. Secondary endpoints included pain relief, complications, mortality, number of interventions, pancreatic function, and quality of life.

Results: 88 patients were randomized according to calculated sample size; 44 to early surgery (41 indeed underwent surgery) and 44 to the step-up approach (44 underwent medical treatment, 39 endoscopic intervention, and 13 surgical intervention thereafter). During 18 months' follow-up patients in the early surgery group had a lower mean Izbicki pain score as compared to patients in the step-up approach (35 vs. 48, p = 0.018). Taken into account the baseline pain score, early surgery showed a larger decrease in Izbicki pain score during follow-up (-26 vs. -16, p = 0.04). Complete or partial pain relief during follow-up was achieved in 54% of patients in early surgery and in 33% of patients in the step-up approach (RR: 1.52 [1.40-1.66], p < 0.001). Fewer interventions were performed in the early surgery group compared to the step-up group (median 1 vs. 3, P < 0.001). Complications, mortality (0%), hospital readmission, pancreatic function and quality of life were comparable between groups.

Conclusion: Early surgery, within the first months of need for opioid use, for patients with chronic pancreatitis and a dilated pancreatic duct provides better pain relief with less interventions than the current step-up approach including endoscopy first, but quality of life is comparable.

Disclosure: Nothing to disclose

MONDAY, OCTOBER 22, 2018   10:30–12:00

Endoscopic resection of polyps – Room B_____

OP005   ASSISTANCE OF A REAL-TIME AUTOMATIC COLON POLYP DETECTION SYSTEM INCREASES POLYP AND ADENOMA DETECTION DURING COLONOSCOPY: A PROSPECTIVE RANDOMIZED CONTROLLED STUDY

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Introduction: Screening colonoscopy can reduce the incidence and mortality of colorectal cancer through detection of polyps. However, a miss rate of up to 27% has been reported for adenomas.

Aims and Methods: The aim of this study was to investigate whether an automatic polyp detection system during colonoscopy increased the polyp and adenoma detection rate. Consecutive patients were prospectively randomized to undergo routine colonoscopy with or without assistance of real-time automatic polyp detection system providing a simultaneous visual notice and sound alarm when a polyp was detected. The automatic polyp detection system used in this study was a previously validated deep-learning polyp detection software[1].

Results: Out of 1,058 patients, 536 were randomized to a colonoscopy (control group), and 522 to a colonoscopy with computer-aided diagnosis (CAD group). There is no statistical difference between 2 groups in demographics and adenoma risk factors, including age (p = 0.16), gender (p = 0.19), BMI (p = 0.99), family/personal adenoma history (p = 0.34/0.8), and family colon cancer history (p = 0.78) etc. A total of 767 polyps, 422 adenomas and 31 serrated adenomas were detected. The polyp detection rate (PDR) of the control and CAD groups were 29.10% and 45.02% respectively (OR = 1.995, 95% CI 1.532-2.544, p < 0.001). The adenoma detection rates (ADR) were 20.34% and 29.12% respectively (OR = 1.61, 95% CI 1.213-2.135, p < 0.001). The average number of polyps detected were 0.50 and 0.95 respectively (Change Folds = 1.89, 95% CI 1.63-2.192, p < 0.001). The average number of adenomas detected were 0.31 and

0.53 respectively (Change Folds = 1.72, 95% CI 1.419-2.084, p < 0.001). There was a total of 39 false alarms and no missed polyp by the automatic polyp detection.

Conclusion: Automatic polyp detection during colonoscopy resulted in an increase in the number of polyps and adenomas found per colonoscopy and improved the overall ADR and PDR.

	Control Group (N = 269)	CAD Group (N = 498)	P value
Pathology. Carcinoma	0 (0%)	0 (0%)	1
Pathology.SSAP	14 (5.20%)	17 (3.41%)	0.541
Pathology. Adenoma	160 (59.48%)	262 (52.61%)	<0.001
Pathology. Benign Lesions	95 (35.32%)	219 (43.98%)	<0.001
Polyp Location			<0.001
Polyp Location. Cecum	3 (1.12%)	5 (1.00%)	0.462
Polyp Location. Transverse	45 (16.73%)	110 (22.09%)	<0.001
Polyp Location. Descending	26 (9.67%)	75 (15.06%)	<0.001
Polyp Location. Rectum	69 (25.65%)	81 (16.27%)	0.254
Polyp Location. Ascending	47 (17.47%)	97 (19.48%)	<0.001
Polyp Location. Sigmoid	79 (29.37%)	130 (26.10%)	<0.001
Polyp Shape			0.076
Polyp Shape. Pedunculated	38 (14.13%)	49 (9.84%)	0.194
Polyp Shape. Not Pedunculated	231 (85.87%)	449 (90.16%)	<0.001
Polyp Size (mm)	Mean 5.03 (SD 3.72)	Mean 4.51 (SD 2.55)	0.05
Polyp Size Category			0.096
Polyp Size Category.0-5 mm	198 (73.61%)	399 (80.12%)	<0.001
Polyp Size Category.6-10 mm	61 (22.68%)	83 (16.67%)	0.047
Polyp Size Category. > 10 mm	10 (3.72%)	16 (3.21%)	0.218

[Comparison of polyp characteristics by automatic polyp detection status]
Disclosure: Nothing to disclose

Reference

1. A Prospective Validation of Deep Learning for Polyp Auto-detection during Colonoscopy. World Congress at ACG2017. https://www.eventscribe.com/2017/wcogacg2017/ajaxcalls/PresentationInfo.asp?efp=SllVTUxLQVozODMy&PresentationID=304929&rnd=0.7090379.

OP006 POTENTIAL ACCEPTABILITY OF A WATCH-AND-WAIT APPROACH FOR DIMINUTIVE COLORECTAL ADENOMAS: FIVE-YEAR INCIDENCE OF ADVANCED COLORECTAL NEOPLASIA IN INDIVIDUALS WITH UNTREATED DIMINUTIVE ADENOMAS

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Introduction: Removal of all colorectal adenomas during colonoscopy (CS) is recommended; however, the increasingly frequent detection of diminutive adenomas raises the question as to whether the removal of all is mandatory, balancing benefit and harms.[1] The increasing use of antithrombotic drugs and possibility of missed diminutive adenomas may also require discussion regarding the acceptability of a watch-and-wait approach for diminutive adenomas. Although the watch-and-wait approach is allowed in Japan,[2] evidence is lacking for it.

Aims and Methods: This study aimed to evaluate the cumulative incidence of advanced colorectal neoplasia (ACN) in individuals with untreated diminutive adenomas, and to compare this with the incidence in those without adenomas. The incidence was also evaluated after identifying and adjusting for risk factors for the incidence of ACN. Data from 1,378 consecutive asymptomatic individuals who underwent first screening CS and at least one follow-up CS without polypectomy at the Cancer Screening Center, National Cancer Center, Tokyo, between February 2004 and March 2013 were analyzed. Those with no adenomas or only nonadvanced diminutive adenomas (<5mm) confirmed by image-enhanced magnifying endoscopy were scheduled to undergo follow-up CS within 5 years after the initial CS without treatment. Thus, participants were classified into two groups; those with untreated diminutive adenomas (group A) and those without any adenomas (group B). The cumulative incidence of ACN in both groups was assessed in March 2018, using Gray's test with consideration of competing risk situations. Multivariate analysis using the Fine and Gray model was performed to identify independent risk factors for the incidence of ACN among the following factors: age, sex, family history of colorectal cancer, smoking, drinking, nonsteroidal anti-inflammatory drugs, body mass index, diabetes mellitus, and the presence and number of untreated diminutive adenomas.

Results: There were 361 and 1,017 participants in groups A and B, respectively. There were 1-6 untreated diminutive adenomas in each group A participant, and 335 participants (92.8%) had less than 3. During a median follow-up of 60.9 months (interquartile range 40.8-64.2), 21 ACNs, including one T1 colon cancer, were detected in 18 individuals. The number of colonoscopies performed per individual was two in both groups (p = 0.93), and the 5-year cumulative incidences of ACN in group A and B were 1.4% (95% CI 0.5-3.4) and 0.8% (95% CI 0.3-1.7), respectively, with no significant difference between the groups (p = 0.23). Endoscopic findings showed that no ACN grew from an untreated adenoma. The only independent risk factor for the incidence of ACN was current smoking (hazard ratio 5.7; p < 0.01); presence and number of untreated diminutive adenomas did not affect the incidence of ACN. After adjustment for smoking status, the 5-year cumulative incidences of ACN in groups A and B were 1.0% (95% CI 0.0-2.2) and 0.7% (95% CI 0.1-1.2), respectively.

Conclusion: The 5-year cumulative incidence of ACN in those with untreated diminutive adenomas was sufficiently low, and was similar to that in those with no adenomas, indicating the potential acceptability of a watch-and-wait approach for diminutive adenomas. The present findings may be useful for consideration of more practical screening and surveillance programs, although further assessment is required particularly for cases with many diminutive adenomas. The potential necessity for consideration of smoking status in surveillance is also worth further investigation.

Disclosure: Nothing to disclose

References

1. Brenner H, et al. *Gastrointest Endosc.* 2017; 85: 1177–9.
2. Tanaka S, et al; Japanese Society of Gastroenterology. *J Gastroenterol.* 2015; 50: 252–60.

MONDAY, OCTOBER 22, 2018   10:30–12:00
Epidemiology and treatment options in NASH – Room E1_____

OP007 SERUM SRAGE LEVELS ARE ASSOCIATED WITH LIFESTYLE AND WITH NON-ALCOHOLIC FATTY LIVER DISEASE

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Introduction: Non-alcoholic fatty liver disease (NAFLD) is strongly related with lifestyle. Advanced glycation end products (AGEs), derived also from diet, have been positively related with NAFLD, while its soluble receptor (sRAGE) acts as a decoy. The association of sRAGE with NAFLD has been scarcely studied. Moreover, little is known about lifestyle-related determinants of sRAGE levels.

Aims and Methods: The aim of this study was to test the association of sRAGE with lifestyle and NAFLD. A cross-sectional study among subjects 40-70 years old, participating in a screening study, undergoing abdominal ultrasonography to diagnose NAFLD and fasting blood tests. Nutritional index consumption was measured by food frequency questionnaire (FFQ) and life-style habits were measured by a structured questionnaire. Low sRAGE levels were defined as a level below the population lower tertile (<1013 pg/ml).

Results: A total of 789 subjects had valid FFQ. High processed and/or red meat consumption (above the third tertile) was associated with higher odds of low sRAGE, respectively (OR = 1.49, 1.00-2.21, p = 0.048), adjusting for gender, age, abdominal obesity and caloric intake. Conversely, greater exercise time (above the median) was associated with reduced odds for low sRAGE (OR = 0.68, 0.49-0.94, p = 0.020). Subjects with low sRAGE had higher odds for NAFLD (OR = 1.51, 1.01-2.27, p = 0.045) and elevated ALT among NAFLD subjects (OR = 1.72, 1.12-2.64, p = 0.014) and among the entire sample (OR = 2.27 95%CI 1.28-4.04, p = 0.005).

Conclusion: Diet and exercise are associated with serum sRAGE levels and, in turn, low levels of sRAGE are associated with NAFLD and elevated ALT levels.

Disclosure: Nothing to disclose

OP008 HYPOXIA-INDUCIBLE FACTOR 2ALPHA IS CRITICAL FOR NASH-RELATED EXPERIMENTAL LIVER CARCINOGENESIS

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Introduction: Hypoxia and hypoxia inducible factors (HIFs) are believed to significantly affect the progression of chronic liver diseases (CLD). Recently, we showed that hepatocyte HIF-2alpha activation is a key feature in both human and experimental NAFLD and significantly contributes to disease progression.

Aims and Methods: In the present study we investigated the contribution of hepatocyte HIF-2alpha in promoting the development of NAFLD/NASH-associated hepatocellular carcinoma (HCC). The role of HIF-2alpha was investigated in human HCC liver specimens from NAFLD/NASH patients and in mice carrying hepatocyte-specific deletion of HIF-2alpha (HIF-2alpha fl/fl/Alb-Cre mice) receiving diethyl-nitrosamine (DEN) administration plus choline-deficient L-amino acid refined (CDAA) diet (DEN/CDAA protocol).

Results: HIF-2 alpha, as detected by mRNA transcript and immunostaining, was expressed in HCC specimens from NAFLD/NASH patients, with higher expression in patients experiencing early tumour recurrence. Following the treatment with the DEN/CDAA protocol, mice carrying hepatocyte specific deletion of HIF-2 alpha showed a significant decrease in either the volume and/or the number of neoplastic liver tumour masses in transgenic mice as compared to control littermates. Liver tumours in HIF-2 alpha transgenic mice were also characterized by: i) a decrease of tumour associated macrophages and fibroblasts/myofibroblasts, as evaluated by F4/80 and alpha-smooth muscle actin immunohistochemistry, respectively; ii) a significant decrease in transcript levels for critical and HIF2alpha-related target genes, including c-Myc and CXCR4.

Conclusion: These results indicate that the activation of HIF-2alpha in hepatocytes has a critical role in the development of experimental liver carcinogenesis in a dietary NAFLD/NASH-related environment.

Disclosure: Nothing to disclose

MONDAY, OCTOBER 22, 2018   10:30–12:00

IBD: From epidemiology to costs and outcome – Room F1_____

OP009 IS THERE A COST-SAVING EFFECT OF BIOLOGICAL THERAPY IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE? RESULTS FROM A PROSPECTIVE EUROPEAN POPULATION-BASED INCEPTION COHORT

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Introduction: The introduction of biological therapy has influenced healthcare expenditures in inflammatory bowel disease (IBD) significantly. However, no prospective long-term analysis of healthcare costs in patients with IBD in the era of biologic treatments exists in Europe.

Aims and Methods: The aim of this study was to perform a cost analysis of a pan-European inception cohort with five years of follow-up. The Epi-IBD cohort is a population-based inception cohort of IBD patients diagnosed from 31 centers in 20 countries in Western and Eastern Europe in 2010. Clinical and direct cost data (investigations, treatments, hospitalization and surgery) were collected prospectively. Patient management was left to the discretion of the treating gastroenterologists. Data are expressed as mean costs (€/patient-year). PY0 represents the inception year, and PY1, PY2, PY3 and PY4 are the four follow-up years.

Results: The cohort included 1,362 IBD patients (Western Europe: 1,104; Eastern Europe: 258), of which 52% had ulcerative colitis (UC), 37% Crohn's disease (CD) and 11% IBD unclassified. The age structure was: ≤40 y 45%, 41-60 y 31%, and ≥ 61 y 24%.

The total expenditures per year in CD and UC patients as well as the proportion of expenditure spent on different categories of direct costs is shown in Table 1. Total expenditure was higher in CD than UC, as was the annual percentage outlay on biological therapy. In Western Europe, total annual costs were highest in PY0 at €4,964, and then decreased as follows: PY1 €1,687, PY2 €1,585, PY3 €1,492, and PY4 €1,113. Expenditure on biologic therapy increased in this time period (PY0 €338, PY1 €410, PY2 €440, PY3 €504, and PY4 €516). In Eastern Europe, while overall healthcare costs were lower, similar observations were made. Total annual costs were highest in PY0 at €2,227, and then decreased: PY1 €934, PY2 €758, PY3 €643, and PY4 €734. Cost of biologic therapy was the following: PY0 €31, PY1 €233, PY2 €355, PY3 €308, and PY4 €292. In both regions this was paralleled by a steady decrease of costs of non-biologic treatment, hospitalization and surgery.

In all centers the expenditure on investigations was highest in the year PY0. No gender differences in costs were observed, however, patients aged ≤ 40 years engendered higher costs than older individuals. The overall outlay on biological therapy, expressed as a percentage of total expenditure, varied by age group: ≤ 40 yrs. 29%, 41-60 yrs. 21%, and ≥ 61 yrs. 11%.

	PY0	PY1	PY2	PY3	PY4
Crohn's disease – total expenditure	5,579€	1,820€	1,714€	1,907€	1,669€
CD – Biological therapy	11%	46%	51%	48%	56%
CD – Other IBD-related medication	5%	13%	11%	11%	12%
CD – Hospitalization	20%	14%	11%	11%	6%
CD – Diagnostic procedures	34%	17%	11%	12%	10%
CD – Surgery	30%	9%	16%	18%	17%
Ulcerative colitis – total expenditure	3,612€	1,421€	810€	983€	674€
UC – Biological therapy	2%	7%	20%	19%	25%
UC – Other IBD-related medication	15%	23%	29%	21%	26%
UC – Hospitalization	35%	29%	21%	33%	17%
UC – Diagnostic procedures	38%	20%	19%	20%	19%
UC – Surgery	10%	21%	10%	8%	13%

[Table 1. Mean total expenditure (€/patient) and as well as the proportion of expenditure spent on different categories of direct costs]

Conclusion: In this large population-based inception cohort of unselected IBD patients, the overall direct expenditure on healthcare decreased over a 5-year follow-up period. This period was characterized by remarkably increasing expenditure on biologics, particularly in CD patients, and decreasing expenditure on standard medical treatments, surgery and hospitalization. Despite their known high acquisition charges, these data indicate a cost-saving effect of biologic medications.

Disclosure: Nothing to disclose

OP010 EFFICACY AND SAFETY OF THE SEQUENTIAL USE OF A SECOND AND THIRD ANTI-TNF DRUG IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Introduction: One-third of inflammatory bowel disease (IBD) patients, both Crohn's disease (CD) and ulcerative colitis (UC), treated with anti-TNF agents do not respond to the drug (primary failure), and a relevant proportion from those who respond experiences loss of response (secondary failure) or intolerance over time. Although the switch to a second or a third anti-TNF drug is not exceptional in clinical practice, data are scarce.

Aims and Methods: The aim was to investigate the efficacy and safety of the sequential use of a second and a third anti-TNF agent after failing or developing intolerance to an anti-TNF drug. Patients diagnosed with IBD from ENEIDA registry (a prospectively maintained registry from GETECCU) who switched to a second or a third anti-TNF after failure or intolerance to a previous anti-TNF drug, were included. Efficacy, loss of response, and safety of the second and third anti-TNF were evaluated by logistic regression, Kaplan-Meier and Cox regression analyses.

Results: 1,022 patients that switched to a second anti-TNF were included (50% men, mean age at diagnosis 31 years, 73% CD). The reasons for withdrawal the first anti-TNF were: primary failure (21%), secondary failure (51%), and intolerance (28%). A second attempt with an anti-TNF agent induced remission in 45% of patients in the short-term. 33% received concomitant immunosuppressive therapy. In the multivariate analysis, factors associated with a lower probability of achieving remission after a second anti-TNF were: combo therapy (OR = 1.9; 95% CI = 1.5-2.5, p < 0.0001), to withdraw the first anti-TNF due to a primary failure (vs. intolerance) (OR = 1.6; 1.1-2.3%, p = 0.007) and to withdraw the first anti-TNF due to secondary failure (vs. intolerance) (OR 1.5; 1.2-2%, p = 0.003). The cumulative incidence of loss of response after achieving remission with the second anti-TNF (median follow-up of 19 months) was 45% (41-49%): 23% at 1 year, 38% at 2, 66% at 3, and 62% at 5 years. The incidence of loss of response to the second anti-TNF was 19% per patient-year of follow-up. The dose of the second anti-TNF was increased in 22% of patients during follow-up (median follow-up of 13 months); of these, 56% regained remission. At 1 year, 91% of these patients were in remission. The factors associated with a higher risk of loss of response were: UC vs. CD (HR = 1.6; 1.1-2.1, p = 0.005) and combo therapy (HR = 2.4; 1.8-3, p < 0.0001). The rate of adverse events after a second anti-TNF was 15%, and led to drug discontinuation in 66%. 71 patients switched to a third anti-TNF (55%men, mean age at diagnosis 32 years, 63% CD). The reasons for withdrawal the second anti-TNF were: primary failure (45%), secondary failure (39%), and intolerance (16%). Remission was achieved with the third anti-TNF in 55% of patients in the short-term. The incidence of loss of response was 22% per patient-year of follow-up (median follow-up of 9 months). The cumulative incidence of loss of response was 38%: 18% at 1 year and 37% at 2 years. 7 patients (11%) had adverse events, but only one discontinued the therapy.

Conclusion: The efficacy of a second anti-TNF in IBD patients was associated with the reason for switching. Almost half of the patients who achieved remission with a second anti-TNF subsequently lost response. Factors associated with loss of response of a second anti-TNF were type of IBD and combo therapy. Almost two-thirds of patients who received a third anti-TNF achieved remission; however, one-third of them lost response subsequently. The sequential use of a second and third anti-TNF is apparently safe.

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OP011 CLINICAL DIFFERENTIAL CHARACTERISTICS OF PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD) OF ONSET IN PEDIATRIC AGE COMPARED TO PATIENTS DIAGNOSED IN ADULTHOOD

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Introduction: Studies comparing the characteristics of childhood-onset and adulthood-onset inflammatory bowel disease (IBD) in the biologic era are scarce.

Aims and Methods: To compare the disease characteristics, the use of immunomodulators and biologic agents, and the need for surgery between childhood and adulthood-onset IBD.

IBD patients diagnosed from 2007 from the ENEIDA registry – prospectively maintained database promoted by GETECCU were included. Patients diagnosed at ≤16 years comprised the childhood-onset cohort (CC), and those diagnosed >16 years were the adult cohort (AC). Cox-regression analysis was performed to identify potential predictive factors to receive immunosuppressants, biological agents or surgery.

Results: From 21,200 patients, 96% comprised the AC and 4% the CC. Median follow-up was 54 months in the CC and 38 months in the AC (p < 0.01). The proportion of male gender, CD and family history of IBD was higher in the CC. CD patients in the CC had more extensive involvement while the proportion of patients with stricturing or fistulizing phenotype was higher in the AC. UC patients in the CC had more extensive involvement. Cumulative incidence of exposure to immunomodulators was higher in the CC: 54% at one year, 63% at 2 years, 70% at 3 years, 73% at 4 years and 87% at 5 years in the CC; and 34% at 1 year, 43% at 2 years, 48% at 3 years, 52% at 4 years and 55% at 5 years in the AC (p < 0.01). The cumulative incidence of exposure to biologic agents was higher in the CC: 25% at 1 year, 39% at 2 years, 45% at 3 years, 50% at 4 years and 65% at 5 years in the CC; and 16% at 1 year, 24% at 2 years, 29% at 3 years, 33% at 4 years and 37% at 5 years in the AC (p < 0.01). The proportions of patients and the cumulative incidence of surgery were similar in the CC and AC (17% vss. 15%, p > 0.05). Childhood-onset IBD was associated with higher risk of immunomodulator and biologic agents exposure. Childhood-onset IBD was not associated with higher risk of surgery (table 1).

Conclusion: IBD patients diagnosed during childhood have differential characteristics (higher prevalence of CD, more extensive disease and more frequent family history). In addition, the use of immunomodulators and biologic agents is higher in childhood-onset patients. Despite of the higher burden of the disease in children, the rate of surgery is similar to that in the adulthood-onset IBD population.

Variable	Hazard ratio (95% confidence interval)
USE OF IMMUNOSUPPRESSANTS	
Childhood-onset vs. adulthood-onset IBD	1.6 (1.5–1.8)
Female gender	0.94 (0.91–0.98)
Crohn's disease (vs. ulcerative colitis)	3.2 (3.09–3.4)
Family history	1.08 (1.01–1.1)
Extraintestinal manifestations	1.2 (1.1–1.3)
Smoking habit	1.1 (1.05–1.16)
USE OF BIOLOGIC AGENTS	
Childhood-onset vs. adulthood-onset IBD	1.5 (1.4–1.7)
Female gender	0.92 (0.8–0.95)
Crohn's disease (vs. ulcerative colitis)	2.5 (2.3–2.7)
Extraintestinal manifestations	1.7 (1.6–1.7)
Smoking habit	1.1 (1.04–1.18)
SURGERY DURING FOLLOW-UP	
Childhood-onset vs. adulthood-onset IBD	0.9 (0.8–1.2)
Female gender	0.79 (0.73–0.86)
Crohn's disease	6.6 (5.8–7.4)
Immunomodulators before surgery	0.36 (0.33–0.39)
Smoking habit	1.2 (1.1–1.3)

[Variables associated with the risk of exposure to immunosuppressants, biological agents and surgery during follow-up.]

OP012 INDIRECT COSTS OF INFLAMMATORY BOWEL DISEASE IN A DANISH POPULATION-BASED INCEPTION COHORT AFTER TEN YEARS OF FOLLOW-UP

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Introduction: Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and Ulcerative Colitis (UC) are chronic disabling diseases diagnosed often in young adulthood. Little is known about the direct and indirect costs of IBD,

especially in the era of biologic therapy. To date, no study has assessed indirect cost of CD and UC patients in a population-based setting.

Aims and Methods: Our aim was to assess the indirect cost of CD and UC patients in a population-based inception cohort with 10 years of follow-up. All incident patients, diagnosed with CD (213) or UC (300) year 2003-2004 in a well-defined Copenhagen area, were followed prospectively until 2014. Employment status, sick-leave and social benefits are automatically registered in national registries through the unique 10 digit personal identification number given at birth or immigration. With use of these national registries, indirect cost of unemployment, sickness- and/or social benefits were assessed. The loss of tax income for the Danish government during unemployment was calculated using the mean income for the Danish population of 41,970 EUR (value of 2017). Data were compared with a population of healthy controls matched by age, sex and municipality at diagnosis with a ratio of 1:20 (n = 10,259). Using multiple linear regression models, associations between indirect cost and multiple variables (gender, age, smoking status at diagnosis, disease behaviour, -location, -extension and diagnostic delay) were assessed.

Results: During follow-up, 139 [65%] CD and 181 [60%] UC patients had at least one paid sick-leave with a median (IQR) length of 8.4 (2.6-19.8) months for CD and 5.1 (1.6-15.9; p = 0.2) for UC. The median cost of sickness benefits during follow-up for CD was 10,2300 (3,900, 32,100) and 8,800 (2,400, 28,500) EUR for UC. No significant difference was found between healthy controls and IBD patients regarding length of paid sick-leaves (5.7 months [1.2, 16.4], p = 0.08) or sickness benefits (9,700 [2,100, 30,200], p = 0.2). Regarding unemployment, a total of 279193 (5439%) (CD: 12377 [5836%], UC: 156116 [5239%]) patients were unemployed at least once during follow-up. In CD, the median length of unemployment was 5.3 (2.3-12) and 6.6 months (2-14.8) in UC (p = 0.55). The median cost for unemployment benefits was 13,30017,900 (4,7003,100, 55,8003,600) EUR for CD, and 12,50014,600 (3,1002,400, 47,1003,500) EUR for UC patients (p = 0.5). These numbers did not differ significantly from the healthy controls (5.9 [1.87, 14.4] p = 0.6 and 13,4000,700 [2,4000,000, 48,60037,300] p = 0.23, respectively). The median loss of tax income for the Danish government because of unemployment was 6,90052,300 (2,20018,500, 17,000121,800) EUR, which did not differ from healthy controls (7,00051,300 [2,50016,400, 16,400126,300], p = 0.6). The total indirect cost accounted for 19.714.4 million EUR (CD: 9.16.9 million, UC: 10.67.5 million). No factors were associated with the indirect cost in CD. In UC, age 17-40 years (OR: 1.53 [1.01, 2.11.6]), being male (OR: 0.9 [0.8, 1.0]) and current smoker (OR: 1.31 [1.10, 1.62]) at diagnosis were significantly associated with the indirect cost of 100,000 EUR.

Conclusion: In this population-based inception cohort with ten years of follow-up, indirect cost of IBD patients did not differ from the general population. Furthermore, no significant increased expenses were found between CD and UC patients. These data indicate that in a country with universal and free access to healthcare current treatment strategies keep patients with IBD on the job market. Except for higher direct costs due to health care utilization, IBD patients did not carry higher indirect costs compared to healthy controls.

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OP013 IS CROHN DISEASE THE PRICE TO PAY TODAY FOR HAVING SURVIVED TO THE BLACK DEATH?

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Introduction: Nucleotide Oligomerisation Domain 2 (*NOD2*) is a key gene of innate immunity which participates to the host defence toward pathogens. Several *NOD2* variations associated with Crohn Disease (CD). Unexpectedly, these loss-of-function mutations are frequent in populations of European ancestry suggesting a model of balancing selection and thus a benefit to mutation carriers. Because NOD2 deficiency has been associated with a resistance to *Yersinia pseudotuberculosis* we hypothesized that *NOD2* mutations have been selected during past plague outbreaks due to *Yersinia pestis*.

Aims and Methods: We performed a Pubmed search looking for the frequencies of CD associated mutations (R702W, G908R and 1007fs) in healthy controls in European and Mediterranean countries. Using historical data on plague outbreaks, we evaluated the rate of exposure to plague of the ancestors of the corresponding populations. Demography of cities and migration rates from the 14th century to the 19th century were also taken into account to evaluate the impact of putative confounding factors.

Results: The rates of the CD-associated *NOD2* mutations in the general population were correlated with the intensities of plague outbreaks in Europe and the Mediterranean Basin. Statistical significance was obtained with the most frequent mutation (R702W, p = 0.03) and with the pooled three mutations (p = 0.023). The association remained significant when putative demographic biases were considered suggesting a robust finding.

Conclusion: This result argues for a selection of CD-associated *NOD2* mutations by the various plague episodes which have occurred in Europe and the Mediterranean Basin since the Middle ages.

Disclosure: Nothing to disclose

OP014 CROHN'S DISEASE: WHAT CAN WE EXPECT FROM THE COURSE OF THE DISEASE?

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Introduction: Crohn's disease (CD) is a chronic and progressive disease that changes its behavior over time. Transmural inflammation in CD leads to stricturing and/or penetrating complications.

Aims and Methods: We aim to evaluate the frequency of the long-term progression of CD phenotypes, and need for surgery, and to determine the main factors associated with this evolution.

A retrospective study was conducted with a prospective follow-up. Patients included had a minimum follow-up of 12 months. Montreal classification was assessed at the moment of the diagnosis and at the end of the follow-up period.

Results: Included 290 patients, 53.8% female. The behavior at presentation was inflammatory (B1) in 64.5%, structuring (B2) in 23.4%, penetrating (B3) 12.1% and perianal disease was present in 18.6%. Behavior at the end of the follow-up was: B1 in 51.4%, B2 in 30.3% and B3 in 18.3%, perianal disease was identified in 20%.

Globally we observed a change in behavior in 46 patients (15.9%); from B1 to B2 in 30 patients, B2 to B3 in 7 patients and B1 to B3 in 9 patients.

Ileocolic location (60.9% vs 45.1%; p = 0.049), age at diagnosis < 16 (8.7% vs 2%; p = 0.017), the use of steroids at diagnosis (43.2% vs 27%; p = 0.031) and less time exposure to biological therapy (15.9 months vs 41.32 months; p < 0.001) were the risk factors associated with changing phenotype.

Regarding surgery, 70 patients (24.1%) were submitted to intestinal resection. Smoking status (42.9% vs 24.8%; p = 0.004), B2 (47.1% vs 15.9%; p < 0.001), B3 (42.9% vs 2.3%; p < 0.001), hospitalizations in the first year of diagnosis (52.3% vs 12.4%; p < 0.001), use of steroids at diagnosis (61.4% vs 23.6%; p < 0.001) were more frequently observed in patients submitted to surgery. Patients submitted to surgery were less frequently treated with biological therapy (8.7% vs 23.4%; p < 0.025).

Conclusion: In our cohort we observed a behavior progression in about one-sixth of patients. The most frequent change in behavior was to stricturing pattern. Stricturing and penetrating behavior, higher number of hospitalizations in the first year of diagnosis, use of steroids at diagnosis, smoking status, age at diagnosis < 16 and Ileocolic localization were factors associated with an unfavorable clinical evolution. Patients that were submitted to surgery were less treated with biological therapy.

Disclosure: Nothing to disclose

MONDAY, OCTOBER 22, 2018   10:30–12:00

Pushing the limits of hepato-pancreatic and biliary diseases – Room G_____

OP015 FIRST-ROUND SCREENING RESULTS IN SUBJECTS AT RISK OF PANCREATIC CANCER FROM THE AISP (ITALIAN ASSOCIATION FOR THE STUDY OF THE PANCREAS) REGISTRY

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Introduction: Surveillance programs on high-risk individuals (HRI) can detect premalignant lesions or early pancreatic cancers (PDAC). We report the results of the first-round of screening of the Italian multicenter program supported by the Italian Association for the study of the Pancreas (AISP).

Aims and Methods: The multicenter surveillance program includes: a) individuals with familial pancreatic cancer (FPC) defined as those with ≥ 3 first- (FDR), second- (SDR) or third-degree relatives with PDAC or individuals with 2 relatives with PDAC with at least 1 FDR; b) BRCA 1/2 or p16 mutation carriers with at least 1 FDR or SDR diagnosed with PDAC; subjects suffering from hereditary pancreatitis (HP) or Peutz-Jegher (PJ) syndrome. The surveillance program consists of at least an annual magnetic resonance cholangiopancreatography (MRCP). An endoscopic ultrasound (EUS) is proposed to patients who refuse or cannot be submitted to an MRCP. Univariate and multivariate analysis were performed using chi-squared test and a binary logistic regression model to identify risk factors the detection of pre-malignant (any IPMN) or malignant lesion.

Results: The study population is represented by 189 HRI who underwent a first-round screening examination with MRCP (174, 92.1%) or EUS (15, 7.9%) from September 2015 to March 2018. Nine (5.1%) received EUS as supplementary investigation due to suspicious findings at MRCP. The mean age was 52 years (range 21-80). 123 (65.1%) FPC, 61 syndromic (32.3%) and 5 (2.6%) HP were included. An overall number of 55 screening abnormalities were found. MRCP detected pancreatic abnormalities in 44 HRI (25.3%), mostly cystic lesions (n = 42, 24.1%); 27 cysts (61.3%) were BD-IPMNs. The mean diameter of BD-IPMNs was 9 mm (range 3-25). EUS detected 6 PDAC (3.1%, 1 BRCA, 1 FPC, 3 PJS, 1 HP). Two patients received resective surgery (pT3N1R0 and pT1N0R0, 1 HP and 1 PJ HRI), 2 were locally advanced (BRCA1 and PJ HRI) and 2 metastatic (1 FPC and 1 PJ HRI). EUS identified 4 further abnormalities (2 undefined cystic lesions and 2 EUS features of chronic pancreatitis) and it was normal in 5 out of 15 cases (33.3%). 2 further patients (PJ-HRI), received surgery due to IPMN with high-risk stigmata with pathology findings of 1 IPMN/invasive carcinoma and 1 low-grade dysplasia mixed-type IPMN (both found at MRCP and confirmed by EUS). An additional solid pseudopapillary tumor was identified and resected. The rate of malignancies detected was higher in the non-FPC cohort than in the FPC one (Fisher's exact test p < 0.05). At the multivariate analysis smoking habit (OR 3.9, 95%CI 1.2–11.8, p < 0.05), > 2 relatives affected by PC (OR 2.7, 95%CI 1-7.2) and age > 50 years (OR 2.5, 95%CI 1-6.2) were found to be independent predictors of detection of pre-malignant and malignant lesions.

Conclusion: The first-round screening results in Italy report a high rate of pancreatic malignancies (3.7%), mostly being advanced at baseline. We confirm that the cohort of HRI suffering from PJ syndrome is the one at highest risk of having pancreatic malignancies (10%). The rate of malignant (invasive carcinoma/IPMN) or pre-malignant lesions (BD-IPMNs and mixed type-IPMN) in the FPC-HRI cohorts was lower (0.5% and 14.8%, respectively, p < 0.05), despite non-negligible. At the multivariate analysis smoking habit, > 2 relatives affected by PC and age > 50 years were independent risk factors for the identification of pre-malignant or malignant lesions. 6 HRI (3.1%) were submitted to surgery after the baseline screening method with nil mortality.

Disclosure: Nothing to disclose

OP016   ACTIONABLE PERTURBATIONS IN THE DNA DAMAGE RESPONSE ESTABLISH SYNERGISTIC THERAPEUTIC ROUTES IN ATM DEFICIENT PANCREATIC CANCER

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) is the 4th leading cause of cancer-associated death in the Western World. PDAC bears a high accumulation of oncogenic mutations. Recent sequencing studies found Ataxia-Telangiectasia Mutated (ATM) frequently mutated in PDAC. Our lab previously showed that the loss of ATM accelerates EMT and promotes genomic instability (1,2). In line with the altered genomic integrity of ATM-mutated PDAC established genotype specific strategies like PARP- and ATR- inhibition. However, these treatment strategies tended to show early resistance and particularly ATR inhibition renders toxicity at least in humans (1).

Aims and Methods: Here, we unravel novel synergistic routes based on actionable perturbations in the DNA damage response (i) to overcome chemoresistance and (ii) to present a genotype tailored cocktail of targeted therapies for *ATM*-mutated PDAC. Based on the Atmfl/fl; Kras+/G12D; Ptf1a+/Cre (AKC) and Kras+/G12D; Ptf1a+/Cre (KC) mouse model primary AKC and KC PDAC cell lines were established.

Results: First, we screened a set of inhibitors and chemotherapeutics for single agent efficiency using conventional MTT assyas. Second, the PreCISE (predictor of chemical inhibitor synergistic effects) software tool was applied to unravel synergy in actionable perturbations of the DNA damage response. Thereby, systematic combinational screening efforts found synergy between inhibition of the DNA-PKC, ATR and PARP signaling leading to synthetic lethality in AKC cell lines. Triple pathway inhibition was then combined with conventional topoisomerase inhibitors, the latter having shown substantially higher activity in AKC lines in our single agent screen. Systematic characterization of the DDR in such treated cell lines provided a coherent understanding of the molecular mechanism behind and key observations were validated in orthotopic and subcutaneous transplantation studies.

Conclusion: Summarized, based on a novel genomic unstable, ATM-depleted PDAC model, we could identify new targeted and synergistic routes to reach highest efficiency with lowest toxicity to pave the way to clinical trials in this subgroup of genomic unstable PDAC patients.

Disclosure: Nothing to disclose

References

1. ATM Deficiency Generating Genomic Instability Sensitizes Pancreatic Ductal Adenocarcinoma Cells to Therapy-Induced DNA Damage. Perkhofer L, Schmitt A, Romero Carrasco MC, Ihle M, Hampp S, Ruess DA, Hessmann E, Russell R, Lechel A, Azoitei N, Lin Q, Liebau S, Hohwieler M, Bohnenberger H, Lesina M, Algül H, Gieldon L, Schröck E, Gaedcke J, Wagner M, Wiesmüller L, Sipos B, Seufferlein T, Reinhardt HC, Frappart PO, Kleger A. *Cancer Res.* 2017 Oct 15; 77(20): 5576–5590.
2. Loss of ATM accelerates pancreatic cancer formation and epithelial-mesenchymal transition. Russell R, Perkhofer L, Liebau S, Lin Q, Lechel A, Feld FM, Hessmann E, Gaedcke J, Güthle M, Zenke M, Hartmann D, von Figura G, Weissinger SE, Rudolph KL, Möller P, Lennerz JK, Seufferlein T, Wagner M, Kleger A. *Nat Commun.* 2015 Jul 29; 6: 7677.

OP017   SINGLE MOLECULE REAL-TIME SEQUENCING UNVEILS THE EVOLUTION OF MULTI-DRUG RESISTANT HEPATITIS C VIRUS CLONES DURING DIRECT-ACTING ANTIVIRAL THERAPY

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Introduction: The recent development of oral direct-acting antivirals (DAAs) has dramatically improved the efficacy of anti-hepatitis C virus (HCV) treatment, however, resistance-associated variants (RAVs) are associated with treatment failure in HCV-infected patients receiving DAA therapy. Although low-abundant RAVs at baseline could expand and contribute to treatment failure, it has been difficult to determine the clonal origin of RAVs using conventional short-read sequencing methods. Thus, in the current study, we investigated the viral dynamics in patients undergoing DAA therapy and explored the clonal origin of multi-drug resistant viral clones using single molecular real-time (SMRT) sequencing, so called third generation sequencing, which can generate extremely long contiguous sequence reads.

Aims and Methods: Among 283 patients with genotype 1b HCV receiving DAAs therapy in our study group, 32 who failed to achieve a sustained virological response (SVR) were included in this study. First, conventional ultra-deep sequencing of NS3 and NS5A regions of HCV genome was performed in all patients using IonProton (ThermoFisher Scientific). Then, using paired sera samples before and after DAA treatment from the representative 6 non-SVR patients, we applied SMRT sequencing using PacBio RSII (Pacific Biosciences) to determine the long contiguous sequences spanning > 3000 bp of the NS3 to NS5A regions of each viral clone.

Results: Ultra-deep sequencing detected representative RAVs in all non-SVR patients at baseline, including NS5A-Y93H or L31M and NS3-D168V. Importantly, at treatment failure, multi-drug resistant HCV clones were detected in all cases as the major population. Then, long contiguous sequences of each viral clone in 12 sera from 6 non-SVR patients (a total of 3601 clones) were determined by PacBio RSII. We found the substantial sequence diversity of viral isolates present at baseline in all cases, showing the high degree of genetic heterogeneity in HCV clones. All the nucleotide substitutions analyzed in each clone before and after treatment were compared, and we found significant linkage between some synonymous substitutions and major resistance-associated substitutions. For example, several synonymous mutations linked to NS5A-Y93H in a subpopulation of pre-existing viral clones at baseline were shared by multi-drug resistant viral clones at treatment failure. Phylogenetic analyses revealed a close genetic distance between pre-existing drug-resistant clones and multi-drug resistant viral clones at treatment failure. In addition, linkage analysis demonstrated that multiple drug-resistant mutations newly developed based on pre-existing RAVs after DAA treatment in all non-SVR cases.

Conclusion: Comprehensive analysis of SMRT sequencing and conventional ultra-deep sequencing revealed that multi-drug resistant viral clones at treatment failure originated from a subpopulation of pre-existing RAVs in HCV-infected patients. Those RAVs were selected for and became dominant with the acquisition of multiple resistance-associated substitutions under DAA treatment pressure. These findings give us a clue to a better understanding of treatment failure with anti-HCV therapy.

Disclosure: Nothing to disclose

OP018 OUTCOMES OF EUS-GUIDED PHOTODYNAMIC THERAPY WITH CHLORIN E6 DERIVATIVES FOR UNRESECTABLE PANCREATIC CANCER: A PHASE I/II TRIAL

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Introduction: Since pancreatic cancer poorly responds to chemoradiotherapy, photodynamic therapy (PDT) has been considered as a promising treatment strategy for minimal invasiveness and selective tumor necrosis. However, the short penetration depth and prolonged photosensitivity of the therapy hindered it from popular usage. Recent progress of a novel photosensitizer with shorter acting time and improved penetration and advancement of the endoscopic ultrasound (EUS) may help overcome such obstacles.

Aims and Methods: This study aims to evaluate the feasibility and safety of EUS-guided photodynamic therapy (EUS-guided PDT) with a second-generation photosensitizer for unresectable pancreatic cancer. Patients with unresectable pancreatic cancer were prospectively enrolled in a single tertiary center between December 2015 and January 2018. Patients were photosensitized with chlorin e6 derivatives (Photolon®, Belmedpreparaty, Belarus) 3.0mg/kg, 3 hours before the procedure. Light at a 660-nm wavelength was delivered through a dedicated flexible laser-light catheter after puncturing the target lesion by 19-gauge fine aspiration needle. Light dose escalation (initial 120 J/cm, 150 J/cm, and 200 J/cm) was achieved. Primary outcome including tumor necrosis volume and fraction on CT or MRI were assessed 2 days after the treatment of EUS-guided PDT, by using an in-built histogram analysis plug-in tool for ImageJ. Criteria for secondary outcomes were technical success, adverse events, time to progression periods, and overall survival.

Results: 29 patients fulfilled the entry criteria and were treated, and a total of 47 EUS-guided PDTs were performed. 20 were male, and median age was 59 (range 36-75), and pre-PDT tumor diameter was median 35 mm (range 18-64). Technical success rate of EUS-guided PDT was 100%. 10 cases with substantial necrotic portion in tumors were excluded because it was not feasible to assess the volume of necrosis by EUS-guided PDT. However, these patients were included for the safety consideration. Among 37 EUS-guided PDTs after exclusion, 120 J/cm was delivered to 9 patients, 150 J/cm to 21, 200 J/cm to 7. Median PDT per session was 5 (range 3-15) with median 3 needle pass (range 1-8). Total necrosis volume was median 4666 mm^3 (range 928-13411), and necrotic fraction was median 35.5% (range 5-100). There was statistical difference of necrotic volume between 120J/cm group and 150J/cm group (613.5 ± 624.5 mm^3 and 1088.8 ± 505.3 mm^3, respectively, p = 0.007), but not with the 200 J/cm group (739.1 ± 422.5 mm^3). Three cases of fever occurred, which was spontaneously recovered. Otherwise, there was no procedure related adverse events including pancreatitis nor photosensitivity. No adverse interactions were seen in patients given chemotherapy or radiotherapy before and after EUS-guided PDT. Progression free survival was median 176 days (95% CI: 141-259), and overall survival was median 304 days (95% CI: 260-NA).

Conclusion: EUS-guided PDT with a second-generation photosensitizer is technically feasible, well-tolerated, and relatively safe for unresectable pancreatic cancer. Especially 150 J/cm may be optimal delivery energy compared to 120 J/cm. EUS-guided PDT could be performed before or after chemotherapy or radiotherapy for unresectable pancreatic cancer. Further randomized trial of comparing EUS-guided PDT with standard care (chemotherapy with or without radiotherapy) and standard care alone for unresectable pancreatic cancer may be warranted. (Clinical trial: CRIS registration number KCT0001763)

Disclosure: Funding: This study was supported by a grant (2018-771) from the Asan Institute for Life Sciences, Asan Medical Center, Seoul, Korea, and the National Research Foundation (NRF) funded by the Ministry of Science & ICT (No. NRF-2018M3C1B9018049).

OP019 TREATMENT WITH OBETICHOLIC ACID IN PATIENTS WITH NASH DOES NOT SHOW INCREASED MARKERS OF LIVER TOXICITY BASED ON EVALUATION OF DRUG-INDUCED SERIOUS HEPATOTOXICITY (EDISH)

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Introduction: Evaluation of drug-induced serious hepatotoxicity (eDISH) is a tool used to assess and identify potential cases of drug-induced liver injury[1]. eDISH was used to evaluate obeticholic acid (OCA) and placebo profiles in 2 double-blind, placebo-controlled studies in patients with nonalcoholic steatohepatitis (NASH). FLINT was a 72-week study, which demonstrated statistically significant improvements in hepatocellular ballooning, steatosis, lobular inflammation, and fibrosis in patients treated with OCA compared to placebo. CONTROL was a 16-week study, which showed that the addition of low-dose atorvastatin reversed OCA-associated changes in LDL-C.

Aims and Methods: The objective of this analysis was to use eDISH to determine if patients with NASH treated with OCA show increased markers of liver injury or whole liver dysfunction. eDISH methodology was applied to 278 patients treated with placebo (n = 140) or 25mg OCA (n = 138) from FLINT and 84 patients treated with placebo (n = 21), 5mg OCA (n = 20), 10mg OCA (n = 21), or 25mg OCA (n = 22) from CONTROL. Individual subject peak values of alanine aminotransferase (ALT) and total bilirubin throughout the double-blind treatment phase were plotted on an x-y chart as logarithm$_{10}$ values of multiples of elevations above the upper limit of the normal reference ranges (x ULN).

Results: Overall, no OCA-treated patients were in the Hy's law quadrant (> 3x ULN for ALT and > 2x ULN for total bilirubin) compared with 1 placebo-treated patient in FLINT. The proportion of patients with peak ALT and total bilirubin values in the lower left quadrant (representing normal or near normal range) was higher in OCA-treated patients compared with placebo (FLINT: 91% OCA vs 84% placebo; CONTROL: 91% OCA vs 86% placebo). 8% of OCA-treated patients from both FLINT and CONTROL presented in the Temple's corollary quadrant (> 3x ULN for ALT and < 2x ULN for total bilirubin) vs 14% (in both studies) for the placebo-treated patients. Across both studies (N = 362), 4 patients were in the cholestasis quadrant (> 2X ULN total bilirubin and < 3X ULN for ALT); 1 placebo-treated patient and 3 OCA-treated patients, including 1 patient with Gilbert's syndrome.

Conclusion: In these 2 placebo-controlled, double-blind NASH studies, the eDISH analysis showed no trend for liver injury with OCA at doses up to and including 25 mg.

Disclosure: This study was funded by Intercept Pharmaceuticals Inc.

Reference

1. Senior JR. *Drug Saf*. 2014; 37(Suppl 1): S9-S17.

OP020 MISFOLDING CARBOXYPEPTIDASE MUTANT INDUCES CHRONIC PANCREATITIS IN MICE

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Introduction: Genetic susceptibility plays an important role in the development of chronic pancreatitis. it has been demonstrated, that loss-of-function mutations in *CPA1*, which encodes the digestive enzyme carboxypeptidase A1, are associated with early-onset chronic pancreatitis[1–3]. *In vitro* functional studies indicate that pathogenic *CPA1* variants exert their effect via the so-called misfolding-dependent pathological pathway characterized by endoplasmic reticulum stress due to mutation-induced misfolding of digestive enzymes. However, *in vivo* evidence has been lacking. The objective of the present study was to generate a murine model that recapitulates features of *CPA1*-associated chronic pancreatitis.

Aims and Methods: To study the mechanism of action of *CPA1* variants *in vivo*, a novel *Cpa1 N256K* knock-in mouse strain was created carrying the most frequently reported human *CPA1* p.N256K mutation in the mouse *Cpa1* gene. Pathological changes in the pancreata and ER stress were assessed in the mutant strain and compared to C57BL/6N and *Cpa1 null* control mice.

Results: In the *Cpa1 N256K* mutant mice we observed characteristic features of chronic pancreatitis that included progressive acinar cell atrophy, inflammatory cell infiltration, fibrosis and pseudo-tubular complex formation. Contrary to the mutant mice both control strains showed no signs of pancreatic damage. Mutation p.N256K induced misfolding of mouse Cpa1 and resulted in elevated expression of ER stress markers *Hspa5* (BiP) and *Ddit3* (CHOP) in the *Cpa1 N256K* strain. Our data clearly demonstrate that *CPA1* mutations lead to enzyme misfolding and cause chronic pancreatitis via an ER-stress related mechanism.

Conclusion: We present the first mouse model of spontaneous chronic pancreatitis associated with digestive enzyme misfolding and endoplasmic reticulum stress. This model may be beneficial in testing the effects of various environmental factors or pharmaceutical drugs on the course of the disease.

Disclosure: Nothing to disclose

References

1. Witt H, Beer S, Rosendahl J, et al. Variants in CPA1 are strongly associated with early onset chronic pancreatitis. *Nat Genet* 2013, 45: 1216–1220.
2. Sahin-Tóth, M. Genetic risk in chronic pancreatitis: The misfolding-dependent pathway. *Curr Opin Gastroenterol* 2017, 33: 390–395.
3. Kujko AA, Berki DM, Oracz G, et al. A novel p. Ser282Pro CPA1 variant is associated with autosomal dominant hereditary pancreatitis. *Gut* 2017, 66: 1728.

OP021 APPLYING EVIDENCE-BASED SOFTWARE FOR NGS IN PANCREATIC CANCER: FIRST RESULTS FROM THE PEPACAKA STUDY

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Introduction: Pancreatic adenocarcinoma (PDAC) is almost resistant to chemotherapy. We performed next-generation sequencing on PDAC tumor tissue and evidence-based, AI-supported evaluation to identify second-line palliative therapies based on biomarker profiles.

Aims and Methods: After first-line therapy, tissue samples were sequenced using a 620-gene panel. Data were analyzed with the MH Guide™ software, a CE-marked medical device. Primary outcome was presence of actionable mutations (drugable targets, effective or ineffective treatments, toxicity markers) and treatment recommendations by the software. Secondary outcomes were implementation of recommendations in patientś treatment and overall survival, stratified for those receiving versus not receiving personalized treatment.

Results: 40 patients were enrolled, 35 tumor samples were analyzed and interpretable results were obtained from 31 patients. At least 1 relevant biomarker was found in all cases. We found mutations in KRAS (n = 24), TP53 (n = 17), SMAD4 (n = 2), BRCA1/2 (n = 4; 3 germline), CDKN2A (n = 9), ATM (n = 6; 3 LOF), APC (n = 4), and MSH3 (n = 15, 1 germline). MH Guide made treatment recommendations in 30/31 cases: PARP-inhibitors (n = 26), MEK/RAF inhibitors (n = 20), CDK inhibitors (n = 9), other kinase inhibitors (n = 3), mTOR inhibitors (n = 2). The molecular tumor board (MTB) agreed in 26 cases, 2 patients received other second-line line therapy and 2 BSC. 3 patients died before and 2 during analysis, 1 prior to the MTB, 2 before start of therapy and 3 shortly after. Toxicity markers were found in 27/31 patients: Platinum (XRCC1 n = 16; 5 homozygous, TPMT n = 1; MUTYH n = 3), paclitaxel (CYP2C8 n = 2), gemcitabine (CDA n = 4; 1 homozygous) and 5-FU (DPYD n = 1), doxorubicin (G6PD n = 1), docetaxel (GSTP1 n = 2), sunitinib (ABCG2 n = 2), irinotecan (ERCC2, n = 6; 5 homozygous, UGT1A1 n = 1). Roughly half of all patients had adverse event CTCAE grade $\geq$ 3 during previous treatment. Chemotherapy for which they had a toxicity marker was given to 13/27 patients and 7 had toxicity of any grade associable with the marker.

Conclusion: Evidence-based personalized treatment recommendation in PDAC is feasible in a clinical setting and molecular stratification of PDAC patients routinely leads to recommendation of off-label use of registered drugs. Toxicity markers for agents commonly used in PDAC treatment are present in a majority of patients and frequently correlate with observed adverse events. The clinical significance of toxicity markers needs further investigation.

Disclosure: ML received honoraria from Abbott, Mylan and Nordmark and has been an advisor to Molecular Health and Pharmcyte.

OP022 STATIN USE AND THE RISK OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CHRONIC HEPATITIS B

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Introduction: Statins have pleiotropic effects including pro-apoptic, anti-angiogenic and immunomodulatory effects, which may exert chemoprevention. Several observational studies have suggested that statins may prevent hepatocellular carcinoma (HCC), but have not yet been fully studied.

Aims and Methods: This study aimed to investigate the association between the use of statins and the risk of HCC in chronic hepatitis B virus infected patients. A hospital-based retrospective study was conducted from 7,714 chronic hepatitis B infected patients enrolled between January 2008 and December 2012. Primary outcome was development of HCC. Statin use was defined when patients had taken statin at least 30 days during follow-up. The association between statin use and the risk of HCC were analyzed.

Results: During a median follow-up of 7.2 years (min-max: 0.5–9.7 years), HCC was newly developed in 702 patients (9.1%). Patients who used statin showed lower cumulative incidence of HCC development compared to patients who did not use statin (8.0% vs 2.2% at 5-years, p < 0.001). When stratified according to cirrhosis status, 5-years cumulative incidence rate of HCC was higher for those who did not use statin compared to those who used statin among patients with cirrhosis (20.2% vs. 5.4%, p = 0.038, n = 1,771), patients without cirrhosis (3.8% vs. 1.9%, p = 0.003, n = 5,578) and patients with missing information on cirrhosis status (7.6% vs. 0%, p = 0.048, n = 365), respectively.

Conclusion: Statin use was associated with reduce risk for HCC development in chronic hepatitis B patients, regardless of cirrhosis status. Statin treatment may decrease HCC risk, which warrants prospective validation.

Disclosure: Nothing to disclose

OP023 MORTALITY, CAUSES OF DEATH AND MALIGNANCIES IN PATIENTS WITH CHRONIC HEPATITIS C: A NATIONWIDE REGISTRY STUDY IN FINLAND

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Introduction: Hepatitis C is associated with increased mortality caused by end-stage liver disease and development of hepatocellular cancer. The estimated number of persons dying from end-stage HCV infection in 2015 was 399,000 globally (1). In addition, HCV-infection is associated with extrahepatic manifestations such as chronic kidney disease and increased risk of for type II diabetes and coronary heart disease (2). In Finland, annually some 1100 new cases of HCV are diagnosed (3) and the number persons with HCV in Finland is some 22,000 with prevalence of 0.3% in the population (4). Some 80% are persons using intravenous drugs who are HCV-positive (4).

Aims and Methods: To assess the mortality, causes of death and associated malignancies with hepatitis C based on nationwide data.

Results: In total 10,058 individuals were included into the analysis, comprising 42,027 person years. Of all the cases 63% were males, 53% were 0-29 years old, 44% 30-59 years and 3.6% older than 60 years. During the study period 800 persons died (8%). For the whole study period HCV-infected persons had markedly increased risk for death: for the whole cohort SMR was 9.43 (95% CI 8.79–10.0), for those 0-29 years, 19.16 (95% CI 16.72–21.76), for 30-59 years 10.56 (95% CI 9.60–11.57), and for those over 60 years 4.37 (95% CI 3.67–5.13), respectively. Main causes of death are summarized in Table 1. During the first year after diagnosis the SMR for men under 30 years for accidental poisonings was 72.17 (95% CI 47.95–104).

Conclusion: Persons with hepatitis C infection have significantly increased mortality, mostly due to accidents and violence (45.6%), intoxications (22%), suicides (13%), infections, cerebrovascular disease and alcohol-related disease (17%), usually associated with iv drug and alcohol use. The results suggest that scaling up treatment of hepatitis C in PIWD is unlikely to have any impact on their mortality.

ICD-10	Diagnosis	Age, years	SMR (95%CI) Whole follow up	SMR (95%CI) <1 year after dg
A00-B99	Infections	0-29	49.7 6.01–179	65.0 1.64–362
		30-59	41.1 20.5–73	71.8 19.6–183
		60+	10.6 1.28–38.3	23.9 0.60–132
C22	Hepatocellular cancer	30-59	8.03 0.97–29.0	19.5 0.49–108
		60+	13.3 4.33–31.12	38.8 7.99–113
E10-E14	Diabetes	30-59	7.14 2.32–16.7	14.8 1.79–53.6
		60+	9.46 1.95–27.6	15.4 0.39–86.0
X40-X44, X46-X49	Accidental poisonings	0-29	47.3 37.4–59	71.1 48.7–100
		30-59	39.1 31.5–47.9	39.0 23.1–61.6
		60+	57.3 18.6–133	57.0 1.44–317
	Alcohol-related diseases	0-29	28.0 14.0–50.1	61.8 24.9–127
		30-59	15.0 12.3–18.0	18.4 12.1–26.7
		60+	10.11 5.7–16.7	16.3 5.30–38.1

[Risk of death in persons infected with hepatitis C in Finland 2008-2016.]

Disclosure: Nothing to disclose

References

1. WHO. GLOBAL HEPATITIS REPORT, 2017. http://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/.
2. Younossi Z, Park H, Henry L, et al. Extrahepatic Manifestations of Hepatitis C: A Meta-analysis of Prevalence, Quality of Life, and Economic Burden. *Gastroenterology* 2016; 150: 1599–1608.
3. https://thl.fi/ttr/gen/rpt/tilastot.html 4. https://www.julkari.fi/handle/10024/125343.

MONDAY, OCTOBER 22, 2018   10:30−12:00
**Risk factors and risk assessment of GI bleeding –
Room K_____**

**OP024 RISK OF BOTH UPPER AND LOWER GASTROINTESTINAL
BLEEDING ASSOCIATED WITH LOW-DOSE ACETYLSALICYLIC
ACID AND PROTON PUMP INHIBITORS AMONG ~400,000
INDIVIDUALS IN ROUTINE GENERAL PRACTICE IN THE UNITED
KINGDOM**

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Introduction: Benefits of low-dose acetylsalicylic acid (ASA) in preventing ischae-
mic vascular events need balancing against gastrointestinal (GI) bleeding risks.
Estimates of proton pump inhibitors (PPIs) effects in reducing ASA-associated
upper but not lower GI bleeds (UGIB/LGIB) from the same study population
are scarce.
Aims and Methods: We used a population-based primary care database of elec-
tronic medical records from the United Kingdom to quantify low-dose ASA-
associated UGIB and LGIB risks with/without PPIs. Among persons aged 40-84
years from 2000-2012, 199,049 new users of low-dose ASA (75-300 mg/day) were
each matched to a non-user by age, sex, time since study entry, and general
practitioner visits in the previous year (proxy for general health). Individuals
(mean age at entry, 64 years) were followed (max. 14 years, median 5.4 years)
to identify incident UGIB/LGIB cases, with validation by manual review of
patient records and linked hospital data. Nested case-control analyses were con-
ducted using cases and controls from both cohorts; controls were frequency-
matched to cases by age, sex and calendar year. Current low-dose ASA or PPI
use was defined as use 0-30 days before the index date (UGIB/LGIB date for
cases, random date for controls). Adjusted relative risks (RRs) with 95% con-
fidence intervals (CIs) were calculated.
Results: There were 1843 UGIB and 2763 LGIB cases; RRs for current use of
low-dose ASA and/or PPIs are shown in the Table. Increased risks were seen for
UGIB (RR = 1.55) and LGIB (R = 2.06) with current low-dose ASA. Compared
with PPI use discontinued >1 year before the index date (suitable reference
group to minimize indication bias), current PPI use of >3 months duration
reduced UGIB risk by 21% (RR = 0.79) but had no effect on LGIB risk
(RR = 1.07) irrespective of low-dose ASA use. Compared with current low-
dose ASA plus past PPI use (>30 days), concomitant PPI and low-dose ASA
therapy reduced UGIB risk by 34% when used for >1 month (RR = 0.66);
UGIB risk increased with shorter-term use (RR = 2.82). However, this increased
risk with short-term (≤1 month) PPI use was lower when PPIs were initiated on/
before the start of ASA therapy (RR = 1.70) than afterwards (RR = 3.35).
Neither short-term nor longer-term PPI use appreciably changed on LGIB risk
among current low-dose ASA users.
Conclusion: Our results suggest that maintaining PPI use (>1 month) reduces
UGIB risk. Prescribing PPIs before starting low-dose ASA and efforts to
improve adherence with PPIs may help reduce UGIB risk. The increased
UGIB risk seen after start of PPI therapy among low-dose ASA users is due
to protopathic bias from first bleeding symptoms prompting PPI use.

	Adjusted RR (95% CI)	
	UGIB	**LGIB**
Low-dose ASA		
Never use (reference)	1.0 (-)	1.0 (-)
Current use	1.55 (1.34–1.80)	2.06 (1.83–2.34)
PPI		
Discontinued use (>1 year before index date; reference)	1.0 (-)	1.0 (-)
Current use ≤3 months duration	2.22 (1.68–2.94)	1.38 (1.09–1.74)
Current use >3 months duration	0.79 (0.65–0.96)	1.07 (0.93–1.24)
Concomitant low-dose ASA and PPI		
Current use of low-dose ASA + past use of a PPI (> 30 days before index date; reference)	1.0 (-)	1.0 (-)
Current use of low-dose ASA + current use of a PPI ≤1 month duration)	2.82 (1.69–4.71)	1.12 (0.73–1.71)
Current use of low-dose ASA + current use of a PPI >1 months duration)	0.66 (0.51–0.85)	0.98 (0.81–1.17)
Current use of low-dose ASA + current use of a PPI ≤1 months duration) with PPI prescribed after start of ASA therapy	3.35 (1.85–6.06)	1.16 (0.73–1.84)
Current use of low-dose ASA + current use of a PPI ≤1 months duration) with PPI prescribed on/before start of ASA therapy	1.70 (0.65–4.45)	0.97 (0.38–2.53)

*[Table. RRs (95% CI) of UGIB/LGIB associated with current use of low-dose
ASA, PPIs and concomitant use of both (nested case-control analysis).]*

**OP025   ACUTE UPPER GASTROINTESTINAL BLEEDING IN
PATIENTS USING ANTITHROMBOTIC AND NON-STEROIDAL
ANTI-INFLAMMATORY THERAPY: CONTRIBUTING FACTORS
AND OUTCOMES**

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Introduction: The most common causes of acute nonvariceal upper gastrointest-
inal bleeding (AUGIB) are peptic ulcer bleeding and haemorrhagic gastritis. The
use of non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose acetylsa-
licylic acid (LDA) are known risk factors for both. COX-2 selective NSAIDs are
considered safer in terms of bleeding.
Aims and Methods: To identify patients with AUGIB who use LDA and
NSAIDs, determine the severity of bleeding, outcomes and potential risk factors
for adverse outcomes. Retrospective, prospective analysis of all patients over 18
years of age consecutively admitted for AUGIB in a tertiary centre in Latvia –
Riga East Clinical University Hospital from November 2013 to December 2014.
Data was collected regarding history of drug use, bleeding-related interventions,
length of hospital stay and outcomes. Forrest classification was used to evaluate
the severity of bleeding, data was entered into the database with consecutive
statistical analysis using SPSS 20.0.
Results: 236 patients with UGIB were enrolled (138 (58%) men, 98 (42%)
women, mean age 62 ± 17.36 years). Peptic ulcer disease (PUD) was the most
common diagnosis (n = 180, 73%). Out of all patients, 90 (38.1%) were NSAIDs
users (more often women (46/44)), 27 (11.4%) used oral anticoagulants (mean
age 73 ± 11.3 years) and 52 (22%) used alcohol (mean age 47 ± 11.61 years).
NSAIDs use was associated with more frequent PUD bleeding (r = 0.347,
p < 0.001). Out of 26 patients with Forrest I type (IA and IB) peptic ulcer
bleeding, 12 (46%) used NSAIDs, 9 (34.6%) were on LDA therapy, 3 (11.5%)
were alcohol users. The most commonly used NSAIDs were diclofenac (n = 24,
26%) and ibuprofen (n = 8, 9%). There was only 1 patient on COX-2 selective
NSAID therapy, who was admitted with Forrest II B bleeding. 108 patients
(45.7%) were hospitalised in intensive care unit, most often with Forrest IIB
PUD bleeding – 36 (33.3%). Transfusion of red blood cells was required in
133 (56.3%) cases, fresh frozen plasma in 106 (44%) cases and cryoprecipitate
in 39 (16.5%) cases. Surgery was performed in 37 (15.6%) patients. Most of the
patients requiring surgical intervention were on NSAID therapy (22/37,
p = 0.004, *Pearson Chi-Square*). Bleeding-related in-hospital death occurred in
24 (10%) cases, mostly in patients with recurrent PUD bleeding. There was a
statistically significant age difference between patients who recovered and those
who died (n = 212, 61 (± 17.14) vs. n = 24, 78 (± 10.04), p < 0.001). The differ-
ence in length of hospital stay between NSAIDs users and non-users was margin-
ally significant (p = 0,058, *Mann-Whitney Test*).
Conclusion: 1. LDA and NSAIDs remain the most common risk factors for
AUGIB and are associated with the need for surgical intervention. 2. Bleeding-
related mortality and need for surgery during hospitalization remain high. 3.
Important prophylactic measures should include patient education about risks,
adequate gastroprotection and minimisation of alcohol use.
Disclosure: Nothing to disclose

**OP026   NO DIFFERENCES IN GI BLEEDING RISK BETWEEN
CLOPIDOGREL-, TICAGRELOR- OR PRASUGREL-BASED DUAL
ANTIPLATELET THERAPY AFTER PERCUTANEOUS CORONARY
INTERVENTION**

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Introduction: Dual antiplatelet therapy (DAPT) decreases major adverse cardiovascular events after a percutaneous coronary intervention (PCI). New and potentially more effective antiplatelet agents such as ticagrelor or prasugrel combined with aspirin (ASA) are being prescribed preferentially to younger and healthier patients based on the potential higher risk of GI bleeding. However, very few data are available concerning the risk and type of GI bleeding associated with these new compounds when compared to classical DAPT with clopidogrel in common clinical practice.

Aims and Methods: We aimed to determine the risk and type of major and minor GI events in patients with DAPT and type of DAPT, and to analyze PPI therapy regimens during and after DAPT withdrawal. This was a retrospective observational cohort study of patients who started DAPT after a PCI from January 2015 to December 2016. The follow-up period was censored either after 15 months of initiation of DAPT, when a major (hospitalization) GI event occurred or when DAPT was discontinued. Development of anemia during the follow-up was considered as a minor GI event. Statistical analyses were performed using SPSS software version 22.0.

Results: 710 patients were included (mean age 66.9 ± 12.6 years; 79% males); 53% (376/710), 36.6% (260/710), and 10.4% (74/710) of patients were on DAPT with either clopidogrel, ticagrelor or prasugrel, respectively. There were statistically significant differences in baseline characteristics between the groups, indicating that younger and healthier people received therapy with the new antiplatelet agents (table 1). Most patients (661/710; 93.1%) received PPI therapy while DAPT was active and after withdrawal (582/661); 88%. 32 patients (4.5% (32/710)) developed a major GI bleeding and 18.9% (134/710) developed anemia. Lower GI bleeding was more frequent than upper GI bleeding (78.1% (25/32) vs 18.8% (6/32)) and 3.1% (1/32) had obscure GI bleeding. There were no differences in the occurrence of major GI bleeding (5.1% vs 3.9%, p = 0.475), non-gastrointestinal bleeding (10.4% vs 10.5%, p = 1.000), ischemic vascular events (13.6% vs 9.6%, p = 0.103) or death (4.8 vs 2.1%, p = 0.066) between patients on DAPT with clopidogrel or new antiplatelets; however, anemia was most common in the group of DAPT with clopidogrel (21.8% vs 15.6%, p = 0.035). After adjusting for main confounding factors, including age, comorbilities, anticoagulant therapy and GI risk, there was no differences in the risk of GI events between groups (clopidogrel vs new agents (overall GI events HR: 0.839 (0.579–1.215), major GI events HR: 1.050 (0.448–2.461), minor GI events HR: 0.801 (0.531–1.207)).

Conclusion: DAPT is more frequently associated with lower than upper GI bleeding. Prasugrel- or ticagrelor-based DAPT was not associated with increased risk of either GI (upper or lower) bleeding when compared to clopidogrel-based therapy. The potential benefits of the new antiplatelets could be extended to all patients undergoing PCI based on GI risk factors.

	Total n = 710	Clopidogrel n = 376	New compounds n = 334	p value
Gender (men)	561 (79.0%)	284 (75.5%)	277 (82.9%)	0.016
Age (median ± ED)	66.9 ± 12.6	71.3 ± 11.8	61.9 ± 11.7	<0.001
Charlson index media ± ED	3.2 ± 2.6	4.3 ± 2.6	1.9 ± 1.9	<0.001
Anticoagulants	81 (11.4%)	75 (19.1%)	9 (2.7%)	<0.001
PPI	661 (93.1%)	344 (91.5%)	317 (94.9%)	0.077
Previous GI risk	114 (16.1%)	76 (20.2%)	38 (11.4%)	0.001

[Table 1]

Disclosure: Nothing to disclose

OP027   OUTCOMES FOR UPPER GASTROINTESTINAL BLEEDING IN ELDERLY PATIENTS: THE EXPERIENCE OF A TERTIARY UNIVERSITY HOSPITAL

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Introduction: Upper gastrointestinal bleeding (UGIB) is one of the main causes of hospital admission and urgent endoscopy in Gastroenterology departments and represents a true emergency, associated with significant morbidity, mortality and healthcare costs. Compared with prior decades, patients with UGIB are older. Current epidemiological data show that elderly patients tend to have comorbidities, and they experience worse outcomes than non-elderly UGIB patients (1).

Aims and Methods: The aim of our study is to compare elderly patients (age 65 and older) (EPs) presenting with UGIB with non-elderly patients (NEPs) as well as to identify predictors of outcomes: in-hospital and delayed 6-months mortality.

Ours was a prospective cohort study on consecutive patients with UGIB (variceal and non variceal) treated in "Virgen de las Nieves" University Hospital from January 2013 to December 2017. All patients underwent upper endoscopy, and information regarding clinical and biochemical data, procedures, and outcomes for 6 months after admission were collected. Clinical outcomes documented were in-hospital and delayed 6-months mortality, rebleeding and delayed 6-months hemorrhagic and cardiovascular events. Descriptive inferential and multivariate logistic regression models were carried out.

Results: 519 patients with a diagnosis of upper gastrointestinal bleeding were included, 279 EPs and 240 NEPs. EPs differed from NEPs in comorbidities (82.1% vs. 37.1%, p < 0.001) and in antiplatelets (31.2% vs. 5.4%, p < 0.001), anticoagulants (26.9% vs.5%, p < 0.001) and NSAIDs (16.1% vs. 30.8%, p < 0.001) use. No differences were found in the need for endoscopic, interventional radiology and surgery procedures; blood units transfusions, days of hospital stay, in-hospital rebleeding and in-hospital mortality.

Independent predictors for in-hospital mortality in EPs were onset as hematemesis (HR 2.750; 95% CI 1.105–6.846; p = 0.030), rebleeding (HR 6.551; 95% CI 2.731–15.719; p < 0.001) and antiplatelets use (HR 0.297; 95% CI 0.084–0.990; p = 0.046). However, elderly patients presented a higher rate of delayed 6-months mortality (15% vs. 7.7%, p = 0.016), 16.7% were related with GI bleeding. Independent predictors for this event in EPs were albumin (HR 0.426; 95% CI 0.426; p = 0.026) and creatinine levels (HR 1.927; 95% CI 1.178–3.150; p = 0.009).

Moreover, the group of elderly patients had a higher rate of delayed hemorrhagic (14.8% vs. 2.9%, p < 0.001) and cardiovascular events (24.5% vs .12.6%).

Conclusion: In this study we demostrate that EPs are more complex regarding to comorbidities and antiplatelets use; however, they don't have worse in-hospital outcomes (need of blood transfusions, days of hospitalizarion, rebleeding and mortality). In fact, antiplatelets use was a independent protective factor for in-hospital mortality. This is in accordance with recent reports showing significantly lower all-cause and cardiovascular mortality rates in patients with UGIB who do not discontinue antiplatelet agents. Practicing clinicians should consider risk and benefits of discontinuing aspirin (2).

On the contrary, EPs group had poor delayed ouomes. This finding is in concordance with ours previous reports stating that the misbalance caused by UGIB on frail patients can entail a delayed mortality even months after the acute episode (3). Serum creatinine and albumin level were independent risk factors of delayed mortality and can be useful prognostic indicators. Further validation in prospective studies is needed.

Disclosure: Nothing to disclose

References

1. Kawaguchi K, Kurumi H, Takeda Y, et al. Management for non-variceal upper gastrointestinal bleeding in elderly patients: the experience of a tertiary university hospital. *Ann Transl Med.* 2017; 5: 181.
2. Derogar M, Sandblom G, Lundell L, et al. Discontinuation of low-dose aspirin therapy after peptic ulcer bleeding increases risk of death and acute cardiovascular events. *Clin Gastroenterol Hepatol.* 2013; 11: 38–42.
3. Jiménez-Rosales R, Valverde-López F, Vadillo-Calles F, Martínez-Cara JG, López de Hierro M, Redondo-Cerezo E. Inhospital and delayed mortality after upper gastrointestinal bleeding: an analysis of risk factors in a prospective series. *Scand J Gastroenterol.* 2018 Mar 26: 1–7. [Epub ahead of print].

OP028   SHOULD WE BE USING THE SHOCK INDEX TO ASSESS PATIENTS PRESENTING WITH UPPER GI BLEEDING?

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Introduction: Upper GI bleeding (UGIB) is a common cause of hospitalisation. The admission Rockall (ARS), Glasgow-Blatchford (GBS) and AIMS65 scores are validated pre-endoscopy risk assessment tools. The UK NCEPOD report into UGIB used Shock Index (SI = pulse/systolic blood pressure) to assess risk of poor outcome. However existing data on SI are mostly from trauma settings. The limited data in UGIB suggest SI > 0.7, or SI > 1 may predict need for endoscopic therapy or mortality. Our aim was to assess the accuracy of SI to predict clinical outcomes after UGIB.

Aims and Methods: We collected demographic, clinical and laboratory data on consecutive patients admitted to 6 large hospitals across the UK, USA, Denmark, Singapore, and New Zealand over 12 months. We compared the SI, ARS, GBS, AIMS65 and the new international bleeding risk score (IBRS) in their ability to predict need for endoscopic therapy, need for major transfusion (≥4 units PRBCs) and death. We also assessed score thresholds for identifying patients at low or high risk of death, and whether adding the SI as a parameter to the IBRS improved its predictive accuracy.

Results: 3012 patients (mean age 65yrs; 58% men) were studied. 574 (19%) required endoscopic therapy and 396 (13.3%) needed major transfusion. 30-day mortality was 7%. This table compares AUROCs of the scoring systems for predicting outcomes

Scoring System	Outcome (AUROC)		
	Endoscopic Therapy	Major (≥4units) Transfusion	30-day Mortality
SI	0.606	0.655	0.611
GBS	0.747*	0.836*	0.692†
AIMS65	0.621	0.692	0.785*
ARS	0.613	0.658	0.759*
IBRS	0.675*	0.726*	0.863*

[*p < 0.001 and †p = 0.001 when compared to SI]

For predicting need for endoscopic therapy or major transfusion, SI had lower accuracy than GBS and IBRS, but similar to AIMS65 and ARS. In contrast to SI≥1, GBS≥7 correctly identified the majority of patients needing endoscopic therapy (80% vs 21%; p < 0.001).

For predicting 30-day mortality, SI had lower AUROC than all other scores. GBS≤1 was superior to SI < 0.7 at predicting low-risk of death (mortality rate 0.35% vs 5.2%; p < 0.001). Patients with S≥I1 had lower mortality than those with IBRS≥8 (15.3% vs 34.1%; p < 0.001) and IBRS correctly identified a greater proportion of those who died as being high risk (49% vs 28%; p < 0.001). Adding SI to the IBRS did not improve its predictive accuracy (AUROC 0.864 vs 0.863).

Conclusion: Existing pre-endoscopy risk scores are superior to the SI in predicting need for endoscopic therapy, major transfusion or mortality after UGIB. Most patients who reach these important clinical endpoints are classified as low risk by SI.

Disclosure: Due to be presented at the British Society of Gastroenterology national meeting in June 2018.

OP029   USE AND COMPARISON OF THE STRATE AND GLASGOW BLATCHFORD SCORES FOR RISK STRATIFICATION OF PATIENTS WITH ACUTE LOWER INTESTINAL BLEEDING

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Introduction: Acute Lower Intestinal Bleeding (ALIB) has variable presentation ranging from minor haemorrhoidal bleeding to life threatening diverticular haemorrhage. Risk stratification and identification of high-risk patients requiring early intervention is difficult but important for good clinical outcome. Similarly, low-risk patients could potentially be discharged early for out-patient management. There is paucity of evidence to support a single clinical tool to identify these patients. The STRATE score was developed for this purpose and using the Blatchford Score (GBS) has also recently been proposed.

Aims and Methods: The aim of our study was to compare the STRATE and GBS scores in risk stratification in patients with ALIB and the identification of high-risk patients requiring urgent intervention. A retrospective cohort study was conducted in a single tertiary hospital with adult patients with ALIB who presented between January 2015 and September 2017. Admission data was analysed to calculate STRATE and GBS scores and divide them into low, moderate and high-risk groups. For the STRATE score low risk was defined as a score of 0 and high-risk as a score > 3. For the GBS, a score > 6 was considered high risk and a score of 0-1 as low risk. Need for intervention, details of intervention performed and any complications were also collated.

Results: 198 patients were identified in the study period with a diagnosis of ALIB. 55 were excluded due to insufficient data to complete the analysis. 143 patients were divided into low, moderate and high-risk groups using the 2 scores. There were 62 females and 81 males in our cohort with a mean age of 73 years. The STRATE score identified 27 patients (18%) as high-risk. 11 patients had therapeutic intervention in this group (37%) with 10 patients undergoing angiography and embolisation. In comparison, the low-risk group (n = 5) did not require any urgent treatment. GBS identified 61 patients as high-risk with 19% requiring urgent intervention. Only 1 patient in the low-risk group for GBS (n = 31) required early treatment. Only 20% of our cohort underwent in patient colonoscopy and no significant endoscopic therapy was required. 2 patients required surgery for ischaemia complicating embolisation.

Conclusion: The STRATE and GBS scores are similar and useful in identifying a low-risk cohort of patients who may only require out-patient management. Similarly, they compare well in identifying a high-risk cohort who require early, aggressive intervention. An approach similar to upper gastro-intestinal bleed could be considered for risk stratification with GBS. This would separate patients with ALIB into high and low-risk groups with high-risk defined as a score greater than 1. This may further improve the assessment.

The management of patients in the moderate-risk group is less well defined with either score. Both scoring systems rely on assessment of clinical parameters within the first 4 hours. Serial monitoring and assessment of scores in the first 24 hours may be beneficial in this cohort. The study is limited by its retrospective design and limited numbers in our cohorts. Further prospective studies are required to determine the ideal risk predictor tools and management pathways in ALIB.

Disclosure: Nothing to disclose

SOP1   A RANDOMIZED CONTROLLED TRIAL COMPARING PERORAL ENDOSCOPIC MYOTOMY (POEM) VERSUS LAPAROSCOPIC HELLER MYOTOMY IN THE TREATMENT OF ACHALASIA

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Introduction: Achalasia cardia (AC) is a primary motor disorder of the esophagus characterized by insufficient lower esophageal sphincter (LES) relaxation and absence of esophageal peristalsis. Its treatment may be endoscopic, pharmacological or surgical. Currently, the laparoscopic Heller myotomy (LHM) is the gold standard treatment but the peroral endoscopic myotomy (POEM) has gained popularity because of its safety and efficacy profile. A recent systematic review and meta-analysis showed POEM to be as effective and safe as LHM for achalasia. However, to date, few randomized clinical trials (RCTs) prospectively compared endoscopic and surgical approach.

We conducted a RCT to assess the efficacy and safety of POEM versus LHM in patients with achalasia.

Aims and Methods: Patients with manometric findings consistent with AC and no obstructive cause without prior therapy were randomly assigned to either LHM or POEM from a single tertiary center. Demographic data, procedure info, Eckardt score, LES pressure, follow-up reflux esophagitis, adverse events and length of stay were collected. Student T's test, Chi square and Logistic regression analyses were conducted.

Results: 40 patients were enrolled (26 M, mean age 48.5) from Mar 16 to Jan 2017. We performed POEM in 20 patients and LHM in other 20. Both groups presented significant reduction in Eckardt scores compared to baseline (1.07 vs 7.87 POEM, p < 0.0001 ; 0.44 vs 8.12 LHM, p < 0.00001) and in LES pressure (12.89 vs 27.03 in POEM, p < 0.00001; 10.03 vs 24.01 in HM, p < 0.00001) at 1 year follow-up. Adverse events were similar in both group (POEM vs LHM) and consisted of empyema (n = 0 vs 1). Mucosal defects requiring clipping were needed in 3 POEM patients. There were no statistical difference between groups regarding Eckardt score and LES pressure reduction, and AEs rate. Patients undergoing POEM were more likely to develop erosive esophagitis (60% vs. 10%, p < 0.001). Operative time was significantly lower for POEM (p < 0.001). There were no differences between POEM and LHM in length of hospital stay (p = 0.173).

Conclusion: POEM as effective and safe as LHM for the treatment achalasia but carries shorter duration of procedure. POEM patients present higher esophagitis rate.

Disclosure: Nothing to disclose

References

1. Vaezi MF, Pandolfino JE, Vela MF. ACG clinical guideline: diagnosis and management of achalasia. *Am J Gastroenterol.* 2013; 108: 1238–49; quiz 50.
2. Ramchandani M, Nageshwar Reddy D, Nabi Z, Chouhan R, Bapaye A, Bhatia S, Mehta N, Dhawan P, Chaudhary A, Ghoshal U, Philip M, Neuhaus H, Deviere J, Inoue H. "Management of Achalasia cardia: Expert consensus statements". *J Gastroenterol Hepatol.* 2018 Jan 29.
3. Inoue H, Minami H, Kobayashi Y et al. Peroral endoscopic myotomy(POEM) for esophageal achalasia. *Endoscopy* 2010; 42: 265–271.
4. Sharata A, Kurian AA, Dunst CM et al. Peroral endoscopic myotomy(POEM) is safe and effective in the setting of prior endoscopic intervention. *J Gastrointest Surg* 2013; 17: 1188–1192.
5. Efficacy of peroral endoscopic myotomy (POEM) in the treatment of achalasia: a systematic review and meta-analysis.
6. Talukdar R, Inoue H, Nageshwar Reddy D. Efficacy of peroral endoscopic myotomy (POEM) in the treatment of achalasia: a systematic review and meta-analysis. *Surg Endosc.* 2015 Nov; 29(11): 3030–46.
7. Vaezi MF, Felix VN, Penagini R, Mauro A, de Moura EG, Pu LZ, Martínek J, Rieder E. Achalasia: from diagnosis to management. *Ann N Y Acad Sci.* 2016 Oct; 1381(1): 34–44.

SOP2   COILS + CYANOACRYLATE VS. COILS ALONE IN THE ENDOSCOPIC ULTRASOUND-GUIDED MANAGEMENT OF GASTRIC VARICES [GOV-II AND IGV-I]: A RANDOMIZED, CONTROLLED THERAPEUTIC TRIAL

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Introduction: Bleeding from gastric varices (GV) is associated with high mortality. Injection of cyanoacrylate (CYA) using standard gastroscopes (SG) presents higher hemostasis and lower re-bleeding rates compared to band ligation or sclerotherapy. Nevertheless, CYA-SG is associated with some adverse events. EUS-guided coils alone technique presents less adverse events, but it shows lower obliteration rate compared with EUS-guided CYA alone, with a

Abstract No: SOP2
Table 1: Baseline characteristics, varices characteristics, therapeutic approach, immediate and mediate outcomes

A. Baseline characteristics				*B. Therapeutic approach characteristics, immediate and mediate outcomes*			
	EUS-guided Coils + CYA (n = 30)	EUS-guided Coils alone (n = 29)	*p-value*		EUS-guided Coils + CYA (n = 30)	EUS-guided Coils alone (n = 29)	*p-value*
Age (years), mean ± SD	61.77 ± 7.8	61.59 ± 12.5	0.947	No. of placed coils, median (range)	2 (1–3)	3 (1–7)	0.009
Cirrhosis etiology (NASH/Alcohol)	7/23	9/20	0.710	CYA volume (ml), median (range)	1.80 (1.20–2.40)	n/a	n/a
Child-Pugh Score, median (range min-max)	6 (5–9)	6 (5–11)	0.362	Complete obliteration, n (%)	30 (100.0)	26 (89.7)	0.112
MELD Score, median (range)	9 (6–13)	9 (6–30)	0.951	Varices disappearance, n (%)	26 (86.6)	4 (13.8)	<0.001
Indication as 1st/2nd Prophylaxis	3/27	4/25	0.707	Re-bleeding, n (%)	2/30 (6.6)	5/29 (17.2)	0.454
Indication due to active bleeding, n (%)	1/27 (3.7)	4/25 (16.0)	0.183	Varices Reappearance, n (%)	3/26 (11.5)	1/4 (25.0)	0.173
Varix type (GOV-II / IGV-I)	19/11	12/17	0.153	Re-intervention, n (%)	4/30 (13.3)	8/29 (27.6)	0.300
Varix diameter (mm), n (%)	21 (10–32)	25 (10–38)	0.329	Adverse events, n (%)	2/30 6.7)	1/29 (3.4)	1.000

significantly higher health care cost. To date, there is no data regarding comparison between EUS-guided coils+CYA vs. EUS-guided coils alone.
Aims and Methods: We aim to compare efficacy and safety of coils+CYA vs. coils alone in the EUS-guided management of GV II and IGV I.
Single-center, randomized, controlled trial (March 2016 – June 2017). Study protocol was approved by Institutional Review Board. Written informed consent was obtained. Selection criteria: 18-80 yo, hepatic cirrhosis with endoscopic evidence of GOV II or IGV I (Sarin classification), >50000 platelets/mL, INR≤2, not into Hepatorenal Syndrome. After randomization, two groups were formed. EUS procedure was performed by a 1° endoscopist, blind to patients' history. EUS follow-up was performed 3 months later by a 2° endoscopist, blind to 1° EUS. Efficacy definition: EUS-Doppler evidenced GV obliteration, immediate GV disappearance, and later reappearance. Safety definition: complications and re-bleeding rate in a 30 days-follow up. Sample size considered 5% α-error, β-error 20%, and success rate for complete obliteration after 1° EUS-guided coils vs. EUS-CYA procedure (82% & 53%) described by Romero-Castro et al. Differences between groups were established through respective hypothesis testing; p < 0.01 was considered to be statistically significant. Endpoints were estimated through relative risk (RR). Analyses were performed using R v3.4.2.
Results: 59 patients were successfully included: 30 to EUS-guided coils+CYA, 29 to EUS-guided coils alone group. There were no statistical differences in baseline characteristics between groups, although a higher number of coils were necessary to manage bleeding in coils alone group (p < 0.01) (table 1A). Compared to coils alone, coils+CYA technique exposes >6 times immediate GV disappearance (RR 6.3, 95% CI 2.5–15.8; p < 0.01), with 10% more cases of complete obliteration, 10% less re-bleeding, preventing 14% GV reappearance and saving 14% re-interventions. There were no difference regarding adverse events in both groups (table 1B).
Conclusion: Due of a significant capability for disappearing GV, higher obliteration rate, lower re-bleeding, and GV reappearance prophylaxis; compared with EUS-guided coils alone, EUS-guided coils+CYA represent an effective technique in the management of GOV II and IGV I. Meanwhile, EUS-guided coils+CYA results to be as safe as EUS-guided coils alone.
Disclosure: Nothing to disclose

resulting in 67 identified genus. Associations between the gut microbiota and IBS and BS-2w were analyzed by logistic regression, and items in VAS-IBS by general linear model, adjusting for age, sex, physical activity and smoking. We further studied if the associations were modified by self-perceived stress.
Results: Of all study participants 15% reported having IBS, 19% having BS-2w, and 47% being stressed. IBS and BS-2w were strongly correlated (r = 0.6), and these subjects were more often females, were younger, had lower physical activity level, were more often smokers and users of probiotics, were more likely to be stressed and suffered from worse psychological well-being, compared to the healthy subjects. The fecal samples of IBS were significantly enriched with *Collinsella* (p = 0.030), *Dorea* (p = 0.019), *Fusobacterium* (p = 0.027), *Streptococcus* (p = 0.008) and *Streptophyta* (p = 0.015), and had significantly less *Barnesinellaceae* (p = 0.018), *Butyricimonas* (p = 0.022), *Christensenellaceae* (p = 0.010), *Facealibacterium* (p = 0.040), *Lahchnobacterium* (p = 0.043), *Rikenellaceae* (p = 0.009), and *SHA98* (p = 0.001). Individuals who reported having bowel symptoms last 2 weeks were significantly enriched with *Blautia* (p < 0.001), *Dorea* (p = 0.013), *Ruminococcus* (p = 0.008), and *Streptophyta* (p = 0.004), and had significantly less *Christensenellaceae* (p = 0.003) and *SHA98* (p = 0.003). Diarrhea was the bowel symptom with most differences compared to health, with the strongest association with higher abundancy of *Lachnospiraceae* (beta = 3.25, p for trend = 0.005). Additionally, we observed significant interactions between gut bacteria and stress, the most significant being for *Lachnospiraceae* on diarrea (p for interaction = 0.002), where the association only occurred in stressed individuals.
Conclusion: This is to the best of our knowledge the first study to investigate relationship between gut microbiota and IBS in a general population. We observed that specific bacteria significantly differed between individuals with and without IBS and bowel symptoms. Diarrhea was the bowel symptom with most and strongest associations of different microbiota. Self-perceived stress was found to modify the composition of gut microbiota in relation to bowel symptoms.
Disclosure: Nothing to disclose

MONDAY, OCTOBER 22, 2018   10:30–12:00
Microbiota in IBS: From bench to bedside –
Room N2

OP030 GUT MICROBIOTA CHARACTERISTICS ASSOCIATE WITH IRRITABLE BOWEL SYNDROME AND SPECIFIC BOWEL SYMPTOMS IN A POPULATION-BASED STUDY FROM SWEDEN

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Introduction: Abdominal pain in association with altered bowel habits, without any obvious organic changes, are called functional bowel disorders, with irritable bowel syndrome (IBS) being the most common entity. The etiology is unknown, but an altered gut microbiota has been observed in some studies, with incongruent results.
Aims and Methods: Our aim was to examine the gut microbiota composition in a large population-based cohort, the Malmö Offspring Study (N = 1988, mean age 40y, 53% women), with respect to presence or absence and severity of bowel symptoms and self-perceived stress. The participants completed questionnaires about socioeconomic factors, lifestyle and medical history, and were asked if they have (yes/no) 1) IBS; 2) experienced any bowel symptoms during the last 2 weeks (BS-2w) and; 3) been constantly stressed during the last 12 months. Participants with BS-2w completed a Visual Analog Scale for Irritable Bowel Syndrome (VAS-IBS) including abdominal pain, diarrhea, constipation, bloating and flatulence, vomiting and nausea and psychological well-being. The 16S rRNA gene was sequenced (2*300bp, V1-V3) from fecal samples. To identify OTUs at genus level the sequences were binned together by FLASH and QIIME and matched to the GreenGenes (13.8) reference database. The OUT data was normalized using cumulative sum scaling, and rare- and low abundancy OTUs were filtered out,

OP031 BACTERIA MODIFIED BILE ACIDS – A POSSIBLE MECHANISM FOR SYMPTOMS SEVERITY IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

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Introduction: The intestinal microbiota has been implicated as an important factor in the pathogenesis of irritable bowel syndrome (IBS) however the mechanisms by which the intestinal microbiota affects the presence and/or severity of IBS symptoms are unclear. Recent advances suggest a role for bile acids in causing alterations in bowel functions including stimulating bowel secretion and increase in peristalsis and symptoms of diarrhea and watery stools that are commonly reported in patients with IBS. It is well known that the conversion of primary bile acids into (highly colonic irritant) secondary bile acids is entirely dependent on intestinal bacterial enzymes. However, the relation between the intestinal microbiota, bile salts and IBS has not been adequately investigated.
Aims and Methods: We aimed to investigate the relationship between the intestinal microbiota, bile salts composition and metabolism and IBS clinical symptoms.

Fresh fecal samples were collected from subjects who met the Rome III criteria for IBS, and non-IBS controls. IBS principal symptoms (abdominal pain, change in bowel movements and bloating) were assessed using validated measures on a daily diary. Overall IBS symptoms were assessed using the IBS symptom severity scale (IBS-SSS) and intestinal sensation by Visceral Sensitivity Index (VSI). The intestinal microbiota was investigated by Illumina Miseq sequencing and analyzed using: an in-house validated, published pipeline(1), predicted metagenomics with PICRUSt(2) and concentrations of fecal bile acids by UPLC-MS system(3). Mann-Whitney test was used for univariate analysis, and PerMANOVA was used for between group comparisons. Pearson correlations were performed with log transformed bile acid concentration and clinical data.

Results: : Fecal samples from 25 IBS and 27 non-IBS subjects were analyzed. We identified 9 major phyla of which Firmicutes ($58.22 \pm 2.56\%$, mean $\pm$ sem), Bacteroidetes (36.32 ± 2.84), Actinobacteria ($2.89 \pm 0.66\%$) and Proteobacteria ($1.37 \pm 0.24\%$) were the most abundant in all subjects. There were no between-groups composition difference at the phylum and community levels. We identified 21 bile acids in stool, with no significant difference in concentration of individual bile acids between IBS and non-IBS samples. In patients with IBS, fecal conjugated primary bile acids ($r = 0.62$, $p = 0.014$), conjugated secondary bile acids ($r = 0.49$, $p = 0.074$) and conjugated tertiary bile acids ($r = 0.74$, $p = 0.022$) showed a positive relationship with IBS-SSS. The 3rd conjugated bile acid also correlated with pain severity in IBS (positive correlation, $r = 0.6809$, $p = 0.0435$) and VSI score (negative correlation, $r = -0.7905$, $p = 0.0195$). No association was found between unconjugated bile acids and any of the clinical variables. Predictive metagenomic analysis of bile salt hydrolase (BSH) bacterial enzymatic activity showed negative correlation with glycine-conjugated primary bile acids ($r = -0.473$, $p = 0.0305$). More interestingly, an inverse trend was found between fecal BSH activity and IBS-SSS ($r = -0.416$, $p = 0.097$).

Conclusion: We discovered novel relationships among fecal microbial derived BSH, the concentration of conjugated bile acids and severity of IBS symptoms. Our findings suggest the involvement of intestinal microbiota in bile acid metabolism contribute to IBS severity in human patients.

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References

1. Chakrabarti A, Siddharth J, Lauber CL, Membrez M, Betrisey B, Loyer C, Chou CJ, Pataky Z, Golay A, Parkinson SJ Resolving microbial membership using Abundance and Variability In Taxonom (AVIT). *Sci Rep*. 2016 Aug 17; 6: 31655.
2. Langille M GI, Zaneveld J; Caporaso J G, McDonald D, Knights D, a Reyes J, Clemente J C, Burkepile D E, Vega Thurber R L, Knight R, Beiko R G, Huttenhower C. Predictive functional profiling of microbial communities using 16S rRNA marker gene sequences. *Nature Biotechnology*, 1–10. 8 2013.
3. Chakrabarti A, Membrez M, Morin-Rivron D, Siddharth J, Chou CJ, Henry H, Bruce S, Metairon S, Raymond F, Betrisey B, Loyer C, Parkinson SJ, Masoodi M. Transcriptomics-driven lipidomics (TDL) identifies the microbiome-regulated targets of ileal lipid metabolism. *NPJ Syst Biol Appl*. 2017 Nov 7; 3: 33.

OP032   RESTORING EPITHELIAL BARRIER IN IRRITABLE BOWEL SYNDROME: THE POTENTIAL ROLE OF ESCHERICHIA COLI NISSLE 1917

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Introduction: Intestinal epithelial barrier alterations play a key role in the pathogenesis of several gastrointestinal diseases, such as inflammatory bowel diseases and Irritable Bowel Syndrome (IBS). Among possible pharmacological interventions to restore epithelial barrier, an interesting perspective is represented by probiotics, which are live microorganisms commonly used in clinical practice. *Escherichia coli* Nissle 1917 (EcN) is a probiotic effective in the maintenance of remission of ulcerative colitis, although the underlying molecular mechanisms remain unclear.

Aims and Methods: The aim of this study was to characterize the potential effect of EcN in reversing the increase of intestinal permeability caused by the mediators spontaneously released by IBS biopsies, by known inflammatory stimuli and to evaluate the molecular mechanisms involved. CaCo-2 cells were used as an in vitro model of intestinal epithelial barrier. Two concentrations of EcN (10^8 and 10^6) were applied to CaCo-2 with or without SLIGRL (a protease-activated receptor-2 activating peptide), tumor necrosis factor (TNF)-a, interferon (IFN)-g and inflammatory mediators spontaneously released (SUP) by mucosal biopsies of patients with IBS and healthy controls (HC). Paracellular permeability was evaluated using sulfonic-acid-conjugated to fluorescein (FITC). qPCR was used to assess mRNA gxpression of tight junction proteins, zonula occludens-1 (ZO-1), claudin- 1 and occludin.

Results: EcN induced a dose-dependent reinforcement of CaCo-2 monolayer of 52% (10^8, $p < 0.05$) and 32% (10^6) compared to untreated CaCo-2 (CTR). SLIGRL 50uM and 200uM induced a significant increase in CaCo-2 permeability compared to CTR ($p < 0.05$); the co-incubation of SLIGRL and EcN induced

a recovery of epithelial integrity compared to SLIGRL alone. TNF-a and IFN-g induced an increase in CaCo-2 permeability compared to CTR reverted by EcN. SUP of patients with IBS induced a significant increase of paracellular permeability compared to HC SUP ($p < 0.05$). The co-incubation of EcN with IBS-D or -C SUP induced a recovery of permeability rate compared to SUP alone ($p < 0.05$). No effect of EcN was observed with IBS-M SUP. qPCR analysis showed EcN induced a significant increase in ZO-1 and occludin expression compared to CTR. Permeability rate significantly correlated with severity and frequency of abdominal pain and distension.

Conclusion: EcN reinforces intestinal epithelial barrier enhancing the expression of tight junction proteins. EcN reverts the increase of epithelial monolayer permeability induced by inflammatory stimuli and IBS SUP. These results pave the way to future studies to understand the potential application of EcN in IBS.

Disclosure: This study was supported by an unrestricted grant from Ca. Di. Group S.r.l., Rome, Italy.

OP033   THE EFFECT OF FAECAL MICROBIOTA TRANSFER ON VISCERAL HYPERSENSITIVITY IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

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Introduction: Increased colorectal perception, so-called visceral hypersensitivity, is one of the hallmarks of patients suffering from irritable bowel syndrome (IBS). A possible role of the gut microbiota in visceral hypersensitivity was suggested by a study that showed that after colonisation with gut microbiota of IBS patients, rats had increased rectal sensitivity compared the control group [1].

Aims and Methods: The aim of this study was to assess the effect of modulating the gut microbiota by faecal microbiota transfer (FMT) on visceral hypersensitivity in IBS patients.

As part of a randomised, placebo-controlled, double-blinded clinical trial (registered at clinicalTrials.gov under NCT02092402), 16 IBS patients were randomised to receive FMT either from a healthy donor (treatment group) or from their own faecal material (placebo group). The faecal material was administered into the caecum by whole colonoscopy after a bowel cleansing. In addition to completing questionnaires for assessing IBS symptoms (IBS-SSS, GSRS-IBS), the patients underwent a barostat procedure at baseline and 8 weeks after FMT. Before assessment, patients fasted overnight and were placed in a left lateral position. The barostat catheter (600 mL, Mui Scientific, Ontario, Canada) was placed 15 cm into the rectum. Rectal distensions were performed according to previous studies using an electronic distension barostat device (Distender series II, G&J Electronic Inc., Toronto, Canada) [2, 3]. In short, intermittent semi-random staircase distensions of 60 seconds duration were separated by intervals of 30 seconds of baseline pressure. During each distension, subjects reported their perception of pain, discomfort, and urge, respectively, using 100 mm visual analogue scales (VAS). VAS scores were fit to a logistic function model and evaluated at fixed pressures of 20, 30, 40, 50 mmHg. The fitted baseline-corrected VAS values were then compared before and after FMT using Wilcoxon signed rank test, and between treatment and placebo using Mann-Whitney U-test.

Results: Evaluable barostat data was available from n = 14 participants. No statistically significant differences in the patients' perception of pain and discomfort were found before and after FMT, neither in the treatment (n = 8) nor the placebo group (n = 6). The perception of urge was significantly lower in the placebo group compared the treatment group at 20, 40, and 50 mmHg 8 weeks after FMT. Even though a relief in symptoms after FMT was found in the treatment group compared to baseline, this was not associated with decreased visceral hypersensitivity.

Conclusion: The beneficial effect of FMT from healthy donors on the symptom scores in IBS patients does not seem to be mediated by reduced hypersensitivity. The reduced perception of urge in the placebo group could be a result of the bowel cleansing prior to the colonoscopy. The absence of this effect on urge in the treatment group might be due to a reaction of the host mucosa to the introduction of a new, foreign microbiota. Further analyses need to be performed to study what contributes to the positive effect of FMT in IBS patients.

Disclosure: Nothing to disclose

References

1. Crouzet L, Gaultier E, DeĺHomme C, et al. The hypersensitivity to colonic distension of IBS patients can be transferred to rats through their faecal microbiota. *Neurogastroenterol Motil*. 2013 Apr; 25(4): e272–82.
2. Kilkens TO, Honig A, van Nieuwenhoven MA, et al. Acute tryptophan depletion affects brain-gut responses in irritable bowel syndrome patients and controls. *Gut*. 2004 Dec; 53(12): 1794–800. doi: 10.1136/gut.2004.041657.
3. Vanhoutvin SA, Troost FJ, Kilkens TO, et al. Alternative procedure to shorten rectal barostat procedure for the assessment of rectal compliance and visceral perception: a feasibility study. *J Gastroenterol*. 2012 Aug; 47(8): 896–903.

OP034   THE MUCOSAL TRANSCRIPTOMIC HOST RESPONSE TO FAECAL MICROBIOTA TRANSFER IN IRRITABLE BOWEL SYNDROME

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Introduction: Faecal microbiota transfer (FMT) consists of the introduction of a new microbiota into the intestine of a patient with the aim to restore a disturbed gut microbiota. Studies have shown that FMT reduces inflammation in ulcerative colitis, and improves insulin sensitivity in metabolomic syndrome (1). However, the colonic mucosal host response to FMT by gene expression has, to the best of our knowledge, not yet been studied.
Aims and Methods: The aim of the study was to investigate the IBS patients' colonic mucosal response to the administration of allogenic (from a donor) or autologous (own) faecal material into the colon. In a recently conducted randomised, double-blinded placebo-controlled clinical trial, 16 IBS patients were treated with FMT by colonoscopy after bowel cleansing. RNA was isolated from colonic biopsies, collected by sigmoidoscopy, at baseline, 2 weeks and 8 weeks after FMT in the group that received allogenic faecal material as well as in the group that received autologous faecal material. Whole genome microarray (Genechip Human Gene 2.1 ST, Affymetrix) was used to analyse gene expression. Pathway analysis was performed by Gene Set Enrichment Analysis.
Results: Pathway analysis of the gene expression data showed that in patients treated with allogenic faecal material, significantly upregulated pathways consisted mainly of immune response-related pathways such as "Allograft rejection" and "Intestinal immune network for IgA production". On the contrary, in the patients receiving autologous faecal material, pathways involving immune response-related processes, such as "Primary immunodeficiency" were significantly downregulated.
Conclusion: This study shows that the host mucosa responds to FMT by up- and downregulating gene expression pathways involved in immunological processes. The upregulated immune-related pathways in the allogenic FMT and downregulated immune-related pathways in the autologous FMT group indicate that the host reacts to the newly introduced, foreign microbiota in a different way than to the bowel cleansing and re-introduction of the own microbiota. Further analysis need to be performed in order to identify which molecular interaction networks are involved, and if these gene expression results are transferable to protein level.
Disclosure: Nothing to disclose

Reference

1. Konig J, Siebenhaar A, Hogenauer C, Arkkila P, Nieuwdorp M, Noren T, et al. Consensus report: faecal microbiota transfer – clinical applications and procedures. *Aliment Pharmacol Ther.* 2017; 45(2): 222–39.

OP035   FECAL MICROBIOTA TRANSPLANTATION ALTERS GUT MICROBIOTA IN PATIENTS WITH IRRITABLE BOWEL SYNDROME: RESULTS FROM A RANDOMIZED, DOUBLE-BLIND PLACEBO CONTROLLED STUDY

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Introduction: Irritable bowel syndrome (IBS) is associated with an intestinal dysbiosis, and fecal microbiota transplantation (FMT) has been hypothesized to have a positive effect in patients with IBS. We performed a randomized, double-blind placebo-controlled trial to investigate if FMT resulted in an altered gut microbiota and improvement in clinical outcome in IBS patients.
Aims and Methods: We performed this study in 52 adult patients with IBS (based on Rome III criteria) with moderate to severe disease activity based on a symptom score of at least 175 in the IBS-severity scoring system (IBS-SSS). Our primary endpoint was the difference in improvement in IBS-SSS after 3 months. At the screening visit, clinical history and symptoms were assessed and fecal samples were collected. Patients were then randomized to FMT or placebo capsules for 12 days and followed for 6 months. Study visits were performed at baseline, 1 month, 3 months and 6 months, where patients were asked to register their symptoms using the IBS-SSS and IBS specific quality of life (IBS-QoL). Prior to each visit fecal samples were collected, inclusive of a sample 3 days after treatment was completed (day 15).
Results: A significant difference in improvement in IBS-SSS score was observed 3 months after treatment (p = 0.012) favoring placebo. This was similar for IBS-QoL data after 3 months (p = 0.003) favoring placebo. Patients receiving FMT capsules had an increase in biodiversity to the extent that this group wasn't statistically distinguishable from the donors, and the placebo patients remained statistically indistinguishable from their pre-treatment state (Mann-Whitney U-test, p < 0.05). All participants completed the treatment and no serious adverse events were registered throughout the study period.
Conclusion: In a randomized double-blind placebo controlled study, we found that FMT changed gut microbiota in IBS patients. But patients in the placebo-group experienced greater symptom relief compared to the FMT-group. Altering

the gut microbiota is not enough to obtain clinical improvement in IBS. However, different study designs and larger studies are required to examine the role of FMT in IBS.
Disclosure: Nothing to disclose

OP036   LONG-TERM RESULTS OF ENDOSCOPIC-RADIOLOGIC RENDEZ-VOUS OF IATROGENIC COMPLETE TRANSECTION OF THE COMMON BILE DUCT

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Introduction: Complete transection of the common bile duct is a dramatic complication after biliary surgery especially after laparoscopic cholecystectomy. Since 1995 we have proposed an endoscopic – radiologic rendez-vous that successfully obtains the reconstruction of the biliary tree in a minimal invasive way. After treatment with 4 or 5 biliary plastic stents left in place for at least one year[1] patients were followed up for at least five years.
Aims and Methods: Since 1995, 91 patients were treated for complete transection of the common bile duct: 3 patients had traumatic biliary section, 88 iatrogenic, (73 after lap.chole. 15 after open surgery).
All patients were successfully treated with endoscopic-radiologic rendez-vous and after right and left transhepatic approach 4 or 5 plastic 10 F stents were radiologically put in place. After 12 months, the stents were endoscopically removed and a control cholangiography with an ERCP was performed. If stones and sludge were found they were removed. In case of duct stenosis a new transhepatic approach was made and several plastic stents put in place again for 12 months. The patients were followed up for 5 years with blood analysis, ultrasounds and MR cholangiography.
Results: 60 patients were evaluated as 21 were lost at follow-up and 10 are under treatment, 44 patients (73%) are well after 5 years without any symptoms of cholestasis and biliary dilatation at MR cholangiography. 2 patients died for sepsis after 6 and 12 months of treatment. 4 patients had cholangitis after 6 and 8 months: the stents were removed and replaced after recovery, 16 patients had stenosis of the main bile duct after stent removal: they were treated again with 4 plastic stents for 1 year, 8 patients had stenosis recurrence during follow up after 2 or 3 years: they were treated endoscopically and a fully covered self-expanding metallic stent left in place for one year. All patients, also those retreated, are well after 5 years of follow up.
Conclusion: The radiologic-endoscopic rendez-vous is a safe and efficient technic for minimal invasive treatment of the common bile duct complete section. It is challenging for the radiologist as the intrahepatic biliary ducts are thin and for the endoscopist that has to puncture the duct often clipped. It requires many sessions for complete treatment and in a few cases treatment for stenosis recurrence but in this way we can avoid surgical treatment on the biliary tree that requires difficult intervention which has a high morbidity and mortality.
Disclosure: Nothing to disclose

Reference

1. Fiocca F, Salvatori FM, Fanelli F et al.: Complete transection of the main bile duct: minimally invasive treatment with an endoscopic-radiologic rendezvous. *GIE* (2011) 74–6: 1393–98.

OP037   ENDOSCOPIC MANAGEMENT OF POSTOPERATIVE PANCREATIC FISTULA: TRANSPAPILLARY VS TRANSMURAL EUS GUIDED DRAINAGE

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Introduction: Postoperative pancreatic fistulas (POPF) are one of the most prevalent clinically relevant complications after partial pancreatic resections. Endoscopic approaches have been proven successful, but literature is scarce on the best route of drainage.
Aims and Methods: Our study aimed at comparing efficacy and safety of transpapillary (ERCP based) and transmural (EUS guided) endoscopic treatment of POPS occurring after distal pancreatectomies. We designed an observational and

analytical retrospective cohort study on all patients (178) with a distal pancreatect-omy since 2000. The primary end point was clinical success of endoscopic treatment defined as a complete resolution of POPF discharge or fluid collection (PFC) or size < 2cm, with association of symptoms resolution, without the need for percu-taneous drainage or surgery. Secondary endpoints were technical success (feasibility and efficacy of stent placement), complication rate of endoscopic procedures, and reintervention rate. Categorical variables were compared using χ^2 test. Normally distributed continuous variables were analyzed by Student *t*-test and non-normally distributed variables by the Mann-Whitney U-test. Patients were divided in 3 groups (ERCP only, EUS drainage only, both EUS and ERCP).

Results: Out of 173 surgical patients, 58 POPF grade B and C were treated by endoscopy. Rate of fistula was not correlated to surgery type (+-splenectomy, body and tail resection or solely tail, enucleation, isthmectomy, combined with other organ resections), neither to indication for surgery (malignancy, trauma, pancreatitis). Fistulas were more severe in older patients (p = 0.043). Patients were treated by ERCP alone (n = 31, 53.4%), EUS alone (n = 13, 22.4%) or both procedures (n = 14, 24.1%). There was a significant shift from ERCP alone (100% of cases between 2000-2005) to EUS alone and combined with ERCP (23% 2006-2010, and 48% 2011-2016). Technical success rates were simi-lar in all groups (87-100-100%). Clinical success in patients treated by ERCP only was 64.5% (20/31) and as high as 96.3% (26/27) in patients in whom EUS was performed at any points during endoscopic treatment (p = 0.003). The over-all re-intervention rate was 44.8%, significantly lower when EUS was part of the treatments (20 and 23% vs. 55%, p < 0.05). The complication rates in the ERCP, EUS and ERCP+EUS groups were respectively 20% (n = 8/40), 30.8% (n = 4/13) and 0% (p = 0.346), with a decrease to only 2 AE in the last 5 years.

Conclusion: Endoscopic treatment was highly successful in treating POPF after distal pancreatectomy, with a significantly better clinical success rate of EUS compared with ERCP, resulting in less reinterventions needed. We therefore sug-gest considering EUS as a primary approach, reserving ERCP for cases with pancreatic ductal strictures or inaccessible post-operative collections or fistulas.

Disclosure: Nothing to disclose

OP038   COMPARATIVE ANALYSIS OF EUS-GUIDED PSEUDOCYST AND WALLED-OFF NECROSIS DRAINAGE BETWEEN DIFFERENT METAL (HOT-AXIOS^{TM}, NAGI^{TM}, SPAXUS^{TM}) AND PLASTIC (DOUBLE PIGTAIL) STENTS: A SINGLE CENTER-EXPERIENCE

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Introduction: Endoscopic Ultrasound-guided Transmural Drainage (EUS-TD) is a minimally invasive first-line modality for the management of 2 types of pan-creatic fluid collection (PFC): pancreatic pseudocyst (PP) and walled-off necrosis (WON). EUS-TD has demonstrated a shorter hospital stay and less morbidity compared to surgical cystogastrostomy. Stents delivery systems are available in different materials and trademarks. Their specific outcomes on PFC types have not been described, particularly in a Hispanic population.

Aims and Methods: We aimed to evaluate the outcomes and seek for differences in the management of EUS-TD of PP and WON, between different stents mate-rials and trademarks.

This was an observational, descriptive, longitudinal, retrospective cohort study. Data from EUS-guided drainages of PFC cases were obtained from medical records, as corresponding: PFC characteristics, type of stent (metal: Hot-AXIOS^{TM}, NAGI^{TM}, SPAXUS^{TM}; plastic: double pigtail), technical success (including time of procedure), clinical success (follow-up: adverse events, further EUS, imaging, possible re-interventions and PFC resolution). Variables were described in mean or median values, according to statistical distribution (Shapiro-Wilk test), and contrasted through follow-up with corresponding hypothesis testing. Analyses were performed using R v3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results: From May-2014 to Oct-2017, 42 consecutive cases were collected: 29/42 PP and 13/42 WON. Median age 48 (10–76) yo, 19/42 (45%) female. PFC etiol-ogy were biliary in 31/42 (74%) cases, and alcoholic in 11/42 (26%). Median size of PFC was 7 (1–14) cm. PFC were more frequently on body-tail (62%). Pain and infection were indication of drainage in 30/42 (71%) and 12/42 (29%) cases, respectively. Clinicopathological chraracteristics are summarized in table 1.

	(n = 42)
PFC in remission during diagnosis, n (%)	7 (16.7)
Patients not attempted & lost follow-up, n (%)	6 (14.2)
Patients addressed to EUS-guided drainage, n (%)	29 (69.0)
No. cases Hot-AXIOS (%)	9/25 (36.0)
No. cases NAGI (%)	10/25 (40.0)
No. cases SPAXUS (%)	6/25 (24.0)
No. cases Double pigtail (%)	4/29 (13.8)

[Table 1. Clinicopathological characteristics.]

In 7/29 PP cases, spontaneous remission was observed; 3/29 PP and 3/13 WON were lost on follow-up. 19/19 PP and 10/10 WON underwent on EUS-guided stent placement, with 100% technical success. Time of procedure per stents was

as following: Hot-AXIOS^{TM} 5 (4-6) min, NAGI^{TM} 19 (18-22) min, SPAXUS^{TM} 20 (18-22) min, double pigtail 20 (18-22) min (p < 0.01). In PP cases, a bleeding episode occurred 48 hours after a Hot-AXIOS^{TM} placement (p = 0.58). In WON cases, an obstruction was reported with a Hot-AXIOS^{TM}, and a bleeding episode occurred 48 hours after a NAGI^{TM} placement (p = 0.69). Both bleeding events required surgical management. Overall adverse events rate was 10% (3/29) with no reports from plastic stent cases. Overall 30-day mortality was 0%. All stents were finally removed. On this series, none of the cases needed percutaneous drainage. Overall median time from stent placement to complete drainage & removal was 8 (1-20) weeks; overall median longest follow-up time was 41 (8-120) weeks. 3 cases (2 SPAXUS^{TM}, 1 NAGI^{TM}) cannot be released due to device failure, and no cases of Hot-AXIOS^{TM} or plastic stent.

Conclusion: Neither stent material nor trademark present a significant impact on PFC outcomes, even in the presence of adverse events. Compared to other stents, Hot-AXIOS^{TM} seems to be more practical and faster for placement.

Disclosure: Nothing to disclose

OP039   TECHNICAL ISSUES DURING EUS-GUIDED PLACEMENT OF LUMEN APPOSING METAL STENTS: DEFINITION AND CLASSIFICATION, INCIDENCE AND RISK FACTORS, ENDOSCOPIC MANAGEMENT AND EFFECT ON PROCEDURE OUTCOMES

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Introduction: Lumen Apposing Metal Stents (LAMS) have been recently intro-duced into clinical practice. A variety of Technical Issues (TIs) can appear during LAMS placement but we lack a common terminology to address them and their consequences on clinical outcomes are unknown.

Aims and Methods: We define TI as any alteration in the normal sequence of LAMS placement (TI is not synonymous with adverse event). Consecutive patients undergoing an endoscopic procedure which includsed the placement of a transmural LAMS between May 2011 and June 2017 in a single tertiary center were included (table 1). Data were prospectively databased and retrospectively analyzed. We propose a novel classification of TIs, categorized in access failure, liberation failures, misplacements and dislodgment. We analyzed their rates, risk factors, endoscopic management and it effect on clinical outcomes.

Results: A total of 289 procedures (47.4% pancreatic fluid collections, 33.7% pancreato-biliary drainages including gallbladder drainages, 13.8% enteric ana-stomoses, 5.1% others) were analyzed. TI occurred in 27% of them, founding a significant higher rate in technical (99.5% vs 52.6%, p < 0.001), procedural (100% vs 82.1%, p < 0.001) and clinical success (88% vs 77.9%, p = 0.03) when compared with procedures without TIs. Distal (25.6%) and proximal flange misplacements (17.9%) and complete liberation failures (17.9%) were the most frequently encountered TIs. Forceps repositioning, placement of a new LAMS or another through-the-LAMS stent were the most frequent rescued techniques. 13 (16.7%) TIs could not be saved. Entero-anastomoses (OR 3.42 (1.22–9.62)) and malignant disease (OR: 3.32 (1.05–10.56)) were risk factors associated to the development of TIs on multivariable analysis.

Conclusion: Even in experts' hands, TIs are frequent in transmural EUS-guided LAMS placement, typically in distal flange misplacement. The knowledge of salvage techniques using other stents makes rescue possible in more than 80% of cases.

Basal Features	N (%)
Age, median (IQR)	71.6 (58.3–83.5)
Male sex, n (%)	184 (63.7%)
Malignant disease, n (%)	75 (26%)
LAMS type, n (%) Hot Cold Missing	170 (58.8%) 116 (40.1%) 3 (1%)
"Free-Hands" Technique	42 (14.5%)
Access, n (%) Stomach Duodenum	215 (74.4%) 63 (21.8%)
Jejunum Esophagus Missing	6 (2.1%) 3 (1%) 2 (0.7%)

[Characteristics of the study population and the procedure]

Disclosure: Nothing to disclose

OP040   ROLE OF EUS-GUIDED TRANSMURAL DRAINAGE IN COMBINED MALIGNANT BILIARY AND GASTRIC OUTLET OBSTRUCTION

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Introduction: Endoscopic management of combined malignant gastric outlet obstruction (GOO) and biliary obstruction remains a challenge. The development of EUS-guided biliary transmural drainage (EUS-D) and EUS-guided gastrojejunal anastomoses (EUS-GJ) has increased the available palliative options. The number of studies comparing intraluminal and transmural approaches regarding follow-up procedures or readmissions is scarce.
Aims and Methods: We performed a retrospective analysis including all patients presenting malignant GOO and biliary obstruction between 2011 and 2017 at a single tertiary care center. Patients were classified according to the biliary and duodenal drainage method, transmural (EUS-D and EUS-GJ) vs transpapillary/intraluminal. Follow-up was started at the time of the first endoscopic procedure. Biliary stent dysfunction was defined as cholangitis and/or obstructive jaundice after endoscopic double stenting. Duodenal dysfunction was accepted if GOO reappeared after successful initial management.
Results: A total of 103 patients with a median age of 76.1 years (IQR: 61.3–84.3), 58 males, were included. Most frequent diagnoses were pancreatic adenocarcinoma (53.4%), cholangiocarcinoma (10.7%) and ampuloma (8.7%). GOO and biliary obstruction were treated within the same week in 39/103 patients. Most biliary obstructions were distal (93/103). Initial management was performed with transpapillary stenting in 69/103 patients and EUS-D in 34/103 (20 choledocoduodenostomies, 13 hepaticogastrostomies, 1 gallbladder drainage). Technical success was achieved in all patients undergoing EUS-D and in 67/69 of the transpapillary drainage group; clinical success was reached in 88.5% EUS-Ds and in 95.6% transpapillary drainages. Duodenal strictures were mostly Mutignani types I (48.5%) and II (49.5%). GOO score at the time of treatment was ≤1 in 87.9% of cases. Initial management was performed with intraluminal SEMS in100/103 cases and with EUS-GJ in 3 patients. Technical success was achieved in 100% and clinical success in 97.5%. Thus, initial management included intraluminal duodenal and biliary stents in 67/103 (65.1%) and EUS-D with intraluminal duodenal stents in 33/103 (32%).
Follow-up was available in 89 patients, with a median time of 247 days (91-547), 68% died during follow-up, 4.4% completed the study period and 27.5% were lost after a median follow-up of 147 days (55-248). We observed a total of 79 biliary events (median 0 events/patients, IQR 0-1). Obstructive jaundice without cholangitis was the most common event (34/79) followed by cholangitis with biliary obstruction (19/79) and cholangitis without obstruction (15/79). EUS-D patients presented a total of 9 events in 6/30 patients while there were 70 events in 36/59 transpapillary drainages. 17/59 patients with transpapillary drainage underwent EUS-D. Transpapillary stenting associated a significantly higher risk of new biliary events, with an incidence-rate ratio of 2.5 (95% CI: 1.14–5.61). We observed 40 episodes of duodenal disfunction in 31/89 patients during follow-up, with the first episode appearing after a median of 95 days (IQR: 37-266); 30/40 (75%) were due to tumor ingrowth. Most episodes (26/40) 65% were salvaged deploying a transluminal stent, although 7 EUS-GJs was performed.
Conclusion: The role of EUS-guided transmural approaches in malignant biliary obstruction and GOO is expanding, but further data are needed before proposing management bundles. Our data suggest EUS-D reduces the need of further endoscopic procedures during follow-up, while EUS-GJ is been increasingly employed.
Disclosure: Dr. Manuel Perez-Miranda is a consultant for Boston Scientific and M.I. Tech and has lectured for Boston Scientific and Olympus. None of the remaining authors has potential conflicts of interests.

OP041 ENDOSCOPIC ULTRASOUND GUIDED GASTROENTEROSTOMY: WHAT IS THE LEARNING CURVE?

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Introduction: Endoscopic ultrasound guided gastroenterostomy (EUS-GE) is a minimally invasive option for patients with gastric outlet obstruction. It involves creating a gastroenterostomy fistula via EUS and deploying a lumen-apposing metal stent (LAMS) across the fistulous tract. It is a technically challenging procedure, requiring skills in EUS, fluoroscopy, and LAMS deployment. The aim of this study was to determine the learning curve for EUS-GE.
Aims and Methods: Consecutive patients undergoing EUS-GE by a single operator were included from a prospective registry from Aug 2014 to Oct 2017. Demographics, procedure info, post-procedure follow-up data, and adverse events were collected. Non-linear regression and CUSUM analyses was conducted for the learning curve. Clinical success was defined as tolerating a diet post-procedure
Results: 23 patients were included (39%M, mean age 65.8 years). 11 (48%) had malignant GOO indication, 9 (39%) had benign GOO, 3 (13%) had other indications. All had a 15mm LAMS placed, 7 (30%) had cautery enhanced LAMS. Clinical success was achieved in 22/23 patients. Average follow-up time 10.8 months (9.1STD). 7 patients had misdeployed LAMS during the procedure, requiring placement of a bridging stent; 2 required NOTES technique for bridging. 5 patients had minor post-procedure complications; 1 patient had a periprocedural esophageal tear treated with clips. 4 patients required repeat intervention for stent revision or removal if no longer needed. Median procedure time was 88 mins (range: 45-140). CUSUM chart shows 88 minute procedure time was achieved at the 7th procedure indicating efficiency. The spikes indicate procedures that required extra time due to bridging of a misdeployed LAMS. Even

with these outliers, the procedure duration further reduced with consequent procedures (non-bridging LAMS stent procedures) indicating continued improvement with experience (nonlinear regression p < 0.0001).
Conclusion: Endoscopists experienced in EUS-GE are expected to achieve a reduction in procedure time over successive cases, with efficiency reached at 88 minutes and a learning rate of 7 cases. Misdeployed stents that require bridging add to the procedure time even after competency is achieved but do not affect the overall learning curve trend.
Disclosure: Michel Kahaleh MD: has received grant support from Boston Scientific, Fujinon, EMcison, Xlumena Inc., W.L. Gore, MaunaKea, Apollo Endosurgery, Cook Endoscopy, ASPIRE Bariatrics, GI Dynamics, NinePoint Medical, Merit Medical, Olympus and MI Tech. He is a consultant for Boston Scientific, Xlumena Inc., Concordia Laboratories Inc, ABBvie, and MaunaKea Tech.-Amy Tyberg MD is a consultant for EndoGastric Solutions. All other authors have nothing to disclose.

MONDAY, OCTOBER 22, 2018   10:30–12:00
Generic profiling and risk assessment in polyps and early CRC – Room L8_____

OP042 SIGNIFICANTLY MUTATED GENE (SMG) ANALYSIS OF EARLY COLORECTAL CANCER (CRC) OBTAINED BY ENDOSCOPIC SUBMUCOSAL DISSECTION (ESD) AND ENDOSCOPIC MUCOSAL RESECTION (EMR) WITH REFERENCE TO BIG DATA OF TCGA ON ADVANCED CANCER

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Introduction: In recent years, Cancer Genome Atlas (TCGA) projects analyzed over 200 colorectal cancer (CRC) tumor-normal pair exome and obtained extremely big data which is available[1]. This TCGA study also revealed dozens of Significantly Mutated Gene (SMG) which are key drivers of CRC development. These results, however, are mostly obtained from advanced CRC. In contrast, we have easy access to early CRC in our daily clinical practice. Thus, we analyzed tissue samples which are mostly early CRC obtained by endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR), and compared to TCGA data on advanced CRC.
Aims and Methods: TCGA data contained data on 149 advanced CRCs which were studied *in silico*, whereas by next generation sequencer we analyzed nucleotides sequences of our 18 endoscopically obtained CRC samples (4 EMR and 14 ESD) by "Colorectal Cancer Panel" which we created in-house. This in-house panel covers 202,842 nucleotides or 67,614 deduced amino acids of 60 SMGs[1,2]. Non-neoplastic portion of the tumor was also analyzed. In addition to the gene sequencing, we undertook immunohistochemical staining of (IHC) of mismatch repair genes (MLH1, MSH2, PMS2, PMS6).
Results: We obtained significant mutations (Total 56, 10 nonsense, 7 frameshift, 39 missense) of 60 SMGs in 18 tumor samples (Cut-off level of Allelic Fraction, AF above 20 %). We also analyzed TCGA data base on 149 advanced CRCs. We then categorized characteristics of those somatic mutation into 4 groups according to presence or absence of 2 major signaling pathways of Wnt signaling (APC, RNF43, CTNNB1) and of MAPK signaling (KRAS, NRAS, BRAF).
Mutations for both Wnt & MAPK; our Early 6/18 (33%) vs 59/149 (40%).
Mutations only for Wnt; our Early 12/18 (67%) vs 49/149 (33%).
Mutation only for MAPK; our Early 0/18 (0%) vs 24/149 (16%).
Mutation negative for both; our Early 0/18 (%) vs 17/149 (11%).
In our study, early CRCs had more Wnt pathway abnormality alone than advanced cases of TCGA data base (67% vs. 33% p < 0.05, Chi-square test). Of interest was that among the molecules involved in Wnt signaling pathway (APC, RNF43 and CTNNB1), the presence of somatic mutations in those molecules were mutually exclusive. This applies for MAPK signaling pathway (KRAS, NRAS and BRAF) as well. All mutation of APC and RNF43 identified in our study were truncating, indicating these mutations were "drivers". Whereas mutation of MAPK genes were all transacting. Among molecule of Wnt pathway, somatic mutation of RNF43 was identified in 2 (11%) early CRC cases. IHC showed that expression of MLH1 and PMS2 were deficient in these 2 cases. In TCGA, only one of 149 (0.7%) advanced CRC had somatic mutation of RNF43. This case was advanced CRC cancer with microsatellites instability high.
Conclusion: Very early stage of CRC now easily available by EMR and ESD tended to have somatic mutation only for genes of Wnt signaling pathway (not both for Wnt and MAPK). In some cases, even in very early stage of CRC, driver mutation of RNF43 with MSI could occur, which might contribute to the initiation of neoplastic changes and transformation to advance stages. However, the rarity of RNF43 mutations in advanced CRC in TCGA data base yet to be confirmed.
Disclosure: Nothing to disclose

References

1. *Nature* 2012; 487: 330–7.
2. *Nat Genet*. 2013; 45: 136–144.

OP043   EICOSAPENTAENOIC ACID (EPA) AND/OR ASPIRIN FOR PREVENTION OF COLORECTAL ADENOMAS (THE SEAFOOD POLYP PREVENTION TRIAL): A MULTICENTRE DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMISED 2X2 FACTORIAL PHASE 3 TRIAL

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Introduction: The omega-3 polyunsaturated fatty acid (PUFA) eicosapentaenoic acid (EPA) and aspirin both have proof-of-concept for colorectal cancer (CRC) chemoprevention, aligned with an excellent safety profile.
Aims and Methods: We performed a randomised, blinded, placebo-controlled, 2×2 factorial trial to determine the effects of EPA and aspirin on preventing colorectal adenomas. We also assessed the safety and tolerability of EPA, in free fatty acid (FFA) or triglyceride (TG) form, and aspirin.
NHS Bowel Cancer Screening Programme (BCSP) patients (aged 55-73) identified as 'high risk' ($\geq$5 small [< 10mm] colorectal adenomas; or $\geq$3 colorectal adenomas, if one $\geq$10mm) at screening colonoscopy were randomly allocated 99%EPA-FFA 2g or 90%EPA-TG 2780mg (equivalent to 2g FFA) daily, or identical placebo capsules; AND aspirin 300 mg daily, or an identical placebo enteric-coated tablet. All participants and research staff were unaware of the treatment allocation.
The primary outcome was the number of participants with $\geq$1 colorectal adenoma (adenoma detection rate [ADR]) at one year surveillance colonoscopy. Outcomes were analysed 'at the margins' on an intention-to-treat basis, adjusted for BCSP site and need for repeat endoscopy at baseline. Secondary outcomes included the total number of colorectal adenomas per patient (mean adenomas per patient [MAP]), 'advanced' ADR, as well as colorectal adenoma location (right/left) and type (conventional/serrated).
Results: 709 participants (80% male, mean [SD] 65 [5] years, 82% BMI > 25kg/m^2) were randomised. The four treatment arms (EPA + aspirin, n = 177; EPA, n = 178; aspirin, n = 178; placebo, n = 176) were well-matched for baseline characteristics. There were no differences between FFA and TG users regarding rectal mucosal/red blood cell PUFA levels or tolerability profile. There was no evidence of any difference in ADR between EPA users (62%) and non-users (61%) (risk difference [RD] -0.9% [95% CI -8.8,6.9]) or for aspirin users (61%) *versus* non-users (62%) (RD -0.6% [-8.5,7.2]). There was no evidence of an interaction between EPA and aspirin for ADR. There was no evidence of any effect on advanced ADR of either EPA (RD -0.6% [-4.4,3.1]) or aspirin (RD -0.3% [-4.1,3.5]). Aspirin use was associated with a reduction in MAP (incidence rate ratio [IRR] 0.78 [0.68,0.90]) with preventive efficacy against conventional (IRR 0.82 [0.71,0.94]), serrated (IRR 0.46 [0.25,0.87]) and right-sided (IRR 0.73 [0.61,0.88]) lesions, but not left-sided (IRR 0.85 [0.69,1.06]) adenomas. There was evidence of chemopreventive efficacy of EPA on conventional (IRR 0.86 [0.74,0.99]) and left-sided (0.75 [0.60,0.94]) adenomas, but not on total MAP (IRR 0.91 [0.79,1.05]), serrated (IRR 1.44 [0.79,2.60]) or right-sided (IRR 1.02 [0.85,1.22]) adenomas. Overall adenoma number was reduced in the EPA + aspirin arm (166) compared with the other groups (238 [EPA], 209 [aspirin] and 231 [placebo]). EPA and aspirin treatment were well tolerated with an excess of mild-moderate GI adverse events (AEs), prominent in the EPA alone arm. There were 6 GI bleeding AEs.
Conclusion: Neither EPA nor aspirin treatment was associated with a reduction in ADR at 1 year in 'high-risk' individuals after clearance colonoscopy. However, both agents displayed evidence of chemopreventive efficacy, based on adenoma number reduction, which was adenoma type- and location-specific, and is compatible with the known anti-(right-sided) CRC activity of aspirin. Best use of EPA and aspirin may need a precision medicine approach to adenoma recurrence based on colorectal adenoma sub-types. ISRCTN05926847

OP044   PRECEDING ENDOSCOPIC SUBMUCOSAL DISSECTION DOES NOT AFFECT FOR THE PROGNOSIS OF PATIENTS WITH T1 COLORECTAL CARCINOMA ADVERSELY AFTER ADDITIONAL SURGERY: A PROPENSITY SCORE-MATCHED ANALYSIS

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Introduction: In Japan, endoscopic submucosal resection (ESD) has become standardized for early colorectal carcinomas (CRCs) as histological complete en bloc resection. According to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016, pT1 CRC resected endoscopically is treated as follows. CRCs with positive vertical tumor margins, unfavorable histology, submucosal invasion depth $\geq$1000 µm, positive vessel invasion, or/and budding grade 2/3 should be considered for additional surgery with lymph node (LN) dissection. Only a few studies have demonstrated that preceding endoscopic resection including ESD did not worsen clinical outcomes in cases after additional surgical resection, however, malignant oncologic behavior of preceding endoscopic resection prior to additional surgery has been controversial. In this study, we analyzed the influence of preceding ESD on the prognosis of patients with pT1 CRCs after additional surgery using propensity score-matching.
Aims and Methods: We retrospectively assessed 1,444 consecutive patients with 1,444 pT1 CRCs who underwent ESD prior to additional surgery or surgery alone between June 1992 and June 2016 at the Hiroshima GI Endoscopy Research Group (Hiroshima University Hospital and 10 affiliated hospitals). A total of 900 patients were excluded due to the following reasons: resected by endoscopic mucosal resection or polypectomy (n = 575); treated by ESD alone (n = 74); no follow-up for more than 12 months (n = 35); previous or synchronous CRCs and other cancers (n = 92); or resected by piecemeal resection (n = 24). Finally, 544 patients with T1 CRCs who underwent ESD prior to additional surgery (group A: n = 163) or surgical resection alone (group B: n = 381) were included in this study. The enrolled patients were treated according to the JSCCR guidelines 2016, and patients who did not meet curative condition of the guidelines were defined as non-endoscopically curable (non-e-curable) patients. After matching the propensity scores, we analyzed pathological characteristics stated in the JSCCR guidelines 2016 and the prognoses of non-e-curable patients between the 2 groups.
Results: The numbers of non-e-curable patients were 157 in group A (including 27 patients with positive vertical tumor margins) and 323 in group B. The rate of LN metastasis was 9.4% (51 patients) and all of them were non-e-curable patients. Recurrence did not occur in e-curable patients (average observation period: 86.1 months); however, 14 recurrences (2.6%) occurred in non-e-curable patients (average observation period: 70.3 months). Five of these were in group A, while the others were in group B. One and three patients died of primary carcinoma in groups A and B, respectively. Propensity scores were calculated using a logistic regression model, and the variables included in the model were age, sex, location, tumor size, and growth type in non-e-curable patients. After propensity score-matching, 134 non-e-curable patients in group A and 134 non-e-curable patients in group B were picked up. The 5-year overall survival rate in group A was significantly higher than that in Group B (97.6% vs. 88.1%). However, there were no significant differences in 5-year disease-free survival rates (95.6% vs. 96.7%) and 5-year disease-specific survival rates (100% vs. 99.1%) after treatment of pT1 CRCs between 2 groups in non-e-curable patients.
Conclusion: The prognoses of e-curable patients with pT1 CRC supported the JSCCR criteria. Preceding ESD with histological en bloc resection for patients with T1 pCRC did not affect their clinical outcomes adversely after additional surgery.

OP045   A STUDY OF POST COLONOSCOPY COLORECTAL CANCER (PCCRC) IN ENGLAND

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Introduction: PCCRC is a key quality indicator for the detection and prevention of colorectal adenocarcinoma (CRC). It is not known whether rates of PCCRC are changing over time. There is limited evidence of factors associated with PCCRC that might be amenable to quality improvement interventions.
This study investigated trends in rates of PCCRC in the NHS in England; the extent of variation between NHS trusts; and potential causal associations with PCCRC.

Aims and Methods: Using linked national Hospital Episode Statistics and National Cancer Registration and Analysis Service data all individuals who had undergone a colonoscopy procedure between 1/1/2006 and 31/12/2012 and who developed a CRC to 31/12/2015 were identified. NHS trust provider status and potential associations with PCCRC were included in the analysis. International consensus methodology was used to calculate the PCCRC – 3 year rate (PCCRC-3yr).[1,2] Colonoscopies were labelled as true positive (CRC within 0 to 6 months of the procedure), false negative (CRC within 6 to 36 months) and true negative (CRC beyond 36 months). The PCCRC-3yr rate was calculated as: false negatives / (true positive + false negative) x 100%. The PCCRC-3yr rate was calculated for each year from 2006 to 2012. In addition, the rate in each colonoscopy provider was calculated, and organisations grouped using quintiles. PCCRC rates were calculated in relation to patient and tumour characteristics.

Results: Between 2006 and 2012 108,908 colonoscopies followed by a diagnosis of CRC were identified. Of these, 93,240 (86%) were labelled true positive, 7,781 (7%) were false negatives, and 7,887 (7%) were true negative tests. There was a significant reduction in PCCRC-3yr rates, from 8.6% in 2006 to 7.5% in 2012 (Chi^2 for trend p < 0.01). There was variation in unadjusted, mean PCCRC-3yr rate between NHS Trusts from 5% (SD +/-2%) in the highest performing quintile to 11% (SD +/-2%) in the lowest. PCCRCs were significantly associated with female sex, right-sided colonic lesions, inflammatory bowel disease and diverticular disease diagnosis, mucinous CRC and in individuals with metachronous CRC.

Conclusion: There has been a significant reduction in PCCRC-3yr rates from 2006 to 2012, likely to be related to improvements in colonoscopic quality: particularly improved caecal intubation and bowel preparation resulting in improved lesion recognition and removal. There appears to be unwarranted variation of PCCRC-3yr rates across NHS trusts. Reasons for this variation need to be explored and subject to quality improvement projects. Evidence from this study can be used to help target those at highest risk of PCCRC.

Disclosure: Nothing to disclose

References

1. Morris EJA, et al. *Gut* 2014; 64: 1248–56.
2. Beintaris I, et al. *UEG J* 2017; 5: PO436.

OP046   MOLECULAR PROFILING OF LONGITUDINALLY OBSERVED SMALL COLORECTAL POLYPS

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Introduction: Knowledge of the natural history of colorectal adenomas is limited because these lesions are removed upon detection. The few studies in which small adenomas have been left *in situ* for a limited period of time have shown that most lesions remain stable or even completely vanish. Lesions that have grown in size more often turn out to be advanced adenomas when resected. Specific DNA copy number changes ('cancer-associated events' or CAEs) are associated with progression of adenomas to cancer.

Aims and Methods: To evaluate whether growth of small colorectal polyps left *in situ* is associated with specific molecular features.
In the CT-colonography (CTC) arm of the COCOS-trial[1], 95 small (6-9mm) colorectal polyps detected on CT-colonography were left *in situ* and re-measured after a surveillance interval of 3 years. Based on volumetric change, polyps were classified as either grown (>30% growth), stable (<30% growth and < 30% regression) or regressed (>30% regression). The surveillance CT-colonography

was followed by colonoscopy, during which all lesions were resected and histologically classified. Using DNA isolated from FFPE material, low-coverage whole genome sequencing was performed to determine DNA copy number profiles, as well as target enrichment mutation analysis and CpG island methylation (CIMP) analysis. In addition, expression of DNA mismatch repair (MMR) genes was determined by immunohistochemistry.

Results: FFPE material could be retrieved from 65 lesions, including 47 (72%) tubular adenomas with low grade dysplasia (LGD), 9 (14%) tubulovillous adenomas with LGD, 1 (2%) sessile serrated lesion without dysplasia and 8 (12%) hyperplastic polyps without dysplasia. Of the lesions 31 (48%) grew, 27 (41%) remained stable and 7 (11%) regressed. Growth rates were higher in lesions having ≥1 CAEs compared to lesions without CAEs (143% (s.e. 56%) vs 52% (s.e. 14%), respectively, p = 0.02). CAEs were absent in lesions that regressed. Mutations occurred in 94% of the lesions, with higher growth rates being associated with lesions having ≥2 mutations compared to lesions with only 0-1 mutations (127% (s.e. 34%) versus 27% (s.e. 13%), respectively, p = 0.03). Mutations in *APC* were most frequently observed, occurring in 56% of the small polyps and only in adenomas and not in serrated lesions. Additional alterations in key genes involved in other pathways of colorectal carcinogenesis were observed, including *KRAS*, and *TP53* mutations. The 2 serrated lesions analysed showed a *BRAF* mutation only. All samples were MMR proficient. No relation between growth and CIMP was observed. Based on the molecular definition of having ≥2 CAEs, 9% of all lesions were classified as being at high risk of progression. These lesions included both grown and stable lesions.

Conclusion: Molecular alterations associated with adenoma to carcinoma progression are more frequent in growing polyps. The observation that high-risk lesions were amongst polyps that remained stable and grew, but not amongst regressing polyps, is relevant for screening and surveillance strategies.

Disclosure: J. Stoker: research consultant Robarts Clinical Trials E. Dekker: FujiFilm: equipment on loan, research grant, personal consultation-fee, Olympus: equipment on loan, research-grant G.A. Meijer: Exact Sciences and Sysmex: provision of materials, equipment or (sample) analyses. Other authors: nothing to disclose

Reference

1. Stoop, E. M. et al. Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: A randomised controlled trial. *Lancet Oncol.* 13, 55–64 (2012).

OP047   DO WE RECOGNIZE EARLY (T1) COLORECTAL CANCER? DATA FROM THE DUTCH NATIONAL SCREENING PROGRAM

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Introduction: The implementation of the Dutch national colorectal cancer (CRC) screening program has led to an increase in diagnosis of early (T1) CRC. However, endoscopic diagnosis of T1 CRC is challenging. In this study we examined how well T1 CRC is recognised in the Dutch CRC screening program and the outcomes for therapy.

Aims and Methods: All participants to the FIT based (faecal immunochemical test) national CRC screening program from February 2014 to August 2015 in the South Limburg region with 1 university hospital (Maastricht University Medical Center) and 3 regional hospitals (Zuyderland Medical Center, location Sittard-Geleen and location Heerlen, and Diagnostic Centre Maastricht) were included. We collected clinical, endoscopic and histopathology data at index colonoscopy and 3-year follow-up data. T1 CRCs were treated by endoscopic resection or surgery (direct surgery or surgery after an initial attempt at endoscopic resection). Pedunculated neoplasms were resected by hot snaring, while sessile and flat neoplasms were resected by endoscopic mucosal resection (EMR).

Results: In total, 2473 patients with 7657 colorectal neoplasms were included. Ninety-seven T1 CRCs, 48 T2 CRCs, 62 T3 CRCs and 3 T4 CRCs were found. At colonoscopy, 19 (19.6%) of the T1 CRCs were endoscopically diagnosed as carcinoma, while 78 (80.4%) were initially diagnosed as adenoma (n = 77) or hyperplastic polyp (n = 1).
Of the 19 endoscopically correctly diagnosed T1 CRCs, 17 (89.5%) were directly surgically resected and 2 (10.5%) underwent surgery after an initial attempt at endoscopic resection. There were no correctly diagnosed T1 CRCs that were solely treated by endoscopic resection.

Of the 78 endoscopically not as such recognised T1 CRCs, 36 T1 CRCs (46.2%) were resected endoscopically and had been followed up according to post-resection surveillance guidelines. 2 lesions showed recurrence within 3 years. (Table 1).

34 endoscopically not as such recognised T1 CRCs (43.6%) underwent surgery after an initial attempt at endoscopic resection. Histopathology of the resection specimen showed no residual submucosal invasion in 16 cases (47.1%).

The remaining 8 endoscopically not as such recognised T1 CRCs (10.3%) were directly referred for surgery, because these lesions were too difficult to resect endoscopically due to their size and location.

Logistic regression analysis showed that distal location (OR 3.83, 95% CI: 2.03–7.25), non-pedunculated shape (OR 2.03, 95% CI: 1.26–3.27) and estimated CRC based on macroscopic appearance (OR 4.90, 95% CI: 2.11–11.35) were independent risk factors for submucosal invasion.

Conclusion: Approximately 80% of the T1 CRCs in our national CRC screening program are not recognised as early CRCs. Uncertainty about diagnosis may lead to additional colonoscopies, delay in surgery and surgical over-treatment. Improvement in the recognition and treatment of early CRC is needed to further optimize the outcomes of our national CRC screening program.

		Endoscopically not recognised T1 CRCs (n = 78)
Endoscopic resection	0	36
- Recurrence within 3 years	0	2
Surgery after initial attempt of endoscopic resection	2	34
- No residual SMI in resection specimen	0	16
Direct surgery	17	8

[Table 1. Treatment strategies of T1 CRCs in the national screening program.]
Disclosure: R.M.M. Bogie and S. Sanduleanu-Dascalescu received an unrestricted research grant from Pentax Europe.

MONDAY, OCTOBER 22, 2018   14:00–15:30
Therapy update in colorectal cancer – Room B_____

OP048 MANAGEMENT OF LOCAL REGROWTHS IN A WATCH-AND-WAIT PROGRAMME FOR RECTAL CANCER

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Introduction: Rectal cancer patients with a clinical complete response to neoadjuvant treatment can be treated with a watch-and-wait approach. However, one of the concerns in a watch-and-wait approach is pelvic failure in patients with local regrowth.

Aims and Methods: The aim of this study was to evaluate the management and oncological outcomes of patients with local regrowth in a watch-and-wait programme. All patients with a local regrowth after an initial watch-and-wait approach between January 2005 -March 2018 were identified from 2 pooled prospectively collected cohorts of rectal cancer patients with a clinical complete response after neoadjuvant treatment treated with a watch-and-wait approach. Type and outcome of salvage treatment were assessed. Long-term oncological outcome was assessed using Kaplan-Meier estimates, calculated from the end of neoadjuvant treatment.

Results: 81 out of 379 (21.3%) watch-and-wait patients developed a local regrowth. Median overall follow-up time was 22 months (range 3-89). Median time to local regrowth was 9 months (range 3-24). Salvage surgery was performed in 78/81 (96%) patients. Reasons for not performing salvage surgery were: refusing salvage treatment (n = 1), presence of distant metastasis (n = 1) and death after diagnosis of regrowth (n = 1). Local excision was performed in 26 (33%) patients with regrowth, of which 5 (6%) patients had a completion TME. Low anterior resection was performed in 26 (33%) patients, an abdominoperineal resection in 24 (31%) patients, and type of resection was unknown in 2 (3%) patients. The R0 rate after TME was 94.5%. 1 patient had a pelvic recurrence after salvage treatment, and received palliative systemic treatment in the setting of widespread metastatic disease. 3-year distant metastasis free survival was 88.7% and 3-year overall survival was 96.7%.

Conclusion: In patients with a regrowth after wait-and-wait salvage surgery was performed in 96%. Pelvic failure was very rare.
Disclosure: Nothing to disclose

MONDAY, OCTOBER 22, 2018   14:00–15:30
Autoimmune hepatitis – Room F1_____

OP049 THE ANTI-INFLAMMATORY RECEPTOR TREM2 PROTECTS THE LIVER FROM CHOLESTATIC INJURY IN MICE

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Introduction: Cholestasis is a common feature of different cholangiopathies such as PSC and PBC. Cholestasis causes liver inflammation and injury in epithelial cells, thereby inducing ductular reaction and activation of non-parenchymal liver cells [i.e. kupffer cells (KC) and hepatic stellate cells (HSC)] that ultimately results in biliary fibrosis. Liver injury leads to alterations in the intestine epithelial barrier, enabling the translocation of bacterial components to the liver via the portal vein. In the liver, these bacterial components bind to toll-like receptors (TLRs) expressed in KC and HSC promoting inflammation and progression of the wound-healing response. The triggering receptor expressed on myeloid cells 2 (TREM2) is an anti-inflammatory receptor that inhibits TLR-mediated signaling.

Aims and Methods: This study aims to evaluate the role of TREM2 in cholestasis. With this purpose, *TREM2* expression was analyzed in the liver of PBC and PSC patients and normal controls. Wild type (WT) and *Trem-2* knock out (*Trem2*-/-) mice were subjected to bile duct ligation (BDL), or sham, for 7 days. Thereafter, sera were collected for the analysis of biochemical markers and livers were obtained for further histological and gene expression analysis. *In vitro*, KCs were isolated from WT and *Trem2*-/- mice, treated with lipopolysaccharide (LPS) and cytokine and chemokine expression was assessed.

Results: *TREM2* expression is upregulated in the liver of PBC and PSC patients as compared to healthy controls; this receptor was also upregulated in a BDL based model of murine cholestasis. After BDL, *Trem2*-/- mice showed exacerbated liver injury with increased hepatocyte necrosis and immune-cell infiltration compared to WT, as assessed by H&E staining. This was accompanied by augmented expression levels of cholangiocyte (*Ck-7* and *Ck- 19*) and proliferation markers (*Ki67* and *PCNA*), indicating that *Trem-2*-/- animals suffered exacerbated ductular reaction. Likewise, *Col1a1* and *α-Sma* mRNA levels revealed enhanced fibrogenesis in *Trem2*-/- livers compared to WT after BDL. In addition, the expression of proinflammatory cytokines (*Il-6* and *Tnf-α*) and chemokines (*Mcp-1* and *Cxcl1*) were upregulated in these mice. The number of neutrophils infiltrating the liver was also increased in *Trem2*-/- mice. LPS-treated *Trem2*-/- KC displayed increased expression of pro-inflammatory (*Il-6*, *Il-1β* and *Tnf-α*) and chemokine (*Cxcl1*) markers, both at mRNA and protein level, as compared to WT-derived KC.

Conclusion: *TREM2* is overexpressed in the livers of PBC and PSC patients and during experimental cholestasis in mice. This receptor negatively regulates TLR4-mediated pro-inflammatory cytokine expression in KC, thereby protecting the liver from cholestatic injury in mice.
Disclosure: Nothing to disclose

OP050 TARGETING LIVER INFLAMMATION USING CD64-TARGETED LIPID NANOPARTICLES AS A NOVEL DRUG DELIVERY SYSTEM

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Introduction: Inflammatory macrophages play a critical role in liver inflammation. Hepatocellular damage, instigated by viral infections, alcohol abuse or metabolic syndrome, results in the recruitment and activation of inflammatory cells mainly macrophages in the liver. The inflammatory macrophages initiates the process of liver injury progressing from liver fibrosis to cirrhosis and hepatocellular carcinoma. Therefore, selective targeted inhibition of the inflammatory macrophages would be a promising approach to attenuate liver inflammation or inflammatory liver diseases. We identified CD64 receptor as a prospective target for pro-inflammatory macrophages.

Aims and Methods: In this study, we developed a novel delivery system i.e. CD64-targeted lipid nanoparticles to achieve M1-specific uptake and to selectively deliver anti-inflammatory drugs to inhibit M1 inflammatory macrophages thereby ameliorating liver inflammation. Specificity of CD64 receptor was evaluated *in vitro* in murine and human macrophages and *in vivo* in CCl$_4$-induced acute liver inflammation mouse model. Novel CD64 targeting peptide was designed and CD64 targeting peptide coated lipid nanoparticles were synthesized, characterized and evaluated for M1-specific uptake in murine and primary human macrophages using FACS. Prednisolone-encapsulated CD64-targeted lipid nanoparticles were synthesized, characterized and investigated for efficacy *in vitro* in RAW macrophages, human THP1 monocytes, primary bone marrow derived macrophages (BMDMs), primary human monocytes, primary human Kupffer cells, and *in vivo* in acute CCl$_4$-induced liver injury mouse model.

Results: Significant up-regulation of CD64 receptor was observed in murine and human LPS- and IFNγ-differentiated M1 macrophages *in vitro*, *in vivo* in liver fibrosis mouse models and in human fibrotic liver tissues. CD64-targeted lipid nanoparticles showed favorable size, stability and drug entrapment efficiency. Significantly, CD64-targeted nanoparticles showed M1-specific uptake, while nanoparticles without targeting moiety/scrambled peptide showed comparatively reduced internalization at different time points. Furthermore, targeted nanoparticles demonstrated significantly reduced uptake in M2 restorative macrophages. No significant uptake in other liver cells was observed. Antibody blocking of CD64 receptor significantly inhibited uptake in M1 macrophages strongly suggesting CD64-mediated uptake. Prednisolone-encapsulated CD64-targeted nanoparticles showed significant reduction in M1-specific inflammatory markers (i.e. CCL2, iNOS, IL-6, IL-1β and TNFα) *in vitro* in RAW cells, human THP1 monocytes, primary murine BMDMs, primary human monocytes and primary human kupffer cells. *In vivo*, prednisolone-encapsulated targeted nanoparticles demonstrated specific liver uptake, highly significant attenuation in intra-hepatic inflammation and fibrotic parameters as compared to free prednisolone and non-targeted liposomes.

Conclusion: This study presents a novel strategy to selectively target M1 Macrophage therefore holds great promise for diagnosis and therapeutic treatment of liver fibrosis and inflammatory liver diseases.

Disclosure: Nothing to disclose

MONDAY, OCTOBER 22, 2018   14:00–15:30
Advances in pancreatio-biliary endoscopy – Room K_____

OP051 IMPACT OF ELECTRICAL PULSE CUT MODE DURING ENDOSCOPIC PAPILLECTOMY: A PROSPECTIVE MULTICENTER RANDOMIZED CLINICAL TRIAL

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Introduction: Endoscopic papillectomy (EP) is increasingly being used for ampullary adenoma removal. Treatment advances including pancreatic stent placement and clipping for distal-side mucosal defects have increased EP safety; however, it remains dangerous and challenging. The ideal power output and mode of electrosurgical current used for EP have not yet been established. Selection of the mode of current generally depends on the endoscopist's preference. To perform the treatment more safely and reliably, we performed this randomized, controlled trial to examine the mode of electrosurgical current at the time of resection during EP.

Aims and Methods: In this randomized, single-blind, prospective, multicenter trial, patients with an ampullary adenoma who were undergoing EP were recruited. EP was performed using a standardized algorithm[1] and patients were randomized to undergo either EP with "Endocut" (EP-E) using a combination of pure cut and soft coagulation, or EP with "Autocut" (EP-A) using pure cut only. The primary outcomes were the incidence of procedure-related bleeding and pancreatitis. Overall successful complete resection, pathological findings, and another adverse event were secondary endpoints.

Results: 60 patients were enrolled during 2 years. Delayed bleeding developed in 9 (15%) patients: 4 (13.3%) in the Ep-E group and 5 (16.7%) in the EP-A group (p = 1.00). Immediate bleeding occurred in 43% (13 of 30) of patients in the Ep-E group and 60.0% (18 of 30) in the EP-A group (p = 0.20). Bleeding severity was mild in all cases. 8 patients (26.7%; 7 mild, 1 moderate) in the EP-E group had pancreatitis versus 9 (30.0%; 8 mild, 1 moderate) in the EP-A group. The primary outcome did not differ between groups (p = 0.77). The rate of crush artifacts due to cauterizing was higher in the EP-E than EP-A group (27% vs 3.3%, p = 0.03). There were no procedure-related deaths.

Conclusion: Autocut mode has similar efficacy and safety to Endocut mode for EP. Crush artifacts of resected specimens may occur frequently in mucosal resection with Endocut mode (Clinical trial registration number: UMIN000021382.)

Disclosure: Nothing to disclose

Reference

1. Tsuji S, Itoi T, Sofuni A et al. Tips and tricks in endoscopic papillectomy of ampullary tumors: single-center experience with large case series (with videos). *Journal of hepato-biliary-pancreatic sciences.* 2015 Jun; 22(6): E22–7.

OP052 LUMEN-APPOSING METAL STENTS (LAMS) FOR PANCREATIC FLUID COLLECTIONS ARE SAFE AND ASSOCIATED WITH A LOW RATE OF DELAYED ADVERSE EVENTS AT THE TIME OF CLINICAL FOLLOW-UP: A MULTICENTER RETROSPECTIVE ANALYSIS

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Introduction: Endoscopic transmural drainage (TMD) with dedicated lumen-apposing metal stents (LAMS) is routinely performed for the management of symptomatic pancreatic fluid collections (PFCs) (pancreatic pseudocyst [PP] or walled-off necrosis [WON]). There has been an increasing concern regarding the timing of LAMS removal given recent reports on higher than expected delayed adverse events at the time of clinical follow-up.

Aims and Methods: Evaluate clinical outcomes at the time of follow-up imaging and endoscopy after LAMS insertion for symptomatic PFCs. Multicenter retrospective analysis of consecutive patients with EUS-guided LAMS placement for symptomatic PFC from January 2010 to May 2017. Main outcomes included resolution of the PFC on follow-up imaging, and findings on follow-up endoscopy after initial LAMS placement, including the rate of adverse events (e.g. delayed bleeding, stent occlusion/migration, buried stent syndrome).

Results: A total of 122 patients (mean age 51 years; 68% male) underwent successful LAMSs insertion for 56 WONs (88%) and 55 PPs (95%). The mean size of the PFC was 10.6 cm. Resolution of PFC on cross-sectional imaging was significantly higher for PP (96%) vs. WON (62%) at a median of 4 weeks after LAMS insertion (p < 0.001). More patients with PP (47; 82.5%) than WON (40; 62.5%) underwent LAMS removal at the time of follow-up endoscopy (p = 0.028). Stent occlusion was the most common adverse event noted on follow-up endoscopy (29.5% in WON vs. 17.5% in PP; p = 0.2), followed by stent migration (4.9% in WON vs. 8.6% PP; p = 0.5) and buried stent syndrome (1.6% WON vs. 1.8% PP; p = 1.0). There were no cases of delayed bleeding. There were no patients lost to follow-up. Size of PFC, diameter of LAMS (10 mm vs 15 mm), additional stents through LAMS (yes vs. no), debridement (yes vs. no) were not associated with the likelihood of stent occlusion seen on follow-up endoscopy on multivariate analysis.

Conclusion: EUS-guided LAMS placement for PFC is safe; with serious adverse events rarely encountered at the time of clinical follow-up and stent removal. The rate of PFC resolution on imaging at a median of 4 weeks after LAMS insertion was significantly lower for WON vs. PP. Future large prospective studies are needed to better define the course of PFCs and optimize management protocol for patients with PFC treated with LAMS.

Disclosure: Nothing to disclose

OP053 OPTIMIZING OUTCOMES OF SINGLE OPERATOR CHOLANGIOSCOPY (SOC)-GUIDED BIOPSIES: RESULTS OF A RANDOMIZED TRIAL

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Introduction: Although considered the most reliable and sensitive method for tissue acquisition in patients with indeterminate bile duct strictures (IBDS), there are scant data on methods to optimize the sampling and specimen processing techniques at single operator cholangioscopy (SOC).

Aims and Methods: The aim was to determine the optimal method of specimen processing and to identify the number of biopsies required to establish a definitive diagnosis in patients undergoing SOC-guided biopsies of IBDS.
Patients with IBDS were randomized at ERCP to undergo specimen processing using the onsite (touch imprint cytology [TIC]) or offsite (cell block) method. A maximum of seven biopsies were performed in each cohort. In onsite cohort, biopsies were performed until the diagnosis was established at TIC. In offsite cohort, to determine the optimum number of biopsies required for establishing diagnosis, three biopsies were placed in the first container and four in the second. Main outcome measure was to compare the operating characteristics of onsite versus offsite specimen processing techniques. Secondary outcome measure was to determine the number of biopsies needed to establish definitive diagnosis. Final diagnosis was established at surgery or a minimum clinical follow-up of 12 months.

Results: 62 patients were randomized: onsite = 32, offsite = 30. Location of stricture was common bile duct (n = 19), common hepatic duct (n = 16), hilum (n = 18) and intrahepatic ducts (n = 9). Final diagnosis was benign disease in

35 and malignancy in 27. There was no significant difference in diagnostic accuracy (93.8 vs. 90.0%, p = 0.67), sensitivity (85.7 vs. 76.9%, p = 0.65), specificity (100 vs. 100%, p = 0.99), positive predictive value (100 vs. 100%, p = 0.99) or negative predictive value (90.0 vs. 85.0%, p = 0.99) between the onsite versus offsite cohorts, respectively. A diagnosis was established with a median of 1 biopsy (IQR 1-1.5) in the onsite cohort; false positives were encountered in 1 patient and false negatives in 2. The diagnostic accuracy was identical (90.0%) whether patients underwent 3 or 4 biopsies in the offsite cohort; false negatives were encountered in 3 patients.

Conclusion: For centers without onsite cytopathology support, performing three SOC-guided biopsies of the biliary stricture and processing the specimen offsite yields a diagnostic accuracy of 90%.

Disclosure: Shyam Varadarajulu and Robert Hawes are Consultants for Boston Scientific Corporation and Olympus America Inc. All other authors have no disclosures to declare.

OP054 APPLICATIONS OF INTRAOPERATIVE PANCREATOSCOPY FOR THE INVESTIGATION OF PANCREATIC IPMNS

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Introduction: Intraoperative pancreatoscopy is a promising tool that might guide surgical resection for suspect main duct involving IPMNs. Data about its diagnostic yield and its clinical impact are lacking.

Aims and Methods: To assess the diagnostic yield and clinical impact of intraoperative pancreatoscopy in patients operated for suspect main pancreatic duct involving IPMNs in a retrospective, single center, cohort study. Patients undergoing surgery for suspect main duct or mixed type IPMNs (MPD ≥ 5 mm) underwent intraoperative pancreatoscopy and frozen section analysis. In all patients undergone extended resection due to suspect pathological pancreatoscopic findings, the final histological specimen was compared with the intraoperative frozen section analysis.

Results: From 2015 to 2017, 46 patients, 52.1% males, median age 67.3 years (45-82 years) underwent intraoperative pancreatoscopy. No procedure related complications were observed. Intraoperative pancreatoscopy changed the operating course in 30 patients (65.2%), leading to extended resections in 20 (43.4%) and to parenchyma sparing procedures in 10 (21.7%). Among patients who underwent extended resections due to pancreatoscopic findings, 6 (30%) have shown skip lesions at final histology, that had not been detected at intraoperative frozen section analysis. The application of both intraoperative pancreatoscopy and frozen section analysis lead to 85.7% sensitivity and 92.3% specificity for the detection of pathological tissue in the remnant pancreas.

Conclusion: Intraoperative pancreatoscopy is a safe and feasible procedure and might allow the detection of skip lesions during surgery for suspect main duct involving IPMN. It has changed the operative management strategy in 65.2% of patients, and in 30% of patients, it significantly impacted the oncological radicality, allowing the detection of early lesions suitable for radical curative surgery.

Disclosure: Nothing to disclose

OP055 ENDOSONOGRAPHY-GUIDED BILIARY DRAINAGE FOLLOWING FAILED ERCP: EXPERIENCE FROM A UK TERTIARY REFERRAL CENTRE

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Introduction: Percutaneous transhepatic biliary drainage (PTBD) is associated with significant morbidity and prolonged hospital stays. [1,2] Endosonography-guided biliary drainage (EUS-BD) is an alternative to PTBD when endoscopic retrograde cholangiopancreatography (ERCP) biliary decompression has failed. EUS-BD transmurally, or facilitated transpapillary drainage is possible via the intrahepatic or extrahepatic bile ducts.

The aims of this study were to review the technical success and adverse events with EUS-BD procedures performed at a tertiary care referral centre.

Aims and Methods: Data were prospectively recorded on EUS-BD procedures performed at Leeds Teaching Hospitals NHS Trust from 1st January 2016 to 26th April 2018. Procedures were performed by 2 experienced endoscopists trained in interventional EUS and ERCP. Recorded variables were technical success, adverse events, length of stay, 30-day re-admission rate and all-cause mortality.

Results: 30 patients (12 male) were included. Indications for drainage were choledocholithiasis (n = 8) and malignant obstruction (n = 22). Reasons for failed ERCP were obscured intradiverticular ampulla (n = 8), Malignant biliary obstruction prohibiting wire guided access (n = 11); duodenal stenosis with inaccessible papilla (n = 8; malignant, n = 6; Crohn's, n = 1), and failed cannulation (tumour infiltration of ampulla, n = 3). The route of attempted biliary drainage was choledochoduodenostomy with lumen-apposing metal stent (LAMS) in 17, EUS-guided rendezvous in 9, and hepaticogastrostomy in 4. Overall technical success was achieved in 29 (97%), with 1 patient requiring PTBD. 29 cases (97%) were achieved under conscious sedation with midazolam and fentanyl. There were 2 significant bleeds; one from the sphincterotomy after a rendezvous procedure and one from a hepaticogastrostomy. Both bleeds were treated with a further endoscopic procedure. There was one instance of LAMS maldeployment, salvaged with fully covered metal stent placement over preserved wire access, and one TIA related to discontinuation of anticoagulation. 8 cases were performed as elective, out-patient procedures. Median length of stay post procedure was 6 days (range 2–80 days) for inpatient cases. There were no re-admissions within 30 days. Of the 14 patients who have died, median survival post procedure was 78 days (range 18–275 days).

Conclusion: This study adds to the existing literature supporting EUS-BD as an effective and safe alternative to PTBD after failed ERCP, which can be performed under conscious sedation, often in the outpatient setting. Our technical success rate is comparable to published series. [3] Adverse event rates compared favourably with accepted rates from PTBD. [1] Experience and improved instruments should lead to further improved results. Definitive prospective, randomised studies are needed to compare outcomes for percutaneous versus EUS-guided drainage.

Disclosure: Nothing to disclose

References

1. Covey AM, Brown KT. Percutaneous Transhepatic Biliary Drainage. *Tech Vasc Interv Radiol* 2008; 11: 14–20. doi:10.1053/j.tvir.2008.05.003 .
2. Winick AB, Waybill PN, Venbrux AC. Complications of percutaneous transhepatic biliary interventions. *Tech. Vasc. Interv. Radiol.* 2001; 4: 200–6. doi:10.1016/S1089- 2516(01)90026-5 .
3. Prichard D, Byrne MF. Endoscopic ultrasound guided biliary and pancreatic duct interventions. *World J Gastrointest Endosc* 2014; 6: 513–24. doi:10.4253/wjge.v6.i11.513.

OP056 EUS GUIDANCE FOR BILIARY AND PANCREATIC DUCT ACCESS AND DRAINAGE IN A TERTIARY CARE CENTER

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Introduction: Endoscopic ultrasonography-guided ductal access & drainage (EUS-D) of biliary or pancreatic ducts offer an alternative to percutaneous drainage after failed ERCP. The actual utility of EUS-D in tertiary care centers is unknown. A complete assessment of EUS-D role requires considering the full spectrum ERCP failure beyond failed cannulation, all populations and indications.

Aims and Methods: Prospective cohort study including procedures aiming at duct drainage performed June 2013-Nov 2015 in a tertiary care center. Referral centers were stratified as primary (no ERCP), secondary (< 200 ERCPs/year) or tertiary (> 200 ERCPs/year & IR). EUS-D was performed after failed ERCP, except in selected patients with altered anatomy or submitted from tertiary centers, where it was performed directly. Procedures were classified as follow-up or index if patients had prior endoscopic duct access or not. Follow-up procedures included ERCP, EUS-D, endoscopic transluminal cholangio-pancreatography (ETCP) through mature transmural duct fistulas, and combined (ERCP with any antegrade approach). Main outcomes: Rates of procedural ERCP failure, EUS-D and PTBD during the study period.

Results: 1625 patients underwent 2205 procedures (median 1 procedure/patient IQR: 1-2), 1274 index and 931 follow-up procedures. Index procedures are summarized in table 1. Overall, EUS-D played a role in 116/1274 (9.1%) index procedures, including 39/67 (58.2%) patients with surgically altered anatomy (SAA) and 77/1207 (6.4%) patients with native anatomy. Most EUS-Ds performed were transmural drainages (88/116; 75.9%), while EUS-guided rendezvous was performed in 12/116 (10.3%), antegrade EUS-D and combined procedures were performed each in 8/116 (6.9%). Direct EUS-D was performed in 30/67 (44.8%) patients with SAA and 15/1207 (1.2%) patients with native anatomy (including 9/25 gastric outlet obstructions and 5 patients from tertiary centers). EUS-guided drainage was performed after failed cannulation in 53 cases, 45/1192 (3.8%) subjects with native anatomy and 8/37 (21.6%) subjects with SAA. Finally, 7 (1.5%) patients with native anatomy and one case of SAA (5%) underwent EUS-D despite successful cannulation. Only 3/1274 index procedures (0.2%) required PTBD. EUS-D was performed more frequently in subjects from tertiary referral centers, 25/69 (36.2%), compared to secondary, 36/228 (15.8%) or primary referral centers 55/977 (5.6%), p < 0.001. EUS-D was performed in 17/87 (19.5%) benign and 67/317 (21.1%) malignant strictures. In the

remaining indications, EUS-D was performed in 32/870 (3.7%) procedures, p < 0.001. 931 follow-up procedures were performed in 352 patients. Overall, the proportion of ERCPs among follow-up procedures was 85.7%, while ETCPs accounted for 7.4%, EUS-Ds for 4% and combined procedures for 2.9%.

Conclusion: EUS-D was performed overall in 6.9% of 2205 biliary and pancreatic duct drainage procedures (7.6% referred from high ERCP volume centers), whereas PTBD was required in 0.1%. The EUS-guided approach integrated with ERCP could be an optimal option of drainage at index and follow-up procedures.

	Overall (n = 1274)	Primary referral centers (n = 977)	Secondary referral centers (n = 228)	Tertiary referral centers (n = 69)
Male sex, n (%)	641 (50.3%)	481 (49.2%)	122 (53.5%)	38 (55.1%)
Age, median (IQR)	76.5 (64.5–83.5)	76.5 (64.5–83.5)	76.5 (64.5–84.5)	70.5 (64.5–80.5)
Surgically altered anatomy, n (%)	67 (5.3%)	35 (3.6%)	18 (7.9%)	14 (20.3%)
Stones, n (%)	476 (37.4%)	380 (38.9%)	74 (32.5%)	22 (31.9%)
Malignant strictures, n (%)	317 (24.9%)	194 (19.9%)	100 (43.9%)	23 (33.3%)
Papillary stenosis, n (%)	276 (21.7%)	243 (24.9%)	25 (11%)	8 (11.6%)
Benign strictures, n (%)	87 (6.8%)	66 (6.7%)	12 (5.3%)	9 (13%)
Other findings, n (%)	117 (9.2%)	93 (9.5%)	17 (7.5%)	7 (10.1%)

[Table 1: Description of index procedures]

Disclosure: Dr. Manuel Perez-Miranda is a consultant for Boston Scientific and M.I. Tech and has lectured for Boston Scientific and Olympus. None of the remaining authors has potential conflicts of interests.

MONDAY, OCTOBER 22, 2018   14:00–15:30
Novel technical developments in basic science – Room M

OP057 DEVELOPMENT OF DECELLULARIZED HUMAN GUT AS A NATURAL 3D-PLATFORM FOR INTESTINAL BIOENGINEERING

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Introduction: As one of the largest and most functionally complex organs of the human body, the intestine is vulnerable to many disorders, which are burdened by high social costs. Options to investigate these functions with direct relevance to the human condition remain severely limited when using conventional two-dimensional (2D) cell cultures and animal models. The field of tissue engineering has extensively explored the development of *de novo* tissue in order to restore diseased phenotype. A major opportunity exists to exploit these natural scaffolds as 3-dimensional (3D) models for the *in vitro* study of gastrointestinal diseases.

Aims and Methods: We here designed 2 decellularization protocols to develop acellular 3D scaffolds from both tubular and small scale cube human gut.

Results: The resultant scaffolds showed preservation of extracellular matrix (ECM) protein composition and 3D architecture. Decellularized human gut scaffolds were reseeded with human epithelial colorectal adenocarcinoma cells (Caco-2) and primary human intestinal myofibroblasts for up to 14 days. Engrafted cells showed excellent viability, motility, proliferation and remodelling of ECM. In addition, mRNA expression changed when comparing primary human intestinal myofibroblasts cultured in 2D versus 3D scaffolds. Compared to fibroblasts cultured in 2D, ACTA2 and COL1A1 mRNA expression were significantly downregulated whereas TGF-β1 and MMP-3 expression were increased in 3D cultured myofibroblasts. Moreover, a long-term treatment with TGFβ1 and PDGF-BB, to mimic a diseased model, induced further gene expression in 3D whereas desensitization towards the stimuli was observed in 2D cell cultures.

Conclusion: Our results present 2 innovative and effective protocols for the decellularization of human gut. These human-derived intestinal scaffolds may

represent an innovative platform for disease modelling, biomarker discovery and drug testing in gastrointestinal fibro-carcinogenic disorders.

Disclosure: Nothing to disclose

OP058 A COHERENT ROADMAP TO GENERATE EITHER PANCREATIC ACINAR OR DUCT-LIKE CELLS FROM HUMAN PLURIPOTENT STEM CELLS CHALLENGES PANCREATIC CANCER BIOLOGY

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Introduction: Cell bioengineering approaches not only hold great promise to replace and regenerate dysfunctional tissue for improved life quality of the diseased patient but may also provide more sophisticated disease models. Engineering approaches to build human pancreatic tissue resembling acinar, ductal and endocrine tissue have been hampered by the complexity of the pancreas. Human pluripotent stem cells (PSCs) may provide the appropriate bioengineering platform for developmental and biomedical studies due to their capability to differentiate into every cell type in the human body.

Aims and Methods: PSCs typically yield heterogeneous population, while certain disease models require homogenous populations. We previously succeeded in generating virtually pure cultures of human pancreatic progenitor cells followed by spontaneous differentiation in a 3D-culture environment to allow acinar ductal commitment (Hohwieler, GUT, 2017). These cultures are the basis of the current approach.

Results: We have implemented signals controlling embryonic lineage fate bifurcations to efficiently yield the desired cell types through exclusion of alternate fates. Specifically, we applied signaling molecules and growth factors inducing either acinar or ductal cells, while inhibiting the respective counter lineage with inhibitors. This approach yields virtually pure pancreatic acinar or duct-like cells generated from human PSCs resembling key features of adult human pancreatic counterparts as shown in an established test battery. Thereby, we provide a coherent roadmap to generate the 2 mature exocrine pancreatic cell types, acinar and ductal cells. Finally, we have applied this novel tool box to dissect the cell type of origin of pancreatic cancer.

Conclusion: The innovative model presented gives novel opportunities to study developmental processes in the pancreas and bears the unique chance to dissect the cell type of origin of pancreatic cancer

Disclosure: Nothing to disclose

MONDAY, OCTOBER 22, 2018   14:00–15:30
TSTM: Stem cells as a therapeutic option – Room 1.61/1.62

OP059 *BIFIDOBACTERIUM ANIMALIS SUBSPECIES LACTIS* ENGINEERED TO PRODUCE MYCOSPORIN-LIKE AMINO ACIDS IN COLORECTAL CANCER PREVENTION

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Introduction: Colorectal cancer (CRC) is the third most common cancer and the third leading cause of cancer-related deaths in Western countries. The pathogensesis of CRC is a multi-step and multi-factorial process. Disruption of the gut microbiota has been associated with gastrointestinal diseases such as colorectal cancer [1]. The genus *Bifidobacterium* is considered an important component of the gastrointestinal microbiota. It has an important role in several aspects of gastrointestinal homeostasis: immunologic, neuro-hormonal, and metabolic. *Bifidobacterium animalis subsp. lactis* is a well documented probiotic form of *Bifidobacterium*. Mycosporin-like Amino Acids (MAAs) are low molecular weight amino acids. MAAs are unique components of red seaweeds and seaweed products are known as nutrional supplements in bowel diseases. *Bifidobacterium animalis* does not produce MAAs. If one could create a *Bifidobacterium animalis* producing MAAs via genetic engineering, it should exert more potent immunostimulatory properties and might become a more potent therapeutic agent in colorectal cancer

Aims and Methods: Abiosynthetic gene cluster for MAAs has been demonstarted in Gram-positive bacteria [2]. Anabaena variabilis PCC 7937 (Cyanobacterium) is able to synthesize MAAs [3]. Genome studies identified a combination of genes, YP_324358 (predicted DHQ synthase) and YP_324357 (O-methyl transferase), which were present only in *A. variabilis* PCC 7937 and missing in other *Cyanobacteria. Anabaenasp. Anabaenasp*. PCC 7120 has been induced to produce MAAs after genomic transfer (YP_324358 and YP_324357 genes) from *Anabaena variabilis* PCC 7937 [3]. The comparative genome analysis revealed that the *Bifidobacterium animalis subsp. Lactis*. KLDS 2.0603 strain has most similar whole genome sequence to the BB-12 strain [4]. It seems that *Cyanobacterium* is the source of MAAs and we hypothesize that the genes of *Cyanobacterium* involved in MAAs biosynthesis could be transferred to the strain *Bifidobacterium animalis subsp. lactis* BB-12 [5].

Results: Genetically modulated *Bifidobacteria* can modulate the immune system to further reduce chronic inflammation and increase colonic mucosal stability. More decreased chronic inflammation and increased mucosal stability might have the promoting role in colorectal tumorigenesis at different stages including tumor initiation, promotion, progression and metastasis [6]. Also experimental data reveal the important role of NF-κB in colon tumor cells as well as in the surrounding "cancerous" and reactive microenvironment [7]. It can be predicted that this combination may be more effective in preventing colorectal cancer through NF-κB pathway. Elevated TBARS levels are associated with colon cancer initiation and progression and this combination can prevent cancer formation by lowering TBARS levels [8].

Conclusion: Significant progress has been made in recent years in recognizing the importance of gut microbiota to colorectal cancer. Key findings include the discovery of oncogenetic mechanisms that link the gut microbiome to colorectal cancer, including reduced SCFA production, chronic inflammation, alterated transcription factors and the immune response. Creating *Bifidobacteria* species producing MAAs viagenetic engineering could result in a bacterium that is more potent in its effect on human health. MAAs produced via genetic engineering can be used not only as a probiotic, also as a pharmacological agent in CRC.

Disclosure: Nothing to disclose

References

1. Zackular JP, Baxter NT, Iverson KD, Sadler WD, Petrosino JF, Chen GY, Schloss PD. The gut microbiome modulates colon tumorigenesis. *MBio*. 2013; 4(6).
2. Miyamoto KT, Komatsu M, Ikeda H. Discovery of gene cluster for mycosporin-like amino acid biosynthesis from Actinomycetales microorganisms and production of a novel mycosporine-like amino acid by heterologous expression. *Appl Environ Microbiol* 2014; 80: 5028–5036.
3. Singh SP, Klisch M, Sinha RP, Hader DP. Genome mining of mycosporine-like amino acid (MAA) synthesizing and non-synthesizing cyanobacteria: A bioinformatics study. *Genomics* 2010; 95: 120–128.
4. Zhu DQ, Liu F, Sun Y, Yang LM, Xin L. Genome-wide identification of small RNAs in Bifidobacterium animalis subsp. lactis KLDS 2.0603 and their regulation role in the adaption to gastrointestinal environment. *PLoS ONE* 2015; 10.
5. Bozkurt HS, Kara B. Bifidobacterium andMycosporin-like Amino Acid Cooperation: A New Era for Intestinal Diseases Treatment? *JGastric Disord Ther* 2017; 3(2).
6. Hu T, Li LF, Shen J, Zhang L, Cho CH. Chronic inflammation and colorectal cancer: the role of vascular endothelial growth factor. *CurrPharm Des*. 2015; 21(21): 2960–7.
7. Perkins ND. The diverse and complex roles of NF-kappaB subunits in cancer. *Nat Rev Cancer* (2012) 12: 121–132.
8. Nayak BS, Pinto S. Protein thiols and thiobarbituric acid reactive substance status in colon cancer patients. *Scand J Gastroenterol*. 2007 Jul; 42(7): 848–51.

OP060 LONG-TERM EFFICACY AND SAFETY OF ALLOGENEIC BONE MARROW-DERIVED MESENCHYMAL STROMAL CELLS FOR PERIANAL FISTULAS IN PATIENTS WITH CROHN'S DISEASE: A 4-YEAR FOLLOW-UP STUDY

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Introduction: Perianal fistulas are regularly observed in patients with Crohn's disease. Very few effective treatment options to accomplish closure of the fistula track have been reported. The results from our dose-finding study (allogeneic bone marrow-derived mesenchymal stromal cell (MSC) therapy for perianal fistulas in Crohn's disease[1]) showed that local administration of MSCs in perianal fistulizing Crohn's disease is safe and local injection of 1×10^7 MSCs and 3×10^7 MSCs promoted fistula healing. In the current study we present the 4-year efficacy and safety data of 2 of the 3 dose cohorts.

Aims and Methods: All patients from cohort 1 (2 patients placebo; 5 patients 1×10^7 MSCs) and cohort 2 (2 patients placebo; 5 patients 3×10^7 MSCs) were invited for evaluation. The patients treated in cohort 3 (2 patients placebo; 5 patients 9×10^7 MSCs) will be seen in the next few months. Adverse events were registered and fistula healing (e.g. no fistula discharge) was evaluated. All MSC-treated patients were asked to undergo a pelvic MRI scan.

Results: From both groups of patients treated with MSCs, 4 out of 5 patients were available for long-term follow-up after 4 years. 1 of the patients in cohort 1 died because of an adenocarcinoma of the cecum[1] and one patient in cohort 2 was lost to follow-up. With regards to therapy efficacy, fistula closure 4 years after MSC-therapy was observed in 3 out of 4 patients treated with 1×10^7 MSCs and in 4 out of 4 patients treated with 3×10^7 MSCs. The single patient with an active fistula never experienced a closed fistula after treatment with MSCs. All 4 placebo-treated patients in cohort 1 and 2, still had draining fistulas at deblinding of the study and were offered post study treatment with MSCs. 2 of these 4 patients were indeed treated, now 2 years ago (both are not included in the current 4-year follow-up study). The 2 placebo-treated patients that denied the post study treatment still have fistula drainage after 4 years follow-up. A total of 6 out of 8 evaluated MSC treated patients were willing to undergo a pelvic MRI in the 4 year follow-up visit. In all 6 patients, the original perianal fistula tract(s) were still seen on MRI.

Several adverse events were reported both in placebo and in MSC-treated patients. Most of the reported adverse events however are in line with the nature of the underlying disease and immunosuppressive medication (e.g., exacerbation of Crohn's disease, pneumonia, uveitis). However, in the long-term follow-up in 1 patient treated with 3×10^7 MSCs, a superficial lesion in the distal rectum showed the presence of Epstein-Barr virus-associated B-cell proliferative disease. This patient is currently being treated with chemotherapy. Molecular and cellular analysis indicated no relation with MSC-therapy.

Conclusion: After 4 years, 8 of 10 patients treated with 1×10^7 or 3×10^7 MSCs could be evaluated and 88% of these patients reported the absence of draining fistulas, compared to 0% of the patients treated with placebo after 3 years of follow-up. 2 serious adverse events have been reported in the long-term follow-up, but found not to be directly related to MSC therapy. The results of cohort 3 will become available in the summer of 2018. Our preliminary data show that long-term fistula closure can be achieved with a single MSC treatment. More long-term data are needed to further complete the safety profile of MSC therapy for Crohn's fistulas.

Disclosure: Nothing to disclose

Reference

1. Molendijk I, Bonsing BA, Roelofs H, et al. Allogeneic Bone Marrow-Derived Mesenchymal Stromal Cells Promote Healing of Refractory Perianal Fistulas in Patients With Crohn's Disease. *Gastroenterology*. 2015; 149: 918–927.

OP061 QUANTITATIVE CHANGES OF ENTERIC NEURONS CORRELATE WITH CLINICAL FEATURES IN PATIENTS WITH SEVERE DYSMOTILITY

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Introduction: Severe gastrointestinal symptoms are often associated with markedly perturbed enteric motility, is a sign of underlying enteric neuropathies. Current methods used to demonstrate enteric neuropathies are mainly based on classic qualitative histopathological / immunohistochemical evaluation. This standard approach, however, is hampered by data interpretation, inter-observer variation and often insufficient expertise of pathologists.

Aims and Methods: In this study, the quantitative analysis of enteric neurons in patients with severe dysmotility (SD) was performed by 3 independent and skilled pathologists and correlated with clinical features.

Jejunal full-thickness biopsies were collected from 32 well characterized SD patients (16-77 years; 22 F); and from n = 8 controls (47-73 years 4F). A symptom questionnaire was fulfilled prior to surgery. Patients were subdivided according to a previous qualitative histopathological evaluation: n = 10 with an apparently normal (AN) neuro-muscular layer; n = 14 with inflammatory (INF) changes throughout the neuromuscular layer; and n = 8 with degenerative neuro-muscular alterations (DEG). Myenteric (MP) and submucosal (SP) neurons were stained using neuron specific enolase antibody and neuronal cell bodies/ganglion were counted in at least 3 sections independently by 3 pathologists. The mean numbers of neuronal cell bodies/ganglion were analyzed by student's t-test and the correlation with symptoms/signs via Spearman correlation test.

Results: The final discordance among the 3 operators was only 20%. MP and SP neuronal cell bodies were decreased in SD vs. controls (p < 0.001). MP and SP neurons also were decreased in AN, INF and DEG vs. controls (p < 0.0001 in MP and p < 0.05 in SP). Furthermore specimens with INF and DEG showed less MP (but not SP) neuronal cell bodies compared to AN (p = 0.0224 and p = 0.0044). The reduction in MP and SP neuronal cell bodies correlated with abdominal distension/pain, early satiety, constipation and gastroparesis (p < 0.05).

Conclusion: This methodological approach with high concordance rate (80%), identified an overall 50% decreased of MP and SP neuronal cell bodies implying a critical loss of the neuronal mass. The 50% neuronal reduction correlated with a variety of symptoms / signs of SD patients. This study indicates that quantitative neuronal abnormalities can be demonstrated in patients with AN histopathology.

Disclosure: Nothing to disclose

OP062   DIFFERENTIATION OF DENTAL PULP-DERIVED MESENCHYMAL STEM CELLS INTO HEPATOCYTES AND THEIR REPOPULATION IN NUDE RAT LIVER

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Introduction: Dental pulp-derived mesenchymal stem cells (DP-MSCs) as a source for regenerative medicine are now the subject of much clinical attention. There are high expectations due to their safety, low tumorigenic risk, and low ethical concerns. Tooth-derived MSCs are known to have a great potential in their proliferation and differentiation capacities, even when compared with bone-marrow-derived MSCs.

Aims and Methods: We aimed to examine the hepatic properties and gene expression patterns of DP-MSC-induced hepatocytes and to investigate the affinity of these cells to liver by using a nude rat model. Dental pulp cells obtained from extracted teeth were cultured under the presence of Activin A, FGF, and then insulin and HGF. Production of liver specific proteins including albumin were investigated. 3 dimentional cultures were perfused with medium containg 5mM NH_4Cl and urea concentration in the eluate was assayed. RT-PCR analysis for the genes that are responsible for the experiments was performed. ^{51}Cr labelled cells (1.51×10^6) were infused via hepatic artery of nude rats and autoradioluminographic images were taken (Dr. Shirai N, Nemoto Science, Co., Ltd, Tsukuba Institute).

Results: Cells differentiated into polygonal hepatocyte-like cells. Production of human albumin fibrinogen, alanine aminotransferase, and hepaplastin in the culture medium were confirmed.

The result of conversion of NH_4Cl to urea (Table 1). Mean and SD values from the 5 hepatocyte cell lines that were independently established were shown.

Urea (mM)

min	5	10	15	20	30
Mean	**0.68**	**2.28**	**3.72**	**4.96**	**7.60**
SD	0.08	0.13	0.13	0.15	0.20

[Table 1.]

The result of RT-PCR showed the expression of HNF4α (transcription factor specific to liver) as well as genes including arginase 1, glutamine synthetase and carbamoyl phosphate synthase that involved in urea production.

Autoradioluminogram of the nude rat that were infused with ^{51}Cr-labelled hepatocytes via hepatic artery showed positive cell spots predominantly located in the liver at both 2 and 168 hrs after the infusion.

Conclusion: Dental pulp MSC-induced hepatocytes had characeric functions of mature hepatocytes including the production of liver specific proteins and the presence of urea cycle. Because the cells repopulated in livers of nude rat even 168 hrs after infusion, they are expected to be a promising cellular resources of regenerative medicine for refractory liver diseases.

Disclosure: Nothing to disclose

OP063   ALTERED MICROVASCULATURE IN CHRONIC INTESTINAL PSEUDO-OBSTRUCTION AND MNGIE: A MORPHOMETRIC AND MOLECULAR ANALYSIS

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Introduction: Chronic intestinal pseudo-obstruction (CIPO) is a rare syndrome characterized by severe gastrointestinal (GI) dysmotility, causing a clinical picture mimicking mechanical obstruction in the absence of any detectable organic abnormality. CIPO is often associated with defective intestinal absorption /

secretion resulting in body weight loss and malnutrition. The microvasculature supplying the gut, may contribute to the severe GI impairment in CIPO, but it has never been formally investigated.

Aims and Methods: This study explored the enteric microvasculature at tissue level in CIPO vs. mitochondrial neurogastrointestinal encefalomyopathy (MNGIE), a genetic condition characterized by the absence of thymidine phosphorylase (TP) expression that is a key regulator of angiogenesis. MNGIE patients show a clinical picture dominated by neurological and GI manifestations, the latter mimicking CIPO features in most cases.

21 clinically and histopathologically characterized CIPO patients (9M; age range: 16-75 yrs); 5 MNGIE patients (4M, 24-32 yrs) and 5 control patients undergoing elective surgery for uncomplicated neoplastic diseases (CTR; 3M, 48-73 yrs) entered the study. In each enrolled patient 2 full thickness biopsies were obtained and processed. The first biopsy was formalin fixed and paraffin embedded. Sections were stained with orcein in order to identify the elastic component associated to blood vessels supplying the jejunal submucosa. The size and number of vessels/mm^2 were quantified in each biopsy using Ima-J software. Submucosal vessels were subdivided in 5 dimensional classes: >500 mm and 499-301 mm (large); 300-101 mm (medium); 100-51 mm and <50 mm (small). The second biopsy was processed to assess TP protein expression by western blot.

Results: CIPO and MNGIE patients show a trend to have more vessels/mm^2 of submucosa (19.6 ± 4.0 and 27.5 ± 4.0 respectively), compared to CTR (11.3 ± 8.7; p = ns). The percentage of the small vessels (<50 mm) in CTR was very low ~15.7%, whereas this drastically increased in CIPO (41.7%; p = 0.014) and MNGIE (53.8%; p = 0.0070). Conversely, the percentage of higher diameter vessels (>500 mm) in CTR is ~9.0% and in CIPO and MNGIE patients decreased to 2.4% and 2.2% (p < 0.0001 and p = 0.0429), respectively. Medium vessels (300-101 mm) represented the most common group (45%) of total CTR GI vessels, whereas the subgroup vessel percentage decreased to 26.1% and 16.7% in CIPO and MNGIE patients (p < 0.0001 and p = 0.0006), respectively. Finally, the biochemical quantification of the angiogenic factor TP showed a significant decrease in the jejunum of CIPO patients (p < 0.0001).

Conclusion: Our results indicate that, compared to CTR, MNGIE and CIPO vasculature shows quantitative abnormalities, large and medium vessel formation vs. small vessels. To the best of our knowledge this is the first attempt to address abnormal vascularization in the small intestine of genetic (MNGIE) and sporadic CIPO as a possible mechanism underlying gut dysfunction.

Disclosure: Nothing to disclose

OP064   CHARACTERISATION OF A NOVEL JUVENILE ONSET DIABETES (JOD) GENE USING HUMAN PLURIPOTENT STEM CELLS

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Introduction: Diabetes represents one of the major burdens in the 21st century with approx. 350 million people affected worldwide. Monogenic diabetes such as juvenile onset insulin-dependent diabetes (JOD) or maturity onset diabetes of the young (MODY) accounts for approximately 1-2% of diabetes cases and results from mutations that primarily reduce β-cell function. The identification of the genetic basis of these diabetes forms has translated into novel avenues of personalized medicine in the diabetes field, but only few of these genes have been identified to date.

Aims and Methods: Based on published data, we hypothesize that a proportion of the genetic contribution to common diabetes (T1D and T2D) may be caused by rare monogenic variants/mutations missed by the current GWAS strategies targeting common variant. The current project reports on such a novel gene relevant as regulator of human pancreatic islet formation but also as a novel juvenile onset diabetes (JOD) gene. For this purpose a stage-specific genome wide profiling complemented with Chip-seq data in differentiating human embryonic stem cells was used.

Results: In our approach we could show that our gene binds and activates Nkx2.2, Nkx6.1 and Pdx1, all belonging to the core suite of isletogenesis transcription factors. Interestingly, this gene co-occupies the enhancer and promoter regions of the latter genes together with Foxa2, Pdx1 and Gata6. Finally, we engineered human embryonic stem cells with previously identified mutations in JOD patients. Directed differentiation studies of these cells shows an altered binding pattern of Nkx2.2, Nkx6.1 and Pdx1 finally leading to reduced amounts of monohormonal b-cells. This reduced target gene binding results from a limited zinc affinity due to the mutation that would be necessary as co-factor for gene binding.

Conclusion: The platform provided allows personalised drug-testing and further sheds light on the mechanism how our JOD gene regulates pancreatic development and leads to diabetes in case of certain mutations in humans.

Disclosure: Nothing to disclose

OP065 LONG-LIVED SECRETORY CELLS RESIDING IN THE MOUSE PROXIMAL COLON SERVE AS RESERVE STEM CELLS UNDER DNA DAMAGE-INDUCED MUCOSAL INJURY

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Introduction: While most intestinal epithelial cells (IECs) are rapidly renewed, small intestinal IECs residing at the +4 position remain quiescent and thereby reside as long-lived IECs. Those long-lived small intestinal IECs are committed to the secretory lineage, and function as reserve stem cells upon massive loss of the genuine intestinal stem cell (ISC) pool. However, the existence of a long-lived IEC counterpart in the colon remains uncertain.

Aims and Methods: We recently reported a newly developed lineage tracing system for secretory IECs by using the Atoh1-CrePGR; ROSA26-LSL-tdTomato (Atoh1$^{\text{tdTomato}}$) mice (Stem Cell Rep, 2018). Using these mice, a pulse-chase experiment combining tdTomato-basedlineage tracing of Atoh1$^+$IECs and BrdU-based nuclear labeling of IECs was conducted to elucidate the lifetime of those Atoh1$^+$IECs in each region of the colon. Also, region-specific gene expression was examined by subjecting tdTomato$^+$cells collected from the proximal or distal colon. To investigate the IEC-intrinsic mechanism required for the maintenance of long-lived Atoh1$^+$IECs, we employed the organoid 3D-culture system. Cell cycle status of organoid IECs derived from different parts of the colon was analyzed by flow cytometry or immunoblotting. *In vitro* tolerance against 5-FU-induced DNA damage was examined by real-time cell viability assay and immunohistochemistry. Finally, we established an IEC-specific 5-FU-induced mucosal injury model to investigate the reserve stem cell capacity of long-lived secretory IECs *in vivo*.

Results: A distinct population of Atoh1$^+$IECs in the proximal colon exclusively retained their tdTomato labeling for over 20 days. These label-retaining Atoh1$^+$IECs were generally post-mitotic, as shown by the BrdU labeling experiment consisting of a 1-month labeling period and a subsequent 3-month chasing period. Microarray analysis of Atoh1$^+$IECs in the proximal colon revealed that they exhibited enhanced expression of genes required to maintain cell quiescence. Consistently, organoids established from the proximal colon showed increased induction of cell cycle arrest and subsequent reduction of proliferation activity, compared to their distal colon counterpart, by promoting Atoh1$^+$IEC differentiation through Notch inhibition. In addition, secretory-lineage committed organoids derived from the proximal colon showed enhanced resistance against 5-FU-induced DNA damage. Atoh1$^+$IECs of the proximal colon *in vivo* were also highly resistant to 5-FU induced DNA damage, as confirmed by the reducedexpression of cleaved caspase 3. By using Atoh1$^{\text{tdTomato}}$mice, we also conducted lineage tracing of Atoh1$^+$IECs in our 5-FU-induced mucosal injury model, and found that Atoh1$^+$IECs in the proximal colon did not only survive but also reacquired ISC properties to completely repair the damaged colonic crypts.

Conclusion: A subpopulation of Atoh1$^+$IECs in the proximal colon reside as long-lived IECs that can serve as reserve ISCs in response to DNA damage-induced mucosal injury.

Disclosure: Nothing to disclose

MONDAY, OCTOBER 22, 2018   14:00–15:30
Transitioning from viral hepatitis to NASH – Room N2_____

OP066 BAVENO VI CRITERIA FOR SCREENING VARICES IS ASSOCIATED WITH THE RISK OF HCC AFTER DAA THERAPY IN PATIENTS WITH HCV INFECTION AND ADVANCED FIBROSIS

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Introduction: The interferon-free antiviral therapies (Direct Antiviral Agent, DAA) for hepatitis C virus (HCV) infection have allowed treatment of a larger number of patients, including those with cirrhosis, advanced age and comorbidity. It is known that the annual incidence of hepatocellular carcinoma (HCC) in HCV infected patients increases with the degree of fibrosis and is between 2 and 8%. Meta-analysis on interferon antiviral therapy showed a risk reduction of HCC incidence of more than 70%, irrespective of fibrosis stage, in patients who achieved an SVR. Data on DAA therapy are more controversial. Despite previous studies reported a high incidence of recurrent HCC in patients treated with DAA and in whom HCC was previously treated, this data was not confirmed by subsequent large multicentric studies. Some concerns on higher incidence of de-novo HCC after DAA treatment have also been reported.

Aims and Methods: The aim of this study was to evaluate which variable are eventually associated to HCC occurrence or recurrence in patients with HCV infection and advanced fibrosis. The study included 297 consecutive HCV patients (M 192/F 105; mean age 60.9 ± 12.1; 54.3% with genotype 1 and 23.8 with genotype 3) with high fibrosis stage detected by transient elastography (81

F3 and 216 F4 sec. Metavir); 16 of whom had a past history of HCC. The following variables were assessed at baseline: liver stiffness, platelets count, Baveno VI criteria for screening varices (stiffness > 20 Kpa and platelet counts < 150,000 mm^3), alphafetoprotein, Child Pugh score, MELD score, presence or absence of esophageal varices, presence or absence of diabetes. All patients received an optimal DAA treatment from April 2015 to May 2017. All treated patients were regularly followed up with a median of 20 months (7-33 months). Chi square analysis for categorical variables was used.

Results: SVR-12 was achieved in 290 patients (97.6%). 23/297 (7.7 %) patients develop HCC de novo or recurrence during the period of follow-up. Among the variable assessed at univariate analysis, liver stiffness > 20 Kpa and platelet counts < 150,000 mm^3 and the presence of diabetes were significantly associated with the occurrence/recurrence of HCC after treatment (82.6% vs 17.4%, p = 0.023 and 15% vs 5.4%, p = 0.021, respectively).

Conclusion: Liver stiffness > 20 Kpa and platelet counts < 150,000 mm^3 known as Baveno VI criteria for screening varices, may be a useful tool to differentiate patients at greater risk of developing hepatocellular carcinoma after DAA treatment. This risk seems to be further increased by the presence of diabetes. Further studies with a larger population of patients will be needed to confirm this observation.

Disclosure: Nothing to disclose

OP067 ASSOCIATION BETWEEN SARCOPENIA AND NONALCOHOLIC FATTY LIVER DISEASE AND ADVANCED FIBROSIS IN THE UNITED STATES

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Introduction: Nonalcoholic fatty liver disease (NAFLD) may be associated with sarcopenia, which share risk factors including chronic inflammation, insulin resistance, vitamin D deficiency.

Aims and Methods: This study aimed to determine whether sarcopenia is independently associated with NAFLD and advanced fibrosis in a nationally representative sample of US adults. Cross-sectional data from 11,325 participants in the third National Health and Nutrition Examination Survey were analyzed. NAFLD was diagnosed by ultrasonographic hepatic steatosis without evidence of other liver diseases. The presence of advanced fibrosis was determined by the NAFLD fibrosis score. Sarcopenia was defined as skeletal muscle index that was measured by bioelectrical impedance analysis.

Results: NAFLD was more common in subjects with sarcopenia than in those without (46.7% vs. 27.5%), which was consistent in analyses stratified by gender, obesity status, and ethnicity. A univariate analysis showed that sarcopenia was associated with NAFLD (odds ratio [OR], 2.31; 95% confidence interval [CI], 2.01–2.64), which remained significant after adjustment for age, gender, ethnicity, metabolic risk factors, and vitamin D deficiency (OR 1.24; 95% CI 1.03–1.48). This finding persisted even after adjustment for c-reactive protein as a marker of chronic inflammation. Furthermore, NAFLD-associated advanced fibrosis was more common in subjects with sarcopenia than in those without (7.8% vs. 1.6%), which was also consistent in analyses stratified by gender, obesity status, and ethnicity. Sarcopenia was associated with NAFLD-associated advanced fibrosis independent of metabolic risk factors, vitamin D deficiency, and chronic inflammation (OR, 1.79; 95% CI, 1.18–2.72). An additional sensitivity analysis was conducted including insulin resistance in the model with similar results.

Conclusion: In this nationally representative sample of American adults, sarcopenia was independently associated with increased risk of NAFLD and NAFLD-associated advanced fibrosis independent of well-defined risk factors. Interventions to strengthen muscle mass may present an opportunity to reduce the burden of NAFLD and advanced fibrosis.

Disclosure: Nothing to disclose

References
1. Koo BK, Kim D, Joo SK, Kim JH, Chang MS, Kim BG, Lee KL, et al. Sarcopenia is an independent risk factor for non-alcoholic steatohepatitis and significant fibrosis. *J Hepatol* 2017; 66: 123–131.
2. Kim D, Kim WR. Nonobese Fatty Liver Disease. *Clin Gastroenterol Hepatol* 2017; 15: 474–485.

OP068 GENETIC SUSCEPTIBILITY TO INCREASED INTESTINAL PERMEABILITY IS ASSOCIATED WITH STEATOHEPATITIS, LIVER FIBROSIS AND TYPE 2 DIABETES MELLITUS IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE

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Introduction: Increased intestinal permeability (IP) has now been considered as a key factor in the pathogenesis of non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM). Given the pivotal role of Gut-Liver Axis in NAFLD pathogenesis, genes involved in the modulation of IP are perfect candidates in exploring SNPs that might significantly impact on fatty liver disease severity.
The aim of our study was to assess whether a single nucleotide polymorphisms (SNP) (rs2542151 G→T) of Protein Tyrosine Phosphatase Non-Receptor Type 2 (PTPN2), known to be involved in regulation of IP, is associated with severity of NAFLD (non-alcoholic steatohepatitis -NASH- and/or liver fibrosis) and type 2 diabetes mellitus.
Aims and Methods: We recruited a prospective consecutive cohort of NAFLD cases and healthy controls among Caucasian patients from 2 Italian tertiary care centers. PTPN2 genotype was assessed both in patients and controls. Anthropometrics, clinical data and laboratory data were collected for each patient. In the entire cohort the presence of fibrosis was non-invasively assessed by FIB-4 score. A subgroup of patients underwent liver biopsy. Unconditional multiple logistic regression models were used to investigate the association between selected SNP (PTPN2 rs2542151 G→T), comorbidities and histological severity of liver disease. Genotype frequencies were consistent with Hardy-Weinberg equilibrium both in control and in patient cohort.
Results: We enrolled 566 cases (males 64.6%, mean age 45.3 ± 13.8 ys) and 377 controls (males 67.1%, mean age 41.3 ± 3.1 ys). PTPN2 genotype distribution was not significantly different between NAFLD patients and controls. Liver biopsy was available for 345 patients; 198/345 (57.4%) had NASH. In the whole study population, considering a genetic dominant model, the analysis showed that PTPN2 rs2542151 G→T is associated with an higher FIB-4 score (OR 1.19 95% CI 1.01-1.41 p < 0.05) and the presence of T2DM (OR 1.82 95% CI 1.14-2.89 p < 0.05) independently from age and sex. At a subgroup analysis of patients who underwent liver biopsy, rs2542151 G→T of PTPN2 was associated with the presence of severe steatosis (OR 2.19 95% CI 1.35-3.55 p < 0.01), NASH (OR 1.81 95% CI 1.13-2.90 p < 0.05) and severe fibrosis (OR 2.55 95% CI 1.50-4.33 p < 0.01) independently from age and sex.
Conclusion: Our study shows that rs2542151 G→T of PTPN2 is associated with the severity of steatosis, fibrosis and NASH histologically assessed. Furthermore, rs2542151 G→T of PTPN2 is associated with the presence of T2DM in patients affected by NAFLD. These results still suggest that in NAFLD patients an individual genetic susceptibility could play a key pathogenetic role on IP impairment and consequently lead to an higher histological severity of fatty liver disease and the presence T2DM.
Disclosure: Nothing to disclose

OP069 THE TRANSCRIPTION FACTOR C-JUN/AP-1 PROMOTES LIVER FIBROSIS DURING NON-ALCOHOLIC STEATOHEPATITIS BY REGULATING OSTEOPONTIN EXPRESSION

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Introduction: The AP-1 transcription factor c-Jun is a major regulator of hepatocyte function in acute and chronic liver diseases. However, its role during non-alcoholic steatohepatitis (NASH) remains poorly defined.
Aims and Methods: To address this issue in more detail, we examined c-Jun expression in liver biopsies of patients diagnosed with steatosis and NASH. The contribution of c-Jun to the pathogenesis of NASH and subsequent fibrosis was further analyzed in hepatocyte-specific (*c-Jun*$^{\Delta li}$) as well as inducible knock-out mice lacking *c-Jun* in both, hepatocytes and non-parenchymal liver cells (NPLCs; *c-Jun*$^{\Delta li*}$) fed a methionine- and choline-deficient diet (MCDD).
Results: Disease progression from steatosis to NASH and NASH-related fibrosis strongly correlated with increased hepatocellular c-Jun expression in patients, while c-Jun expression in NPLCs strongly correlated with fibrosis stage. Analysis of MCDD-treated *c-Jun*$^{\Delta li}$ and control mice further revealed that c-Jun expression in hepatocytes promotes hepatocyte survival and triggers an exacerbated compensatory response called ductular reaction (DR), expression of pro-fibrogenic genes and subsequent fibrosis. The DR correlated with increased numbers of non-parenchymal Sox9 and Osteopontin (Opn) co-

expressing cells as well as expression of the Opn receptor CD44, which have all been implicated in fibrogenesis. Interestingly, c-Jun and Opn expression co-localized in both, human and murine hepatocytes as well as NPLCs and we therefore wondered whether the increased fibrosis observed in *c-Jun*$^{\Delta li}$ mice could be rescued by additional deletion of *c-Jun* in NPLCs (*Jun*$^{\Delta li*}$). Indeed, NASH in *c-Jun*$^{\Delta li*}$ mice was characterized by reduced liver damage, impaired Opn expression, impaired ductular reaction and subsequently less fibrosis. A comparable phenotype was observed in *Opn*$^{-/-}$ mice, indicating that the phenotype observed in *Jun*$^{\Delta li*}$ mice was indeed very likely Opn-dependent.
Conclusion: These results suggest that c-Jun exerts cell-type specific functions during NASH pathogenesis: c-Jun expression in hepatocytes promotes hepatocyte survival and protects against the NASH-related DR and fibrosis. In contrast, c-Jun expression in NPLCs rather promotes the DR and subsequent fibrosis by regulating Opn expression.
Disclosure: Nothing to disclose

OP070 LIVER AND CARDIOVASCULAR MORTALITY AFTER DAAS: DATA FROM THE RESIST-HCV COHORT

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Introduction: Large scale, real-life data on the long-term course of liver disease after HCV clearance obtained with DAAs are still scanty, and the separate effects on hepatic and non-hepatic causes of death still unclear.
Aims and Methods: Between March 2015 and December 2016, 5,166 patients (mean age 65.7 ± 11.5 years, 57.6% males) were included in the prospective RESIST-HCV cohort (22 centres in Sicily) and started DAAs treatment. 199 with previous HCC and 299 with previous OLT were excluded. All patients were followed after antiviral therapy to register liver-related and unrelated outcomes. The primary endpoint was the evaluation of survival since starting DAAs. Cox regression analysis was used to assess the predictors of liver-related and unrelated death.
Results: In 200 patients viral outcome was not assessable (14 patients stopped therapy for adverse events, 27 died and 159 dropped out during or after therapy). 4,468 patients were observed for a mean of 72 ± 32 weeks, 990 (22.1%) had diagnosis of chronic hepatitis (F3 in > 90%), 3095 (69.3%) had Child A cirrhosis and 383 (8.6%) had Child B cirrhosis. Overall, 4,234 patients (94.8%) achieved SVR while 234 patients (5.2%) were HCV-RNA positive at the last control. 62 patients (1.4%) died during the observation: 31 of them died for liver-related causes, 19 for cardiovascular disease, 4 for cancer (not liver), 6 for other causes. No liver death occurred among patients with chronic hepatitis. By multivariate Cox regression analysis, the lack of SVR (hazard ratio [HR] 18.5; 95% confidence interval [CI], 6.8–50.8; p < 0.001) and albumin < 3.5 g/dl (HR: 6.0; 95% CI, 2.3–15.7; p < 0.001) were independently associated with an increased incidence of liver related mortality in Child A patients. Lack of SVR was the unique predictor of liver deaths also in Child B patients (HR 3.49, 95% CI: 1.09–11.22. p = 0.036). Independent predictors of cardiovascular mortality were no SVR (HR: 10.6, 95% CI: 3.4–32.5; p < 0.001) and diabetes (HR: 4.1, 95% CI:1.3–13.00, p = 0.011).

Conclusion: In this real-world setting using a variety of DAA regimens SVR reduced overall mortality and risk of liver-related and unrelated deaths at all stages of disease, but mostly in Child A cirrhosis. Deaths linked to cardiovascular diseases are reduced after viral eradication regardless of the stage of fibrosis. The biological basis and ultimate lifetime impact should be assessed.
Disclosure: Nothing to disclose

OP071 BLOOD-BORNE HEV TRANSMISSION: TRANSFUSION-TRANSMITTED HEPATITIS E VIRUS INFECTIONS AND EXPERIENCE WITH ROUTINE HEV SCREENING AT A TERTIARY CENTRE

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Introduction: Hepatitis E virus (HEV) infection has become a relevant topic with increasing attention and is a major threat for immunosuppressed patients. Routine HEV testing of blood products has recently been implemented in Great Britain and the Netherlands. The relevance of blood-borne hepatitis E virus (HEV) infections for these patients has been discussed controversially within the last months and still requires further investigations.
Aims and Methods: We report (A) our experience of routine HEV testing of blood products at a tertiary centre and (B) cases of immunosuppressed patients developing transfusion associated chronic HEV infection.
From 10/2016 onwards all blood donors at the University Hospital Hamburg-Eppendorf were routinely screened for HEV RNA (pools of 24 donations) by PCR using the Roche cobas 6800® (LLOD single: 19 IU/ml, 24 pool: 456 IU/ml). HEV RNA positive blood products were not transfused. All immunosuppressed patients with HEV infection (2011-2017) were retrospectively studied. All blood products given to chronically HEV-infected patients were retrospectively analyzed.
Results: (A) 30/28981 donors (0.1%) were HEV-RNA-positive (median viral load 960 IU/ml), whereas only 3 of them (10%) presented with elevated serum transaminases at time of donation (ALT: 83 U/l, 192 U/l and 101 U/l). Retrospective analysis of all HEV-positive donors revealed that 4 donors with asymptomatic infection had been HEV-viraemic for up to 3 months.
(B) 37 immunosuppressed patients with HEV infection were identified whereas 11 of these (30%) developed chronic HEV infection. In 4/11 (36%) we were able to identify an HEV positive blood donation as source of HEV transmission. 2 of these (50%) acquired chronic HEV infection by plasmapheresis/rituximab as treatment for heart transplant rejection.
Conclusion: Overall incidence of HEV RNA in asymptomatic blood donors in our cohort is higher than previously reported although most donors had low viral load. However, blood products are a relevant source of HEV-infection in particular for immunosuppressed individuals as 36% of chronic HEV infections were transfusion associated. Therefore routine screening of blood products should be implemented in standard of care.
Disclosure: Nothing to disclose

MONDAY, OCTOBER 22, 2018   14:00–15:30
Gastric carcinogenesis – Room L7

OP072 *HELICOBACTER PYLORI*, GASTRIC CARCINOGENESIS AND THE ASSOCIATION WITH ER-STRESS AND AUTOPHAGY

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Introduction: *Helicobacter Pylori* (HP) is one of the most successful pathogens in the world, infecting nearly half of the world's population. Importantly, HP is the biggest risk factor in the development of gastric pathology including gastric atrophy, intestinal metaplasia (IM) and dysplasia, all of which are considered precursor lesions to gastric cancer. Autophagy is a cellular degradation mechanism, the physiological role of which is to recycle cytoplasmic components. A specialized form of autophagy, xenophagy, contributes to clearance of intracellular pathogens. Recently it has been shown that HP may modulate autophagy through activation of the endoplasmic reticulum stress (ER stress) pathway. Our previous studies have shown that a single nucleotide polymorphism (SNP) in the autophagy gene ATG16L1 (rs2241880) modulates intestinal ER stress. The aim of this study was to investigate the role of this SNP in HP-mediated autophagy, ER stress and intestinal metaplasia.
Aims and Methods: DNA (n = 262) was isolated from EDTA blood of a cohort of IM patients (PROREGAL Cohort), and the ATG16L1 SNP (rs2241880) status was determined by PCR-RFLP. ER stress and autophagy experiments were performed with gastric cancer cell line SK-GT-2 and immortalized gastric cell line GES-1. ER stress was induced by tunicamycin. ER stress (GRP78) and autophagy (LC3B) were detected by western blot analysis. HP (ATCC 43504) was cultured on Columbia sheep blood agar and heat-killed before cell stimulation. Antral biopsies were taken from 47 patients with IM of which 23 were actively infected with HP (determined by histology), these same patients were biopsied 1 year after eradication. The other 24 biopsies were from patients

IM who have never been infected with HP (determined by serology). Immunohistochemistry was performed on these biopsies using GRP78 as a marker for ER stress. Positivity was scored using the Allredscore taking the average of 4 high powered fields. Statistical significance was determined by Students T-test.
Results: The minor allele frequency (MAF) of rs2241880 (i.e. the A allele, associated with lower intestinal ER stress levels) was calculated as 0.53 in the IM cohort, which was significantly higher than the reference population (Rotterdam study, MAF 0.45, p = 0.0003). After stimulation with HP, ER stress levels in gastric cell lines were reduced, whereas autophagy was induced, as determined by LC3BI to LC3BII conversion. These differences were not observed when cells were stimulated with non-pathogenic *E. coli* bacteria. Biopsies from patients actively infected with HP showed a reduced amount of GRP78 positivity as compared to uninfected patients (p = 0.0171) and the same patients one year after eradication (p = 0.0006).
Conclusion: These results show that HP upregulates the autophagy pathway and thereby reduces ER-stress *in vitro* and *in vivo*. Furthermore we show that a genetic variant of the ATG16L1 gene which causes reduced levels of ER stress is more prevalent in patients who have developed precancerous gastric lesions, suggesting that promotion of autophagy and thereby reduction of ER stress contributes to HP-induced changes of the gastric epithelium.
Disclosure: Nothing to disclose

OP073 HELICOBACTER PYLORI INFLUENCES THE METAGENOMIC PROFILE OF HUMAN GASTRIC MUCOSA

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Introduction: The discovery of *H. pylori* superseded the long-held conception of the stomach being a sterile organ that does not contain specific microbiota. Further research has shown that *H. pylori* is not the only inhabitant of the stomach, and other microorganisms can also colonize it. However, the influence of *H. pylori* on other members of the gastric microbiota remains poorly understood. Research on the bacterial biodiversity within the stomach in *H. pylori*-positive versus *H. pylori*-negative gastric mucosa is still controversial.
Aims and Methods: The aim of the study was to characterize the microbial composition of the gastric mucosa in *H. pylori*-positive and *H. pylori*-negative subjectsby high-throughput 16S rRNA sequencing. Ten gastric mucosal biopsy samples were obtained for metagenomic analysis. According to the rapid urease test combined with cytology results, 6 *H. pylori*-positive and 4 *H. pylori*-negative samples were detected. Total RNA from each sample was extracted, which then was used to synthesize cDNA. This step was needed to detect only the living microorganisms of the stomach. DNA libraries of V3-V4 variable region of the 16S rRNA gene were sequenced on the Illumina MiSeq platform. Trimmed reads were analyzed by the QIIME software to characterize the composition of the microbiota.
Results: There is a significant difference in bacterial composition between *H. pylori*-positive and *H. pylori*-negative samples. In case of *H. pylori*-positive patients, a significant dominance of the *Helicobacter* genus was found, which in 2 out of 6 samples represented up to 99% of the total microbiota. In the absence of *H. pylori* infection the predominance of the *Streptococcus* genus was shown as well as the presence of the *Rothia, Prevotella, Gemellaceae, Fusobacterium* and *Neisseria* genera, which are usually recognized as the normal gastric microbiota. It is interesting to note that *H. pylori* occurs in small quantities even in cases when no evidence of *H. pylori* infection is detected according to the rapid urease test and cytology. It is worth noticing that in 4 samples quite a large number of the *Nesterenkonia* and *Halomonas* bacterial genera was found, which are usually isolated from the environment, e.g. soil or marine samples, and have not previously been detected in the human digestive tract. Thereby, their role among the other gastric microbiota representatives needs further study.
Shannon diversity index was calculated to analyze the biodiversity in all studied samples. The biodiversity decreased in all *H. pylori*-positive samples and was in average three times lower than in *H. pylori*-negative patients.
Conclusion: Microbial composition differs significantly in *H. pylori*-positive and *H. pylori*-negative samples; *H. pylori* tends to prevail in the stomach of *H. pylori*-positive patients. Bacterial biodiversity is shown to be decreasing in the presence of *H. pylori* infection. This allows assuming that *H. pylori* has some sort of inhibitory effect on other inhabitants of the gastric microbiota.
Disclosure: All authors have declared no conflicts of interest.

OP074 CLINICOPATHOLOGICAL FEATURES OF EPSTEIN-BARR VIRUS ASSOCIATED GASTRIC CARCINOMA WITH SUBMUCOSAL INVASION

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Introduction: The frequencies of lymph node metastasis (LNM) in pT1a and T1b gastric cancer (GC) are 3% and 20%, respectively, namely the majority of them has no LNM. The Cancer Genome Atlas Research Network proposed the concept of molecular phenotype classifying GC into 4 phenotypes including Epstein-Barr virus-CIMP (EBV). The EBV group accounts for 8.8% and is considered to have low prevalence of LNM. This study aimed to evaluate clinicopathological features of submucosal invasive (pT1b) EBV GC without lymphovascular invasion to choose lower risk group for LNM from pT1b GC, for expanding indications of endoscopic submucosal dissection (ESD).
Aims and Methods: 411 pT1b GCs without lymphovascular invasion that underwent surgical resection between 2005 and 2014 at the Cancer Institute Hospital, were enrolled and retrospectively analyzed. Tissue microarray was made and EBV-encoded RNA in situ hybridization was performed for evaluation of EBV status. Patients' age, sex, tumor location, macroscopic type, predominant histologic type, tumor diameter, depth of submucosal invasion, the presence of ulceration and the presence of LNM were compared between EBV group and non-EBV group.
Results: The EBV group accounted for 11.4% (47/411). Compared to the non-EBV group, the EBV group was more frequent in men (80.8% vs. 64.8%, p = 0.032), located more frequent in upper third region (44.6% vs 18.1%, p < 0.0001), showed deeper submucosal invasion depth (mean 1200 μm vs 600 μm, p = 0.0001) and lower frequency of having ulceration (21.2% vs 42.8%, p = 0.004). The predominant histologic type of "carcinoma with lymphoid stroma" was more frequent in EBV group than in non-EBV group (44.6% vs 2.2%, p < 0.0001). No LNM was found in EBV group (0% vs 7.7%, p = 0.059).
Conclusion: pT1b EBV GC without lymph vascular invasion showed low prevalence of regional LNM regardless of tumor diameter and the extent of submucosal invasion. This group will be a good candidate to be included curative resection criteria of ESD.
Disclosure: Nothing to disclose

OP075 FGFR2 SIGNALING CROSSTALKS WITH HIPPO PATHWAY TO DRIVE GASTRIC CARCINOGENESIS

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Introduction: FGFR2 (fibroblast growth factor receptor 2) has been reported to be associated with cellular growth and carcinogenesis. However, the mechanism underlying its functional role in gastric cancer (GC) remains elusive.
Aims and Methods: We seek to elucidate the function of FGFR2 and comprehensively reveal its regulatory mechanisms during gastric carcinogenesis. Firstly, we performed expression profiling based on 9 GC cell lines to identify FGF18 and FGFR2 as the predominant members in the FGF-FGFR cascade. The mRNA and protein expression of FGFR2 were examined by qRT-PCR and Western blot. The correlation of FGFR2 expression with other clinical parameters was investigated by immunohistochemistry on tissue microarray. The biological role of FGFR2 was determined by MTT proliferation, monolayer colony formation, cell invasion assays through siRNA-mediated knockdown. Expression microarray was employed for the downstream signalling analysis.
Results: Among the ligands and receptors of FGF family, FGF18 and FGFR2 possessed the highest expression levels. Given that our previous work has demonstrated the oncogenic role of FGF18 in GC, we continued to delineate the expression and function of FGFR2 in gastric carcinogenesis. According to TCGA dataset, FGFR2 owns the highest gene amplification rate among the family, and copy number gain and amplification are associated with mRNA upregulation (p < 0.001). FGFR2 upregulation also indicated poor survival among GC patients (overall survival, HR = 1.69, p < 0.001, n = 641; first progression survival, HR = 1.63, p < 0.001, n = 641, multiple GEO cohorts). Gene set enrichment analysis (GSEA) suggested that FGFR2 abundance was correlated with downregulation of PTEN (ES = 0.391, NES = 1.614, p = 0.031, n = 300, NCBI/GEO/GSE62254). Multivariate cox regression analysis revealed that FGFR2 upregulation predicted poor prognosis independently. In vitro experiments demonstrated that siFGF18 led to inhibition of cell growth (p < 0.001), colony formation (p < 0.001) and invasion (p < 0.001), suggesting its oncogenic role during gastric carcinogenesis. Moreover, MAPK signalling pathway was confirmed to be the main downstream of FGFR2 in GC, which showed good concordant with the driver oncogenic role of YAP1. Finally, we confirmed that FGFR2 exhibits oncogenic role through activating YAP1, thus to stimulate MAPK signalling.
Conclusion: FGFR2 is abundantly expressed in GC tissues with gene amplification and its overexpression indicates poor outcomes. FGFR2 overexpression in GC exhibited oncogenic property through YAP1 activation. Our findings not only identified novel prognostic marker but also provided a translational potential for clinical intervention.
Disclosure: Nothing to disclose

OP076 MODIFICATION OF INFLAMMATORY MICRORNAS IN GASTRIC MUCOSA BY ASPIRIN, NSAIDS AND PROTON-PUMP INHIBITORS

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Introduction: Gastric carcinogenesis is a multistep *H. pylori*-related process. Deregulation of microRNA (miRNA) expression is one of the crucial contributing events in the progression from chronic inflammation to preneoplastic conditions and gastric cancer. Several miRNAs have been suggested as potential biomarkers for preneoplastic conditions. However, nothing is known regarding the modulating effects of non-steroidal anti-inflammatory drugs (NSAIDs) or proton pump inhibitors (PPI) on the miRNA expression.
Aims and Methods: The aim of this study was to investigate the effect of aspirin, NSAIDs and PPI on the expression of mucosal inflammatory miRNAs (miR-155 and miR-223) in *H. pylori*-infected and non-infected subjects. The study was performed in 2 cohorts: 1) interventional study in 20 healthy subjects with and without *H. pylori* infection (each n = 10), and 2) prospective case-control observational study (n = 188). In interventional study, low-dose aspirin (100mg) was given for 7 days and upper GI-endoscopy including histological sample collection was accessed on the days 0, 1, 3, 7. 9 *H. pylori*-eradicated subjects repeated the protocol following eradication treatment. Patients from the second cohort underwent upper GI endoscopy including histological evaluation, *H. pylori* testing (incl. cultivation), biopsy collection and were systematically questioned about NSAIDs and PPI use. MiR-155 and miR-223 levels were assessed in total RNA extracted from the biopsies using TaqMan Assay and subsequently correlated with COX-2 expression level.
Results: miR-155 and miR-223 expression is strongly dependent on *H. pylori* infection in gastric mucosa and in short-term view shows a trend for reversal following eradication treatment. Daily low-dose aspirin as well as NSAIDs intake did not influence the expression both in healthy subjects and in patients. However, regular PPI intake was associated with a substantial reduction of miR-155 expression predominantly in antral mucosa of patients with chronic gastritis independently of the density of neutrophils and mononuclear cell infiltrates. Furthermore, miR-155 expression was inversely associated with COX-2 levels in subjects without *H. pylori* infection.
Conclusion: PPI but not NSAIDs or low-dose aspirin are associated with changes in expression of mucosal inflammatory miRNAs in *H. pylori*-dependent manner. Further studies are needed to elucidate the potential clinical and prognostic benefit of PPI-related miR-155 modification.
Disclosure: Nothing to disclose

OP077 *PSCA* SNP-*HELICOBACTER PYLORI* INTERACTION ASSOCIATES TO GASTRITIS PROGRESSION IN THE GASTRIC CANCER SEQUENCE AND *PSCA* EXPRESSION

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Introduction: In addition to *H. pylori* virulence, host genetic backgrounds and other environmental factors also exhibit complex interactions in gastric cancer development. *Prostate stem cell antigen* (*PSCA*) single nucleotide polymorphism (SNP) and its decreased expression are associated with gastric cancer[1]. Gastric cancer develops through a multiple step process known as the gastritis-gastric cancer sequence that is triggered by *H. pylori* infection. Severe gastritis has been proven to be a precursor condition[2].
Aims and Methods: Here, we investigated *PSCA* SNP rs2294008 and *PSCA* expression of background gastric mucosa in the gastritis-gastric cancer sequence and revealed host-bacterial interactions in the disease pathogenesis.
A total of 280 subjects with *H. pylori* infection and 28 *H. pylori*-negative controls who underwent EGD in Toyoshima Endoscopy Clinic were enrolled in this study[3]. Genotyping results of 509 *H. pylori*-negative controls and 2,329 gastric cancer patients analyzed in our previous study[4] were used in this study. DNA was purified from peripheral blood leukocytes. mRNA was purified from remaining biopsy tissues from the gastric mucosa of the incisura angularis. Quantitative real-time PCR was conducted. The expression of the *actin, beta* gene was used for normalization. To grade the neutrophil activity according to the updated Sydney system, we used 2 biopsy specimens from the greater curvature of the corpus and the antrum. We topographically classified the gastritis into 4 categories

and defined no gastritis and antrum-predominant gastritis as mild gastritis, and pangastritis and corpus-predominant gastritis as severe gastritis.

Results: As previously reported[1], the T allele of *PSCA* rs2294008 was significantly associated with gastric cancer risk when we used *H. pylori*-negative individuals as a control ($p = 4.5 \times 10^{-6}$; odds ratio (OR) = 1.37; T vs C). SNP rs2294008 is associated with the progression of gastritis ($p = 9.4 \times 10^{-5}$; OR = 3.88; TT+ TC vs CC, $p = 1.0 \times 10^{-3}$; OR = 1.93; T vs C), but not with *H. pylori* infection *per se* ($p = 0.15$; OR = 1.14; T vs C) nor with the progression from active gastritis to gastric cancer ($p = 0.37$; OR = 0.90; T vs C). The *PSCA* polymorphism was significantly associated with the expression of *PSCA* mRNA in the gastric mucosa of both *H. pylori*-negative controls and *H. pylori*-infected patients ($p = 1.8 \times 10^{-4}$, 1.3×10^{-12}, respectively). *H. pylori* infection reduced *PSCA* expression ($p = 5.1 \times 10^{-8}$) while eradication therapy increased *PSCA* expression ($p < 1 \times 10^{-11}$). In addition, *PSCA* expression was decreased in the gastric mucosa in severe gastritis compared with mild gastritis only among T allele carriers (CC: $p = 0.36$, CT: 0.048, TT: 0.032).

Conclusion: Our findings revealed the interaction between host genetic variations (*PSCA* SNP) and bacterial infection that contributes to gastritis progression after *H. pylori* infection in the gastritis-gastric cancer sequence and its possible implications for risk prediction and personalized disease prevention.

Disclosure: Nothing to disclose

References

1. Sakamoto, H. et al. Genetic variation in PSCA is associated with susceptibility to diffuse-type gastric cancer. *Nat Genet* 2008.
2. Malfertheiner, P. et al. Management of Helicobacter pylori infection–the Maastricht IV/ Florence Consensus Report. *Gut* 2012.
3. Mori, J. et al. EPSIN 3, a novel p53 target, regulates the apoptotic pathway and gastric carcinogenesis. *Neoplasia* 2017.
4. Tanikawa, C. et al. A genome-wide association study identifies two susceptibility loci for duodenal ulcer in the Japanese population. *Nat Genet* 2012.

MONDAY, OCTOBER 22, 2018   14:00−15:30
Translational research in liver, biliary and pancreas – Room L8_____

OP078 THE ROLE OF METABOLOMICS IN THE DISEASE PROGRESSION AND DEVELOPMENT OF BILIARY DYSPLASIA AND CHOLANGIOCARSINOMA IN PRIMARY SCLEROSING CHOLANGITIS (PSC)

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Introduction: PSC is a chronic inflammatory liver disease leading to strictures intra- and extrahepatic bile ducts and finally to cholestasis and secondary biliary cirrhosis. The etiopathogenesis of the PSC is unknown [1]. PSC is a premalignant condition associated with high risk for cholangiocarcinoma (CCA) [2,3]. Currently there are no sensitive surrogate markers to predict the risk. High-throughput metabolomics analysis could offer as a potential source to identify reliable markers.

Aims and Methods: We aimed to discover metabolomics profiles of serum and biliary samples in 1) controls and PSC patients to find new noninvasive markers for screening and diagnosing PSC, 2) PSC patients with non-advanced disease compared to those with advanced disease to assess the disease progression, 3) PSC patients with and without biliary dysplasia or CCA to find more sensitive and specific markers to detect biliary dysplasia and CCA.

The patients ($N = 184$) were recruited from the PSC registry of Clinic of Gastroenterology; serum and bile samples are collected and stored at -80C. Samples are extracted using acentonitrile, and analysed using WATERS Acquity UPLC coupled to XEVO-TQ-S QQQ MS for targeted and quantitative metabolomics analysis [4].

Results: Model-based analyses (Generalized Estimating Equations) pinpointed 60 metabolites with significant p-values in bile and/or serum after correction for type-I error. In both bile and serum samples, 2-Aminoisobutyric acid, Acetoacetic acid, Asymmetric dimethylarginine, Citrulline, Dodecanoylcarnitine, Guanosine, Homocysteine, Inosinic acid, L-Glutamic acid, L-Glutamine, L-Palmitoylcarnitine, L-Tyrosine, Sorbitol, Stearoylcarnitine, Symmetric dimethylarginine, and Tetradecanoylcarnitine showed consistent differences between healthy controls and PSC patients. All of the above except Citrulline, Inosinic acid, L-Glutamine, and Stearoylcarnitine also allowed differentiating between healthy controls and all affected patients (non-advanced PSC, advanced PSC and dysplasia).

In bile samples alone, Adenine, Chenodeoxycholic acid, Creatine, Creatinine, Cyclic GMP, Glycocholic acid, Hippuric acid, Hydroxykynurenine, O-Phosphoethanolamine, S-Adenosyl-L-Homocysteine, and Taurocholic acid Tetradecanoylcarnitine showed consistent differences between healthy controls and PSC patients. With the exception of Chenodeoxycholic acid, and Hippuric acid, all the above also allowed differentiating between healthy controls and all

affected persons. Importantly, Cytidine, L-Kynurenine, L-Tyrosine, and Propionylcarnitine, also differentiated between PSC and dysplasia patients.

In serum samples alone, 5-Hydroxyindoleacetic acid, Adenosine monophosphate, Carnosine, D-Ribose-5-phosphate, Decanoylcarnitine, Dimethylglycine, Folic acid, Gamma-Glutamylcysteine, L-Asparagine, L-Kynurenine, L-Tryptophan, NAD, Neopterin, Niacinamide, Nicotinic acid, Normetanephrine, Spermidine, and Xanthosine showed consistent differences between healthy controls and PSC patients. With the exception of L-Tryptophan, and Spermidine, all the above also allowed differentiating between healthy controls and all affected persons.

Conclusion: This study detected a consistent group of metabolites characterizing PSC and dysplasia patients in both serum and bile samples. In addition, fluid-specific candidate biomarkers were pinpointed. Of these, alterations in bile L-Tyrosine, Cytidine, L-Kynurenine and Propionylcarnitine characterized dysplasia in particular.

Disclosure: Nothing to disclose

References

1. Hirschfield GM, KarlsenTH, Keith D Lindor KD, Adams DH. Primary sclerosing cholangitis. *Lancet*. 2013; 382: 1587–99.
2. Bergquist A, Ekbom A, Olsson R, et al. Hepatic and extrahepatic malignancies in primary sclerosing cholangitis. *J Hepatol* 2002; 36: 321–327.
3. Burak K, Angulo P, Pasha TM, et al. Incidence and risk factors for cholangiocarcinoma in primary sclerosing cholangitis. *Am J Gastroenterol* 2004; 99: 523–526.
4. Roman-Garcia P, Quiros-Gonzalez I, Mottram L, Lieben L, Sharan K, et al. Vitamin B12-dependent taurine synthesis regulates growth and bone mass. *The Journal of Clinical Investigation* 2014; 7: 2988–3002.

OP079 CYSTIC FIBROSIS RELATED PANCREATIC DUCTAL DAMAGE IN THE CYSTIC FIBROSIS NEWBORN FERRET AND PIG MODEL

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Introduction: Several animal models are available to study the cystic fibrosis (CF) related pancreatic damage although they have clear limitations. Recently cystic fibrosis transmembrane regulator (CFTR) knockout ferret and pig models have been generated.

Aims and Methods: We aimed to characterize the fluid and bicarbonate secretion of CF and wild type (WT) ferret and pig pancreatic ducts. Pancreatic ducts were isolated from newborn CF and WT ferret and pig pancreas. In the ferret model the expression of CFTR was detected by immunohistochemistry and resting pH, buffer capacity and Cl^-/HCO_3 exchange activity were evaluated by microfluorometry. Fluid secretion of ducts from CF and WT ferrets and pigs were examined by videomicroscopy.

Results: Our results indicate that the bicarbonate secretion is significantly decreased in CF ferret ducts compared to WT. Videomicroscopy revealed a significant increase in fluid secretion to HCO_3^- and to 5μM forskolin and 100 μM IBMX stimulation in both WT pig and WT ferret ducts. In CF ferret and pig ducts increase of the fluid secretion were not detected during the stimulation period.

Conclusion: Concerning our data, absence of the CFTR can lead to decreased or completely abolished pancreatic ductal fluid secretion. Our interesting results revealed the importance of studying pancreatic ductal secretion of these new CF animal models more closely.

Disclosure: Nothing to disclose

OP080 MUSCLE MIR-34A IS ACTIVATED DURING NAFLD PROGRESSION, PROMOTING INSULIN RESISTANCE AND MITOCHONDRIAL DYNAMICS DYSFUNCTION

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Introduction: Intramyocellular lipid deposition associates with mitochondrial dysfunction and insulin resistance (IR), constituting a key pathophysiological event in non-alcoholic fatty liver disease (NAFLD). Our group has previously shown that human muscle IR correlates with NAFLD severity, while microRNAs (miRNAs/miRs), including pro-apoptotic miR-34a, are progressively regulated during disease progression, in both liver tissue and plasma.

Aims and Methods: Now, we aimed to investigate the functional role of miRNAs in the skeletal muscle of NAFLD patients modulating local mitochondrial dysfunction and IR and, hence, contributing for development of metabolic syndrome and NAFLD.

Skeletal muscle biopsies were obtained from morbid obese NAFLD patients undergoing bariatric surgery. Muscle RNA was run in TaqMan[TM] array microRNA cards. qPCR array data was analyzed using the HTqPCR package in Bioconductor. C57BL6 mice were fed with different NAFLD-inducing diets, including a fast food diet for 25 weeks; a choline-deficient, high-fat diet for 14 weeks; and a choline-deficient amino acid-defined diet for 32 weeks. C2C12 muscle cells were incubated with palmitic acid (PA) in the presence or absence of A-769662, a AMPK specific activator, or upon miR-34a functional modulation.

Results: 47 muscle miRNAs were found to increase from simple steatosis to non-alcoholic steatohepatitis (NASH), including miR-34a ($p < 0.05$). Concomitantly, expression of SIRT1, a direct target of miR-34a, and activation of AMPK, a metabolic SIRT1-mediator, were decreased ($p < 0.05$). Mitochondrial dynamics dysfunction was evidenced by decreased Mfn2, a mitochondrial fusion protein and increased Drp1, a mitochondrial fission protein (at least $p < 0.05$). Activation of the miR-34a/SIRT1/AMPK pathway, IR and mitochondrial dysfunction were also evident in the skeletal muscle of all three NAFLD animal models, as well as in C2C12 cells incubated with PA (at least $p < 0.05$). Of note, *in vitro*, miR-34a inhibition alleviated PA-repressed SIRT1/AMPK and mitochondrial deregulation (at least $p < 0.05$). Inversely, miR-34a overexpression mimicked PA-induced dysfunction, an effect that was abolished when downstream AMPK was activated ($p < 0.05$).

Conclusion: Altogether, these results indicate that activation of the miR-34a/SIRT1/AMPK pathway leads to impairments in IR and mitochondrial dynamics in skeletal muscle of NAFLD patients. As the role of miR-34a in global NAFLD pathogenesis keeps expanding, its further exploitation as a putative therapeutic target is warranted.

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Disclosure: Nothing to disclose

OP081 THE SERUM LEVELS OF SERINE PALMITOYLTRANSFERASE LONG-CHAIN SUBUNIT 3 ARE ASSOCIATED WITH NONALCOHOLIC FATTY LIVER DISEASE-RELATED HEPATOCARCINOGESIS

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Introduction: In recent years, the prevalence of nonalcoholic fatty liver disease (NAFLD) has been increasing, and accordingly, the proportion of hepatocellular carcinoma (HCC) patients with a background of NAFLD has also been on the rise. Although it is important to identify patients with HCC among NAFLD patients, a useful biomarker has not yet been established, so its discovery is an urgent matter in the medical treatment of NAFLD.

Aims and Methods: We previously reported that a high-fat diet aggravated the pathophysiological findings in the liver in nonalcoholic steatohepatitis (NASH) mouse models, and the hepatic expression of serine palmitoyltransferase long-chain subunit 3 (SPTLC3) mRNA was suggested to be potentially associated with NASH progression and carcinogenesis of the liver. However, the role of SPTLC3 in NAFLD patients has not been fully elucidated. The aim of this study was to clarify the role of SPTLC3 in patients with NAFLD. We analyzed 61 patients with biopsy-proven NAFLD, including 19 with hepatocellular carcinoma, and 6 healthy volunteers (HVs) and investigated the association between the serum SPTLC3 levels and the clinical features. In addition, we compared the serum SPTLC3 levels before and after the HCC treatment of 18 NAFLD patients with HCC. The serum SPTLC3 levels were measured by an enzyme-linked immunosorbent assay.

Results: 38 of the NAFLD patients were female, and the median age was 58 years. The median platelet count was $2.06 \times 10^5/\mu L$, serum ALT was 68.0 U/L, hyaluronic acid was 55.8 ng/dL, and SPTLC3 was 1.089 ng/mL. In the NAFLD patients with HCC (19 patients), the age, HbA1c, hyaluronic acid, AFP, and DCP were higher than in those without HCC (42 patients). The serum SPTLC3 levels were significantly higher in the HCC group than in the non-HCC group (6 HVs and 42 NAFLD patients) (HV vs. NAFLD group vs. HCC group = 0.6 vs. 1.0 vs. 1.6 ng/mL, respectively; $p < 0.01$). In multivariate analysis, SPTLC3 was an independent factor related to NAFLD-related hepatocarcinogesis. A receiver operating characteristic (ROC) analysis revealed that the SPTLC3 cut-off value of 1.42 ng/mL discriminated between HCC and non-HCC (area under the curve-ROC, 0.745) better than AFP (0.665). SPTLC3 and DCP (0.777) had equivalent diagnostic capabilities. The diagnostic rate of HCC using SPTLC3 (cut-off value: 1.42 ng/mL) was 63.2%. The rate using the 3 parameters of AFP, DCP, and SPTLC3 (if one or more exceeded the cut-off value, it was regarded as 'positive')

was 84.2%. The serum levels of SPTLC3 of patients who received HCC treatments were lower than the levels before treatments (before: 1.412, after: 1.094, $p < 0.001$).

Conclusion: The overexpression of SPTLC3 in the liver was associated with NASH-related hepatocarcinogenesis, and the levels of serum SPTLC3 were high in the NAFLD patients with HCC. SPTLC3 might be a novel biomarker for identifying patients with HCC among NAFLD patients in conjunction with existing biomarkers.

Disclosure: Nothing to disclose

OP082 THE EFFICACY OF PENTOXIFYLLINE ON ACUTE PANCREATITIS

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Introduction: Acute pancreatitis is an inflammatory condition that occurs in the pancreatic parenchyma and systemically affect other organs. The first phase of the disease, usually during the first week, is caused from the patient's systemic inflammatory response elicited by acinar cell injury. During this phase, the severity of acute pancreatitis is directly related to extrapancreatic organ failure, and several intercellular signaling proteins such as tumor necrosis factor-a (TNF-a) are involved. Although there is currently no specific treatment for such condition, there is evidence in animals model showing that the administration of pentoxifylline, a competitive nonselective phosphodiesterase inhibitor, is able to reduces inflammation through TNF-a inhibition. However, its benefit in acute pancreatitis in human remains unclear.

Aims and Methods: We aimed to study clinical outcomes of pentoxifylline in APACHE II score in acute pancreatitis patients at 72 hours after treatment and to study effects of pentoxifylline on inflammatory markers level (i.e., CRP, ESR, procalcitonin, and Interleukin-6).

54 acute pancreatitis patients with associated risk factors of severe pancreatitis development were evaluated for the severity of disease and inflammatory markers prior to treatment. Participant were allocated within 48 hours of diagnosis into pentoxifylline or control arm. Severity of disease as well as inflammatory markers were re-evaluated 72 h after treatment.

Results: Pentoxifylline did not decrease severity of disease determined by a reduction in APACHE II score and a percent reduction of APACHE II compared with control group (0 vs. 2; $p = 0.267$ and 0% reduction vs. 3% reduction; $p = 0$, respectively). Interestingly, the incidence of the systemic inflammatory responds syndrome (SIRS) after 72 hours of treatment was significantly lower than those without pentoxifylline. (7.7% vs. 29.2%; $p = 0.048$). Noticeably in subgroup analysis, patients with acute alcoholic pancreatitis who received pentoxifylline tended to have lower C-reactive protein (CRP) levels than those who did not (-14.53 ± 61.40 vs -3.72 ± 153.27; $p = 0.82$).

Conclusion: Pentoxifylline is an anti-TNF-a drug that seems to reduce the inflammatory process of early phase of acute pancreatitis, particularly in patients presented within 24 hours of onset. However, the overall severity of the disease and clinical benefit was similar to control group. A future study of pentoxifylline is needed to confirm its efficacy.

Disclosure: Nothing to disclose

OP083 DELETION OF BRG1 PREVENTS LIVER FIBROSIS AFTER CCL4 INJECTION IN MICE

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Introduction: Liver fibrosis is known to be a progressive pathological process that results in the accumulation of excess extracellular matrix proteins, ultimately leading to the development of cirrhosis and, at times, hepatocellular carcinoma. Brg1, a core subunit of the SWI/SNF chromatin-remodeling complex, is known to modulate proliferation in the liver and genes regulating extracellular matrix. Up to now, the role of Brg1 in liver fibrosis remains unclear. In this study, we investigate the effect of Brg1 on the progression of liver fibrosis.

Aims and Methods: A hepatocyte-specific Brg1 knockout mice model was being used by intercross of Brg1^{fl/fl}and AlbCre single mutant mice on a mixed genetic background. Carbon tetrachloride (CCl$_4$) was injected in order to induce liver fibrosis for 4, 6, 8, and 12 weeks. Brg1 expression was determined by immuno-histochemistry. Liver fibrosis was assessed by analysis of liver to body weight ratio, Sirius red staining, alpha-smooth muscle actin (α-SMA) staining, and serum ALT ELISA.

Results: Brg1 expression was significantly increased in fibrotic liver tissue of wildtype mice compared to non-treated wildtype mice. Brg1 knockout mice showed reduced liver fibrosis after chronic liver injury caused by CCl$_4$injection. After 6 weeks of CCl4 treatment, the liver to body weight ratio of Brg1

liver-specific knockout mice was decreased compared to wildtype mice. In addition, less fibrosis was seen in Brg1 knockout mice as shown by Sirius red staining and α-SMA staining. Moreover, serum ALT levelswere lower in Brg1 liver-specific knockout mice compared to wildtype mice.

Conclusion: We were able to show that hepatocyte-specific Brg1 deletion prevents liver fibrosis after CCl$_4$ injection in mice. We conclude that Brg1 promotesprogression of hepatic fibrosis and may, thus, be used as a potential therapeutic target for the treatment of patients with liver fibrosis due to chronic injury.

Disclosure: Nothing to disclose

MONDAY, OCTOBER 22, 2018   15:45–17:15
Cutting-edge endoscopy – Room E1_____

OP084   THE EFFICACY OF SCISSOR-TYPE KNIFE IN ENDOSCOPIC SUBMUCOSAL DISSECTION FOR SUPERFICIAL ESOPHAGEAL CANCER: A MULTI-CENTER RETROSPECTIVE STUDY

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Introduction: Scissor-type knife was invented as a device for endoscopic submucosal dissection (ESD) for gastrointestinal neoplasms, which enabled to perform ESD-like biopsy procedure. Therefore, ESD with scissor-type knife (ESD-S) is considered as a technically easier procedure than ESD with non-scissor-type knife (ESD-N). However, there are few reports suggesting efficacy of ESD-S by comparing with ESD-N.

Aims and Methods: This study aimed to compare the technical outcomes of ESD-S with those of ESD-N by propensity score matching analysis. Superficial esophageal cancer treated by ESD between October 2015 and March 2018 at 3 hospitals were retrospectively reviewed. Lesions treated by ESD-S (n = 48) and lesions treated by ESD-N (n = 114) were compared. Multivariate analyses and propensity score matching were used to compensate for the differences in age, gender, tumor size, tumor location, tumor depth, degree of tumor circumference, operator level and traction method use, including factors which were previously reported to affect the outcomes of ESD. Primary outcome was the procedure time during ESD. Secondary outcomes were the rate of en-block/complete resection and the rates of complication (perforation/delayed bleeding) among 2 groups.

Results: Before matching, non-experts had a higher rate of selecting scissor-type knife than experts. Propensity score matching analysis created 34 matched pairs. Adjusted comparisons between 2 groups showed a significant difference in procedure time (median; 42.5min in ESD-C vs 68.5min in ESD-O, p = 0.014). In addition, they also showed similar treatment outcomes (en-block resection rate: 100% vs 97.1%, p = 1; complete resection rate: 88.2% vs 82.4%, p = 0.734; perforation during ESD: 0% vs 5.9%, p = 0.493, delayed bleeding: 0% in both groups).

Conclusion: ESD using scissor-type knife achieved shorter procedure time than ESD using non-scissor-type knife without increase of complication. Therefore, scissor-type knife may become one option as an endo-knife of ESD for superficial esophageal cancer, especially for non-experts.

Disclosure: Nothing to disclose

OP085   FEASIBILITY AND SAFETY OF ENDOSCOPIC SUBMUCOSAL DISSECTION FOR ESOPHAGEAL CANCER IN PATIENTS WITH A HISTORY OF ESOPHAGECTOMY OR GASTRECTOMY, A PILOT STUDY

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Introduction: Patients with a history of esophagectomy of gastrectomy may have a higher risk of suffering from esophageal squamous cell carcinoma (ESCC) due to tumor recurrence or reflux of alimentary juice. Early ESCC can be found by endoscopy examination during the follow up in part of patients. Esophagectomy has been viewed as the gold standard for ESCC, however, a second alimentary tract reconstruction is extremely difficult, which remains esophageal replacement with the colon the only method. What makes matter worse is that this method is companied by high risks of adverse events and leads to bad quality of life and survival rate. ESD has been proved to be useful for early ESCC within indications, but without analysis of this special group of people.

Aims and Methods: This is a single-center retrospective study. Early ESCC patients receiving ESD between 01/01/2012 and 12/31/2016 in our institution were analyzed. Patient and cancer characteristics, adverse events were compared between the groups.

Results: 49 patients (53 lesions) with early ESCC are included in the study (Table 1). Most of the cases are male (93.9%) and 44 cases had a history of gastrectomy,

while 5 cases had a history of esophagectomy. Among the 53 lesions, 32 (60.4%) lesions invaded epithelium or lamina propria mucosa, and 9 (17.0%) lesions invaded muscularis mucosa, both of which are viewed as indications of ESD for early ESCC. 12 (22.6%) lesions invaded submucosa. En bloc resection and R0 resection were achieved in 50 (94.3%) and 42 (79.2%) cases respectively. 4 (7.5%) cases had the lymphovascular invasion. All patients who didn't get an R0 resection or had submucosal or lymphovascular invasion didn't receive a second surgery, and some of them accepted radiotherapy. No fatal perioperative adverse events were found. 1 patient had bilateral pleural effusion and treated by improvement of respiratory function and antibiotics, without surgery or drainage. 3 patients suffered from stricture and were treated by endoscopic dilation to relieve stenosis.

Conclusion: ESD is found to be safe and technically feasible in treating early ESCC in patients with a history of esophagectomy and gastrectomy. More follow-up data are needed to be analyzed by further studies to prove its efficacy in these groups of patients in a long run.

Age (years), mean ± SD	64.6 ± 7.5
Gender	
Male	46 (93.9%)
Female	3 (6.1%)
History of surgery	
Gastrectomy	44 (89.8%)
Esophagectomy	5 (10.2%)
Lesion location	
Upper esophagus	6 (11.3%)
Middle esophagus	26 (49.1%)
Lower esophagus	21 (39.6%)
anastomotic lesion	4 (7.5%)
Depth of invasion	
Epithelium or Lamina propria mucosa	32 (60.4%)
Muscularis mucosa	9 (17.0%)
Submucosal invasion	12 (22.6%)
Lesion size (cm), mean ± SD	3.0 ± 1.5
En bloc resection	50 (94.3%)
R0 resection	42 (79.2%)
Hospital stay (day), median (IQR)	3 (1-7)

[Patient demographics, cancer characteristics, pathology and outcomes]
Disclosure: Nothing to disclose

OP086   COMPARISON OF OUTCOMES OF PER-ORAL ENDOSCOPIC MYOTOMY (POEM) IN ACHALASIA PATIENTS WITH OR WITHOUT PRIOR LAPAROSCOPIC HELLER'S MYOTOMY (LHM)

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Introduction: Recurrence of achalasia symptoms after laparoscopic Heller's myotomy (LHM) occurs in about 10% of patients due to inadequate myotomy or fibrosis at the site of myotomy. Re-operation can be technically challenging with increased perioperative complications and decreased response. POEM is emerging as a less invasive treatment modality for redo-myotomy in such patients. In this study, we compared the outcomes of POEM in patients with and without prior LHM.

Aims and Methods: Achalasia patients who underwent POEM between April 2014 and June 2017 with at least 2-month post-treatment follow-up were included in the study. Patients were categorized as those with prior LHM and those without prior LHM. Patient demographics, pre-treatment and 2 month post-treatment timed barium oesophagram (TBE), high resolution oesophageal manometry (HREM) and pH study parameters were compared between the 2 groups. All POEM procedures were performed under general anesthesia and with standard steps. Fisher's exact test and Mann-Whitney U test was used to assess the significance of differences for categorical and continuous variables respectively.

Results: A total of 138 patients (No LHM = 109; prior LHM = 29) were included and 53.8% were females. There was no significant difference in the age, gender, prior treatments for achalasia (apart from LHM), pre-treatment Eckardt's score, length of stay and complication rates in both groups. The length of POEM procedure (110 [91-130] vs. 97.5 [79.5–110.5 minutes]; p = 0.023) and duration of symptomatic achalasia (5 [4-8] vs. 2 [1-6] years; p = 0.002) were significantly longer in the prior LHM group. 2-month post treatment Eckhardt's scores and

HREM parameters improved significantly in both groups. Post-treatment, patients with prior LHM showed improvement in all the TBE parameters except for height of barium column at 1 minute, which did not change significantly. On comparing pre-treatment TBE and HREM parameters, patients in the no LHM group had smaller width of barium column at 5 minutes and significantly higher mean basal LES pressure and lower LES integrated relaxation pressure (LES-IRP) as compared to the prior LHM group. All TBE parameters (except, height at 1 cm) improved more significantly in the no LHM group as compared to prior LHM group. Abnormal pH study with increased DeMeester scores (>14.72) was not significantly different in the 2 groups.

Conclusion: POEM takes longer procedure time but is safe and effective for palliation of symptoms in patients with recurrent symptoms after prior LHM. Clinical improvement reflected by a decrease in Eckhardt's scores is similar in both groups, although objective improvement in TBE parameters is more impressive in patients without prior LHM.

Factors	No prior LHM group (n = 109)	Prior LHM group (n = 29)	p-value
Pre-POEM findings			
Eckardt's score	7 (5-9)	7 (5-8.5)	0.618
Basal mean pressure on HREM (mmHg)	45 (29.6–58.7)	28.7 (14.1–46.5)	0.004
Lower esophageal sphincter Integrated relaxation pressure (LES-IRP) (mmHg)	25.5 (16.8–34.5)	20.5 (6.6–31.7)	0.03
Height at 1 minute on TBE (cm)	11 (7.5–15)	9.3 (6.4–15)	0.35
Width at 1 minute on TBE (cm)	3 (2-4)	3.5 (3-4.5)	0.056
Post-POEM findings			
Eckardt's score	0 (0-1)	0 (0-2)	0.858
Basal mean pressure on HREM (mmHg)	14.7 (9.5–21.5)	10.3 (5.6–18.2)	0.05
Lower esophageal sphincter Integrated relaxation pressure (LES-IRP) (mmHg)	6.7 (3.4–9.4)	5.9 (1.1–7.6)	0.207
Height at 1 minute on TBE (cm)	4.5 (0-8)	6.7 (3.5–8.8)	0.88
Width at 1 minute on TBE (cm)	0 (0-1.5)	2.5 (1.9–3.5)	<0.001
Height at 5 minute of TBE (cm)	0(0-5)	3.5 (0-7)	0.024
Width at 5 minute on TBE (cm)	0 (0-1.5)	2 (0-3)	0.001

[Comparison of pre-treatment and post-treatment Eckardt's score, HREM and TBE findings in patients without and with prior LHM]

Disclosure: This Abstract has been accepted to be presented at Digestive Disease Week (DDW) meeting in Washington DC, 2018, USA

OP087   EFFICACY AND SAFETY OF ENDOSCOPIC RESECTION FOR SMALL SUBMUCOSAL TUMORS ORIGINATING FROM THE MUSCULARIS PROPRIA LAYER IN THE GASTRIC FUNDUS

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Introduction: Gastrointestinal submucosal tumors (SMTs) are most commonly found in the stomach, as often as 1 in every 300 endoscopies. Small tumors may be asymptomatic or only present with nonspecific gastrointestinal symptoms, and are usually detected incidentally during upper gastrointestinal endoscopy. Recently, as the widespread use of digestive endoscopy and advances in endoscopic ultrasonography (EUS), the diagnostic rate of small SMTs, including gastrointestinal stromal tumors (GISTs) with malignant potential, have been increasing. According to guidelines set by the National Comprehensive Cancer Network (NCCN), surgical referral should be considered for non-metastatic GISTs > 2 cm, whereas GISTs < 2 cm lacking high-risk features upon EUS can be followed up at 6-month to 12-month. However, distinguishing GISTs from other SMTs with similar features by EUS is difficult. Furthermore, when the tumor grows, patients may lose the opportunity to receive minimally invasive treatment. Therefore, the minimally invasive resection approach for these small SMTs is crucial.

Endoscopic resection (ER) including endoscopic submucosal excavation (ESE) and endoscopic full-thickness resection (EFTR) which are derived from endoscopic submucosal dissection (ESD) have been used to curatively resect gastric SMTs in an en bloc fashion. When the tumor is in the fundus, the dissection is more challenging and more time is comsumed for the resection because of the retroflexion of the endoscope and specific anatomical features. Formerly, large consecutive studies analyzing of small SMTs treated by ER technique, particularly in gastric fundus, have not been reported. The aim of this study was to evaluate the efficacy, safety and feasibility of resection for small gastric SMTs using the ESE and EFTR technique in a large series of patients with long-term outcomes.

Aims and Methods: In this study, we investigated the efficacy, safety, and long-term outcomes of ER for small SMTs of the gastric fundus in a large series of patients which were lacked before. 537 consecutive patients with SMTs no more than 20mm of the gastric fundus originating from the muscularis propria (MP) layer and treated with endoscopic submucosal excavation (ESE) or endoscopic full-thickness resection (EFTR) were included in this retrospective study at Zhongshan Hospital of Fudan University from January 2013 to September 2016. Clinicopathological, endoscopic and follow-up data were collected and analyzed.

Results: The en bloc resection was achieved in 100% of patients and complete resection was achieved for 530 (98.7%) lesions. Although total rate of complications was 9.3%, serious adverse events only occurred in 3 (0.6%) patients including major pneumoperitoneum, major hydrothorax and bleeding. Unlike lager tumor size and longer procedure time, endoscopist experience had positive impact on decreasing complications. Based on statistical analysis, tumors with greater size, near cardia and treated by EFTR were the significant contributors to longer operative times. A median follow-up of 32 months was available and all patients were free from local recurrence or distant metastasis during the study period.

Conclusion: Although technical difficulties present in gastric fundus, ER is quite effective and safe for resection of small gastric SMTs with high complete resection rate and rare serious adverse events.

Disclosure: Nothing to disclose

OP088   ENDOSCOPIC RESECTION VIA ANTRAL SUBMUCOSAL TUNNELING FOR SAFE EN BLOC REMOVAL OF TUMORS IN THE DUODENAL BULB

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Introduction: Generally, endoscopic submucosal dissection (ESD) of the duodenal tumor remains less prevalent due to anatomical characteristics of the duodenum, technical difficulties of the procedure, and a high risk of complications including delayed bleeding and perforations which may require invasive surgical intervention [1]-[3].

Aims and Methods: Herein, we describe a novel endoscopic technique, endoscopic resection via antral submucosal tunneling (ERAST), for the en bloc removal of tumors in the duodenal bulb. The specific steps of the ERAST are the following. First, a mucosal incision is made using a Hybrid knife (I-type, ERBE, Germany) approximately 5 cm proximal to the pylorus. A submucosal tunnel extending to the duodenal tumor via the pylorus is then created. To completely expose the tumor, submucosal tunneling following entry into the duodenal bulb is continued until approximately 10 mm distal to the tumor. Soft coagulation (80 W on effect 4, ERBE, Germany) is recommended for hemostasis in the bulb to prevent potential perforation of the thin duodenal muscularis propria. Next, a mucosal incision is made from the inner side of the submucosal tunnel towards the duodenal lumen. The circumferential mucosa of the tumor is then incised in a step-by-step manner to remove the tumor en bloc. An endoclip tied with floss is used to extract the tumor out from the duodenum. Finally, the mucosal defect in the bulb and the mucosal incision in the antrum are closed using endoclips (Micro-Tech, Nanjing, China) combined with endoloop (MAJ-254; Olympus). ERAST takes advantage of submucosal tunneling to facilitate tumor resection and has the potential to increase the safety of ESD and overcome difficulties in resecting tumors that are anatomically challenging to access.

In this preliminary study, we evaluated the feasibility and safety of ERAST for the treatment of lesions in the duodenal bulb.

Results: As shown in Table 1, 4 tumors, independent of their location in the duodenal bulb, were successfully resected by ERAST and 100% en bloc resection was achieved. No major bleeding or perforation occurred during ERAST and no postoperative complications such as delayed bleeding, perforation or hyperpyrexia was observed. Esophagogastroduodenoscopy carried out 2 months after the ERAST revealed that the indicated wound had healed completely without recurrence or biliary reflux and no patients reported any discomfort. Leveraging the use of submucosal tunneling to facilitate endoscopic resection, the endoscopic view enabled by ERAST facilitates recognition of anatomic layers of the thin duodenal wall and hence, demarcation of a clear and safe dissection line above the muscularis propria. In addition, ERAST facilitates the dissection of tumors in anatomically difficult locations, such as locations close to the pyloric ring or superior angle; exploiting the submucosal tunnel, ERAST enables the endoscope to approach the tumor easily with an adequate visual and operating field.

Conclusion: In conclusion, our findings suggest that ERAST is feasible and safe for the removal of lesions in the duodenal bulb, particularly for those in challenging anatomical locations. However, further prospective studies with a larger number of cases are warranted to investigate the long-term recurrence rates and potential adverse effects.

[Clinical characteristics of the 4 cases of duodenal tumors that have been successfully resected by ERAST.]

Disclosure: Nothing to disclose

Abstract No: OP088

Characteristic	Age,y (Sex)	Location (D1)	Size (mm×mm)	Depth	Pathology	Estimated blood loss (ml)	Procedure time (min)	Intraoperative perforation	Postoperative complications
Case 1	48 (F)	Anterior	20 × 30	M	High grade intraepithelial neoplasia	10	300	Minute perforation due to force coagulation	None
Case 2	63 (F)	Superior	15 × 15	SM	Neuroendocrine neoplasm	30	300	None	None
Case 3	53 (F)	Greater curvature	11 × 13	SM	Neuroendocrine neoplasm	3	122	None	None
Case 4	41 (M)	Lesser curvature	25 × 30	SM	Adenoma of Brunner's gland	5	210	None	None

References

1. Yamamoto H, Miura Y. Duodenal ESD: conquering difficulties. *Gastrointest Endosc Clin N Am* 2014; 24: 235–44.
2. Hoteya S, Furuhata T, Takahito T, et al. Endoscopic Submucosal Dissection and Endoscopic Mucosal Resection for Non-Ampullary Superficial Duodenal Tumor. *Digestion* 2017; 95: 36–42.
3. Bourke MJ. Endoscopic resection in the duodenum: current limitations and future directions. *Endoscopy* 2013; 45: 127–32.
4. Hayashi Y, Sunada K, Takahashi H, Shinhata H, Lefor A, Tanaka A, et al. Pocket-creation method of endoscopic submucosal dissection to achieve en bloc resection of giant colorectal subpedunculated neoplastic lesions. *Endoscopy*. 2014 Oct 14; 46(S 01): E421–2.
5. Sakamoto H, Hayashi Y, Miura Y, Shinozaki S, Takahashi H, Fukuda H, et al. Pocket-creation method facilitates endoscopic submucosal dissection of colorectal laterally spreading tumors, non-granular type. *Endosc Int Open*. © Georg Thieme Verlag KG; 2017 Feb 13; 05(02): E123–9.

OP089 THE POCKET-CREATION METHOD FACILITATES ENDOSCOPIC SUBMUCOSAL DISSECTION OF LARGE SESSILE AND SUBPEDUNCULATED TUMORS

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Introduction: Large sessile and subpedunculated tumors are frequently associated with severe submucosal fibrosis and retraction of the muscularis (1,2). Therefore, endoscopic en bloc resection by endoscopic submucosal dissection (ESD) is challenging. Despite the non-lifting sign, endoscopic resection may be curative since the fibrosis is often benign without tumor invasion and many of these tumors are limited to the mucosa. The pocket-creation method (PCM) provides adequate submucosal traction enabling ESD, even with submucosal fibrosis (3). We previously reported that the PCM facilitates ESD of laterally spreading colorectal tumors, non-granular type, frequently complicated by submucosal fibrosis (4).

Aims and Methods: The aim of this study is to assess the utility of PCM to overcome the difficulties caused by even severe fibrosis associated with large sessile and subpedunculated tumors by comparing ESD using the PCM with conventional methods (CM).

A total of 887 colorectal lesions were resected by ESD between April 2010 and January 2017 at Jichi Medical University Hospital. Of 887 lesions, 109 were sessile or subpedunculated tumors. Of the 109 lesions, 18 were smaller than 20mm in diameter and one non-neoplastic lesion was excluded. This is a retrospective review of the remaining 90 colorectal large sessile and subpedunculated tumors in 89 patients. The lesions are divided into PCM (n = 40) and CM groups (n = 50). The primary outcome measure was en bloc resection rate. Secondary outcome measures included (1) R0 resection (en bloc resection with histologically negative resection margins); (2) complications; (3) dissection time (min); (4) dissection speed (mm²/min).

Results: PCM and CM achieved high en bloc resection rates. (PCM, 100% [40/40] vs. CM 94% [47/49] p=0.55). ESD of 2 lesions in the CM group were stopped during the procedure, 1 after immediate perforation was recognized, and 1 with a deeply invasive tumor converted to Endoscopic Mucosal Resection. 1 lesion in the CM group was resected in a piecemeal fashion. Tumor diameters (mm) were similar (median (range), PCM: 30.5 (20-57) vs. CM: 30.5 (20-90), p=0.77) There were no differences in R0 resection rates (88 %, 35/40 vs. 78%, 38/49, p = 1.0) or incidence of adverse events (perforation and late delayed bleeding, 5%, 2/40 vs. 8%, 4/50, p = 0.69). When the PCM was used, the rate of pathologically negative vertical margins (p = 0.04) was significantly greater, dissection time (p = 0.04) shorter and dissection speed (p = 0.02) faster than when CM was used.

Conclusion: ESD using PCM increases the rate of negative vertical margins with rapid dissection for the treatment of large colorectal sessile and subpedunculated tumors.

Disclosure: Nothing to disclose

References

1. Toyonaga T, Tanaka S, Man-I M, East J, Ono W, Nishino E, et al. Clinical significance of the muscle-retracting sign during colorectal endoscopic submucosal dissection. *Endosc Int Open*. 2015 May 5; 3(03): E246–51.
2. Choi YS, Lee JB, Lee E-J, Lee SH, Suh JP, Lee DH, et al. Can endoscopic submucosal dissection technique be an alternative treatment option for a difficult giant (≥ 30mm) pedunculated colorectal polyp? *Dis Colon Rectum*. 2013 May; 56(5): 660–6.

MONDAY, OCTOBER 22, 2018 15:45–17:15
Clinical features in IBD – Room F1

OP090 EOSINOPHILIC OESOPHAGITIS WITH INFLAMMATORY BOWEL DISEASE: EPIDEMIOLOGY AND OUTCOMES FROM A LARGE POPULATION-BASED ANALYSIS

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Introduction: Eosinophilic oesophagitis (EoE) is an immune-mediated condition that shares some immunological pathways with inflammatory bowel diseases (IBD). Few case reports have suggested an overlap between EoE and IBD, although the epidemiology and implications of this relationship are unknown.

Aims and Methods: The primary objectives of this study were to estimate the prevalence of EoE in IBD and to identify potential adverse outcomes of co-diagnosis. Given the rarity of EoE in IBD, we relied on a very large population-based cohort to maximize the sensitivity and precision of our analyses. All enrollees in the Truven Health MarketScan® Research Database (2007–2016), the largest health claims database in the United States, were included in this study. Patients with EoE, Crohn's disease (CD), and ulcerative colitis (UC) were identified based on recurrent diagnoses using the International Classification of Diseases 9 and 10 codes. Descriptive analyses were used to estimate the prevalence and characterize the demographics of IBD patients with or without EoE. Cox proportional hazards models were used to compare the longitudinal risk of major adverse outcomes (corticosteroid use, initiation or change in biologic therapy, hospitalization, and abdominal surgery) between IBD patients with and without EoE. Regression models controlled for age, sex, and geographic region.

Results: There were 153,232,283 individuals with a median follow-up time of 1.8 years (interquartile range 0.8 to 3.8). The overall prevalence of EoE was 68.5 per 100,000 individuals. The prevalence rates of EoE were significantly higher in patients with CD (508.0 per 100,000; p < 0.01) and UC (325.0 per 100,000; p < 0.01) than in the general population. CD and UC patients with EoE were predominantly male (CD: 61.8% vs. 38.2%, p < 0.01; UC: 56.6% vs. 43.4%, p < 0.01) and younger (CD: 33.9 vs. 46.1 years, p < 0.01; UC: 41.4 vs. 49.8 years, p < 0.01) than IBD patients without EoE. For CD patients, EoE was associated with an increased risk of corticosteroid use (adjusted hazard ratio [aHR] 1.16; 95% CI 1.07 to 1.25; p < 0.01) and the initiation or change in biologic therapy (aHR 1.21; 95% CI 1.05 to 1.39; p < 0.01), but not hospitalization or surgery. For UC patients, EoE was similarly associated with an increased risk of corticosteroid use (aHR 1.26; 95% CI 1.13 to 1.40; p < 0.01) and the initiation or change in biologic therapy (aHR 1.50; 95% CI 1.03 to 2.20; p = 0.04), but not hospitalization or abdominal surgery.

Conclusion: In this first population-based study of EoE in IBD, EoE was found to be 5- to 8-fold more prevalent in IBD than the general population. For IBD patients, EoE was significantly more common in younger and male patients. EoE was associated with an increased need for corticosteroids and biologic therapy, but not hospitalization or abdominal surgery. Given the observed relationship between EoE and IBD, further investigation into the epidemiology and patho-physiology of both diseases may provide insight into shared mechanisms of pathogenesis.

Disclosure: Nothing to disclose

OP091 LONG-TERM OUTCOME OF CROHN'S DISEASE COMPLICATED BY UPPER GASTROINTESTINAL STRICTURE : A GETAID COHORT STUDY

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Introduction: The most frequent location of inflammatory lesions in Crohn's disease (CD) are the terminal ileum and the colon. Disease activity can lead to the developpement of stenosis and their management is well known. Upper gastrointestinal (UGI) locations of CD are less frequent thus the risk of stenosis is high. Few studies are avalaible to evaluate the efficacy of medical, endoscopic and surgical treatment.
Aims and Methods: The aim of the present study was to evaluate outcomes and treatments efficacy in Crohn's disease patients with severe strictures of the upper gastrointestinal tract. We performed a retrospective study in 18 centers from the GETAID, including all CD patients with an nonpassable UGI stricture on upper endoscopy. The primary outcome was the surgery-free survival from diagnosis of stricture. Short and long-term clinical efficacy (defined as a relief of obstructive symptoms) and endoscopic efficacy (defined as ability to pass the scope beyond the stricture) of medical, endoscopic and surgical treatments and identification of predictors of surgery were also evaluated.
Results: From 1988 to August 2017, 43 CD patients with a non-passable stricture on upper endoscopy were included: 40% were female and 9% were active smokers. Median age at CD diagnosis was 22 (IQR: 17-30,5) years with a median disease duration from CD to stricture diagnosis of 7 (IQR: 0-13,5) years. Location of stenosis was : 4 (9%) esophagus, 6 (14%) stomach, 28 (65%) duodenum, 3 (7%) proximal jejunum, and 2 (5%) evolving both pylorus and duodenum. 40 (93%) patients had primary stricture and 3 (7%) anastomotic stricture. The median follow-up from stricture diagnosis to last news was 5 (IQR: 2-10.5) years. Surgical-free survival was 80%, 75%, 61% and 49% at 1, 3, 5, and 7 years respectively. Medical treatment of the stricture consisted in: immunosupressant in 27 cases with as short-term clinical efficacy in 13 (48%) cases and endoscopic efficacy in 3 (11%) cases; anti-TNF therapy in 28 cases with a short-term clinical efficacy in 17 (60%) cases and endoscopic efficacy in 7 (25%). 39 endoscopic procedures (30 dilations, 7 stents, 2 gastroenteroanastomosis) were realized with a short-term clinical efficacy in 31 (79%) cases and endoscopic efficacy in 23 (59%) cases; a complication occurred in 4 (10%) cases (3 perforations and 1 hemorrhage). At the end of follow-up 21 (49%) patients were not operated. 25 surgeries were performed with a short-term clinical efficacy in 21 cases (84%) for a median time of 61 (12-127) months. A complication occurred in 8 (32%) cases (2 perforations, 1 death, 1 pulmonary embolism, 1 anastomotic stricture, 1 hematoma, 1 hemorrhage, 1 gastroenteroanastomosis dysfunction). In multivariate analysis, the risk of surgery was greater for active smokers (p = 0.04), and was lower for patients receiving anti-TNF treatment at stricture diagnosis (p = 0.02).
Conclusion: Surgery is often necessary in CD patients with severe stricture of the UGI, especially in active smokers. Medical and endoscopic treatments are efficient in the majority of the patients at short term and allow avoiding surgery in almost half the patients at long term.
Disclosure: Nothing to disclose

OP092 ADICROHN PILOT STUDY: AN INNOVATIVE TREATMENT FOR REFRACTORY PERIANAL FISTULAS IN CROHN'S DISEASE: LOCAL INJECTION OF AUTOLOGOUS FAT AND ADIPOSE DERIVED STROMAL VASCULAR FRACTION

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Introduction: Mesenchymal cell therapy is promising for the treatment of perianal Crohn's fistulas refractory to conventional therapy. Autologous adipose-derived stromal vascular fraction (ADSVF) is recognized as an easily accessible source of cells with angiogenic, anti-inflammatory, immunomodulatory and regenerative properties. ADICROHN pilot study is based on the innovative hypothesis that combined action of ADSVF associated with trophic charasteristics of microfat graft could be beneficial to Crohn's patients with refractory perianal fistulas
Aims and Methods: This is a prospective, open, non-comparative, single center, phase I-II clinical trial. Eligible patients were aged > 18 years and diagnosed with complex perianal fistula associated with Crohn's disease at least for 6 months with controlled luminal disease (CDAI < 220). Fistula(s) had to be refractory to conventional treatment. 10 patients were enrolled. Patients were first subjected to an exam under anaesthesia with drainage by seton placement if indicated, followed at least 1 week later on the same day by adipose tissue extraction, ADSVF and microfat preparation then injected into the fistula. Patients were monitored at baseline and at 1, 2, 6, 12, 16 and 48 weeks after injection for safety and efficacy analysis. Safety analysis included at every visits clinical assessment of adverse events. Efficacy analysis included at every visit clinical evaluation of fistula closure, evaluation of disease activity by PDAI/CDAI scores, and assesment of quality of life by SIBDQ. Fistula closure was also evaluated via radiological assessment with MRI (confirmation of absence of collections > 2 cm of the treated perianal fistula) at week 12 and 48. Complete response was defined as a complete cessation of suppuration on week 12, despite not achieving a complete re-epithelization. Partial response was defined as an evident decrease in suppuration. Remission was defined as complete closure of all the external openings that were draining at baseline despite gentle pressure, also confirmed via radiological assessment with MRI (absence of collections > 2 cm of the treated perianal fistula).
Results: Since October 2015 and March 2017, 10 patients were treated by this innovative local treatment (among 10 cc of microfat and about 30 millions of ADSVF viable cells subsequently injected into the soft tissue around the fistulas). No serious adverse events have been described. The most frequent side effect (40% of patients) was moderate pain on lipoaspiration site. No case of incontinence post treatment was described. About efficacy, 70% of response was found at week 12 (50 % of partial response and 20% of remission) and 80% of response at week 48 (40% of remission, 20% of complete response, 20% of partial response). These results were associated to significant reduction of severity of perianal disease with a PDAI score that passed from 7.3 at baseline at 3.8 at week 12 and 3.4 at week 48 (p = 0.002) and significant improvement of quality of life score (p = 0.038).
Conclusion: This first study evaluating co-local administration of ADSVF in association with fat graft appears to be a simple, safe and efficient surgical regenerative therapy for perianal Crohn's fistula refractory to conventional therapy.
Disclosure: Nothing to disclose

OP093 A PROPENSITY SCORE-MATCHED COMPARISON OF INFLIXIMAB AND ADALIMUMAB IN NAïVE AND NON-NAïVE PATIENTS WITH CROHN'S DISEASE: REAL-LIFE DATA FROM THE SICILIAN NETWORK FOR INFLAMMATORY BOWEL DISEASE (SN-IBD)

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Introduction: In the absence of head-to-head trials, there is an unmet need to better understand the effectiveness of different biologics in inflammatory bowel disease (IBD). The Sicilian Network for Inflammatory Bowel Disease (SN-IBD) is a group composed by 16 Sicilian centres which continuously enter in a web based software all clinical data of IBD patients treated with biologics.

Aims and Methods: Data of all incident Crohn's disease (CD) patients treated with infliximab (IFX) and adalimumab (ADA) from January 2013 to April 2017 were extracted from the cohort of SN-IBD. Patients were divided in biologic-naïve and non-naïve, and the 2 groups were analyzed singularly. We used a 1-to-2 propensity score matching (2 ADA: 1 IFX) accounting for the main baseline characteristics in naïve patients, and a 1-to-1 propensity score matching (1 ADA: 1 IFX) in non-naïve. Clinical outcomes were evaluated at 12 weeks and 1 year.

Results: 632 patients (735 total treatments) were included. After propensity score matching, 321 naïve (ADA: 214; IFX: 107) and 81 non-naïve patients (total treatments: 94; ADA: 47; IFX: 47) were analyzed. Among naïve patients, a clinical benefit was achieved in 175/214 (81.8%) patients treated with ADA and in 84/107 (77.6%) patients treated with IFX (adjusted OR: 1.23, 95% CI 0.63–2.44, p = 0.547) at 12 weeks; after 1 year, a clinical benefit was achieved in 148/214 (69.2%) patients treated with ADA and in 69/107 (64.5%) patients treated with IFX (adjusted OR: 1.10, 95% CI 0.61–1.96, p = 0.766). The rate of adverse events was significantly higher in patient treated with IFX (incidence rate ratio = 1.71, p-value = 0.020). Conditional logistic regression model showed that previous surgery (adjusted OR: 0.19, 95% CI 0.04–0.78, p = 0.021), upper GI localization (adjusted OR: 0.20, 95% CI 0.05–0.84, p = 0.028), and fistulizing behavior (adjusted OR: 0.29, 95% CI 0.10–0.87, p = 0.027) were independent risk factors for a reduced rate of clinical benefit at 1 year. Among non-naïve patients, a clinical benefit was achieved in 29/47 (61.7%) patients treated with ADA and in 32/47 (68.1%) patients treated with IFX (adjusted OR: 0.72, 95% CI 0.21–2.44, p = 0.600) at 12 weeks; after 1 year, a clinical benefit was achieved in 23/47 (48.9%) patients treated with ADA and in 19/47 (40.4%) patients treated with IFX (adjusted OR: 1.23, 95% CI 0.54–2.86, p = 0.620). The rate of adverse events was significantly higher in patient treated with IFX (incidence rate ratio = 2.57, p = 0.009). No prognostic factor of clinical benefit was found among non-naïve patients.

Conclusion: In the first study comparing the clinical effectiveness of ADA and IFX in moderate to severe CD patients via propensity score, there was no significant difference between the 2 drugs, neither in naïve nor in non-naïve patients.

Disclosure: Ambrogio Orlando served as an advisory board member for AbbVie, MSD, Takeda Pharmaceuticals and received lecture grants from AbbVie, MSD, Sofar, Chiesi, and Takeda Pharmaceuticals. Fabio Salvatore Macaluso served as an advisory board member for MSD, and received lecture grants from MSD and Takeda Pharmaceuticals. Sara Renna served as an advisory board member for AbbVie and MSD Pharmaceuticals, and received lecture grants from AbbVie, MSD and Takeda Pharmaceuticals. Filippo Mocciaro served as an advisory board member for AbbVie and MSD, and received lecture grants from AbbVie, MSD and Takeda Pharmaceuticals. Maria Cappello served as an advisory board member for AbbVie, MSD, Takeda Pharmaceuticals, and received lecture grants from AbbVie, MSD, Chiesi, and Takeda Pharmaceuticals.

OP094 TREATMENT PATTERNS AMONG PATIENTS WITH MODERATE-TO-SEVERE ULCERATIVE COLITIS IN WESTERN EUROPE

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Introduction: The goal of treatment in ulcerative colitis (UC) is to induce clinical response and maintain steroid-free disease remission in the long term. The aim of the present study is to examine how moderate-to-severe UC is currently managed in real-world clinical practice across select Western European countries.

Aims and Methods: Data from the 2017 Adelphi Inflammatory Bowel Disease Specific Programmes (IBD-DSP) were used. The IBD-DSP is a database of patient chart information abstracted by selected gastroenterologists across the European Union Five ([EU5]; i.e., France, Germany, Italy, Spain, and the United Kingdom [UK]). Eligible gastroenterologists who agreed to participate were asked to complete patient record forms for the next 7 consecutive eligible adult patients with UC. Only charts from patients with moderate-to-severe UC were included in the analysis (defined as those with documented administration of either an immunomodulator [IM] or a biologic). Treatment usage by line of therapy (defined as the sequential order of treatments after diagnosis) and the prevalence of dose escalation was reported using descriptive statistics (mainly percentages).

Results: A total of N = 1191 patient charts were included (France: N = 331, Germany: N = 271, Italy: N = 207, Spain: N = 250, UK: N = 132; 56.5% male; mean age = 39.6 [SD = 13.7]). Patients had been diagnosed for a mean of 4.9 years (SD = 5.9). For those with complete treatment history (N = 1060), 47.1% used 5-ASAs and/or steroids as their first-line therapy. The remaining 52.9% used either an IM or biologic as first-line therapy (IM without biologic = 27.4%; infliximab [IFX] = 13.3%; adalimumab [ADA] = 9.8%; golimumab [GOL] = 1.3%, vedolizumab [VDZ] = 0.8%). Use of IM therapy (without a biologic) was higher in subsequent lines: second-line = 41.5%, third-line = 38.3%. Similarly, the use of a biologic also increased in second-line (IFX = 19.0%,

ADA = 10.4%, GOL = 3.6%, VDZ = 2.4%) and then again in third-line (IFX = 19.9%, ADA = 14.4%, GOL = 4.0%, VDZ = 6.6%). The percentage of patients treated with biologic therapy who were also using a concomitant IM increased over time from first-line to third-line: IFX = 19.9% to 32.0%, ADA = 12.5% to 25.9%, GOL = 7.1% to 20.0%, VDZ = 11.1% to 20.0%. Among patients currently using a biologic therapy, dose escalation during maintenance therapy (i.e., a higher than indicated dose or greater than indicated dosing frequency) was observed as follows: IFX = 39.1%, ADA = 36.1%, VDZ = 30.9%, GOL = 20.8%.

Conclusion: Among patients with UC in the EU5 who go on to use an IM or biologic treatment, many patients use these treatments as their first therapy after diagnosis. Combination therapy with both IM and biologic therapy is also common and increases over the course of the disease. For patients who use biologic therapy, between 20-40% of patients use a higher than indicated dose and/or frequency. These findings suggest a number of patients experience sub-optimal levels of disease control.

Disclosure: A Armuzzi has received research support from MSD, lecture fees from AbbVie, AstraZeneca, Chiesi, Ferring, Hospira, MSD, Mundipharma, Nikkiso, Otsuka, Pfizer Inc, Takeda, TiGenix, Zambon, and consultancy fees from AbbVie, Allergan, Biogen Idec, Celltrion, Eli Lilly, Ferring, Hospira, Janssen, MSD, Mundipharma, Pfizer Inc, Samsung Bioepis, Sofar, Takeda; M Tarallo, M DiBonaventura, D Bargo, L Salese, J Cappelleri, G Gigante are employees and shareholders of Pfizer Inc; J Lucas, D Bluff and B Hoskin are employees of Adelphi Real World.

OP095 EFFICACY AND SAFETY OF USTEKINUMAB INTRAVENOUS INDUCTION IN A COHORT OF PATIENTS WITH CROHN'S DISEASE REFRACTORY TO ANTI-TUMOR NECROSIS FACTOR AGENTS

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Introduction: Ustekinumab is a fully human IgG1k monoclonal antibody targeting the p40 subunit of interleukins-12 and 23 thus inhibiting their receptors on T cells and natural killer cells. Ustekinumab is effective to induce clinical response and remission in patients with moderately to severely active Crohn's disease (CD) that is refractory to either TNF antagonists or conventional therapy in phase III trials. The aim of the study was to describe the real-life experience with Ustekinumab intravenous induction in anti-TNF and/or vedolizumab resistant or intolerant CD patients.

Aims and Methods: We perfomed a retrospective observational open-label study on CD patients receiving ustekinumab intravenous induction between August 2014 and November 2017 in 2 gastroenterology departments at University Hospital Nord (Marseille) and University Hospital Saint-Eloi (Montpellier). The primary outcome was clinical response at 8 weeks, defined by reduction in Harvey-Bradshaw Index (HBI) of ≥3 points.

Results: A total of 100 patients was included. 99 patients (99%) were resistant or intolerant to ≥1 anti-TNF and 54 (54%) to Vedolizumab.

Ustekinumab was given to 84 (84%) patients for luminal disease activity, to 8 (8%) for intolerance to a previous treatment, to 7 (7%) for absence of endoscopic or imaging remission and to 1 patient (1%) for reduce the risk of post operative recidive.

Clinical response at week 8 was achieved in 74 patients (74%) and clinical remission in 50 patients (50%). 79 patients were still under treatment at 6 month. No factors predicted the initial clinical response with ustekinumab at week 8.

An adverse event developed in 11 patients (11%) during the induction phase and 1 severe adverse event resulting in death was reported 5 months after treatment initiation.

Conclusion: Ustekinumab intravenous induction is effective in almost three-quarters of patients with CD refractory to at least 1 anti-TNF agent and/or vedolizumab therapy. Moreover, it seems to be sustainable over time and safe.

Disclosure: Nothing to disclose

MONDAY, OCTOBER 22, 2018   15:45–17:15
Management of Barrett's – Room K_____

OP096 QUALITY INDICATORS FOR BARRETT'S ENDOTHERAPY (QBET): UK CONSENSUS STATEMENTS FOR PATIENT'S UNDERGOING ENDOSCOPIC THERAPY FOR BARRETT'S ESOPHAGUS NEOPLASIA

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Table 1: Final list of Appropriate Quality Indicators based on all 4 statistical methods

	Appropriate QI	Median Score	Performance Threshold Median % (Range)
Pre-endoscopy	BET should be performed in high-volume centres within a local cancer network	9	100 (90, 100)
Pre-endoscopy	Patients considered for BET, should be discussed in a Oesophago-Gastric MDT	9	93 (85, 100)
Pre-endoscopy	It is recommended that endoscopist undertaking BET should have undergone formal hands on training at a high-volume centre	9	100 (90, 100)
Pre-endoscopy	Centres should carry out sufficient numbers of BET cases per year to meet efficacy and safety standards	9	N/A
Intra-procedural (Resection)	Adherence to the Prague and Paris classification is recommended	9	95 (80, 100)
Intra-procedural (Resection)	It is recommended that all patients undergoing BET and follow-up should have assessment with High-definition white light (WL) endoscopy with chromoendoscopy	9	93 (80, 100)
Intra-procedural (Resection)	Where appropriate ALL visible lesions should be entirely resected with EMR or ESD	9	93 (80, 100)
Intra-procedural (Resection)	For patients having BET, the use of EUS is not routinely recommended	8.5	90 (70, 100)
Intra-procedural (Resection)	Lesions with SM invasion should only be considered for curative BET if low risk of metastasis	8.5	90 (80, 100)
Intra-procedural (Ablation)	Low and High grade dysplasia without visible lesions should be considered for endoscopic ablation	9	95 (80, 100)
Intra-procedural (Ablation)	Following endoscopic resection, patients should undergo ablative therapy, every 2-4 months in order to achieve CR-IM	9	90 (80, 100)
Intra-procedural (Ablation)	For patients undergoing RFA with a focal device, the recommended dose is 12 J / cm^2 × 3 (without cleaning)	8	N/A
Intra-procedural (Ablation)	Centres undertaking BET should achieve CR-D ≥ 90 % and CR-IM ≥ 80 % within 18 months after the first treatment	8	N/A
Intra-procedural (Ablation)	Patients with residual dysplasia after 18 months, should be re-discussed at a Oesophago-Gastric MDT	9	90 (80, 100)
Intra-procedural (Ablation)	Post-BET symptomatic stricture rate should not exceed 10-15 %	8	N/A
Post Endoscopy	Following successful BET, patients should undergo follow up endoscopies at appropriate intervals stratified according to risk of recurrence	9	90 (80, 100)
Post Endoscopy	At follow-up endoscopy, biopsies should be taken from the Squamo-columnar junction and within the extent of the original BE length, for the first 2 years; thereafter biopsies should be taken from the Squamo-columnar junction and any visible lesion	8	90 (80, 100)
Post Endoscopy	All centres should regularly audit their outcomes and adverse events	9	N/A

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Introduction: Barrett's Endoscopic Therapy (BET) for the management of patients with BE neoplasia has significantly developed in the past decade. Despite recent national and international guidelines, UK and European registries and national audits demonstrate variation in the management of these patients resulting in variable outcomes. Healthcare systems and processes need to be aligned to ensure a streamlined, efficient and high quality service provision to all patients. Quality Indicators (QI) for BET in the UK are lacking.
Aims and Methods: The **aim** of this project was to develop expert physician-led QBET to define best practice in patients with BE neoplasia.
Method: The RAND UCLA Appropriateness Method (RAM) was utilised to combine the best available scientific evidence with the collective judgment of experts to develop QBET in 4 sub-groups: Pre-endoscopy, intra-procedural (resection), intra-procedural (ablation) and post endoscopy. National and International experts including gastroenterologist (n = 20), surgeons (n = 2), BE pathologist (n = 1), clinical nurse specialist (n = 1) and patient representative (n = 1) participated in a 3-round process (Round 0, 1 and 2) to develop 18 QIs in BET that fulfilled the definition of appropriateness using 4 statistical methods: 1) mean absolute deviation from median MAD-M, 2) BIOMED Concerted Action on Appropriateness definition, 3) p-value and 4) inter-percentile range adjusted for symmetry (IPRAS). Performance threshold was also set for each of the QIs, indicating the target to be achieved by each service provider.
Results: A total of 17 experts participated in Round 1 and 20 in Round 2. Of the 24 proposed QIs in round 1, 20 were ranked as appropriate (put through to round 2) and 4 as uncertain (were discarded). At the end of round 2, a final list of 18 QIs were scored appropriate and are listed in Table 1.
Conclusion: This UK national consensus QBET project has successfully developed QIs for patients undergoing BET. These QIs can be used by service providers to ensure that all patients with BE neoplasia receive uniform and high quality care based on the best available evidence and expert opinion.
Disclosure: Nothing to disclose

References

1. Fitzgerald, R. C. et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut* 7–42 (2014). doi:10.1136/gutjnl-2013-305372.
2. Haidry, R. J. et al. Improvement over time in outcomes for patients undergoing endoscopic therapy for Barrett's oesophagus-related neoplasia: 6-year experience from the first 500 patients treated in the UK patient registry. *Gut* 64, 1192–1199 (2015).
3. Fitch, K. et al. The RAND / UCLA Appropriateness Method User's Manual. (2001).

OP097 BARRETT'S OESOPHAGUS: ENDOSCOPIC TREATMENT OR SURVEILLANCE? A COMPARATIVE COST-EFFECTIVENESS ANALYSIS

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Introduction: Barrett's oesophagus (BO) is a known precursor lesion to oesophageal adenocarcinoma (OAC). All clinical guidelines recommend surveillance and/or treatment of BO patients depending on the severity of the precursor lesion. However, the optimal management strategy for non-dysplastic BO (NDBO) and low-grade dysplasia (LGD) patients remains controversial. Prior modeling studies have reported conflicting results on the management of these patients.

Aims and Methods: We aimed to identify the optimal management strategy for BO patients through a comparative modeling analysis. We used 3 independently developed population-based models from the NIH Cancer Intervention and Surveillance Modeling Network (CISNET). A cohort of 60-year-old US men with BO was simulated and followed until death without surveillance or treatment (natural history). Then, we implemented 78 unique BO management strategies. The strategies varied in (a) LGD management: with or without confirmation of LGD by a repeat endoscopy at 2 months, and surveillance with different intervals or endoscopic treatment; and (b) NDBO management: no surveillance or surveillance with different intervals. In all strategies, patients with high-grade dysplasia received endoscopic treatment. An incremental cost-effectiveness analysis, assuming a willingness-to-pay threshold of $100,000 per quality-adjusted life-year (QALY), determined the optimal strategy using the average results of the 3 models. To assess the robustness of our findings, we also analysed the separate results of each model and simulated a cohort of US women with BO.

Results: The models' average OAC incidence in the natural history was 110 (93-120) and the average cost was $5.7 million ($4.5–6.7 million) per 1000 BO patients. Surveillance and/or endoscopic treatment of BO patients prevented 23-77% of OAC cases, but they increased costs to $6.3–17.0 million. Considering cost-effectiveness, all strategies with only surveillance for LGD patients were dominated by those with LGD treatment. Repeated endoscopy to confirm LGD was more cost-effective than strategies without confirmatory endoscopy. The optimal strategy was treatment after confirmation by repeat endoscopy for LGD patients and surveillance every 3 years for NDBO patients (incremental cost-effectiveness ratio: $64,322/ QALY). The separate results of each model and the female cohort were consistent with the average results of the male cohort on management of LGD, but suggested intervals for surveillance of NDBO patients varied (2-5 years) (Table 1).

Conclusion: Our analyses show that endoscopic treatment of patients with LGD is cost-effective, but only if these patients undergo repeat endoscopy to confirm LGD before treatment. The optimal strategy for NDBO patients is surveillance using 3-year intervals in men and 5-year in women.

BO: Barrett's oesophagus, LGD: low-grade dysplasia, m: month, mln: million ND: no dysplasia, QALY: quality-adjusted life-year, Tx: treatment, y: year. 1. The numbers in the column show the optimal surveillance interval. 2. Per 1,000 BO patients compared with natural history. 3. Confirmatory endoscopy at 2 months, if LGD is confirmed then treatment. 4. Only men.

Analysis	NDBO[1]	LGD	OAC prevented[2]	Net cost ($)[2]	QALY gained[2]
Men (average)	3y	2m, Tx[3]	69%	4.1 mln	351
Women (average)	5y	2m, Tx	62%	3.2 mln	217
Erasmus/University of Washington model[4]	2y	2m, Tx	71%	6.4 mln	431
Massachusetts General Hospital model[4]	3y	2m, Tx	63%	3.2 mln	371
Fred Hutchinson Cancer Research Centre model[4]	5y	2m, Tx	73%	3.1 mln	262

[Table1. Optimal management strategy for BO patients]
Disclosure: Nothing to disclose

OP098 ACETIC ACID GUIDED BIOPSIES VERSUS MAPPING BIOPSIES FOR BARRETT'S SURVEILLANCE: THE ABBA STUDY

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Introduction: Barrett's surveillance traditionally requires mapping biopsies to identify neoplasia. Acetic acid (AA) allows only targeted biopsies, potentially reducing the number of biopsies required.

Aims and Methods: To compare neoplasia detection with AA targeted biopsies and protocol guided non-targeted biopsies during Barrett's surveillance. This was a multicentre randomized crossover feasibility study in UK secondary care. Patients under surveillance for Barrett's metaplasia (>2cm) with no history of dysplasia or cancer were recruited. Endoscopists were trained in the acetic acid technique through a structured training programme developed for the study. All patients underwent 1 gastroscopies 8 weeks apart, 1 with AA guided biopsy of abnormal areas only (Portsmouth Protocol) and 1 with non-targeted mapping biopsies (Seattle Protocol). Neoplasia yield (low grade dysplasia LGD, high grade dysplasia (HGD) and cancer) from each strategy was evaluated and the number of biopsies recorded.

Results: 200 patients recruited from 6 centres. Mean age 66 yrs. 145 were male. Mean length C4M6. 174 patients completing both procedures. The prevalence of LGD, HGD and cancer was 9/192 (4.7%). All HGD and cancer was found with both protocols and confirmed with definitive treatment. 1 LGD was found with both Portsmouth and Seattle protocol. 1 LGD was found with Portsmouth protocol not found with Seattle. 3 LGD were found with Seattle protocol not found with Portsmouth. This difference was not significant, and on follow-up gastroscopy no neoplastic changes were found in any of the LGD cases. 2139 biopsies were taken using Seattle protocol at a cost of £125,987 (357 biopsies per neoplasia, £18,023). 226 biopsies with Portsmouth Protocol at a cost of £13,311 (57 biopsies per neoplasia, £3,357) a 6-fold difference. In terms of HGD / cancer, 1070 biopsies / neoplasia found using Seattle protocol and 113 biopsies / neoplasia using Portsmouth Protocol, a 9.5-fold difference.

Conclusion: This is the first RCT comparing these techniques. No HGD or cancer was missed with either technique. There was a 4-fold reduction in biopsies per neoplasia detected with Portsmouth compared to Seattle protocol and a 9.5-fold difference when restricted to high-risk neoplasia. If implemented nationally then this could lead to a massive reduction in histopathology work load and costs. LGD remains controversial and we believe inflammation could have resulted in false positive LGD as subsequent OGD and biopsies did not reveal any LGD. This feasibility data would support a definitive trial of AA targeted biopsies in a surveillance population.

Disclosure: Nothing to disclose

OP099 OUTCOMES OF 360 EXPRESS RADIO-FREQUENCY ABLATION FOR BARRETT'S OESOPHAGUS RELATED NEOPLASIA

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Introduction: Radio-frequency ablation (RFA) for the treatment of Barrett's oesophagus (BE) related neoplasia is the preferred ablative intervention after endoscopic resection (ER). For circumferential BE, the 3cm HALO 360 balloon is used to treat large areas. A new device, the HALO 360 Express self-sizing catheter was recently launched and can potentially allow quicker ablation times and better coverage of the mucosa due to the improved tissue/ catheter contact and 4cm balloon length. We have previously presented initial data of 3 month follow up in these patients but now present more extensive data including end of treatment biopsies.

Aims and Methods: Specialist centres in the UK and Ireland submitted cases where Halo 360 express had been used. Patients returned for follow-up at 3 months after index RFA express treatment. The primary outcome was surface area regression of BE at 3 months. Secondary outcomes were stricture formation and regression of intestinal metaplasia (EoT (End of Treatment) CR-IM) and dysplasia (EoT CR-D) were analysed.

Results: 11 centres submitted 123 patients treated with the HALO 360 Express catheter. 112 of these cases had 3 month follow-up. The mean age was 67 years +/-10. 83% were male. 43 patients (35%) had low-grade dysplasia (LGD) as initial histology; 62 had high-grade dysplasia (HGD) 50%, 19 had intramucosal carcinoma (15%), 1 had invasive adenocarcinoma as baseline histology. 54 (44%) had had previous endoscopic mucosal resection (EMR). The mean pre-treatment circumferential Barrett's segment length (C) was 5.5cm +/- 4.3cm and the mean mucosal length (M) was 7.8cm +/- 3.6cm. The mean % reduction in C of 78% +/-36% and mean reduction in M of 55% +/-36% at this first 3 month follow-up. 17 patients (15%) developed strictures which required dilation at this 3 month follow-up. The median number of dilations was 2 (IQR2-4). 4/17 (24%) were treated with 12J/no clean, 10/17 were treated with 10J/no clean (59%), 3/17 (17%) had been treated with 10J/clean protocol. 8/17 (47%) had had previous EMR. 47 patients had 12 month EoT biopsies, 40 (85%) had CR-D and 34 (76%) had CR-IM. 4/112patients (<4%) had progressed to invasive cancer at the time of writing. The median number of treatments (focal RFA, EMR, APC (argon plasma coagulation)) to EoT was 2(IQR1-4).

Conclusion: The HALO 360 Express catheter shows good reduction in C and M length at 3 months, and effective eradication of IM and Dysplasia in those at 12 months. However, as previously reported by us the stricture rate is higher than previous series with the HALO 360 catheter which showed a stricture rate of 6-10% compared to 15% in this study.

Disclosure: Nothing to disclose

OP100 MULTICENTER FEASIBILITY STUDY OF COMBINED INJECTION AND ARGON PLASMA COAGULATION (HYBRID-APC) IN THE ABLATION THERAPY OF NEOPLASTIC BARRETT ESOPHAGUS

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Introduction: Neoplastic Barrett esophagus (BE) is usually treated by a combination of endoscopic resection for (visible) neoplasia followed by ablation of the remaining BE mucosa with the aim to eradicate the entire BE. For ablation, radiofrequency ablation (RFA) which has been used in most studies, has recently been challenged by other methods such as but argon plasma coagulation (APC) with prior submucosal injection (Hybrid-APC, H-APC).

Aims and Methods: Multicenter study in 9 European centers on patients with biopsy proven neoplastic BE. Following endoresection (EMR/ESD) a maximum of 5 H-APC sessions was allowed; exclusive ablation for neoplastic BE (LGIN/HGIN) could be performed at the discretion of the endoscopists for neoplastic BE (LGIN or HGIN) without visible lesions. Primary therapeutic success was defined as one follow-up endoscopy showing normal endoscopic neo-Z-line with negative biopsies.

Results: 130 of 164 included patients (112 male, 18 female, mean age 63.8 years) have completed therapy with 3 month follow-up, 19 were excluded from the therapeutic concept for a variety of reasons. Final diagnoses were mucosal cancer (n = 79), high-grade (HGIN, n = 23), low-grade dysplasia (LGIN n = 26) and normal BE (n = 2). Therapy: Combined resection and ablation (n = 117), exclusive ablation (n = 13). Mean number of H-APC sessions: 2.69 (range 1-5). Short-term treatment outcome: Endoscopic treatment success (normal Z line) was seen in 99 cases, but in 6 cases histopathology showed intestinal metaplasia (minor residual BE disease) or (n = 1) residual cancer. 31 further cases each had either indeterminate endoscopy (minor residual BE possible) but either negative biopsies (n = 27) or minor residual normal BE on biopsies. Based on histopathologic proof, short-term eradication rates were 89.2% (116/130). Treatment for minor residual BE is currently ongoing in some patients. Immediate complications: bleeding n = 5, post-procedure fever n = 9 and 1 perforation treated conservatively by clipping. Later strictures requiring dilatation: n = 5 (5/130 = 3.8 %). In the 12 months follow-up (n = 101 at present), the endpoint of a macroscopically normal Z-Line with negative biopsies was maintained in 88/101 cases (87.1%), with 2 cases included who had indeterminate endoscopy (suggesting minor residual BE) but negative biopsies. Of the 13 cases with positive biopsies (macroscopically visible BE in 2 of them), all had non-dysplastic BE.

Conclusion: H-APC for BE ablation appears to be feasible and safe with a short- and mid-term efficacy of close to 90% in this interim analysis; final results of this large prospective study have to be awaited. The comparative value of H-APC to RFA will be assessed in a prospective randomized trial.

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OP101 FEASIBILITY, SAFETY, TOLERABILITY AND DOSE-RELATED EFFICACY OF A NOVEL SWIPE CRYOBALLOON ABLATION (90°-SCBA) DEVICE IN DYSPLASTIC BARRETT'S ESOPHAGUS

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Introduction: Cryotherapy has been used for years to eradicate flat dysplastic Barrett's esophagus (BE), since it may be better tolerated and result in lower stricture rates when compared to heat-based ablation techniques. Cryoballoon ablation (CBA) is a new technique comprising a through-the-scope catheter with a conformable balloon that is inflated and cooled using nitrous oxide. Thus far, focal CBA has been promising, but only suitable for treatment of limited BE. The novel 90°-swipe CBA (90°-SCBA) covers 90° of the esophageal circumference over 3cm in a single step. The controller software allows for adjustment of the dose (the rate at which the diffuser traverses the 3cm long axis of the balloon catheter while emitting cryogen). 90°-SCBA has been feasible and safe in animal and pre-esophagectomy studies.

Aims and Methods: The aim of this study is to assess feasibility, safety and dose-related efficacy of 90°-SCBA in patients with dysplastic BE. Patients with flat BE (circumferential extent ≤3cm) and low or high-grade dysplasia (LGD/HGD) or residual BE after endoscopic resection(ER), were enrolled in 5 Dutch BE expert centers. Half of the esophageal circumference was treated, starting with 0.8mm/sec (dose 1). The dose was then escalated with 0.1mm/sec (6 patients per dose) until the effective dose (ED) was found. ED was defined as the lowest dose resulting in median BE regression ≥80% in the absence of dose-related serious adverse events (DR-SAE). ED was subsequently confirmed in a confirmation cohort. DR-SAEs included severe pain (VAS > 6) for ≥7 days or stenosis requiring dilation. Pain (VAS 0-10), dysphagia (0-4) and other adverse events were evaluated at days 0, 1, 7 & 30. Primary outcomes were technical success, DR-SAEs and efficacy (BE regression at 8 weeks follow-up (FU) endoscopy assessed by 2 independent endoscopists by systematic comparison of baseline and FU videos).

Results: In total, 25 patients were included (74% male, median BE C0M3). Baseline pathology was LGD (76%), HGD (12%) and adenocarcinoma (12%). Five patients were treated with ER before inclusion. The 90°-SCBA procedure was technically successful in 23 patients (92%). Device malfunctions occurred in 2 other patients (8%) and were resolved with device replacement. No DR-SAEs occurred (Table). BE regression at FU was 78% (IQR 68-86) with 0.8mm/sec (dose 1, N = 6) and 85% (75-95) with 0.7mm/sec (dose 2, N = 7), which was in turn defined as ED. ED was confirmed in 12 extra patients resulting in a median BE regression of 85% (IQR 75-94). Median pain scores after treatment with the ED (dose 2, N = 19) were 4 (IQR 2-5), 2 (0-4), 0 (0-0) and 0 (0-0) at days 0, 1, 7 & 30 respectively. Median dysphagia score was 0 at all FU timepoints.

Conclusion: Our multicenter pilot study suggests that semi-circumferential treatment with 90°-SCBA is feasible, safe and well tolerated for eradication of flat dysplastic BE. It results in a median BE regression of 85% in the 19 patients treated at a dose of 0.7mm/sec (ED) and is a promising new modality for endoscopic eradication.

	Dose-finding phase		Confirmation phase
	Dose 1 (0.8mm/second)	*Dose 2 (0.7mm/second)*	*Dose 2 (0.7mm/sec)*
Baseline	**N = 6**	**N = 7**	**N = 12**
Male, n(%)	5 (83)	4 (57)	10 (83)
Age, median (IQR)	67 (52-80)	67 (53-70)	67 (62-71)
Worst pathology prior to first treatment, n(%)	LGD 6 (100) HGD 0 (0) EAC 0 (0)	LGD 4 (57) HGD 1 (14) EAC 2 (29)	LGD 9 (75) HGD 2 (17) EAC 1 (8)
Previous EMR, n(%)	1 (17)	3 (43)	1 (8)
Median Prague prior to 90°-SCBA (IQR)	C 0.5 (0-1) M 3 (2-3)	C 0 (0-2) M 4 (2-5)	C 0 (0-1) M 4 (3-5)
Treatment & follow-up			
Median ablation time in minutes (IQR)	9 (9-13)	9 (7-10)	10 (6-17)
Dose-related SAEs	0 (0)	0 (0)	0 (0)
Median BE regression (IQR)	78 (68-85)	85 (75-95)	85 (75-94)

[Baseline, treatment and follow-up characteristics.]

Disclosure: This study was sponsored by C2 Therapeutics, Inc.

MONDAY, OCTOBER 22, 2018 15:45–17:15
IBD pathogenesis – Room N1

OP102   MIS-G, A MOLECULAR MEASURE OF INFLAMMATION IN IBD PATIENTS BASED ON TRANSCRIPTIONAL PROFILES FROM 2495 INTESTINAL BIOPSIES: DEFINITION, CHARACTERIZATION AND POTENTIAL USES

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Introduction: The disease state of IBD patients have been described by clinical, macro, and microscopic approaches. However, despite extensive efforts for standardization, those measurements are still subject to certain degree of subjectivity that limits their reliability. More objectives and molecularly defined measures of gut inflammation are of particular interest in IBD, as they allow to objectively subset patients according to disease activity or use as part of the treat-to-target strategy. Such molecular scores can also be used to remove the inflammation component from transcriptome data, increasing our ability to identify non-inflammatory processes of IBD pathophysiology, such as tissue homeostasis and epithelial barrier function or to measure the mucosal healing.

Aims and Methods: We present a more objective molecular characterization of disease activity based on transcription profiles of 719 inflamed (I) and 1776 non-inflamed (NI) intestinal biopsies from 1160 patients in the MSCCR cohort (498 CD, 419 UC, 243 non-IBD control) undergoing routine endoscopy at Mount Sinai Hospital. Genes differentially expressed between I and NI biopsies (FDR < 0.05, FCH > 2) were used to generate a biopsy-level molecular inflammation score (MIS-B) via GSVA[1]. For each patient, multiples MIS-B scores from different regions were combined to create a patient-level gut inflammation score (MIS-G) using mixed-effect models.

Results: MIS-G strongly correlated with clinical disease severity as measured by the disease activity scores (HBI for UC, SCCAI for UC), as well as commonly used Inactive/Active disease categories. MIS-G also correlated with endoscopic measures of IBD severity (SES-CD for CD, and Mayo endo for UC), with higher MIS-G in more severe disease and significant pairwise differences between each Inactive/Mild/Moderate/Severe category. The observed associations were stronger for MIS-G than for CRP measured the day of the endoscopy. Specifically,

UC patients with Inactive and Mild disease could be differentiated by MIS-G ($p < 10^{-10}$), but not by CRP (p = 0.5). MIS-G was also associated with disease location in CD according to Montreal classification, with higher scores in patients with ileo-colonic disease (L3) than those with terminal ileum (L1) or colonic (L2). Although no differences were found in clinical or endoscopic severity between patients in early stage of disease (<2 years since diagnosis) and late disease (>5 years), nor for CRP values (d = 0.07, p = 0.8), patients with late disease had higher MIS-G than those recently diagnosed (d = 3.2, p < 0.02), highlighting the granularity of our molecular score. In UC patients, MIS-B was positively associated in UC A in biopsies from distal colonic regions (Rectum, Sigmoid and Left colon), but not with more proximal regions of colon or ileum.

Conclusion: We generated a measure of transcriptionally based intestinal inflammation in IBD patients, MIS-B, that provides an objectively defined measure of disease state in IBD relevant tissues. Patient-level MIS-G represents a molecular measure of disease activity that differentiates between IBD categories according to clinical and endoscopic evaluations, potentially allowing for further subsetting of IBD patients. We identified biopsies macroscopically defined as NI with high MIS-B, defining regions with latent disease. Investigation of such regions may help determining sub-clinical disease state, either to identify biological mechanisms regulating clinical manifestations, or to predict risk of upcoming flares.

Disclosure: This work was funded through a collaboration between Janssen Research & Development and the Mount Sinai Hospital

Reference

1. Hänzelmann S, Castelo R, Guinney J. GSVA: gene set variation analysis for microarray and RNA-seq data. *BMC Bioinformatics*. 2013 Jan 16; 14: 7.

OP103   LUMINAL PROTEASE ACTIVITY IS INCREASED IN PATIENTS WITH POUCH INFLAMMATION

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Introduction: Restorative proctocolectomy and ileal pouch-anal anastomosis (IPAA) is the surgical therapy of choice for patients with refractory or complicated ulcerative colitis (UC). Approximately 60% of these patients develop pouch inflammation (pouchitis).

The hypothesis is that pouchitis may occur due to compromise of the epithelial barrier function and exposure of the intestinal immune system to microbial antigens. Increased luminal protease activity was associated with exacerbation of colitis in animal models as well as in patients with inflammatory bowel diseases.

Aims and Methods: We aimed to study whether luminal proteolytic activity is increased in UC patients with pouchitis and what are the functional implications on epithelial barrier function.

Fecal supernatants were extracted from patients with a normal pouch (NP), active pouchitis (AP) and healthy controls (HC). Fecal protease activity was determined using FITC-casein florescence assay. Caco-2 cell monolayers were exposed to fecal supernatants. Epithelial integrity and permeability were determined by measuring trans-electrical epithelial resistance (TEER) and permeability of a 4 kDa FITC-dextran across the monolayers. Immunofluorescence and Western blot were performed on Caco-2 cells to assess for tight junction proteins integrity (ZO-1, occludin) after exposure to fecal supernatants.

Results: Fecal supernatants were obtained from 25 patients: 6 NP, 10 AP and 9 HC participants. Proteolytic activity was 4.3–fold increased in patients with AP compared to NP and HC (p < 0.05). Fecal supernatants from patients with AP disrupted occludin and ZO-1 proteins, as assessed by Western blot and immunofluorescence. TEER in patients with AP was reduced by 1.6 fold (p < 0.05), and epithelial permeability to FITC-dextran increased by 18.36 (p < 0.05) and 73 fold (p < 0.01), compared to the effects of fecal supernatants from patients with NP and HC, respectively.

Conclusion: Pouch inflammation is associated with increased luminal proteolytic activity. Fecal supernatants from patients with pouchitis disrupt tight junction proteins of Caco-2 cell monolayers and increase epithelial cells permeability suggesting that proteolytic activity affects epithelial barrier function and may be a step in the mechanism of pouchitis.

Disclosure: Nitsan Maharshak reports consulting fees from Janssen, Neopharm, BiomX and Mybiotics. Speaking fee from Abbvie and Takeda

OP104 PATHOGENICITY OF IN-VIVO GENERATED INTESTINAL TH17 LYMPHOCYTES IS IFNG DEPENDENT

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Introduction: Th17 cells are crucially involved in the immunopathogenesis of inflammatory bowel diseases in humans. Nevertheless, pharmacological blockade of IL17A, the Th17 signature cytokine, yielded negative results in patients with Crohn's disease (CD), and attempts to elucidate the determinants of Th17 cells pathogenicity in the gut have so far proved unsuccessful.

Aims and Methods: Here, we aimed to identify and functionally validate the pathogenic determinants of intestinal IL-17-producing T cells. *In-vivo* generated murine intestinal IL-17-producing T cells were adoptively transferred into immunodeficient $Rag1^{-/-}$ recipients to test their pathogenicity. Human IL-17-, IFNγ/ IL-17 and IFNγ- actively secreting T cell clones were generated from lamina propria lymphocytes of CD patients. The pathogenic activity of intestinal IL-17-producing T cells against the intestinal epithelium was evaluated.

Results: IL-17-producing cells with variable colitogenic activity can be generated *in vivo* by different experimental colitis models. Pathogenicity of IL-17-secreting cells was directly dependent on their IFNγ secretion capacity, as demonstrated by the reduced colitogenic activity of IL-17-secreting cells isolated from $IFN\gamma^{-/-}$ mice. Moreover, IFNγ production is a distinguished attribute of CD-derived lamina propria Th17 cells. IFNγ secretion by CD-derived IL-17-producing intestinal clones is directly implicated in the epithelial barrier disruption through the modulation of tight junction proteins.

Conclusion: Intestinal Th17 cell pathogenicity is associated to IFNγ production, which directly affects intestinal permeability through the disruption of epithelial tight junctions.

Disclosure: Nothing to disclose

OP105 HUMAN BONE MARROW-DERIVED MESENCHYMAL STEM CELLS MEDIATE IMMUNOSUPPRESSION IN EXPERIMENTAL CROHN'S DISEASE BY SECRETING PROSTAGLANDIN E$_2$ AND REPROGRAMMING MACROPHAGES TO AN IMMUNOSUPPRESSIVE PHENOTYPE

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Introduction: Locally injected mesenchymal stem cells (Alofisel®, TiGenix and Takeda) are now an approved therapy in European Union for treatment of perianal fistulising Crohn's disease (CD)[1]. However, clinical studies have shown limited efficacy of systemic mesenchymal stem cells (MSC) therapy for luminal CD[2]. The reasons for low efficacy for luminal CD is inadequately investigated with majority of the studies performed demonstrating the benefit of MSC therapy in murine models that require manipulation (genetic, chemical) to develop inflammation and focus on colonic inflammation. Thus, we studied the SAMP-1/YitFc (SAMP), a chronic and spontaneous murine model of small intestine (SI) inflammation that closely resembles human CD for treatment with human bone marrow derived MSC (hMSC)[3]. We previously reported that hMSCs injected intraperitoneally (i.p) into SAMP reduced the severity of SI inflammation (Phosphate buffered saline[PBS] control: 17 ± 1.1 vs. hMSC: 9.4 ± 2.4; p < 0.01)[4].

Aims and Methods: The aim of this study was to determine the mechanism(s) by which hMSCs mediate immunosuppression in SAMP. hMSC mediated immunosuppression was studied by enzyme immunoassay, flow cytometry, differentiation assays, mixed lymphocyte reaction (MLR), macrophage co-culture, RT-PCR, and nanostring immune profiling. hMSCs were transduced with lentivirus vector containing shRNA for COX-2 (hMSCshCOX-2) to knockdown secretion

of Prostaglandin E$_2$ (PGE$_2$) and lentivirus with scrambled shRNA was used as control (hMSCshRNA control).

Results: Using NanoString mouse immune cell profiling assay that examined the gene expression of 561 inflammation related genes, SAMP mice treated with hMSC i.p had increased abundance of macrophages and decreased abundance of lymphocytes in the SI. In co-culture assay, hMSCs reprogrammed SAMP macrophages to alternatively activated antiinflammatory phenotype with higher gene expression of arginase I (3.9–fold increase, p = 0.01) and lower gene expression of IL-6 (0.8–fold decrease, p = 0.03) and TNF-α (0.7–fold decrease, p = 0.09) compared to SAMP mice treated with PBS and dead hMSCs. In MLRs set up with irradiated allogeneic splenocytes to stimulate naïve T lymphocytes from SAMP mice, hMSCs profoundly suppressed T cell proliferation in a dose dependent manner as measured by [^{3}H] thymidine incorporation (95% CI of difference: 3,885–10,456 cpm; ANOVA p < 0.001 for 5x10^4 hMSCs and 8,573–14,335 cpm; ANOVA p < 0.0001 for 2x10^5 hMSCs). By enzyme immunoassay we determined that hMSCs basally secrete PGE$_2$ at a concentration of 4850 ± 86 pg/mL per 100,000 cells. The supernatants from suppressed T cells co-cultured with hMSCs contained higher amounts of PGE$_2$ than proliferating T cells not co-cultured with hMSCs (5609 ± 364 pg/mL vs.49.6 ± 57 pg/mL; p < 0.0001). Indomethacin, a COX-1/2 inhibitor (10 μM) decreased PGE$_2$ secretion from hMSC (1219 ± 56 pg/mL vs. 7187 ± 42 pg/mL; p < 0.0001) and abrogated the suppression of T cell proliferation in MLR (95% CI of difference: -914–2442 cpm; p not significant). MLR performed with PGE$_2$ inhibited hMSC (hMSCshCOX-2) in comparison to hMSC shRNA control again demonstrated abrogation of suppression of T cell proliferation (95% CI of difference: 3,885–10,456 cpm; ANOVA p < 0.001 for hMSCshRNA control and 95% CI of difference: -1,859–7580 cpm; ANOVA p not significant for hMSCshCOX-2) confirming the role of PGE$_2$ in mediating immunosuppression by hMSC.

Conclusion: hMSCs mediate immunosuppression by secreting PGE$_2$ and reprogramming macrophages to immunosuppressive phenotype in SAMP model of experimental CD.

Disclosure: Nothing to disclose

References

1. Panés J, García-Olmo D, Van Assche G, et al., Long-term Efficacy and Safety of Stem Cell Therapy (Cx601) for Complex Perianal Fistulas in Patients With Crohn's Disease. *Gastroenterology*. 2018 Apr; 154(5): 1334–1342.e4.
2. Dave M, Mehta K, Luther J, et al., Mesenchymal Stem Cell Therapy for Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *Inflamm Bowel Dis*. 2015 Nov; 21(11): 2696–707.
3. Cominelli F, Arseneau KO, Rodriguez-Palacios A, et al., Uncovering Pathogenic Mechanisms of Inflammatory Bowel Disease Using Mouse Models of Crohńs Disease-Like Ileitis: What is the Right Model? *Cell Mol Gastroenterol Hepatol*. 2017 Mar 6; 4(1): 19–32.
4. Dave M, Di Martino L, Somoza R et al. *Gastroenterology* 2016; 150: S196.

OP106 THE INTERLEUKIN-6 RECEPTOR AS A DRUG TARGET IN INFLAMMATORY BOWEL DISEASE; A MENDELIAN RANDOMIZATION STUDY

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Introduction: Excessive production of interleukin-6 is associated with active inflammatory bowel disease (IBD). Blockade of the interleukin-6 receptor (IL6R) with a monoclonal antibody (tocilizumab) is licensed for treatment of rheumatoid arthritis. Clinical trials of IL6R inhibitors in IBD have been small in numbers, with varying efficacy. The *IL6R* SNP rs2228145 associates with a similar pattern of effects to tocilizumab therapy (higher soluble IL6R, lower c-reactive protein and fibrinogen), making it an attractive genetic instrument for drug target validation.

Aims and Methods: We performed a two sample Mendelian randomization study using rs2228145 (a variant associated with impaired IL6R signaling) to evaluate the role of IL6R inhibition for primary prevention of IBD. Gene – soluble IL6R biomarker associations were estimated in 1650 individuals, as a proxy for defective IL6R signaling. Gene – IBD associations were estimated in 49833 cases and 61630 ancestry matched controls from publically available IBD genome-wide association study (GWAS) summary statistics.

Results: In a fixed-effects meta-analysis of 26788 cases with Crohn's disease (CD), 23045 with ulcerative colitis (UC)) and 61630 controls, genetically elevated soluble IL6R was associated with decreased odds of Crohn's disease (CD) (odds ratio (OR) 0.87, 95% CI 0.82–0.92, p = 0.00001463) and ulcerative colitis (UC) (OR 0.92, 95% CI 0.89–0.99, p = 0.0378) per 2-fold increment.

Conclusion: On the basis of genetic evidence in human beings, defective IL6R signaling seems to protect against the development of both CD and UC; its inhibition is an attractive drug target suitable for further exploration. Genetic studies in populations could be used more widely to help validate and prioritize novel drug targets or to repurpose existing agents for new therapeutic and preventive uses.

Disclosure: Nothing to disclose

References

1. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. *Nat Immunol*. 2015; 16(5): 448–457. doi:10.1038/ni.3153.
2. Neurath MF. Current and emerging therapeutic targets for IBD. *Nat Rev Gastroenterol Hepatol*. 2017; 14(5): 269–278. doi:10.1038/nrgastro.2016.208.
3. Coskun M, Vermeire S, Nielsen OH. Novel Targeted Therapies for Inflammatory Bowel Disease. *Trends Pharmacol Sci*. 2017; 38(2): 127–142. doi:10.1016/j.tips.2016.10.014.
4. Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium, Swerdlow DI, Holmes M V, et al. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. *Lancet*. 2012; 379(9822): 1214–1224. doi:10.1016/S0140-6736(12)60110-X.
5. IL6R Genetics Consortium Emerging Risk Factors Collaboration, Sarwar N, Butterworth AS, et al. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. *Lancet*. 2012; 379(9822): 1205–1213. doi:10.1016/S0140-6736(11)61931-4.
6. Liu JZ, van Sommeren S, Huang H, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet*. 2015; 47(9): 979–986. doi:10.1038/ng.3359.
7. de Lange KM, Moutsianas L, Lee JC, et al. Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease. *Nat Genet*. 2017; 49(2): 256–261. doi:10.1038/ng.3760.
8. Hartwig FP, Borges MC, Horta BL, Bowden J, Davey Smith G. Inflammatory Biomarkers and Risk of Schizophrenia. *JAMA Psychiatry*. November 2017. doi:10.1001/jamapsychiatry.2017.3191.

OP107   CD103+SIRPα+ DENDRITIC CELLS ARE SPECIFICALLY DECREASED IN THE INFLAMED COLON FROM PATIENTS WITH ULCERATIVE COLITIS BUT NOT IN CROHN'S DISEASE

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Introduction: Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammation of the human gastrointestinal (GI) tract. Dendritic cells (DC), the most potent antigen presenting cells, are essential to maintain the mechanisms of GI-homeostasis towards nutrients and commensal in health, while initiating immune responses towards pro-inflammatory invading pathogens. However, despite the relevance of DC modulating GI-immune responses, there is not much information about DC composition in the human GI-tract both in health and IBD.
Aims and Methods: Our aim was to characterize human GI-DC subsets, phenotype and function both in health and in IBD patients. To that end, human intestinal biopsies were obtained from healthy controls and IBD patients (including UC and CD; both active and quiescent). Tissue was disaggregated and the lamina propria mononuclear cells (LPMC) characterized by flow cytometry.
Results: Human intestinal DC were identified within singlet viable leukocytes as CD14−CD64−HLA-DR+CD11c+. Type 1 conventional DC were defined as CD103+SIRPα− while type 2 conventional DC were identified as SIRPα+ and further divided into subsets based on the expression of CD103. Total DC numbers changed throughout the healthy human gut as they were higher in the colon (either distal or proximal) compared with the ileum. DC numbers were indeed further decreased in the duodenum. Type 1 (minority) and type 2 (majority) conventional DC did not change their proportion throughout the healthy gut. However, CD103+SIRPα+ DC were the main subset in the duodenum as opposed to CD103−SIRPα+ DC which were predominant in the colon and the ileum. Compared with their CD103−SIRPα+ type 2 counterparts, CD103+SIRPα+ had higher levels of HLA-DR, CD40, CD86, CCR7, CD137L, ICOSL and PD-L1. CD103+SIRPα+ were also more phagocytic and had lower expression of blood-related markers like CLA and CCR2 suggesting that they are derived from CD103−SIRPα+ DC following mucosal conditioning. Indeed, CD103+SIRPα+ numbers were increased following LPMC culture, although this process was reverted in the presence of pro-inflammatory LPS. CD103+SIRPα+ DC displayed an enhanced production of IL-10, both in resting conditions and in the presence of LPS, confirming therefore their tolerogenic phenotype. Type 1 CD103+SIRPα− DC, on the contrary, displayed a decreased production of IL-1β (both resting and with LPS) in agreement with their different lineage. Referred to the colonic mucosa in IBD, type 2 DC constitutively displayed lower expression of SIRPα both on the inflamed and non-inflamed mucosa from IBD patients. Nevertheless, the inflamed colon from UC patients, but not CD, specifically displayed lower numbers of tolerogenic CD103+SIRPα+ confirming therefore a differential DC signature in both conditions.
Conclusion: Human GI-DC can be divided into 3 different subsets with different phenotype and function based on the expression of CD103 and SIRPα. CD103+SIRPα+ DC display a tolerogenic phenotype and function and are likely derived from their CD103+SIRPα− counterparts following mucosal conditioning. The specific reduction of CD103+SIRPα+ DC in the inflamed mucosa from UC patients, but not CD, suggests the presence of different pathogenic mechanisms occurring in IBD.
Disclosure: Nothing to disclose

Coeliac disease: From basics to therapy – Room N2_____

OP108   ARYL HYDROCARBON RECEPTOR HAVE A PROTECTIVE EFFECT IN CELIAC DISEASE MUCOSA AND IN A MOUSE MODEL OF POLY I:C-INDUCED SMALL INTESTINAL ATROPHY

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Introduction: Aryl hydrocarbon receptor (AhR) is a transcription factor activated by a large variety of natural and synthetic ligands and represents an important link between the environment and immune-mediated pathologies. Celiac disease (CD) is an immune-mediated enteropathy driven by gluten.
Aims and Methods: We characterized the expression and role of AhR in CD-related inflammation. AhR expression was analysed in duodenal mucosal samples, lamina propria mononuclear cells (LPMC) and intraepithelial lymphocytes (IELs) of active CD patients, inactive CD patients and normal controls (NC) by flow cytometry and real-time PCR. To evaluate the factors that regulate AhR expression in CD mucosa, specific neutralizing antibodies against IL-21, IL-15 or IFN-γ were added to *ex vivo* organ cultures of active CD mucosal explants. Moreover, duodenal samples taken from inactive CD patients were treated with peptic-tryptic digest of gliadin (PT). After 24 hours, AhR and inflammatory cytokines expression were evaluated by real-time PCR. Transcripts of inflammatory cytokines were also analysed in CD mucosal explants either left untreated or treated with 6-formylindolo[3,2-b]carbazole (Ficz), a natural ligand of AhR. Finally, we evaluated whether Ficz ameliorated poly I:C-driven small intestine atrophy in mice.
Results: AhR expression was significantly reduced in duodenal biopsy samples, LPMC and IELs taken from active CD patients compared to inactive CD patients and NC. The addition of PT to *ex vivo* organ cultures of duodenal biopsies taken from inactive CD patients reduced AhR expression, while neutralizing IL-21 or IL-15 specific antibodies increased AhR expression in *ex vivo* organ cultures of duodenal samples of active CD patients. Treatment with Ficz of *ex vivo* organ cultures of duodenal biopsies, IELs and LPMC taken from active CD patients reduced the expression of IFN-α, IFN-γ and TNF-α. Moreover, Ficz reduced the expression of perforin and granzyme B in IELs and LPMC isolated from active CD patients. Mice given Ficz were protected from poly I:C-driven intestinal atrophy and showed reduced levels of IFN-α, IFN-γ, TNF-α, perforin and granzyme B in small intestinal mucosa.
Conclusion: These data indicate that AhR-driven signals inhibit pathogenic responses in the gut of CD patients.
Disclosure: Nothing to disclose

OP109   TOLEROGENIC IMMUNE-MODIFYING NANOPARTICLES CONTAINING GLIADIN RESTORE TOLERANCE & ABROGATE DISEASE IN MURINE MODELS OF COELIAC DISEASE

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Introduction: In coeliac disease (CD), tolerance to gluten (gliadin) proteins from cereals is lost. Tolerogenic immune modifying nanoparticles (TIMP) are effective at restoration of antigen-specific immune tolerance in various autoimmune conditions. The identification of gliadins as dietary antigens and drivers of immune-mediated pathology in CD suggests that TIMP containing gliadin (TIMP-GLIA) may serve as a cure.
Aims and Methods: Here, we tested immunomodulatory effects of TIMP-GLIA vs. control TIMP in 3 different mouse models of CD, 1) a delayed-type hypersensitivity, 2) a HLA-DQ8 transgenic, and 3) a gliadin memory T cell enteropathy model. Nanoparticles were administered intravenously.
Results: Treatment with TIMP-GLIA reduced gliadin-specific T cell proliferation, inflammatory cytokine secretion, circulating gliadin-specific IgG/IgG2c, earswelling, gluten-dependent enteropathy, and body weight loss in mouse models of CD. Therapeutic effects were antigen-specific, and dose-dependent. RNA sequencing and Foxp3 RT-qPCR of gliadin-restimulated splenocytes from HLA-DQ8 transgenic mice revealed a tolerogenic signature of TIMP-GLIA in T cells and antigen-presenting cells.
Conclusion: The results demonstrate efficacy of TIMP-GLIA in modulating the immune response to gliadin *in vivo*, by inducing regulatory T cell tolerance and reversing T helper 1/T helper 17 cell skewing. Safety and efficacy testing of TIMP-GLIA in restoring gluten tolerance in CD patients is warranted.
Disclosure: N.J.C.K, S.D.M, L.D.S and D.R.G are share holders of Cour Pharmaceutical Development Company. D.M, N.J.C.K, S.D.M, L.D.S and D.R.G are inventors on patent applications describing TIMP-GLIA. Based on

an agreement between the University of Helsinki and Cour Pharmaceuticals Development Company, T.L.F. and S.M. received funding to conduct experiments.

OP110   ABERRANT INTRA-EPITHELIAL LYMPHOCYTES CAUSE VILLOUS ATROPHY IN REFRACTORY CELIAC DISEASE TYPE II BY GRANZYME-B-INDUCED APOPTOSIS OF ENTEROCYTES MEDIATED VIA CD103(αE)β7-E-CADHERIN-INTERACTIONS

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Introduction: Refractory celiac disease type II (RCDII) is an indolent intestinal tumor of aberrant intraepithelial T-lymphocytes (IEL). The severe enteropathy found in RCDII is caused by aberrant IEL that exert cytotoxicity against the enterocytes. In this study, we investigated the cell death mechanisms that are responsible for villous atrophy in RCDII and their potential diagnostic and therapeutic implications.

Aims and Methods: mRNA and protein expression were determined using RT-MLPA analysis, immunofluorescence and flow cytometry, respectively. Enterocyte killing and degranulation by aberrant IEL were measured in the presence of a transwell, specific inhibitors or therapeutic agents, using flow cytometry. Secretion of granzyme B was detected by ELISA.

Results: mRNA and protein expression of granzyme B were significantly upregulated in the cytoplasm of aberrant IEL of patients with RCDII compared to levels of granzyme B expression in patients with celiac disease on a gluten-free diet (GFD). The level of granzyme B expression in RCDII patients correlated with the severity of villous atrophy and with clinical response to therapy. RCDII cell lines also demonstrated increased levels of granzyme B expression. Furthermore, in RCDII patients and RCDII cell lines degranulation and secretion of granzyme B was observed in the presence of epithelial cells. Incubation of RCDII cell lines with epithelial cell line Caco2 showed that aberrant IEL induced apoptosis of Caco2. Treatment with a granzyme B inhibitor demonstrated that killing of enterocytes was granzyme B dependent and that degranulation by IEL was imperative. In addition, we found that the aberrant IEL induced cell death through triggering of the intrinsic apoptosis pathway via mitochondrial membrane depolarization and caspase-3 and -9 activation. For degranulation of granzyme B and killing of the enterocytes, binding of the aberrant IEL to the epithelial cell was necessary. CD103(αE) expression was significantly increased in RCDII patients compared to CD patients on GFD. Functional studies revealed that CD103(αE)β7-E-cadherin interaction was essential for release of granzyme B and loss of enterocytes. Treatment with therapeutic agent etrolizumab, an anti-β7 mAb, inhibited degranulation of granzyme B and killing of the epithelial cells by RCDII cell lines.

Conclusion: Killing of enterocytes in RCDII is dependent on upregulated expression and degranulation of granzyme B and on interaction with the aberrant IEL through CD103(αE)β7-E-cadherin binding. These data contribute to a better understanding of the pathogenesis of villous atrophy in RCDII and therefore can be important for diagnostic purposes and during follow-up of RCDII patients. Moreover, our preclinical findings support the potential use of etrolizumab as a novel therapeutic agent for the treatment of RCDII patients.

Disclosure: Nothing to disclose

OP111   CHILDREN FROM COELIAC FAMILIES BENEFIT FROM EARLY DIAGNOSIS AND TREATMENT: AN ANALYSIS OF THE PREVENTCD COHORT

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Introduction: Because of their increased risk for coeliac disease (CD), ESPGHAN and other guidelines advise to screen children with affected first-degree relatives. However, in the literature there is little information about the benefit of early diagnosis and treatment in these children.

Aims and Methods: Our aim was to prospectively assess whether children from coeliac families benefit from screening, early diagnosis and treatment.

We analyzed the data from the European, multicentre PreventCD cohort involving 944 newborns recruited from 2007-2010, who are being prospectively assessed for CD development. All the children are positive for HLA-DQ2 and/or HLADQ8 and have at least 1 first-degree relative with CD. Health status using (parental) questionnaires on CD-related symptoms and CD antibodies (IgA against transglutaminase 2 (TGA)) were assessed at the age of 4, 6, 9, 12, 18, 24 and 36 months, and thereafter at least every 2 years (www.preventcd.com). TGA was centrally measured using from 2007-2014 the Celikey Varelisa test and from 2015, the Celikey ELIA method, with cut-off values of 5 U/ml and 7 U/ml respectively. If the children presented symptoms and/or increased TGA level indicating CD, diagnostic small bowel biopsies were offered. The biopsies were assessed centrally by an independent pathologist blinded to the clinical and antibody results. All CD diagnoses were discussed and agreed upon by the diagnostic committee of PreventCD. Measured outcomes were improvement of the reported symptoms and of TGA level on a gluten-free diet (GFD) at follow-up 1 and 2 years after diagnosis.

Results: As on 01 December 2017, 130 children (mean age: 9.1 years; range: 7.3–10.9; 59.8% female) had been diagnosed with CD at a mean age of 3.8 years (range: 1.1– 9.2). Since 4 asymptomatic CD children did not follow a GFD, 126 CD children were included in this analysis. 71 children (56.3%) were symptomatic at diagnosis and reported 1 or more symptoms, as shown in the table. In total 80.0% and 87.8% of the symptomatic children at diagnosis were symptom-free after 1 and 2 year on a GFD, respectively. All symptoms at diagnosis, except constipation and vomiting, significantly improved after treatment. The mean TGA level in symptomatic children decreased from 81.2 U/mL to 4.0 U/mL and 2.2 U/mL after 1 and 2 year of treatment, respectively.

	At diagnosis – no. (%) N = 71	After one year (mean 11.3 months) no. (%) N = 12**	After two years (mean 30.0 months) no. (%) N = 10***#	p-value (diagnosis-two years after GFD)
Diarrhoea	29 (40.8)	4 (6.7)	1 (1.8)	<0.01
Abdominal pain	26 (36.6)	5 (8.3)	4 (7.0)	<0.01
Failure to thrive §	23 (32.4)	2 (3.3)	2 (3.5)	<0.01
Abdominal distention	21 (29.6)	2 (3.3)	0 (0)	<0.01
Anorexia	13 (18.3)	2 (3.3)	1 (1.8)	<0.01
Other¥	11 (15.5)	2 (3.3)	0 (0)	<0.01
Constipation	10 (14.1)	1 (1.7)	3 (5.3)	0.159
Vomiting	4 (5.6)	0 (0)	1 (1.8)	0.321
Missing	0	11	11	

[Symptoms in 126 included children*]
*One or more symptoms, ** 12/ 60 children had symptoms after 1 year on a GFD, *** 10/ 57 children had symptoms after 2 years on a GFD; #3 children with less than 2 years GFD after the diagnosis
§FTT = reduction of 0.5 SD weight/length per 6 months and/or length < -2SD),
¥Other = extra-intestinal symptoms e.g. irritability, fatigue

Conclusion: Our prospective data show that most children from CD families develop the disease very early in life and about half of them have CD-related symptoms that improve significantly after treatment with a GFD. These results support early screening, diagnosis and treatment in children from CD families.

Disclosure: Nothing to disclose

OP112   COELIAC DISEASE DIAGNOSIS IN INDIVIDUALS ON A GLUTEN-FREE DIET

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Introduction: Coeliac disease (CD) is a gluten-dependent enteropathy that develops in genetically susceptible individuals. Current treatment is a gluten-free diet (GFD), which leads to the recovery of the normal morphology and function of the intestine, with the subsequent disappearance of clinical symptoms and specific antibodies. Therefore, CD diagnosis needs to be established under gluten containing diet, a problem due to the increasing number of individuals following a GFD.

Aims and Methods: Based on the study of Han et al. (1), we studied the utility of detecting activated $\gamma\delta$ and CD8 T cells expressing gut-homing receptors after a 3-day gluten challenge aimed to diagnose CD in individuals on a GFD.
We studied 18 previously diagnosed seropositive CD patients: 14 with high HLA genetic risk (all HLA-DQ2.5) and 4 with low or even non-HLA genetic risk (two HLA-DQ2.2, one HLA-DQ7.5 and one non-HLA-DQ2/DQ8). All patients showed clinical and serological response to GFD. A group of 35 non-CD controls was also included, mainly composed by healthy volunteers that followed a GFD for at least 1 month. All subjects were exposed to 12-15 g of gluten every day for 3 consecutive days. Peripheral blood was collected before (day 0) and 6 days (day 6) after starting gluten consumption, and the expression of CD103, β7 and CD38 in gd and CD8 T cells was assessed by flow cytometry.

Results: The 3-day gluten challenge was completed by all participants. In all of them, the studied T cell populations were undetectable or barely present at day 0, but on day 6, gd and CD8 T cells coexpressing CD103, β7^{hi} and CD38 were observed in every CD patient, but only in 1 control. No differences were observed between patients with high and low/non-HLA risk genetics.

Conclusion: A short gluten challenge elicits the activation of CD103$^+$ β7^{hi} CD8/$\gamma\delta^+$ T cells in CD. These cells can be detected by flow cytometry in peripheral blood, even in those patients with a more difficult diagnosis, opening new possibilities for CD diagnosis in individuals on a GFD.

Disclosure: Nothing to disclose

Reference

1. Han A, Newell EW, Glanville J, et al. Dietary gluten triggers concomitant activation of CD4+ and CD8+ alphabeta T cells and gammadelta T cells in celiac disease. *Proceedings of the National Academy of Sciences of the United States of America* 2013; 110: 13073–8.

OP113   CLASSIFICATION OF REFRACTORY CELIAC DISEASE WITH FLUORESCENCE-ACTIVATED CELL SORTING OF INTESTINAL LYMPHOCYTES: DATA FROM A TERTIARY REFERRAL CENTER

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Introduction: Refractory celiac disease (RCD) is classically categorized into two different entities: RCD type I is an autoimmune disease that responds to immunosuppressants, while in RCD type II a monoclonal transformation of IEL is found[1]. This is usually detected by means of TCR clonality analysis. Patients with RCD type II have a poor prognosis and a high risk of development of enteropathy-associated T-cell lymphoma (EATL), so that it has been proposed to consider RCD type III as a low-grade intraepithelial lymphoma (pre-EATL)[2]. Recently, flow cytometric analysis of isolated intestinal lymphocytes has been introduced as new diagnostic modality for the detection of so-called aberrant intestinal lymphocytes (ILs)[3,4].

Aims and Methods: The aims of this study were (i) to detect aberrant ILs in a cohort of non-celiac, celiac and RCD patients by means of flow cytometry, (ii) to verify whether there is an association between clinical characteristics of RCD patients and presence of aberrant ILs, (iii) to evaluate the diagnostic accuracy of aberrant ILs for RCD II/pre-EATL in our cohort.
Immunostaining (CD3, CD4, CD8, CD7, CD103, TCR$\gamma\delta$, lineage markers) and flow cytometric analysis of isolated ILs from duodenal biopsies of patients with RCD, uncomplicated CD and controls were performed. Aberrant ILs were defined by means of different gating strategies including cytCD3+surfCD3-CD7+ and surfCD3-CD7+CD103+. Aberrant ILs and clinical characteristics in different patient groups were compared.

Results: A total of 130 flow cytometry analyses were performed on 109 patients (42 controls, 21 active CD, 16 CD on gluten-free diet and 30 RCD). RCD patients were initially grouped according to TCR clonality (TCRclon+, n = 17, TCRclon-, n = 13). The presence of aberrant ILs was compared between the two subgroups, with increased aberrant IL numbers being exclusively in the RCDclon+ (Table 1). Patients with evidence of aberrant ILs also showed significantly more criteria for severe malabsorption (as assessed by a cumulative malabsorption score). A cut-off of 11% ILs for the most reliable strategy allowed to identify a subgroup of low risk RCD patients (= 21/30) and a small group of

high-risk RCDs (n = 5) that were classified as pre-EATL (2 of them with a later EATL diagnosis). Nevertheless, sensitivity gaps were uncovered: 1 patient with ulcerative jejunoileitis who later developed an EATL was not identified as pre-EATL. Furthermore, 2 overt EATL cases were false negative (i.e., overall sensitivity 67%, NPV 89%). Alternative, simpler gating strategies for aberrant ILs showed similar accuracy to the main strategy.

Conclusion: In clinical practice, flow cytometry of aberrant ILs may be a simple predictor of high-risk RCD. However, its use as the only diagnostic strategy for classifying patients in RCD I (low risk) and RCD II/pre-EATL may also lead to misdiagnosis. A multimodal diagnostic approach for the diagnosis of RCD (including TCR clonality and malabsorptionscore) maximizes diagnostic accuracy.

	Controls (n = 42)	Active CD (n = 21)	CD on GFD (n = 16)	RCD clon- (n = 13)	RCD clon+ (n = 17)
N of assays	42	22	16	18	31
%Lymphocytes	13 (6-21)	24 (11-35)	15 (7-28)	16 (7-22)	20 (7-33)
%CD4+	14 (4-38)	9 (2-21)	11 (5-30)	10 (2-27)	8 (2-30)
%CD8+	33 (4-75)	44*(14-73)	40 (8-76)	37 (7-76)	31*(5-61)
%TCR$\gamma\delta$+	3 (0-8)	15 (2-29)	12 (3-35)	11 (2-36)	7 (1-47)
Aberrant ILs					
%CytCD3+surfCD3-CD7 within lin-TCR$\gamma\delta$	3 (1-8)	1 (0-3)	1 (0-12)	1 (0-6)	2 (0-36)
CD7+CD103+ within surfCD3-	4 (0-11)	1 (0-2)	1 (0-12)	1 (0-5)	1 (0-41)

*p = 0.048. Data are expressed as median, 10th and 90th percentile.
[Table 1. Flow cytometry results]
Disclosure: Nothing to disclose

References

1. Malamut G, Cellier C. Complications of coeliac disease. *Best Pract Res Clin Gastroenterol* 2015; 29: 451–8.
2. Nijeboer P, Malamut G, Bouma G, et al. Therapy in RCDII: Rationale for Combination Strategies? *Dig Dis* 2015; 33: 227–30.
3. Verbeek WH, Goerres MS, von Blomberg BM, et al. Flow cytometric determination of aberrant intra-epithelial lymphocytes predicts T-cell lymphoma development more accurately than T-cell clonality analysis in Refractory Celiac Disease. *Clin Immunol* 2008; 126: 48–56.
4. Van Wanrooij RL, Schreurs MW, Bouma G, et al. Accurate classification of RCD requires flow cytometry. *Gut* 2010; 59: 1732.

MONDAY, OCTOBER 22, 2018   15:45–17:15
Unsolved issues in cirrhosis – Room L7_____

OP114   RISK SCORE MODEL TO PREDICT EARLY READMISSION IN DECOMPENSATED CIRRHOSIS

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Introduction: Cirrhosis has shown an increase of 45.6% in mortality from 1990 to 2013. Medicare expenditures for potentially preventable readmissions may be as high as $12 million per year and the cost for an individual readmission is reported around $20, 000. Besides the costs, the readmission is related with a significant negative effect on quality of life for the patients. Early hospital re-admissions (during the next 30 days after discharge) among patients with decompensated cirrhosis predict a poor outcome and increase the 1-year follow-up mortality. We believe that in some cases early re-hospitalization could be predictable and therefore, potentially preventable. This study aimed to develop a score that identifies patients at high risk for 30-day readmission.

Aims and Methods: This prospective study was conducted in 2 hospitals from Spain. We included 253 patients with diagnosis of cirrhosis, and admitted due to a decompensation. Before discharge, we collected demographic, socioeconomic, clinic and laboratory data. Readmissions were categorized into 3 stages, within 30 days, from 1-6 month, and from 6-12 months after discharge.

Statistical Analysis: We established significant risk factors for early readmission identified by Cox proportional hazards model. We assigned weighted-points that were proportional to their β regression coefficient values. We calculated a prognostic score in patients with complete data for multivariate model (N = 245). After internal validation (Bootstrap validation), patients were categorized into 3 groups that were significantly distinct in predictive risk for early readmission (low, medium, and high risk).

Results: The predictors for ER in the Cox-model (p < 0.05) included: SBP during hospitalization (HR: 4.34; 95% CI 1.43–13.17; p = 0.01), ascites grade ≥2 (HR: 2.16; 95% CI 1.21–3.86; p = 0.01), number of medications at discharge

(HR: 1.16; 95% CI 1.03–1.32; p = 0.02), ECOG performance status ≥1 (HR: 4.13; 95% CI 1.25–13.65; p = 0.02), Child-Pugh ≥10 (HR: 2.43; 95% CI 1.33–4.45; p = 0.004) and MELD-Na ≥15 (HR: 2.25; 95% CI 1.19–4.26; p = 0.01). The use of beta-blockers was a protective factor for readmission (HR: 0.46; 95% CI 0.26–0.82; p = 0.01).

After assigning weighted-points to the previous factors, the model (Table 1) was able to predict 30-day readmissions with a good discrimination. The c-statistic value was 0.79 (95% CI: 0.72–0.84). The total sum of the 7 values plus 4 (scaling factor) was the final risk score number. Patients were divided in 3 groups according to the risk of ER:

- *Low-risk group (< 17 points):* 93/245 subjects; 30-day readmission rate of 4.3%.
- *Medium-risk group (17-24 points):* 85/245 subjects; 30-day readmission rate of 21.2%
- *High-risk group (≥25 points):* 67/245 subjects; 30-day readmission rate of 49.3%

1-year follow up showed a survival rate of 47.8% in the high-risk group, 65.3% in the medium-risk group, and 83.9% in the low-risk group.

Conclusion: The risk score is useful to identify patients at high risk of early readmission. This group can be the target to implement strategies to reduce the 30-day readmission. It is necessary external validation of the score and future studies to establish appropriate interventions.

SBP during hospitalization	YES = +10	NO = +0
Ascites at discharge grade ≥2	YES = +5	NO = +0
ECOG performance Status grade ≥1	YES = +9	NO = +0
Child-Pugh score ≥10	YES = +6	NO = +0
MELD-Na ≥15	YES = +5	NO = +0
Beta blocker use	YES = −5	NO = +0
Number of medications at discharge (n)	+ n	
RISK SCORE	TOTAL AMOUNT + 4 ("4" is the scaling factor used to generate only positive risk scores)	

[Predictive model for Early readmission in decompensated cirrhosis.]

Disclosure: Nothing to disclose

References

1. Kanwal F, El-Serag H. Improving quality of care in patients with cirrhosis. *Clin Liver Dis.* 2013; 2(3). doi:10.1002/cld.189.
2. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2015; 385: 117–71.
3. Seraj SM, Campbell EJ, Argyropoulos SK, Wegermann K, Chung RT, Richter JM. Hospital readmissions in decompensated cirrhotics: Factors pointing toward a prevention strategy. *World J Gastroenterol.* 2017; 23(37): 6868–6876. doi:10.3748/wjg.v23.i37.6868.
4. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *New England Journal of Medicine* 2009; 360: 1418–28. doi:10.1056/NEJMsa0803563.
5. Kanwal F. Quality of care assessment in chronic liver disease. *Clin Liver Dis.* 2014; 4(6): 149–152. doi:10.1002/cld.435.
6. Joynt KE, Jha AK. Thirty-Day Readmissions — Truth and Consequences. *N Engl J Med.* 2012; 366(15): 1366–1369. doi:10.1056/NEJMp1201598.
7. Morales BP, Planas R, Bartoli R, et al. Early hospital readmission in decompensated cirrhosis: Incidence, impact on mortality, and predictive factors. *Dig Liver Dis.* 2017; 49: 903–909. doi:10.1016/j.dld.2017.03.005.

OP115   RISK FACTORS FOR THE EMERGENCE OF MULTIDRUG-RESISTANT ORGANISMS IN LIVER CIRRHOSIS

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Introduction: Infections in patients with liver cirrhosis (LC) are common and one of the major causes of hospitalization. Multidrug-resistant organisms (MDROs) are a current reality that can alter the paradigm of treatment and prevention of infection in these patients.

Aims and Methods: The aim of this study is to identify the risk factors for the occurrence of MDROs in patients with LC.

Prospective study from October 2017 to March 2018 in consecutively hospitalized patients with uncompensated LC with infection. Blood, urine and ascitic fluid cultures were analyzed.

Results: 52 episodes of infection (43 males, mean age 63 ± 14.6 years, 30 Child-Pugh C, 20 Child-Pugh B). In 15 episodes no microorganisms were identified in cultural examinations. Of the remaining, MDROs were isolated in 18 (15 males, mean age 63 ± 12.3 years; 7 Child-Pugh C, 10 Child-Pugh B). Klebsiella ESBL was the most frequently isolated MDRO (44.4%). MDROs were associated with the use of proton pump inhibitors (PPI) (72.2% vs. 36.8%, p = 0.0312), antibiotic therapy in the last 90 days (including norfloxacin prophylaxis) (94.4% versus 47.4%, p = 0.0033) and hospitalization for more than 48 hours or discharge for less than 30 days (100% versus 68.4%, p = 0.0082). The presence of Diabetes Mellitus (38.9% versus 31.6%) and hepatocellular carcinoma (33.3% versus 31.6%) were not relevant as factors predisposing to MDROs infection (p = 0.6526 and p = 0, 9124, respectively).

Conclusion: The indiscriminate use of antibiotics and PPIs increases the risk of MDROs infections, suggesting that the prescription of these drugs should be restricted to formal indication. Also hospitalization for more than 48 hours or hospital discharge for less than 30 days have been shown to influence the onset of MDROs. This suggests that hospitalizations in LC patients should be limited to the minimum number of days required. The authors consider relevant the investigation of other factors predisposing to the emergence of these microorganisms.

Disclosure: Nothing to disclose

OP116   EFFICACY AND SAFETY OF TRANSJUGULAR PORTOSYSTEMIC SHUNT IN DIFFICULT-TO-MANAGE HYDROTHORAX IN CIRRHOSIS

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Introduction: Pleural effusions complicate end-stage liver disease in 5% of patients. Early and careful identification of cause and related complications is imperative for appropriate management and patient survival. Unlike refractory ascites, data is limited on safety and efficacy of TIPS in cirrhotic patients with refractory refilling pleural effusion.

Aims and Methods: We analyzed a consecutive cohort of hospitalized cirrhotic patients having pleural effusion (PE) at admission. Baseline HVPG and PE tap was done to determine etiology and presence of infection. We determined the rate and predictors of PE resolution with standard medical treatment (SMT), need for intercostal drainage (ICD) for repeated pleurocentesis, and efficacy and safety of TIPS in hepatic hydrothorax.

Results: Of 1149 admissions involving 762 cirrhotics (mean CTP- 10.6 ± 1.8) with PE, 967 (84.2%) had hepatic hydrothorax (HH), 181 (15.8%) had tubercular PE (TBPE) and despite comparable HVPG, CTP and MELD scores at baseline, patients with HH in comparison to TBPE developed more complications (HE- 41.6% vs 30.2%, AKI- 48.6% vs 37%, pneumonia- 16.1% vs 7.2%, bacteremia- 11.7% vs 6.1% and septic shock-14.1% vs 8.3%; all p < 0.01) on follow-up. Of patients with HH, 475 (49.2%) were symptomatic (mainly dyspnea-30.1%, cough-24% and chest pain-16.1%) at admission and PE tap revealed SBE in 219 (22.9%) patients. Presence of co-existing SBP (52.5%; Odd's ratio, OR: 5.2) and ICD placement (24.2%; OR: 3.1) were independent predictors for SBE. Baseline HVPG (16.6 ± 4.4 vs. 16.4 ± 5.1; p-0.6) and MELD scores (22.3 ± 6.9 vs. 21.9 ± 7.3; p-0.1) were comparable in SBE and no SBE patients. 43% patients of HH responded to SMT alone and 133 (13.8%) required ICD placement for repeated pleurocentesis. 41 patients were carefully selected for TIPS [based on lower CTP score (TIPS vs no TIPS- 9.9 ± 1.6 vs 10.7 ± 1.8; p-0.02), lower MELD (18.7 ± 5.5 vs. 21.5 ± 7.5; p-0.03) and higher HVPG (19 ± 4.7 vs. 16.4 ± 4.8; p-0.08)]. Despite reduction in pressure gradient (mean portal venous – mean right atrial pressure) from 23.1 ± 3.8 mm Hg to 7.2 ± 2.5 mm Hg), only 20 (48.2%) had complete resolution of HH, with no difference in mortality rates. Main complications of TIPS in HH were post TIPS encephalopathy (8 patients, 6 resolved) and ischemic hepatitis (4 patients, 2 resolved). 321 (35.9%) patients with HH had in-hospital mortality and independent predictors were MELD > 25, SBE non-response to SMT and septic shock requiring vasopressors.

Conclusion: Only 1-half of hepatic hydrothorax resolves with standard medical therapy and need for any intervention including TIPS generally heralds poor outcomes. Role of hepatic hemodynamics in predicting complications and response to HH is limited. Early referral for liver transplantation is imperative.

Disclosure: Nothing to disclose

OP117   RANDOMIZED PLACEBO-CONTROLLED STUDY OF ORPHENADRINE IN TREATMENT OF MUSCLE CRAMPS IN PATIENTS WITH LIVER CIRRHOSIS

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Introduction: Muscle cramps are common in patients with liver cirrhosis and adversely influence quality of life with no available highly effective treatment.

Aims and Methods: The aim of this study was to assess the efficacy and safety of orphenadrine in treatment of muscle cramps in cirrhotic patients.

Methods: 122 patients with liver cirrhosis were enrolled in this study who suffering from frequent muscle cramps (≥3 per week), randomized to receive either orphenadrine 100 mg twice daily or placebo for 1 month twice daily as a control.

33 patients in the orphenadrine group and 36 patients in the placebo group were on diuretic therapy. Muscle cramp questionnaire was fulfilled. Severity, duration, and frequency of muscle cramps were assessed before, after 1 month of treatment and 2 weeks after washout of treatment. Side effects were recorded every visit to determine safety of the drug.

Results: 1 month after treatment with orphenadrine; the frequency of muscle cramps decreased significantly to 0.91 ± 1.07 compared to 11.08 ± 4.55 at baseline per week (p < 0.001), the duration of muscle cramps decreased from 4.36 ± 1.24 to 1.86 ± 2.25 minute after treatment (p < 0.001). The pain score improved significantly from a score of 7.27 ± 2.38 to 3.27 ± 3.46 (p < 0.001). The side effects were few such as dry mouth, drowsiness, and nausea, with no significant difference between their occurrences in the 2 groups.

Conclusion: Orphenadrine is safe and effective in treatment of muscle cramps in patients with liver cirrhosis.

Disclosure: Nothing to disclose

Reference

1. Abd-Elsalam S, El-Kalla F, Ali LA, et al. Pilot study of orphenadrine as a novel treatment for muscle cramps in patients with liver cirrhosis. *United European Gastroenterol J* 2018; 6(3): 422–7.

OP118 EFFECTIVENESS OF ACTIVE OUTPATIENT FOLLOW-UP PROGRAM ON LONG-TERM SURVIVAL OF PATIENTS WITH ALCOHOLIC LIVER DISEASE

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Introduction: Alcoholic liver disease (ALD) is the most prevalent cause of advanced liver disease and liver-related mortality in Europe and Russia. Abstinence is the first line and the basic therapeutic procedure for any form and stage of ALD. Combined comprehensive supportive and behavioral (repeated short brief intervention sessions) treatments provided by clinicians may increase abstinence rate followed by liver function stabilization and improves patient's outcome.

Aims and Methods: The main aim of this study was to estimate the effectiveness of the active outpatient follow-up (AOF) program in achieving and maintaining abstinence, liver function compensation and improving the long-term outcome of patients with ALD.

In this historical control study 29 patients with ALD were enrolled in the group of AOF that included active supervision by hepatologist: physical and motivation assessment, motivational interviewing, liver panel lab tests with the rate once at 3 months. The duration of the AOF was 12 months with 1 follow-up visit after 12 month. The historical control group included 36 patients with ALD and history of 2-year follow-up in the hepatology department, who received comprehensive therapy and simple advice to avoid alcohol.

Results: There were significant differences in adherence to abstinence between AOF and control groups at 6 (88% vs 43%, p < 0.001), 9 (84% vs 44%, p = 0.002), 12 (84% vs 41%, p = 0.001) and 24 (80% vs 40%, p = 0.017) months of follow-up, respectively. The 24-month alcohol relapse occurred in 2 (8%) patients in the AOF group comparing with 13 (36%) patients in the control group (p = 0.005). Univariable analysis showed that only AOF was significantly associated with achieving and maintaining of abstinence. Multivariable regression analysis of alcohol relapse during the 24 month showed that AOF is independent factor for being abstinent (OR: 0.80 [95% CI 0.14-0.479]; p = 0.006). The proportion of patients with decompensated cirrhosis (Child-Pugh B+C) was higher in the control group at 12 (14.2% vs 56%, p = 0.002) and 24 (19% vs 52%, p = 0.021) months after enrollment. Medians of MELD were 11 (10-12.5) points in the AOF group vs 14 (11.75-17.25) points in the control group (p = 0.01) after 12 months and 11 (10-12.5) points in the AOF group vs 13 (11-15) points in the control group (p = 0.009) after 24 months. The overall mortality in AOF-patients vs those in control group was 14% vs. 28% (p = 0.02), respectively. Multivariable regression analysis of mortality showed that decompensated cirrhosis at baseline was an independent risk factor for higher mortality (OR: 88.01 [95% CI 3.1-2498.51]; p = 0.009) whereas in contrast AOF was an independent factor for being alive (OR: 0.026 [95% CI 0.001-0.618]; p = 0.024).

Conclusion: The program of active outpatient follow-up provided by hepatologist can increase likelihood of achieving and maintaining abstinence, prolonged compensation of liver function and improve the long-term survival of patients with ALD.

Disclosure: Nothing to disclose

OP119 THE BENEFICIAL EFFECTS OF NON-SELECTIVE BETABOCKERS IN SECONDARY PROPHYLAXIS ARE MOST PRONOUNCED IN PATIENTS WITHOUT REFRACTORY ASCITES

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Introduction: Endoscopic band ligation (EBL) is used for primary (PP) and secondary prophylaxis (SP) of variceal bleeding. For SP, current guidelines recommend combined use of non-selective beta-blockers (NSBBs) and EBL for SP, while either NSBB or EBL should be used in PP.

Aims and Methods: (Re-) bleeding rates and mortality were retrospectively assessed with and without concomitant NSBB therapy after first EBL in PP and SP.

Results: 766 patients with esophageal varices underwent EBL from 01/2005-06/2015. In PP, among 284 patients undergoing EBL, n = 101 (35.6%) received EBL only, while n = 180 (63.4%) received EBL+NSBBs. In 482 patients on SP, n = 163 (33.8%) received EBL only, while n = 299 (62%) received EBL+NSBBs. In PP, concomitant NSBB therapy neither had an impact on bleeding rates (log-rank p = 0.353) nor on mortality (log-rank p = 0.497) as compared to EBL alone. Patients in SP with EBL+NSBB showed similar rebleeding rates as compared EBL alone (log-rank p = 0.247). However, in SP, a concomitant NSBB therapy resulted in a significantly lower mortality rate (log-rank p < 0.001) with fewer deaths related to liver failure, bleeding, and infections with EBL+NSBB combination therapy. A decreased risk of death with EBL+NSBB in SP (hazard ratio, HR:0.50; p < 0.001) but not of rebleeding, transplantation or further decompensation was confirmed by competing risk analysis. Interestingly, in SP, NSBB intake reduced 6-months mortality (HR:0.53; p = 0.008) in patients without severe/refractory ascites (HR:0.37; p = 0.001) only but this effect was not seen in patients with severe/refractory ascites (HR:0.80; p = 0.567).

Conclusion: EBL alone seemed to be sufficient for PP of variceal bleeding. In SP, concomitant NSBB to EBL improves survival within the first 6 months after EBL, as compared to EBL alone. In patients with severe/refractory ascites these beneficial effects of NSBB therapy have to be weighted against their potential side-effects.

Disclosure: Nothing to disclose

Diagnosis and risk factors of pancreatic diseases – Room L8

OP120 DEFINING PANCREATITIS AS A RISK FACTOR FOR PANCREATIC CANCER: THE ROLE, INCIDENCE, AND TIMELINE OF DEVELOPMENT

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Introduction: Pancreatic cancer has a high mortality rate and is the third leading cause of cancer related deaths in the United States. Risk factors for developing pancreatic cancer-include age > 55, male sex, obesity, tobacco, and diagnosis of diabetes. Additionally, acute and/or chronic pancreatitis has been implicated as an important risk factor for pancreatic cancer; however, the incidence and temporal relationship of pancreatitis prior to the diagnosis of pancreas cancer is unclear.

Aims and Methods: We aim to establish the role and incidence of pancreatitis temporally with the development of pancreatic cancer. A population-based study, with a web-based platform called Explorys was used to collect de-identified patient data. Over 50 million patients, spanning nationally in over 20 healthcare systems' electronic medical records is in this cloud-based, HIPPA-enabled platform. Data was obtained using ICD-9 code criteria with search terms "acute pancreatitis," "chronic pancreatitis," and "malignant tumor of the pancreas." A temporal relationship between pancreatitis diagnoses, followed by pancreatic cancer diagnosis was investigated. Intervals of 3, 6, 12, 24, and 36 months were observed. Demographical data, including age, gender, and race was also recorded and analyzed.

Results: A total 50,080 patients were found to have a diagnosis of pancreatic cancer. 7,420 (14.8%) of these patients were found to have diagnoses of pancreatitis prior to their cancer diagnoses. Of those, 91.6% were between the ages of 45-89. Interestingly, there was a higher incidence of pancreatic cancer in the African-American population vs. the Caucasian population (21.2% vs 14.8%, p < 0.05) group with prior pancreatitis diagnosis. Further analysis of pancreatic cancer diagnosis revealed that 6,030 of the 7,420 patients were diagnosed within 3 months of their acute and/or chronic pancreatitis (81.3%) diagnosis. Finally,

7,340 (98.9%) patients had established diagnoses of pancreatic cancer within 3 years of the pancreatitis diagnosis.

Conclusion: Treatment of pancreas cancer is often challenging because symptoms are not common or specific until advanced stage disease occurs. Early detection of pancreatic cancer may lead to improved survival. This study shows that almost 15% of patients with a diagnosis of pancreatic cancer have prior diagnoses of pancreatitis, of which 90% of these cases occur over age 45. Additionally, nearly 99% of pancreas cancer diagnoses occur within 3 years of the pancreatitis diagnosis. Given our large sample size, early detection and screening in patients with pancreatitis over the age of 40 with unclear etiology of pancreatitis may be reasonable, especially in the African American population. Limitations include inability to track etiology of pancreatitis as well as unclear histologic types of pancreas cancer in this database.

Diagnosis	Pancreatitis	Pancreatic Cancer	Pancreatitis Prior to Cancer (%)
N	7,420	50,080	14.8
Males	4,030	25,540	15.8
Age – yr			
20-29	10	150	6.7
30-39	90	470	19.1
40-49	420	1,790	23.5
50-59	1,330	6,490	20.5
60-69	2,100	12,830	16.4
70-79	1,930	14,430	13.4
80-89	1,140	10,230	11.1
90+	340	3,420	9.9
Ethnicity			
Caucasian	5,470	37,030	14.8
African-American	1,360	6,410	21.2

[Demographics of Pancreatitis prior to diagnosis of Pancreatic Cancer]
Disclosure: Nothing to disclose

OP122 THE WAY FROM ABDOMINAL PAIN TO PEDIATRIC PANCREATITIS – THE PINEAPPLE STUDY

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Introduction: The documented incidence of pediatric pancreatitis (PP) is low, but it shows a rising pattern from Eastern to Western Europe and the USA. The cause of this phenomenon is not clear, but based on a single center study the amylase and lipase measurements correlate with the incidence of the disease.

Aims and Methods: The aim of the PINEAPPLE (Pain IN EArly phase of Pediatric Pancreatitis) study is to investigate the current diagnostic practice for PP and to estimate the occurrence of pancreatitis among children suffering from abdominal pain worldwide. Furthermore we would like to develop an EBM guideline to establish a scoring system in order to evaluate the necessity of diagnostic steps for PP in children with abdominal pain. PINEAPPLE is a registered (ISRCTN35618458), observational, multinational clinical trial and the pre-study protocol is published (http://www.ncbi.nlm.nih.gov/pubmed/26641250). The PINEAPPLE-R is a retrospective review of ER medical records of children and adults. The PINEAPPLE-P is a prospective study in which serum pancreatic enzyme measurement (sPEM) and abdominal imaging are performed in every children with abdominal pain. Until now we have reviewed 35277 patient records for the PINEAPPLE-R and involved 496 patients in the PINEAPPLE-P from 13 centers from 3 countries.

Results: PINEAPPLE-R: 9.7% (2775/28707) of the children appeared at ER unit had abdominal pain. In case of abdominal pain sPEM was performed in 14% whereas 32% of the patients had transabdominal ultrasonography. In our cohort the number of sPEM decreases from the USA (21.6%) to Eastern Europe (13% in Hungary and 0.6% in Romania) and it correlates (r = 0.97) with the incidence of PP (8/2775). PINEAPPLE-P: 8 pancreatitis from 496 patients with abdominal pain were diagnosed. Positive family history and upper abdominal pain were characteristic for PP but fever and forced posture were not typical.

Conclusion: The PINEAPPLE-R shows that the incidence of PP is 0.3% among children with abdominal pain based on the current diagnostic practice. Better awareness of PP results 1.6% incidence of PP as a reason of abdominal pain. These data strongly suggest that acute pancreatitis is underdiagnosed in children.

Disclosure: Nothing to disclose

OP123 IS DIABETES BEING IGNORED IN PATIENTS WITH PANCREATIC CANCER?

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Introduction: Many risk factors have been implicated in pancreatic cancer, including age > 55, male gender, obesity, tobacco use, pancreatitis and diabetes mellitus (DM). It has been reported in literature that as high as 80% of patients with pancreatic cancer have glucose intolerance or frank diabetes.

Aims and Methods: We aim to evaluate if physicians are diagnosing, reporting, and managing diabetes in patients with pancreatic cancer. A population-based study, using an IBM platform called Explorys, was used to collect de-identified patient data. Over 50 million patients, spanning nationally in over 40 healthcare systems' electronic medical records (EMR) is in this cloud-based, HIPPA-enabled platform. Data was obtained using ICD-9 code criteria with search terms "diabetes mellitus" and "malignant tumor of the pancreas." Further, patients were also included if they were on anti-diabetic medications, including metformin, sulfonylureas, and insulin. These search terms were observed to ensure diagnosis of DM after pancreatic cancer as a first occurrence. Subsequently, HbA1c levels were observed in correlation to rates of mortality within this cohort.

Results: A total of 50,080 patients in the Explorys database with diagnosis of pancreatic cancer. Of those, 20,160 (40.3%) had concomitant diagnosis of DM in their EMR. African-Americans had a higher rate of DM development when compared to Caucasians (50.2% vs. 39.9%, p < 0.001). Majority of the diabetic patients were aged 60-89, with predominance between 70-79. As levels of HbA1c increased, rates of mortality did as well. Patients with HbA1c levels between 4-6.4% were found to have a lower mortality rate than those with HbA1c levels in the range between 6.5–8% (44.8% vs. 46.6%, p = 0.0293) and 9–12% (44.8% vs. 47.6%, p = 0.00672).

Conclusion: It has been reported in literature that as high as 80% of patients with pancreatic cancer have concomitant diagnoses of DM. We found drastically different percentages; these variations may be due to several factors. Firstly, it is very possible clinicians are underdiagnosing diabetes, especially in patients with pancreatic cancer. It is possible because of the high mortality of these patients, their other diagnoses, including DM, are being overlooked. Secondly, if DM is being diagnosed, physicians are not adequately reporting it in a patients' EMR. Moreover, patients with DM with HbA1c levels greater than 6.5% have a higher rate of mortality as compared to patients with HbA1c levels below 6.5%. Clinicians need to be aware of the high incidence of DM in patients with pancreatic cancer, so proper diagnosis and management can be implemented to possibly decrease mortality. Increased awareness should be also be in elderly patients between 60-89, as well as the African-American population where prevalence was highest.

Factors	Pancreatic Cancer	Diabetes and Cancer	Rate (%)
N	50080	20160	40.3
Males	25540	10660	41.7
Age 20-29	150	20	13.3
Age 30-39	470	110	23.4
Age 40-49	1790	510	28.5
Age 50-59	6490	2160	33.3
Age 60-69	12830	5260	41.0
Age 70-79	14430	6600	45.8
Age 80-89	10230	4210	41.1
Age 90+	3420	1290	37.7
Caucasian	37030	14770	39.9
African-American	6410	3220	50.2
Tobacco users	22610	12650	55.9
Alcohol users	11700	7010	59.9
BMI > = 30	19400	12550	64.7

[Demographics and Risk Factors of Pancreatic Cancer with concomitant Diabetes]
Disclosure: Nothing to disclose

OP124 PANCO: AN OPEN-LABEL, SINGLE-ARM PILOT STUDY OF ONCOSIL[TM] IN PATIENTS WITH UNRESECTABLE LOCALLY ADVANCED PANCREATIC ADENOCARCINOMA IN COMBINATION WITH FOLFIRINOX OR GEMCITABINE+NAB-PACLITAXEL CHEMOTHERAPIES

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Introduction: Locally advanced pancreatic cancer (LAPC) is associated with a poor prognosis. Current standard treatment is limited to chemotherapy or chemo-radiotherapy. Novel treatment approaches are crucial in attempting to combat this unmet medical need. Phosphorus-32 (P-32) Microparticles is a brachytherapy device that implants a predetermined dose of the beta radiation emitting isotope (P-32) directly into pancreatic tumours via endoscopic ultrasound (EUS) guidance. The presented data are early results from an ongoing international, multi-institutional, single-arm pilot study. The study objective is to determine the safety and efficacy of P-32 Microparticles in a patient population undergoing standard chemotherapy for unresectable LAPC.

Aims and Methods: Eligible patients were allocated to receive either gemcitabine+nab-paclitaxel or FOLFIRINOX by physician choice. P-32 implantation took place during the 4th or 5th week following the initiation of chemotherapy. P-32 was implanted directly into the pancreatic tumour via EUS guidance, using a fine needle aspiration (FNA) needle. Each patient's dose was calculated from the tumour volume where the absorbed dose of P-32 to the tumour was calculated to equal 100 Gy. Diffusion pattern of the P-32 suspension following implantation was assessed by EUS and by Bremsstrahlung SPECT/CT imaging. Chemotherapy was continued after the implantation. Safety data was collected weekly and toxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE). Centrally read CT scans were conducted every 8 weeks to assess response defined as complete response [CR], partial response [PR], and stable disease [SD]) rate, according to RECIST 1.1 criteria. FDG-PET scans were performed at baseline and at week 12.

Results: Data is reported on the first 20 implanted patients (12 males and 8 females, median age 65 years [range 54-84]) up to week 16 of follow-up. At 16 weeks, the objective response rate was 20% – PR in 4/20 patients. The local disease control rate (CR, PR and SD) was 85% – either PR or SD in 17/20 patients. Median change in tumour volume from baseline to week 16 was -33% (range +36% to -80%). Total lesion glycolysis (TLG) as measured via FDG-PET scan showed a median reduction of 54% (range +45% to -100%) from baseline to week 12.

The EUS-guided implantation was carried out successfully in all patients and without any complications. By week 16, 318 adverse events (AEs) were reported. 33 Grade 3 AEs (10%) and 6 (2%) Grade 4 toxicities were reported. The most common AEs of Grade 3 and 4 severity were neutropenia (7), anaemia (2), constipation (2), vomiting (2) and fatigue (2). None of the G3 and G4 AEs were attributable to the device or the implantation procedure.

Conclusion: Early data indicates that the use of EUS-guided implantation of P-32 is highly feasible, well tolerated and has an acceptable safety profile in combination with standard first-line chemotherapy for LAPC. Preliminary data shows evidence of tumour regression and local disease control. These results, however, warrant further evaluation. The clinical trial is ongoing and additional safety and efficacy data will be presented.

References: ClinicalTrials.gov Identifier: NCT03003078

OP126 ANTIREFLUX METAL STENT VS. CONVENTIONAL COVERED METAL STENT FOR NONRESECTABLE DISTAL MALIGNANT BILIARY OBSTRUCTION: A MULTICENTER RANDOMIZED CONTROLLED TRIAL

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Introduction: An antireflux metal stent (ARMS) for nonresectable distal malignant biliary obstruction may prevent recurrent biliary obstruction (RBO) caused by the duodenobiliary reflux and thereby provide long time to RBO (TRBO). The superiority of the ARMS over conventional covered self-expandable metal stents (SEMSs) has not fully examined.

Aims and Methods: We conducted a multicenter randomized controlled trial to examine whether TRBO of an ARMS with a funnel-shaped valve was longer than that of a covered SEMS in patients without a history of SEMS placement. Secondary outcomes included causes of RBO, adverse events, and patient survival.

Results: We enrolled 104 patients (52 patients per arm) from September 2014 to June 2016 at 11 tertiary care centers in Japan. The median TRBO did not differ significantly between the ARMS and covered SEMS groups (251 and 351 days, respectively; p = 0.11). RBO due to biliary sludge or food impaction was observed in 13% and 9.8% patients who received an ARMS and covered SEMS, respectively (p = 0.083). The ARMS appeared to be associated with a higher rate of stent migration compared with the covered SEMS (31% vs. 12%, respectively; p = 0.038). No significant between-group difference was observed for adverse events or patient survival.

Conclusion: The current ARMS was not associated with longer TRBO compared with the covered SEMS. Further modifications including addition of an anti-migration system are required to justify the use of the current ARMS as a first-line palliative treatment modality for distal malignant biliary obstruction.

OP127 EUS-GUIDED BILIARY DRAINAGE VERSUS ERCP FOR THE PRIMARY PALLIATION OF MALIGNANT BILIARY OBSTRUCTION: A MULTICENTER RANDOMIZED CLINICAL TRIAL

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Introduction: Although ERCP for the palliation of malignant biliary obstruction is the standard care, post-procedure pancreatitis and stent dysfunctions are not uncommon. While endoscopic ultrasound (EUS)-guided biliary drainage (EUS-BD) has garnered interest as a viable alternative when ERCP is impossible, its role as a primary palliation of malignant distal biliary obstruction is yet to be proven.

Aims and Methods: The aim of the study was to determine whether EUS-BD is comparable to conventional transpapillary stenting with ERCP in the primary palliation of malignant distal biliary obstruction. We performed random allocation to EUS-BD or ERCP in 125 patients with unresectable malignant distal biliary obstruction at four tertiary academic referral centers in South Korea.

Results: Technical success rates were 93.8% (60/64) for EUS-BD and 90.2% (55/61) for ERCP (difference 3.6%, 95% 1-sided confidence interval lower limit -4.4%, p = 0.003 for noninferiority margin of 10%). Clinical success rates were 90.0% (54/60) in EUS-BD and 94.5% (52/55) in ERCP (p = 0.49). Lower rates of overall adverse events (6.3% vs 19.7%, p = 0.03) without post-procedure pancreatitis (0 vs 14.8%), reintervention (15.6% vs. 42.6%), and higher rate of stent patency (85.1% vs. 48.9%) were observed with EUS-BD at the study end. EUS-BD was associated with more preserved QOL than transpapillary stenting after 12 weeks of the procedure.

Conclusion: This study demonstrated comparable technical and clinical success rates between EUS-BD and ERCP in relief malignant distal biliary obstruction. Coupled with longer duration of bile duct patency, lower rates of adverse events and re-intervention, EUS-BD should be considered as a viable primary treatment option in patients with distal biliary obstruction from unresectable malignancy.

Disclosure: Nothing to disclose

TUESDAY, OCTOBER 23, 2018   08:30–10:00

Oesophageal disorders: Mechanisms and management – Room G

OP128 HYPERCONTRACTILE (JACKHAMMER) ESOPHAGUS DEMONSTRATES EXCESSIVE EXCITATORY AND ABNORMAL INHIBITORY DYSFUNCTION ON PROVOCATIVE TESTING DURING HIGH RESOLUTION MANOMETRY (HRM)

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Introduction: Excessive excitation of the esophageal smooth muscle is thought to induce esophageal hypercontractility. Abnormal inhibition can lead to premature esophageal contractions, with or without abnormal lower esophageal sphincter (LES) relaxation. Esophageal provocative testing (multiple rapid swallows, MRS) during HRM evaluates esophageal excitation and deglutitive inhibition, and could provide insights into the pathophysiology of hypercontractile esophageal disorders.

Aims and Methods: We aimed to evaluate interrelationships between excessive excitation and abnormal inhibition in esophageal hypercontractile disorders, using MRS. Esophageal HRM fulfilling Chicago Classification 3.0 criteria for hypercontractile esophagus (HE) with and without esophagogastric junction (EGJ) obstruction were reviewed from 5 centers (4 in Europe, 1 in US). Incomplete studies, and prior foregut surgery were exclusions. Upper endoscopy and barium studies excluded structural processes (rings, hiatus hernia, stricture). Single swallows (SS) and MRS were analyzed using HRM software tools assessing integrated relaxation pressure (IRP, >15 mmHg $=$ EGJ obstruction), distal latency (DL) and distal contractile integral (DCI); MRS:SS DCI ratio >1 defined contraction reserve. Comparison groups were achalasia type 3 (positive control for EGJ obstruction) and healthy volunteers (negative control). Symptoms, HRM metrics, and MRS contraction reserve were analyzed within HE subgroups and comparison groups.

Results: Study groups consisted of 40 patients with HE (62.6 ± 2.0, 63% F), 30 with HE and EGJ obstruction (65.6 ± 2.7, 55% F); 72 with achalasia type 3 (66.2 ± 2.0, 56% F) and 18 normal controls (27.4 ± 0.7, 56% F). Higher mean DCI values were noted in HE and HE with EGJ obstruction groups (p = ns between SS and MRS, and between groups), these DCI values were significantly higher than comparison groups (p < 0.0001 for each comparison). MRS/SS DCI ratio was lower in HE with obstruction compared to achalasia type 3 (p = 0.03) and normal controls (p < 0.001), and trended toward significance in HE vs. achalasia type 3 (p = 0.16). Proportions with contraction reserve were lower in HE subgroups (p = 0.03 across groups). Incomplete inhibition was similar between EGJ obstruction categories (HE with obstruction, achalasia type 3, p = ns), and lower in HE without obstruction (p = 0.04 vs. achalasia type 3, p = 0.06 vs all obstructive categories). On symptom analysis, perceptive symptoms (heartburn, chest pain) were common in HE subgroups (p = 0.009 across groups), while transit symptoms (dysphagia) were more frequent in the setting of EGJ obstruction (p = 0.03 across groups).

		HE	HE with obstruction	Achalasia type 3	Normal controls
SS mmHg.cm.s	DCI	8910 ± 515*†	8552 ± 1043*†	3912 ± 398†	1762 ± 335
MRS mmHg.cm.s	DCI	9640 ± 1602*†	9088 ± 2357*†	4222 ± 479	2699 ± 652
MRS:SS DCI ratio		1.08 ± 0.15†	0.88 ± 0.11*†	1.42 ± 0.16	1.78 ± 0.30
% with contraction reserve		38%†	40%†	49%	78%
% with abnormal inhibition		50%*	60%	69%	50%
Dysphagia		53%*	70%	76%	
Heartburn/chest pain		86%*	77%	58%	

*[*p < 0.05 compared to achalasia type 3; †p < 0.05 compared to normal controls]*

Conclusion: The esophageal smooth muscle demonstrates excessive excitation at baseline in HE subgroups, manifest as high DCI and diminished contraction reserve on MRS. In contrast, abnormal inhibition is predominant in achalasia type 3, and participates in the pathophysiology of HE with obstruction. Our findings indicate that the balance of excitation and inhibition defines the clinical and motor manifestations in HE, HE with obstruction and achalasia type 3. Provocative testing, particularly MRS, has diagnostic value in the evaluation of hypercontractile esophageal disorders.

Disclosure: Nothing to disclose

OP129 MANAGEMENT OF SUPRAGASTRIC BELCHING: PREDICTORS OF SUCCESS AND FOLLOW UP OUTCOMES 6-12-MONTHS AFTER INITIAL TREATMENT WITH COGNITIVE BEHAVIOURAL THERAPY (CBT)

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Introduction: Esophageal pH-impedance monitoring (MII-pH) can identify a type of belching disorder that seems to have a significant behavioural component – supragastric belching (SGB). SGB involves an intake of air from the mouth into the esophagus, followed immediately by expelling the air via abdominal straining, without the air entering or originating from the stomach. We have recently reported our experience on treatment of SGB using cognitive behavioural therapy (CBT) (Glasinovic et al., 2018). Our 10 weeks CBT protocol consisted of: explaining the possible mechanism of SGB, raising awareness of the initial warning signals for the onset of the belch, and teaching patients abdominal breathing manoeuvers and a mouth/tongue position to prevent it. Out of the 39 patients who completed treatment, 25 patients (64%) recorded at least 50% improvement in either their subjective and/or objective outcomes at the end of the 5 CBT sessions (10-week treatment)

Aims and Methods: We **aimed** to assess predictors of success and to audit subjective outcomes at 6-12 months after completion of CBT.

Methods: To identify determinants of treatment success, patients who reported at least 50% symptom improvement (improved group, IG n = 25) were compared with those who did not (including treatment drop-outs, unimproved group, UG n = 14) on a range of baseline and in-treatment variables. All treatment completers (N = 39) were contacted via phone 6-12-months post treatment and 31 (79%) responded. The outcome was measured subjectively using the 4 item Visual Analogue scale (VAS) score adapted from Hemmink et al (2010). Patients were asked to rate how bothered they are by their belching, their ability to control belching, the impact of the belching on daily activities, and the impact on social activities.

Results: Of baseline variables, IG and UG differed only in the proportions of patients from ethnic minorities. Successful treatment outcome was related to being able to identify signals for the onset of belching, acceptance of the behavioural explanation of the condition and adherence to treatment exercises. The differences between IG and UG groups in symptom change were significant already after the first week of treatment (t = 2.6; p < 0.05). At baseline VAS score was: 6.53 ± 2.06; at the end of CBT treatment 3.45 ± 2.11 and at the 6-12 month follow up it was: 3.82 ± 2.04. The difference between the baseline VAS and 6-12-months VAS statistically significant (p < 0.001). At the TE interview patients were asked if they still continued to use the abdominal breathing technique and mouth opening. 24/31 (77.4%) stated that they continue to follow the CBT treatment on a regular basis.

Conclusion: Awareness of signals preceding belching and accepting the behavioural explanation of the condition were factors that predicted success. The follow up audit at 6-12 month after treatment support the long-term efficacy of CBT in the treatment of SGB.

Disclosure: Nothing to disclose

References

1. Glasinovic E, Wynter E, Arguero J, Ooi J, Nakagawa K, Yazaki E, Hajek P, Woodland P, Sifrim D. Treatment of supragastric belching with cognitive behavioral therapy improves quality of life and reduces acid gastroesophageal reflux. *Am J Gastroenterol*. 2018 Apr; 113(4): 539–547. doi: 10.1038/ajg.2018.15. Epub 2018 Feb 20.

2. Glasinovic E1,2, Wynter E1, Arguero J1, Ooi J1, Nakagawa K1, Yazaki E1, Hajek P, Psych CC3, Woodland P1, Sifrim D1. Hemmink, G.J.M., Ten Cate, L., Bredenoord, A.J., Timmer, R., Weusten, B.L.A.M., & Smout, A. J. (2010). Speech therapy in patients with excessive supragastric belching – a pilot study. *Journal of Neurogastroenterology and motility*, 22(1): 24-E23.

OP130   LARYNGOPHARYNGEAL REFLUX AND COUGH REFLEX SENSITIVITY

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Introduction: Cough reflex sensitivity to inhaled irritants is influenced by the functional state of cough-triggering afferent nerve terminals in the larynx and large airways. Laryngopharyngeal reflux (LPR) causes irritation of the larynx and possibly large airways. However, the relationship between the cough reflex sensitivity and LPR is incompletely understood.

Aims and Methods: We hypothesized that cough reflex sensitivity in patients with LPR is positively correlated with LPR. Our hypothesis predicts that patients with more frequent LPR have lower cough reflex threshold. Consecutive patients referred for LPR were evaluated and those with positive reflux symptom index (RSI > 13) and/or reflux finding score (RFS > 7) were evaluated. LPR was evaluated by 24 hour dual pharyngeal and distal esophageal 24-hour pH/impedance monitoring. Appropriate distance between pharyngeal and distal esophageal pH sensors was chosen based on manometrically determined LES and UES. LPR event was inferred from the pharyngeal reflux following reflux detection in the distal esophagus. For each LPR event we determined the maximum drop of pH at the pH levels < 6, < 5.5, < 5.0, < 4.5 and < 4.0 to perform the analysis independent of the assumption how acidic the pH of LPR is required to affect the sensitivity of cough reflex. Cough reflex sensitivity was determined by single breath capsaicin inhalation challenge of doubling concentrations of capsaicin (0.49–1000μmol/l) using KoKo PFT system. Cough threshold was defined as the lowest concentration of capsaicin that evoked at least 2 coughs (C2) or 5 coughs (C5). For statistical analysis C2 and C5 values were -log transformed and Pearson coefficients were calculated for correlation with reflux parameters.

Results: 27 consecutive patients were evaluated. The number of LPR events that reached pH 6.0, 5.5, 5.0, 4.5 and 4.0 was 14[8-21], 4[2-7], 1[0-2], 1[0-1], 0[0-1]. Correlations between cough reflex sensitivity expressed as C5 and the numbers of LPR episodes with pH drop to < 6.0, 5.5, 5.0, 4.5 and 4.0 expressed as the R value were 0.07, 0.04, 0.01, 0.02, 0.23, respectively (p > 0.1 not significant in all cases). Correlations between cough reflex sensitivity expressed as C2 and the numbers of LPR episodes with pH drop to < 6.0, 5.5, 5.0, 4.5 and 4.0 expressed as the R value were 0.18, 0.03, 0.11, 0.04, 0.14, respectively (p > 0.1 not significant in all cases). There was no correlation between the cough sensitivity expressed as either C5 or C2 and the number of LPR episodes, irrespective of the acidity of the LPR event.

Conclusion: The number of LPR episodes does not correlate with the cough reflex sensitivity in patients with laryngopharyngeal reflux, irrespective of the acidity of LPR event. This suggests that a direct simple relationship between the intensity of laryngeal irritation and cough is improbable.

Support: Biomedical Center Martin [ITMS 26220220187]

Disclosure: Nothing to disclose

OP131   ANTI-REFLUX ENDOSCOPIC SURGERY: ENDOSCOPIC CARDIOPLASTY USING ENDOSCOPIC MUCOSAL RESECTION MAY EFFECTIVELY TREAT REFRACTORY GASTROESOPHAGEAL REFLUX DISEASE

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Introduction: Anti-Reflux Endoscopic Surgery (ARES) is a new efficacious treatment of option for gastroesophageal reflux disease (GERD). We propose to define "esophageal remodeling" as the functional restoration of the esophagogastric junction (EGJ) that involves increased lower esophageal sphincter (LES) pressure. ARES is a endoscopic fundoplication technique using endoscopic mucosal resection (EMR) to treat such refractory GERD patients. This study investigated the clinical outcomes of ARES for refractory GERD patients.

Aims and Methods: ARES was performed in 106 patients with drug-refractory GERD from December 2015 to July 2017. We analyzed data from a prospectively collected database of ARES subjects, which included preprocedure and 6-month postprocedure of GERD-Q symptom scores, and results from esophageal high resolution manometry (HRM) and 24-hour pH monitoring. Symptom control rates were compared according to clinical and surgical factors to identify predictive factors of successful surgical outcomes.

Results: ARES was performed for 106 patients (55% male; mean age 46.8 years) with PPI-refractory GERD. Mean PPI medication periods were 5.7 (1-30) years and median ARES procedure time was 32.6 (15-83) minutes. The GERD-Q score and 24hr pH monitoring were significantly improved after ARES. Mean post-treatment GERD-Q score was 7.54 ± 2.6, compared to 10.87 ± 2.7 pre-treatment (p < 0.001). In impedance planimetry, the mean distensibility was 16.1 ± 8.3 prior to and 9.1 ± 5.7, respectively (p < 0.001). No serious complications after ARES were occurred. But 6 patients underwent post-treatment stricture, and were treated using balloon dilation and steroid injection. 3 patients suffered from minor post-ARES bleeding, successfully treated with argon plasma coagulation.

Conclusion: ARES is a very effective and safe treatment option for PPI-refractory GERD patients. ARES can be a good alternative treatment for refractory GERD.

Disclosure: Nothing to disclose

OP132   EFFICACY OF RPC4046, AN ANTI-INTERLEUKIN-13 MONOCLONAL ANTIBODY, IN PATIENTS WITH ACTIVE EOSINOPHILIC ESOPHAGITIS: ANALYSIS OF THE STEROID-REFRACTORY SUBGROUP FROM THE HEROES STUDY

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Introduction: The HEROES study was a 16-week double-blind, placebo-controlled phase 2 multicenter trial that evaluated the efficacy and safety of RPC4046 in adult patients with active eosinophilic esophagitis (EoE). The study included subjects who were considered steroid refractory based on prior corticosteroid use and investigator judgment. Both pre-specified and post-hoc analyses were undertaken to assess the effect of RPC4046 treatment on this important subgroup.

Aims and Methods: In this study, 99 adult patients with active EoE were stratified by steroid-refractory status (yes/no) and randomized 1:1:1 to receive RPC4046 360 mg, 180 mg, or placebo weekly for 16 weeks. The primary endpoint was change from baseline in mean esophageal eosinophil count at week 16. Secondary endpoints included mean change from baseline to week 16 in EoE Endoscopic Reference Score (EREFS), improvements in dysphagia determined by the Daily Symptom Diary (DSD), Eosinophilic Esophagitis Activity Index (EEsAI) score, and EoE histology scoring system (EoEHSS) based on grade and stage.

Results: Of the steroid-refractory patients, 17 were randomized to RPC4046 360 mg, 14 to RPC4046 180 mg, and 16 to placebo. The differences in change in mean esophageal eosinophil counts from baseline to week 16 between RPC4046 360 mg and placebo as well as RPC4046 180 mg and placebo were statistically significant. The difference in mean change in EREFS between each RPC4046 group and the placebo group was statistically significant for total score over all esophageal locations. The mean change in DSD composite score in the RPC4046 360 mg group compared to the placebo group approached statistical significance. Statistically significant improvements from baseline to week 16 in the RPC4046 treatment groups also were observed on histology as determined by EoEHSS and on symptom severity as determined by EEsAI. The most frequently reported adverse events in the study were headache, upper respiratory tract infection, arthralgia, nasopharyngitis, diarrhea, and nausea.

Conclusion: RPC4046 treatment improved mean and peak eosinophil count and histopathologic parameters, improved endoscopic features, and improved symptoms in steroid-refractory EoE patients. Although this pre-specified analysis was undertaken in a subgroup of patients in the HEROES trial, these data provide support that treatment with RPC4046 results in marked improvement in multiple EoE-related disease measures in steroid-refractory EoE patients. In the overall study population, ozanimod was generally safe and well-tolerated.

	Placebo (n = 16)	RPC4046 180 mg (n = 14)	RPC4046 360 mg (n = 17)
Esophageal Eosinophil Count (eosinophils/hpf)			
Baseline mean (SD)	79.2 (47.1)	146.9 (83.1)	127.5 (78.2)
Week 16 mean (SD)	101.6 (64.7)	27.5 (35.4) p = 0.0001	28.3 (34.8) p < 0.0001
Week 16 number (proportion) < 15 peak	0/15	5/12 (0.42) p = 0.0066	8/15 (0.53) p = 0.0012
EREFS (Total)			
Baseline mean (SD)	10.7 (3.8)	9.9 (4.8)	9.7 (3.9)
Week 16 mean (SD)	10.4 (4.7)	5.8 (4.9) p = 0.0026	5.3 (3.7) p = 0.0016
DSD Composite Score			
Baseline mean (SD)	32.7 (12.0)	26.9 (14.6)	29.3 (9.4)
Week 16 mean (SD)	31.0 (18.1)	25.6 (17.8) p = 0.8284	16.9 (19.0) p = 0.0547

DSD = Daily Symptom Diary; EREFS = EoE Endoscopic Reference Score; hpf = high-powered field; SD = standard deviation.

[Esophageal Eosinophil Counts, EREFS, and DSD Score in the Steroid-Refractory Subgroup]

OP133   FIRST-LINE THERAPEUTIC OPTIONS AND EFFECTIVENESS RATES IN EUROPEAN PATIENTS WITH EOSINOPHILIC ESOPHAGITIS: INITIAL RESULTS FROM THE *EOE CONNECT* REGISTRY

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Introduction: Eosinophilic esophagitis (EoE) is a chronic immune-mediated inflammatory esophageal disorder characterized by symptoms of esophageal dysfunction and dense eosinophil-predominant infiltration. EoE constitutes a particular non-IgE-mediated food allergy; avoiding specific food triggers is the only therapy that targets the cause of the disease. Limitations from dietary therapy hampering its implementation in clinical practice promoted the use of anti-inflammatory drugs, mainly swallowed topic steroids and proton-pump inhibitors (PPI) as first-line therapies for EoE patients. Comparative studies among available options are lacking. The *EoE CONNECT* registry resulted from the UEG Link Award program is a suitable way to document and understand how new patients diagnosed from suffering EoE are being managed in Europe.

Aims and Methods: To describe the use and effectiveness of diets, drugs, esophageal dilation and its combinations as first-line therapies for children and adults with EoE and to identify potential variables that influence the choice of therapy. Initial therapy in patients diagnosed with EoE from *EoE CONNECT* registry (a prospectively maintained registry of EoE patients from EUREOS) were analysed; effectiveness was defined in terms of histologic response and symptomatic improvement. Demographic and clinical variables were considered to identify on decision-determining factors. Frequency tables were generated for each treatment category while contingency tables were analysed by chi-square test using GraphPad software.

Results: 352 patients (186 male) were recruited at 8 centers in Spain and 1 in Italy. PPIs were the preferred option for first-line therapy (69.3%), followed by dietary interventions (16.5%) and topical steroids (fluticasone propionate in all cases) (9.1%), whereas endoscopic dilation (1.4%) and combination therapy (3.7%)

were rarely prescribed. Within PPI drugs, omeprazole and rabeprazole were the most (49%) and the least (2.7%) frequently prescribed drugs, respectively. As for dietary options, empiric elimination diets (EED) were the most commonly chosen alternative (78.3%), with the six-food elimination diet representing 46.8% of them. A complete symptomatic improvement was more frequently achieved after an EED (61.1%) while PPI displayed the highest ratio of no response (28.4%). Topic steroids were the most effective option to achieve histologic response (69.2%), but they were assessed in only 13 patients. Overall, PPIs and EED achieved some degree of histologic response in 54% and 51.2% of patients, respectively.

Age was identified as an explicative factor for treatment choice: EED were the most common option for children and teenagers (25.3%) while PPI use increased with age, reaching a highest rate in patients over 50 years-old (82.1%). Severity of symptoms revealed a significant explicative factor, with PPIs constituting the preferred therapy in 88.6% of patients with any degree of dysphagia, while EED was the first therapy prescribed in 29.8% of non-dysphagic patients at the moment of treatment initiation (p < 0.001). Finally, Spanish patients received dietary therapy more frequently than Italian ones (p < 0.05), who doubled the use of topic steroid after diagnosis. Differences were also observed among hospitals in Spain (p < 0.001).

Conclusion: PPI therapy is the preferred first-line option for EoE patients in Europe, despite of a high rate of absence of clinical response. Patients' age and severity of symptoms determined the choice of therapy. Efforts are needed to harmonize the treatment of EoE patients to reduce variability in clinical management.

Disclosure: Nothing to disclose

TUESDAY, OCTOBER 23, 2018   08:30–10:00
Help! I've got a bleeder! – Room K_____

OP134   APPROPRIATE USE OF RED BLOOD TRANSFUSION IN ACUTE LOWER GASTROINTESTINAL BLEEDING

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Introduction: Unnecessary blood cell transfusion (RBCT) increases the risk of side effects and the cost of the treatment of gastrointestinal bleeding, without providing benefits.

Aims and Methods: We aimed to assess the appropriateness of RBCTin acute lower gastrointestinal bleeding (LGB).

This was a retrospective study from January 2013 to June 2017 at a university tertiary care hospital. Patients with acute LGB were identified using the International Classification of Diseases (9th Revision) and Clinical Modification codes for admission diagnosis. A *transfusion episode* was defined as the interval between the prescription of RCBT and completion of its administration.

The following variables were defined for each transfusion episode:

● *Appropriateness of the RBCT prescription:* the prescription was evaluated with restrictive criteria, based on pre-transfusional hemoglobin (Hb) and the clinical characteristics of each patient in accordance with the recommendations of the AABB (American Association of Blood Banks): a threshold of Hb ≥7 g/dL in stable patients, and one of Hb ≥8 g/dL in patients with stable coronary and cerebrovascular disease, hemodynamic instability or cardiac failure.

● *Appropriateness of the RBCT volume:* over-transfusion was defined when post-transfusion Hb levels were ≥2 g/dL above the relevant Hb transfusion threshold for each particular RBCT indication. The number of red blood cell (RBC) units over-transfused was estimated as the sum of the differences between actual and target post-transfusion Hb for each transfusion episode, assuming that one RBC unit increased theHb level by 1 g/dL. Finally the number of transfusion episodes with use of one unit of RBC ("1-in-1 transfusion") was considered.

Patients with massive hemorrhage, previous transfusion < 90 days, acute coronary syndrome, symptomatic peripheral vascular disease or stroke < 90 days were excluded.

Results: A total of 407 consecutive patients with LGB were identified 106 of whom (26%) were transfused. We included 115 transfusion episodes in 74 patients (18.2%) with a total of 206 RBC units transfused. Median age was 82.6 years; 59 (79.4%) of patients were over 70, and 54.1% were men.

75 transfusion episodes (65.2%) were appropriate. Over-transfusion occurred in 34 episodes (29.6%). A "1-in-1 transfusion" was performed in only 25 (21.7%) transfusion episodes. The number of over-transfused RBC units was 69 (33.5%). Table 1 summarizes the characteristics of patients and transfusional episodes.

Conclusion: RBCT in LGB is inadequate in a third of the cases due to over-transfusion, caused by an inappropriate assessment of the relevant Hb threshold of each patient. More measures should be implemented to increase the appropriateness of RBCT.

Patients	74
Male	40 (54.1%)
Age (years Median/> 70 years	82.6/59 (79.7%)
Shock (SBP < 100 bpm + heart rate > 100 bpm)	8 (10.8%)
Charlson index >3	51 (68.9%)
Diagnosis: Diverticular/angyodisplasia/ no diagnosis/Ischemic colitis	22 (29.7%)/20 (27. %)/ 10 (13.5%)/6 (8.1%)
Treatment: Antivit K/ acetylsalicilic acid/selective serotonine reuptake/ NSAID/Clopidogrel/Direct oral antic-oagulants/proton pump inhibitors	27 (36.5%)/33 (44.6%)/ 11 (14.9%)/11 (14.9%)/ 7 (9.5%)/5 (6.8%)/54 (73%)
N° of transfusional episodes	115
Total RBC units transfused. Median. (1/2/3)	206. (21.7%/ 77.4%/0, 9%)
Appropiateness of transfusion	75 (65.2%)
Over transfusion	34 (29.6%)
Total over-trasfused RBC units	69 (33.5%)
Pre-trasfusional Hb (gr /dL) (<6/ 6-6.9/ 7-7.9/8- 8.9/>9)	(14.8%/20%/36.5%/27.8%/ 0.9%)

[Table 1: Characteristics of patients and transfusional episodes]
Disclosure: Nothing to disclose

References

1. Sadana D, Pratzer A, Scher LJ, et al. Promoting HighValue Practice by Reducing Unnecessary Transfusions With a Patient Blood Management Program. *JAMA Intern Med.* 2018 Jan 1; 178(1): 116–122.
2. Carson JL, Guyatt G, Heddle NM. et al Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. *JAMA.* 2016 Nov 15; 316(19): 2025–2035.

OP135   RISK OF POST-POLYPECTOMY BLEEDING WITH UNINTERRUPTED CLOPIDOGREL THERAPY: AN INDUSTRY-INDEPENDENT, DOUBLE-BLIND, RANDOMIZED TRIAL

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Introduction: Current guidelines recommend clopidogrel to be interrupted for at least 5 to 7 days before polypectomy. We investigate whether uninterrupted clopidogrel therapy will increase the risk of post-polypectomy bleeding.
Aims and Methods: In this double-blind randomized trial, we screened for patients receiving clopidogrel due to cardiovascular disease who required polypectomy. Patients were instructed to stop taking their prescriptions of clopidogrel 7 days before colonoscopy and were randomized to 7 days of clopidogrel (75mg daily) or its placebo daily until the morning of colonoscopy. All patients resumed their usual prescriptions of clopidogrel after colonoscopy. Primary endpoint was delayed post-polypectomy bleeding defined as rectal bleeding starting after the colonoscope has been retracted from the anus to 30 days after the procedure, with hypotension, a decrease in hemoglobin of ≥ 2 g/dL from baseline, requirement of transfusion, prolonged hospitalization, hospitalization, and or hemostatic intervention. Secondary endpoints were immediate post-polypectomy bleeding and serious cardiothrombotic events. Immediate post-polypectomy bleeding was defined as bleeding at the time of polypectomy that persisted despite continuous irrigation with diluted epinephrine solution for 5 minutes. Serious cardiothrombotic events were defined as non-fatal myocardial infarction, non-fatal stroke, or death from a vascular cause within 6 months of colonoscopy.
Results: A total of 387 patients received colonoscopy of who 216 required polypectomy: 106 patients in uninterrupted clopidogrel group, 110 patients in interrupted clopidogrel group. The cumulative incidence of delayed post-polypectomy bleeding was 3.8% (95% CI 1.4% – 9.7%) in the uninterrupted clopidogrel group and 3.6% (95% CI 1.4% – 9.4%) in the interrupted clopidogrel group (log-rank test p = 0.945). Immediate post-polypectomy bleeding (8.5% versus 5.5%, p = 0.380) and cardiothrombotic events (1.5% versus 2%, p = 0.713) were noted.
Conclusion: Contrary to current guidelines, our study does not show any clinically meaningful increase of post-polypectomy bleeding with uninterrupted clopidogrel therapy in patients undergoing polypectomy. This study was supported by the Research Grant Council of Hong Kong [Grant number: 460912].

Characteristic	Uninterrupted clopidogrel (n = 106)	Interrupted clopidogrel (n = 110)
Male sex- no. (%)	88 (83.0)	89 (80.9)
Age (year)- mean (SD)	62.0 (8.3)	62.9 (8.2)

(continued)

Continued

Characteristic	Uninterrupted clopidogrel (n = 106)	Interrupted clopidogrel (n = 110)
ASA grading 1,2,3,4 – no. (%)	0, 34 (32.1), 72 (67.9), 0	0, 33 (30.0), 77 (70.0), 0
Concomitant aspirin use – no. (%)	84 (79.2)	86 (78.2)
Total polyps removed	232	217
Polyp number per patient- mean (SD)	2.2 (1.5)	2.0 (1.5)
Polyp size (mm)- mean (SD)	4.7 (3.1)	4.6 (2.8)
Polyp size- no (%) < 5mm, 5-9mm, $\geq$ 10mm	144 (62.1), 67 (28.9), 21 (9.1)	132 (60.8), 71 (32.7), 14 (6.5)
Largest polyp removed- mm	20.0	18.0
Polyp morphology- no (%) Sessile, Pedunculated, Flat	195 (84.1), 23 (9.9), 14 (6.0)	180 (82.9), 13 (6.0), 24 (11.1)
Polypectomy technique- no (%)		
Cold biopsy	81 (34.9)	72 (33.2)
Hot biopsy	20 (8.6)	24 (11.1)
Cold snare	24 (10.3)	15 (6.9)
Hot snare	107 (46.1)	106 (48.8)

[Characteristics of patients and polyps]
Disclosure: Nothing to disclose

OP136   CAN PROPHYLACTIC ARGON PLASMA COAGULATION REDUCE DELAYED POST-PAPILLECTOMY BLEEDING? A PROSPECTIVE RANDOMIZED MULTICENTER TRIAL

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Introduction: Endoscopic post-papillectomy bleeding usually occurs in 3 to 20% of cases or higher prevalence. Moreover, delayed post-papillectomy bleeding within 1 week is also problematic. However, there is no definite guideline or consensus for prevention or reduction of delayed post-papillectomy bleeding. Additive role of prophylactic argon plasma coagulation (APC) after papillectomy was not defined.
Aims and Methods: The aim of this study was to evaluate the efficacy of prophylactic APC to minimize delayed post-papillectomy bleeding and reduce the recurrence or persistence of residual tumors.
A prospective randomized study was performed at 6 tertiary referral centers. Patients with ampulla of Vater adenoma were enrolled and followed from January 2016 to March 2018, and were randomized to either the prophylactic APC or non-APC group. Endoscopic papillectomy was performed using a conventional snaring papillectomy method without submucosal injection. Then, the prophylactic APC group underwent APC on the resection margin. Immediate post-papillectomy bleeding needing hemostasis was not included. On the next day after papillectomy, all patients underwent follow-up duodenoscopy to identify post-papillectomy bleeding and followed up with duodenoscopy at 1, 6, and 12 months. The main outcome measurements were delayed (> 24 h) post-papillectomy bleeding rate and tumor persistent rate between 2 groups.
Results: In total, 48 patients underwent endoscopic papillectomy. Delayed bleeding rates in the prophylactic APC and non-APC groups were 33.3% (8/24) and 16.7% (4/24), respectively (p = 0.336). Tumor persistence at 1 month did not differ between the 2 groups (8.3% vs. 4.2%, p = 0.401). However, both groups did not have tumor recurrence at 6 months (0/24 and 0/24). The mean tumor length and width were 11 and 12 mm in the prophylactic APC group, and 13.6 and 12.7 mm in the non-APC group. En-bloc resection rates in the prophylactic APC and non-APC groups were 83.3% (20/24) and 95.8% (23/24), respectively. Positive resection margin rates in the prophylactic APC and non-APC groups were 66.7% (16/24) and 33.3% (8/24), respectively (p = 0.076). Post-procedure pancreatitis rates were 20.7% (5/24) in the prophylactic APC and 37.5% (9/24) in the non-APC groups, respectively (p = 0.295). The severity of pancreatitis did not differ between the 2 groups. There were no procedure-related mortalities or serious complications.

Conclusion: The prophylactic APC may be not effective in reducing delayed post-papillectomy bleeding or remnant tumor ablation. The prophylactic APC seemed to have a higher tendency of delayed post-papillectomy bleeding without statistical difference, and might be not have additive role on tumor persistent or ablative effect during short-term follow-up.
Disclosure: Nothing to disclose

OP137 EUS-GUIDED MULTI-MODALITY TREATMENT OF PERIPANCREATIC PSEUDO-ANEURYSMS

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Introduction: Pseudoaneurysms may occur in both acute and chronic pancreatitis. Gastrointestinal bleeding is the most common presentation after rupture. Pseudoaneurysm can be of different size and can have different wall thickness. Managing peripancreatic pseudoaneurysms is complex and challenging. Failure in radiological intervention is followed by surgery. We present a series of Endoscopic ultrasound (EUS) guided treatment of 6 patients with pseudoaneurysms involving splenic artery (1 patient), gastroduodenal artery (GDA) (3 patients) and hepatic artery (2 patient)
Aims and Methods: All 6 patients were male. 4 patients presented with gastrointestinal bleeding. 3 patients had chronic pancreatitis while 2 were associated with acute pancreatitis. Initial selection of treatment by EUS was made by size and wall of pseudoaneurysm which can be thin walled or thick walled. As per inner diameter, they can be of 3 types: small ($<$2cm), large (2-4 cm) or giant ($\geq$ 4cm). There were 3 giant, 1 large and 2 small pseudoaneurysms. 4 had thick wall while 2 had thin wall. Different modalities of EUS guided treatment were used singly or in combination. These modalities were coils, thrombin and glue. The sizes of coils were dependant on the size of aneurysm. It was inserted with 19 Gauge needle. Thrombin was injected in boluses of 500 IU per ml using 25 Gauge needle. Cyanoacrylate glue was injected around 1 or 2ml using 22 Gauge needle. 2 thin walled pseudoaneurysm were treated with thrombin injection. 1 giant splenic artery pseudoaneurysm was treated with combination of coil, thrombin and glue. 1 large GDA pseudoaneurysm was treated with combination of coils and thrombin. 1 small thick wall GDA pseudoaneurysm was treated with 2 ml of glue injection. 1 giant hepatic artery pseudoaneurysm was treated with 2 sessions of coiling.
Results: There were no major complications. All 6 patients had complete or near complete occlusion of pseudoaneurysm which was evaluated by abdominal ultrasound and endoscopic ultrasound. Multiple sessions were required in 4 patients while 2 were treated with single session.
Conclusion: ● EUS guided treatment of pseudoaneurysms appears as effective, feasible and safe technique with many choices of obliteration i.e. Coil, thrombin and glue at the disposal of endosonographer
● It can ensure complete obliteration of pseudoaneurysm with no major complications
● It is evolving technique which requires further standardization, more studies and comparative studies with interventional radiology
● The operator should be familiar with all three modalities of treatment i.e. Coil, thrombin and glue
● Whether single or multimodality EUS guided treatment will be decided by operator preference, type of aneurysm, local availability and further studies
Disclosure: Nothing to disclose

OP138 HEMOSTATIC ENDOSCOPIC TREATMENT OF GASTRODUODENAL VARICES BY CHEMICAL GLUE MIXED WITH GLUCOSE SERUM: EXPERIENCE OF HASSAN II UNIVERSITY HOSPITAL CENTER

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Introduction: Gastrointestinal haemorrhage by rupture of gastroduodenal varices has an incidence of 3 to 30% and represents approximately 10% of all upper gastrointestinal haemorrhages associated with portal hypertension (PHT). The aim of this work is to evaluate the therapeutic efficiency and complications of diluted chemical glue injection in glucose serum as an endoscopic haemostasis technique.
Aims and Methods: This is a retrospective study of 24 patients compiled between January 2012 and April 2018. All patients were admitted with upper gastrointestinal bleeding. They all had benefited from a gastroscopic fibroscopy that had objectified bleeding caused by rupture of gastroduodenal varices. Methacryloxysulfolane-associated n-butyl-2-cyanoacrylate (Glubran 2) was prepared with glucose serum. The endoscopic treatment performed under sedation, consists of the injection of chemical glue at the level of gastroduodenal varices.
Results: The average age of our patients was 51 years [23 years -76 years]. A female predominance was noted, with a sex ratio F/M: 2.4. Glucose injection into

gastric varices was performed in 22 patients (91.7%) of whom 12 had GOV2 (55%), 8 had IGV1 (36%), 2 had GOV1 (9%). Ectopic duodenal varicose veins were found in 2 patients (8.3%). The injection was performed at 1 or 2 sites of the ruptured varice. The initial haemostasis was obtained in 100% of cases. Recurrence was noted in 2 patients. No immediate or delayed complication was noted.
Conclusion: Our results confirm that endoscopic hemostatic treatment of hemorrhages from ruptured gastroduodenal varices by chemical glue diluted in glucose serum is effective and less expensive compared to dilution in Lipiodol which is not always available in our context.
Disclosure: Nothing to disclose

OP139 EUS-GUIDED THROMBOLYSIS OF PORTAL VENOUS SYSTEM

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Introduction: Portal venous system (PVS) is one of the most inaccessible systems of the body. Acute thrombosis of portal venous system, resulting in mesenteric ischemia has a high morbidity and mortality. Endoscopic ultrasound (EUS) guided access to the PVS is possible. We report EUS guided thrombolysis of acute portal venous system thrombosis in 6 cases.
Aims and Methods: Between December 2015 and march 2018, all symptomatic patients presenting with acute thrombosis of portal venous system with/ without mesenteric ischemia were included in the study. Informed consent was taken. Diagnosis was achieved by clinical evaluation (abdominal pain, vomiting, abdominal distension) and CT abdomen (thrombus in PVS with/ without abnormal thickening of ischemic bowel wall). Only patients without indication for surgery, i.e. bowel infarction, bowel perforation, were included. All patients had variable extent of acute thrombus along with dilated portal venous system and clinical features of impending mesenteric ischemia. All patients received intravenous fluids, antibiotics and low molecular weight heparin (LMWH). Patients without clinical improvement to anticoagulation therapy at 48 hours were taken for EUS guided thrombolysis.
Entry into the portal venous system was possible by EUS-guided puncture and injection of streptokinase was given as continuous catheter thrombolysis with 30000 unit/hour in three cases. Bolus injections of 50000 units were given in portal vein, splenic vein and superior mesenteric vein in 3 cases. For bolus injection, the splenic vein was punctured from body of stomach, the portal vein was punctured from duodenal bulb and the superior mesenteric vein (SMV) was punctured from descending duodenum. For continuous catheter thrombolysis SMV was punctured through the pancreas with a 22 gauge EUS- FNA needle. A .018 inch guide wire was placed into a tributary of SMV. A tapered tip cannula was advanced over the wire and cannula was positioned in the tributary of SMV. The scope was removed while leaving the cannula in place, the cannula was routed through the nose and a syringe pump was fitted for infusion of thrombolytic agent. The thrombolysis was continued for 72 hours to 10 days depending on symptom improvement. Regular follow-up was done to monitor for GI bleed. The thrombolysis catheter was removed in all cases under endoscopic guidance to monitor for a possible bleed from catheter site.
Results: *Procedure related:* Technical success as defined by successful catheter placement in PVS was achieved in all patients (100%). During hospital course, 1 patient had catheter site bleed while catheter was *in situ*, for which hemostasis was achieved by inflating an enteroscope assisting device of balloon, fitted over the scope. 1 patient had mild ooze on catheter removal which was controlled by inflating an enteroscope assisting device of balloon fitted over the scope. 1 patient developed splenic infarct on day 7. Despite infarction, thrombolysis could be continued till the resolution of ileus on day 10.
Patient related: All patients tolerated the procedure well. All patients had resolution in pain and ileus. There was no mortality.
There was complete resolution of thrombus in 4 cases with partial resolution in 2 cases
Conclusion: EUS-guided thrombolysis should be considered in life-threatening acute PVS thrombosis. Multicentre trials in larger number of cases are required and comparison with interventional radiology methods needs to be planned. We require dedicated accessories to ensure continuous delivery.
Disclosure: Nothing to disclose

TUESDAY, OCTOBER 23, 2018   08:30–10:00
TSTM: Mechanisms of intestinal inflammation – Room 1.61/1.62_____

OP140   FOOD-DERIVED BIOACTIVE PEPTIDE LUNASIN EXERTS AN IMMUNOMODULATORY ROLE IN THE HEALTHY HUMAN INTESTINAL MUCOSA

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Introduction: The gastrointestinal mucosa represents the main interface between dietary components and the organism. Lunasin is a 43-amino acid peptide naturally present in soybean protein with a variety of biological functions demonstrated by *in vitro* assays, cell cultures and animal models. Nevertheless, its physiological relevance in human primary intestinal cells has been scarcely investigated.

Aims and Methods: Our aim, therefore, was to evaluate the *ex vivo* biological activity of peptide lunasin in the healthy human intestinal mucosa. Peptide was obtained by chemical synthesis. Colonic biopsies from healthy controls were conditioned with peptide lunasin (5, 50, and 200 μM), both in the presence and absence of pro-inflammatory lipopolysaccharide (LPS). The cytokine milieu (IL-1β, IFN-α2, IFN-γ, TNF-α, MCP-1, IL-6, IL-8, IL-10, IL-12p70, IL-17A, IL-18, IL-23, and IL-33) was subsequently assessed on the culture supernatants following overnight culture. The stability and/or modification of peptide during culture was evaluated by liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS).

Results: Peptide lunasin exerted immunomodulatory effects on the human intestinal mucosa determined by changes on the global cytokine milieu. While lunasin 5 μM was not biologically active, it regulated the cytokine profile at 50 μM expanding the production of IL-10 and IL-33 by intestinal mucosa. Moreover, at higher doses (lunasin 200 μM), this peptide lowered the production of IFN-γ, IL-6 and MCP-1, as well as enhanced an innate immune response characterized by induction of intestinal IL-1β and TNF-α cytokines. Nevertheless, this peptide did not modulate the global cytokine profile when intestinal mucosa was exposed to LPS. The response of colonic biopsies towards the conditioning with peptide lunasin was monitored by HPLC-MS/MS, confirming its presence during cultures.

Conclusion: Bioactive food peptides may exert physiological effects related to digestive health given their direct and continuous contact with immune mucosa. Peptide lunasin modulated in resting conditions the immune cytokine profile of the healthy intestinal mucosa. This peptide might represent, therefore, a novel agent as functional compound for the prevention of immune and inflammatory-mediated intestinal disorders.

Disclosure: Nothing to disclose

OP141   PREVENTIVE EFFECT OF SPONTANEOUS PHYSICAL ACTIVITY ON GUT-ADIPOSE TISSUE CROSS-TALK IN MICE MODEL MIMICKING CROHN'S DISEASE SUSCEPTIBILITY

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Introduction: Crohn's disease (CD) is a chronic inflammatory characterized from an aberrant immune response favoring by gut microbiota in genetically predisposed individuals and/or under the influence of environmental factors like a high-fat diet. In this context, CD is characterized by an abnormal ileal colonization by adherent-invasive *E. coli* (AIEC) and an expansion of mesenteric adipose tissue (AT). Currently, immunosuppressive or biological treatments used in CD are not curative and have many side effects. In this context, physical activity (AP) could be an attractive alternative therapy through its anti-inflammatory properties, its ability to effectively decrease TA and favorably modulate the gut microbiota composition.

Aims and Methods: The aim of this study is to analyze the preventive effect of spontaneous PA on gut-adipose tissue cross-talk in CEABAC10 mice exposed by AIEC bacteria after training. 36 male CEABAC10 mice were divided in spontaneous PA (WHEEL; n = 24) and the control group (CONT; n = 12) during 12 weeks. The distance and the speed performed in WHEEL group were weekly recorded. After this period, both groups were exposed to AIEC LF 82 for 6 days and were killed 4 days later. Animals were fed with high fat/high sugar diet (HF/HS) over all study duration and a per feeding was performed on CONT group. Body composition was analyzed by EchoMRI and the weighing of tissue was realized post-mortem. Glycemic control was evaluated through fasting glycaemia, insulinemia and an oral glucose tolerance test. The level of AT cytokines secretion (IL-6 and KC) was measured by ELISA. The expression of tight junction proteins (ZO-1 and occludin) was determined by western-blot and used as a marker of intestinal permeability. Gut microbiota was analyzed using 16S rRNA gene sequencing on an Illumina MiSeq Platform. Fecal short-chain fatty acids (SCFA) concentrations were determined using gas liquid chromatography.

Results: Over the 12 weeks, WHEEL group ran an average of 3.6 ± 0.4 km per day at an average speed of 8.5 ± 0.7 m.min^{-1}. The mean total mass in WHEEL group was lower compared to CONT from week 7 to the end of protocol (p < 0.05). Total fat mass at 12 weeks was inferior in WHEEL group compared to CONT group (p < 0.05). Before bacterial exposition, glycemic control (fasting glycaemia, insulinemia and plasma glucose OGTT responses) were not affected by spontaneous PA, however, the distance run and the speed were associated with lower fasting glucose and an increase of glucose tolerance (p < 0.05). Mesenteric AT was lower in WHEEL group, and a negative correlation was found between mesenteric AT and distance ran (r = −0.6, p < 0.05). Tight junction protein content increased with spontaneous PA. Beneficial and anti-inflammatory genera (Bifidobacterium and Lactobacillus) in CONT group decreased while the AP favors slimming-related genera (Oscillospira) and SCFA producers (Ruminococcus). Concomitantly, propionate and butyrate were higher in WHEEL group (p = 0.05).

Conclusion: Spontaneous PA favors a modification of the gut microbiota composition of CEABAC10 mice in response to HF/HS diet and bacterial exposition. This modification could be related to the decrease of total fat mass and more likely to the mesenteric AT reduction. These effects were greater when the average distance performed and the mean speed were higher. These preliminary results obtained in a rodent model could be expanded to patients with CD in therapeutic clinical protocols. Physical activity could then be considered in patients with CD in order to substantially improve their quality of life.

Disclosure: Nothing to disclose

OP142   SMALL INTESTINAL EPITHELIAL ENDOPLASMIC RETICULUM STRESS DRIVES A MICROBIOTA-INDEPENDENT IGA RESPONSE THAT PREVENTS FROM EXTENSIVE SMALL INTESTINAL INFLAMMATION

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Introduction: Genome-wide association studies identified many risk genes for inflammatory bowel disease (IBD).[1] Amongst these, many genes encode proteins that are involved in proteostasis, including endoplasmic reticulum (ER) stress. Understanding how such defects in proteostasis induce anti-inflammatory protective responses could lead to novel therapy.[2] An important mechanism of protection in the intestine is the production of Immunoglobulin A (IgA) by plasma cells.[3] Interestingly, plasma cell accumulation around the intestinal crypts, so-called basal plasmacytosis, is a phenomenon often observed in inflammatory bowel disease.

We set out to investigate whether ER stress induces protective IgA responses.

Aims and Methods: To model the role of ER in the intestine, mice were developed in which X-box binding protein-1 is deleted specifically in the intestinal epithelium ($Xbp1^{\Delta IEC}$). IgA deficient (IgA$^{-/-}$), B cell deficient μMT mice, and TCRβ deficient (TCRβ$^{-/-}$) mice were crossed to $Xbp1^{\Delta IEC}$ mice to generate double KO animals. PP-deficient animals were generated by injecting pregnant females at gestational day 13.5 with anti-IL7Rα, which abrogates PP ontogeny. Germ free (GF) $Xbp1^{\Delta IEC}$ mice were generated as previously described.

Intestinal lamina propria (LP), Peyer's patch (PP) and peritoneal immune cell populations were studied using flowcytometry and immunohistochemistry. Inflammation was assessed on H&E stained tissue sections from small intestines, by an expert pathologist, as previously described.[4]

Results: $Xbp1^{\Delta IEC}$ mice exhibited inflammation particularly in the terminal ileum, as previously described.[5] Interestingly, $Xbp1^{\Delta IEC}$ mice had significantly increased levels of LP IgA+ plasma cells and increased luminal and serum IgA as compared to littermate controls. IgA protected from inflammation as IgA−/−$Xbp1^{\Delta IEC}$ mice or B cell deficient μMT-$Xbp1^{\Delta IEC}$ mice had increased small intestinal inflammation.

IgA+ plasma cells were not derived from Peyer's patches (PP), as no increase in either Fas+GL7+germinal center B cells or CXCR5+PD1+T follicular helper cells was observed. In addition, PP deficient $Xbp1^{\Delta IEC}$ mice or TCRβ−/−$Xbp1^{\Delta IEC}$ mice had a similar increase in LP IgA+ plasma cells compared to PP deficient and TCRβ+/+littermate controls. Instead, a significant increase in peritoneal B1 cells was observed, an innate-like limb of the B cell system. Interestingly, the IgA response occurred independent of the presence of inflammation or microbiota as germ free (GF) $Xbp1^{\Delta IEC}$ mice, that lack microbes and do not develop inflammation, had increased levels of LP IgA+plasma cells as well.

Conclusion: We here show that innate-like, peritoneal B1 cell-derived IgA responses are under the control of epithelial ER stress. The IgA response is not induced in the Peyer's Patches and does not require T-cell help. It occurs independently of either microbes or inflammation making it a self-contained, host-derived response. We further show that such a response serves a critical role in protecting the mucosa and requires secretion of IgA into the lumen. We propose that this homeostatic function of epithelial ER stress is conceptually a novel and beneficial "eustress" response that is functionally opposed to its well-described involvement in pro-inflammatory pathways.

Disclosure: Nothing to disclose

References

1. A. Kaser, S. Zeissig, R. S. Blumberg, Inflammatory bowel disease. *Annu Rev Immunol* 28, 573–621 (2010).
2. J. Grootjans, A. Kaser, R. J. Kaufman, R. S. Blumberg, The unfolded protein response in immunity and inflammation. *Nat Rev Immunol* 16, 469–484 (2016).
3. C. Gutzeit, G. Magri, A. Cerutti, Intestinal IgA production and its role in host-microbe interaction. *Immunol Rev* 260, 76–85 (2014).
4. T. E. Adolph et al., Paneth cells as a site of origin for intestinal inflammation. *Nature* 503, 272–276 (2013).
5. A. Kaser et al., XBP1 links ER stress to intestinal inflammation and confers genetic risk for human inflammatory bowel disease. *Cell* 134, 743–756 (2008).

OP143 CATESTATIN AMELIORATES INTESTINAL INFLAMMATION BY ORCHESTRATING TIGHT JUNCTION DYNAMICS *VIA* STAT3-DEPENDENT PATHWAY

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Introduction: Inflammatory bowel disease (IBD) is characterized by aberrant regulation of tight junctions (TJ), which leads to intestinal barrier defects. Signal transducer and activator of transcription 3 (STAT3) and interleukin (IL)-8/18 have a pivotal role in intestinal epithelial cells (IEC) for restoration of gut mucosal barrier defect during colitis. Previously, we showed that Catestatin (CST), a chromogranin-A (CHGA)-derived peptide, regulates immune communication and STAT-3 in the gastrointestinal tract.

Aims and Methods: Here, we aimed to investigate the effect of CST on IEC functions during the development of colitis using human biopsies from patients with active ulcerative colitis (UC), human colonic epithelial cells, and an experimental model of UC (dextran sulfate sodium [DSS]-colitis). The expression of CST and its correlation with mRNA levels of TJ proteins (Claudin-1 [*CLDN1*], zonula occludens-1 [*ZO1*], occludin [*OCLN*]), epithelial-associated cytokines (*IL8, IL18*), and *STAT3* were quantified in patients with UC using ELISA and RT-qPCR. Acute colitis (5% DSS, 5 days) was induced in C57BL/6 mice. Preventive CST (1.5 mg/kg/day) treatment or vehicle started 1-day before colitis induction and lasted for 5-days. Disease activity index (DAI), TJ proteins (Cldn1, Zo1, Ocln), and IL-18 were determined. Caco-2 epithelial cells were treated with CST (100 ng/ml) for 24 h in presence or absence of STAT3-inhibitor (STATTIC) then exposed for LPS (1 mg/ml) or 5 % DSS for an additional 24 h. Proliferation, viability, and migration of caco-2 cells were quantified using proliferation, MTT and wound healing assay. Levels of phospho-STAT3 (p-STAT3), TJ proteins (CLDN1, ZO1, OCLN), IL-8, and IL-18 in LPS- & DSS-stimulated caco-2 cells were quantified.

Results: In UC patients, level of CST, TJ proteins (CLDN1, ZO1, OCLN), and STAT3 are significantly decreased and IL-8, IL-18 increased when compared with healthy individuals. Colonic expression of CST showed a strong positive linear relationship with TJ proteins (CLDN1, ZO1, OCLN) and STAT3, and a strong negative correlation with IL8 and IL18. Experimentally, CST reduced the onset and severity of colitis and the colonic levels of IL-18, and maintained colonic expression of *Cldn1, Zo1, Ocln*, and enhanced the level of phosphorylated (p)-STAT3. *In vitro*, CST significantly increased proliferation, viability, and migration of caco-2 cells in naïve conditions and in response to LPS- & DSS-induced epithelial injury. CST enhanced the p-STAT3 in both LPS- & DSS-stimulated epithelial cells. CST also reducedthe release of IL-8/IL-18 and maintained the expression of TJ proteins in response to LPS and DSS. In parallel, the presence of STATTIC, the beneficial effect of CST on IL-8 and IL-18 release and expression of *CLDN1, ZO1, OCLN* was abolished.

Conclusion: Here, we extend our previous findings by showing that CST is associated with epithelial functions in human patients suffering from UC and we provide additional experimental insights into how CST regulates intestinal homeostasis and mucosal wound healing via the STAT3-dependent pathway. Targeting CST in IEC should be a promising therapeutic approach in situations when the intestinal epithelial cell homeostasis is disturbed in UC patients.

Disclosure: Nothing to disclose

OP144 HPMSCS COTRANSPLANTED WITH CHITOSAN-IGF-1C HYDROGEL AMELIORATE TNBS-INDUCED COLITIS BY SECRETING PGE2

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Introduction: Mesenchymal stem cells (MSCs) transplantation is a promising strategy for inflammatory bowel disease (IBD). However, low cell retention and engraftment after transplantation diminish the clinical application of MSCs in IBD. In our previous report, a synthesized bioactive hydrogel by immobilizing the C domain peptide of insulin-like growth factor-1(IGF-1C) on chitosan formed a hydrogel matrix which can refresh stem cells by mimicking niche. Hence we aim to investigate whether co-transplanting this hydrogel with human placenta-derived mesenchymal stem cells (hP-MSCs) into the damaged colon could ameliorate trinitrobenzene sulfonic acid (TNBS)-induced colitis and illustrate its mechanism.

Aims and Methods: Utilizing the lentivirus transfected into hP-MSC which steadily express fireflyluciferase (Fluc) and green fluorescent protein (GFP) thereby can be measured proliferation effect of CS-IGF-1C hydrogel for hP-MSCs and tracked by bioluminescence imaging (BLI) and histology, respectively. Colitis was induced with TNBS via enema, mesenteric injection of PBS, chitosan hydrogel, or chitosan-IGF-1C hydrogel with hP-MSCs or PBS without hP-MSCs were performed. After living imaging by BLI for measuring the survival of hP-MSCs and reactive oxygen species (ROS), intestinal tissues were collected for histopathologic analyses. Interleukin-1 (IL-1) and interleukin-6 (IL-6) were tested by real time PCR. Western blot and immunofluorescence analyses are conducted for detecting the phenotype of macrophages after transplantation. Enzyme linked immunosorbent assay (ELISA) was performed for testing PGE2 from the supernatant of hP-MSCs.

Results: Comparing with free hydrogel or chitosan hydrogel only, the CS-IGF-1C hydrogel significantly increased stem cell proliferation demonstrated by BLI. Moreover, in vivo studies indicated that CS-IGF-1C hydrogel promoted hP-MSCs survival confirmed by BLI and co-transplantation of CS-IGF-1C hydrogel with hP-MSCs ameliorated mice colitis dramatically: increased body weight decreasing IL-1, IL-6 and ROS, alleviated intestinal inflammation, achieved histological improvement compared with free hydrogel or chitosan hydrogel only. Additionally, CS-IGF-1C hydrogel could promote hP-MSC releasing PGE2, polarizing M2 macrophages accompanying expression of Interleukin-10 (IL-10), furthermore reducing the level of M1 macrophages *in vitro* and *in vivo*.

Conclusion: Topical application of CS-IGF-1C hydrogel implanted hP-MSCs significantly ameliorates mouse colitis via promoting these donor cells releasing PGE2, which polarizes M2 macrophages accompanying IL-10 expression. To our knowledge, this is the first report on co-transplantation with CS-IGF-1C hydrogel and MSCs on IBD as well as the local-injection as administration which improve the therapeutic effectiveness of MSCs on TNBS-induced colitis significantly. These data could benefit the expansion of application of MSCs transplantation on IBD treatment.

Disclosure: Nothing to disclose

References

1. *Gastroenterology*. 2018 Apr; 154(5): 1334–1342.e4.
2. *Lancet*. 2016 Sep 24; 388(10051): 1281–90.
3. *Gastroenterology*. 2015 Oct; 149(4): 918–27.e6.
4. *J Am Soc Nephrol*. 2016 Aug; 27(8): 2357–69.

OP145 POLYUNSATURATED FATTY ACIDS INDUCE FERROPTOTIC INFLAMMATION IN THE INTESTINE

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Introduction: Crohn's disease (CD) is a chronic remittent inflammatory condition of the gastrointestinal tract that arises from a deranged interplay of the immune system, microbiota and unknown environmental factors in genetically susceptible hosts. GWAS studies recently revealed a genetic association of gluthatione peroxidase 4 (GPX4) with the development of CD (1). Reduced GPX4 activity leads to a form of iron-dependent regulated cell death that is termed ferroptosis. Recent findings linked ferroptotic cell death with incorporation of polyunsaturated fatty acids into biological membranes, including arachidonic acid (AA) (2). AA is contained within a western style diet and especially animal products. The consumption of these fatty acids paralleled the increased IBD incidence in the last decades. However, the role played by AA in intestinal inflammation is unknown.

Aims and Methods: In this study we aimed to investigate the influence of AA on intestinal epithelial cells, with reduced GPX4 expression evoked by siRNA silencing. For *in vivo* analysis we crossed $Gpx4^{flox/flox}$ (3) mice with *Villin-Cre*$^{+/-}$ mice to obtain $Gpx4^{flox/wt}$;*Villin-Cre*$^{+/-}$ ($Gpx4^{+/-IEC}$) mice. We investigated an inflammatory phenotype in *Gpx4*-deficient murine MODE-K small intestinal epithelial cells (IEC) and organoids from $Gpx4^{+/-IEC}$ mice upon AA treatment.

Results: IECs that were *Gpx4* silenced, showed increased lipid peroxidation and ferroptotic cell death which was aggravated by AA. Ferroptosis was paralleled by production of IL-6 and the IL-8 homologue CXCL1. Cytokine production and death were governed by ferric iron. Ferroptotic IECs also released damage associated molecular patterns that induced neutrophil chemotaxis. Organoids from $Gpx4^{+/-IEC}$ mice showed diminished viability and a distorted morphology upon treatment with AA and ferric iron. Moreover, $Gpx4^{+/-IEC}$ mice that were orally challenged with AA and ferric maltol showed neutrophilic infiltration in the proximal small intestine as well as increased CXCL-1 expression, while wildtype littermates were unaffected. Treatment with a-tocopherol protected $Gpx4^{+/-IEC}$ mice from neutrophilic inflammation.

Conclusion: Our data shows that AA and ferric iron promote lipid peroxidation and cytokine release in GPX4-deficient IECs which trigger neutrophilic inflammation in mice with reduced GPX4 levels in the intestinal epithelium. As such, we identified an environmental trigger within a western diet that instigates intestinal inflammation in susceptible hosts.

Disclosure: Nothing to disclose

References

1. L. Jostins et al., Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* 491, 119–124 (2012).
2. V. E. Kagan et al., Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis. Nat. *Chem. Biol.* 13, 81–90 (2017).
3. S. E. Yoo et al., Gpx4 ablation in adult mice results in a lethal phenotype accompanied by neuronal loss in brain. *Free radical biology & medicine* 52, 1820–1827 (2012).

OP146 EMERGING ROLE OF MIRNA-320 INDUCED BY IL-33 IN PROMOTING RECOVERY AND GUT MUCOSAL WOUND HEALING AFTER ACUTE COLITIS

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Introduction: It is now well-established that IL-33 and its receptor, ST2, are important factors in the pathogenesis of IBD. However, animal studies to uncover their mechanistic function(s) during gut mucosal inflammation have yielded ambiguous results.

Aims and Methods: The aim of our study was to characterize the precise role of the IL-33/ST2 axis following acute epithelial injury and mucosal repair in DSS-induced colitic mice. 3% DSS was administered for 5d to C57/BL6 wild-type (WT), *Il-33*$^{-/-}$ and *St2*$^{-/-}$ mice. DSS was then replaced with drinking water for 2 wks (recovery period). Another group of WT mice received DSS for 5d and IL-33 (33ug/kg, i.p.) or vehicle (VEH) every other day during the recovery period. Mice were sacrificed either after DSS challenge or after 1 or 2 wks of recovery. Control mice (CT) not exposed to DSS were sacrificed at similar time points. Body weight, occult blood test, and stool consistency were measured daily to calculate the Disease Activity Index (DAI), and endoscopic and histological evaluation of colons were performed using established scoring systems. IHC, qPCR and western blot were done on full-thickness colons for IL-33 and ST2 localization, mRNA expression and evaluation of protein isoforms, respectively. Intestinal epithelial cells (IECs) were isolated from colitic mice treated with IL-33 or VEH during recovery and processed for qPCR. Caco-2 cells were grown to 80% confluency, cultured with or without rhIL-33, collected after 6 and 24h, and evaluated for cell proliferation by XTT assay and scratch assay. Another group of cells was collected after 6h, RNA was extracted and submitted for microarray analysis. Results were tested at qPCR. Based on these data, *MIR320* was selectively knocked-down trough reverse transfection in Caco-2 cells. Control Caco-2 were processed with transfection reagents only (Control). Cells were then cultured with rhIL-33 following the abovementioned protocol and evaluated at XTT and scratch assay.

Results: IL-33, ST2L and sST2 mucosal levels were elevated after DSS challenge and further increased after 1 week of recovery, before returning to baseline by 2 weeks of recovery *vs.* CT. IHC showed intense IL-33 and ST2 staining within the inflamed and ulcerated mucosa of DSS-treated mice. ST2 staining was more evident during the recovery phase following DSS, notably localized to IEC and SEMF in close proximity to areas of re-epithelialization. Both *Il33* and *St2* deficiency in mice reduced the severity of colitis after acute DSS, but interestingly dampened epithelial repair throughout the recovery period *vs.* WT. IL-33 treatment during recovery decreased endoscopic and histologic score, promoting mucosal healing, a faster body weight recuperation and disease activity amelioration *vs.* VEH. At XTT and scratch assay, IL-33 significantly increased cell proliferation and wound healing *vs.* untreated Caco-2 cells. Microarray analysis showed IL-33-mediated activation of intracellular proliferative pathways. In particular, IL-33 administration potently upregulated miR-320 *vs.* untreated cells. These results were confirmed at qPCR in both Caco-2 *vs.* untreated cells and IECs isolated from IL-33 treated mice *vs.* VEH. Specific knockdown of *MIR320* significantly decreased both epithelial proliferation and wound healing *vs.* Control at XTT and scratch assay, respectively.

Conclusion: Taken together, IL-33 can play a dichotomous role during gut mucosal inflammation, stimulates epithelial restitution and repair, and promotes overall recovery during colitis potentially through a mechanism involving upregulation of miR-320.

Disclosure: Nothing to disclose

TUESDAY, OCTOBER 23, 2018   08:30–10:00
Small bowel disorders – Room N2_____

OP147 CHRONIC INTESTINAL FAILURE: WHEN CHILDREN BECOME ADULTS

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Introduction: Major advances in recent years have resulted in improved survival for patients with chronic intestinal failure (CIF). There is very little data on the future of children that became adult with CIF.

Aims and Methods: The aim of our work was to describe this population since the creation of our center.

Methods: In an approved HPN centre for adults with a dedicated activity for CIF, we collected retrospectively all data related to patients treated with home parenteral nutrition during infancy (at least 4 years before transition to our centre) and transferred in our centre since 1984. We evaluated demographic data, social evolution and main complications at theadulthood. Results were expressed as median [±SD].

Results: Among a total of 870 HPN patients followed between 1984 and december 2017, 44 young adults (17F/27M) were transferred from 3 paediatric hospitals. Age of transition was 19 ± 2 years. The principal etiologies of CIF were short bowel syndrome (n = 18), CIPO (n = 21), mucosal disease (n = 5). At the end of follow up, defined as the last news or death, 7/44 patients had died (2 after intestinal transplantation, 3 after sepsis, 2 due to liver failure), 3/44 were weaned off PN (2 due to growth factors, 1 after intestinal transplantation), 33/44 were alive requiring HPN (6 ± 1.7 infusions/week; 2.2 ± 1.3l/day; 29 ± 13kcal/kg/day). Oral intake was 2000 ± 1085kcal/day but 9/44 presented remaining oral disorders. Seventeen/44 had a regular work (35 ± 6.5hours/week). 23 lived with their parents; 17 lived in partnership and 7 had at least one child.

Conclusion: Despite progress in survival and quality of life in HPN, many children who become adults stay with their parents and do not work. The transition requires probably a better social, educational and psychological preparation if we want to improve the future of these patients.

Disclosure: Nothing to disclose

OP148   OUTCOMES OF TEDUGLUTIDE TREATMENT AT 6 MONTHS IN ADULT PATIENTS WITH SHORT BOWEL SYNDROME AND CHRONIC INTESTINAL FAILURE: A NATIONWIDE FRENCH PROSPECTIVE OBSERVATIONAL COHORT STUDY

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Introduction: Short bowel syndrome with intestinal failure (SBS-IF) is a rare condition that requires parenteral support (PS). Pivotal trials with teduglutide (TED) in SBS-IF have demonstrated a PS volume reduction $\geq 20\%$ from baseline (BL) in 63% of treated patients at 6 months (M6). In France, TED has been available since October 2015, and initial results demonstrated an early response at M3 in 59% of treated patients. The objectives of the current analysis are to evaluate in the "real-world" setting the outcomes of treatment and to assess the predictive factors of response and of PS wean-off at M6 in adults with SBS-IF.
Aims and Methods: This is a French, multicenter, observational study looking at the characteristics and outcomes of all adult patients with SBS-IF who have initiated TED (N = 74). All patients on treatment for ≥ 6 months between October 2015 and September 2017 are included in this analysis (n = 54). Clinical response is defined as $\geq 20\%$ of PS volume reduction from BL at Week 24 of treatment. Descriptive summary statistics are presented as mean (range) values, and univariate analysis adjusting for nutritional variables (age, sex, body weight) have been conducted to identify predictors of response and of PS wean-off.
Results: 54 patients with SBS-IF were treated with TED (0.05 mg/kg/day) for ≥ 6 months. 22 (40.7%) were women, age was 52.3 years (range, 22−84) PS duration was 9.8 years (range, 0.5−31), PS days/week was 4.3 (range, 2−7), PS volume was 11,163 mL/week (range, 2000−38,500), and oral energy intake was 6347 kcal/week (range, 0−16,800). 19 patients (35%) had a jejunostomy, 27 (50%) a jejunocolic anastomosis, and 8 (15%) a jejunoileal anastomosis with a remaining small bowel length of 61 cm (range, 0−200). At M6, 46/54 (85%) were responders and were on 2.8 PS days/week (range, 0−7). 13 of 54 patients (25%) were weaned off PS. The predictive factors of response at M6 were a high oral energy intake at BL (p = 0.024). The predictive factors of wean-off at M6 were a jejunocolic anastomosis (p = 0.007), a low PS volume at BL (p = 0.001), a high oral energy intake (p = 0.018).
Conclusion: This is the largest real-world adult cohort with SBS-IF treated with TED. The results of this analysis confirm the efficacy at M6. Our study identified that net volume PS reduction is higher for patients with high baseline PS while all types/causes of SBS may benefit from TED with a similar relative reduction in PS needs. Furthemore, patients with colon in continuity, low baseline PS volume requirements and high oral intake are most likely to fully wean-off PS.
Disclosure: SHIRE

OP149   EFFICACY AND SAFETY OF LANREOTIDE IN POSTOPERATIVE DUMPING SYNDROME: A PHASE III, DOUBLE-BLIND PLACEBO-CONTROLLED CROSS-OVER STUDY

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Introduction: Data on the efficacy and safety of long-acting somatostatin-analogues for postoperative dumping syndrome are scarce. We previously reported the efficacy of monthly intramuscular long-acting (LAR) compared to daily subcutaneous octreotide injections using the Arts dumping score (DS) and its subscales for early and late dumping symptoms (1).
Aims and Methods: We performed a double-blind, randomized and placebo controlled cross-over study of monthly subcutaneous lanreotide in postoperative dumping syndrome. Adults with positive prolonged oral glucose tolerance test or spontaneous hypoglycemia and global DS ≥ 10 despite dietary advice were treated with lanreotide (Somatuline® Autogel 90 mg) and placebo (each 3 monthly injections) in a randomized double-blind cross-over fashion with 4-week wash-out period between treatments. Primary outcome was the effect of lanreotide on DS and overall treatment assessment 3 weeks after the last injection. Secondary outcomes were (serious) adverse events (AE) and quality of life (QoL-SF36). Non-parametric analyses were performed on pooled results (2 periods combined) comparing baseline, lanreotide and placebo.
Results: In total, 24 patients (66.7% female, mean age 49.1 ± 2.1 yrs, BMI 23.7 ± 0.8 kg/m2) were included with 12 randomized to lanreotide and 12 to placebo first. Pooled DS after 3 injections were significantly decreased compared to baseline after lanreotide (median (IQR) 14 (11.5−23) vs. 22 (16-27); p = 0.032) but not placebo (20 (15-27) vs. 23 (13-29); p > 0.05). A similar improvement was seen for early (7.5 (4.5−13) vs. 12 (9-16); p = 0.03) but not late (7 (6-10.3) vs. 9 (6-13); p > 0.05) DS. The overall treatment assessment correlated negatively with change in DS, indicating lower scores with increase in DS (r = −0.703, p < 0.002)

and validating the Arts DS. Of the 90 reported AE, 53 (59%) occurred on lanreotide vs. 37 on placebo (p > 0.05) with 20 events of diarrhoea (14 lanreotide vs. 6 placebo; p > 0.05). All 7 serious AE occurred during lanreotide treatment with (sub-) obstruction in 4 patients. Symptom improvement was not associated with significant changes in the QoL-SF3 and the vitality subdomain scored higher after placebo vs. baseline (40 (30-50) vs. 25 (15-32.5); p < 0.01) but not lanreotide.
Conclusion: Lanreotide is effective for treating postoperative dumping symptoms, although side effects are common and quality of life is not significantly affected. Future studies should focus on optimal dosing to enhance tolerability while maintaining efficacy.
Disclosure: Nothing to disclose

Reference

1. Arts J et al. *CGH* 2009.

OP150   PROTEIN-LOSING ENTEROPATHY AFTER FONTAN SURGERY IS ASSOCIATED WITH LIVER DAMAGE AND HIGH LEVELS OF FECAL CALPROTECTIN: A CASE-CONTROL STUDY FROM A PROSPECTIVE DATABASE

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Introduction: The Fontan procedure is used in patients with a single functioning ventricle due to a complex congenital heart disease. This results in sustained systemic venous hypertension that in the long term cause liver damage and, in some patients, protein-losing enteropathy (PLE). The association between liver disease and PLE is unknown. Addittionally, PLE is thought to be associated with intestinal inflammation. However, data supporting this hypothesis is scarce and fecal calprotectin (FC) has not been assessed in this population.
Aims and Methods: We aim to evaluate if PLE is associated with liver damage through non-invasive methods and to assess if FC is increased in PLE. This is a case-control study from an unicentric prospective-database. Patients were evaluated by blood tests; Fibroscan®; abdominal Doppler-US, MRI or CT (if pacemaker); and echocardiography and other cardiological test. PLE was defined as Alpha-1-Antitrypsin clearance > 27 ml/day. Controls were matched by age and Fontan procedure (atriopulmonary/extracardiac). IBD was an exclusion criteria. Univariate analysis using non-parametric tests with adjustment for multiple comparisons was performed.
Results: 14 cases and 15 controls were included. Baseline and cardiological characteristics are detailed in Table 1. Patients with PLE presented worse cardiological function. Non-invasive methods suggested more advanced liver disease in PLE (median): platelets/mm^3 (117,000 vs 153,000, p = 0.01), hepatic Fibroscan® (25.4 vs 14.5 Kpa, p = 0.03), ascites in US (43% vs 7%, p = 0.03), esophageal varices or intrabdominal collateral circulation on CT/MRI (64.3% vs. 33.3%, p = 0.03), FIB-4 index (1.4 vs 0.9, p = 0.016) and LSPS index (2.2 vs 0.38, p < 0.001). No differences were detected in bilirubin, transaminases or cholestasis parameters.
PLE patients had higher FC values (median) (80 vs 30 µg/g, p < 0.001). No differences were found in NSAID, anticoagulants or antiagregants consumption. Calprotectin levels were directly correlated with alpha-1 antitrypsin clearance (rho = 0.6, p = 0.004) and inversely with the cardiac index (rho = −0.65, p = 0.006), total proteins (rho = −0.68, p = 0.004) and the body mass index (rho = −0.5, p = 0.01)
Conclusion: 1. PLE is associated with more advanced liver disease.
2. Fecal calprotectin is increased in PLE and correlates with its severity. Our study suggest that FC could be a useful biomarker in PLE after Fontan surgery.

Variable	Patients with PLE (n = 14)	Patients without PLE (n = 15)	P values
Age years	28.1 (13 -38)	28.2 (13- 39)	
Male Sex	71.4% (10/14)	53.3% (8/15)	0.31
Antiagregant	57.1% (8/14)	73.3% (11/15)	0.45
Fontan surgery: – Atriopulmonar – Extracardiac	42.9% (6/14) 57.1% (8/14)	40% (6/15) 60% (9/15)	
Time since Fontan (years)	17.9	18.8	
Body Mass Index (kg/m2)	21.4	24.3	0.24
Ejection Fraction MRI	58.5%	63.5%	0.05
Cardiac index (Hemodynamic)	2.54 (1.4–5.1)	4.25 (2.4–6.1)	0.016
Alpha 1-antitrypsin fecal clearance (ml/day)	84 (27 -784)	5.8 (3.1–13)	< 0.001

[Baseline characteristics. Median (range)]
Disclosure: Nothing to disclose

OP151 ORAL ANTIBIOTICS PREVENT INTESTINAL NECROSIS IN ACUTE MESENTERIC ISCHEMIA: A PROSPECTIVE COHORT STUDY

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Introduction: The high mortality of acute mesenteric ischemia (AMI) closely correlates with the occurrence of intestinal necrosis leading to extensive intestinal resection. Recent studies showed that a multimodal and multidisciplinary management of AMI, including a prompt revascularization, decreased the overall mortality as well as the rate of intestinal resection in this setting. These results demonstrated that AMI is potentially reversible and that preventing its progression to irreversible transmural intestinal necrosis (ITIN) should be a primary therapeutic goal. Alongside prompt revascularization, other treatments may help avoid, limit or delay ITIN and its complications. The aim of this study was to assess the efficacy of these therapeutic measures in terms of their effect on the occurrence of ITIN.

Aims and Methods: We conducted a prospective observational cohort study in our intestinal stroke center including all consecutive patients admitted for AMI between January 1st, 2009 and December 31st, 2014. The primary outcome was the occurrence of pathologically proven ITIN in patients who underwent surgery within 90 days from admission. Patients with superficial and non-transmural ischemic necrosis upon pathological assessment and those who recovered from AMI with no need for intestinal resection at 90 days after admission were considered not to have ITIN. Resected specimens were retrospectively reviewed in order to confirm ITIN by a senior pathologist, expert in gastrointestinal diseases and blinded to the treatments administered before surgery. The origin of AMI, epidemiological and clinical data as well as treatment provided (oral and/or IV antibiotics, antithrombotic drugs, revascularization and delays) were collected. A Cox regression model with time-dependent variables was performed for statistical analysis.

Results: A total of 67 patients [(29 (43%) women; median age 54 (40-63) years)] were included. The origins of AMI were arterial, venous, mixed and non-occlusive in 52%, 37%, 6% and 2% of cases, respectively. Pharmacological treatment immediately provided upon admission included intravenous antibiotics (n = 53; 79%), oral antibiotics (n = 37, 55%), anticoagulant therapy (n = 63; 94%), anti-platelet (n = 29; 83% of arterial AMI patients), and revascularization therapy (n = 18; 51% of arterial AMI patients). Median follow-up was 12 months [95% confidence interval (CI) = 9.6–21.7]. 28 (42%) patients underwent intestinal resection and ITIN was noted in 23 (34%) of cases. In multivariate analysis, oral antibiotics was associated with a significant decrease in the risk of ITIN [HR: 0.16 (95%CI = 0.03–0.62); p = 0.01] whereas organ failure was associated with an increased risk [HR: 15.4 (95%CI = 3.2–73.7); p = 0.001]. Overall mortality was 13% and ranged from 2% to 35% in patients without and with ITIN, respectively.

Conclusion: Our results suggest a protective effect of oral administration of antibiotics against the occurrence of irreversible transmural intestinal necrosis in the setting of AMI. A management strategy including at least oral antibiotics in addition to early revascularization might reduce or prevent progression of AMI to intestinal necrosis, avoid surgery and improve survival. Such a strategy should be confirmed with further prospective interventional studies.

Disclosure: MSD Avenir grant

OP152 BOWEL PREPARATION FOR SMALL BOWEL CAPSULE ENDOSCOPY – THE LATER, THE BETTER!

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Introduction: In small bowel capsule endoscopy (SBCE), the presence of residue in the small bowel lumen limits the observation, hampers the interpretation and may lead to diagnostic mistakes.

Aims and Methods: We aimed to assess differences in the diagnostic yield of SBCE using 3 different preparation protocols, as well as the rate of complete examinations and small bowel transit time (SBTT).

Prospective, randomized, blind study, including 101 patients that consecutively preformed SBCE (PillCam® SB3, Given Imaging). Protocol A: Clear liquids diet the day before the examination with fasting from 8p.m.; Protocol B: Protocol A + 2 pouchs of Moviprep® (polyethylene glycol electrolyte solution) in 1 liter of water from 8p.m. of the day before the examination; Protocol C: Protocol A + 2 pouchs of Moviprep® in 1 liter of water to be consumed after real-time confirmation of SBCE arrival at small bowel.

Small bowel preparation was classified by an experienced physician, considering the percentage of the examination in which mucosal observation was adequate: Excelent (>90%), Good (90-75%); Fair (75-50%); Poor (<50%).

Results: 101 patients were randomized to the 3 protocols (A 37, B 31 and C 33 patients). Protocol C had an excellent or good small bowel preparation in a higher percentage of examinations (A:37.8% vs B:45.2% vs C:78.8%, p = 0.002). No significant differences were found between the 3 protocols regarding diagnostic yield (A:59.5% vs B:48.4% vs C:63.6%, p = 0.445), however protocol C had a higher detection of angiectasia (A:5.4% vs B:9.7% vs C:27.3%, p = 0.022).

No differences were found between the 3 protocols regarding SBTT (A:278 ± 123minutes vs B:275 ± 107minutes vs C:244 ± 148 minutes = 0.504) or complete examinations rates (A:89.2% vs B:100.0% vs C:93.9%, p = 0.171).

Conclusion: In SBCE the administration of Moviprep® after the confirmation of capsule arrival at the small bowel associated with a better small bowel preparation and a higher detection of angiectasia. Therefore, this innovative protocol should be systematically used to improve procedure results.

Disclosure: Nothing to disclose

TUESDAY, OCTOBER 23, 2018   08:30–10:00

Murine models of intestinal inflammation – Room L7

OP153 LOSS OF PTPN2 IN DENDRITIC CELLS PROMOTES T CELL ACTIVATION AND DIFFERENTIATION INTO TH1 CELLS BUT DOES NOT AFFECT REGULATORY T CELLS

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Introduction: Variants within the gene locus encoding protein tyrosine phosphatase non-receptor type 2 (PTPN2) are associated with the development of inflammatory disorders, including IBD. The role of PTPN2 in T cells and intestinal epithelial cells has been investigated in depth, but its role in dendritic cells (DCs) remains unclear. Understanding the DC specific role of PTPN2 is of particular interest, since DCs play a crucial role in activation of T cells and orchestrating immune responses in general. Here, we addressed whether loss of PTPN2 in DCs affects the expression of co-stimulatory molecules and subsequently activation and differentiation of T cells.

Aims and Methods: Mice with a LoxP flanked PTPN2 gene were crossed with mice expressing Cre-recombinase under control of the CD11c promoter in order to specifically delete PTPN2 in DCs (PTPN2-CD11cCre mice). Using multicolour flow cytometry, we analysed immune cells in the spleen, mesenteric lymph nodes, lung, liver, kidney, and skin in PTPN2-CD11cCre mice and their wild-type littermate controls.

Results: PTPN2-CD11cCre mice show symptoms of splenomegaly and skin inflammation, as well as inflammatory infiltrates in the liver and lung in some mice. Severity of the inflammation varies between individuals, resulting in spontaneous death in some mice. We found increased expression of co-stimulatory molecules CD80 and CD86 on PTPN2-deficient DCs. Of note, there was no difference regarding the expression of MHCII on CD11c+ cells between PTPN2-CD11cCre and their littermate controls. Consistent with increased expression of co-stimulatory molecules, we observed increased numbers of CD44+ effector/memory CD4+ and CD8+ T cells in lymph nodes (p < 0.05), liver, lung (p < 0.01) and spleen (p < 0.01) but not in kidney of PTPN2-CD11cCre mice, indicating an enhanced T cell activation capacity of PTPN2-deficient DCs. Of note, levels of CD62L+ naïve T cells were reduced in liver, lung and spleen. In addition, frequencies of IFN-gamma+CD4+ Th1 T cells were increased in lung (p < 0.05), skin (p < 0.05), spleen (p = 0.056), and liver but reduced in the kidney. However, there was no difference regarding differentiation into IL13+ Th2 and IL17+ Th17 T cells. Moreover, loss of PTPN2 in DCs did not affect gamma delta T cells. Further, there was an increase of FoxP3+ regulatory T cells in mesenteric lymph nodes (p < 0.05) but we did not observe any difference in frequencies of FoxP3+ regulatory T cells in kidney, liver, lung and spleen of PTPN2-CD11cCre mice.

Conclusion: In conclusion, our results show that PTPN2 has an important anti-inflammatory role in DCs. Loss of PTPN2 in DCs promotes T cell activation as well as increased expression of co-stimulatory molecules CD80 and CD86. Further, it affects differentiation into Th1 but not Th2 or Th17 T cells. However, PTPN2 in DCs does not play a major role in the differentiation of regulatory T cells. Further studies will investigate the interaction of PTPN2-deficient DCs and T cells in terms of antigen presentation and subsequent T cell proliferation and differentiation.

Disclosure: Nothing to disclose

OP154 LACK OF SUCNR1 PROTECTS FROM INTESTINAL FIBROSIS

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Introduction: Intestinal fibrosis is a common complication associated with Crohn's Disease (CD) which cannot be reverted with any drug and forces repeated surgery. It has been reported that succinate, a metabolite accumulated in inflammatory pathologies, plays an important role in the activation of synovial fibroblasts and hepatic stellate cells through its receptor called SUCNR1 or GPR91.

Aims and Methods: We aim to analyze the relevance of SUCNR1 receptor in intestinal fibrosis.

Intestinal resections from CD patients and colon carcinoma patients were obtained and the expression of SUCNR1 and α-sma were analzyed by immunostaining. Primary intestinal fibroblasts from human resections or from colon of wild-type (WT) or SUCNR1-/- (KO) mice were isolated, maintained in culture and treated with different concentrations (0, 0.1, 0.5, 1, 5mM) of succinate for 24 hours. Intestinal fibrosis was induced *in vivo* introducing one intestinal graft from WT or KO mice into the neck of a receptor mice for 7 days. The expression of pro-fibrotic markers was analyzed by qPCR. Sirius Red staining was performed and the collagen layer was quantified using ImageJ. Results are expressed by mean $\pm$ SEM (n$\geq$5). Statistical analysis was performed with one-way ANOVA followed by Newman-Keuls test. Correlations were analyzed with the Spearman coefficient.

Results: SUCNR1 is expressed in epithelial cells and α-sma+ cells of intestinal resections from CD patients. The SUCNR1 expression positively and significantly correlates with the expression of α-sma (r = 0.759, p < 0.0001, n = 24) and co1lA1 (r = 0.82, p < 0.001, n = 24). In primary fibroblasts isolated from CD patients (13.54 $\pm$ 4.6) the expression of SUCNR1 was significantly higher than in those obtained from control patients (2.07 $\pm$ 0.86). In these cells, succinate induced the expression of profibrotic markers such as Col1A1, α-sma, Tgfb, and TIMP1 in a dose-response manner. This profibrotic effect of succinate was also observed in fibroblasts from WT mice and it was completely reverted in fibroblasts obtained from KO mice. The murine model of intestinal fibrosis *in vivo* revealed that: a) the thickness of the collagen layer was significantly reduced in colons from KO mice compared with those from WT mice; b) the expression of pro-fibrotic markers such as col1A1, α-sma and vimentin was also significantly reduced in colons from KO mice vs colons from WT mice (19.7 $\pm$ 10.1 vs 69.8 $\pm$ 26.6, 0.9 $\pm$ 0.1 vs 2.5 $\pm$ 0.5, 1.7 $\pm$ 0 vs 12.4 $\pm$ 0.3, respectively).

Conclusion: An increased expression of SUCNR1 receptor is detected in fibroblasts from CD patients the activation of which induces a pro-fibrotic effect. This receptor mediates murine intestinal fibrosis and we propose its blockade as a new pharmacological target in CD treatment.

Disclosure: Nothing to disclose

OP155 RELEASE OF UNCONTROLLED ACTIVE ELASTASE BY INTESTINAL EPITHELIAL CELLS PARTICIPATES TO MUCOSAL INFLAMMATION IN IBD

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Introduction: Imbalance between proteases and their inhibitors appears to be crucial to the development of Inflammatory Bowel Diseases (IBD). We have previously shown that colonic biopsies from IBD patients released higher elastolytic activity compared to biopsies from healthy controls. In addition, expression of ELAFIN, an endogenous elastase inhibitor, was significantly downregulated in mucosa from IBD patients, compared to heathly controls.

Aims and Methods: The aim of our study was to identify the source of elastase hyperactivity released by IBD biopsies and to examine its impacts on colonic barrier function and inflammatory response. *In situ* zymography with FITC-elastin was performed on cryosections of colonic biopsies from healthy and IBD patients taken from inflamed and non-inflamed areas. Immunostaining for epithelial elastase was performed on cryosections from human biopsies, human organoïds, or from mouse colon. A Caco2 epithelial cell line overexpressing epithelial elastase (Tg-ELA) was constructed and the potential of elastase hyperactivity to modulate the release of cytokines and permeability changes was evaluated. Transgenic murine model, which over-expressed the epithelial elastase specifically in epithelial cells in a temporally controlled manner, was developed (pVillin-CRE[ERT2]-ELA) and analyzed at macroscopic and molecular levels.

Results: *In situ* zymography evidenced strong elastolytic activity in enterocytes of healthy human colonic tissues, which was greatly enhanced in inflamed biopsies as well as in non-inflamed biopsies from IBD patients. An elastase cDNA was cloned from human enterocytes. Immunostaining of colonic tissues showed that this elastase was only expressed in epithelial cells and secreted into the lumen. In IBD, the expression of this elastase was enhanced in the epithelium. Tg-ELA

epithelial cells exhibited defective barrier function accompanied by an increase of pro-inflammatory cytokine expression. Western blot analyses revealed that the major elements of tight junction, Occludin and Claudin-1, were targeted by elastase hyperactivity secreted in the medium.

In addition, *in vivo*, over-expression of elastase in the intestinal epithelium (pVillin-ELA mice) for 3 weeks led to increased permeability and overexpression of antimicrobial peptides (Reg3g and Reg3b). Macroscopic damage scoring highlighted intestinal inflammation, with strong adhesive phenotype.

Conclusion: We demonstrate the presence of an epithelial form of elastase in the intestine. Imbalance between elastase and its inhibitor in the epithelium participates in the generation of IBD-associated symptoms.

Disclosure: Nothing to disclose

OP156 LOSS OF PTPN2 IN DENDRITIC CELLS RESULTS IN REDUCED TUMOR BURDEN IN THE AOM/DSS COLON TUMOR MOUSE MODEL

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Introduction: Protein tyrosine phosphatase non-receptor type 2 (PTPN2) has been recetly identified as potential cancer immunotherapy target. We have previously recognised PTPN2 as a key regulator for inflammatory responses in the intestine. Our recent data demonstrate that loss of PTPN2 in myeloid cells using PTPN2xLysMCre conditional PTPN2 knock-out mice results in reduced tumour burden in the azoxymethane (AOM)-dextran sodium sulphate (DSS) induced model of colitis-associated colorectal carcinoma. However the role and mechanism of action how PTPN2 is involved in colon carcinoma development has not yet been studied in detail. Here, we showed that the tissue specific loss of PTPN2 in dendritic cells results in reduced tumour load in AOM/DSS mice model.

Aims and Methods: We generated a mouse line lacking PTPN2 in specifically in dendritic (PTPN2-CD11cCre) cells. We then induced colon tumor formation in wild-type (WT) and PTPN2-deficient mice using the AOM/DSS model of colitis-associated cancer and analysed immune cells in spleen, mesenteric lymph nodes (LN) and lamina propia in PTPN2-CD11cCre and their WT littermate controls using flow cytometry and RNA expression levels.

Results: AOM/DSS treatment resulted in the formation of colon tumours in both WT and KO mice. Tumour burden varied between individual mice, however PTPN2-CD11cCre mice had less and smaller tumours comparing to their WT littermate controls. In turn, PTPN2-CD11cCre mice exhibited significantly increased levels of CD44+ effector/memory CD4+ and CD8+ T cells in spleen, lymph nodes and lamina propia, showing an enhanced T cell activation by PTPN2-deficient dendritic cells. In addition, we observed that PTPN2-deficient mice also presented significantly increased levels of CD4+ PD-1 and CD8+ PD-1 cell surface receptors on the T cells in spleen and LN. While expression of PDL-1 checkpoint inhibitor molecule did not differ between WT and KO in treated and untreated groups, PDL-2 expression was significantly decreased in the spleen of the treated KO mice comparing to the DSS/AOM treated WT mice.

Conclusion: In conclusion, our results demonstrate a role for PTPN2 in the pathogenesis of colorectal carcinoma in vivo. Loss of PTPN2 in dendritic cells exerts anti-tumour effect and results in lower colon tumour burden in AOM/DSS treated mice. This effect is likely mediated via promoting anti-cancer immune responses by modulating checkpoint inhibitor molecule expression.

Disclosure: Nothing to disclose

OP157 TP53 MUTATION ENHANCES CELL PROLIFERATION AND STEMNESS IN HUMAN COLON EPITHELIAL ORGANOIDS AND PROMOTES A RESISTANCE AGAINST LONG-TERM INFLAMMATION

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Introduction: In colitis-associated cancer (CAC), tumor protein p53(TP53) mutation often occurs in the early phase of colon carcinogenesis known as dysplasia-carcinoma sequence. Although there are some reports about the relation between TP53 mutation and colon carcinogenesis in mice model, a direct effect of TP53 mutation on colon epithelial cells and carcinogenesis in human are still unknown. We therefore aimed to assess the influence of TP53 mutation by using a CRISPR Cas9 system on human colon epithelial organoids under long-term inflammation model which we originally launched.

Aims and Methods: TP53 mutation was generated by using lentiviral CRISPR Cas9 system in 3 different epithelial organoids derived from individual human colonic mucosa with wild-type TP53 (WT-TP53). Written informed consent was obtained from all included patients and this study was approved by the Ethics Committee of Tokyo Medical and Dental University. The guide RNA was designed to bind exon 10 of TP53. TP53 mutation in organoids was confirmed by direct sequencing. The expression of TP53 protein was assessed by immunohistochemistry. Loss of function of TP53 was assessed by Nutlin3a-resistance and the expression of TP53 target genes. Gene expression was assessed by microarray analysis and quantitative PCR. The long-term inflammation model was established by culturing organoids with inflammatory factors (TNF-a, Flagellin and IL-1β) for 60 weeks. Inflammatory response in the organoids was assessed by gene expression of inflammatory-related genes and the level of reactive oxygen species (ROS). Phenotypes of each organoids were assessed by MTS Assay, sphere formation assay for cell proliferation and stemness, respectively.

Results: At first, we successfully established TP53 mutation in 3 different human colon epithelial organoids. Mutant TP53 was strongly expressed in nuclei of all organoid cells as often shown in dysplastic lesion of ulcerative colitis (UC), whereas WT-TP53 was not expressed in naive organoids. Mutant TP53 also showed Nutlin3a-resistance and down-regulation of TP53 target genes, indicating the loss of function of TP53. Moreover, microarray analysis revealed up-regulated genes in the organoids with mutant TP53, suggesting the gain of specific function of mutant TP53. We then assessed the effect of mutant TP53 with or without inflammatory stimulation for 60 weeks. Long-term inflammatory stimulation attenuated cell proliferation and sphere formation of the organoids with WT-TP53. Mutant TP53 however enhanced cell growth and stemness with increased gene expression of c-myc and Lgr5 compared to WT-TP53 under the inflammatory situation, nevertheless inflammatory response in the organoids with mutant TP53 was equal to that in the organoids with WT-TP53.

Conclusion: We for the first time showed TP53 mutation alone enhances cell proliferation and stemness of human colonic organoids under long-term inflammation. Mutant TP53 cancelled epithelial cell damage by chronic inflammation, suggesting that these results might mimic the early step of colitis associated carcinogenesis.

Disclosure: Nothing to disclose

OP158 THE CHANGE OF THE TH17/TREG ON EXPERIMENTAL COLITIS MICE AND THE RESEARCH ABOUT PROTECTIVE EFFECT OF MICA

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Introduction: Inflammatory bowel disease (IBD) is a chronic nonspecific intestinal inflammatory disease, and its incidence and prevalence have been increasing in recent years. To date, the etiology and pathogenesis of IBD are still not very clear, and the latest research indicates that the imbalance of Th17/Treg cells may play an important role in the occurrence of IBD. The drugs for IBD mainly include 5-aminosalicylic acid, glucocorticoid and immunosuppressants and biological agents; although these medications in many cases are effective, most of the patients are not stable and can not get good control. Therefore, to explore the pathogenesis of IBD and find new therapeutic drugs is an urgent problem to be solved in clinical. Mica is one of the silicate mineral drugs. Previous studies have shown that mica has the effect of promoting the regeneration and maintenance of mucosal barrier and anti-inflammatory action of gastrointestinal mucosal epithelial cells. In this study, the role of Thl7/Treg cells in the pathogenesis of ulcerative colitis and the protective effect and possible mechanism of mica were investigated by observing the changes of Foxp3/ROR- in mice with ulcerative colitis induced by TNBS.

Aims and Methods: Observation the change of the Foxp3/ROR-γt on tnbs-induced experimental colitis mice. Investigation of the role of Th17/Treg in ulcerative colitis and investigation of the prevention and possible mechanism of mica. 30 male balb/c mice of clean grade were randomly divided into control group, model group and mica group, 10 mice in each group. In first day, the model group and mica group were initiated by intrarectal administration of TNBS to establish the model. From the second day, the control group and model group were intrarectally administrated with normal saline, the mica group was intrarectally administrated with mica for three days. On day 5, all the mice were killed, specimens were taken. We observed the gross and histological damage of colon in mice, tested the expression of ROR-γt, Foxp3, IL-17A, IL-10 in the colon tissue used by RT-qPCR, immunohistochemistry, ELISA.

Results: 1. General situation: The disease activity index score in model group mice was significantly higher than control group. After the intervention of mica, the disease activity index score had obviously decreased comparing with model group. 2. The macroscopic and histological damage score: The model group was higher than control group. After the intervention of mica, the score had obviously decreased comparing with model group. 3. RT-qPCR comparing with control group the ROR-γt, Foxp3, IL-17A, IL-10 mRNA of model group all were higher expression. The ROR-γt, IL-17A mRNA of mica group was obviously more decreased than model group, but the Foxp3, IL-10 mRNA of mica group was higher expression compared with model group. 4. Immunohistochemistry: Comparing with control group, Foxp3, IL-10, ROR-γt of model group were higher expression comparing with model group, ROR-γt of mica group was obviously more decreased than model group. Foxp3, IL-10 of mica group further increased than model group. 5. ELISA: IL-17A of model group was higher expression than control group. Mica group was obviously decreased than model group.

Conclusion: The Th17/Treg and inflammation-related cytokines was imbalanced in TNBS-induced ulcerative colitis mice; this may be the important pathogenesis. Mica has a protective effect on ulcerative colitis mice and its mechanism may be related to adjust the imbalance of Th17/Treg, increase the expression of IL-10, restrain the expression of IL-17 and ultimately reduce inflammation.

Disclosure: Nothing to disclose

TUESDAY, OCTOBER 23, 2018 08:30–10:00

The gut-brain axis in the lower GI – Room L8

OP159 ELASTOLYTIC HOMEOSTASIS: A MAJOR COMPONENT OF COLONIC HYPERSENSITIVITY ASSOCIATED WITH IRRITABLE BOWEL SYNDROME

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Introduction: While increased Trypsin activity was described in tissues from IBS patients, the presence and activity of other proteases have been barely studied. We have recently demonstrated that human intestinal epithelium is capable of producing a form of epithelial elastase, as well as its endogenous inhibitor Elafin. In inflammatory bowel disease patients, epithelial elastase is up-regulated, while its inhibitor Elafin is down-regulated. Here, we wanted to investigate the role of this epithelial elastolytic balance in Irritable Bowel Syndrome (IBS).

Aims and Methods: We used different mouse models of colon hypersensitivity: one model induced by intracolonic administration of Protease-Activated Receptor-2 (PAR2) agonist, the mustard oil intracolonic administration model, the post-infectious visceral hypersensitivity model induced by *Citrobacter rodentium* infection associated with water avoidance stress, and the intracolonic administration of IBS patient tissue supernatants. Visceral nociceptive response to colorectal distension was measured in those mouse models. We also used tissues from IBS patients to perform *in situ* zymography, and immunohistochemistry. Transgenic murine model, which over-expressed specifically epithelial elastase in a temporally controlled manner, was developed (pVillin-CRE^{ERT2}-ELA) and was used to analyse nociception and barrier function.

Results: Elastolytic activity was significantly increased in colonic tissues from mice showing visceral hypersensitivity symptoms after combined stress and *C. rodentium* infection, but stayed at basal levels in mice that did not develop signs of hypersensitivity. Elastolytic activity was also up-regulated in tissue exudates from IBS patients, and this activity was localized in intestinal epithelial cells by *in situ* zymography. Elafin, the endogenous elastase inhibitor was also up-regulated in epithelial cells from IBS patients, compared to healthy controls, suggesting that tissues from IBS patients try to re-equilibrate elastolytic balance. However, Elafin production does not seem to be sufficient to bring back elastolytic activity to control levels in IBS. We therefore tried to deliver exogenously Elafin, by the mean of food-grade bacteria (*L. lactis*) recombinant for the expression of Elafin. In hypersensitive mice (that have received intracolonically PAR2 agonists, mustard oil or IBS tissue supernatants), oral treatment with Elafin-expressing *L. lactis* significantly inhibited allodynia and hyperalgesia, while the wild-type *L. lactis* had no significant effect. *In vivo*, over-expression of elastase in the intestinal epithelium (pVillin-CRE^{ERT2}-ELA mice) for 10 days provoked visceral hypersensitivity in response to colorectal distension. Increased intestinal permeability was also a phenotype observed in mice over-expressing epithelial Elastase.

Conclusion: We demonstrate up-regulated elastolytic activity associated with IBS and visceral hypersensitivity. Elastase inhibitor protects against visceral hypersensitivity. A form of epithelial elastase up-regulated in IBS generates IBS-

associated symptoms (hypersensitivity and barrier defects), and could constitute a new target for the treatment of colonic hypersensitivity.

Disclosure: Nothing to disclose

OP160 NO UNCONSCIOUS ATTENTIONAL BIAS FOR GI-SALIENT TERMS IN SUBJECTS WITH FUNCTIONAL GI DISORDERS OBJECTIVELY MEASURED BY ELECTROENCEPHALOGRAPHY (EEG)

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Introduction: Individuals suffering from functional gastrointestinal (GI) disorders have been shown to have altered central processing of visceral stimuli relative to healthy controls (1). Further such individuals appear to have selective attention to gastrointestinal words (2) suggesting an attentional bias towards GI-relevant terms which may explain this phenomenon. They also have increased threat perception (3). However it remains unclear how much of the attention given to GI words is conscious versus unconscious. Understanding the extent to which individuals suffering from functional GI symptoms are unconsciously biased towards GI words may offer insights into therapeutic approaches to individuals in whom organic pathology has been ruled out. One previous study inferred an unconscious attentional bias for GI words through indirect means (Stroop test) (4) but its methodology was not designed to specifically measure the pre-attentional phase of central processing.

Aims and Methods: This study aimed to objectively identify differences between GI symptomatic and asymptomatic control individuals in unconscious (pre-attentional) processing of GI words using electroencephalography (EEG) which has fine temporal resolution. 26 GI symptomatic and 23 asymptomatic individuals were recruited from the community. Organic pathology and current mood disorders were ruled out by self-report. All subjects viewed 20 GI-related words, 20 negative but non-GI words and 20 neutral words from a validated word bank six times in a randomised order. Reactions were measured through ERP peak amplitude in the Occipital region in the P100 period (75-125 milliseconds) as this clearly corresponds to pre-attentional processing.

Results: Subjects generally exhibited distinctive peak amplitudes in response to all word types for the P100 period. However there was no difference in P100 peak amplitude across word type for the GI symptomatic subjects (p = 0.3). There was no difference in P100 peak amplitude for GI-relevant words between symptomatic and asymptomatic subjects (p = 0.6), nor was there an interaction between symptomatic status and word type (p = 0.8). Hence there was no suggestion of difference in P100 peak amplitude across GI-relevance of words nor symptomatic status.

Conclusion: In contrast to previous work, our data suggest that attentional bias in FGID individuals is not due to pre-attentional (unconscious) central processing and that this occurs at a later (conscious) stage. This finding has positive consequences for the development of psychological therapies targeting functional GI symptom burden since unconscious biases are much more difficult to change.

	Subject group	
Word type	Symptomatic (n = 26)	Asymptomatic (n = 23)
Gastrointestinal	-3.22 (2.68)	-3.60 (3.67)
Negative	-3.39 (2.44)	-3.57 (3.58)
Neutral	-3.35 (2.86)	-3.75 (3.75)
Combined	-3.32 (2.63)	-3.64 (3.61)

[Table. Mean (SD) peak amplitude by subject group and word type for the P100 period in the Occipital region]

Disclosure: Nothing to disclose

References

1. Rubio A, Pellissier S, Van Oudenhove L, Li GH, Dupont P, Tack J, et al. Brain responses to uncertainty about upcoming rectal discomfort in quiescent Crohn's disease – a fMRI study. *Neurogastroenterology & Motility*. 2016.
2. Gibbs-Gallagher N, Palsson OS, Levy RL, Meyer K, Drossman DA, Whitehead WE. Selective recall of gastrointestinal-sensation words: evidence for a cognitive-behavioral contribution to irritable bowel syndrome. *The American Journal of Gastroenterology*. 2001; 96(4): 1133–8.
3. Naliboff BD, Fresé MP, Rapgay L. Mind/Body Psychological Treatments for Irritable Bowel Syndrome. *Evidence-based Complementary & Alternative Medicine (eCAM)*. 2008; 5(1): 41–50.

4. Afzal M, Potokar JP, Probert CS, Munafo MR. Selective processing of gastrointestinal symptom-related stimuli in irritable bowel syndrome. Psychosom Med. 2006; 68(5): 758–61.

OP161 ANTI-TNF-A ALTERS CONNECTIVITY BETWEEN INTEROCEPTIVE SENSORY CORTEX AND AMYGDALA IN CROHN'S DISEASE PATIENTS

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Introduction: Inflammatory Bowel Disease (IBD) increases TNF-a release from peripheral mononuclear cells as the immune system responds to inflammation in mucosal tissue. This immune response is closely linked with the intensity of gastrointestinal symptoms and extra-intestinal comorbidities such as depression or anxiety. We have previously demonstrated that anti-TNF-a treatment impacts on implicit health cognition via altering brain function (Gray et al., 2018). Increased psychiatric symptoms in IBD are commonly explained as driven by an interoceptive mechanism, however there is scant direct evidence to support these interpretations. To address this mechanism, we experimentally engaged core interoceptive circuitry and then examined the influence of anti-TNF-a therapy on brain function in patients with Crohn's disease.

Aims and Methods: 10 patients with Crohn's disease (age 29.3 ± 13.0 yrs, 5 female, 5 ileocolonic, 2 colonic and 3 ileal disease) on stable anti-TNFα therapy (6 adalimumab, 4 infliximab) were studied twice, in randomized order, before and after anti-TNFα administration. On each occasion patients underwent visceral sensory testing (standardized nutrient challenge) and then functional magnetic resonance imaging (fMRI) of the brain during an interoception task. During sensory testing 600ml of enteral feeding solution was consumed over 15 minutes while the intensity of GI symptoms was quantified. We used a recognized and commonly employed experimental protocol to recruit interoceptive neural circuits, heartbeat perception (See Brener et al., 2016 for a review of experimental methods)

Results: Within 72 hrs after administration of anti-TNF-a unpleasant visceral sensation during nutrient challenge (subjective fullness) was significantly reduced. Prior to anti-TNF-a, our experimental task robustly activated core interoceptive circuitry including the interoceptive sensory (anterior insula) cortex and interoceptive motor (anterior cingulate) cortex. Surprisingly, activation of interoceptive circuits was not significantly altered following anti-inflammatory therapy. Instead, we observed the functional connectivity between the right anterior insula and the right amygdala was significantly reduced following anti-TNF-a.

Conclusion: Anti-TNFα agents significantly reduce symptoms during a standardized nutrient challenge, and alter the strength of communication between primary interoceptive sensory cortex (anterior insula) and limbic circuitry (amygdala). Our findings are consistent with previous observations that greater amygdala functional connectivity is associated with visceral hypersensitivity (Icenhour et al., 2017). Our findings however are the first to demonstrate altered amygdala connectivity specific to interoceptive processing. These findings suggest that the functional coupling between interoceptive circuits and limbic circuits may be implicated in the translation of inflammatory conditions into psychological symptoms such as depression and anxiety. These findings support further examination of how cytokines including TNF-a may impact on mental health in gastrointestinal patients.

Disclosure: Nothing to disclose

References

1. Brener J, Ring C. (2016). Philos Trans R Soc Lond B Biol Sci. 371(1708). Gray MA, Chao CY, Staudacher HM, Kolosky NA, Talley NJ, Holtmann G. (2018). *PLoS One*. 13(3): e0193542.
2. Icenhour A, Witt ST, Elsenbruch S, Lowén M, Engström M, Tillisch K, Mayer EA, Walter S. (2017). *Neuroimage Clin*. 15: 449–457.

OP162 PROLIFERATION AND MORPHOLOGICAL ALTERATIONS OF ENTERIC GLIA STIMULATED BY STRESS MEDIATORS ARE ASSOCIATED WITH INDUCTION OF NEURONAL ELONGATION FACTORS: POSSIBLE MECHANISM(S) OF VISCERAL HYPERSENSITIVITY IN THE ENTERIC NERVOUS SYSTEM

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Introduction: Sensitization of enteric neurons occurs under stress conditions such as pathogenesis of irritable bowel syndrome (IBS). Various phenomena such as changes in some receptor affinity, production of inflammatory cytokines and chemical mediators, elongation of enteric neurons appeared around the enteric nervous system. In addition, morphological alterations of colonic glial cells occur, and glia-neuronal system contributes to the colonic hypercontraction of an IBS model (*Neurogastroenterol Motil,* 2015). However, it is unknown whether enteric glial cells changes or not under stress conditions.

Aims and Methods: We investigated whether stress-related mediators of the pathogenesis of IBS such as tryptase and corticosterone affect enteric glial cell (EGC) on cellular activation, cell proliferation, morphological alterations, and gene induction of neurotrophic factors and axon guidance factors. EGC (CRL-2690 purchased from ATCC) were used for the consequent experiments after reaching to sub-confluent condition. Presence of tryptase-protease-activated receptor-2 (PAR-2), glucocorticoid receptor, and morphological changes of EGC was evaluated by immunofluorescence method. For EGC activation, we evaluated expressions of phosphorylated extracellular signal-regulated kinase (pERK) 1/2 by stimulations with tryptase (100 nM) and corticosterone (1 μM) by western blotting, and mRNA expression of glial fibrillary acid protein (GFAP) by real-time RT-PCR. For induction of neurotrophic factors and an axon guidance factor after stimulation with tryptase (100 nM) (0.5–6 hrs) and corticosterone (1 μM) (0.5–6 hrs), nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), and netrin-1 were analyzed using a real-time RT-PCR. Expression of netrin-1 was histologically evaluated. To evaluate cell proliferation, we used the MTT assay method and cell number count.

Results: PAR-2 was localized in the nucleus of EGC, and glucocorticoid receptor was observed in the cytoplasm of EGC. Expressions of pERK1/2 were about 2-fold higher than those of the basal control, and peaked at 2 min and 5 min after stimulation with tryptase and corticosterone, respectively. Tryptase but not corticosterone stimulation induced cell proliferation (1.8–fold). Tryptase significantly increased mRNA expression levels of GFAP (1.7–fold) at 30 min and 1 hrs. Regarding with morphology of EGC, corticosterone (1 μM, 6 hrs) but not tryptase remarkably caused EGC process elongation and long thin process connecting with another distant EGC. Extended cytoplasm of EGC also appeared by stimulation with corticosterone alone. Tryptase increased NGF mRNA expression at 1 hr (about 2.5–fold) and GDNF mRNA expressions at 30 min (2.9–fold) and 1 hr (3.7–fold). Then, increased NGF mRNA expression was continued until 6 hrs, but GDNF mRNA expressions were gradually decreased. While, corticosterone significantly decreased mRNA expression levels of NGF by 90% (1 μM), but increased GDNF mRNA (4-fold, 1μM) at 30 min. Netrin-1 was expressed in the cytoplasm of EGC. Netrin-1 mRNA expression was increased by both stimulations (2.5–fold higher, tryptase: 1.8–fold higher, corticosterone), and its higher expression levels continued until 6 hr.

Conclusion: There appeared different responses of EGC between proliferation and morphological changes stimulated by stress mediators. Imbalanced responses of EGC may associate with induction of neuronal factors (NGF, GDNF, netrin-1), which possibly regulates neuronal elongation under stress conditions.

Disclosure: Nothing to disclose

OP163 UNDERSTANDING THE ROLE OF NEURO-IMMUNE INTERACTIONS AND NERVE SPROUTING IN PATIENTS WITH DIVERTICULAR DISEASE

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Introduction: Colonic diverticula are an age-dependent event in Western countries occurring in up to 65% of people over the age of 60 years. Symptomatic uncomplicated diverticular disease (SUDD) is a syndrome characterized by abdominal symptoms similar to irritable bowel syndrome (IBS) attributed to diverticula. A role for inflammation, sensory-motor dysfunction, and dysbiosis may have a role in diverticular disease in a clinical picture that mimics IBS. We hypothesized that mucosal immune activation, nerve fiber density and sprouting may play a role in symptom generation in patients with SUDD.

Aims and Methods: The aim of the present study was to characterize immune cells, nerve density and sprouting in patients with SUDD, diverticulosis and healthy controls (HC). 14 HC, 16 patients with diverticulosis and 10 with SUDD were enrolled in the study. In patients with diverticula, mucosal biopsies were obtained close to diverticula (peridiverticular region) and in the normal mucosa. In HC, biopsies were performed at sigmoid and at descending colon. Immunohistochemistry was used to stain and quantify immune cells (mast cells, T cells, macrophages), nerve fibers (using anti-neuronal specific enolase [NSE] antibody) and neuronal outgrowth (using anti-growth-associated protein 43 [GAP-43] antibody). Correlation analyses were performed between immune cell counts and nerve fiber ones.

Results: No differences were detected in mast cell nor in T cell counts among the three groups. Macrophages were significantly increased in patients with SUDD and diverticulosis as compared to HC, both in the peridiverticular ($5.8 \pm 0.4\%$, $6.9 \pm 0.6\%$, $4.9 \pm 0.4\%$, respectively; $p < 0.05$) and in normal mucosa ($7.1 \pm 0.7\%$, $6.6 \pm 0.4\%$, $4.0 \pm 0.3\%$, respectively; $p < 0.001$). The density of NSE+ fibers was significantly enhanced in patients with SUDD and diverticulosis in comparison with HC ($5.1 \pm 0.7\%$, $5.5 \pm 0.8\%$ vs $3.4 \pm 0.4\%$, respectively; $p < 0.05$) in the peridiverticular region. GAP-43+ fibers were significantly increased only in patients with SUDD as compared to HC ($p < 0.05$) in the peridiverticular region. The peridiverticular region of patients with SUDD was characterized by a higher number of GAP43+ fibers close to immune cells compared to HC ($p < 0.05$).

Conclusion: Patients with SUDD and diverticulosis are characterized by increased macrophage counts. The colonic mucosa of patients with SUDD is characterized by nerve fiber sprouting and neuro-immune interactions which could be involved in symptom generation.

Disclosure: Nothing to disclose

OP164 GENETIC ASSOCIATIONS OF IRRITABLE BOWEL SYNDROME AND DEPRESSIVE DISORDER THROUGH WHOLE EXOME POOLED-SEQUENCING

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Introduction: Irritable bowel syndrome (IBS) is the most commonly diagnosed functional gastrointestinal disorder with a psychological distress comorbidity rate of 15.5%-39.5%, especially with depressive disorder (DD). Twins' studies and population genome wild association studies (GWAS) suggest there is a genetic contribution to development of IBS, rare results could display the high comorbidity rate of IBS and depression.

Aims and Methods: The aim of this study was to distinguish the genetic associations of IBS and depressive disorder. 35 diarrhea dominated IBS patients (IBS) and 35 depressive disorder patients (DD) were recruited according the Rome III criteria and MINI Diagnostic, 35 matched healthy volunteer (HC) without any gastroenterology or mental disease were also recruited at the same time in Peking university third hospital and Beijing HuiLongGuan Hospital. Peripheral blood DNA of each sample in the same group were extracted and mixed as a pool, the whole exome single nucleotide polymorphism (SNPs) of 3 pools were measured through the pooled-sequencing (Pool-seq)[1]. The study was approved by the Ethics Committee of Peking University Health Science Center (no. 2013-112).

Results: 10 SNPs in IBS and 12 SNPs in DD significantly different from HC and located in extronic, nonsynonymous and damage protein structure. 7 of them are the same: Methylation in SSPO gene were positively correlated with HAD depression scores in IBS patients [3, 4]. Methyl-CpG binding domain 1 (MBD1) gene, have the ability to bind DNA at methylated CpG sites. MBD1 rs125555 was found in a singleton Caucasian family and was carried by each family member who diagnosed with anxiety or depression [5]. Mbd1−/− mouse is also showing increased anxiety, greater susceptibility to depression. RECQL4 rs4251691 and SLC7A6OS rs8063446 are the risk variants in IBS while ANKRD11 rs113527563 is the protective one. RECQL4 rs4251691 is reported in Rothmund-Thomson syndrome patients. Detailed clinical data were collected from 16 patients having RECQL4 mutations and diarrhea was reported in 12 out of 14 patients [6, 7]. For depressive disorder patients, COMT rs6267, EDN3 rs11570255 and PPBP rs201450284 are risk variants, SCARF1 rs3744644 and VASN rs3810818 show some protective effect. Catechol-O-methyltransferase (COMT) associated with experimental pain sensitivity. COMT rs6267 minor alleles in the high pain sensitive haplotype coding for 20-fold reductions in COMT enzymatic activity and correlated with schizophrenia or Parkinson's disease [8, 9].

Conclusion: This is the first study using whole exome pool-seq to look at genetic associations of IBS and depressive disorder together in Chinese population. Our results show IBS and DD patients have the same risk mutation which are associated with neuronal modulation or depression. Meanwhile, specific SNPs are found in IBS or DD patients respectively. The results support that same genetic variants may leading to the high comorbidity of IBS and depression.

SNPs	ORIBS	ORDD
SSPO rs12536873	3.98	2.83
MBD1 rs125555	1.18	1.07
RECQL4 rs4251691	2.58	-
ANKRD11 rs113527563	0.33	-
SLC7A6OS rs8063446	2.41	-
EDN3 rs11570255	-	3.77
PPBP rs201450284	-	12.63
SCARF1 rs3744644	-	0.15
VASN rs3810818	-	0.45
COMT rs6267	-	1.56
others		

[Odd ratio of significant variants in IBS and DD]

Disclosure: Nothing to disclose

References

1. Anand S, et al. Next Generation Sequencing of Pooled Samples: Guideline for Variants' Filtering. *SCI REP-UK* 2016: 6(1).
2. Mahurkar S, et al. Genome-wide DNA methylation profiling of peripheral blood mononuclear cells in irritable bowel syndrome. *Neurogastroenterol Motil* 2016: 28(3): 410–422.
3. Giddaluru S, et al. Genetics of structural connectivity and information processing in the brain. *Brain Struct Funct* 2016: 221(9): 4643–4661.
4. Cukier HN, et al. Novel variants identified in methyl-CpG-binding domain genes in autistic individuals. *Neurogenetics* 2010: 11(3): 291–303.
5. Siitonen HA, et al. The mutation spectrum in RECQL4 diseases. *Eur J Hum Genet* 2009: 17(2): 151–158.
6. Suter AA, et al. Rothmund-Thomson Syndrome: novel pathogenic mutations and frequencies of variants in the RECQL4 and USB1 (C16orf57) gene. *Mol Genet Genomic Med* 2016: 4(3): 359–366.
7. Nackley AG, et al. Low enzymatic activity haplotypes of the human catechol-O-methyltransferase gene: enrichment for marker SNPs. *PLoS ONE* 2009: 4(4): e5237.
8. Lin CH, et al. Depression and Catechol-O-methyltransferase (COMT) genetic variants are associated with pain in Parkinson's disease. *Sci Rep* 2017: 7(1): 6306.

access to technologies and continuous medical education by primary care physicians.

	Duodenal Ulcer	Gastric Ulcer	Non-investigated Dyspepsia	Investigated Dyspepsia	1st Degree family of cancer	Afraid of cancer	GERD	Anaemia
Never	19%	20%	29%	29%	51%	70%	30%	52%
Occasionally	16%	14%	24%	25%	21%	21%	31%	31%
Usually	21%	23%	30%	28%	15%	5.6%	25%	11%
Always	44%	43%	17%	18%	13%	3.3%	15%	6.7%

[Do you diagnose H. pylori in the following patients?]

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TUESDAY, OCTOBER 23, 2018   10:30–12:00

Clinical management and consequences of H.pylori eradication – Room F1_____

OP165   SPANISH PRIMARY CARE SURVEY ON THE MANAGEMENT OF *H. PYLORI* INFECTION: PREFERENCES, ACCESS TO TECHNOLOGY, AND DECISIONS

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Introduction: The *H. pylori* management preferences and decisions of primary care physicians, or their access to different health technologies (i.e. diagnostic methods), courses and information have not generally been taken in consideration by the literature even though they currently manage most of the infections.
Aims and Methods: To evaluate the preferences, decisions and access to health technology of Spanish Primary Care physicians. A multidisciplinary committee formed by *H. pylori* experts from the Spanish Association of Gastroenterology (AEG) and the 3 societies of primary care in Spain (SEMFyC, SEMERGEN and SEMG) designed an online survey registering 140 variables regarding demographics, type of practice, continuous education received, preferences on management and access to health technology. Survey was submitted via e-mail to the members of the three societies. Responses were anonymously codified. Truncated responses were considered up to disconnection, in identified duplicates the most complete and/or latest response was used. Responses were weighted by province, gender, age and type of practice. Survey was performed using the AEG-REDCap platform. Margin of error of the survey is 2.5%.
Results: A total of 1,581 responses were received between December 2017 and March 2018. After removing blank and duplicate responses 1,425 were valid for analysis. 66% (95% CI = 64-68%) were women and the average age was 48 years (SD = 11). 59% were from urban context, 20% from semi-urban and 21% from rural. 93% provided public practice. Only 84% of GPs have direct access to diagnostic methods (55% stool antigen test SAT, 50% to upper GI endoscopy, 44% to urea breath test UBT, and 30% to serology). 19% of GPs prescribed eradication treatment without diagnostic testing (14% occasionally, 3.4% usually, and 1.4% always). Table shows strategy taken based on the conditions of the patient. The most common management option for patients below 55 years old and no-alarm symptoms was antisecretory treatment (67%) mostly alone (33%) although sometimes combined with SAT (15%), UBT (9%), Serology (3%) or derivation to gastroenterologist (3%). The next most common were SAT (35%, alone 14%), and UBT (25%). For patients with alarm symptoms or above 55, the most common strategies were endoscopy (48%), derivation to gastroenterologist (45%) and antisecretory treatment (20%). After treatment 68% perform confirmatory test, 5% never and 28% depending on the clinical situation (If symptoms persist 96%, in duodenal ulcer 74%, gastric ulcer 83%, non-investigated dyspepsia 50%, investigated dyspepsia 32%, if symptoms disappear 10%). Only 67% tested 4 weeks or more after treatment. The most common first-line treatment of choice was triple (59%; with a Proton pump inhibitor (PPI), clarithromycin and amoxicillin 56% and other triple 3%) followed by non-bismuth quadruple concomitant with clarithromycin, metronidazole, amoxicillin and a PPI (28%), bismuth quadruple therapy (single capsule 6.8% or doxycycline combination 3.0%), other (1.1%).
Conclusion: Our survey shows there is a significant deviation from recommended strategies in Spain to the real access to health technology and decisions taken by primary care physicians. A strong national program is needed to ensure adequate

OP166   PCR TEST FOR *HELICOBACTER PYLORI* DETECTION AND CLARITHROMYCIN RESISTANCE PREDICTION ON FECAL AND BIOPTIC SAMPLES: COMPARISON OF ACCURACIES

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Introduction: *Helicobacter pylori* (Hp) infection treatment is still a challenge for clinicians. Eradication rates of first-line clarithromycin-based regimens have fallen in the last 20 years, mainly due to the increase of clarithromycin resistant Hp strains. Hp culture is difficult, time consuming, not always successful and it requires an invasive procedure. 12 point mutations in the 23SrRNA gene related to clarithromycin resistance have been so far identified, in particular A2142C, A2142G, A2143G are present in 90% of cases.
Aims and Methods: To evaluate the accuracy of RT-PCR performed on stool samples to detect the presence of *Hp* DNA while concurrently detecting point mutations in the 23SrRNA gene. Results were compared with RT-PCR carried on bioptic samples.
Methods: Between January and April 2018, 93 dyspeptic patients (30 males, 63 females, mean age 49.5 years) referred to our Unit to perform an upper endoscopy, were enrolled. Composite reference method (CRM): [13]C urea breath test (^{13}C UBT), rapid urease test, histology and culture were performed to establish Hp status. On Hp positive cultures, antibiogram was performed with the E-test method. On the day of endoscopy, stools specimens were collected and rapidly frozen at -20°C.
Results: With the CRM method 69 patients resulted Hp positive and 24 Hp negative. In stools, 64 out of the 69 positive specimens were deemed *true positive* and all the negative specimens were detected properly (accuracy: 94.6%, 95% CI: 87.9% to 98.2%). Among the 64 positive samples, 30 out of 32 were deemed *true sensitive* and 22 out of 32 *true resistant* (accuracy: 81.3%, 95% CI: 69.5% to 89.9%). In biopsies, 66 out of the 69 positive specimens were deemed *true positive* and all the negative specimens were detected properly (accuracy: 97.8%, 95% CI: 92.4% to 99.7%). Among the 66 positive samples, 32 out of 33 were deemed *true sensitive* and 23 out of 33 *true resistant* (accuracy: 83.4%, 95% CI: 72.1% to 91.4%). PCR on stools and biopsies were highly concordant, being Cohen K coefficient 0.9 for Hp detection and 0.8 for resistance prediction.
Conclusion: *Helicobacter pylori* DNA and 23SrRNA point mutations can be detected in human stool specimens with high accuracy, obtaining the same performance of DNA extraction from biopsies. RT-PCR on stools can therefore be used to determine the presence of the bacterium and the genotypic resistance to clarithromycin, facilitating the choice of the right therapeutic approach when endoscopy or culture can't be performed.
Disclosure: Nothing to disclose

OP167 GENOTYPIC RESISTANCE GUIDED VERSUS EMPIRICAL THERAPY FOR REFRACTORY *HELICOBACTER PYLORI* INFECTION – A RANDOMIZED TRIAL

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Introduction: Randomized controlled trials comparing susceptibility testing guided therapy and empirical therapy for patients who fail after 2 or more eradication therapies for *H. pylori* are lacking.
Aims and Methods: We aimed to compare the efficacy of genotypic resistance guided therapy versus empirical therapy for eradication of refractory *H. pylori* infection. This multicenter, open label, parallel group, randomized trial was conducted between Oct 2012 and Sep 2017. Adult (≥20 years old) patients who failed after at least 2 eradication therapies for *H. pylori* infection were enrolled. Eligible patients were randomized to receive either (A) genotypic resistance guided therapy for 14 days; or (B) empirical therapy according to medication history for 14 days. Eradication status was determined by ^{13}C-urea breath test. The primary outcome was the eradication rate at least 6 weeks after eradication therapy according to intention-to-treat (ITT) analysis. Genotypic resistances of clarithromycin (23S rRNA) and levofloxacin (gyrase A) were determined by PCR with direct sequencing.
Results: Upon recruitment of 41 patients, trial 1 was terminated because of low efficacy of doxycycline sequential therapy (57.7%, 15/26). We replaced doxycycline with tetracycline in trial 2 and a total of 410 patients were randomized as the original design. The overall prevalence of resistance for clarithromycin, metronidazole, levofloxacin, amoxicillin, tetracycline, and rifabutin were 90.4% (381/411), 66.2% (272/411), 61.1% (251/411), 13.3% (55/411), 7.5% (31/411), and 1.5% (6/411), respectively. The eradication rates of genotypic resistance guided therapy and empirical therapy were 81% (17/21) and 60% (12/20) in trial 1 (p = 0.181), respectively, and were 78% (160/205) and 72.2% (148/205) in trial 2 (p = 0.170), respectively, according to ITT analysis. The frequencies of adverse effects and compliance were not significantly different in the 2 treatment groups in trial 1 and trial 2.
Conclusion: Properly designed empirical therapy according to medication history in this trial may be an alternative strategy to genotypic resistance-guided therapy for eradication of *H. pylori* infection after 2 or more eradication failures if susceptibility testing is not available.
Disclosure: Nothing to disclose

OP168 SHIFTS IN HUMAN GUT MICROBIOTA AFTER HELICOBACTER PYLORI ERADICATION THERAPY: SHORT AND LONG-TERM EFFECTS

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Introduction: Antibiotics treatment may affect the indigenous gut microbiota and lead to a violation in the host-microbiota balance.
Aims and Methods: The aim of the study was to assess the human gut microbiota composition in *H.pylori*-positive patients before, immediately after and 1 month after eradication therapy.
Stool samples from 83 *H.pylori*-positive patients before and immediately after eradication therapy as well as 14 stool samples one month after the eradication from the same patients were collected. Eradication therapy included amoxicillin (1000 mg), clarithromycin (500 mg), proton pump inhibitor and bismuth subsalicylate (240 mg) bid for 14 days.
Stool samples total DNA shotgun sequencing was performed on SOLiD 5500xl-W platform. Overall microbial composition as well as Shannon diversity index were used for evaluating the changes in gut microbiome.
Results: In general, 4 fila were predominant in gut microbiota of *H.pylori*-positive patients before eradication therapy: Firmicutes (56.73 ± 21.8)%, Bacteroidetes (35.97 ± 23.65)%, Actinobacteria (2.42 ± 4.23)%, Proteobacteria (2.37 ± 6.99)%. The relative abundance of Firmicutes decreased immediately after therapy (48.76 ± 23.66)% vs. (56.73 ± 21.8)% (p = 0.06) and 1 month after: (40.85 ± 18.26)% vs. (56.73 ± 21.8)% before therapy (p = 0.047). However relative abundance of Bacteroidetes increased immediately after therapy and one month after the eradication therapy, thus becoming the most represented phyla. Abundance of Actinobacteria, Euryarchaeota, Verrucomicrobia reduced, whereas the number of Proteobacteria increased immediately after eradication, however, the tendency to return to the initial level was observed in a month after the treatment.
Bacteria of the following genus: Bacteroides (15.1 ± 17.32)%, Prevotella (14.1 ± 21.60)%, Eubacterium (13.79 ± 10.49)%, Faecalibacterium (6.26 ± 5.85)%, Ruminococcus (5.61 ± 5.77)%, Subdoligranulum (5.3 ± 5.77)%, Butyrivibrio (4.6 ± 13.26)%, Coprococcus (4.57 ± 13.26)%, Roseburia (4.0 ± 4.56)%, which could be considered as "core microbiota" members, were the most represented before the initiation of therapy. Immediately after eradication therapy the relative abundance of almost all these bacterial genera decreased, except Bacteroides, which representation increased: (21.9 ± 19.71)%

vs. (15.1 ± 17.32)% before therapy (p = 0.049). The abundance of Escherichia and Klebsiella increased as well: (6.02 ± 13.68) % vs. (1.73 ± 6.32)% initially (p = 0.0019) and (3.02 ± 13.26)% vs. (0.17 ± 0.79)% before therapy (p = 0.0068), respectively. These bacteria are considered to be potentially pathogenic and could have a negative effect on human health.
There was a tendency to return to the initial level for the abundance of most of bacterial genus by 1 month after eradication therapy, except for the Subdoligranulum, Ruminococcus, Eubacterium genera.
The Shannon index was found to be significantly decreased immediately after the eradication therapy compared with baseline: (2.43 ± 0.61)% vs. (2.66 ± 0.55)% (p = 0.015), which may indicate the instability of the gut microbiota, reduction of the overall bacterial diversity and the possible dominance of 1 or several particular species. 1 month after the end of therapy the Shannon index increased, but was still slightly lower than the baseline level (2.54 ± 0.33)% vs. (2.66 ± 0.55)% (p = 0.103).
Conclusion: So *H.pylori* eradication therapy causes significant changes in the gut microbiota composition, which can indirectly affect human health. Changes are individual in the majority of patients. Apart from the tendency to return to baseline level, some changes persist even 1 month after completion of eradication therapy.
Disclosure: Nothing to disclose

OP169 THE IMPACT OF *HELICOBACTER PYLORI* INFECTION, ERADICATION THERAPY AND PROBIOTIC SUPPLEMENTATION ON GUT MICROENVIRONMENT HOMEOSTASIS: AN OPEN-LABEL, PROSPECTIVE CLINICAL TRIAL

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Introduction: It was estimated that approximately 4.4 billion individuals were infected with *Helicobacter pylori (H. pylori)* worldwide by year 2015. As we know, *H. pylori* is the dominant bacterial species of gastric microbiota in *H. pylori*-infected patients. The domination of *H. pylori* can change the gastric microenvironment and result in the reconstitution of gastric microbial community. However, the influence of *H. pylori* infection on gut microbiota homeostasis is still largely unknown.
As is well known, eradication therapy of *H. pylori* is followed by gastric and gut microbiota alterations. Whether the alterations are beneficial or detrimental, and the effect of eradication therapy on gut microbiota were not thoroughly studied. As a typical butyric acid-producing bacterium, *Clostridium butyricum* (*C. butyricum*) has been studied in several test models and human for the eradication of *H. pylori*. However, most studies of *C. butyricum* were conducted with standard triple eradication therapy, analyzed gut microbiota alterations using bacterial culture, and emphasized the effect on eradication rate and side effects. Our study analyzed the effect of *C. butyricum* supplementation on gut microbiota homeostasis using 16S rRNA sequencing.
Aims and Methods: Our study aimed to investigate the impact of *H. pylori* infection, 14-day BQ therapy and probiotic supplementation on gut microbiota homeostasis and to provide suggestions for clinical decision. A total of 70 *H. pylori*-positive patients and 35 *H. pylori*-negative patients were enrolled. *H. pylori*-positive patients were randomly assigned to group A and group B. Patients in Group A received 14-day BQ therapy consisting of pantoprazole, amoxicillin, furazolidone and colloidal bismuth pectin. Patients in Group B were supplemented with *C. butyricum*. Stool samples of *H. pylori*-positive patients were collected on day 0, day 14 and day 56 while stool samples of *H. pylori*-negative patients were collected on day 0. Gut microbiota was investigated by 16S rRNA sequencing. *H. pylori* status was reassessed by ^{13}C urea breath test on day 56 for patients in group A and group B. *H. pylori*-negative status indicated the success of eradication treatment.
Results: 63 *H. pylori*-positive patients and 35 *H. pylori*-negative patients completed this study. Several important metabolism pathways were predicted to be more abundant in *H. pylori*-positive community while some human diseases pathways were with higher potential in *H. pylori*-negative community through KEGG pathway analysis. The abundances of most butyric acid-producing bacteria significantly decreased and those of several detrimental bacteria increased immediately after 14-day BQ therapy. The gut microenvironment homeostasis was not completely reconstituted 6 weeks after treatment in spite of a recovery tendency. Although no significant improvement of eradication rate was observed, more gastrointestinal symptoms were relieved with the supplementation of *C. butyricum*.
Conclusion: The role of *H. pylori* in human disease and gut microenvironment homeostasis may not be necessarily detrimental. The eradication of *H. pylori* should be based on comprehensive analysis of individual patients, especially for asymptomatic *H. pylori*-infected patients. The gut microbiota was extremely changed immediately after eradication therapy and 6 weeks was not enough to thoroughly reconstitute gut microenvironment balance in spite of a recovery tendency. *C. butyricum* might promote the recovery of gut microenvironment balance through immunological and non-immunological mechanisms.
Disclosure: Nothing to disclose

OP170 HELICOBACTER PYLORI ERADICATION THERAPY IN LOCALIZED GASTRIC MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMA: A PROSPECTIVE, NATIONWIDE, MULTICENTER STUDY IN JAPAN

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Introduction: *Helicobacter pylori* eradication therapy induces clinical and histological regression of gastric extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) in the majority of cases and was approved for the first-line, standard treatment of *H. pylori*-positive gastric MALT lymphoma by Japanese government in 2010. Although several retrospective studies or small-scale single-centre studies have been reported, a prospective, large-scale, multi center study has not yet been conducted in Japan.

Aims and Methods: We have conducted a prospective, nationwide, multicenter study to evaluate the clinical efficacy of rabeprazole-based triple *H. pylori* eradication therapy for the patients with localized gastric MALT lymphoma in practice-based clinical trial (ClinicalTrials.gov, NCT01264822). The 108 *H. pylori*-positive patients with clinical stage I/II1 (Lugano staging system) underwent *H. pylori* eradication therapy. The primary endpoints were complete remission (CR) rate and the rate of transfer to secondary treatment. The secondary endpoints were CR maintenance duration and overall survival (OS).

Results: *H. pylori* eradication was successfully achieved in all 97 patients of the efficacy analysis set. CR of lymphoma was achieved in 84 of the 97 patients (86.6%), during the period of 2.0–44.7 months (median, 5.3 months) following *H. pylori* eradication treatment. CR was maintained in 77 of 81 patients (95.1%), who were followed for 0.4–53.2 months (median, 33.1 months). Kaplan-Meier estimates for the cumulative probability of CR maintenance were 97.3% (95% CI; 89.6–99.3%) at 12 months and 94.2% (95% CI; 85.3–97.8%) at 24 months, 36 months and 48 months. Secondary treatments (radiotherapy, rituximab, or gastrectomy) for gastric MALT lymphoma were needed in 10 of the 97 patients (10.31%). During follow-up, OS rate was 96.9% (94/97). 3 patients died of causes unrelated to gastric lymphoma.

Conclusion: *H. pylori* eradication therapy demonstrated a high CR rate, long CR maintenance for patients with localized and *H. pylori*-positive gastric MALT lymphoma in this prospective, practice-based, nationwide, multicenter study. The results suggested that the follow-up interval could be extended after 24 months of CR maintenance by *H. pylori* eradication in the patients with the same clinical characteristics enrolled in this study.

Disclosure: This study was supported by Eisai Co., Ltd.

TUESDAY, OCTOBER 23, 2018   10:30–12:00

IBD: From drug monitoring to immunogenicity – Room G_____

OP171 INDUCTION AND EARLY MAINTENANCE VEDOLIZUMAB TROUGH LEVELS PREDICT MUCOSAL HEALING IN INFLAMMATORY BOWEL DISEASE

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Introduction: Vedolizumab (VDZ), an anti-$\alpha_4\beta_7$ integrin monoclonal antibody, is effective for the treatment of inflammatory bowel disease and leads to long-term mucosal healing. There is emerging data that early trough levels (TL) predict mucosal healing (1), while the correlation of maintenance TL and mucosal healing remains unknown.

Aims and Methods: We investigated the correlation between induction and maintenance VDZ TL on mucosal healing in a prospectively followed cohort.
We measured TL at weeks 2, 6, 10, 14, 22, 38, 54 and at the infusion closest to endoscopy or treatment discontinuation using the apDia Vedolizumab ELISA in all patients starting vedolizumab treatment at our centre between May 2016 and April 2017. Our main outcome was mucosal healing, defined as SES-CD < 4 and Mayo endoscopic subscore 0 or 1, assessed at endoscopy between w30 and w54, evaluated centrally by a blinded expert endoscopist. Patients who discontinued treatment due to inefficacy were considered to have active disease. Predictive cut-off values were identified using receiver operating curve analysis.

Results: Of the 54 patients in the study population, 25 (46%) had ulcerative colitis. The vast majority (83%) had failed treatment with anti-TNFα agents. 21 (39%) achieved mucosal healing by week 54. Patients with mucosal healing had significantly higher median VDZ TL at weeks 6, 10, 22, but not later on in the maintenance phase (Table 1). A cut-off of 19.1 µg/ml at week 6 predicted mucosal healing with 81% sensitivity and 70% specificity (AUC 0.742, 95% confidence interval: 0.587–0.897; $p = 0.007$), while a cut-off of 10.1 µg/ml at week 22 identified patients with mucosal healing with 53% sensitivity and 76%

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specificity (AUC 0.783, 95% confidence interval: 0.646–0.920; $p = 0.001$). Among patients with both TL below the cut-offs 5/23 (21.7%) achieved mucosal healing, while 16/25 (64%) of those with at least one of the TL above the cut-off achieved mucosal healing ($p = 0.003$).

Median vedolizumab trough level (IQR) [µg/mL]	Mucosal healing by week 54 (n = 21)	No mucosal healing by week 54 (n = 33)	P-value
Week 2	24.7 (10.9)	18.2 (9.2)	0.073
Week 6	**25.9 (7.6)**	**14.4 (12.8)**	**0.004**
Week 10	**20.3 (7.0)**	**12.7 (14.5)**	**0.012**
Week 14	12.1 (9.2)	5.2 (13.6)	0.060
Week 22	**14.2 (9.4)**	**4.0 (7.4)**	**0.004**
Week 38	11.7 (5.5)	5.3 (13.3)	0.193
Week 54	11.2 (5.6)	11.5 (23.3)	0.706
At endoscopy	11.7 (10.0)	9.6 (15.8)	0.499

[Vedolizumab trough levels during the first year and mucosal healing by week 54 of treatment. IQR – interquartile range]

Conclusion: Induction vedolizumab trough levels, particularly at weeks 6 and 22, were significantly higher in patients achieving mucosal healing by week 54 and could serve as predictors of endoscopic outcomes.

Disclosure: Dr Drobne has served as a speaker, a consultant and an advisory board member for MSD, Abbvie, Takeda, Pfizer, Janssen, Krka. Dr Novak has served as a speaker, a consultant and an advisory board member for Takeda, MSD, Abbvie, Dr. Falk Pharma, Ferring, Pfizer. Dr Ferkolj has served as a speaker, a consultant and an advisory board member for MSD, Abbvie, Takeda and Krka. Dr Štabuc has served as a speaker, a consultant and an advisory board member for Krka, Bayer, Takeda and has received research funding from Krka. Dr Gils reports grants and speaker fees from Pfizer, speaker fees from MSD, Janssen Biologicals, Takeda and Abbvie. Other authors have no disclosures.

Reference

1. Yacoub W, Williet N, Pouillon L, et al. Early vedolizumab trough levels predict mucosal healing in inflammatory bowel disease: a multicentre prospective observational study. *Aliment Pharmacol Ther*. 2018 Apr; 47(7): 906–912.

OP172 MAINTENANCE LEVELS OF VEDOLIZUMAB DO NOT CORRELATE WITH CLINICAL REMISSION IN IBD PATIENTS

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Introduction: Therapeutic drug monitoring (TDM) has an established role in the use of anti-TNF therapies in inflammatory bowel disease (IBD). The role of TDM for vedolizumab (VDZ) therapy has not been well characterized. Suggested trough levels associated with clinical and endoscopic remission range from 5.1ug/ml to >11ug/ml in previous studies.

Aims and Methods: We aimed to determine whether maintenance VDZ levels correlate with clinical remission and mucosal healing in patients with IBD.
We performed a cross-sectional, observational study in a single IBD centre. Included patients had a minimum of 3 VDZ infusions and VDZ levels drawn within 14 days of their infusion. Chart review was performed to determine the Harvey-Bradshaw Index (HBI) score or the partial Mayo score at the time of VDZ level as well as endoscopic scores if applicable. The primary endpoint was clinical remission (HBI score of < 5, partial Mayo score of < 2, or pouch disease activity index score < 7). The secondary endpoint was mucosal healing, defined as an SES-CD score of < 5 or a Mayo endoscopic subscore of < 2. Endoscopy data was included if performed within 8 weeks of drug level testing. Serum VDZ levels and antibodies-to-vedolizumab (ATV) were obtained using a drug-tolerant assay (Prometheus Labs, San Diego, California). VDZ levels were expressed as median with inter-quartile ranges (IQR). Statistical analysis was performed using the Kruskill-Wallis test, Chi-squared test and ROC curves.

Results: 60 patients were included (25 Crohn's disease, 34 ulcerative colitis/IBD-U, and 2 with pouchitis). 38 (63%) were anti-TNF experienced and 1 patient was co-treated with anti-TNF therapy. 9 patients (15%) were on concomitant immunomodulator therapy. 25 patients (42%) were on q4week dosing, 31 (52%) were on q8week dosing, and 4(6%) were on q6week dosing. Median VDZ level was 10.6ug/ml (6.3–18.6). Patients receiving VDZ q4weeks had significantly higher levels than those receiving q8week dosing (20.6ug/ml vs 8.35ug/ml, p < 0.0001) without significant differences in remission rates (40% vs 45%, p=0.530). 2 patients had low-titre detectable ATV although both these patients had detectable drug levels. Clinical remission rates were not significantly higher in patients with higher levels (14.6ug/ml vs 10.1ug/ml, p=0.287). The area under the curve (AUC) for VDZ levels and clinical remission was 0.619. Of the cohort studied, 24 (40%) had endoscopic data available. Of these, 10 patients (42%) achieved mucosal healing while 14 (58%) did not. There was no difference between VDZ maintenance levels of those with mucosal healing when compared to

those without mucosal healing (17.56 ug/ml vs 16.10ug/ml, p = 0.682). The AUC for VDZ levels and mucosal healing was 0.55.

Conclusion: In a single-centre cohort of IBD patients, there was no association between maintenance VDZ levels and clinical remission or endoscopic mucosal healing. Shortening the dosing interval achieves higher VDZ levels, but this did not correlate with improved clinical response. This finding supports our observation that dose escalation of VDZ does not improve clinical response rates in patients with IBD. Interestingly, few patients had detectable ATV despite lower rates of concomitant immunomodulator use than previously studied populations, supporting the suggestion that VDZ has lower immunogenicity than other biologics.

Disclosure: Nothing to disclose

OP173   INTEREST IN THE ADDITION OF AZATHIOPRINE (AZA) TO THE SWITCH OF ANTI-TNF IN IBD PATIENTS IN CLINICAL RELAPSE WITH UNDETECTABLE ANTI-TNF TROUGH LEVELS AND ANTI-DRUG ANTIBODIES: A PROSPECTIVE RANDOMIZED TRIAL

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Introduction: In patients experiencing a loss of response to an anti-TNF with unfavorable pharmacokinetics (undetectable levels and anti-drug antibodies), the algorithms propose a switch of the anti-TNF but is frequently accompanied by the subsequent appearance of antibodies directed against the second anti-TNF.

Aims and Methods: Between 2012 and 2016, all patients with IBD in loss of response to a first optimized anti-TNF given in monotherapy at induction or 6 months later and with an undetectable level of anti-TNF with a high level of anti-drug antibodies were included. They were randomized to receive either AZA or nothing and induction by a second anti-TNF was performed at standard doses. They were followed for 2 years after the switch, with a measurement of the clinical activity and pharmacokinetics of the second TNF at 6, 12 and 24 months. Non-primary responders after the change were excluded. A clinical failure was defined as a disease outbreak defined on a Harvey Bradshaw score > 5 associated with a faecal calprotectin level 250 µg/g stool for Crohn's disease or a Mayo score > 3 with an endoscopic sub-score > 1 in the case of ulcerative colitis and the need for a therapeutic change (dose intensification, change in treatment, addition of corticosteroids or AZA, use of surgery). The appearance of unfavorable pharmacokinetics was defined by the appearance of low or undetectable levels of anti-TNF with anti-drug antibodies.

Results: 90 patients (48 CD, mean age: 39.5 years, sex ratio M/W: 0.95) were included. The second anti-TNF was adalimumab (ADA) and infliximab (IFX) in 40 and 50 patients, respectively. 45 patients were randomized to receive AZA (2 to 2.5 mg/kg mg/kg). Groups with or without AZA were comparable. At 12 months and 24 months, clinical safe survival rates and unfavorable pharmacokinetics were significantly higher in combination therapy (Log rank < 0.0001): 85% vs. 62% and 80% vs. 59% at 12 months and 80% respectively *vs* 20% and 84% vs. 30% at 24 months. These rates were not different at 6 months (90% vs. 76% and 85% vs. 68%; p = 0.1). These results did not differ according to the type of anti-TNF. With the ADA for reference, hazard ratios (HR) were for the IFX of 1.2 [0.6–2.3], for ADA-AZA combination therapy of 0.1 [0-0.4] and for combotherapy IFX-AZA of 0.2 [0.1–0.4]. In univariate and multivariate analysis, only the use of combination therapy was significantly associated with a favorable change after anti-TNF switch. The type of IBD, the duration of the disease or the characteristics of the patient were not associated to clinical outcome.

Conclusion: During a switch of anti-TNF (IFX to ADA or ADA to IFX) required for a loss of response due to unfavorable pharmacokinetics with the presence of anti-drug antibodies, it is necessary to associate the second anti-TNF with AZA.

Disclosure: Nothing to disclose

OP174   PREDICTORS OF IMMUNOGENICITY TO ANTI-TNF THERAPY IN IBD: RESULTS OF THE ABIRISK STUDY

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Introduction: ABIRISK is a multicenter, prospective, non-interventional study based on cohorts of patients with IBD, multiple sclerosis, rheumatoid arthritis. Patients are included at the start of biopharmaceuticals. Biological samples are collected, to find biomarkers predictive of efficacy and immunization. We herein report the results observed in the IBD cohort of patients treated with anti-TNFs.

Aims and Methods: Patients treated with adalimumab (ADL) or infliximab (IFX) as a first-line therapy for active IBD were eligible. Anti-drug antibodies (ADAb) were measured a chemo-luminescence drug tolerant capture ELISA assay at W0, W6, W12 and W52. Immunogenicity was defined as ADAb within the first 12 months of anti TNF treatment. Clinical activity was assessed at W6, W12, W52 and at withdrawal if the drug was discontinued. Surgical and medical history, including previous medications were reported at inclusion, while adverse events, including those related to ADAb, and concomitant medications were reported at any time points. Clinical remission was defined as a HBI≤3 in CD patients and a Mayo subscore ≤4 in UC patients. Patients who discontinued ADL or IFX or who were lost to follow-up were considered as treatment failures.

Results: 204 eligible patients were recruited from 17 centers (France, Belgium and Israel). 197 were included (7 screen failures) of whom 184 patients could be assessed (mean age was 36.9 (SD:13.7), 48.4% were women). There were 148 patients with CD and 36 with UC. 86 patients were treated with IFX (n = 86, REM or CT-P13) and 98 with ADL. Median disease duration was 3.69 (IQR: 10.37) years. In CD, median Harvey-Bradshaw index was 6, 27 had a penetrating phenotype (B3) (IFX, n = 17; ADL, n = 10) and 23 had perianal fistulas (IFX, n = 18 ADL, n = 6). In UC, median Mayo subscore was 6. 19.6% had extraintestinal manifestations. Concomitant immunosuppressants were prescribed in 68% and 40% of patients treated with IFX and ADA respectively. 82% and 35 % of patients treated with IFX and ADL received corticosteroids, respectively. At 1 year, 95 patients (51.6%) were in clinical remission, including 73 (40%) without optimization of anti-TNF therapy. ADAb were detected in 51 patients (27.7%). The immunogenicity rate for ADL and IFX was 38.8% and 15.1%, respectively. Mean time to onset of ADAb was 2.5 months, and ADAb persisted over time in 72%. Drug levels at 6 weeks of therapy were significantly lower in patients who developed ADAb. Immunogenicity was associated with non-remission at 1 year (58.6% in patients with ADAb vs 35.7% in patients without ADAb, p = 0.008). In multivariate cox regression analysis of time to ADAb development, immunogenicity was associated with concomitant immunosuppressant (HR: 0.39 [95% CI 0.2–0.75]), anti-TNF levels at 6 weeks of therapy (HR: 0.86 [95% CI 0.8–0.91]), antibiotics usage during the study (HR: 0.3 [95% CI 0.14–0.65]) and vaccine in the year before start of anti-TNF therapy (HR: 3.1 [95% CI 1.5–6.3]).

Conclusion: In IBD patients, immunogenicity towards anti-TNFs is associated with a lower remission rate and lower drug levels. Concomitant immunosuppressants and antibiotics are associated with a lower risk of immunogenicity while vaccine received before the start of anti-TNF are associated with an increased risk of immunogenicity.

Disclosure: Nothing to disclose

OP175 MAGNETIC RESONANCE ENTEROGRAPHY ASSESSMENT OF MUCOSAL HEALING WITH VEDOLIZUMAB IN PATIENTS WITH MODERATE-SEVERE CROHN'S DISEASE: RESULTS FROM THE VERSIFY STUDY

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Introduction: Magnetic resonance enterography (MREn) may be used in clinical practice to assess disease activity in Crohn's disease (CD).[1,2] Vedolizumab (VDZ) is clinically effective in patients (pts) with moderately to severely active CD,[3] but healing with VDZ on MREn has not been previously measured. This study evaluated the effect of VDZ on radiologic remission using MREn at weeks (wks) 26 and 52 in pts with active CD.

Aims and Methods: VERSIFY (NCT02425111) was a Phase 3b, open-label study evaluating endoscopic remission with VDZ in 101 pts at 26 wks, and in 56 eligible pts at 52 wks following a protocol amendment extending treatment duration. Only patients receiving VDZ at the time of the amendment, or enrolled after the amendment was implemented, were eligible to be treated to wk 52. Pts were enrolled with moderate-severe CD ($\geq$3 months; CD Activity Index 220-450; Simple Endoscopic Score for CD $\geq$7; $\geq$1 mucosal ulceration on centrally read endoscopy) and who had prior failure to a corticosteroid, immunomodulator, and/or $\geq$1 TNF [tumour necrosis factor] antagonist). The MREn substudy enrolled 37 pts, of whom 21 were eligible to continue treatment to wk 52. The exploratory endpoint was Magnetic Resonance Index of Activity (MaRIA) score;[4] quantified in 6 ileocolonic segments (1 ileal and 5 colonic). MaRIA-7 remission of all active lesions and MaRIA-11 remission of only severe lesions were defined as scores of < 7 and < 11, respectively, in all segments, and were assessed at wk 26 and wk 52. Data were analysed in the full analysis set (FAS; all treated pts) and in the per-protocol set (PPS; treated pts with sufficient data at baseline and post-baseline). Only pts with an abnormal MaRIA score of $\geq$7 or $\geq$11 in $\geq$1 segment at baseline, respectively, were included in the analysis. If no relevant post-baseline MaRIA scores were available then they were considered non-responders in the FAS. Subgroup analyses of the FAS and PPS by prior TNF exposure were performed.

Results: Of 37 pts enrolled into the MREn substudy, 32 pts had a baseline MaRIA score $\geq$7 in $\geq$1 segment and 32 had a baseline score $\geq$11 in $\geq$1 segment. These pts were included in the MaRIA-7 and MaRIA-11 remission analysis. The 5 pts who did not meet the threshold for inclusion in the MaRIA-7 remission analysis were classified as having 'suboptimal' MREn exams at baseline. 27/32 pts had 26 wk observations. 15/21 MREn pts had 52 wk observations. At baseline, in the FAS-MREn population (n = 32), the mean MaRIA score for the most severely affected segment was 24.8. MaRIA-7 and MaRIA-11 remission at wk 26 and wk 52 for the FAS-MREn population are shown in Table 1. MREn remission rates at wk 26 and wk 52 in the PPS-MREn population (n = 26) were similar to those observed in the FAS-MREn population (overall and in anti-TNF naïve and failure pts) (Table 1).

Conclusion: VDZ can induce radiologic remission (MaRIA-7) in a difficult-to-treat population with moderately to severely active CD, both in those naïve to, or who had failed, anti-TNF therapy.

References

1. Rimola J, et al. *Gut* 2009; 58: 1113–20.
2. Rimola J, et al. *Inflamm Bowel Dis* 2011; 17: 1759–68.
3. Danese S, et al. *J Crohns Colitis* 2018; 12(Suppl. 1): S016-S017.
4. Ordas I, et al. *Gastroenterology* 2014; 146: 374–82.e1.

OP176 SOLUBLE MUCOSAL ADDRESSIN CELL ADHESION MOLECULE 1 AND RETINOIC ACID ARE POTENTIAL TOOLS FOR THERAPEUTIC DRUG MONITORING IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE TREATED WITH VEDOLIZUMAB: A PROOF OF CONCEPT STUDY

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Introduction: Vedolizumab (VDZ), a humanized monoclonal antibody targeting $\alpha 4\beta 7$ integrin, is effective in induction and maintenance therapy in patients with inflammatory bowel disease (IBD) who have not adequately responded to standard therapies, and high levels of vedolizumab trough levels (VTL) have been associated with clinical remission. The $\alpha 4\beta 7$ integrin binds to endothelial MAdCAM-1 and is up-regulated by retinoic acid (RA).

Aims and Methods: To determine the relations between soluble MAdCAM-1 (sMAdCAM-1) and RA concentrations with clinical remission during VDZ maintenance therapy.In a retrospective study performed in IBD patients treated with VDZ we measured VTL, sMAdCAM-1 and RA concentrations.

Results: Among the 62 included patients (38 Crohn's disease) 24 relapsed and 38 stayed in remission between weeks 10 to 30 after VDZ initiation. During this maintenance therapy, median values of VTL and RA were 15.4 µg/mL and 0.97 ng/mL, whereas sMAdCAM-1 was undetectable (<0.41 ng/mL) in 67.3%

Abstract No: OP175
Table 1: Overall remission by MREn

	FAS-MREn		PPS-MREn	
	Wk 26	Wk 52	Wk 26	Wk 52
Overall population	**N = 32**	**N = 21**	**N = 26**	**N = 14**
MaRIA-7 remission, n (% [95% CI])	7 (22% [9.3-40.0])	8 (38% [18.1-61.6])	7 (27% [11.6-47.6])	8 (57% [28.9-62.3])
MaRIA-11 remission, n (% [95% CI])	11 (34% [18.6-53.2])	9 (43% [21.8-66.0])	11 (42% [23.4-63.1])	9 (64% [35.1-67.2])
TNF naïve subgroup	**N = 20**	**N = 13**	**N = 16**	**N = 11**
MaRIA-7 remission, n (% [95% CI])	5 (25% [8.7-49.1])	8 (62% [31.6-86.1])	5 (31% [11.0-58.7])	8 (73% [39.0-94.0])
MaRIA-11 remission, n (% [95% CI])	7 (35% [15.4-59.2])	8 (62% [31.6-86.1])	7 (44% [19.8-70.1])	8 (73% [39.0-94.0])
TNF failure subgroup	**N = 12**	**N = 8**	**N = 10**	**N = 3**
MaRIA-7 remission, n (% [95% CI])	2 (17% [2.1-48.4])	0	2 (20% [2.5-55.6])	0
MaRIA-11 remission, n (% [95% CI])	4 (33% [9.9-65.1])	1 (13% [0.3-52.7])	4 (40% [12.2-73.8])	1 (33% [0.6-90.6])

of samples. The positive predictive value (PPV) of undetectable sMAdCAM-1 for clinical remission was 80.0% with a corresponding sensitivity of 74.6%. On multivariate analysis undetectable sMAdCAM-1 and high VTL (> 19 µg/mL) were independently associated with clinical remission (OR = 7.5, p = 0.006 and OR = 2.2, p = 0.045, respectively). The combination of sMAdCAM-1 < 0.41 ng/mL and VTL > 19 µg/mL was the best pharmacokinetic profile with a PPV of 95.2%. Median values of sMAdCAM-1 and RA were significantly higher (p = 0.0001) before VDZ therapy than during the follow-up (sMAdCAM-1: 40.5 vs. < 0.41 ng/mL; RA: 1.7 vs. 0.97 ng/mL). Only RA > 1.86 ng/mL before VDZ therapy was predictive of clinical remission during the follow-up (AUROC = 80.7%).

Conclusion: Undetectable sMAdCAM-1 appears strongly associated with clinical remission during VDZ maintenance therapy. Combination of undetectable sMAdCAM-1 with high VTL is also potentially interesting for therapeutic drug monitoring. Baseline RA concentrations are predictive of clinical remission. These findings need to be confirmed in further prospective studies.

Disclosure: Nothing to disclose

TUESDAY, OCTOBER 23, 2018   10:30−12:00
Faecal transplantation in C. difficile: How to do it right? – Room K_____

OP177 DEVELOPING MICROBIOME RESTORATION BIOMARKERS FOR *CLOSTRIDIUM DIFFICILE* INFECTIONS: CONTINUED EVALUATION OF A PROTOTYPE MICROBIOME HEALTH INDEX

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Introduction: Intestinal microbiome disruption (dybiosis) is linked to many human diseases and chronic conditions, most notably recurrent *Clostridium difficile* infections (rCDI). In response, there are numerous efforts to develop FDA-approved microbiota-based drugs to restore a healthier microbiome. These include RBX2660, a standardized, stabilized liquid microbiota suspension delivered by enema, and RBX7455, a lyophilized, non-frozen, orally administered microbiota product. Given the lack of established biomarkers for microbiome restoration, we are evaluating unidimensional Microbiome Health Indices (MHI) to measure microbiome restoration, which are based on the associations of *Bacteroidia* and *Clostridia* with colonization resistance, and *Gammaproteobacteria* and *Bacilli* with dysbiosis. Herein we evaluate MHI data from three clinical trials for preventing rCDI, including 2 controlled Phase 2 trials of RBX2660 and 1 Phase 1 trial of RBX7455.

Aims and Methods: Patient fecal samples were collected as part of three clinical trials for preventing rCDI in which treatment success was freedom from CDI recurrence at 8 weeks after treatment. Fecal samples and RBX2660 or RBX7455 product samples were extracted and sequenced using standard 16S or shallow shotgun methods, and the resulting operational taxonomic units (OTU) data were used to calculate MHI values. MHIs from the 2 RBX2660 trials were pooled, and receiver operator characteristic (ROC) analysis was used to define an MHI cut-point for distinguishing rCDI subjects prior to RBX2660 treatment (baseline) from the RBX2660 drug product. Post-treatment MHIs from patients in all trials were assessed longitudinally and by outcome.

Results: Baseline MHI values were not significantly different among all 3 trials (p > 0.05). ROC analysis indicated that the pooled baseline samples from RBX2660 trials could be distinguished from the pooled RBX2660 profile with a maximum likelihood ratio of 121 (AUC = 0.99, sensitivity = 0.96, specificity = 0.99, cutpoint = 8.2). Among patients who responded to treatment, MHIs were significantly higher 7 days after treatment (p < 0.001) for the RBX2660 trials, with 58% of responders having an MHI > 8.2, and an increasing percentage of participant MHIs above the cutpoint at 30 and 60 days post-treatment. Similar results were observed in the RBX7455 trial, with 38%, 75%, and 87% of participants above MHI = 8.2 at 7, 30, and 60 days post treatment. Among patients who failed treatment, MHIs were also significantly higher 7 ± 4 days after treatment (p < .001), but only 21% were above the MHI = 8.2 cut-point. More importantly, among pooled data from all 3 trials, MHI of successes could be distinguished from failures at 7 ± 4 days post-treatment.

Conclusion: MHI values and trends pre- and post-treatment are consistent across 2 controlled Phase 2 clinical trials for RBX2660 and 1 Phase 1 trial of RBX7455, suggesting potential for prospective evaluation of MHI as an exploratory microbiome endpoint. MHI can also effectively distinguish patients with dysbiosis from healthier patients. Significant MHI increases can be measured post-treatment, and in this analysis MHI can differentiate successes from failures at 7 ± 4 days post-treatment. These results generate prospectively evaluable hypotheses for future clinical trials and emphasize the value of a unidimensional MHI.

Disclosure: This analysis was funded by Rebiotix, Inc., Roseville, MN.

OP178 TWO YEARS OF EXPERIENCES IN *CLOSTRIDIODES DIFFICILE* TREATMENT OF THE NETHERLANDS DONOR FECES BANK

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Introduction: Since 2016, the Netherlands Donor Feces Banks (NDFB) is facilitating the treatment of patients with multiple recurrences of *Clostridiodes difficile* infections (rCDI) with fecal microbiota transplantations (FMT).

Aims and Methods: An observational study was performed using a standardized approach of data collection and guidance of an expert team of medical microbiologists, infectious diseases physicians and gastroenterologists. Furthermore, microbiota analysis was performed on 10 patient fecal samples before and after FMT, and their corresponding donor fecal samples. Shotgun metagenomics was performed on an Illumina Nextseq. The sequencing data was quality controlled and taxonomically profiled with the One Codex platform and afterwards all reads were cross-assembled with the MegaHit assembler. Taxonomic annotation was performed with Megablast/LCA.

Results: Between March 2016 and March 2018, 260 of 472 donor candidates completed a questionnaire; 220 (85%) were excluded, mainly because age above 50 and an unhealthy BMI. 39 (15%) donor candidates were invited for laboratory screening of blood and feces of which 15 (38%) passed this screening. Carriership of *Blastocystis hominis*, *Dientamoeba fragilis* and Multi Drug Resistant Organisms were the most observed exclusion criteria. Of 15 donors, 6 failed at a following screening test, which is performed every 2 months. Finally, 9 (3.5%) active donors were enrolled. Between March 2016 and April 2018, 99 patients were evaluated by our FMT expert team. Of these 99 patients, 76 (77%) were considered as suitable candidates for FMT treatment and 23 (23%) were interpreted as patients with underlying bowel disease who concomitantly carried *C. difficile*. The mean age of the 76 FMT treated patients was 72 year, 58.6% was female, and the mean recurrence rate was 3.4 CDI episodes. The treatment was performed in 28 different hospitals with a success rate of 89%. 8 patients suffered a CDI relapse, of which 4 were associated with antibiotic use within one month after FMT. All 8 were successfully treated, of which 7 with anti-CDI antibiotics again. 2 serious adverse events (SAE) of faecal regurgitation were reported without further complications. The microbiota analysis indicated that patients with active CDI had a reduced diversity and extremely diversity composition of their microbiota compared to healthy donors, and compared to the microbiota after FMT. The patient microbiota after FMT was more similar to its donor microbial community than to the other microbiota samples in the study.

Conclusion: Only a low percentage (3.5%) of healthy volunteers are qualified as suitable feces donors. Critical evaluation of FMT applications in a multidisciplinary setting is useful, as a high percentage (23%) of FMT request was rejected due to *C. difficile* carriership instead of infection. An high success rate (of 89%) of FMT for multiple recurrent CDI was observed. Furthermore, we observe that antibiotic stewardship after FMT is of importance as a high proportion of CDI relapses after FMT is caused by antibiotic use. Microbiota analysis confirmed that FMT is associated with an increase in diversity of the microbiota.

Disclosure: Research funding: The NDFB is supported by a grant of the Netherlands Organization for Health Research and Development, ZonMW (VIMP number 1708810011) The NDFB receives an unrestricted grant Vedanta for microbiota analysis

OP179 FROZEN DONOR STOOL FOR FECAL MICROBIOTA TRANSPLANTATION IS AS EFFECTIVE AS FRESH STOOL IN INDUCING RESPONSE AND REMISSION IN ACTIVE ULCERATIVE COLITIS

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Introduction: Recently, double-blind randomized studies investigating fecal microbiota transplantation (FMT) in chronic active ulcerative colitis (UC) have shown promising results. The use of variable FMT protocols used for this indication raises questions concerning the route and frequency of application and preparation of donor stool. The use of frozen stool in *Clostridium difficile* infection has been shown to be as effective as fresh donor stool and increases availability of FMT for this indication.

Aims and Methods: The aim of this analysis was to assess the clinical efficacy of frozen and fresh donor stool for FMT in ulcerative colitis. 49 patients suffering

from chronic active ulcerative colitis received repeated fecal microbiota transplantation (5 times every second week) using the same protocol, except for donor stool preparation. 25 patients (mean age 36 y ± 15) were treated with frozen donor stool (mixed with sodium chloride and glycerol, stored at -80°C), 24 patients (mean age 44y ± 9) with freshly prepared donor stool (not older than 6 hours). Remission and response were determined by the total Mayo score (TMS) before FMT and after 90 days. Clinical response was defined as a decrease of ≥3 points in TMS from baseline, along with either a decrease of >1 point in the rectal bleeding subscore or the absolute rectal bleeding subscore of 0 or 1. Remission was defined as a TMS < 2 and an endoscopic subscore of 0 or 1.
Results: The mean TMS was 9.2 ± 2.2 (frozen stool) and 8.9 ± 1.8 (fresh stool) at baseline and was reduced to 5.1 ± 2.7 in the frozen donor stool group and to 5.3 ± 3.6 in the fresh donor stool group at day 90. The mean improvement in TMS between baseline and day 90 was statistically not significant different between the two groups (p = 0.691). Furthermore, remission and response rates were comparable between frozen donor stool and fresh donor stool cohorts (No response/Response/Remission: 40%/40%/20% vs. 42%/33%/25%; p = 1.00/ 0.769/0.742).
Conclusion: In chronic active ulcerative colitis frozen donor stool for FMT is as effective as fresh donor stool in inducing response and remission in ulcerative colitis. By using frozen donor stool FMT may become more available for the clinical use in this patient group.
Disclosure: Nothing to disclose

OP180 A CULTUROMICS-BASED SYNTHETIC MICROBIOTA CONSORTIUM, DERIVED FROM SUCCESSFUL BACTERIAL ENGRAFTERS, IS A SAFE AND EFFECTIVE TREATMENT FOR RECURRENT *CLOSTRIDIUM DIFFICILE* INFECTION: A PILOT STUDY

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Introduction: Although faecal microbiota transplantation is a highly effective treatment against recurrent *Clostridium difficile* infection (CDI) its dissemination is prevented by many issues, including regulation, long-term safety, screening costs, identification of optimal protocols. Specific microbiota suspensions may help overcoming these concerns and provide a fine-tuning therapeutic option for CDI and other dysbiosis-related disorders.
Aims and Methods: The aim of this study is to assess the safety and efficacy of a culturomics-based synthetic microbiota suspension, derived from successful bacterial engrafters, in treating patients with recurrent CDI.
The synthetic microbiota consortium was composed of 15 bacterial species belonging to the phyla Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria. To select bacterial species composing the consortium we assessed the engraftment between 5 patients with recurrent CDI and a single healthy donor after clinically successful FMT, and selected those engrafting the recipients' gut. Then, selected bacterial strains were cultured on each one conditions and resuspended in NaCl 0.9% solution in order to obtain a final concentration of 2 MCFarland unit in a total of 500 ml per patient.
Each patient received a 500 ml-suspension of synthetic microbiota consortium by colonoscopy after a 3-day vancomycin course and a bowel lavage. The primary end point was the cure of *C. difficile*-associated diarrhea 8 weeks after the end of the treatment. Safety was evaluated by monitoring adverse events.
Results: From November 2016 to December 2017, 10 patients (6 males; mean age 75 years old) with recurrent CDI were enrolled. 6 patients had resolution of *C. difficile*-associated diarrhea after the first infusion of microbiota consortium, while the 4 remaining patients cured CDI after a second infusion. Overall, the synthetic microbiota consortium cured all 10 patients (100% both in per-protocol and intention-to-treat analyses). No serious adverse events associated with the treatment were observed. We found significant shifts in the microbiota composition of treated patients. Additional metagenomic analyses are currently running and will be presented at the UEG Week if this abstract is selected.
Conclusion: In our pilot study, a culturomics-based synthetic microbiota consortium, derived from successful bacterial engrafter, cured all patients with recurrent CDI, and had a favorable safety profile. Should these preliminary results be confirmed, synthetic microbiota suspensions may be considered as a potential therapy for the treatment of recurrent CDI.
Disclosure: Nothing to disclose

OP181 RANDOMISED CLINICAL TRIAL: SINGLE INFUSION- VERSUS MULTIPLE INFUSION-FAECAL MICROBIOTA TRANSPLANTATION FOR THE TREATMENT OF SEVERE *CLOSTRIDIUM DIFFICILE* INFECTION REFRACTORY TO ANTIBIOTICS

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Introduction: Faecal microbiota transplantation (FMT) is a highly effective treatment against recurrent *Clostridium difficile* infection. Far less evidence exists on the efficacy of FMT in treating severe *Clostridium difficile* infection refractory to antibiotics.
Aims and Methods: The aim of our study was to compare the efficacy of 2 FMT-based protocols associated with vancomycin in curing subjects with severe *Clostridium difficile* infection refractory to antibiotics.
Subjects with severe *Clostridium difficile* infection refractory to antibiotics were randomly assigned to 1 of the 2 following treatment arms: 1) FMT-S, including a single faecal infusion via colonoscopy followed by a 14-day vancomycin course; 2) FMT-M, including multiple faecal infusions plus a 14-day vancomycin course. In the FMT-M group, all subjects received at least 2 infusions, while those with pseudomembranous colitis (PMC) underwent further infusions until the disappearance of pseudomembranes. The primary outcome was the cure of refractory *Clostridium difficile* infection.
Results: 56 subjects, 28 in each treatment arm, were enrolled. 21 patients in the FMT-S group and 28 patients in the FMT-M group were cured, respectively (75% versus 100%, respectively, both in PP and ITT analyses; p = 0.01). No SAEs associated with any of the 2 treatment protocols were observed.
Conclusion: A vancomycin-associated and PMC-driven FMT protocol based on multiple faecal infusions was significantly more effective than a vancomycin-associated single-shot FMT protocol in curing severe *Clostridium difficile* infection refractory to antibiotics.
Disclosure: Nothing to disclose

OP182 A NON-FROZEN, LYOPHILIZED, ORAL MICROBIOTA-BASED DRUG RBX7455 IS SAFE, REDUCES *CLOSTRIDIUM DIFFICILE* INFECTION RECURRENCE, AND RESTORES THE MICROBIOME: CLINICAL EVIDENCE FROM 3 PATIENT COHORTS

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Introduction: To broaden access to microbiota-based therapeutics therapies, RBX7455, a non-frozen, lyophilized, orally-administered microbiota-restoring drug candidate was developed. We report additional interim results from an open-label Phase 1 trial of RBX7455 for preventing recurrent *Clostridium difficile* infections (rCDI).
Aims and Methods: 25 patients with ≥2 CDI episodes following ≥2 courses of antibiotic therapy have been enrolled to date in 3 cohorts as follows: 1) 4 RBX7455 capsules twice daily for 4 days, n = 10; 2) 4 RBX7455 capsules twice daily for 2 days, n = 10; 3) 2 RBX7455 capsules twice daily for 2 days, n = 5 to date. Success was defined as absence of CDI recurrence through 8 weeks after treatment completion, and adverse events were monitored during and after treatment.
Recipient stool samples prior to and at 1, 7, 30, and 60 days after treatment were collected. Stool and representative RBX7455 product samples were sequenced using an ultra-shallow shotgun sequencing method. Operational taxonomic unit (OTU) data were grouped by cohort and compared using a Bray-Curtis dissimilarity calculation. Relative OTU abundances at the class level were compared among time points.
Results: 9 of 10 patients in cohort 1, 8 of 10 patients in cohort 2, and 5 of 5 patients in cohort 3 were recurrence-free at the 8-week endpoint, with an overall success rate of 88% (22/25). A total of 37 non-serious adverse events (AEs) have been recorded to date, with gastrointestinal AEs being most common. No serious AEs have been observed.
Prior to treatment, the taxonomic compositions of responder microbiomes were significantly dissimilar from the RBX7455 composition and were dominated by Gammaproteobacteria and Bacilli. After treatment, patient microbiomes converged toward the RBX7455 composition, with Bacteroidia and Clostridia becoming more predominant. Microbiome changes were similar among responders from all cohorts.
Conclusion: 3 different dosing regimens of RBX7455 had a high success rate in preventing rCDI with no serious AEs. In addition, RBX7455 appears to restore patient microbiomes toward the RBX7455 composition. Microbiome and safety data collection will continue for 6 months after treatment.
Disclosure: This analysis was funded by Rebiotix Inc., Roseville, MN.

TUESDAY, OCTOBER 23, 2018   10:30–12:00
Cirrhosis: It's all about varices! – Room N1_____

OP183 TREATMENT OF GASTRIC FUNDAL VARICES WITH EUS-GUIDED EMBOLISATION COMBINING COIL PLACEMENT WITH THROMBIN INJECTION

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Introduction: Gastric varices are present in 5-33% of patients with portal hypertension with incidence of bleeding of around 25% in 2 years[1]. If gastric varices are identified as the source of bleeding, therapeutic options include endoscopic methods, TIPSS, surgery and non-selective beta blockade[2]. There are reports of EUS-guided coiling combined with cyanoacrylate glue[3] but limited literature on safety and efficacy of EUS-guided coil embolisation with human thrombin injection. We report our experience.
Aims and Methods: We analysed data of all EUS-guided interventions for the management of bleeding gastric varices between 2015-2017 at a liver transplant center. Olympus EUS linear scope was used to inject human thrombin (Tisseel®; 500IU/ML) in gastric varices with or without coils (Nester® Embolization Coils).
Results: A total of 10 EUS-guided interventions in 6 patients (4M & 2F), aged 55 (41-59) yrs for secondary prophylaxis. 67% patients had cirrhosis with MELD score of 14 (10-21) and 75% were Child-Pugh class C. The remainder had non-cirrhotic portal hypertension. All patients had previous bleeding from gastric varices and 2/3rd were intolerant of beta-blockers. 67% had previous thrombin injection that had failed to obliterate the gastric varices. EUS-guided coil embolisation was undertaken with thrombin injection in 6, and thrombin alone in 40 (2 had previous coils embolisation). The largest feeding vessel was 120 (7-16) mm with a median 5 (2-10) coils placement followed by thrombin injection of 3500 (2500- 5000) IU.
Most (8/10) stayed overnight after intervention and only 2 required longer stays. Median F/U was 9 (3-20) months with zero 30-day mortality. 1 patient had fever 2 days post procedure requiring IV antibiotics. No reported episodes of re-bleeding except in 1 patient at 23 months. 4 had follow up EUS (5-7 months) and showed no flow at the level of the coils. 1 patient died within 3 months of procedure secondary to hepatic decompensation.
Conclusion: In our experience EUS-guided coil embolisation and injection of thrombin is a technically safe and well-tolerated procedure even in patients with advanced liver disease especially who have failed eradication of gastric varices from single modality therapy. Due to the lower incidence of gastric variceal bleeding in comparison to oesophageal varices bleeding, we recommend multi-center prospective data collection evaluating the modalities being used and reporting of outcomes to help inform national guidelines.
Disclosure: Nothing to disclose

References

1. *Hepatology* 1992; 16: 1343–1349.
2. *Gut* 2015; 64: 1680–704.
3. *Gastrointest Endosc*. 2016 Jun; 83(6): 1164–72.

OP184 PHARMACOKINETIC/PHARMACODYNAMIC MODELING AND SIMULATION OF LUSUTROMBOPAG, A NOVEL THROMBOPOIETIN RECEPTOR AGONIST, FOR TREATMENT OF THROMBOCYTOPENIA IN PATIENTS WITH CHRONIC LIVER DISEASE UNDERGOING INVASIVE PROCEDURES

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Introduction: Patients with thrombocytopenia (TCP) associated with chronic liver disease (CLD) have an increased risk of bleeding during planned invasive procedures. Lusutrombopag (LUSU) is a small-molecule orally active agonist of human thrombopoietin receptor. At the 2015 and 2017 annual meetings of the American Association for the Study of Liver Diseases (AASLD), Izumi N et al and Afdhal NH et al reported the results from phase 3 studies (L-PLUS 1 in Japan and L-PLUS 2 in multiple nations) evaluating LUSU treatment of TCP in patients with CLD who were undergoing non-emergency invasive procedures, and concluded that LUSU 3 mg once daily was an effective and safe alternative to platelet transfusions (1, 2). Here we report the further analysis for characterizing the pharmacokinetics/pharmacodynamics (PK/PD) of LUSU based on the multiethnic data and assessing a risk of platelet overshooting during the treatment.
Aims and Methods: Population PK/PD analyses were performed using a total of 4196 plasma LUSU concentrations from 427 subjects (78 healthy subjects and 349 thrombocytopenic patients with CLD) and 3526 platelet counts from 347 of the above 349 patients. Covariates were explored from subjects' background data. PK/PD simulations were performed to calculate platelet metrics, ie, the probabilities of platelet counts $\geq$50 G/L on Days 9 to 14 (efficacy index) and >200 G/L (safety index defined as overshoot) for assessing dose response.
Results: The developed models well described the PK/PD of LUSU. Body weight was an influential covariate on PK, but no effects of covariates (including ethnicity, body weight, age, sex, and Child-Pugh score) on response profiles of thrombopoiesis were clinically significant. In the simulations, the 3-mg dose provided a probability of 87.1% and 80.8% of platelet count $\geq$50 G/L on Days 9 to 14 in Japanese and non-Japanese patients, respectively. The probabilities of platelet

overshooting (>200 G/L) at the 3-mg dose were low in Japanese and non-Japanese patients: 1.52% and 0.43%, respectively.
Conclusion: The modeling and simulation in the multiethnic data support that oral LUSU 3 mg once daily for 7 days has no ethnic differences in efficacy and has low risk for platelet overshoot in treating TCP in patients with CLD undergoing invasive procedures.
Disclosure: This study was supported by Shionogi & Co., Ltd. The authors, Takayuki Katsube, Ryosuke Shimizu, Takahiro Fukuhara, Takeshi Kano, and Toshihiro Wajima, are all employees of Shionogi & Co., Ltd.

References

1. Izumi N et al. *Hepatology*. 2015; 62: 1397A [abstract LB-30].
2. Afdhal NH et al. *Hepatology*. 2017; 66: 1254A [abstract LB-1].

OP185 MEASUREMENT OF SPLENIC STIFFNESS IN THE PREDICTION OF ESOPHAGEAL VARICES AND THE RESPONSE TO CARVEDILOL THERAPY IN PORTAL HYPERTENSIVE PATIENTS

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Introduction: Esophageal Varices is one of the dreadful complications of portal hypertension [1]. Upper endoscopy is the gold standard for diagnosing esophageal varices [2]. Noninvasive methods were applied in order to predict the presence of esophageal varices and their response to medical treatment [3].
A recent method is the assessment by splenic stiffness measurement [4]. Many studies were carried out for evaluating this technique, all of them agreed on the benefit, however, their results were different regarding a specific united cut-off value and the capability of identifying the size of the varices [5]. These differences were thought to be due to readings exceeding the maximum value (75 kPa) of the machine [6].
Carvedilol is a nonselective β-blocker used to reduce portal pressure in order to prevent variceal bleeding [7], being a potent therapeutic agent with dual action (non-selective β-blocker and α1-adrenergic blocker) [8]. Effective dose of carvedilol for reducing portal pressure with the least arterial hypotension was found to be 12.5mg/d [9].
Aims and Methods: The aim of this study is to investigate the possibility of using the spleen stiffness measurement by transient elastography as a noninvasive approach to detect esophageal varices, and comparing the results obtained to liver stiffness measurement and platelet count to spleen diameter ratio in detecting and grading the size of varices. The study also aims to monitor changes in spleen stiffness before and after carvedilol therapy.
This was a single-center, prospective cross-sectional study, conducted on 110 individuals (90 chronic HCV patients and 20 healthy controls). Patients were divided into 4 groups; **Group 1:** Healthy controls, **Group 2:** Chronic Hepatitis, **Group 3:** Cirrhotics without varices, **Group 4:** Cirrhotics with varices.
All patients enrolled were over 18 years of age. Patients with transient elastography technical difficulty, contraindication to β-blockers, pregnant females, those receiving portal hypotensive medications, and those undergone previous endoscopic management of esophageal varices were excluded from the beginning. Each patient underwent abdominal ultrasound and laboratory investigations, cirrhotic patients (60) were furtherly subjected to doppler ultrasonography to confirm portal hypertension, then upper endoscopy to verify the presence of esophageal varices, patients with esophageal varices were prescribed carvedilol (6.25mg twice daily) (30). Liver and spleen stiffness was done for all patients once and it was repeated again for patients who received carvedilol after three month of treatment as described.
Results: There was statistical significant difference between all groups in terms of both liver and spleen stiffness (p < 0.001). An inverse correlation was found in **group 4** between spleen stiffness before treatment and the spleen size (R-value -0.438, p = 0.016). Patients in **group 4** showed a statistical significant difference in spleen stiffness measurement before and after treatment (p < 0.001). Spleen stiffness measurement was capable of predicting the presence of esophageal varices at cut off 59.85kPa with AUC 0.768, showing sensitivity 80% and specificity 70%. However, neither spleen stiffness nor platelet count to spleen size ratio were capable of predicting the size of the varices.
Conclusion: Spleen stiffness measurement by transient elastography is a reliable noninvasive method in predicting the presence of esophageal varices compared to other noninvasive methods and monitoring of treatment by carvedilol; however, it was not capable of identifying the size nor the risk of variceal bleeding.
Disclosure: Nothing to disclose

References

1. Garcia-Tsao G, Abraldes J, Berzigotti A, Bosch J. (2017) *Hepatology*. 2017; 65(1): 310–35. https://doi.org/10.1002/hep.28906.
2. Seo, Y. S. (2018) *Clinical and Molecular Hepatology,* 24(1), 20–42. http://doi.org/10.3350/cmh.2017.0064.
3. Kraja, B., Mone, I., Akshija, I., et al. (2017) *World Journal of Gastroenterology,* 23(26), 4806–4814. http://doi.org/10.3748/wjg.v23.i26.4806.
4. Bae J, Sinn DH, Kang W, et al. (2018) *Liver Int*. 2018; 00: 1–7. https://doi.org/10.1111/liv.13732.

5. Ma X, Wang L, Wu H et al. (2016): *PLoS One* 2016; 11: 1–15 https://doi.org/10.1371/journal.pone.0165786.

6. Calvaruso V, Bronte F, Conte E, et al. (2013) *J Viral Hepat*. 2013; 20: 867–874. https://doi.org/10.1111/jvh.12114.

7. Abd ElRahim, A.Y., Fouad, R., Khairy, M. et al. (2018) *Hepatol Int* 2018; 12: 75. https://doi.org/10.1007/s12072-017-9835-9.

8. Bosch J, Abraldes JG, Fernández M, et al. (2010) *J Hepatol* 2010; 53: 558–567. https://doi.org/10.1016/j.jhep.2010.03.021.

9. Schwarzer R, Kivaranovic D, Paternostro R, et al. (2018) *Aliment Pharmacol Ther*. 2018; 47: 1162–1169. https://doi.org/10.1111/apt.14576.

OP186 RANDOMISED TRIAL OF BALLOON-OCCLUDED RETROGRADE TRANSVENOUS OBLITERATION VERSUS CYANOACRYLATE INJECTION FOR PREVENTION OF GASTRIC VARICEAL REBLEEDING

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Introduction: Gastric variceal bleeding is less common than esophageal variceal bleeding; however, it is associated with a high morbidity and mortality rate. The aim of our study was to compare the balloon-occluded retrograde transvenous obliteration (BRTO) with cyanoacrylate injection for the prophylaxis of recurrent gastric variceal bleeding.

Aims and Methods: Between June 2015 and June 2018, 64 patients with variceal bleeding were randomly assigned either balloon-occluded retrograde transvenous obliteration (n = 32) or cyanoacrylate injection (n = 32). The mean duration of follow−up period was 415 ± 250 days in the BRTO group and 404 ± 210 days in the cyanoacrylate group. Foam sclerotherapy using lauromacrogol by BRTO was performed.

Results: The technical success rate was 100% (32/32 patients) in the BRTO group. The amount of lauromacrogol used was 12.5 ± 4.5 ml (range, 3-20 ml). Significant rebleeding occurred in 1 patients (21.9%) of the BRTO group, and 7 patients (21.9%) of cyanoacrylate injection group (p = 0.023). The cumulative probability of remaining free of all-cause rebleeding was significantly higher in the BRTO group than in the cyanoacrylate group; the probability at 1 year was 88.9% in the BRTO group and 78.1 % in the cyanoacrylate group (p = 0.024). There was no difference in survival with estimated 1-year survival rates for BRTO and cyanoacrylate injection treated patients of 90.5% and 86.3%, and 2-year survival rates of 69.6% and 86.3%, respectively.

Conclusion: These results suggest that the BRTO is more effective than cyanoacrylate injection in prevention of gastric variceal rebleeding. Survival is similar in the 2 groups.

Disclosure: Nothing to disclose

OP187 FEASIBILITY OF DIRECT EUS-GUIDED EMBOLISATION OF RECURRENT BLEEDING PARASTOMAL VARICES

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Introduction: Recurrent bleeding from stomal varices secondary to portal hypertension can be challenging to treat. Treatments available include transjugular intrahepatic portosystemic shunt (TIPSS) and/or coil embolisation of the dominant vein passing to the stoma or surgical portosystemic shunt formation[1]. A more recent approach to treat gastric varices is using endoscopic ultrasound (EUS) guidance using coil embolisation or in combination with cyanoacrylate glue[2]. Endoscopic use of human thrombin in gastric varices has also been proposed as a treatment[3]. To date there are no publications on the EUS-guided thrombin injection combined with coil embolisation. We have experience of adopting this approach to treat stomal varices by EUS guidance

Aims and Methods: We analysed data and outcomes of all EUS-guided intervention for bleeding stomal varices from January 2014 to October 2017 at a regional liver transplant centre. All cases were done using Olympus EUS linear scopes, human thrombin (Tisseel®; 500IU/ML) ± coils (Nester® Embolization Coils). After intubation of the stoma with the EUS scope, the dominant feeding vessel to the stoma was targeted for injection with thrombin ± coils. All procedures were undertaken without sedation, and the majority without analgesia. Data presented as median (lower and upper quartile), unless stated otherwise.

Results: 19 patients (7 M & 12 F) aged 63.5 (54-70) years with recurrent bleeding from parastomal varices despite optimal medical therapy for portal hypertension had a total 27 EUS-guided injections of 3000 (2500-4500) IU of human thrombin. 47% (9/19) had thrombin alone and 53% (10/19) had concomitant coil embolisation. 68% (13/19) required single intervention, 21% (4/19) required 2 interventions and 11% (2/19) required 3 interventions with median follow-up of 8 (6-17) months, 3 lost f/u and 3 died due to primary disease. Failure of treatment was defined as bleeding requiring transfusion or hospital admission. Only 1 patient failed treatment and went on to have an emergency venogram + embolisation. No immediate complications or 30-day mortality were encountered.

Conclusion: EUS-guided injection of thrombin ± coil embolisation appears to be technically feasible and safe with good efficacy. To our knowledge this is the first series of EUS-guided thrombin injection ± embolisation of stomal varices. Due

to the relative low number of patients and short follow-up, further prospective evaluation of this promising technique is required.

Disclosure: Nothing to disclose

References

1. *Aliment Pharmacol Ther*. 2008 Aug 1; 28(3): 294–303.
2. *Cadiovasc Intervent Radiolo*. 2011 Feb; 34 Suppl 2: S210–3.
3. *Eur J Gastroenterol Hepatol*. 2014 Aug; 26(8): 846–52.

TUESDAY, OCTOBER 23, 2018   10:30−12:00
New insights in cholestatic liver diseases – Room N2

OP190 SURVIVAL OF PRIMARY SCLEROSING CHOLANGITIS: A POPULATION-BASED STUDY IN FINLAND

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Introduction: Primary sclerosing cholangitis (PSC) is a rare chronic cholestatic liver disease that leads to liver cirrhosis and predisposes the development of cholangiocarcinoma[1]. At present, no medication has been shown to delay the disease progression and liver transplantation (LT) is the only effective treatment for end stage liver disease. In previous studies mean time from diagnosis to liver transplantation or death varies between 12 and 20 years[1]. Concomitant inflammatory bowel disease (IBD) is present in 20-80% of patients, most commonly (80%) ulcerative colitis. Very few large population-based studies of PSC are available[2].

Aims and Methods: Aim of the study: to assess the survival of PSC patients in a large population-based cohort in Finland. All PSC patients from 1990 to 2015 in a defined area of Finland, the Hospital District of Helsinki and Uusimaa (HUS), were retrieved. HUS has a comprehensive register that includes all hospital admissions and discharge diagnoses, procedure codes and admission and discharge dates. In 2015 the HUS area comprised 29% (1,616,321) of the total Finnish population. Medical records of all patients included were reviewed to confirm the diagnosis and establish the time of the diagnosis. Cumulative survival and cumulative relative survival were calculated. Four endpoints for survival calculations were used: 1) death or LT 2) PSC-related death or LT 3) PSC-related death and 4) all deaths. PSC-related death was defined as death from liver disease, cholangiocarcinoma or colorectal cancer.

Results: 580 patient were retrieved of whom 54% were male. All resided in the HUS area at diagnosis and the diagnosis was established within the study period of 1990-2015. Median age at diagnosis was 40.6 years. Age at diagnosis was categorized into 4 groups: < 20 years, 20-39 years, 40-59 years, and ≥ 60 years. Within the study period 45 patients underwent LT and 68 died. Of the 68 deaths 39 were PSC-related. Estimated mean survival from diagnosis were 18.3 years (death or LT), 19.8 years (PSC-related death or LT), 23.1 years (PSC-related death) or 21.9 years (all deaths). The estimated mean time from diagnosis to death or LT for the age-groups at diagnosis were 18.7 (<20 years), 20.1 (20-39 years), 17.7 (40-49 years) and 13.7 (≥ 60 years), respectively. The relative survival decreased for both sexes with time from diagnosis. The cumulative and relative survival for males was slightly poorer than that for females. For patients who had a LT median time from diagnosis to LT was 6.4 years. The time to LT did not differ between males and females. Patients with IBD had a better prognosis than non-IBD patients, this was also true for ulcerative colitis and Crohn's disease versus non-IBD patients.

Conclusion: We confirm the longer survival in PSC previously reported. PSC patients in Finland with IBD have a better prognosis than non-IBD patients, in contrast to previously published data[3].

Disclosure: Nothing to disclose

References

1. Dyson JK1, Beuers U2, Jones DEJ3, et al. Primary sclerosing cholangitis. *Lancet*. 2018 Feb 13. pii: S0140-6736(18)30300-3. doi: 10.1016/S0140-6736(18)30300-3. [Epub ahead of print].

2. Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. *J Hepatol*. 2012 May; 56(5): 1181–8. doi: 10.1016/j.jhep.2011.10.025. Epub 2012 Jan 13.

3. Weismüller TJ1, Trivedi PJ2, Bergquist A3, et al. Patient Age, Sex, and Inflammatory Bowel Disease Phenotype Associate With Course of Primary Sclerosing Cholangitis. *Gastroenterology*. 2017 Jun; 152(8): 1975–1984.e8. doi: 10.1053/j.gastro.2017.02.038. Epub 2017 Mar 6.

OP191 LIPIDOMICS ANALYSES IN BILE IDENTIFIED SEVERAL CANDIDATE BIOMARKERS FOR DIAGNOSIS AND DISEASE PROGRESSION OF PRIMARY SCLEROSING CHOLANGITIS AND BILIARY DYSPLASIA

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Introduction: Primary sclerosing cholangitis (PSC) is a chronic, progressive structuring disease of bile ducts that may eventually lead to cirrhosis and cholangiocarcinoma (CCA). The etiopathogenesis is heterogeneous, involving both genetic and environmental factors. Early diagnosis and better tools for monitoring progression of PSC and detection of biliary dysplasia is a major medical challenge. Novel biomarkers enabling a more precise diagnostic and prognostic markers of both PSC and biliary dysplasia are urgently needed.

Aims and Methods: This study aimed identifying a set of lipids in bile that would serve as biomarkers for detection and prognosis of PSC and biliary dysplasia. After informed consent, bile samples (n = 151) were drawn from participants (n = 147) distributed across 4 experimental groups: non-advanced PSC (n = 63), advanced PSC (n = 58), biliary dysplasia (n = 24), and healthy controls (n = 6). The samples were subsequently analyzed using a novel lipid-screening platform (Lipidyzer^{TM}, Sciex) to determine the concentration of 1134 lipids species across 13 lipid classes.

Results: Model based analyses (Generalized Estimating Equations) pinpointed the following set of lipids as altered in PSC patients with respect to healthy controls, after correcting for type-I error: lysophosphatidylcholines (LPC(18:3), LPC(20:4), LPC(20:5), LPC(22:5), and LPC(22:6); lowest p = 6.4610^{-12}), lysophosphatidylethanolamines (LPE(20:3); p = 3.0610^{-6}), phosphatidylcholines (PC(14:0/16:1), PC(14:0/20:4), PC(17:0/18:1), PC(17:0/20:4), PC(18:0/18:1), and PC(18:0/18:3); lowest p = 3.2710^{-6}), phosphatidylethanolamines (total PE, PE(16:0/16:1), PE(16:0/18:1), PE(16:0/18:2), PE(16:0/18:3), PE(16:0/20:4), PE(18:0/18:3), PE(18:0/20:3), PE(18:0/20:4), PE(18:1/18:1), PE(18:1/18:2), PE(O-18:0/18:1); lowest p = 3.2710^{-6}), and multiple fatty acids in LPC (alpha-linolenic acid, arachidonic acid, eicosapentaenoic acid, docosapentaenoic acid and docosahexaenoic acid; lowest p = 6.4610^{-12}), LPE (eicosatrienoic acid; p = 3.0610^{-6}), PC (pentadecanoic acid and heptadecanoic acid; p = $2.0110^{-5}$and 1.6510^{-5}, respectively), and PE (hexadecanoic acid, heptadecanoic acid, oleic acid, alpha-linoleic acid, eicosatrienoic acid and arachidonic acid; lowest p = 1.8510^{-9}). All the above except PC(18:0/18:3) PE(16:0/18:2), PE(16:0/20:4), and eicosatrienoic acid in PE were also altered when comparing all affected patients (PSC and dysplasia) to healthy controls.

Conclusion: From the extensive lipid panel initially screened, this study was capable of detecting a set of 34 candidate bile biomarkers that allowed differentiating between persons affected with PSC and biliary dysplasia from the healthy controls.

Disclosure: Nothing to disclose

OP192 INFLUENCE OF ANTIBIOTIC DURATION IN CHOLANGITIS AFTER SUCCESSFUL DRAINAGE BY ERCP

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Introduction: The cornerstone of treatment in cholangitis exist of adequate drainage of the biliary tract by means of an ERCP in combination with antibiotics. Recommendations in current international guidelines regarding the duration of antibiotic treatment after adequate drainage vary from 3 days or less up to 10 days. The Dutch (SWAB) guideline recommends antibiotics for 3 days or less. However, high level of evidence to justify this recommendation is lacking. Our aim was to assess the incidence of infectious complications after adequate drainage of ascending cholangitis and to evaluate the potential influence of the antibiotic duration.

Aims and Methods: We performed a retrospective multicenter study in 7 medical centers in the Amsterdam region. Patients with cholangitis due to choledocholithiasis between January 2012 and January 2017 were extracted from local prospective endoscopy databases. Adequate drainage by means of ERCP was required. The primary outcome was number of infectious complications within 3 months after the initial ERCP. An infectious complication was defined as the need for antibiotics within 3 months after ERCP. Secondary outcomes included duration of hospital stay and guideline adherence.

Results: 426 patients with cholangitis due to choledocholithiasis were identified of which 303 patients met all inclusion criteria. During follow-up 68 infectious complications occurred in 64 patients (21%). The median duration of antibiotics given after adequate drainage was 4 days (IQR 2-6 days). In 141 patients (47%) the Dutch guideline was adhered, and antibiotics were given for 3 days or less. 39 of 68 complications (24%) occurred in patients receiving antibiotics more than 3 days versus 29 (21%) in the patients treated less than 3 days (p = 0.615). Severity of cholangitis (according to Tokyo guideline) did not differ between patients receiving antibiotics for 3 days or less or longer. The median duration of hospital stay was 6 days (IQR 4-9 days). Hospital stay in patients receiving antibiotics for 3 days or less was shorter in comparison with patients receiving antibiotics for more than 3 days; 6 days (IQR 4-8.5 days) and 7 days (IQR 5-9.5 days) respectively (p = 0.026).

Conclusion: The Dutch guideline regarding duration of antibiotics in cholangitic patients after successful ERCP is not consistently followed. Our data confirms that antibiotics for less than 3 days after adequate drainage does not lead to an increase in infectious complications in comparison with longer treatment. Moreover, treating for more than 3 days increases, likely unnecessary, hospital stay. We therefore recommend stricter adherence to the Dutch guideline.

Disclosure: Nothing to disclose

OP193 HUNTING THE ENVIRONMENTAL TRIGGER IN PRIMARY SCLEROSING CHOLANGITIS: DISEASE CLUSTERING WITH AFFLUENCE AND RURAL LOCATION

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Introduction: Primary sclerosing cholangitis (PSC) is a complex, chronic cholestatic disease with unknown aetiology. Genetic factors have been identified and whilst an environmental trigger has been postulated its identity is unknown (1-4). This is a unique study examining the role of putative environmental risk factors in a comprehensive, well-defined cohort of PSC patients.

Aims and Methods: The study aimed to identify all patients with PSC in a defined geographical region within England and examine whether there was evidence of environmental factors related to disease prevalence. The study was based in the Academic Health Science Network for the North East and North Cumbria (AHSN NENC); a region with a heterogeneous mix of urban and rural landscapes including areas of intensive historical and well-documented industrialisation.

Extensive, multi-source case-finding methodology was used. Besag-York-Mollie models were used to estimate the relative risk (RR) of PSC in individual postcode districts in relation to putative risk factors for disease. The null model was developed to look for clusters of disease. Models were then fitted with various single spatial covariates: urban-ness, traffic, landfill sites, coal mines, lead mines, sandstone quarries, limestone quarries, Townsend score (a measure of social deprivation), cadmium, arsenic, lead, manganese, iron, stream sediment pH) and a multi-covariate model containing covariates shown to be significant at 95% Bayesian Credibility Intervals (BCIs). Deviance Information Criterion (DIC) was used to compare the fits of models. All analyses were performed after controlling for the area size of each postcode district. There were 3 main questions:

1. Is the prevalence of PSC in a defined area greater than that expected by chance i.e. disease clustering?
2. If so, is elevated risk associated with any environmental risk factors local to the cases?
3. Is elevated risk dependent on socio-economic status?

Results: 472 patients were identified (diagnosed between 1972 and 2018); 321/472 (68%) male, median age at diagnosis 51 (11-92) years. The null model showed evidence of disease clustering with areas of high and low disease prevalence (controlled for population size). The areas of highest risk were in rural Cumbria (RR 1.755) and lowest risk in urban Darlington and Teeside (RR 0.6243).

Models using single spatial covariates showed that only urban-ness and Townsend score significantly improved the 'null model' with 2.5% and 97.5% confidence intervals not crossing 0. A multi-covariate model (combining urban-ness and Townsend score) did not improve the model further. There was a statistically significant difference in the Townsend scores of the 20 patients living in areas of highest and lowest prevalence (p < 0.0001) with lower Townsend scores (i.e. less social deprivation) seen in areas of high disease prevalence.

Conclusion: A higher prevalence of PSC was seen in more rural, less deprived areas. This inverse association with social deprivation is the opposite to that seen in epidemiological studies of many other diseases, including liver diseases, and warrants further investigation into potential disease triggers. The association with rurality raises the possibility of an association with processes in these areas e.g. farming, pesticide use.

References

1. Ji SG, Juran BD, Mucha S et al. Genome-wide association study of primary sclerosing cholangitis identifies new risk loci and quantifies the genetic relationship with inflammatory bowel disease. *Nat Genet.* 2017; 49(2): 269–273.
2. Alberts R, de Vries EMG, Goode EC et al. Genetic association analysis identifies variants associated with disease progression in primary sclerosing cholangitis. *Gut.* 2017 doi: 10.1136/gutjnl-2016-313598. [Epub ahead of print].
3. Eaton JE, Juran BD, Atkinson EJ et al. A comprehensive assessment of environmental exposures among 1000 North American patients with primary sclerosing cholangitis, with and without inflammatory bowel disease. *Aliment Pharmacol Ther.* 2015; 41(10): 980–90.
4. Boonstra K, de Vries EM, van Geloven N et al. Risk factors for primary sclerosing cholangitis. *Liver Int.* 2016; 36(1): 84–91.

OP194   DURABLE RESPONSE IN THE MARKERS OF CHOLESTASIS THROUGH 36 MONTHS OF OPEN-LABEL EXTENSION STUDY OF OBETICHOLIC ACID IN PRIMARY BILIARY CHOLANGITIS

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Introduction: Obeticholic Acid (OCA) is a selective and potent farnesoid X receptor agonist indicated for treatment of primary biliary cholangitis (PBC). POISE is a 12-month double-blind (DB), placebo (PBO)-controlled, Phase 3 PBC study including an open-label extension (OLE).
Aims and Methods: The purpose of the OLE is to assess safety and durability of the OCA effect on serum markers of cholestasis. Key POISE inclusion criteria: PBC diagnosis, ALP ≥1.67x ULN and/or total bilirubin (TB) >ULN to < 2x ULN, stable UDCA dose or unable to tolerate UDCA. During the DB phase, 216 patients were randomized and dosed to: daily PBO, n = 73; OCA 5-10 mg (titration after 6 months based on response and tolerability), n = 70; or OCA 10 mg, n = 73. In the OLE, all patients were initially treated with OCA 5 mg regardless of DB treatment with the option to increase after 3 months based on response and tolerability.
Results: 193 of 198 (97%) patients completing the DB phase of the study enrolled in the OLE; 165 reached 36 months of the OLE: PBO, n = 49; OCA 5-10 mg, n = 59; OCA 10 mg, n = 57. At the end of the DB phase, patients on OCA had significant reductions in ALP and patients on PBO did not (Table 1). ALP reduction observed in OCA-treated patients was durable through 36 months OLE. PBO-treated patients experienced a significant reduction in ALP after switching to OCA, which was durable through 36 months OLE. Similar durable improvements were seen for GGT, ALT, and AST (data not shown). For OCA-treated patients, mean TB remained below BL through 36 months OLE. For PBO-treated patients, mean TB increased at 12 months DB, but trended back toward baseline (BL) with 36 months of OCA during OLE. During the OLE, 28 (15%) patients discontinued treatment, 7 (4%) patients for pruritus.
Conclusion: OCA treatment results in improvement in liver biochemistry; this improvement is shown to be durable in this analysis. For patients initially treated with PBO, switching to OCA is also associated with a durable biochemical response. Consistent with the DB phase, pruritus was the most common side effect of OCA, but discontinuation due to pruritus continues to be infrequent.

DB Phase Treatment Group	PBO	OCA 5-10 mg	OCA 10 mg
ALP (U/L)			
DB BL	327 (115)	326 (116)	316 (104)
ΔDB 12 Mo	−8 (88)	−104 (87)***	−118 (73)***
ΔOLE 24 Mo	−101 (87)***	−121 (97)***	−103 (79)***
ΔOLE 36 Mo	−113 (90)***	−101 (110)***	−85 (137)***
TB (μmol/L)			
DB BL	11.8 (7.2)	10.2 (5.5)	11.3 (6.6)
ΔDB 12 Mo	1.5 (4.1)	−0.5 (3.4)**	−1.2 (4.3)***
ΔOLE 24 Mo	1.9 (7.6)	−0.4 (3.6)	−0.6 (4.8)
ΔOLE 36 Mo	0.5 (3.6)	−0.5 (3.4)	−0.9 (4.1)

*p < 0.05, **p < 0.01, ***p < 0.0001. Values are Mean (SD). DB: P-value for comparing active treatments to PBO is obtained using an ANCOVA model with BL value as a covariate and fixed effects for treatment and randomization strata factor. OLE: P-value for the within treatment comparisons are obtained using the Students t-test.
[Table 1: ALP and TB mean change from BL through 36 Months of OLE]
Disclosure: This study was funded by Intercept Pharmaceuticals, Inc.

TUESDAY, OCTOBER 23, 2018   14:00–15:30
IBD clinical trials I – Room F1_____

OP195   EFFICACY AND SAFETY OF UPADACITINIB AS AN INDUCTION THERAPY FOR PATIENTS WITH MODERATELY-TO-SEVERELY ACTIVE ULCERATIVE COLITIS: DATA FROM THE PHASE 2B STUDY U-ACHIEVE

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Introduction: Janus Kinase (JAK) inhibitors are emerging as a promising treatment option for ulcerative colitis (UC). The efficacy and safety of upadacitinib (UPA), a JAK1-selective inhibitor, was assessed in an 8-week double-blind placebo (PBO)-controlled dose-ranging Phase 2b induction study in patients (pts) with moderately-to-severely active UC who had inadequate response, loss of response or intolerance to corticosteroids (CS), immunosuppressants (IS), or biologic therapies.
Aims and Methods: Adult pts with moderately-to-severely active UC (Adapted Mayo Score [Mayo score without Physician Global Assessment] 5-9 points and centrally-read endoscopy subscore 2-3) were randomized to receive extended-release UPA 7.5, 15, 30, 45 mg once daily (QD) or PBO for 8 weeks. Pts were stratified by previous biologic use, baseline (BL) CS use, and BL Adapted Mayo score (≤7/> 7). A dose-response relationship between UPA doses and PBO for the primary endpoint, clinical remission per Adapted Mayo Score at week 8 (defined as stool frequency subscore [SFS]≤1, rectal bleeding subscore [RBS] = 0, endoscopic subscore [ES]≤1), was tested by Multiple Comparison Procedures Modeling (MCP-Mod) using pre-specified candidate models in the intent-to-treat population. Pairwise comparisons between UPA doses and PBO for the primary and ranked secondary endpoints were also conducted using the Cochran-Mantel-Haenszel test stratified by randomization factors. Non-responder and last observation carried forward imputations were utilized for missing

Abstract No: OP195

Endpoints	Placebo n = 46	UPA 7.5 mg QD n = 47	UPA 15 mg QD n = 49	UPA 30 mg QD n = 52	UPA 45 mg QD n = 56
Clinical remission per Adapted Mayo Score at week 8[a] (stool frequency subscore ≤1, rectal bleeding score = 0, endoscopic score ≤1)	0	4 (8.5)	7 (14.3)*	7 (13.5)*	11 (19.6)**
Endoscopic Improvement (endoscopic subscore ≤1) at week 8[b]	1 (2.2)	7 (14.9)*	15 (30.6)***	14 (26.9)***	20 (35.7)***
Clinical remission per Full Mayo (Full Mayo ≤2 with no subscore >1) at week 8[b]	0	4 (8.5)	5 (10.2)*	6 (11.5)*	11 (19.6)**
Clinical response per Adapted Mayo (decrease from baseline ≥2 points and ≥30% and in RBS ≥1 or RBS = 0 or 1) at week 8[b]	6 (13.0)	14 (29.8)*	22 (44.9)***	23 (44.2)***	28 (50.0)***

[a]Primary Endpoint; [b]Ranked Secondary Endpoints; ***, **, * significant at 0.001, 0.01, and 0.05 levels, respectively

values in categorical and continuous efficacy variables. Treatment-emergent adverse events (AEs) were reported from first dose of study drug up to 30 days after last dose.

Results: A total of 250 pts were randomised with a mean (SD) age of 42.3 (14.2) years and a disease duration of 8.2 (2.5) years. At BL, 77.6% had prior use of biologics, 36% had an Adapted Mayo Score > 7, and 79% had an ES of 3. A significant and consistent dose-response relationship was observed with UPA for the primary and secondary endpoints with highest rates observed with 45 mg QD treatment. At Week 8, the primary endpoint and secondary endpoints of endoscopic improvement, clinical remission per full Mayo score, and clinical response per adapted Mayo score were achieved with all doses from 15 mg to 45 mg QD (Table). Incidences of AEs and AEs leading to discontinuation were similar across UPA groups, and numerically higher in the PBO group. Rates of serious AEs (SAE) were 10.9%, 0%, 4.1%, 5.8% and 5.4%,for PBO, 7.5, 15, 30, and 45 mg QD, respectively; UC worsening was reported in 4.3%, 0%, 2.1%, 5.8% and 1.8% among SAEs, respectively in each arm. Serious infections occurred in pts receiving PBO (4.3%, n = 2), 15mg QD (2.0%, n = 1), and 45mg QD (3.6%, n = 2). One event of herpes zoster with 45 mg QD and no events of TB were reported. One malignancy (malignant melanoma) occurred with 7.5mg QD. No venous thromboembolic events or deaths were reported.

Conclusion: In this dose-ranging 8-week induction study, UPA demonstrated statistically significantly greater efficacy compared to PBO in pts with moderately-to-severely active UC. A dose-response relationship of efficacy was demonstrated by MCP-Mod in doses up to 45 mg QD. UPA was well-tolerated, and no new safety concerns were identified compared to previous studies of UPA.[1]

Disclosure: WJ Sandborn: consulting fees from Abbvie, Akros Pharma, Allergan, Ambrx Inc., Amgen, Ardelyx, Arena Pharmaceuticals, Atlantic Pharmaceuticals, Avaxia, Biogen, Boehringer Ingelheim, Bristol Meyers Squibb, Celgene, Conatus, Cosmo Technologies, Escalier Biosciences, Ferring, Ferring Research Institute, Forward Pharma, Galapagos, Genentech, Gilead Sciences, Immune Pharmaceuticals, Index Pharmaceuticals, Janssen, Kyowa Hakko Kirin Pharma, Lilly, Medimmune, Mesoblast, Miraca Life Sciences, Nivalis Therapeutics, Novartis, Nutrition Science Partners, Oppilan Pharma, Otsuka, Palatin, Paul Hastings, Pfizer, Precision IBD, Progenity, Prometheus Laboratories, Qu Biologics, Regeneron, Ritter Pharmaceuticals, University of Western Ontarion (owner of Robarts Clinical Trials), Salix, Seattle Genetics, Seres Therapeutics, Shire, Sigmoid Biotechnologies, Takeda, Theradiag, Theravance, Tigenix, Tillotts Pharma, UCB Pharma, Vascular Biogenics, Vivelix; research grants from Atlantic Healthcare Limited, Amgen, Genentech, Gilead Sciences, Abbvie, Janssen, Takeda, Lilly, Celgene/Receptos; payments for lectures/speakers bureau from Abbvie, Janssen, Takeda; and holds stock/stock options in Escalier Biosciences, Oppilan Pharma, Precision IBD, Progenity, Ritter Pharmaceuticals. S Ghosh: consulting fees from Boehringer-Ingelheim, Gilead Pfizer, Janssen, AbbVie, BMS, Celgene and speaker's fees from AbbVie, Ferring, Janssen, Takeda, Shield, and Falk Pharma J Panés: consulting fees from AbbVie, Arena Pharmaceuticals, Boehringer Ingelheim, Celgene, Celltrion, Ferring,, Genentech, Janssen, MSD, Oppilan, Pfizer, Robarts, Roche, Second Genome, Takeda, Theravance, Tigenix, and Topivert, speaker's fees from AbbVie, Ferring, Janssen, MSD, Shire Pharmaceuticals, Takeda and Tillots; and research funding from AbbVie and MSD S. Schreiber: consultancy and lecture fees from AbbVie, Boehringer Ingelheim,,Celltrion, Falk Pharma, Ferring, Genentech, Gilead, Janssen, Novartis, MSD, Pfizer, Genenech/Roche, Shire, Takeda G D'Haens: consulting and/or lecture fees from AbbVie, ActoGeniX, AIM, Boehringer Ingelheim GmbH, Centocor, Chemo Centryx, Cosmo Technologies, Elan Pharmaceuticals, enGene, Dr Falk Pharma, Ferring, Galapagos, Giuliani SpA, Given Imaging, GlaxoSmithKline, Janssen Biologics, MSD, Neovacs, Novo Nordisk, Otsuka, PDL BioPharma, Pfizer, Receptos, Salix, SetPoint, Shire Pharmaceuticals, Schering-Plough, Takeda, Tillotts Pharma, UCB Pharma, Versant, and Vifor Pharma; research grants from AbbVie, Janssen, Given Imaging, MSD, Dr Falk Pharma, and PhotoPill; speaking honoraria from AbbVie, Tillotts, Tramedico, Ferring, MSD, UCB Pharma, Norgine, Shire S Tanida: Consulting fee from Kissei pharmaceutical Co., Ltd and research funding from EA Pharma Co., Ltd. J Siffledeen: consultancy and/or speaking honoraria fees from Abbvie Inc, Janssen Pharmaceuticals, Allergan, Takeda, Ferring Pharmaceuticals, Shire, Pfizer. Educational grants from Abbvie Inc. P Higgins: consultancy fees from AbbVie, PRIME Medical Education, UCB, Takeda, Amgen, Lilly, Lycera, research funding from Janssen, Abbvie, Pfizer, Lilly, UCB, Takeda, Janssen, Arena, NIH, CCF W Zhou, A Othman,B Huang, J Enejosa: Abbvie employees; may own AbbVie stock and/ or options

Reference

1. Sandborn WJ et al., *Gastroenterology* 2017; 152(5) S1: S1308-S1309.

OP196   CANNABIS INDUCES CLINICAL RESPONSE BUT NO ENDOSCOPIC RESPONSE IN CROHN'S DISEASE PATIENTS

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Introduction: Many patients with Crohn's disease (CD) report that the use of medical cannabis improves their symptoms, however studies evaluating objective disease parameters including inflammatory markers and endoscopic score are lacking.

Aims and Methods: To assess the effect of cannabis treatment on Crohn's disease patients.

Methods: In a double blind, randomized, placebo-controlled trial on CD patients with active disease Patients were randomized to receive either cannabis oil with 15%Cannabidiol (CBD) and 4%tetrahydrocannabinol (THC) or placebo for 8 weeks. All other medications remained unchanged. Disease-related outcome measures including Crohn's disease activity index (CDAI), C-reactive protein (CRP), fecal calprotectine, simple endoscopic score for Crohn's disease (SES-CD) and SF-36 quality of life (QOL) were assessed before, during and after treatment.

Results: A total of 46 patients, 31 males (62%), mean age 35 ± 12, were investigated. Each study group included 23 patients. CDAI before the treatment was 288.4 ± 78.0 and 298.5 ± 112.2 (p = 0.71), after 8 weeks of treatment the CDAI was 143.1 ± 96.0 and 209.5 ± 113.0 in the cannabis and placebo groups, respectively (p < 0.05). Remission rate (defined as CDAI < 150) was achieved in 65% of the cannabis group and 35% of the placebo group (p < 0.05). Median quality of life score after 8 weeks was 90.1 (IQR 83-102) in the cannabis group and 76 (IQR 68-92) in the placebo group (p < 0.05). CRP before treatment was 3.1 ± 4.4mg/dl and 3.6 ± 5.4mg/dl (p = 0.62), after treatment it was 2.4 ± 8mg/dl and 4.1 ± 8.8mg/dl in the cannabis and placebo groups, respectively (p = 0.40). Calprotectine before treatment was 182 ± 133 and 122 ± 91 (p = 0.37), after treatment it was 170 ± 115.6 and 137 ± 115 (p = 0.76) in the cannabis and placebo groups, respectively. SES-CD was $9.5 \pm 6.5 11.9 \pm 6$ (p = 0.93) before treatment and 7.17 ± 6 and 9.8 ± 5.4 (p = 0.17) after treatment in the cannabis and placebo groups, respectively.

Conclusion: 8 weeks of CBD-rich cannabis treatment induced significant clinical improvement but no change in inflammatory parameters or endoscopic score. Cannabis treatment in Crohn's disease could be considered for temporary symptom relief. The potential anti-inflammatory properties of cannabis treatment in IBD/Crohn's disease requires further investigation.

Disclosure: Bar-Lev Schlieder Lihi is an employee of Tikun Olam, a supplier of medical cannabis

OP197   TOFACITINIB 15 MILLIGRAMS TWICE DAILY FOR PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS: RESULTS FROM 8-WEEK INDUCTION STUDIES OCTAVE INDUCTION 1 & 2

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Introduction: Tofacitinib is an oral, small molecule Janus kinase inhibitor that is being investigated for ulcerative colitis (UC). The efficacy and safety of tofacitinib 10 mg twice daily (BID) induction therapy for UC was previously reported in 2 8-week, Phase 3 trials (OCTAVE Induction 1 & 2 [NCT01465763 & NCT01458951]).[1] The initial trial protocols called for patients to be randomised (2:2:1) to either tofacitinib 10 or 15 mg BID or placebo. Randomisation to the tofacitinib 15 mg BID dose ceased after a protocol amendment.

Aims and Methods: We report pooled efficacy and safety analyses from OCTAVE Induction 1 & 2 for the tofacitinib 15 mg BID dose alongside data from the placebo and tofacitinib 10 mg BID groups previously reported.[1] Patients were ≥18 years of age and had failed, or were intolerant to, corticosteroids, immunomodulators or tumour necrosis factor inhibitors. Remission (total Mayo score ≤2, no subscore > 1 and rectal bleeding subscore of 0), mucosal healing (Mayo endoscopic subscore ≤1) and clinical response (decrease from baseline total Mayo score of ≥3 points and ≥30%, plus decrease in rectal bleeding subscore ≥1 or absolute subscore ≤1) were evaluated based on central reading of endoscopic subscore. Differences from placebo and 95% confidence intervals (CI) were calculated using an exact method.

Results: Baseline demographics and disease characteristics of the 22 patients who received tofacitinib 15 mg BID during OCTAVE Induction 1 & 2 were generally consistent with the overall study population. At Week 8 in the tofacitinib 15 mg BID group, the primary efficacy endpoint of remission was achieved by 9 (40.9%) patients, mucosal healing by 13 (59.1%) patients, and clinical response by 19 patients (86.4%). Treatment effect sizes (ie difference from placebo [95% CI]) were 34.9% (15.6, 56.4) for remission, 45.4% (23.5, 65.3) for mucosal healing, and 55.6% (32.3, 67.8) for clinical response. There were numerically greater rates of adverse events (AEs) and infections with tofacitinib 15 mg BID compared with tofacitinib 10 mg BID and with placebo. There were no deaths, serious AEs, serious infections, herpes zoster, gastrointestinal perforations, opportunistic infections, malignancies, non-melanoma skin cancers or major adverse cardiovascular events with tofacitinib 15 mg BID (Table).

Conclusion: Based on a small sample size of 22 patients who received tofacitinib 15 mg BID in OCTAVE Induction 1 & 2, efficacy with tofacitinib 15 mg BID was greater than with placebo, and there were numerically greater rates of AEs and infections with tofacitinib 15 mg BID compared with tofacitinib 10 mg BID and placebo.

Table. Baseline demographics and disease characteristics, and summary of efficacy and safety at Week 8, in OCTAVE Induction 1 & 2

	Placebo N = 234	Tofacitinib 10 mg BID N = 905	Tofacitinib 15 mg BID N = 22
Baseline demographics and disease characteristics			
Age in years, mean (SD)	41.1 (14.4)	41.2 (13.8)	38.4 (12.7)
Male, n (%)	132 (56.4)	536 (59.2)	12 (54.5)
Disease duration in years, median (range)	6.1 (0.4–36.2)	6.3 (0.3–42.5)	6.9 (0.5–21.9)
Total Mayo score, mean (SD)	9.0 (1.5)	9.0 (1.4)	9.0 (1.5)
Prior TNFi failure, n (%)	124 (53.0)	465 (51.4)	10 (45.5)
Efficacy outcomes at Week 8, n (%)			
Remission	14 (6.0)	159 (17.6)	9 (40.9)
Difference (95% CI) from placebo	–	11.6 (7.7, 15.5)[a]	34.9 (15.6, 56.4)[b]
Mucosal healing	32 (13.7)	271 (29.9)	13 (59.1)
Difference (95% CI) from placebo	–	16.3 (11.0, 21.6)[a]	45.4 (23.5, 65.3)[b]
Clinical response	72 (30.8)	521 (57.6)	19 (86.4)
Difference (95% CI) from placebo	–	26.8 (20.1, 33.5)[a]	55.6 (32.3, 67.8)[b]
Summary of safety up to Week 8, n (%)			
AEs	132 (56.4)	501 (55.4)	16 (72.7)
SAEs	14 (6.0)	34 (3.8)	0 (0.0)
Discontinuations due to AEs	10 (4.3)	35 (3.9)	0 (0.0)
Infection AEs	36 (15.4)	189 (20.9)	7 (31.8)
Infection SAEs	0 (0.0)	7 (0.8)	0 (0.0)
Herpes zoster	1 (0.4)	5 (0.6)	0 (0.0)
Herpes zoster SAEs	0 (0.0)	0 (0.0)	0 (0.0)

Efficacy data are full analysis set with non-responder imputation based on central read endoscopy.
[a]Calculated based on the normal approximation for the difference in binomial proportions; [b]Calculated using an exact method.
AE, adverse event; BID, twice daily; CI, confidence interval; N, number of evaluable patients; n, number of patients; SAE, serious adverse event; SD, standard deviation; TNFi, tumour necrosis factor inhibitor.
[Table]
Disclosure: DT Rubin has received research support from AbbVie, Genentech, Janssen, Takeda, UCB; and consultancy fees from AbbVie, Amgen, Janssen, Pfizer Inc, Takeda, UCB; S Motoya has received research support from AbbVie, Eisai, Mitsubishi Tanabe Pharma, Zeria, and honoraria from AbbVie, Eisai, Mitsubishi Tanabe Pharma; S Schreiber has received consulting fees from AbbVie, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Galapagos, Janssen, MedImmune, MSD, Pfizer Inc/Hospira, Shire, Takeda, UCB, and lecture/speaker fees from AbbVie, Falk, Ferring, MSD, Takeda, UCB; D Quirk, CI Nduaka, N Lawendy, DA Woodworth, W Wang, C Su are Pfizer Inc employees and shareholders; PDR Higgins has received consultancy fees from AbbVie, Amgen, Genentech, JBR Pharma, Lycera.

Reference

1. Sandborn WJ et al. *N Engl J Med* 2017; 376: 1723–36.

OP198 EFFICACY AND SAFETY OF GASTRO-RESISTANT PHOSPHATIDYLCHOLINE (LT-02) FOR INDUCTION OF REMISSION IN PATIENTS WITH MILD-TO-MODERATE ULCERATIVE COLITIS REFRACTORY TO MESALAZINE: A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY (PCG-2)

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Introduction: An observed deficiency of phosphatidylcholine (PC) in the intestinal mucus in patients with ulcerative colitis (UC) [1] led to the hypothesis that daily oral administration and subsequent gastro-resistant release of PC into the ileum could restore the protective mucus barrier function.
Aims and Methods: This was a prospective, double-blind, randomised, multicenter phase 3 trial to compare the efficacy and safety of 2 different dosing regimen of LT-02 (LT-02 0.8 g QID, LT-02 1.6 g BID) with placebo over 12 weeks for induction of remission in patients with active ulcerative colitis (mDAI score 4-10, with $\geq$ 1 point in each of the four subscores) refractory to mesalazine despite either continued treatment with oral 5-ASA $\geq$ 2.4 g/d for $\geq$ 6 weeks or combination of oral 5-ASA $\geq$ 2.4 g/d and a rectal 5-ASA preparation for $\geq$10-14 days. Subjects had to have fecal calprotectin (FCP) $\geq$ 250 µg/g at screening or FCP $\geq$ 100 µg/g and < 250 µg/g and Histological Index (HI) > 1. Primary endpoint was the percentage of patients in deep remission defined as mDAI Score $\leq$ 1 with a score of '0' points for rectal bleeding and stool frequency, and $\geq$ 1 point reduction from baseline in the mucosal appearance score. After a pre-specified interim-analysis, the study was stopped for futility.
Results: The full analysis set (FAS) comprised 465 patients. Both the primary and the secondary efficacy endpoints did not show significant differences across treatment groups:

	LT-02 0.8 g QID (n = 155)	LT-02 1.6 g BID (n = 155)	Placebo (n = 155)
Number (%) of patients with deep clinical remission	15 (9.7%)	22 (14.2%)	21 (13.5%)
Number (%) of patients with remission (total mDAI $\leq$ 2 with no subscore >1)	21 (13.5%)	16 (10.3%)	15 (9.7%)
Number (%) of patients with improvement (total mDAI decrease $\geq$3)	28 (18.1%)	38 (24.5%)	33 (21.3%)
Number (%) of patients mucosal healing (mucosal appearance score $\leq$1, min. 1 point decrease)*	51 (32.9%)	57 (36.8%)	56 (36.1%)
Change from baseline in Total mDAI: Mean (SD)	−2.6 (3.08) N = 126	−2.8 (2.91) N = 134	−2.8 (3.04) N = 128
Change from screening in Histological Index**: Mean (SD)	−0.4 (1.05) N = 125	0.6 (1.02) N = 133	−0.4 (0.97) N = 126
Calprotectin changes from Screening in µg/g: Mean (SD)	−587 (3386) N = 148	−512 (2107) N = 152	−443 (2617) N = 148

*scored by site endoscopist
**Riley et al.

[Primary & secondary efficacy endpoints at week 12 (LOCF)]
Numbers of AEs, SAEs and ADRs were comparable between patients in the LT-02 groups and the placebo group. Frequencies of withdrawals due to AE were similar across treatment groups and low. Tolerability of LT-02 was assessed as very good or good in the vast majority of patients by both the investigators and patients.
Conclusion: This study failed to prove superiority of both dosing regimen of LT-02 treatment over placebo for the induction of remission across various efficacy parameters in patients with mildly to moderately active UC refractory to mesalazine.
Disclosure: Employed by Dr. Falk Pharma GmbH

Reference

1. Braun et al., *InflammBowel Dis.* 2009; 15(11): 1705–20.

OP199 A PHASE 3 STUDY OF VEDOLIZUMAB IN JAPANESE PATIENTS WITH ULCERATIVE COLITIS: EFFECTS ON TIME TO DISEASE WORSENING AND TREATMENT FAILURE

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Introduction: Vedolizumab (VDZ), a humanized monoclonal antibody inhibiting $\alpha_4\beta_7$ integrin, is approved globally for the treatment of ulcerative colitis (UC). However, data on its safety and efficacy is limited in the Asian population. We conducted a phase 3, randomized, double-blind, placebo (PBO)-controlled study in Japanese patients (pts) with UC (NCT02039505), where 1 of 2 primary endpoints were met: clinical response at Week 10 (induction phase, IP) was numerically greater but not significant, and clinical remission at Week 60 (maintenance phase, MP) was statistically superior, in the VDZ compared with the PBO arm. Here we report the results of predefined exploratory endpoints for the MP: the effect of VDZ on time to disease worsening (TDW) and time to treatment failure (TTF).

Aims and Methods: Japanese pts with moderate-to-severe UC received 300mg VDZ or PBO at Weeks 0, 2 and 6 in the IP. Pts showing a clinical response to VDZ at Week 10 were then randomized 1:1 to receive VDZ (N = 41) or PBO (N = 42) in the MP, at Weeks 14, 22, 30, 38, 46 and 54. Disease worsening in the MP was defined as an increase of the partial Mayo score (range: 0-9 points) by ≥3 points compared with that of Week 10 for 2 successive visits, and a partial Mayo score of ≥5 points (or ≥9 points in 2 successive visits, in the case of >6 points at Week 10). Treatment failure was defined as any of the following: disease worsening, use of rescue medication, or study discontinuation due to drug-related adverse events.

Results: Kaplan-Meier analysis of TDW showed that at Month 6, the proportion of pts without disease worsening was higher for the VDZ group (89.6%) compared with the PBO group (74.4%); this difference was sustained at Month 12 with rates of 89.6% for VDZ and 67.0% for PBO groups. The proportion of pts without treatment failure was 82.5% in the VDZ and 61.5% for PBO groups at Month 6, and was 68.8% and 52.4%, respectively, at Month 12. In a stratified log-rank test based on prior TNFα antagonist use, statistically significant differences were observed between the treatment groups for both TDW (p = 0.0446) and TTF (p = 0.0166).

Conclusion: VDZ showed statistically significant difference between treatment groups on TDW and TTF in Japanese pts with UC.

OP200 ROLE OF CONCOMITANT IMMUNOSUPPRESSION IN THE EFFICACY AND SAFETY OF USTEKINUMAB: POST-HOC ANALYSES OF UNITI

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Introduction: Unlike anti-TNFs, ustekinumab (UST, an anti-IL-12/23 monoclonal antibody) appears minimally immunogenic, and therefore may not require combination with immunosuppressants (IS) AZA, 6-MP, or MTX to achieve maximum efficacy. As previously reported, UST is superior to PBO across a wide range of subgroups, including combo & mono therapy. In this post hoc

Abstract No: OP200

Table 1: Role of concomitant immunosuppression in the efficacy of UST induction

	No AZA/6-MP/MTX		With AZA/6-MP/MTX		Difference mono: UST-PBO	Difference combo: UST-PBO	p-value
UNITI-1: UST ~6 mg/kg (TNF-failures)	PBO (n = 137)	UST (n = 138)	PBO (n = 73)	UST (n = 71)			
CR-100 Week 6	21.0	36.3	22.5	28.2	15.3	5.7	0.33
Remission Week 8	6.6	19.9	8.8	23.1	13.3	14.3	0.74
UNITI-2: UST ~6 mg/kg (Conventional failures)	PBO (n = 167)	UST (n = 171)	PBO (n = 80)	UST (n = 78)			
CR-100 Week 6	28.7	50.0	28.8	66.2	21.5	37.4	0.48
Remission Week 8	18.3	37.7	21.9	45.1	19.4	23.2	0.92
IM-UNITI: UST 90 mg Q8W	PBO (n = 87)	UST (n = 85)	PBO (n = 44)	UST (n = 43)			
CR-100 Week 44	41.3	57.7	50.0	62.8	16.4	12.8	0.77
Remission Week 44	32.2	51.8	43.2	55.8	19.6	12.6	0.58
IM-UNITI: UST 90 mg Q12W	PBO (n = 87)	UST (n = 78)	PBO (n = 44)	UST (n = 51)			
CR-100 Week 44	41.3	55.1	50.0	62.8	13.8	12.8	0.58
Remission Week 44	32.2	46.2	43.2	52.9	14.0	9.7	0.80

analysis of the UNITI program, we further investigate the role of combining IS with UST.

Aims and Methods: The efficacy of UST in induction and maintenance was stratified according to IS use, then tested for potential correlation between the effect size of the response of UST and the use of IS (Chi-square, without corrections or error control). For the safety population, we created odds ratios for all AEs and infections, for combo and mono groups. Safety data was corrected for follow-up and stratified by concomitant IS use.

Results: We compared the efficacy of UST and PBO at primary and major secondary endpoints for the induction and maintenance ph3 trials. During the induction trials (UNITI-1 & -2) we could not detect an association between concomitant IS use and efficacy at any endpoint (Data for approved ~6mg/kg induction dose in Table 1), nor was there any consistently obvious benefit for combo therapy with IS. During maintenance therapy (IM-UNITI), we failed to detect significant interactions between concomitant IS use and efficacy in either Q8W or Q12W UST groups (Table1). Rates of total AEs were not obviously different between groups, though combo therapy tended to have lower rates than monotherapy. When examining rates of infections, there were no trends when contrasting dose groups or IS use. PBO pts treated with concomitant IS had infections rates of 156, 182, and 114 per 100 pt-yrs (PBO, UST 90mg Q12W, and UST 90mg Q8W) vs. 167, 130, 173 per 100 pt-yrs (PBO, UST 90mg Q12W, and UST 90mg Q8W) without IS. Odds ratios did not appear different when contrasting mono and combo therapy; with 95% CI's were broadly overlapping and crossing 1.0.

Conclusion: In this analysis, we were unable to detect a significant interaction between any dosage of UST and IS. Taken with previously presented data on serum [UST] being independent of IS use, and low overall immunogenicity; these data suggest that similar benefit is achieved when UST is administered as monotherapy or given as combination therapy with IS in patients with moderate to severe CD.

Disclosure: This study was supported by Janssen Research & Development, LLC.

TUESDAY, OCTOBER 23, 2018　　　　　　　　　　　　　　14:00–15:30
Managing colorectal polyps – Room K＿＿＿＿＿＿＿＿＿＿＿

OP201　COLD SNARE POLYPECTOMY IS SAFE YET UNDER-UTILISED: AN ANALYSIS OF 281,194 POLYPECTOMIES BY UK ENDOSCOPY TRAINEES OVER 9 YEARS

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Introduction: Multiple techniques exist for the management of colorectal polyps. Recent (2017) ESGE guidelines [1] have defined an evidence based approach to the optimal technique for removing different sizes of polyps.

Aims and Methods: Previously the decision on optimal polypectomy technique often depended on an individual operator's experience and training. We sought to examine current polypectomy practice amongst United Kingdom endoscopy trainees with reference to these guidelines.

The ESGE polypectomy guideline 2017 suggests polyps < 10mm should be removed using cold snare polypectomy (CSP) or cold biopsy forceps (CBF) [< =3mm only], 10-19mm using endoscopic mucosal resection (EMR) or hot snare polypectomy (HSP) and 20mm or larger using EMR. The JETS database is a prospectively collected record of trainee colonoscopic procedures in the United Kingdom and its use during training is mandatory for accreditation. Data is entered by trainees on their own endoscopic procedures. Adverse events were classified as delayed bleeding or delayed perforation. We retrospectively analysed procedures entered into the JETS database from Jan 2008 to December 2017 for polypectomy technique and compared this to the 2017 ESGE guideline.

Results: 291,778 polypectomies were performed in 176,569 trainee-performed procedures by 3395 trainees over the study period. 10,584 polypectomies were missing data. 281,194 polypectomies were analysed.

Of 250,783 polyps < 10mm in size removed, 29.5% were performed using CBF, 27.9% by CSP, 25.1% by hot snare polypectomy HSP, 9.5% by hot biopsy forceps HBF, and 8.0% by endoscopic mucosal resection EMR. Of 26,605 polyps 10-19mm in size, 55.3% were removed by HSP, 31.0% by EMR and 3.5% by CSP. 8.4% of lesions were biopsied and not removed. Of 3806 polyps ≥ 20mm in size, 39.4% were removed by EMR, 36.3% by HSP, 1.1% were removed by CSP and 21.9% of these lesions were biopsied and not removed.

Overall, adherence to the ESGE guidance was observed in 154,948 polypectomies (55.1%). Nurse endoscopists were more adherent (61.7%), versus physicians (57.9%) versus surgeons (44.3%), p < 0.001.

Of 219 (0.1%) adverse events reported amongst all polypectomies, 50.8% were amongst HSP, 19.2% EMR, 16.9% CSP and 12.7% after HBF, p < 0.001. Of 20 delayed perforations (event rate 0.01%), 55% were due to EMR, 30% to HSP and 15% to HBF. No perforations resulted from CSP. 0.03% of all polypectomies resulted in unplanned hospital admission. Of these admissions 45.1% were after EMR, 35.1% after HSP and 6.4% after CSP, p < 0.001.

Conclusion: Cold snare polypectomy is under-utilised for diminutive polypectomy, despite its proven safety and efficacy; its use amongst trainees should be promoted in line with ESGE guidance. Trainees are likely to follow the example of their trainers and, as such, this study likely provides an insight into current polypectomy practice in the wider UK endoscopic community. Trainees in the United Kingdom predominantly remove diminutive polyps with extremely low reported rates of adverse events, but do not often perform more complex polypectomy.

Disclosure: Nothing to disclose

Reference

1. Ferlitsch M, Moss A, Hassan C, Bhandari P, Dumonceau J-M, Paspatis G, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy*. 2017 Mar 1; 49(03): 270–97.

OP202　LONG TERM RATES OF SURGERY AND ADENOMA RECURRENCE ARE SIMILAR FOR LATERALLY SPREADING LESIONS RESECTED EN BLOC OR BY PIECEMEAL ENDOSCOPIC MUCOSAL RESECTION

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Introduction: Endoscopic mucosal resection (EMR) allows safe and effective resection of large laterally spreading lesions ≥ 20mm (LSL). Adenoma recurrence is commonplace when resection is performed piecemeal. En bloc EMR, however, has been shown to achieve low adenoma recurrence rates but long term outcomes are unknown.

Aims and Methods: Over 9 years to April 2017 analysis of LSL resected by EMR from a prospectively collected database at 8 Australian Tertiary Referral Centres was performed. LSL ≤ 25mm in the left colon and ≤ 20mm in the right colon were included. Multiple LSL in the same patient were excluded. Standard inject and resect EMR was performed. LSL resections were identified as piecemeal or en bloc (single snare resection) and their outcomes were compared. Scheduled surveillance colonoscopy was performed at desired intervals of 4-6 months and 18 months after EMR. Late recurrence described adenoma recurrence after a negative surveillance procedure.

Results: 587 LSL were included of which 267 (46.1%) were resected en bloc, with histologic clear margins in 80.4%. Larger and previously attempted LSL were more likely to be removed piecemeal (p = 0.015 and p < 0.001 respectively). Neither colonic location nor morphology predicted en bloc resection. En bloc resections took less time, median 10 versus 20 minutes, p < 0.001. Muscularis propria injury was more common with en bloc resection (p = 0.038). Other adverse events were not more common between the groups (table 1).

406 (69%) LSL underwent first surveillance with recurrence in 5 (2.6%) LSL which were resected en bloc and 23 (9.3%) resected piecemeal (p = 0.004). 251 (63%) LSL underwent second surveillance at median 19.5 months (interquartile range 15.5–25). Recurrence was present in 1 (0.8%) EMR scar where the LSL was resected en bloc and 7 (5.4%) resected piecemeal (p = 0.066). In the piecemeal group 4/7 of these recurrences were after treatment of a previous recurrence. Need for surgery was infrequent in both groups during surveillance and was due to inability to resect recurrence in all cases.

	En bloc (n = 267)	Piecemeal (n = 320)	P
Underwent first surveillance, n (%)	195 (77)	246 (77)	
Time to first surveillance, months, median (IQR)	6.0 (4.0–11.2)	5.0 (3.9–7.1)	0.01
Recurrence (%)	5 (2.6)	23 (9.3)	0.004
Surgery after this procedure (%)	3 (1.5)	2 (0.8)	0.659
Underwent second surveillance, n (%)	126 (66)	130 (54)	
Time to second surveillance, months, median (IQR)	21.2 (16.1–28.0)	18.0 (15.0–22.7)	0.006
Recurrence, n (%)	1 (0.8)	7 (5.4)	0.066

[Table 1; Characteristics of laterally spreading lesions (LSLs) removed by endoscopic mucosal resection during follow-up split by piecemeal or en bloc]

Conclusion: LSL resected piecemeal by EMR have higher recurrence rates at first surveillance, but comparable rates of late recurrence at second surveillance compared to those resected en bloc. Adenoma recurrence at surveillance procedures is readily treated endoscopically. En bloc resection may lead to higher rates of adverse events versus piecemeal resection. Unless there is concern for invasive disease, en bloc resection need not be pursued at all costs.

Disclosure: Nothing to disclose

OP203 A NEW METHOD OF ENDOSCOPIC RESECTION FOR COLORECTAL ADENOMA, "UNDERWATER COLD SNARE POLYPECTOMY": A PROPENSITY SCORE MATCHING ANALYSIS WITH CONVENTIONAL COLD SNARE POLYPECTOMY

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Introduction: Cold snare polypectomy (CSP) for colorectal adenomas is used worldwide because of its excellent safety. However, the rate of R0 resection is not adequately high [1]. Few studies have reported on the efficacy of underwater endoscopic mucosal resection for colorectal adenomas [2]. We hypothesized that CSP for colorectal adenomas in underwater environment may combine high safety and high R0 resection rate; we named this procedure underwater CSP (UCSP). We prospectively analyzed the safety and efficacy of UCSP.
Aims and Methods: [Study 1] Between May 2017 and January 2018, 161 lesions from 53 patients were resected using UCSP. Patients with pathologically confirmed adenomas underwent follow-up colonoscopy 3 weeks after UCSP whether or not they achieved R0 resection. Any post-UCSP scars were biopsied to confirm the presence or absence of residual adenomas.
[Study 2] We used propensity score-matching (PSM) analysis to compare the safety and efficacy of UCSP in the resection of 175 adenomas and to confirm the presence of residual adenomas in the 102 lesions resected using conventional CSP, between March 2015 and April 2017; the follow-up schedule for both groups was the same. The location, macroscopic type, and size of the lesions were used as covariates.
Results: [Study 1] The patients included 33 men and 20 women (mean age, 68.0 ± 8.1 years). The number of lesions in the cecum, ascending colon, transverse colon, descending colon, sigmoidal colon, and rectum, was 15, 51, 53, 22, 35, and 15, respectively. The number of lesions with type Ip, Isp, Is, and IIa macroscopic appearance was 3, 49, 62, and 78, respectively. The mean lesion size was 4.5 ± 1.5 mm (range, 2-8 mm; median, 4 mm). The en bloc resection and complete retrieval rates of specimens were 100% and 99.5%, respectively. In the final pathological diagnoses, 13, 157, 6, 8, 1, 1, and 4 lesions were non-tumor, low-grade tubular adenoma, low-grade tubulo-villous adenoma, high-grade tubular adenoma, high-grade tubulo-villous adenoma, intra-mucosal carcinoma, and SSA/P, respectively. The R0 resection rate of 177 tumorous lesions was 74.0% (131/177). No cases of perforation or delayed bleeding were found. Of the 177 scars post-CSP for adenomas, 175 (98.9%) were identified, and one residual adenoma (0.57%) was pathologically identified from all the biopsied scar specimens.
[Study 2] For PSM analysis, 204 lesions (102 pairs) were included. No significant differences were observed in the location, macroscopic type, or size of the lesions between the two groups. The R0 resection rate of UCSP was significantly higher than that of CSP (75.5% vs. 32.4%; p < 0.001). The rate of pathological residual adenomas 3 weeks after resection was 0.98% in both groups (1/102).
Conclusion: The R0 resection rate of UCSP was significantly higher than that of conventional CSP, with both procedures showing similar safety. Therefore, UCSP may be adequate therapy for small colorectal adenomas.
Disclosure: Nothing to disclose

Reference

1. Maruoka D, et al. Endoscopy. 2018 [Epub ahead of print]; 2. Binmoeller KF, et al. *Gastrointest Endosc.* 2012; 75: 1086–91.

OP204 ENDOSCOPIC FULL THICKNESS RESECTION IN THE COLON: 3-YEAR MULTICENTRE UK EXPERIENCE

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Introduction: Endoscopic full thickness resection (eFTR) of the colon using the full thickness resection device (FTRD) is a novel method for removing lesions involving, or tethered to, deeper layers of the colonic wall. The UK FTRD registry collects data from multiple centres performing this procedure. We describe the feasibility and early outcomes of this technique.
Aims and Methods: Registry data from April 2015 – January 2018 was analysed. Main outcome measures were technical success, procedural time, specimen size, R0 resection, endoscopic clearance, and adverse events. Reported technical difficulties were collated.

Results: 38 cases were performed across 8 centres (median 2 cases per centre, range 1-23). Mean patient age was 70 years (39-93). Indications for eFTR include non-lifting adenoma (18 cases), T1 tumour resection (10), submucosal tumour (7), and appendix base adenoma (3).
In 97.4% (37/38) of patients the lesion was reached with the FTRD. 1 caecal lesion could not be reached due to sigmoid diverticulosis. The procedure was technically successful in 91.9% of patients (34/37). Median procedure time was 41 minutes (11-86), median resection time 6 minutes (2-36), and median specimen size 22mm (10-30). R0 resection was achieved in 76.5% of patients (26/34). R0 resection was not achieved in 8 patients, of which 5 had no residual lesion on follow up, giving a total endoscopic clearance rate of 91.2% (31/34).
Technical difficulty occurred in 9 patients; 6 due to snare failure and 3 due to lesion slippage on clip deployment. Of these 9 cases, 7 achieved R0 resection by use of further snare. Of the 2 patients with R1 resection, one has had follow-up at 4 months with no evidence of residual lesion.
Resection was unsuccessful in 3 patients; 2 due to significant tethering restricting lesion capture, and 1 due to haemodynamic instability from atrial fibrillation whilst pulling lesion into cap.
Complications occurred in 2 patients; 1 acute appendicitis at day 6 after resection of appendix base adenoma, and 1 with mild asymptomatic stricture at eFTR site at follow-up. There were no cases of bleeding, perforation, or fistula.
Conclusion: eFTR has a high success rate in treating lesions not previously amenable to endoscopic therapy. Whilst technical difficulties may arise, complication rates are low and outcomes acceptable, making eFTR a viable alternative to surgery.
Disclosure: Nothing to disclose

OP205 LIMITATIONS OF ENDOSCOPIC RESECTION FOR COLORECTAL SUBMUCOSAL INVASIVE CARCINOMA ARISING IN SESSILE SERRATED ADENOMA/POLYP

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Introduction: Among early colorectal carcinomas, lesions with little possibility of lymph node metastasis are usually treated endoscopically [1]. However, to the best of our knowledge, no report has described the problem with endoscopic treatment for early carcinomas arising in sessile serrated adenoma/polyps (SSA/Ps). Although invasive carcinomas with SSA/Ps (CA-SSA/Ps) are rare, these tumours are critical because SSA/Ps may grow into subsequent SSA/Ps with high-grade dysplasia or those with submucosal carcinoma more rapidly [2]. Furthermore, mucinous histology has also been found in CA-SSA/Ps [3], [4].
Aims and Methods: The aim of this study was to elucidate the clinicopathological features of CA-SSA/Ps and to investigate the possibility of endoscopic resection for these lesions. We reviewed all lesions pathologically diagnosed as T1 colorectal carcinomas that were endoscopically or surgically resected at Juntendo University Hospital and our affiliated hospitals between 2006 and 2017. We identified 45 CA-SSA/P lesions (from 45 patients) that were endoscopically (n = 18) or surgically resected (n = 27). For comparison, we randomly selected 200 invasive carcinomas with adenomas (CA-ADs) that were endoscopically (n = 87) or surgically resected (n = 113) from 200 patients.
Results: The clinicopathological characteristics of the studied lesions are summarized in Table 1. The patients with CA-SSA/P were older than those with CA-AD and were predominantly female. CA-SSA/Ps were more frequently located in the proximal colon than CA-ADs. Furthermore, CA-SSA/Ps more frequently exhibited sessile morphology than CA-ADs. CA-SSA/Ps were significantly smaller than CA-ADs. Well to moderately differentiated adenocarcinomas were predominant in both groups. In addition, a mucinous component in the submucosa was more common in CA-SSA/Ps than in CA-ADs. CA-SSA/Ps invaded less deeply into the submucosal layer than CA-ADs. Lymphatic invasion was observed more often in CA-SSA/Ps than in CA-ADs, as was lymph node metastasis.
Conclusion: Although CA-SSA/Ps were smaller and invaded less deeply into the submucosal layer than CA-ADs, they frequently had a mucinous component and exhibited a higher potential for lymphatic invasion and lymph node metastasis. Therefore, the risk of lymph node metastasis should be considered when performing endoscopic treatment for CA-SSA/Ps even if the lesions are small.

Variable	SSA/P-CA (n = 45)	AD-CA (n = 200)	P value
Age (years)	71.3 ± 8.2 (55–89)	66.2 ± 10.0 (40–86)	0.002
Sex			
Male	19 (42%)	124 (62%)	0.019
Female	26 (58%)	76 (38%)	
Location			
Proximal colon	43 (96%)	38 (19%)	< 0.001
Distal colon	2 (4%)	162 (81%)	
Macroscopic type			
Sessile	31 (69%)	87 (43%)	0.002

Continued

Variable	SSA/P-CA (n = 45)	AD-CA (n = 200)	P value
Semipedunculated	12 (27%)	60 (30%)	
Pedunculated	2 (4%)	53 (27%)	
Size of tumour (mm)	14.8 ± 8.8 (5–54)	21.7 ± 14.4 (6–99)	< 0.001
Differentiation			
Well differentiated	27 (60%)	119 (59%)	NS
Moderately differentiated	17 (38%)	78 (39%)	
Poorly differentiated	1 (2%)	3 (2%)	
Mucinous component	15 (33%)	7 (4%)	< 0.001
Depth of invasion (μm)	1496 ± 941 (100–4500)	2188 ± 1878 (100–10000)	0.046
Lymphatic invasion	13 (29%)	25 (13%)	0.011
Venous invasion	3 (7%)	20 (10%)	NS
Lymph nodes metastasis	8/27 (30%)	8/113 (7%)	0.003

[Table 1. Clinicopathological characteristics of colorectal lesions studied.]
Disclosure: Nothing to disclose

References

1. Tanaka S, Kashida H, Saito Y, et al. JGES guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. *Dig Endosc.* 2015; 27: 417–434.
2. Lazarus R, Junttila OE, Karttunen TJ, et al. The risk of metachronous neoplasia in patients with serrated adenoma. *Am J Clin Pathol.* 2005; 123: 349–359.
3. Fujita K, Yamamoto H, Matsumoto T, et al. Sessile serrated adenoma with early neoplastic progression: a clinicopathologic and molecular study. *Am J Surg Pathol.* 2011; 35: 295–304.
4. Sheridan TB, Fenton H, Lewin MR, et al. Sessile serrated adenomas with low- and high-grade dysplasia and early carcinomas: an immunohistochemical study of serrated lesions "caught in the act". *Am J Clin Pathol.* 2006; 126: 564–571.

OP206   ENDOSCOPIC RESECTIONS IN INFLAMMATORY BOWEL DISEASE

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Introduction: Cumulative colon cancer risk is estimated at 2-18% depending on the duration of colitis. The management of neoplasia in colitis remains controversial. BSG guidelines recommend colectomy if complete endoscopic resection isn't guaranteed.
Aims and Methods: The aim of this study was to assess the need for surgery in the management of neoplasia in colitis. This is a multicentre cohort study of all neoplasia endoscopically resected in patients with colitis from 5 tertiary European centres between 2008-2017. The following endoscopic resection techniques were used: endoscopic mucosal resection (EMR) and hybrid endoscopic submucosal dissection (ESD).
Results: 101 neoplasia were resected in 85 patients at 5 European centres. Mean age 61 years (range 28-82). Mean size of lesions 34 mm (range 8-120mm).
40% of the lesions were treated by hybrid ESD. There was no difference in lesion location between EMR and hybrid ESD. Lesions >20mm in size were removed more by hybrid ESD than EMR. More of the lesions removed by hybrid ESD (26) had fibrosis compared to EMR (15). 7 complications occurred in the cohort; 3 cases of bleeding and 4 perforations. Bleeding was controlled endoscopically. 3 perforations were managed endoscopically and 1 required surgery. 7/86 (8.1%) lesions with follow up data had recurrence.
Multi-variate regression analysis concluded;
• EMR leads to higher recurrence rates, irrespective of size, location and fibrosis (p-value of 0.048)
• Hybrid ESD leads to higher complication rates in the colon compared to the rectum (p-value of 0.045)
• Hybrid ESD shows a trend towards better en-bloc resection (p-value 0.063)
5 lesions underwent surgery; 3 due to cancer; 1 due to perforation; 1 due to failure of endoscopic resection. Histology; 88 adenomas (low-grade dysplasia), 6 adenomas (high-grade dysplasia), 3 cancers and 4 sessile serrated polyps.
Conclusion: This is the largest reported cohort of endoscopic resections of neoplasia in colitis. We demonstrate that both hybrid ESD and EMR are feasible in colitis with only 5% of patients requiring surgery. Fibrosis is very common in colitis. Recurrence is higher with EMR and complications higher with hybrid ESD. Our data shows that lesions with fibrosis are best treated by hybrid ESD, and those without fibrosis and < 20mm in size can be managed by EMR.
Disclosure: Nothing to disclose

TUESDAY, OCTOBER 23, 2018   14:00–15:30
From bench to the bedside in pancreatic cancer – Room L7

OP207   INTERNATIONAL VALIDATION OF THE 8TH EDITION AMERICAN JOINT COMMITTEE ON CANCER (AJCC) TNM STAGING SYSTEM IN PATIENTS WITH RESECTED PANCREATIC CANCER

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Abstract No: OP206
Table 1: Endoscopic Resections According to Location, Presence of Fibrosis and Size.

LESION LOCATION	Hybrid ESD Colon (26)	Hybrid ESD Rectum (13)	EMR Colon (54)	EMR Rectum (8)	Total (101)
Recurrence	2	0	5	0	7
Complications	5	0	2	0	7
En-bloc	14	11	33	5	63
FIBROSIS	Hybrid ESD Fibrosis (26)	Hybrid ESD No Fibrosis (13)	EMR Fibrosis (15)	EMR No Fibrosis (47)	Total (101)
Recurrence	1	1	0	5	7
Complications	5	0	1	1	7
En-bloc	15	10	8	30	63
LESION SIZE	Hybrid ESD 0-20mm	Hybrid ESD >20mm	EMR 0-20mm	EMR >20mm	Total
Recurrence	0	2	3	2	7
Complications	0	5	1	1	7
En-bloc	4	21	37	1	63

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Introduction: The American Joint Committee on Cancer (AJCC) has proposed the 8th edition of the TNM staging system in pancreatic cancer in order to improve prognostic accuracy and guide treatment decisions. An international validation study in a cohort with representative heterogeneity and sufficient long-term follow-up is currently lacking. The objective of this study is to validate the proposed 8th edition of the AJCC TNM staging system in an international cohort of resected pancreatic cancer.

Aims and Methods: Patients who underwent pancreatoduodenectomy for non-metastatic pancreatic ductal adenocarcinoma between 2000-2015 at 5 referral centers from 4 countries were retrospectively staged according to the 8th edition of the TNM staging system, based on tumor size (T1: $\leq$2cm, T2: >2 and $\leq$4cm, T3: $>$4cm, T4: involves celiac axis/superior mesenteric artery) and number of positive lymph nodes (N0: no positive lymph nodes (LN), N1: 1-3 positive LNs, N2: $\geq$4 positive LNs). Prognostic accuracy on overall survival was evaluated by Kaplan-Meier estimates and concordance statistics (Uno's C-statistic) with 95% confidence intervals (CI) to compare both editions of the TNM staging system.

Results: In total, 1528 patients were included for analysis. Distribution among stages changed from 2.7%, 3.0%, 13.2%, 80.4%, 0.8% in the 7th edition to 7.9%, 9.6%, 1.4%, 42.0%, 39.1% in the 8th edition for stage IA, IB, IIA, IIB and III, respectively. With the 8th edition, 781 patients (51.1%) migrated to a different stage, of whom 188 patients (12.3%) to a lower stage and 593 patients (38.7%) to a higher stage. Median overall survival for the entire cohort was 24.4 months. Five-year survival rates changed from 37.6%, 39.3%, 35.1%, 16.5%, 0% (log-rank p < 0.0001) in the 7th edition, to 39.4%, 34.2%, 27.6%, 21.0% and 10.8% (log-rank p < 0.0001) in the 8th edition for stage IA, IB, IIA, IIB and III, respectively. T-stage for node-negative patients (stage IA, IB, IIA only differ in T-stage) was neither predictive for survival in the 7th edition (log-rank p = 0.96), nor in the 8th edition (log-rank p = 0.24). The 8th edition N-stage was highly prognostic with 5-year survival rates of 35.6%, 20.1% and 10.9% for N0, N1 and N2 patients, respectively (log-rank p < 0.0001). When comparing prognostic accuracy, the C-statistic improved from 0.55 (95% CI, 0.52–0.57) in the 7th to 0.58 (95% CI, 0.55–0.60) in the 8th edition.

Conclusion: In this international cohort, the AJCC 8th edition of the TNM staging system for pancreatic cancer demonstrated a better distribution among different stages and an increased prognostic accuracy compared to the AJCC 7th edition. The new T-stage alone is still not predictive for survival, whereas the new N-stage is highly prognostic.

Disclosure: Mauna Kea Technologies for J.F. Tseng (Board Member, stipend and equity).

OP208   THE ROLE OF GASTROKINE 1, A GASTRIC TUMOR SUPPRESSOR, IN PANCREATIC CARCINOGENESIS

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Introduction: Pancreatic ductal adenocarcinoma (PDAC), a poor prognostic cancer, commonly arises from premalignant pancreatic intraepithelial neoplasia (PanIN) stages. After accumulation of mutations, these lesions further evolve into PDAC. Poor understanding of the patho-mechanisms and inability of early detection of PDAC necessitates better understanding of mechanisms leading to PDAC development and identifying biomarkers for early detection.

While understanding the biological role of PanIN lesions in pancreatic cancer using a genetic mouse model of pancreatic cancer (KC mice), we discovered high gastrokine 1 (GKN1) expression in premalignant pancreatic lesions in mice. We also detected GKN1 in peri-tumoral regions of human PDAC samples. GKN1 has been well described in gastric mucosa and suggested as a gastric specific tumor suppressor. However, GKN1 has never been associated with pancreatic carcinogenesis before. Therefore, we aim to investigate gastrokine expression and function in the pancreas, to understand the early events that underlie the development of premalignant lesions leading to pancreatic tumor formation.

Aims and Methods: GKN1 expression in human and mouse pancreas samples was analyzed by qPCR, western blot and immunohistochemistry (IHC). Mouse pancreatic juice and serum were analyzed by proteomic analysis. To clarify the role of GKNs in pancreatic carcinogenesis, we intercrossed KC mice with Gkn1-/- mice. To study contribution of peripheral gastrokine in tumor development, syngeneic tumor cells (Panc02) were injected subcutaneously and orthotopically into Gkn wt and Gkn1-/- mice. Tumors were assessed by IHC, qPCR and FACS.

Results: Thorough analysis of human and mouse pancreatic tissues showed, that GKN1 expression is absent in healthy pancreatic cells and on malignant tumors.

GKN1 expression is restricted to low-grade premalignant lesions, it is abundant in the cytoplasm of dysplastic epithelium. Proteomic analysis in KC mice confirmed the secretion of GKNs into pancreatic juice but not in the serum. Analysis of pancreatic tissue from GKN1-/- KC mice, at 3 months, showed faster development of PanIN with accelerated tumor development. Investigating the cellular and molecular mechanisms focused on tissue remodeling (epithelial mesenchymal transition, tight junctions), apoptosis, senescence and inflammatory environment. Gkn1-/- mice injected with Panc02 cells developed significantly smaller subcutaneous tumors, possibly due to increased CD8+/CD4+ T cells ratio within tumors.

Conclusion: Collectively, our data establishes a role for Gastrokine 1 in PanIN and PDAC development. The accelerated PanIN development in the absence of GKN1 *in vivo* suggest that gastrokines expression can delay PanIN formation and subsequent PDAC development. Secretion of gastrokine in pancreatic juice during carcinogenesis could make them potential early biomarker(s) to detect PDAC.

Disclosure: Nothing to disclose

OP209   EXPRESSION OF TN ANTIGEN PROMOTES PANCREATIC CARCINOGENESIS IN A TRANSGENIC MOUSE MODEL

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Introduction: Dysfunctionalities of Cosmc result in the expression of Tn antigen (Tn) and thereby in formation of truncated O-glycosylation with pathophysiological implications.[1–4] Tn is a hallmark of cancer and appears early in carcinogenesis.[5,6] Tn expression also arises in up to 90% of pancreatic ductal adenocarcinomas (PDAC) and is associated with poor prognosis.[7] This is of particular relevance, since PDAC is one of the most aggressive human tumors with a dismal overall prognosis.[8]

Aims and Methods: The aim of the present study was to investigate the impact of Tn expression on PDAC development *in vivo*. Therefore, we hypothesized that Tn expression promotes oncogenic properties and in this way pancreatic carcinogenesis. For this purpose, we generated a transgenic mouse model with a conditional *Cosmc* knockout and concomitant activation of oncogenic *Kras*^{G12D}, mediated by the *pancreas specific transcription factor 1a* (*Ptf1a*)-cre mouse strain.[9] Tn-modified proteins were identified using the plant lectin *Vicia villosa agglutinin* (VVA) for purification and subsequent mass spectrometric proteome analysis.

Results: Additional deletion of *Cosmc* in *Ptf1a*$^{+/Cre}$;*Kras*$^{+/G12D}$ mouse strain induces Tn expression in murine pancreas. We observed an activation of the PI3K/AKT/mTOR pathway with consecutive increased Ki-67 proliferation rate in *Ptf1a*$^{+/Cre}$;*Kras*$^{+/G12D}$;*Cosmc*$^{-/-}$ mouse strain. Moreover, histopathological analyses reveal an advanced tumor stage in *Ptf1a*$^{+/Cre}$;*Kras*$^{+/G12D}$;*Cosmc*$^{-/-}$ mice with pronounced tumor stroma formation. Furthermore, *Ptf1a*$^{+/Cre}$;*Kras*$^{+/G12D}$;*Cosmc*$^{-/-}$ mice display an early epithelial-to-mesenchymal transition phenotype.

Conclusion: In summary, in our transgenic mouse model presented here, causality between Tn expression and accelerated carcinogenesis of PDAC is shown, which highlights the pathophysiological relevance of truncated O-glycan formation. Moreover, it is conceivable that the identified Tn-modified proteins may also be relevant as potential new biomarkers for early detection of PDAC.

Disclosure: Nothing to disclose

References

1. Ju, T. & Cummings, R.D. Protein glycosylation: chaperone mutation in Tn syndrome. *Nature* 437, 1252 (2005).
2. Wang, Y., et al. Cosmc is an essential chaperone for correct protein O-glycosylation. *Proc Natl Acad Sci U S A* 107, 9228–9233 (2010).
3. Hofmann, B.T., et al. COSMC knockdown mediated aberrant O-glycosylation promotes oncogenic properties in pancreatic cancer. *Mol Cancer* 14, 109 (2015).
4. Stowell, S.R., Ju, T. & Cummings, R.D. Protein glycosylation in cancer. *Annu Rev Pathol* 10, 473–510 (2015).
5. Schietinger, A., et al. A mutant chaperone converts a wild-type protein into a tumor-specific antigen. *Science* 314, 304–308 (2006).
6. Ju, T., et al. Tn and sialyl-Tn antigens, aberrant O-glycomics as human disease markers. *Proteomics Clin Appl* 7, 618–631 (2013).
7. Springer, G.F. T and Tn, general carcinoma autoantigens. *Science* 224, 1198–1206 (1984).
8. Siegel, R.L., Miller, K.D. & Jemal, A. Cancer statistics, 2018. *CA Cancer J Clin* 68, 7–30 (2018).
9. Hingorani, S.R., et al. Preinvasive and invasive ductal pancreatic cancer and its early detection in the mouse. *Cancer Cell* 4, 437–450 (2003).

OP210 AN R0-RESECTABLE, GENETICALLY ENGINEERED MOUSE MODEL OF PANCREATIC CANCER MIMICS THE RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN HUMAN PANCREATIC CANCER

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Introduction: The understanding of the complex tumor-stromal interactions in pancreatic cancer (PDAC) microenvironment has been dramatically enhanced by the development of mouse models. However, recent studies demonstrated that the immune response in existing murine models does not correspond to that of the human disease. In this study, we analyzed the effects of neoadjuvant chemotherapy (neoCTx) on the histopathological features of a novel R0-resectable, genetically induced mouse model (termed Pfl mice) and compared it to human PDAC.

Aims and Methods: Using double immunofluorescence stainings with multiple markers and software-based analysis, we quantified the angiogenesis, tumor desmoplasia (activated stroma index/ASI), and the tumor-associated infiltration with cytotoxic T-lymphocytes, myeloid-derived-suppressor cells/MDSC and natural killer cells (NK) in tissue specimens of 36 neoadjuvantly treated PCa patients and 6 Pfl mice and compared the results with matched cohorts of primarily resected specimens.

Results: In contrast to human PDAC, the stromal activity in the murine tumor microenvironment remained constant after neoCTx. No significant change was observed in the microvessel density in both human and mice ($p = 0.179$; $p = 0.560$). NeoCTx led to a reduction of the CD45+ leucocytes (human: 266.7 ± 22.75 vs 186.6 ± 25.33; mice: $6.3 \times 10^{-4} \pm 1.0 \times 10^{-4}$ vs $1.3 \times 10^{-4} \pm 5.0 \times 10^{-5}$; $p = 0.005$) as well as to an increase of the CD8+ T-lymphocytes/CD45+ leucocyte ratio in both populations (human: 0.22 ± 0.01 vs 0.37 ± 0.01; $p < 0.001$; mice: 0.01267 ± 0.03972; $p = 0.035$). Simultaneously, our findings showed a marked decrease of MDSCs (human:16.95 ± 2.36 vs 5.58 ± 0.88; $p < 0.0001$; mice: $6.4 \times 10^{-5} \pm 1.0 \times 10^{-5}$ vs $2.6 \times 10^{-5} \pm 1.8 \times 10^{-5}$; $p = 0.074$) and NCAM+ NK cells (human: $1.33 \times 10^{-4} \pm 2.13 \times 10^{-4}$ vs $2.13 \times 10^{-5} \pm 3.03 \times 10^{-6}$; $p < 0.0001$; mice: $12.2 \times 10^{-5} \pm 3.2 \times 10^{-5}$ vs $2.5 \times 10^{-5} \pm 1.7 \times 10^{-5}$; $p = 0.069$) after neoCTx in human and murine tissue specimens.

Conclusion: Our data suggest that the reactivation of anti-tumoral immune responses in the tumor microenvironment of the Pfl PDAC mouse model after neoCTx strongly mimics that of the human disease and therefore proved its suitability for its use in future preclinical trials for molecular immunotherapy.

Disclosure: This abstract has also been submitted for presentation at the 2018 meeting of the European Pancreatic Club.

OP211 SITE-SPECIFIC ANGIOGENESIS MAY PROMOTE ISOLATED PULMONARY METASTASIS IN PANCREATIC CANCER

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Introduction: Pancreatic cancer (PCa) has the worst prognosis among all gastrointestinal cancers. Recent studies identified a remarkably better prognosis of PCa patients with isolated pulmonary metastasis. The reason behind this peculiarly better prognosis of this interesting patient subgroup is yet unknown.

Aims and Methods: In the present study, we hypothesized that some subtypes of PCa might preferentially foster the growth of endothelial cells in the lung, and less in the liver and thereby lead to isolated pulmonary metastases. For this purpose, we made use of endothelial cells specifically isolated from the human liver and lung, and treated these with several types of human pancreatic cancer cell lines. The proliferation and the tube formation rate by each PCa cell line was digitally quantified and compared. Cell lines that preferentially increased the growth of lung versus liver endothelial cells were subjected to a secretomics analysis comprising more than 600 secreted soluble factors. Tissue sections from primary tumours, lung metastasis and liver metastasis derived from human PCa patients and from the genetically engineered KPC (*Ptf1-Cre;LSL-Kras^{G12D};p53$^{lox/+}$*) mouse model of PCa were further analyzed for the expression of the pro-angiogenic factor Angiopoetin-2 (*Angpt2*) and of the anti-angiogenic receptor *Dscr1*.

Results: In humans and mouse tissue sections, we identified lower levels of *Dscr1* in cancer cells within lung metastases and relatively higher levels of *Angpt2*. In vitro, certain types of PCa cell lines preferentially induced the growth of lung endothelium and not of the liver endothelium. Comparative secretomic analysis of lung- versus liver endothelium growth-promoting cell lines revealed selectively increased secretion of *plasminogen* and *transferrin* from cancer cells that specifically promote lung endothelial growth.

Conclusion: Occurrence of isolated pulmonary metastasis in PCa may be due to the selective promotion of lung endothelial growth by cancer cell subgroups. In this pulmonary pro-angiogenic capacity of PCa cells, *plasminogen* and *transferrin* may be among the key mediators.

Disclosure: Nothing to disclose

OP212 IDENTIFICATION OF PERINEURAL INVASION-PROMOTING GENETIC ALTERATIONS IN PANCREATIC CANCER VIA PIGGYBAC-TRANSPOSON-MUTAGENESIS

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Introduction: Pancreatic cancer is characterised by an unparalleled degree of neural invasion (NI). NI is associated with reduced overall survival, increased local recurrence rate, and with neuropathic pain. One of the major mechanisms leading to NI is the specific affinity of tumor cells to neurons. This affinity can be mimicked by means of 3-dimensional migration assays that include neurons and cancer cells.

Aims and Methods: The aim of the study was to identify genetic alterations that specifically promotes neural invasion in pancreatic cancer by means of *in vivo* piggyback-transposon mutagenesis. A set of genetically pre-characterized mouse pancreatic cancer cell lines, which were generated by means of piggybac-transposon mediated mutagenesis, was used in three-dimensional migration assays with neurons. The cell lines with the highest affinity to neurons were analyzed for the sites of transposon integration in a pre-existing sequencing data base. The identified loci were were functionally analyzed in the cells by means of Crispr/Cas9 gene editing.

Results: In the genetically pre-characterized group of 22 mouse pancreatic cancer cell lines, 3 cell lines were identified to exhibit a high neuroaffinity. In the analysis of their transposon insertion sites, we found a specific, de-activating integration in the *Galnt2* and *St3Gal6* genes. In accordance, Crispr-Cas9-mediated gene editing resulted in increased migration of pancreatic cancer cells to Neurons.

Conclusion: The *in vivo* mutagenesis screen allows identification of neural invasion-promoting genetic alterations in pancreatic cancer. These results suggest that galactoaminyltransferases may promote neural invasion in pancreatic cancer.

Disclosure: This abstract was previously presented at the VBC 2017 congress in Germany

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TUESDAY, OCTOBER 23, 2018   14:00–15:30
Barrett's oesophagus: Pathogenesis and biomarkers – Room L8

OP213 BARRETT'S METAPLASIA ORIGINATES FROM *HOXA13*-POSITIVE CELLS IN THE GASTRO-ESOPHAGEAL JUNCTION

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Introduction: Barrett's esophagus (BE) is an intestinal metaplasia characterized by crypt-structured columnar epithelium with distal gastrointestinal (GI)-tract characteristics. This homeotic transformation predisposes to adenocarcinoma of the esophagus. *HOX* genes are known mediators of homeotic transformations. HOX genes encode master regulators of anterior to posterior specification in organogenesis and tissue homeostasis. The 3' to 5' sequence of *HOX* genes corresponds to the sequence in which they act along the anterior to posterior axes of the body. This property is termed collinearity and links clustering to function. HOX collinearity has not been thoroughly investigated in the human gut. Recent evidence from human and mouse studies has shown BE might originate from the glands at the gastro-esophageal junction (see refs). If it can be shown that these glands contain elements associated with positional misspecification, this theory could be substantially bolstered.

Aims and Methods: The aim of this study was firstly to characterize *HOX* gene expression in physiology, metaplasia and heterotopia of the GI-tract. The second aim was to find *HOXA13* expression in the gastro-esophageal junction. The third aim was to find the effect of *HOXA13* expression in BE. Expression of 39 *HOX* genes was determined by RT-qPCR and verified by RNA-ISH in tissues along the gut, BE, gastric intestinal metaplasia, and gastric heterotopia in the esophagus, Meckel's diverticula, and colon. *HOXA13* RNA-ISH was performed to verify the findings. Published data was analyzed to for *HOX* gene expression in epithelium specific stem cells. Squamous esophageal cell lines were exposed to acid and bile to simulate gastro esophageal reflux disease (GERD). A *Hoxa13*-GFP mouse model was employed to study the *Hoxa13* promotor activity in the

colon and gastro-esophageal junction. Mouse embryonic stem cells were differentiated to definitive endoderm, the progenitor cell of intestinal epithelia, as a model of the cell of origin of BE. *HOXA13* was transduced and overexpressed in a primary immortalized squamous esophageal cell line and knocked down in a primary immortalized BE cell line. HOXA13 function in the BE cell line was further studied in an *in vivo* organotypic model.

Results: *HOX* cluster gene expression in the gastrointestinal tract is collinear in men and mice, this coding is established at the level of the location specific stem cell. Metaplasias and heterotopias in the upper GI-tract are characterized by high *HOXA13* expression, while HOXA13 expression is characteristic for the colon. HOX coding is paralleled in epithelium specific stem cells of squamous and BE and stomach. *HOXA13* expression is epithelial and is not upregulated in squamous epithelium *in vivo* and *in vitro*. The *Hoxa13* promotor is regulated binary along the rostral-caudal body axis in the murine and human large intestine alike. Strikingly, we found a specific mouse to human- and lifespan-conserved patch of *HOXA13* positive cells at the gastro-esophageal junction. These cells might represent the cells of origin of BE. In the model of the cell of origin of BE, forced *HOXA13* confers a relative competitive advantage through upregulation of *Nanog* signaling and downregulation of *Wnt* signaling. *HOXA13* downregulates the chromosome 1q21.3 epidermal differentiation complex and other cornified envelope genes and has pro-oncogenic characteristics *in vitro*. The *in vivo* organotypic culture model showed *HOXA13* conveys typical characteristics of the BE phenotype.

Conclusion: *HOXA13* offers an explanation for the etiology, phenotype, and oncogenic potential of Barrett's esophagus.

Disclosure: Nothing to disclose

References

1. Jiang, M., Li, H., Zhang, Y., Yang, Y., Lu, R., Liu, K., Lin, S., Lan, X., Wang, H., Wu, H., et al. (2017). Transitional basal cells at the squamous-columnar junction generate Barrett's oesophagus. *Nature* 550, 529–533.
2. Quante, M., Bhagat, G., Abrams, J.A., Marache, F., Good, P., Lee, M.D., Lee, Y., Friedman, R., Asfaha, S., Dubeykovskaya, Z., et al. (2012). Bile acid and inflammation activate gastric cardia stem cells in a mouse model of Barrett-like metaplasia. *Cancer Cell* 21, 36–51.

OP214   NOTCH SIGNALING PROMOTES PROGRESSION FROM BARRETT ESOPHAGUS TO ADENOCARCINOMA THROUGH NFKB SIGNALING

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Introduction: Barrett's esophagus (BE) is a metaplastic precursor lesion of esophageal adenocarcinoma (EAC) and current evidence supports an origin from stem cells in the gastric cardia. There is an ongoing discussion about the importance and role of intestinal metaplasia (IM), with the presence of goblet cells, in the definition of BE, as many patients seem not to show IM before the diagnosis of EAC. It was recently demonstrated that the appearance of goblet-like cells is indicative of intestinal metaplasia and inversely correlates with carcinogenesis. Notch signaling supports stem cell maintenance and potentially attenuates goblet cell maturation in the intestine, suggesting a role during esophageal carcinogenesis.

Aims and Methods: To unravel the functional impact of Notch signaling on BE and EAC development we crossed the IL-1b mouse model of BE with conditionally overexpressing (pL2.Lgr5.N2IC) or knockout (pL2.Lgr5.N2$^{fl/fl}$) mice of Notch2 specifically in Lgr5$^+$ stem cells (Lgr5CreTm). The triple transgenic mice were aged and histopathological, gene expression and FACS analysis were performed to characterize tumor development. Moreover, we utilized a p65 floxed mouse model (pL2.Lgr5.p65$^{fl/fl}$) to analyse the effect of NFkB activation in Lgr5 stem cells in our IL-1b mouse model.

Results: In IL-1b mice and in human tissue gene expression analyses indicated that in particular Notch2 receptor appears to be a relevant player during metaplastic and neoplastic transformation and inversely correlated with goblet cell maturation. In pL2.Lgr5.N2IC mice in contrast to the conditional knockout of Notch2, (pL2.Lgr5.N2$^{fl/fl}$) Notch signalling activation lead to mitigated goblet-like cell maturation, increased crypt fission, and accelerated tumour progression. Lgr5-cell derived BE organoids from all mouse lines and treatment with g-secretase inhibitor (DAPT) supported the *in vivo* observations of Notch-dependent differentiation and organoid growth. Furthermore, global gene expression profiling and immunohistochemistry hinted to a Notch-associated activation of NFkB activity specifically in Lgr5+ stem cells which prompted the generation of a conditional p65 knockout mouse model. Indeed, in pL2.Lgr5.p65$^{fl/fl}$ mice, the occurrence of dysplastic tissue was significantly reduced while the frequency of goblet cells increased accordingly, indicating a concomitant enhancement of both pathways during disease progression. Moreover, 3D BE organoid culture supported the implications of NFkB on cell proliferation and differentiation.

Conclusion: In conclusion, we show an importance of activated Notch signaling during progression from BE to EAC, whereas elimination of Notch signaling leads to goblet cell differentiation and reduced carcinogenesis. Activated Notch signaling induces NFkB pathway activation leading to increased stem cell expansion. In contrast elimination of NFkB signaling, results in intestinal differentiation and attenuated carcinogenesis. These data point to a novel role of Notch signaling in NFkB dependent stem cell expansion during esophageal carcinogenesis and introduce Notch activation as a novel biomarker for BE to EAC progression.

Disclosure: Nothing to disclose

OP215   SHORTENING OF TELOMERES ACCELERATES CARCINOGENESIS IN A MOUSE MODEL FOR BARRETT'S ESOPHAGUS AND EMERGES AS A BIOMARKER FOR PROGRESSION TO ESOPHAGEAL ADENOCARCINOMA

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Introduction: Barrett's esophagus (BE) is a premalignant, inflammation-dependent condition of the esophagus and a known precursor of esophageal adenocarcinoma (EAC). The incidence of EAC has increased at a rate of 4 to 10% annually in parts of the Western World. Though endoscopic surveillance is utilized to detect and treat dysplasia and early malignancy, it may not detect early cancers in nearly half of patients. Furthermore endoscopic therapy shows durable response in only up to 75% of cases and treatment specific risks have to be factored in. Novel biomarkers would ideally help in identifying patients with BE at increased risk of disease progression, prompting extended surveillance programs. A number of predictive markers have been reported in the literature including DNA content abnormalities. Genomic instability is a known driver for carcinogenesis and can occur with impaired telomere function. However, the functional role of short telomeres has not been evaluated during esophageal carcinogenesis.

Aims and Methods: Here we utilize the L2-IL-1β[1] transgenic mouse model of BE that recapitulates the human histopathologic progression to EAC while inducing chronic inflammation in the esophagus. To study the role of telomerase dysfunction and shortening of telomeres we crossed a telomerase k.o. mouse model (mTerc-/-) into our IL-1β model and analyzed progression to dysplasia as well as its implication for cellular differentiation in different backcrossed IL-1β.mTerc generations. Telomere length was measured quantitatively with *in situ* Hybridization (FISH) on a per cell basis. Results were compared to a human cohort of which full-length resected surgical esophagi were histopathologically scored and epithelial telomere length was measured at different stages of disease for each individual (27 samples of 9 individuals).

Results: In the mouse model, significant dysfunction of telomeres was observed in the second generation (IL-1β.mTerc-/- G2). Therefore we compared IL-1β.mTerc-/- G2 mice (n = 16) with IL-1β mice (n = 16). IL-1β.mTerc-/- G2 mice exhibited significantly shorter telomeres (p = 0.02) and a significantly higher grade of dysplasia (p = 0.02) than their age-matched IL-1β counterparts. Telomere length assessment of human biopsies of EAC precursor lesions confirm prior findings that BE- and LGD- epithelial cells possess significantly shorter telomeres than epithelial control cells of the gastric cardia with reduced ratios in BE-Cardia (p < 0.01) and LGD-Cardia (p < < 0.01) samples, suggesting a progressive shortening with accelerated malignant transformation. Importantly, discrimination of epithelial cells into columnar cells and goblet cells displayed significantly shorter telomeres in columnar lined cells than in goblet cells of human BE tissue (p < 0.01) and LGD tissue (p < 0.01).

Conclusion: Shortening of telomeres accelerated dysplastia in our mouse model of BE. This proves for the first time the functional importance of dysfunctional telomeres as a potential driver in early stages of esophageal carcinogenesis. In addition epithelial telomere shortness was correlated with disease progression and cellular de-differentiation in murine and human EAC precursor lesions. Thus telomere length qualifies as a potential biomarker in EAC precursor lesions and should therefore be further tested in large human cohorts to prove its validity. Remarkably the result that goblet cells possess longer telomeres than columnar cells within the same histologically defined samples complements earlier findings that higher goblet-to-columnar-cell ratios are more likely to be found in stages of metaplasia than dysplasia.

Disclosure: Nothing to disclose

Reference

1. Barrett esophagus: what a mouse model can teach us about human disease. Quante M, Abrams JA, Lee Y, Wang TC. *Cell Cycle*. 2012 Dec 1; 11(23): 4328–38. doi: 10.4161/cc.22485. Epub 2012 Oct 24. Review.

OP216 MINICHROMOSOMAL MAINTENANCE COMPONENT COMPLEX 5 (MCM5) AS A MARKER OF BARRETT'S OESOPHAGUS RELATED NEOPLASIA – A FEASIBILITY STUDY

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Introduction: Minichromosome maintenance component complex 5 (MCM5) is an integral component of the cell cycle, forming part of the DNA replicative helicase and facilitating cell replication and proliferation. Exfoliated cells obtained from patients with urothelial and oesophageal cancer demonstrate aberrant expression of MCM5. Barrett's oesophagus (BE) is a premalignant condition, but up to 36% of BE associated neoplasia is missed on endoscopic surveillance in the year preceding diagnosis. Quantification of potential biomarkers in aspirated gastric fluid from patients undergoing upper endoscopy may allow the identification of those with BE or early neoplasia. Such a validated biomarker also has potential as a screening test for Barrett's oesophagus or OAC, to stratify symptomatic patients presenting to clinicians. We assess whether MCM5 expression, quantified using a proprietary assay, can be used to discriminate between patients undergoing endoscopy with a macroscopically normal oesophagus (NE), non-dysplastic Barrett's oesophagus (NDBE), dysplastic Barrett's oesophagus (DBE) and OAC.

Aims and Methods: Patients were recruited from a UK referral centre between Aug 2017 and Apr 2018. All patients with NDBE, DBE or OAC had endoscopic and matched histologic confirmation of the diagnosis. High-grade dysplasia was considered DBE. Patients previously treated with radiofrequency ablation, chemo-radiotherapy, with systemic inflammatory disease, BE low-grade dysplasia or other malignancy were excluded. The oesophagus was carefully intubated to avoid mucosal disruption and no fluid was passed through the working channel before aspiration of 5ml of gastric fluid via a white tube and suction. Aspirated Gastric fluid was refrigerated at 4C prior to centrifugation at 4400rpm. Cells were then resuspended in lysis buffer and stored at -80°C prior to MCM5 quantification using a proprietary MCM5 assay. Normality was assessed by Shapiro-Wilks testing. Median MCM5 expression and interquartile range (IQR) was calculated and a two-tailed t-test was used to assess for differences in expression levels between the groups.

Results: 61 patients were recruited (15 NE; 14 NDBE; 18 HGD and 14 OAC). We demonstrate a stepwise increase in MCM5 expression for patients with acid reflux, NDBE, DBE and BE associated OAC. The median expression for each group was 47pg/ml (IQR 32.8 [26.92–59.77]) for NE, 116.6pg/ml (IQR 411.3 [17.23–428.54]) for NDBE, 229.9pg/ml (IQR 1070.4 [29.59–1099.96]) for DBE and 279pg/ml (IQR 1462.7[10.09–1500]) for OAC. There was a significant difference in MCM5 expression between patients with a macroscopically normal oesophagus and those with DBE or adenocarcinoma (p < 0.001). We also observed a trend towards higher mean MCM5 expression in patients with NDBE compared to those with a normal oesophagus (p = 0.06). There was no significant difference between patients with NDBE and DBE/OAC, although 2 patients in the NDBE group demonstrated very high expression compared to the rest of the group.

Conclusion: We demonstrate that raised MCM5 expression in exfoliated cells obtained from aspirating gastric fluid at upper endoscopy is a feasible approach to differentiating patients with a normal oesophagus from those with DBE and OAC. Further work should focus on appropriately powered multi-centre trials to assess for significant differences in MCM5 expression in patients with AR (NE), NDBE compared to DBE/OAC.

Disclosure: Materials and assays were performed by Arquer

OP217 PREDICTION IN SURVEILLANCE OF BARRETT'S ESOPHAGUS: THE EFFECT OF MULTIPLE MEASUREMENTS OF BIOMARKERS ON THE ESTIMATED NEOPLASTIC PROGRESSION RISK

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Introduction: Barrett's esophagus (BE) is a premalignant condition, where surveillance is carried out to reduce morbidity and mortality related to esophageal adenocarcinoma (EAC). The harm-benefit ratio of this strategy is questionable, because identification of high-risk patients is difficult. To improve risk stratification, additional biomarkers, and their variations between and -in particular-within patients should be taken into account. P53 and SOX2 are immunohistochemical markers which have been shown to be valuable in predicting progression to high-grade dysplasia (HGD) or EAC in BE patients. To date, no more

than 2 time points have been included when studying the risk of neoplastic progression.

Aims and Methods: We aimed to develop a model incorporating *all* follow-up (FU) measurements of low-grade dysplasia (LGD), p53, and SOX2 to study their predictive performance. In this multicenter prospective cohort study, we included consecutive BE patients from 15 hospitals in the Netherlands with histologically confirmed BE, a segment of $\geq$2 cm, and a FU time of at least 0.5 year. The study endpoint was identification of HGD or EAC. The surveillance guidelines of the American College of Gastroenterology were followed. Data were collected during every FU. 2 BE expert pathologists independently reviewed all H&E slides and immunohistochemistry of p53 and SOX2. We incorporated the dynamic values of LGD, p53, and SOX2 as registered at each endoscopy in a multivariate joint model, adjusted for age, sex, length of BE, and esophagitis.

Results: The median FU time was 7.2 years (IQR 5.4–9.9) of 628 patients included (69% male, median age 60 years, 76% length of BE $\geq$3 cm); 48 developed HGD or EAC. If a patient would have only 2 FU moments, 1 with normal (0) expression of the biomarker, 1 with aberrant (1), the hazard ratio (HR) of neoplastic progression was 1.2 for LGD (p = 0.61), 1.5 for p53 (p = 0.004), and 5.0 for SOX2 (p = 0.004), annually. With more FU endoscopies, these multiple observations will set the probability of aberrant expression to a value between 0 and 1, with a ditto proportion of the previously mentioned hazard ratios. Dynamic risk profiles of neoplastic progression could be estimated for individual patients during their FU, based on these biomarker patterns.

Conclusion: The risk of neoplastic progression can be estimated better by p53 and SOX2 than LGD if measurements of all FU endoscopies are taken into account. In the future, this prediction model will provide an updated prediction of neoplastic progression based on new observations in ongoing FU. The combination of dynamic observations of biomarkers such as p53 and SOX2 merits further study to improve the identification of high-risk patients in a personalized surveillance program, eventually reducing the burden of surveillance.

Disclosure: Nothing to disclose

OP218 OMEPRAZOLE INHIBITS CDX2 AND SOX9 EXPRESSION THROUGH EFFECTS ON HEDGEHOG SIGNALING AND BMP4 SIGNALING IN BARRETT'S ESOPHAGUS CELLS

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Introduction: Barrett's Esophagus (BE) is a premalignant condition defined by replacement of the squamous epithelium in the distal esophagus by specialized intestinal metaplasia. Previous work implicated that hedgehog signaling and BMP4 signaling were involved in the differentiation of squamous epithelium toward intestinal-type columnar epithelium[1], which was charactered by increased expression of columnar cell transcription factors, such as sox9[2] and CDX2[3]. Conceivably, inhibitors targeting hedgehog signaling and BMP4 signaling might block progression of BE, however, drugs mostly used to treat BE in the present are associated with acid suppression and reflux control. Drugs targeting BE progression is to be discovered.

Clinical studies revealed that the use of proton pump inhibitors (PPIs) but not histamine receptor antagonists was associated with a decreased risk of oesophageal adenocarcinoma[4−5]. Huo, X. et al revealed that PPIs exerted anti-inflammatory effects on reflux oesophagitis independent of effects on gastric acid secretion[6]. This research indicated that PPIs could benefit BE patients by Acid-Independent Mechanism.

Noting that BE might be driven by increased columnar cell transcription factors targeted by hedgehog signaling and BMP4 signaling, and that PPIs can benefit BE patients through acid-independent mechanisms, we hypothesized that PPIs might interfere with activation of hedgehog signaling and BMP4 signaling, expression of columnar cell transcription factors, such as sox9 and CDX2, and that this acid-independent mechanism might contribute to the efficacy of PPI therapy in BE progression.

Aims and Methods: We exposed CPA and CPB cells to omeprazole, and evaluated its effects on activation of hedgehog signaling and BMP4 signaling, expression of CDX2 and SOX9 by realtime PCR and western blot. Moreover, miRNA microarray technology was used to identify the differentially expressed miRNAs in BE organoids treated with Omeprazole, realtime PCR validated these results. Dual Luciferase Assay was used to validated miRNA/mRNA interactions.

Results: Omeprazole inhibited activation of hedgehog signaling and BMP4 signaling,and reduced expression of CDX2 and SOX9. Moreover, Omeprazole inhibited hedgehog signaling and BMP4 signaling by up-regulating hsa-miR-2116-3p and hsa-miR-18a-5p, respectively.

Conclusion: In Barrett's Esophagus cells, omeprazole inhibits CDX2 and SOX9 expression through effects on hedgehog signaling and BMP4 signaling, which is entirely independent of effects on gastric acid secretion. These previously unrecognized PPI effects might contribute to blocking progression of BE.

Disclosure: Nothing to disclose

References

1. Wang, D. H. et al. 170405Aberrant epithelial-mesenchymal Hedgehog signaling characterizes Barrett's metaplasia. *Gastroenterology* 138, 1810–1822, doi:10.1053/j.gastro.2010.01.048 (2010).
2. Blache, P. et al. SOX9 is an intestine crypt transcription factor, is regulated by the Wnt pathway, and represses the CDX2 and MUC2 genes. *J Cell Biol* 166, 37–47, doi:10.1083/jcb.200311021 (2004).
3. Huo, X. et al. Acid and bile salt-induced CDX2 expression differs in esophageal squamous cells from patients with and without Barrett's esophagus. *Gastroenterology* 139, 194–203 e191, doi:10.1053/j.gastro.2010.03.035 (2010).
4. Falk, G. W. et al. A combination of esomeprazole and aspirin reduces tissue concentrations of prostaglandin E(2) in patients with Barrett's esophagus. *Gastroenterology* 143, 917–926 e911, doi:10.1053/j.gastro.2012.06.044 (2012).
5. Singh, S., Garg, S. K., Singh, P. P., Iyer, P. G. & El-Serag, H. B. Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. *Gut* 63, 1229–1237, doi:10.1136/gutjnl-2013-305997 (2014).
6. Huo, X. et al. 170408In oesophageal squamous cells exposed to acidic bile salt medium, omeprazole inhibits IL-8 expression through effects on nuclear factor-kappaB and activator protein-1. *Gut* 63, 1042–1052, doi:10.1136/gutjnl-2013-305533 (2014).

TUESDAY, OCTOBER 23, 2018   14:30–15:00

Endoscopic submucosal dissection: When the going gets tough – Room 1.61/1.62

OP219   VONOPRAZAN FOR PREVENTING POST-ESD BLEEDING SHOULD BE FIRST ADMINISTERED SHORTLY AFTER ESD

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Introduction: Proton pump inhibitors (PPIs) and vonoprazan are widely used for healing post-ESD ulcers and they both prevent post-ESD bleeding[1,2] in Japan. However, PPIs take about 72 hours to inhibit gastric acid secretion. Therefore, patients must take PPIs a few days before ESD to increase gastric pH effectively. On the other hand, vonoprazan (VPZ), a potaissium-competitive acid blocker, is a new class of acid-suppressing agents, and takes only 3 hours to inhibit gastric acid secretion[3].

Aims and Methods: Data for 129 patients was reviewed, who underwent gastric ESD from December 1, 2016 to December 31, 2017 at Osaka City General Hospital and were treated with VPZ. We compared the incidence of bleeding after gastric ESD between subjects to whom VPZ was first administered on the day of ESD (the A group, $n = 70$) and those to whom VPZ was first administered by the day before ESD (the B group, $n = 39$). The patients exclusion criteria for the study included the following: (1) patients who underwent multiple sites ESD on the same day ($n = 14$), (2) patients to whom second-look GI endoscopy was not performed ($n = 5$), (3) patients whose ESD was cancelled ($n = 1$). A case which has active bleeding or exposed vessels on post-ESD gastric ulcers with hematemesis, melena or a decline in hemoglobin levels from not less than 2 g/dl within 4 weeks after ESD was defined as "post-ESD bleeding". In addition, we perform second-look endoscopy on the day after ESD. A case in which hemostasis was needed with hemorrhage of Forrest Ia and Ib when we underwent the second-look GI endoscopy was defined as "next-day hemostasis case". We investigated retrospectively post-ESD bleeding rate and next-day hemostasis rate in the A group and the B group.

Results: Gender, use of anti-thrombotic agents, dialysis, mean age, and ulcer size were not significantly different in both groups. 4 of the 70 patients in the A group (5.7%) and 3 of the 39 patients in the B group (7.7%) had Post-ESD bleeding. In addition, 17 patients in the A group (24.3%) and 8 patients in the B group (20.5%) had next-day hemostasis. There was no significant difference in both groups regarding post-ESD bleeding ($p = 0.813$) and next-day hemostasis ($p = 0.699$) (Table). That is possibly because VPZ rapidly inhibits gastric acid secretion within 3 hours after administration, prevents acid exposure, and reduces the percentage of bleeding on post-ESD gastric ulcers. In our hospital, 38 patients underwent gastric ESD and esomeprazole (EPZ) was first administered by 2 days before ESD, from December 1, 2014 to December 31, 2017. 4 of those 38 patients (10.5%) had post-ESD bleeding, and 8 of them (21.1%) had next-day hemostasis. We did not investigate VPZ vs. EPZ in this study. However, the effect on bleeding after gastric ESD was similar with the case with first administration of VPZ a few hours after ESD. Therefore, patients do not need to start taking PPIs a few days in advance of ESD but should start taking VPZ by a few hours after ESD.

	A group, n = 70	B group, n = 39	P – Value
Post-ESD bleeding	4 (5.7%)	3 (7.7%)	0.813
Next-day hemostasis	17 (24.3%)	8 (20.5%)	0.699

ESD, endoscopic submucosal dissection. Univariate analysis was performed by Fisher's exact test.

[Incidence of post-ESD bleeding and next-day hemostatsis]

Conclusion: Vonoprazan should be first administered shortly after ESD for preventing post-ESD bleeding.
Disclosure: Nothing to disclose

References

1. Uedo N, Takeuchi Y, Yamada T, et al. Effect of a proton pump inhibitor or an H2-receptor antagonist on prevention of bleeding from ulcer after endoscopic submucosal dissection of early gastric cancer: A prospective randomized controlled trial. *J Gastroenterol*. 2007; 102: 1610–1616.
2. Kagawa T, Iwamoto M, Ishikawa S, et al. Vonoprazan prevents bleeding from endoscopic submucosal dissection-induced gastric ulcers. *Aliment Pharmacol Ther* 2016; 44: 583–591.
3. Sakurai Y, Mori Y, Okamoto H, et al. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects: A randomized open-label cross-over study. *Aliment Pharmacol Ther* 2015; 42: 719–730.

OP220   COMPARISON OF THE EFFECTS OF ANTITHROMBOTIC THERAPY ON DELAYED BLEEDING AFTER ENDOSCOPIC RESECTION: A PROPENSITY SCORE-MATCHED CASE-CONTROL STUDY

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Introduction: Antithrombotic therapy has been known to increase post-endoscopic resection (ER) bleeding risk; however, there are few studies quantifying the effect of antithrombotic agents.

Aims and Methods: This study aimed to analyze the incidence of delayed bleeding (DB) based on antithrombotic agents administered and to identify the proper timing of drug cessation. Between January 2011 and March 2017, 7752 patients with 8242 lesions underwent ER for single gastric neoplasm. After a 2:1 propensity score matching using age, sex, specimen size, tumor location, diagnosis, chronic kidney disease and bleeding history, 798 and 399 lesions were classified as belonging to the matched control (MC) group and antithrombotics (AT) group respectively. The clinical outcomes were compared between the two groups.

Results: The DB rate of the MC and AT groups was 6.3% and 10.0%, respectively. There was no significant difference in the early DB rate between the 2 groups; however, the late DB rate of the AT group was higher than the MC group. The continuation group of the AT group had a higher incidence of DB than their matched controls (15.9% vs. 5.1%, OR 3.55 [95% CI 1.24–10.14]; p = 0.018). In patients taking anticoagulants, heparin bridging therapy (HBT) increased the incidence of DB compared with non-HBT (35.7% vs. 10.0%, OR 5.00 [95% CI 1.11–22.50]; p = 0.036). A thromboembolic event was not observed in all patients taking antithrombotic agents.

Conclusion: Patients receiving antithrombotic therapy had a higher incidence of DB than those not receiving antithrombotic therapy, especially with the continued administration of antithrombotic agents and HBT.
Disclosure: Nothing to disclose

OP221   ENDOSCOPIC SUBMUCOSAL DISSECTION FOR GASTRIC TUMORS UNDER THE CONTINUOUS ADMINISTRATION OF ANTICOAGULANTS

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Introduction: Endoscopic submucosal dissection (ESD) is sometimes accompanied by serious adverse events such as postoperative bleeding and perforation. Tentative guidelines concerning the continuation and cessation of anticoagulants have been published by several societies including the Japan Gastroenterological Endoscopy Society and the European Society of Gastrointestinal Endoscopy. According to the Japanese guidelines, heparin bridge therapy is commonly performed during the cessation of warfarin in patients with a high risk of thromboembolism; however, heparin bridge therapy may increase the risk of postoperative bleeding. Although direct oral anticoagulant drugs (DOACs) are increasingly used in clinical practice, the association between DOACs and the risk of post-ESD bleeding is not fully understood. Recently, the continuous administration of anticoagulants (no bridge to heparin) has been recommended in Japan.

Aims and Methods: The aim of this study was to evaluate the effect of continuous anticoagulants including DOACs on postoperative adverse events after ESD for gastric tumors. A total of 76 patients who had taken anticoagulants underwent gastric ESD between April 2005 and March 2018. ESD was performed in 49 patients under the cessation of anticoagulants or bridging anticoagulants to heparin before March 2013 and in 27 patients under the continuous

administration of anticoagulants after April 2013. The clinical outcomes of ESD were retrospectively compared between the non-continuous and continuous groups.

Results: The study population included 60 men and 16 women (median age, 77.5 years). Warfarin was taken by all 49 patients in the non-continuous group and 16 patients in the continuous group. The remaining 11 patients received DOACs (dabigatran, n = 3; apixaban, n = 4; and rivaroxaban, n = 4). The clinical characteristics (including age, gender, tumor location, macroscopic appearance, tumor size, presence of ulcer scar and tumor depth) did not differ between the two groups to a statistically significant extent. *En-bloc* resection was achieved in all patients with a complete resection rate of 96% in the non-continuous group (47 of 49 patients) and 100% in the continuous group (27 of 27 patients). The median procedure time was 78 minutes in the non-continuous group and 70 minutes in the continuous group (p = 0.99). Postoperative bleeding occurred in 4 patients in the non-continuous group (8.2%) and 2 patients in the continuous group (7.4%); the difference was not statistically significant (p = 1.00). None of the patients developed perforation during the study period. One patient in non-continuous group suffered from cerebrovascular disease.

Conclusion: The continuous administration of anticoagulants did not significantly increase the incidence of adverse events in our cases. Considering the risk of cerebrovascular disease, the continuous administration of anticoagulants might be feasible and safe in gastric ESD.

Disclosure: Nothing to disclose

OP222 THE SIMPLENESS AND EASINESS OF HEMOSTASIS IN ENDOSCOPIC SUBMUCOSAL DISSECTION USING DUAL RED IMAGING

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Introduction: Endoscopic submucosal dissection (ESD) still has not been widely adopted around the world because endoscopists sometimes face difficulty in achieving hemostasis during ESD. Our group developed dual red imaging (DRI), a novel endoscopic imaging technology. We push the operation button of the endoscope once and we can change White Light Imaging (WLI) to DRI easily. DRI may facilitate hemostasis management due to being able to clearly identify the bleeding point as a yellow color. However, there is no evidence for easiness of hemostasis management using DRI. In this study, we examined the safety and efficacy of DRI for hemostasis management during ESD.

Aims and Methods: We performed 3 prospective studies. Study 1. DRI and WLI were used alternately for the management of 380 bleeding events in patients undergoing ESD. Study 2. 46 patients underwent ESD using DRI for hemostasis management during ESD. The endoscopist commenced the ESD using WLI, switched to DRI immediately when bleeding was detected, then switched back to WLI upon obtaining hemostasis. Study 3. 45 patients underwent ESD using DRI throughout the entire intervention. The psychological stress experienced by the endoscopist and time required to achieve hemostasis (hemostasis time) were examined in Study 1. We also examined the treatment result and ESD operation time in Study 2 and 3. We evaluated psychological stress with 5 phases of score depending on degree of the stress. We also compared the treatment results and operation time between DRI and WLI.

Results: Study1. The average hemostasis time was significantly shorter in the DRI group than in the WLI group (60.7 vs 50.8 seconds, p = 0.012), and the average score for psychological stress in the DRI group was significantly lower (2.30 vs 1.68, p < 0.0001). Study 2. The success rates of intervention, en bloc resection, and en bloc R0 resection were 46/46 (100%), 46/46 (100%) and 43/46 (93.4%), respectively, and the rates of perforation and delayed bleeding were 1/46 (2.1%) and 3/46 (6.5%), respectively. Study 3. The rates of intervention success, en bloc resection, and en bloc R0 resection, perforation, and delayed bleeding were 42/45 (93.3%), 42/42 (100%), 38/42 (90.4%), 5/45 (11.1%), and 2/45 (4.4%), respectively. All of the perforation cases were lesions with severe fibrosis. The operation time in the DRI groups was shorter than the control groups, however, there was no significant difference between the DRI and control groups when DRI was used throughout the entire ESD procedure or used only for hemostasis management.

Conclusion: DRI is a novel endoscopic imaging technology that facilitates hemostasis during ESD. DRI can only be safely used for hemostasis management during the ESD procedure, because dissection by DRI poses a high risk of perforation in lesions with fibrosis.

Disclosure: Nothing to disclose

OP223 EFFICACY OF ORAL MIXTURE OF HYDROCORTISONE SODIUM SUCCINATE AND ALUMINUM PHOSPHATE GEL FOR THE PREVENTION OF STRICTURE AFTER ≥2/3 CIRCUMFERENTIAL ENDOSCOPIC SUBMUCOSAL DISSECTION(ESD) FOR ESOPHAGEAL CANCER

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Introduction: ESD has been performed on many patients with early esophageal cancer. However, postoperative stricture after ≥2/3 circumferential ESD is the most important issues for quality of life in patients which is drastically decreased and repeat, periodic endoscopic balloon dilation (EBD) is usually required. We developed an innovative strategy with oral mixture of hydrocortisone sodium succinate and aluminum phosphate gel for prevention of the stricture and evaluate the efficacy of this mixture in single center of Beijing, China.

Aims and Methods: 27 patients who underwent more than 2/3 circular circular ESD from September 2014 to November 2017 were included. They were randomized into control and study groups. 13 patients received endoscopic intralesional steroid injection accompanied with systemic steroid treatment(IT+ST group; control group), 14 patients received oral mixture of hydrocortisone sodium succinate and aluminum phosphate gel (OHA group; study group). IT+ST group started with 80mg introlesional steroid at the end of ESD procedure, and 30mg/day prednisolone on the second day post-ESD, then continued with a gradually tapering prednisolone dose, finally discontinuing systemic steroid administration 8 weeks later. OHA group started with mixture of hydrocortisone sodium succinate 50mg and aluminum phosphate gel 20g, qid for 2weeks and continued with a gradually tapering OHA dose on the second day post-ESD. EBD was performed when patients experienced persistent dysphagia. If the patient had no complaint of dysphagia, esophagogastroduodenoscopy (EGD) was performed 8 weeks after ESD to evaluate any possible stricture. The primary end point in this part was the stricture rate after ESD. The secondary end point was the number of EBD sessions required to resolve the stricture. A stricture was defined as a difficulty in swallowing solids or an inability to pass an EGD (9.2mm diameter endoscope).

Results: No significant differences were seen among the 2 groups in terms of demographic parameters including age, sex, tumor location, resection size. The stricture rates of IT+ST, OHA group after ESD were 53.8% (7 of 13 patients), 7.1% (1 of 14 patients), respectively (95% confidence interval, p = 0.013). OHA group needed less EBD sessions than IT+ST group (median 0, interquartile ranged from 0 to 0 vs. median 0.5, interquartile ranged from 0 to 1; p = 0.018).

Conclusion: Oral mixture of hydrocortisone sodium succinate and aluminum phosphate gel showed promising results for the prevention of stricture after ESD for early esophageal cancer.

Disclosure: Nothing to disclose

OP224 A RANDOMIZED CONTROLLED ANIMAL STUDY TO EVALUATE THE TECHNICAL FEASIBILITY OF CHEMICALLY ASSISTED SUBMUCOSAL DISSECTION TECHNIQUE WITH THE CONTINUOUS APPLICATION OF MESNA

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Introduction: Mesna is a mucolytic agent, which chemically dissolves disulfide bonds in connective tissues. We previously reported that the use of mesna as an injectate to create a submucosal fluid bleb shortened the procedure time of gastric and esophageal ESD reducing the need for electrosurgical dissection. However, the chemical effect of mesna is inactivated within a short period of time and the substance with a low osmotic pressure quickly dissipates into surrounding tissues. A novel infusion pump system was recently developed to enable mesna to be continuously applied onto tissues while dissecting the submucosal tissue plane.

Aims and Methods: To explore the procedural feasibility of ESD with the chemical blunt dissection technique (COLD ESD) using the newly developed mesna infusion pump (CADISS Remote System, Auxin surgery) in *in vivo* porcine models evaluating the effect of mesna as a chemical tissue dissector comparing with saline. In this study, 5 porcine models were used under general anesthesia. We created 2 tentative lesions sized about 20mm in the body and the antrum of the stomach respectively. A total of 4 lesions were created for each pig. Then, each lesion was randomly assigned into the mesna group or the saline group as a control. After the circumcision around the lesion was made, mesna or saline was injected into the submucosal layer underneath the isolated lesion with the CADISS Remote System. The information of the injectate used was blinded to the operator. First, the blunt cleavage of the submucosa was attempted while continuously applying one of the injectates using a Hook Knife J (Olympus medical systems), connected to the pump. However, the use of electrosurgical dissection was allowed when the operator felt excessive tissue resistance ad lib. We counted the number of electrosurgical incisions used with the VIO Doku software in real-time (ERBE). All endoscopic procedures were performed by 2 endoscopists. The levels of procedural difficulty were evaluated with a 5-point analogue scale. The burned area ratio (burned area/specimen area) of the excised specimen was evaluated with a picture of the specimen using Image J software (NIH).

Results: En bloc resection rate was 100% in both groups. The total procedure time (mesna group 18.1 ± 7.9 min vs. saline group 20.9 ± 12.5 min, p = 0.54), the submucosal dissection time (mesna group 11.1 ± 8.0 vs saline group 12.5 ± 9.4

minutes, p = 0.57), the total amount of injectate used (mesna group 19.0 ± 7.5 ml vs saline group 23.7 ± 10.3 ml, p = 0.30), the number of electrosurgical incisions (mesna group 26.6 ± 17.2 vs saline group 33.0 ± 42.4 times, p = 0.62), the subjective sore of the procedural difficulty (mesna group 3.8 ± 1.0 vs saline group 3.1 ± 1.0, p = 0.17) showed no significant difference between the 2 groups. However, the burned area ratio was significantly smaller in the mesna group (mesna group $9.0 \pm 8.9\%$ vs saline group $17.7 \pm 8.7\%$, p = 0.02).

Conclusion: In this randomized controlled animal study, the procedural feasibility of the mesna assisted cold-ESD using the novel pumping system was confirmed. The results of this study indicated that the continuous topical application of mesna would minimize the thermal damage on the tissues, which may provide optimal tissue sampling for accurate histological evaluation of specimens and reduce bystander tissue burns associated with electrosurgical incisions.

Disclosure: Nothing to disclose

TUESDAY, OCTOBER 23, 2018   15:45–17:15
Champion session in surgery and endoscopy – Room E1_____

OP225   LAPAROSCOPIC VERSUS OPEN PANCREATODUODENECTOMY (LEOPARD-2): A MULTICENTER, PATIENT-BLINDED, RANDOMIZED CONTROLLED TRIAL

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Introduction: Laparoscopic pancreatoduodenectomy (LPD) is gaining popularity because of potential advantages including less operative blood loss, less delayed gastric emptying, and shorter hospital stay but concerns exist regarding increased pancreatic fistula rates and, in low-volume centers, increased postoperative mortality. Multicenter randomized trials investigating this subject are lacking. In the Netherlands, LPD was introduced according to the IDEAL framework for surgical innovation including a training program (LAELAPS-2) with a 3.5% 90-day mortality and 34% pancreatic fistula rate in the first 114 LPDs in 4 centers. According to the IDEAL framework, we hereafter initiated an RCT to assess whether LPD could reduce time to functional recovery.

Aims and Methods: A multicenter randomized controlled, patient-blinded, trial comparing LPD with OPD was performed in 4 centers that each perform ≥ 20 pancreatoduodenectomies annually (median 37 (range 23-77)), completed the LPD training program, and had performed at least 20 LPDs during the 18 months training period (range 23-34). Adult patients with an indication for pancreatoduodenectomy because of a neoplasm without signs of vascular involvement were included. Primary outcome was time (days) to functional recovery.

Results: The data safety monitoring board (DSMB) recommended early termination of the trial because of a difference in 90-day complication-related mortality (LPD 5 (10%) vs. OPD 1 (2%), p = 0.2). The DSMB stated that the possible harm for patients did not outweigh the hypothesized patient benefit of faster recovery. In total, 99 of the projected 136 patients were included (50 LPD and 49 OPD). Time to functional recovery was 9 days (95% CI 6-12) after LPD vs. 8 days (95% CI 6-10) after OPD (p = 0.9). The conversion rate with LPD was 20% (N = 10). Operative blood loss was 300 mL (IQR 200-519) vs. 400 mL (300-975) (p = 0.13) and operative time 383 (IQR 231–454) vs. 215 (IQR 180–299) minutes (p < 0.001) for LPD and OPD respectively. Clavien-Dindo grade ≥ 3 complications were seen in 25 (50%) vs. 19 patients (39%) (p = 0.3), pancreatic fistula grade B/C in 14 (28%) vs. 12 (24%) (p = 0.8), hepaticojejunostomy leakage grade B/C in 6 (12%) vs. 5 (10%) (p = 0.8) and postpancreatectomy haemorrhage grade B/C in 5 (10%) vs. 7 (14%) (p = 0.5) for LPD and OPD respectively. Hospital stay was 11 days (IQR 7-20) after LPD and 10 (IQR 7-20) after OPD (p = 0.8). The median annual volume of LPD per center during the trial was 11 (range 6-15).

Conclusion: This early terminated first multicenter RCT showed comparable time to functional recovery and morbidity after LPD versus OPD. The mortality rate after LPD raises concerns, especially in the absence of patient benefits, even in trained centers. Potentially, the learning curve for LPD is longer than previously perceived and possibly a greater annual volume is required.

References: Trial registration: Netherlands Trial Register (NTR5689). Registered on March 2, 2016.

Disclosure: A investigator initiated grant was received from Ethicon/ Johnson&Johnson, IIS 15-707

OP226   A STEP-UP APPROACH OR OPEN NECROSECTOMY FOR NECROTIZING PANCREATITIS: LONG-TERM OUTCOMES OF A RANDOMIZED TRIAL

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Introduction: In 2010, the PANTER trial demonstrated that a step-up approach for infected necrotizing pancreatitis led to a reduction in the combined primary endpoint of major complications and death, as compared to open necrosectomy. A third of patients was successfully treated with catheter drainage only. The step-up approach could be associated with more reinterventions in the long term. We therefore performed a long-term follow-up study.

Aims and Methods: We prospectively evaluated the 73 surviving out of 88 randomized patients at a mean follow-up of 86 months (± 11 months). We collected data on clinical and health care resource utilization endpoints throughout follow-up. Primary endpoint was a composite of major complications and death, in accordance with the PANTER trial. During a final follow-up visit, we measured pancreatic exocrine function, quality of life (SF-36, EQ-5D) and Izbicki pain-scores.

Results: From index admission to final follow-up, the primary endpoint occurred in 19 (44%) patients in the step-up group and in 33 (73%) patients in the open necrosectomy group (p = 0.005). Patients in the step-up group had fewer incisional hernias (23% vs. 53%; p = 0.004), less pancreatic exocrine insufficiency (29% vs. 56%; p = 0.03) and less endocrine insufficiency (40% vs. 64%; p = 0.05). There were no differences in additional drainage procedures (11% vs. 13%; p = 0.99), pancreatic surgery (11% vs. 5%; p = 0.43), recurrent acute pancreatitis [b1] and Izbicki pain-scores. Quality of life increased during follow-up without a significant difference between groups. Combined medical costs were similar in both groups.

Conclusion: A step-up approach for necrotizing pancreatitis remains superior to open necrosectomy during long-term follow-up, without an increased risk for reinterventions.

Disclosure: Nothing to disclose

OP227 WIRE-GUIDED BILIARY CANNULATION IN ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY: A PROSPECTIVE RANDOMIZED COMPARISON BETWEEN MICRO AND CONVENTIONAL GUIDEWIRE

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Introduction: Wire-guided biliary cannulation is reported to be an appropriate first-line cannulation technique, since it is associated with a high success rate and low risk of post-ERCP pancreatitis (PEP). However, the conventional guidewire (CGW; 0.025 inch) is sometimes too rigid to pass through the long curved narrow distal segment, resulting in increased biliary cannulation time and even an unsuccessful biliary cannulation. At UEGW 2017, we reported that a micro guidewire (GTW; GT wire; 0.016 inch, 300 cm, TERUMO, Japan) designed for superselective angiography was helpful in such cases. Rapid biliary cannulation is desirable because a prolonged procedure may induce PEP. The use of GTW-assisted cannulation as the first-line cannulation technique for ERCP could reduce biliary cannulation time.

Aims and Methods: We aimed to evaluate whether biliary cannulation was achieved in lesser time using GTW than when using CGW in ERCP. In total, 118 consecutive ERCP-naïve patients were randomly assigned to undergo biliary cannulation with GTW (GTW group) or CGW (CGW group). We measured the cannulation time (from the time the cannula advanced out of the endoscope channel to the time successful deep cannulation was confirmed) and the serum amylase level on the following day. The endoscopist performed ERCP with the designated guidewire for less than 10 min and was permitted to switch to the other guidewire to achieve cannulation after 10 min from initiation of the procedure. The primary outcome was the success rate of biliary cannulation within the first 10 min, which was then compared between both groups. The secondary outcome was the overall success rate of biliary cannulation as well as the incidence of PEP and asymptomatic hyperamylasemia in both groups. Additionally, among patients in whom biliary cannulation was successful, we compared the frequency of switching to the other guidewire and the biliary cannulation success rate between both groups.

Results: The biliary cannulation success rate within the first 10 min was significantly higher in the GTW group than in the CGW group (39/59 patients, 66% and 29/59 patients, 49%, respectively; p = 0.047 by Fisher's exact test). The overall biliary cannulation success rate (57/59 patients, 97% and 57/59 patients, 97%) and incidence of PEP (1/59 patients, 1.7% and 1/59 patients, 1.7%) was equal in both groups. The overall asymptomatic hyperamylasemia was 13.6% (8/59 patients) in the GTW group and 15.3% (9/59 patients) in the CGW group. Among the 114 patients in whom biliary cannulation was successfully achieved, 32% (18/57 patients) in the CGW group were switched to GTW. No patients in the GTW group were switched to CGW after 10 min from initiation of the procedure. The biliary cannulation success rate in the GTW group was significantly higher than that in the CGW group (p = 0.036, by the Kaplan-Meier method and log rank test).

Conclusion: The use of GTW-assisted cannulation as the first-line cannulation technique for ERCP significantly improved the biliary cannulation success rate and reduced biliary cannulation time.

Disclosure: Nothing to disclose

OP228 MOTORIZED SPIRAL ENTEROSCOPY: FINAL RESULTS A TWO-CENTER PROSPECTIVE CLINICAL TRIAL

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Introduction: Currently available methods for small bowel endoscopy are complex to use and time consuming. Novel Motorized Spiral Endoscopy (NMSE) represents a new technology which offers all advantages of spiral enteroscopy with a faster and less invasive approach.

Aims and Methods: To prospectively study the efficacy and safety of peroral NMSE. Primary objective: diagnostic yield of NMSE in patients with suspected small bowel diseases. Secondary objectives: procedural success, – time, depth of maximal insertion, therapeutic yield, adverse events.

Patients with occult gastrointestinal bleeding, indeterminate iron-deficiency anemia or positive findings of small bowel imaging examinations were included in a 2-center prospective clinical trial. A novel reusable endoscope with an integrated electric motor was used for rotating a disposable short spiral overtube mounted on the insertion tube portion. Rotation of the spiral allows to "pleat" or "unpleat" the bowel either on or off the insertion tube as the spiral thread rotates in a clockwise or counter-clockwise direction.

Results: 140 procedures were performed in 132 patients (63 f, 79 m; mean age [range]: 62 [20-100] years) with suspected small bowel disease and positive findings of video capsule endoscopy or other small bowel imaging modality. Technical success of NMSE (advancement of the endoscope beyond the ligament of Treitz) was 98%. Mean insertion time to the jejunum was 4.7 [1-25] min and to the deepest point of insertion distal from ligament of Treitz 28.4 [3-122] min. The mean maximum insertion depth from ligament of Treitz was 425 [0-600] cm. Anterograde panenteroscopy to cecum was achieved in 14 patients (10%). The diagnostic yield of NMSE was 76% (arteriovenous malformations AVM n = 80, benign polyps n = 22, other findings n = 51). 167 interventions were performed in 116 procedures (biopsies n = 39, argon plasma coagulation APC n = 69, ink injection n = 33, clipping n = 17, EMR n = 9). Mean withdrawel time without interventions was 14.6 [4-45] min. 1 delayed perforation of the terminal ileum following APC of AVM resolved without consequences after laparoscopic suturing (anticipated serious adverse event, 0.7%). Mild adverse events (mainly asymptomatic superficial mucosal lesions) occurred in 12% of the procedures.

Conclusion: Final results of a first prospective clinical trial demonstrate that NMSE is safe and effective for diagnostic and therapeutic anterograde enteroscopy. The novel technique seems to offer advantages over traditional methods in terms of procedural duration and ease of use.

Disclosure: Authors H.N., J.D., T.B. received consultancy honoraria and lecture fees from Olympus Medical Corporation.

OP229 REAL-TIME ARTIFICIAL INTELLIGENCE "FULL COLONOSCOPY WORKFLOW" FOR AUTOMATIC DETECTION FOLLOWED BY OPTICAL BIOPSY OF COLORECTAL POLYPS

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Introduction: Colon polyp detection and optical biopsy are key performance indicators in colonoscopy. Artificial Intelligence (AI) has the potential to greatly improve both. However, practical real-time applications with standard scopes are elusive.

Aims and Methods: We have published on real-time optical biopsy of diminutive colon polyps using AI, surpassing the 90% negative predictive value (NPV) for adenomas, as per PIVI guidelines. We sought to use latest AI techniques to further improve our optical biopsy performance. In relation to polyp detection, most AI detection tools are trained using still images or videos with obvious polyps. In contrast, we planned our tool around difficult sequences from clinical screening videos that start when the polyp first becomes visible. Finally, an AI model capable of detecting NBI light was the cornerstone that allowed us to propose a "full clinical workflow" for colon polyp detection immediately followed by optical biopsy. Our workflow was optimized to allow for real-time clinical use, a first in this field.

The full workflow captures the video feed from a tower and consists of 3 distinct AI models: a NBI light detector, a polyp detector, and an optical biopsy. The NBI light detector runs continuously and triggers either the detection mode (white light) or the optical biopsy mode (NBI). This allows a seamless interface without the need for a switching signal from either the tower or operator.

Results: The NBI light model was tested on 21,804 unseen frames and achieved a near-perfect accuracy of 99.94%.

The polyp detection model was tested on the polyp approach sequence part of 30 previously unseen colonoscopy videos (>20min each). The model detected polyps with a sensitivity of 79.0% while triggering on 13.7% of frames without polyps. Notably, polyps are detected, on average, 403 milliseconds after their first appearance.

The optical biopsy was tested on videos of 125 previously unseen polyps and achieved a sensitivity of 95.95%, specificity of 91.66%, and NPV of 93.6%. Even if the model can abstain when unsure, it committed to a prediction for 97.6% of polyps, an absolute increase of 12.8% over our previous work[1].

Finally, results are displayed in real-time and the user interface is updated 30 times per second.

Conclusion: We propose the first real-time AI full colonoscopy workflow for automatic detection followed by optical biopsy of colorectal polyps. It consists of three separate AI models allowing for real-time detection of colon polyps, automatic recognition of the switch from white light to NBI, followed by immediate optical biopsy of detected polyps. Detection shows very promising results, especially on difficult approach sequences, and our AI optical biopsy has been even further improved. A clinical trial is planned for the near future.

Disclosure: MF Byrne—founder "ai4gi", shareholder Satis Operations Inc. N Chapados, F Chandelier—shareholders Imagia Cybernetics Inc.

Reference

1. Byrne MF, Chapados N, Soudan F, et al Real-time differentiation of adenomatous and hyperplastic diminutive colorectal polyps during analysis of unaltered videos of standard colonoscopy using a deep learning model *Gut* Published Online First: 24 October 2017. doi: 10.1136/gutjnl-2017-314547.

OP230 OPTICAL DIAGNOSIS OF DIMINUTIVE POLYPS IN THE DUTCH CRC SCREENING PROGRAM: ARE WE READY TO START?

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Introduction: Implementation of the optical diagnosis of diminutive polyps increases the efficacy and reduces the economic burden of a colorectal cancer (CRC) screening program. To adopt such strategy in clinical practice, the ASGE PIVI thresholds should be met: ≥90% negative predictive value (NPV) for diagnosis of adenomatous histology and ≥90% agreement between optical diagnosis and histological diagnosis in determining the post-polypectomy surveillance intervals. We evaluated these performance parameters in the Dutch CRC screening program.

Aims and Methods: We collected endoscopic and histopathologic data from participants to the FIT Dutch CRC screening program from February 2014 to August 2015 at 4 endoscopy units (1 academic centre and 3 non-academic centers). All endoscopists were familiarized with optical diagnosis of colorectal polyps. High-definition white light colonoscopy was used, and if necessary (virtual) chromoendoscopy was used. The classification options were: adenomatous polyp, hyperplastic polyp, sessile serrated polyp, carcinoma and other. The 'diagnose and leave in place' scenario was applied to hyperplastic polyps ≤5mm in the rectosigmoid while the 'resect and discard' scenario was applied to polyps ≤5mm in the entire colon. We measured the agreement between optical diagnosis and histological diagnosis in determining the post-polypectomy surveillance intervals according to the post-polypectomy colonoscopy surveillance guideline from the ESGE[1]. For this, the percentage of congruent pairs was calculated.

Results: A total of 3.028 diminutive polyps were included and 14 certified endoscopists participated in this study. Optical diagnosis of diminutive adenomatous polyps predicted histology with 76% (95% CI 74-77) accuracy and 69% (95% CI 66-73) NPV. Optical diagnosis of diminutive hyperplastic polyps in the rectosigmoid (n = 1.222) predicted histology with 71% (95% CI 69-74) accuracy, 61% (95% CI 56-66) PPV and 72% (95% CI 68-76) NPV. In 2.470 patients both optical diagnosis and histopathological data for index colonoscopy were available. Applying the 'diagnose and leave in place' strategy resulted in 96% agreement on surveillance intervals, while applying the 'resect and discard' strategy resulted in 91% agreement on surveillance intervals (Table 1).

Conclusion: In the Dutch CRC screening program the optical diagnosis of diminutive polyps remains difficult. According to the ASGE PIVI thresholds, the NPV for optical diagnosis in this setting was too low but the thresholds for determining surveillance intervals, based on optical diagnosis, are met. Systematic training in optical diagnosis can optimize the efficacy of our nationwide CRC screening program.

		Based on histopathology			
		3 year	10 year	No surveillance	Total
Based on optical diagnosis	3 year	**928**	82	2	1012
	10 year	32	**706**	57	795
	No surveillance	3	36	**624**	663
	Total	963	824	683	**2470**

[Table 1.]

Disclosure: Roel M.M. Bogie and S. Sanduleanu-Dascalescu received an unrestricted research grant from Pentax Europe.

Reference

1. Hassan C, Quintero E, Dumonceau JM, Regula J, Brandao C, Chaussade S, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy*. 2013 Oct; 45(10): 842–5.

OP231 HIGH-DEFINITION CHROMOENDOSCOPY (HDCE) USING 0.03% INDIGO CARMINE VERSUS 0.2% INDIGO CARMINE FOR DETECTING DYSPLASIA IN PATIENTS UNDERGOING IBD COLITIS SURVEILLANCE. A RANDOMIZED CONTROLLED TRIAL – INTERIM ANALYSIS

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Introduction: Patients with ulcerative colitis (UC) and Crohn's colitis are known to have an increased risk of colorectal cancer compared with that of the background population. The recent SCENIC consensus statement endorses high definition chromoendoscopy (HDCE) with targeted biopsies for dysplasia detection but required more evidence regarding optimal dye concentrations and mode of delivery. No trials have previously studied this. Our aim was to compare 0.2% indigo carmine (IC) using a spray catheter with that of 0.03% IC via a foot pump, for dysplasia detection in patients undergoing surveillance in IBD colitis.

Aims and Methods: A parallel group randomized controlled trial (ClinicalTrials.gov ID: NCT03250780) in which patients undergoing surveillance endoscopy for IBD colitis were randomized into either HDCE using 0.2% IC using a spray catheter or HDCE using 0.03% IC via a foot pump. HD scopes (Olympus CF-HQ290L) and processors (Elite CV 290) were used. 2 expert GI histopathologists confirmed presence of dysplasia. Time of withdrawal and ampoules of IC were also recorded.

Results: There were 75 patients in each arm (total n = 150). Baseline characteristics including colitis phenotype, disease duration, BSG risk category, number of biopsies, concomitant PSC and previous dysplasia were similar in both arms. Dysplasia within the colitic area was found in 12 patients (16.0%) in the 0.2% IC group and 13 patients (17.3%) within the 0.03% IC group, p = 0.666 (table 1). Withdrawal was significantly (p < 0.001) quicker in the 0.03% IC group (16.36 ± 5.92, 95% CI 14.9–17.7) than in the 0.2% IC group (21.23 ± 6.69, 95% CI 19.7–22.8). The 0.03% IC group used significantly less IC ampoules (2, IQR 2-3) compared with 0.2% IC group (5, IQR 4-5.25), p < 0.001). Dysplasia on random biopsies only, was found in 3.3% (n = 5) of the cohort. Univariate analysis for dysplasia on random biopsies showed association with BSG high-risk category group (p < 0.001), concomitant PSC (p = 0.033) and having previous dysplasia (p < 0.001).

Conclusion: There is no significant difference in dysplasia detection between 0.2% and 0.03% IC concentration. 0.03% IC seems to be on average 5 minutes quicker and uses less ampoules of IC. There maybe still a place for random biopsies in patients defined by the BSG as high-risk.

Disclosure: Nothing to disclose

OP232 SIMPLE ENDOSCOPIC TREATMENT OF ADENOMA RECURRENCE AFTER WIDE FIELD ENDOSCOPIC MUCOSAL RESECTION IS EFFECTIVE: A PROSPECTIVE STUDY OF 1558 LESIONS WITH LONG-TERM FOLLOW-UP

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Introduction: Adenoma recurrence after wide field endoscopic mucosal resection (EMR) of laterally spreading colonic lesions ≥ 20mm (LSLs) is a major limitation. Data on the optimal methods and outcomes of endoscopic treatment of recurrence (ETOR) is absent and no evidence based standard exists. We examined the techniques and success of ETOR over time in a large prospective cohort.

Aims and Methods: Over 100 months to January 2017 data on all recurrences after consective EMR procedures for LSLs at the lead centre of the Australian Colonic Endoscopic Resection Study (ACE) was recorded. Recurrence at the EMR scar was 1 discerned using high definition endoscopic imaging as previously described. ETOR comprised coagulation snare 2 resection (ERBE Effect 2, 30W), cold avulsion forceps with adjuvant snare tip soft coagulation [CAST] (ERBE Effect 4, 80W) or a combination of the two. The primary outcomes were complete adenoma clearance using ETOR at first surveillance (desired interval 4-6 months) and absence of recurrence at subsequent surveillance procedures.

Results: 1558 patients with 1558 LSLs were included. 150 LSLs (9.6%) had recurrence at first surveillance colonoscopy. The mean age of patients with recurrence was 68 years and 55% were male. Recurrent LSLs were median 50mm in size (IQR 35-60mm) and located distal to the hepatic flexure in 52.7%. They were commonly of Paris 0-IIa+Is morphology (46.7%) and displayed tubulovillous adenoma at histopathology (75.3%), with high grade dysplasia in 23.3%. 4 (2.7%) were resected en-bloc.

Recurrence at the EMR scar was ≤ 5mm in size (64%), uni-focal (75%) and within the scar (55%) or at the edge (45%). The commonest modality used to resect recurrence was hot snare with adjuvant snare tip soft coagulation (35%). CAST was used in 30% and was also used in combination with hot snare (9%). CAST was more commonly used in the second temporal half (62.5%) than the first half (10.6%, p < 0.001) of the cohort. Prior injection was performed in a minority (16%). In 124/143 (86.7%) cases where tissue was retrieved, there was histologic confirmation of recurrence.

ETOR achieved clearance of recurrent adenoma in 94.7% of cases at first surveillance colonoscopy with 8 (5.3%) referred for surgery primarily due to an

inability to resect recurrence. For LSLs that underwent further surveillance, 89% (1 further surveillance), 86.5% (2 further surveillances) and 89.5% (3 further surveillances) respectively showed no evidence of recurrence.

	First Half of Cohort	Second Half of Cohort	Whole Cohort	P
Number of recurrences	69/785 (8.8)	81/773 (10.5)	150/1558 (9.6)	0.259
Size of recurrence (%) <2mm	9 (13.0)	17 (21.0)	26 (17.3)	0.226
2.1–5mm	34 (49.3)	36 (44.4)	70 (46.7)	
5.1–10mm	22 (31.9)	18 (22.2)	40 (26.7)	
>10mm	4 (5.8)	10 (12.3)	14 (9.3)	
Recurrence treatment	N = 146			
Use of CAST (%)	7 (10.6)	50 (62.5)	57 (39.0)	<0.001
Histologic correlate of recurrence/n = 143 (%)	62 (95.4)	62 (79.5)	124 (86.7)	0.006
Endoscopic cure at SC1 (%) n = 150	64 (92.8)	78 (96.3)	142 (94.7)	0.471
1 negative FU after treatment/109 (%)	55 (91.7)	42 (85.7)	97 (89.0)	0.323
2 negative FU after treatment /37 (%)	26 (92.9)	6 (66.7)	32 (86.5)	0.081

[Table 1: Features of LSLs that demonstrated recurrence at first surveillance colonoscopy and their outcomes, FU – follow up, SC1 – first surveillance]

Conclusion: Adenoma recurrence after EMR of LSLs is commonly diminutive and can be effectively treated using simple endoscopic techniques with rates of long-term remission approaching 90%. Based on this data, more technically complex, morbid and resource intensive endoscopic or surgical techniques are unnecessary to resect LSL recurrence after EMR.

Disclosure: Nothing to disclose

References

1. Desomer 2017 (10.1016/j.gie.2016.06.031).
2. Tate 2017 (10.1055/s-0043-119215).

OP233   BLEEDING DURING ENDOSCOPIC SUBMUCOSAL DISSECTION: A RANDOMISED CONTROLLED TRIAL OF A NOVEL HAEMOSTATIC AGENT

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Introduction: Endoscopic submucosal dissection (ESD) is associated with intra-procedural bleeding which is usually treated with heat applied to the visible bleeding vessel. Prolonged and repeated applications of heat can increase the risk of perforation. Purastat® is a transparent gel with a novel extracellular scaffold matrix which forms a mechanical barrier over the bleeding point. It may be an alternative non diathermic option for intraprocedural bleeding.

Aims and Methods: The aim of this study was to assess the efficacy of Purastat® in reducing the use of intraprocedural heat therapy during ESD.

This was a randomised controlled trial conducted in a tertiary referral centre between May 2016 and April 2018. Patients undergoing ESD in the oesophagus or colorectum were randomised in equal proportions to receive Purastat® as the primary haemostat during intraprocedural bleeding (intervention) or heat therapy (control). Patients in the Purastat® arm were not excluded from heat therapy treatment when required to achieve haemostasis. The primary endpoint was the reduction in the amount of heat therapy required for intraprocedural haemostasis between Purastat® and control groups.

Results: 100 patients were recruited to the study. There were 2 withdrawals (ESD aborted) and 7 had no bleeds. An intention to treat analysis was performed on 91 patients (see table).

	Purastat group (n = 46)	Control group (n = 45)	Significance
Total number of bleeds	232	269	
Total number of bleeds requiring treatment	221 (95.3%)	262 (97.4%)	p = 0.20
Mean number of bleeds per patient	5.04	5.96	p = 0.29
Number and % of bleeds treated with heat	110 (49.8%)	261 (99.6%)	p < 0.001
Number and % of bleeds treated with Purastat alone	111 (50.2%)	N/A	N/A

(continued)

	Purastat group (n = 46)	Control group (n = 45)	Significance
Number and % of bleeds treated with Purastat and heat	121 (54.8%)	N/A	N/A
Mean length of time taken for haemostasis per bleed (seconds)	70.0	77.6	p = 0.67
Total procedure time (minutes)	74.2	80.7	p = 0.56

[Intraprocedural bleeding during ESD]

Both groups were well matched in terms of baseline characteristics (mean lesion size 33.7mm in the Purastat® group and 36.6mm in the control group, age 68.6 vs 71.5 years, adenocarcinoma and high-grade dysplasia 60.9% vs 53.3%). There were 221 bleeds requiring haemostasis in the Purastat® group compared to 262 in the control group with no significant difference in the mean number of bleeds per patient. There was a significant reduction in the proportion of bleeds treated with heat therapy in the patients receiving Purastat® compared to controls (110/221 or 49.8% vs 261/262 or 99.6%, p < 0.001). Purastat® was used in 54.8% of bleeds in the interventional group and haemostasis was achieved with this device as a single agent in 91.7% (111/121) of cases when used.

All bleeds were managed endoscopically with no blood transfusion or hospital admission for management required. There were no complications related to the application of Purastat® in this study and it did not interfere with subsequent use of diathermy for haemostasis if required.

Conclusion: This is the first randomised controlled trial of this haemostatic device and our results show that Purastat® successfully reduced the use of intraprocedural heat therapy for haemostasis in ESD by almost 50%. The device was easy to use and did not prolong the time taken for haemostasis or the total procedure time. This study supports its use as a safe and effective haemostat for bleeding during endoscopic resection.

Disclosure: Nothing to disclose

TUESDAY, OCTOBER 23, 2018   15:45–17:15
IBD on fire – Room F1_____

OP234   DEVELOPMENT OF A SUBCUTANEOUS FORMULATION OF CT-P13 (INFLIXIMAB): MAINTENANCE SUBCUTANEOUS ADMINISTRATION MAY ELICIT LOWER IMMUNOGENICITY COMPARED TO INTRAVENOUS TREATMENT

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Introduction: Intravenous (IV) use of CT-P13, an infliximab biosimilar, has resulted in comparable efficacy, safety and immunogenicity as innovator infliximab in various indications including Crohn's disease (CD)[1] and rheumatoid arthritis (RA)[2]. A subcutaneous (SC) formulation of CT-P13 is developed to provide patients with opportunities for self-injection, thereby enhancing convenience and flexibility in treatment.

Aims and Methods: This work aimed to investigate immunogenicity by post-hoc analysis of 2 randomised controlled trials comparing pharmacokinetics of CT-P13 IV and CT-P13 SC. Patients with active CD (Crohn's Disease Activity Index [CDAI] score of 220–450) and RA (presence of 6 or more swollen and tender joints [of 28 assessed], and serum C-reactive protein [CRP] concentration >0.6 mg/dL) were treated with CT-P13 IV at Weeks 0 and 2. At Week 6, patients were randomised for continuation with IV or SC administration. The IV cohorts received CT-P13 IV (5 mg/kg for CD and 3 mg/kg for RA) every 8 weeks and the SC cohorts were treated with CT-P13 SC (120, 180 and 240 mg for CD and 90, 120, 180 mg for RA) every 2 weeks up to Week 30. Trough serum concentrations (C_{trough}) were assessed at Weeks 6, 14 and 22 for IV and Weeks 6, 8, 10, 14, 22, 24, 26 and 28 for SC. Target exposure level was considered as 5 µg/mL for CD[3,4] and 1 µg/mL for RA[5,6]. Anti-drug antibody (ADA) was assessed before study drug administration at Weeks 0, 6, 14, 22 and 30 by a drug-sensitive, enzyme-linked immunosorbent assay (ELISA).

Results: In total, 92 CD (n = 44) and RA (n = 48) patients were randomised at Week 6 to IV (CD: n = 13, RA: n = 13) or SC (CD: n = 31, RA: n = 35). Among CD patients, immunomodulators (azathioprine, 6-mercaptopurine or methotrexate) were used at Week 6 by 9 (69.2%) and 15 (48.4%) patients in IV and SC cohorts, respectively. All RA patients used methotrexate as concomitant medication throughout the study. Efficacy results in each indication (CDAI-70 responder rate for CD and EULAR [CRP] responder rate for RA) were comparable between the IV and SC cohorts. Systemic safety profiles observed from CT-P13 SC after randomisation were also comparable to those of IV. A sub-therapeutic C_{trough} level below target exposure was detected at least once in 23 (92.0%) and 9 (14.1%) patients in IV and SC cohorts, respectively. ADA were detected at least once in 16 (64.0%) versus 11 (18.1%) of patients in the IV and SC cohorts (p < 0.0001), respectively.

Efficacy	IV cohort	SC cohort	p value [a]
CDAI-70 responder rate at Week 30 in CD patients	8/10 (80.0%)	24/26 (92.3%)	0.3048
EULAR (CRP) responder rate at Week 30 in RA patients	12/13 (92.3%)	32/32 (100%)	0.2889
C_{trough}	IV cohort (N = 25)	SC cohort (N = 64)	p value [a]
C_{trough} < target exposure at least once	23 (92.0%)	9 (14.1%)	< 0.0001
$C_{trough} \geq$ target exposure throughout the study	2 (8.0%)	55 (85.9%)	
Immunogenicity	IV cohort	SC cohort	p value [a]
Anti-drug antibody positive at least once	16/25 [b] (64.0%)	11/61 [b] (18.1%)	< 0.0001
− CD patients	7/12 [b] (58.3%)	3/28 [b] (10.7%)	0.0033
− RA patients	9/13 (69.2%)	8/33 [b] (24.2%)	0.0071

Note: [a]p value was derived from Fisher's exact test. [b]Patients who reported ADA positive at Week 0 or 6 (before randomisation) were excluded.

[Efficacy, C_{trough} and immunogenicity among CD and RA patients]

Conclusion: After initial loading two doses of infliximab IV, patients subsequently receiving biweekly maintenance treatment with injections of CT-P13 SC achieve more stable steady state therapeutic blood levels of infliximab and have lower rate of anti-infliximab antibodies compared with patients receiving continued IV treatment. Further work to corroborate these findings is ongoing through a confirmatory efficacy trial.

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References

1. Kim, et al. LB04 Phase III randomized controlled trial to compare biosimilar infliximab (CT-P13) with innovator infliximab in patients with active Crohn's disease: 1-year maintenance and switching results. *United European Gastroenterol J.* 2017 Dec; 5(8): 1138–1150.
2. Yoo, et al. A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study. *Arthritis Res Ther* 2016; 18: 82.
3. Papamichael, et al. Role for therapeutic drug monitoring during induction therapy with TNF antagonists in IBD: Evolution in the definition and management of primary nonresponse. Inflamm. *Bowel Dis.* 2015; 21: 182–197.
4. Vaughn, et al. Biologic concentration testing in inflammatory bowel disease. *Inflamm. Bowel Dis.* 2015; 21(6): 1435–42.
5. Takeuchi, et al. Impact of trough serum level on radiographic and clinical response to infliximab plus methotrexate in patients with rheumatoid arthritis: results from the RISING study. *Mod Rheumatol.* 2009; 19(5): 478–487.
6. Mori S. A relationship between pharmacokinetics (PK) and the efficacy of infliximab for patients with rheumatoid arthritis: characterization of infliximab-resistant cases and PK-based modified therapy. *Mod Rheumatol.* 2007; 17(2): 83–91.

OP235 NOVEL PROTEIN BIOMARKERS IN SERUM EXTRACELLULAR VESICLES FOR THE DIAGNOSIS OF PRIMARY SCLEROSING CHOLANGITIS (PSC) IN PATIENTS WITH ULCERATIVE COLITIS (UC)

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Introduction: Primary sclerosing cholangitis (PSC) is a chronic cholestatic biliary disease of unknown etiology, which increases the risk of developing cholangiocarcinoma (CCA). In addition, PSC patients frequently (80%) present inflammatory bowel disease, mainly ulcerative colitis (UC) (PSC-UC). Currently, there are not available accurate non-invasive biomarkers for surveillance or early diagnosis of PSC in UC patients, which is warranted to monitor disease progression and to guide therapeutic strategies. We recently showed [1] that serum extracellular vesicles (EVs) contain protein biomarkers for the differential diagnosis of PSC, CCA and hepatocellular carcinoma (HCC).

Aims and Methods: The aim of this study was to investigate the usefulness of protein biomarkers in serum EVs for the differential diagnosis of PSC-UC and UC patients, which could help in the early diagnosis of PSC in UC patients.

Methods: Serum EVs were isolated from PSC-UC (n = 21), UC (n = 64; without PSC) and healthy individuals (n = 62) using ultracentrifugation/filtration methods. EV characterization was performed by transmission electron microscopy (TEM), nanoparticle tracking analysis (NTA) and immunoblot. The proteome of EVs was analyzed by mass spectrometry-based proteomics.

Results: Serum EVs showed round morphology (by TEM), similar size (180 nm diameter by NTA) and markers (CD9, CD63 and CD81 by immunoblotting) consistent with exosomes and small-size microvesicles. The proteomic profiles of serum EVs revealed 45 proteins to be differentially expressed in UC vs. controls, 66 in PSC-UC vs. controls, and 62 in PSC-UC vs. UC patients with high diagnostic performance(sensitivity and specificity). In particular, proteins such as Aminopeptidase N (AMPN), Polymeric immunoglobulin receptor (PIGR), G-protein coupled receptor family C group 5 member C (GPC5C) and Pantetheinase (VNN1) were exclusively upregulated (p < 0.05) in PSC-UC patients compared to UC and healthy controls. In contrast, proteins such as Complement factor I (CFAI), Ficolin-2 (FCN2) and Fibronectin (FINC) were downregulated (p < 0.05) in PSC-UC patients compared to UC and healthy controls.

Conclusion: Proteomic signatures found in serum EVs of PSC-UC and UC patients show potential as non-invasive tools for diagnosis and follow-up.

Disclosure: Nothing to disclose

Reference

1. Arbelaiz A, Azkargorta M, Krawczyk M, Santos-Laso A, Lapitz A, Perugorria MJ, et al. Serum extracellular vesicles contain protein biomarkers for primary sclerosing cholangitis and cholangiocarcinoma. *Hepatology.* 2017; 66(4): 1125–43.

OP236 IMPROVEMENT IN PATIENT-REPORTED OUTCOMES WITH UPADACITINIB IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE: 52-WEEK DATA FROM THE CELEST STUDY

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Introduction: Upadacitinib (UPA), an oral selective JAK1 inhibitor was associated with clinical and endoscopic efficacy over 52 weeks in patients with moderate to severe refractory Crohn's disease.[1] This is the first study assessing the long-term effects of a JAK inhibitor (UPA) on patient-reported outcomes (PROs) in Crohn's disease.
Aims and Methods: The 52-week data from the phase 2, randomised, double-blind CELEST study (M13-740; NCT02365649) were analysed for long-term effects of 4 UPA regimens on PROs. All patients who completed the 16-week induction period were re-randomised 1:1:1 into an Extension Phase to receive UPA 3 mg twice daily (BID), 12 mg BID or 24 mg daily (QD) for 36 weeks. The 24 mg QD arm was later stopped and a 6 mg BID arm was initiated to evaluate an intermediate maintenance dose. Patients completed the Inflammatory Bowel Disease Questionnaire (IBDQ), EuroQol (EQ-5D) and Work Productivity and Activity Impairment (WPAI) PROs at baseline, week 16, and week 52. Outcomes at week 52 for patients who received UPA induction therapy and achieved clinical response at week 16 were assessed. Percentages of patients who achieved IBDQ response (defined as minimum clinically important differences (MCID) ≥16-point increase in IBDQ score from baseline) and who achieved IBDQ remission (IBDQ score ≥170) at week 52 were determined using non-responder imputation (NRI). Changes from baseline to week 52 were calculated using observed cases and analysis of covariance for IBDQ score, EQ-5D visual analogue score (VAS) and WPAI.
Results: Among 220 patients enrolled in CELEST, 180 were re-randomized into the Extension Phase. Of these, 153 patients received UPA induction therapy, of whom 94 achieved clinical response at week 16. Among week-16 clinical responders, a greater proportion of patients in the BID dose groups attained IBDQ response (43.8%-78.6%) and achieved IBDQ remission (43.8%-50.0%) at week 52 than those in the 24mg QD dose group (Table). Dose-related improvements in mean IBDQ scores (range 43-71) and EQ-5D VAS (range 18-36) were observed in the 3mg, 6mg and 12mg BID dose groups at week 52. At week 52, improvements in WPAI including reduction of activity impairment (26-42%) and work impairment (23-38%) were numerically greater for the BID dose groups.

Mean ± SD (n)	UPA 3mg BID n = 32	UPA 6mg BID n = 14	UPA 12mg BID n = 29	UPA 24mg QD n = 19
IBDQ at week 52 (NRI), n (%)				
Remission (IBDQ≥170)	14 (43.8)	7 (50.0)	12 (41.4)	6 (31.6)
Response (Δ≥16)	14 (43.8)	11 (78.6)	20 (69.0)	6 (31.6)
Mean change from baseline to week 52 (observed cases)				
IBDQ	43 ± 44 (n = 22)	47 ± 28 (n = 13)	71 ± 47 (n = 23)	27 ± 53[+] (n = 14)
EQ-5D VAS	18 ± 19 (n = 22)	22 ± 17 (n = 13)	36 ± 26[+] (n = 22)	9 ± 18* (n = 14)
WPAI: % activity impairment	−29 ± 32 (n = 22)	−26 ± 22 (n = 12)	−42 ± 28 (n = 21)	−15 ± 27[+] (n = 14)
WPAI: % overall work impairment[a]	−23 ± 36 (n = 12)	−37 ± 32 (n = 5)	−38 ± 35 (n = 15)	−21 ± 26 (n = 6)

*, [+] statistically significant at 0.05 and 0.1 level for each group vs 3 mg BID for mean change from baseline.
[a] Only employed patients.
[Table. Patient-Reported Outcomes Results for Week-16 Clinical Responders]

Conclusion: Maintenance treatment with UPA among week-16 clinical responders resulted in improved quality of life based on IBDQ, EQ-5D and work productivity over 52 weeks. Numerically greater improvements were reported in the patients who received 12 mg BID.
Disclosure: Financial support for the study and medical writing services (Rebecca Wylie, Fishawack) was provided by AbbVie. AbbVie participated in interpretation of data, review, and approval of the abstract. All authors contributed to development of the abstract and maintained control over final content. L Peyrin-Biroulet: Consulting fees: Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Therakos, Pharmacosmos, Pilège, BMS, UCB-pharma, Hospira, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, Pfizer, HAC-Pharma, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis. Lecture fees: Merck, AbbVie, Janssen, Takeda, Ferring, Norgine, Tillots, Vifor, Therakos, Mitsubishi, HAC-pharma. E Louis: Educational grants: MSD, Abbvie, Takeda. Speaker fees: Abbvie, Ferring, MSD, Chiesi, Mitsubishi Pharma, Hospira, Janssen, Takeda. Advisory board: Abbvie, Ferring, MSD, Takeda, Hospira, Mitsubishi Pharma, Celltrion, Prometheus. EV Loftus Jr: Consulting: AbbVie, Takeda, Janssen, UCB, Amgen, Pfizer, Eli Lilly, Celgene, Celtrion Healthcare. Research support: AbbVie, Takeda, Janssen, UCB, Amgen, Pfizer, Genentech, Receptos, Gilead, Celgene, Seres, MedImmune, Robarts Clinical Trials. S Ghosh: Steering committee: Pfizer, Janssen, AbbVie, BMS, Celgene, Boehringer-Ingelheim. Speaker honorarium: AbbVie, Janssen, Takeda, Shield, Ferring, Falk Pharma. WJ Lee, A Lacerda, F Cataldi: Employees, stock: AbbVie.

Reference

1. Sandborn WJ, et al. *Gastroenterology*. 2017; 152(5) Suppl 1: S1308-S1309.

OP237 DEEP MURAL HISTOLOGICAL ALTERATIONS AT ILEAL RESECTION MARGINS ARE ASSOCIATED WITH A HIGHER RISK OF POST-OPERATIVE ENDOSCOPIC RECURRENCE IN CROHN'S DISEASE

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Introduction: Recurrence after ileocaecal resection for Crohn's Disease (CD) is frequent. Severity of post-operative endoscopic recurrence, evaluated by the Rutgeerts score, is a predictive factor of long-term outcome. Histological alterations of the ileal resection margins could be a predictor of this post-operative endoscopic recurrence as suggested by previous studies focused on myenteric or submucosal plexitis.
Aims and Methods: We aimed to study whether microscopic lesions at ileal resection margins could predict endoscopic recurrence after surgery.
We conducted a prospective multicentric study including CD patients who undergo an ileocaecal resection. Clinical and biological data are collected and analyzed in a network of gastroenterology research expert centers to define predictors of recurrence.
Patients operated from April 2010 to December 2016 were included. An ileocolonoscopy was performed between 6 and 12 months after surgery. Endoscopic recurrence was defined by a Rutgeerts score ≥ i2. Whole paraffin-embedded ileal resection margins were blindly analyzed by 2 expert pathologists to grade inflammatory lesions of mucosa, submucosa, muscularis (plexitis) and subserosa. Correlation with post-operative endoscopic recurrence was evaluated by both univariate (Chi-2) and multivariate analyses (Logistic regression) for each item of the analysis grid. Transcriptome analyses on ileal resection margins were performed using microarrays after extraction of total RNA from whole intestinal mucosa biopsies
Results: Of the 228 patients included, 211 (92.5%) ileal resection margins were available for histological analysis. 91 (43.1%) patients were male, 70 (33.2%) active smokers and 52 (24.6%) received an anti TNF treatment after surgery. 101 patients (49.3%) presented endoscopic recurrence.
At histological examination, 98.1% (207) of patients had inflammation on ileal margin, (limited to an increased lymphocyte count in the lamina propria in 21.7%) and only 4 patients (1.9%) had a strictly normal ileal wall. Histological items significantly associated with recurrence were active Epithelial alterations (Erosion, ulceration or cryptitis) (45.7% vs 61.2%, p = 0.05), Submucosa Fibrosis (44.6% vs 59.2%, p = 0.04) and Subserosa inflammation (44.6% vs 60.3%, p = 0.04). Myenteric and Submucosa plexitis were not associated with recurrence.
We defined a score based on the presence of the three histological abnormalities associated with recurrence (0 to 3). Post-operative recurrence was observed in 44%, 44%, 50% and 75% in patients with a score of 0, 1, 2 or 3 respectively. Severe endoscopic recurrence (i3 or i4) was observed in 10%, 26%, 31% and 36% respectively. Patients with a histologic score of 3 had a clear transcriptomic signature, corresponding to a strong inflammatory state (DUOX2, CXCL6, CXCL8, Calprotectin genes).
Conclusion: Deep mural histological alterations defined by the presence of Epithelium alterations, Submucosa fibrosis and Subserosa inflammation were associated with a higher risk of endoscopic recurrence. A strong inflammatory transcriptomic signature was associated with these severe lesions.
Disclosure: Nothing to disclose

OP238 TIME TO THERAPEUTIC INTERVENTION FOLLOWING ILEOCECAL RESECTION COMPARED TO INFLIXIMAB FOR ILEOCECAL CROHN'S DISEASE: LONG-TERM FOLLOW UP OF THE LIR!C TRIAL

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Introduction: Crohn's disease patients who fail corticosteroids and immunomodulator therapy are generally upscaled to biological treatment. The LIR!C trial showed that laparoscopic ileocecal resection (ICR) is a valid alternative to infliximab (IFX) therapy for immunomodulator refractory ileocecal Crohn's disease (1). Our aims were to compare the long-term efficacy of both interventions and identify predictive factors associated with time to therapeutic intervention.

Aims and Methods: Long-term follow-up data was retrospectively collected for patients who participated in the LIR!C trial; a multicenter, randomized controlled trial that compared laparoscopic ICR with IFX induction and maintenance therapy for adult patients with non-stricturing and immunomodulator refractory ileocecal Crohn's disease (≤40cm). Primary outcome was the time to therapeutic intervention defined by the initiation or modification of medical therapy or surgery for disease flare or intolerance to treatment. Time to intervention was analyzed by Kaplan-Meier survival analysis. Potential predictive factors were defined a priori, identified through Cox proportional hazards regression analysis and expressed as hazard ratio (HR) [95% confidence interval (CI)]. The following baseline explanatory variables were included: gender, age, disease duration, smoking, continued immunomodulator use, family history, extra intestinal manifestations, corticosteroid use, perianal disease and C-reactive protein.

Results: Data were obtained for 128 of the 143 randomized patients (89.5%). Median time of follow up was 25.5 [IQR 10.3–57.8] months. In the ICR group, 24 (36.4%) patients received prophylactic immunomodulator treatment after randomization as opposed to 37 (59.7%) in the IFX group. An intervention was observed in 38 (57.6%) patients in the ICR and 38 (61.3%) in the IFX group. No difference was observed in the distribution of interventions between groups (log-rank p = 0.560). The incidence rate of an intervention was 18% and 20% per patient-year in the ICR and IFX group respectively. The median time without an intervention was 33 [IQR 3.1–62.9] and 34 [IQR 0.0–68.9] months respectively. Cumulative incidences are presented in table 1. Eventually, 18 (27.3%) patients allocated to the ICR arm needed anti-TNF. Conversely, 28 (45.2%) patients in the IFX group underwent an ICR. In both the ICR group (HR 0.306 [95%CI 0.144–0.648] p = 0.002) and the IFX group (HR 0.457 [95%CI 0.224–0.932] p = 0.031), prophylactic use of an immunomodulator was associated with lower risk of a therapeutic intervention in multivariable analysis.

Conclusion: No difference in the need for additional therapeutic intervention was observed for ICR compared to IFX in adult patients with immunomodulator refractory ileocecal Crohn's disease. These long-term data corroborate the results of the LIR!C trial. Prophylactic use of an immunomodulator in conjunction with either treatment significantly decreased the need for additional therapeutic intervention.

Treatment group	6M	12M	24M	36M	48M	60M	72M	84M
IFX total (%)	16.1	37.1	43.5	48.4	50.0	59.7	59.7	61.3
IFX: disease activity (%)	*8.0*	*19.4*	*25.8*	*30.7*	*30.7*	*38.7*	*38.7*	*38.7*
IFX: intolerance (%)	*8.1*	*17.7*	*17.7*	*17.7*	*19.3*	*21.0*	*21.0*	*22.6*
ICR (%)	10.6	24.2	40.9	48.5	51.5	53.0	56.1	57.6

[Table 1. Cumulative incidence of therapeutic interventions at different time points]
Disclosure: Nothing to disclose

Reference

1. Ponsioen CY et al. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. *Lancet Gastroenterol Hepatol*. 2017.

OP239   PRESENCE OF MUCOSA-ASSOCIATED ESCHERICHIA COLI, ESPECIALLY ADHERENT-INVASIVE E. COLI, ON THE SURGICAL SPECIMEN IN ILEAL CROHN'S DISEASE AS A GOOD PREDICTOR OF ENDOSCOPIC POSTOPERATIVE RECURRENCE: A STUDY FROM THE REMIND GROUP

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Introduction: The majority of patients with ileal Crohn's disease (CD) undergo at least one intestinal resection during the course of their disease. Postoperative recurrence is a major issue, as up to 70% of them develop new lesions in their neoterminal ileum within 1 year of surgery. We aim to determine whether the presence of adherent and invasive *Escherichia coli* (AIEC) bacteria at the time of surgery was associated with endoscopic post-operative recurrence at 6 months.

Aims and Methods: The REMIND group (9 centers) has established a homogeneous, prospective, multicenter cohort (POP-REMIND) of operated CD patients. Tissue samples were taken from the surgical specimen (M0) and at endoscopy (M6), and stored centrally in a bio-bank. The inclusion criteria were: age ≥18 years, ileal or ileocaecal CD requiring intestinal resection. Postoperative treatment was prescribed according to a standardized algorithm. Clinical outcome, therapeutic, biological and endoscopic data (Rutgeerts score) were collected 6 months after surgery. Clinical factors (demographic variables, phenotypic and postoperative treatments) associated with endoscopic recurrence were investigated by univariate analysis and logistic (multivariate) regression. The search for mucosa-associated *E. coli* bacteria was carried out by culturing on Drigalski medium, and adherent-invasive characteristics of *E. coli* was performed using Int-407 cells, and survival within THP-1 macrophages.

Results: The presence of mucosa-associated *E. coli* strains was determined on the surgical specimen in 241 patients; 110 harbored mucosa-associated *E. coli* (45.6%). The presence of mucosa-associated *E. coli* on the surgical specimen was not correlated with age, disease duration, smoking, previous surgical resection and with preoperative anti-TNF exposure. Of the 241 patients included, 172 had a postoperative colonoscopy at M6. Among these, 76 (44.2%) harbored mucosa-associated *E. coli*. The presence of mucosa-associated *E. coli* on the surgical specimen was associated to increase risk of endoscopic post-operative recurrence (defined as Rutgeerts scores i2b, i3 and i4): 32 among 76 patients mucosa-associated *E. coli* + (42.1%) versus 32/96 (33.4%) for mucosa-associated *E. coli*-. In contrast, mucosa-associated *Enterococci* have been isolated in 119 patients (49.4%) but was not correlated with endoscopic recurrence at month 6. Among the 76 patients colonized by mucosa-associated *E. coli*, 27 of them were carriers of adherent-invasive *E. coli* at the time of surgery. The presence of AIEC on the surgical specimen was predictive of severe endoscopic post-operative recurrence (defined as Rutgeerts scores i2b, i3 and i4): 14 among 27 patients AIEC + (52%) versus 50/145 (34%) for AIEC -; p = 0.01. After adjusting for age, sex, pre- or post-operative exposure to TNF antagonists and antibiotics, the presence of AIEC on the surgical specimen was associated with endoscopic recurrence i3-i4 (OR = 3.42 CI95% [1.31–8.84], p = 0.011).

Conclusion: In this prospective POP-REMIND cohort of 172 patients, abnormal colonization of ileal mucosa by *E. coli* increased the risk of recurrence, and this is not the case for *Enterococci* bacteria. Of interest, the presence of AIEC on the surgical specimen was an independent risk factor for severe endoscopic post-operative recurrence of Crohn's disease. Thus, the detection of AIEC at the time of surgery appears essential to adapt the postoperative treatment.
Disclosure: Nothing to disclose

OP240   MOLECULAR PROFILING OF ULCERATIVE COLITIS PATIENTS FROM THE TURANDOT TRIAL UNCOVERS NOVEL PHARMACODYNAMIC AND CLINICAL EFFICACY BIOMARKERS AND A MECHANISTIC RATIONALE FOR A NON-MONOTONIC DOSE RESPONSE

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Introduction: PF-00547659 (SHP647)[1] is a human anti-mucosal addressin cell adhesion molecule-1 (MAdCAM-1) IgG2 monoclonal antibody that decreases intestinal inflammation through blockade of MAdCAM-dependent lymphocyte recruitment. A phase 2 study (NCT 01620255), in patients with moderate to severe, active ulcerative colitis in the TURANDOT study showed the therapeutic efficacy of PF-00547659 in a non-monotonic dose responsive manner, with the intermediate 22.5 mg dose cohort demonstrating greater efficacy than the highest 225 mg dose cohort[1].

Aims and Methods: We aimed to define novel pharmacodynamic and efficacy biomarkers and to elucidate potential mechanisms underlying the observed non-monotonic dose response.

Transcriptome (RNA seq), protein (Olink), and immunohistochemistry (IHC) data were generated from the peripheral blood and intestinal biopsies of 310 patients from this phase 2 trial.

Results: Compared to the placebo group, C-C Motif Chemokine Receptor 9 (CCR9) gene expression demonstrated a 1.2, 2.0, 3.0 and 2.5-fold increase in the 7.5 mg, 22.5mg, 75mg, and 225mg cohorts, respectively (p = 0.21, 3e-8, 7.5e-18 and 1.8e-12) in peripheral blood; while in inflamed intestinal tissue, it demonstrated a 0.3, 0.4, 0.5 and 0.5-fold decrease in the 7.5 mg, 22.5mg, 75mg and 225mg cohorts, respectively (p = 0.046, 0.0070, 0.0015, 0.0028). Oncostatin M (OSM) gene or protein expression in peripheral blood or intestinal tissue demonstrated a 0.2 to 0.9-fold decrease among patients who showed efficacy (response, remission, or mucosal healing, p = 0.01 to 2.6e-8). Compared to the placebo group, intestinal T regulatory cells measured by IHC demonstrated a 5.4-fold increase in the intermediate 22.5 mg dose cohort (p = 0.02), but not in the highest 225 mg dose cohort (p = 0.58).

Conclusion: These results reveal CCR9 and OSM as pharmacodynamic and efficacy biomarkers, respectively. Furthermore, the increased number of regulatory cells in the intermediate 22.5 mg cohort could suggest a greater sensitivity for T effector versus T regulatory cells to PF-00547659-mediated blockade, implicating a potential mechanistic rationale for the observed non-monotonic efficacy response. Taken together, these findings may have significant implications for our understanding of UC disease pathophysiology and the development of future therapeutic approaches.

Disclosure: Nothing to disclose

Reference

1. Vermeire S, Sandborn WJ, Danese S, Hebuterne X, Salzberg BA, Klopocka K, Tarabar D, Vanasek T, Gregus M, Hellstern PA, Kim JS, Sparrow MP, Gorelick K J, Hinz, M, Ahmad A, Pradhan V, Hassan-Zahraee M, Clare R, Cataldi F, and Reinisch W (2017). Anti-MAdCAM antibody (PF-00547659) for ulcerative colitis: the TURANDOT study. *The Lancet* 2017, 390 (10090): 135–144.

OP241 PRO-INFLAMMATORY/PRO-FIBROTIC MACROPHAGES MAY ACT AS A SOURCE OF WNT2B IN INTESTINAL TISSUE FROM B3 CROHN'S DISEASE PATIENTS

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Introduction: Macrophages contribute to fibrosis through the release of different mediators and the pattern of secretion may vary according to their phenotype. Strong evidence identifies the Wnt signalling pathway as an emerging modulator of fibrosis. We have recently reported differences in the Wnt signalling pathway in surgical resections from Crohn's disease patients presenting a stricturing (B2) or a penetrating (B3) behavior (1).

Aims and Methods: The aim of the present study is to analyze the pattern of expression of macrophages and the expression of Wnt ligands in surgical resections from Crohn's disease (CD, n = 43) patients with different disease behavior. CD patients were categorized according to Montreal classification (B2 or B3) and unaffected mucosa of patients with colorectal cancer was used as control. mRNA was isolated and the expression of macrophage markers, pro-inflammatory cytokines and Wnt2b was analyzed by RT-PCR (Gene/b-actin) mRNA expression; fold induction vs control group). The number of macrophages positive for the different markers (CD206, CD86, CD16 and WNT2b) was analysed by flow cytometry. Human peripheral blood mononuclear cells (PBMCS) were isolated from healthy donors and treated with secretomes from control, B2 or B3 surgical resections for 5 days. mRNA from PBMCS was isolated and the expression of macrophage markers and wnt2b was determined. Results are expressed by mean ± SEM (n ≥ 5). Statistical analysis was performed by ANOVA + Newman-Keuls test. Correlations between data were analysed using Pearson's correlation coefficient (p < 0.05).

Results: The expression of pro-inflammatory cytokines, IL-1β and IL-6 and WNT2b was significantly higher in intestinal samples from B3 CD patients (8.9 ± 2.0, 8.7 ± 1.8 and 2.3 ± 0.4, respectively) than in controls (2.3 ± 0.4, 2.4 ± 0.6 and 1.1 ± 0.1, respectively) or B2 CD patients (3.6 ± 1.0, 5.0 ± 0.8 and 0.7 ± 0.1, respectively). The number of CD16 or CD86 positive macrophages was significantly higher in intestinal tissue from B3 CD patients (69.7 ± 24.4% and 88.8 ± 18.4%, respectively) than in that from B2 CD patients (36.12 ± 5.8% and 30.58 ± 10.9%, respectively). A high percentage of CD16 positive macrophages were also positive for Wnt2b in intestinal tissue from B3 CD patients (24.7 ± 8.8%). A significant and positive correlation between WNT2b and CD16 (r = 0.8, p = 0.001) or CD86 (r = 0.7, p = 0.001) as well as CD16+ cells and CD86+ cells (r = 0.7, p = 0.002) was detected in intestinal tissue from B3 CD patients. The mRNA expression of CD16, CD86 and WNT2b was significantly higher in PBMCS treated with B3-secretomes (138.6 ± 20.9, 35 ± 8.0 and 12 ± 3.2, respectively) than in those treated with B2- (3.3 ± 1.8, 3.3 ± 1.8 and 3.3 ± 1.8, respectively) or control (1.2 ± 0.5, 1.2 ± 0.5 and 1.2 ± 0.5, respectively) secretomes.

Conclusion: A pro-inflammatory/profibrotic macrophage phenotype may act as a source of Wnt2b in intestinal tissue from Crohn's disease patients with a penetrating (B3) behavior.

Disclosure: Nothing to disclose

Reference

1. P008-Differences in macrophage infiltration and Wnt ligands expression between stricturing and penetrating behavior in Crohńs disease. P. Salvador, D.C. Macías-Ceja, J. Cosín-Roger, R. Alos J. Hinojosa Del Val; F. Navarro-Vicente, J. Manyé, S. Calatayud, M.D. Barrachina, D. Ortiz-Masiá. ECCO Congres 2018.

OP242 A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF A SELECTIVE, ORAL SPHINGOSINE 1-PHOSPHATE RECEPTOR MODULATOR, ETRASIMOD (APD334), IN MODERATE TO SEVERE ULCERATIVE COLITIS: RESULTS FROM THE OASIS STUDY

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Introduction: The efficacy and safety of etrasimod, a selective, oral sphingosine 1-phosphate receptor 1, 4, and 5 modulator, was evaluated in patients (pts) with moderate to severe ulcerative colitis (UC).

Aims and Methods: This randomized, double-blind, parallel-group, 12-week (wk) phase 2 induction study evaluated etrasimod in pts with moderate to severe UC, defined as a 3-component Mayo Clinic Score (MCS) of 4-9 with endoscopic subscore ≥ 2 and rectal bleeding (RB) subscore ≥ 1. The 3-component MCS (range 0-9) includes RB, stool frequency, and endoscopy. Pts received once-daily etrasimod 1 mg (n = 52) or 2 mg (n = 50), with no dose titration, or placebo (PBO; n = 54). The primary endpoint (EP) was change from baseline (BL) in 3-component MCS at wk 12. Secondary EPs included the proportion of pts with endoscopic remission (≤ 1 point). Exploratory EPs included the proportion of pts achieving clinical remission and clinical response at wk 12 and change in lymphocyte count (LC). Changes in MCS were assessed by analysis of covariance with treatment as a factor and current oral corticosteroid (CS) use, prior anti-tumour necrosis factor (TNF)α use, and BL measures as covariates; LC was assessed by mixed-effects model and parameters with proportions of pts by the Mantel-Haenszel method with adjustment for current oral CS and prior anti-TNFα use.

Results: Of 156 pts randomized, 90% completed the study. BL characteristics, including age, sex, disease duration, current CS use, and prior biologic use, were balanced among groups. At wk 12, dose-dependent improvements occurred with etrasimod in all efficacy measures vs PBO (Table). Etrasimod 2 mg improved change from BL in 3-component MCS vs PBO (difference, 0.99 points; 90% confidence interval, 0.30–1.68; p = 0.009). More pts receiving etrasimod 2 mg achieved endoscopic improvement (41.8% vs 17.8% for PBO; p = 0.003). At wk 12, there was a significant decrease in circulating LCs from BL with etrasimod 1 and 2 mg relative to PBO (37.2% and 57.3%, respectively; p < 0.001 for both). Adverse events (AEs) were mostly mild to moderate and similar among groups. More PBO-treated pts (11.1%) had a serious AE (SAE) vs etrasimod-treated pts (2 mg, 0%; 1 mg, 5.8%), reflecting disease worsening. No SAEs related to bradycardia or atrioventricular block were noted.

Conclusion: In pts with moderate to severe UC, etrasimod was more effective than PBO in achieving dose-dependent improvements in clinical response, clinical remission, and endoscopic appearance. Etrasimod was safe and well tolerated in this short-term study.

Efficacy Measure	PBO (n = 54)	Etrasimod 1 mg (n = 52)	Etrasimod 2 mg (n = 50)
Primary Endpoint: Change from baseline in 3 component MCS (RB + SF + endoscopy), LS mean difference vs PBO[a]	−1.50	−1.94 -0.43 p = 0.146	−2.49 -0.99 p = 0.009
Secondary Endpoint: Patients with endoscopic improvement (MCS 0 or 1), % Difference vs PBO[b]	17.8	22.5 4.1 p = 0.306	41.8 24.4 p = 0.003
Exploratory Endpoints: Patients with clinical response, % Difference vs PBO[b]	32.5	43.7 11.4 p = 0.131	50.6 18.9 p = 0.028
Patients with clinical remission, % Difference vs PBO[b]	8.1	16.0 7.1 p = 0.136	33.0 25.8 p < 0.001

LS, least-squares; MCS, Mayo Clinic Score; PBO, placebo; RB, rectal bleeding; SF, stool frequency.
[a]Analysis model estimated difference from PBO for some measures using analysis of covariance with treatment as a factor and current oral corticosteroid use, prior anti-TNFα use, and baseline value as covariates.
[b]Difference of proportion using Mantel-Haenszel model and adjusted for current oral corticosteroid and prior anti-TNFα use.
p values are 1-sided vs PBO.
[Efficacy Results at Week 12]

TUESDAY, OCTOBER 23, 2018   15:45–17:15

Evaluation of colorectal cancer screening programmes – Room K_____

OP243 THE EFFECT OF THE TWO-WEEK WAIT REFERRAL SYSTEM ON THE DETECTION OF AND MORTALITY FROM COLORECTAL CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS OF OVER 90000 PATIENTS

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Introduction: In 2000 the UK two-week-wait (TWW) suspected cancer pathway was launched, with comparable fast-track pathways in place across Europe. The service utilises substantial time at primary and secondary care level and with significant financial cost to NHS trusts, yet national TWW performance data is lacking. This systematic review is the first to comprehensively evaluate the latest evidence on colorectal cancer (CRC) conversion rate, polyp detection rate and stage at diagnosis through the TWW pathway for suspected lower gastrointestinal malignancy.

Aims and Methods: This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses [PRISMA] 2009 statement. Cochrane, EMBASE, Medline via Pubmed, NHS Evidence, Trip and the British Library Catalogue were searched, plus references were hand-searched. Disagreements were resolved via consensus. Cancer conversion rates were expressed as proportions along with their corresponding 95% confidence intervals. Random effects models were used to estimate pooled cancer conversion rates, polyp detection rates and cancer stage at diagnosis using R package metaphor. Proportions of non-CRC malignancy and other diagnoses were also calculated. Forest plots were produced for each outcome measure.

Results: 95 full papers and 28 conference abstracts were reviewed, 49 met eligibility criteria. 77.5% of full papers reported cancer conversion rate, corresponding weighted mean was calculated with a cancer conversion rate of 7.7% (95% CI 6.9–8.5). Cancer stage at diagnosis was reported in 28.5% of papers. Pooled data showed the proportion presenting at Dukes A = 11.2% (95% CI 7.4–15.6), B = 36.7% (95% CI 30.8–42.8), C = 35.7% (95% CI: 30.8–40.8) and D = 11.1% (95% CI 7.3–15.5). 30.6% of papers reported polyp detection rate with an overall value of 10.8% (95% CI 8.5–16.3), adenoma detection rate was 8.5% (95% CI 6.6–10.6). Diagnosis of non-CRC cancer and IBD were very low at 3.2% (95% CI: 0.9–6.6) and 3.9 (95% CI: 2.9–4.9) respectively. 54.6% (95% CI: 46.2–62.8) of patients had a diagnosis of normal or haemorrhoids.

Conclusion: The pooled cancer conversion rate via TWW is similar to the cancer detection rate in the asymptomatic Bowel Cancer Screening Population (latest figure 8%) and is not having its intended impact on cancer diagnosis. When compared with the recent national staging data no statistically significant difference in stage distribution was seen in the TWW cohort compared with CRC diagnosed via any non-TWW route combined (excluding emergencies). Nearly half of patients presented with stage 3 or 4 disease with corresponding survival of 47.7% and 6.6% respectively[1]. The results provoke a reconsideration of the benefits of the TWW pathway for CRC. Re-evaluation of the referral criteria needs consideration with focus on symptoms with higher positive predictive value (PPV) in cancer.

Disclosure: Nothing to disclose

Reference

1. Colorectal cancer survival by stage. National Cancer Intelligence Network. 2009. Available at: www.ncin.org.uk/databriefings (accessed 5th Jan 2018).

OP244 RESULTS OF THE DUTCH FIT-BASED COLORECTAL CANCER SCREENING PROGRAM IN 2016: IMPACT OF INCREASING THE CUT-OFF LEVEL ON PARTICIPATION AND YIELD IN THE SECOND ROUND

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Introduction: In the Netherlands, a colorectal cancer (CRC) screening program was initiated in January 2014, using biennial fecal immunological testing (FIT). 6 months later, a higher than expected participation and FIT positivity rate combined with a low positive predictive value (PPV) necessitated an increase in the FIT cut-off level to increase the PPV and to alleviate the colonoscopy capacity. This study presents the impact of the increased FIT cut-off level on the results of the second round of the CRC screening program.

Aims and Methods: We present outcomes of the Dutch national CRC screening program in 2016. The target population for this year consisted of 3 groups of individuals: first-time invitees; second-time invitees that had been invited to FIT at a cut-off level of 15 μg Hb/g feces in 2014; and second-time invitees invited to FIT at a cut-off level of 47 μg Hb/g feces in 2014. All participants in 2016 underwent screening with a 47 μg Hb/g feces FIT cut-off level. The FIT positivity rate and PPV for detecting CRC and/or Advanced Adenoma (AA) among FIT positive participants was compared between the three groups of individuals. Data were collected from Screen-IT, the national screening database covering the whole Dutch CRC screening program from selection of individuals for invitation to the colonoscopy and pathology reports.

Results: A total of 1,497,591 individuals were invited for FIT in 2016: 1,038,998 first-time invitees, 57,936 second-time invitees with a previous 15 μg Hb/g feces cut-off level and 400,657 second-time invitees with a previous 47 μg Hb/g feces cut-off level (Table). Participation was high in both first- and second-time invitees: 71.8% and 76.2% respectively. As expected, FIT positivity was highest among first-time invitees (6.0%, 95%CI: 5.9–6.1). In second-time invitees, positivity rate was lower in those previously invited for a FIT with cut-off of 15 μg Hb/g feces (3.3%, 95%CI: 3.1–3.5), compared to those previously invited for a FIT with cut-off of 47 μg Hb/g feces (4.3%, 95%CI: 4.3–4.4). Results for detection rates and PPV showed a similar pattern (Table).

Conclusion: Participation in the Dutch CRC screening program remains among the highest in the world. The increase in FIT cut-off level in 2014 has not jeopardized participation. As expected, an increased FIT cut-off level in the first screening round resulted in relatively more positive FIT results and higher PPV

AbstractNo: OP244
Table 1: Age, Participation rate, Positivity rate, Detection rate and Positive Predictive Value per screened subgroup in 2016.

		First-time invitees (n = 1038998)	Second-time invitees, previously invited for FIT at 15 μg Hb/g feces (n = 57936)	Second-time invitees, previously invited for FIT at 47 μg Hb/g feces (n = 400657)
Age	Median years (IQR)	63 (61-71)	67 (65-69)	
Participation rate	% (95%CI)	71.8 (71.7-71.9)	76.2 (76.0-76.3)	
Positivity rate	% (95%CI)	6.0 (5.9-6.1)	3.3 (3.1-3.5)	4.3 (4.3-4.4)
Detection rate	Per 1,000	26.4 (26.0-26.8)	10.4 (9.4-11.4)	15.0 (14.5-15.4)
Positive Predictive Value	% (95%CI)	53.7 (53.1-54.2)	36.8 (34.0-40.0)	41.0 (40.0-41.9)

in the subsequent screening round. This suggests that most of the missed findings due to use of an increased FIT cut-off level are detected in the subsequent round, emphasizing the importance of repeated screening, especially within screening settings with high cut-off levels.

Disclosure: Nothing to disclose

OP245 COST-UTILITY ANALYSIS OF COLONOSCOPY OR FAECAL IMMUNOCHEMICAL TEST FOR COLORECTAL CANCER SCREENING

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Introduction: Organized programs for colorectal cancer (CRC) screening have been associated with a substantial degree of CRC prevention in terms of its incidence and mortality. However, these programs demand a high burden of medical and economic resources. The 2 preferred screening methods are faecal immunochemical test (FIT) and primary colonoscopy. Our aim was to perform a cost-utility analysis between these 2 tests in an European setting.
Aims and Methods: A Markov cost-utility analysis was performed for the Portuguese population from a societal perspective comparing FIT or colonoscopy screening versus non-screening. Clinical data and utilities were collected from a systematic review and costs from published national data. Population was screened from 50 to 74 years-old by biennial FIT or colonoscopy every 10 years and efficacy was evaluated in quality-adjusted life years (QALY). For the base case scenario, FIT cost was €3, with 50% acceptance, sensitivity 70% and specificity 95%; colonoscopy cost was €397 with 38% acceptance. An annual discount of 3% was used and the threshold was set at €39,760/QALY. The primary outcome was the incremental cost-effectiveness ratio (ICER); deterministic and probabilistic sensitivity analysis was done and colonoscopy burden was addressed according to the screening option.
Results: Biennial FIT screening and primary colonoscopy every 10 years screening resulted in a degree of CRC incidence and mortality prevention of 30% and 30%, and 38% and 38%, respectively. This translated in an incremental utility of 0.00157 QALY and 0.00185 QALY, as compared with no screening. The overall cost was €17.9 for FIT and €199.4 for colonoscopy, resulting in an additional cost of €10 and €191 vs. no screening, respectively. At cost-effectiveness analysis, FIT was the most cost-effective option providing an ICER of €6,383/QALY while colonoscopy every 10 years provided an ICER of €103,633/QALY. FIT screening was the most cost-effective option in 96% of simulations in sensitivity analysis. Colonoscopies capacity would have to increase 1.3% for a FIT programme (26,000 colonoscopies/year/million screened) or 31% for a colonoscopy programme (48,000 colonoscopies/year/million screened).
Conclusion: Biennial FIT is a more suitable choice compared to primary colonoscopy screening resulting in a more rational exploitation of the limited endoscopic capacity. This further supports the progressive implementation of FIT-based programs in Europe.

Disclosure: Nothing to disclose

OP246 PREDICTION OF ADVANCED COLONIC NEOPLASM IN SYMPTOMATIC PATIENTS: A SCORING SYSTEM BASED ON THE FAECAL IMMUNOLOGICAL TEST TO PRIORITIZE COLONOSCOPY IN THE FAST-TRACK REFERRAL SYSTEM (COLONOFIT STUDY)

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Introduction: The fast-track colonoscopy program to detect patients with colorectal cancer (CRC) based on high-risk symptoms is associated with low sensitivity and specificity.
Aims and Methods: Derive a predictive score of advanced colonic neoplasia (ACN) in symptomatic patients with indication of a fast-track colonoscopy.

All the patients referred for colonoscopy with fast-track indication were evaluated in the three participating centres. We performed in the included patients: faecal immunological occult haemoglobin test (FIT) (3 samples) considering positive >4 µg Hb/g faeces; and a face-to-face survey to register clinical variables of interest. The main outcome was ACN defined as CRC or advanced adenoma (>1 cm or high-grade dysplasia or villous component). The overall maximun faecal haemoglobin (MAXFIT) value, which maximizes the probability of ACN through the assessment of the diagnostic odds ratio (OR) was calculated, and was 11 µg Hb/g faeces. We assumed 3 categories for the MAXFIT variable: ≤4, >4 to 11, >11 µg Hb/g faeces. A minimum sample size of 600 individuals was calculated for each phase of the study: Phase 1 (derivation cohort) and Phase 2 (validation cohort). A Bayesian logistic regression analysis using R software was performed to derive a predictive score and stratify the risk of ACN.
Results: 1495 patients were included (Phase 1 + 2). Differences were found between the derivation and the validation cohort in the variables related to the FIT (in Phase 2 there were 3 CRCs with negative FIT), but not in the rest of the study variables. Overall, there were 6/116 (5%) CRC patients with only 1 out of 3 faecal samples positive. Age (OR, 21), MAXFIT (OR, 2.3) and number of positive samples (OR, 28) presented the highest ORs. The predictive clinical variables adjusted for age and FIT in Phase 1 were previous colonoscopy (last 5 years) and smoking (no, ex/active). No clinical symptom was a significant predictor after adjusting for age and FIT. With these variables (age, FIT, previous colonoscopy, smoking) a predictive score of ACN was derived (-4 to 24 points). Applying the score to Phase 2: patients with a Score >20 had an ACN probability of 66%, while in those with a Score ≤10, the probability was 10% (CRC, 1%). Prioritizing patients with Score >10, 49.4% of patients were referred for fast-track colonoscopy, diagnosing 98.3% of CRCs and 77% of advanced adenomas.
Conclusion: A scoring system was derived and validated to prioritize fast-track colonoscopies according to risk, which was shown to be efficient, simple and robust.
Disclosure: Sponsored by a Grant 'Fundació la Marató de TV3' (785/U/2013). This sponsor had no role in the study design, nor in the acquisition, analysis, or interpretation of the data, or the writing of the report.

OP247 POST-COLONOSCOPY COLORECTAL CANCER IN THE ENGLISH NATIONAL HEALTH SERVICE BOWEL CANCER SCREENING PROGRAMME

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Introduction: Post-Colonoscopy Colorectal Cancer (PCCRC) rate is a key quality indicator of colonoscopy. The Word Endoscopy Organization has reached consensus agreement to use one method for calculating 3-year PCCRC rates (termed PCCRC-3y) to enable international benchmarking of rates (1). This methodology, used previously by Morris et al (2), showed a PCCRC-3y rate of 8.6% across the English National Health Service (NHS) from 2001-2007(2) with a rate of 7.3% in 2007. This study aimed to determine the rate of PCCRC-3y in the English NHS Bowel Cancer Screening Programme (BCSP).
Aims and Methods: Data from each colonoscopy in the BCSP is entered into a national database, the Bowel Cancer Screening System. All colorectal adenocarcinomas, within and outside the BCSP, are validated and registered by the National Cancer Registration and Analysis Service. This retrospective observational study interrogated these databases to identify those BCSP colonoscopies detecting colorectal cancers within 6 months (true positive colonoscopies) and those BCSP colonoscopies in patients who subsequently developed a colorectal cancer 6 months – 3 years after the colonoscopy (false negatives) between 2006 and 2013.
Results: Of the 200 PCCRCs, 115 were detected at a subsequent BCSP procedure and 85 detected outside the BCSP.

Year	True Positive Colonoscopies	False Negative Colonoscopies	To year end	PCCRC-3y Rate
2006-2008	2288	47	2009-2011	2.05% (95% CI 1.5–2.7)
2009	2303	62	2012	2.62% (95% CI 2.0–3.3)
2010	3180	91	2013	2.78% (95% CI 2.2–3.4)
Total	7771	200		2.50%(95% CI 2.2–2.9)

[Results]
Conclusion: 1. The overall English NHS BCSP PCCRC-3y rate from 2006-2010 is 2.5% – less than half the 7.3% PCCRC rate seen in the symptomatic English NHS for 2007, providing further evidence that high quality colonoscopy, such as that performed by screening-accredited colonoscopists in the BCSP, results in a lower rate of PCCRC (3)(4).

2. Despite the high quality of colonoscopy in the BCSP, PCCRCs still occur, showing the importance of vigilance during all colonoscopies.

3. Diagnosis of >2000 colorectal cancers (true positive colonoscopies) each year indicates there is an adequate sample size for annual reporting of PCCRC-3y rate within the BCSP and comparison with PCCRC-3yr rates in symptomatic services.

Disclosure: Nothing to disclose

References

1. Beintaris I et al. *United European Gastroenterology Journal* Vol 5 Issue 5_Suppl PO436.
2. Morris EJA et al. *Gut* 2014; 0: 1–9.
3. Corley DA et al. *N Engl J Med* 2014; 370: 1298–306.
4. Kaminski MF et al. *N Engl J Med* 2010; 362: 1795–803.

OP248 HIGH-RISK LESIONS ARE A STRONGER PREDICTOR FOR INTERVAL CANCER THAN ADENOMA DETECTION RATE

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Introduction: After index colonoscopy patients with high-risk adenomas (≥ 2 polyps or ≥ 10 mm or high-grade dysplasia or villous or tubulovillous histology) should undergo surveillance colonoscopy after 3 years, patients with low-risk adenomas after 10 years. Although endoscopic screening reached high quality standards, interval cancers still occur in a significant number of patients and the underlying risk factors are poorly understood.

Aims and Methods: To evaluate if patients with high-risk adenomas are at increased risk for interval cancers. Screening colonoscopies performed between 1/2009 and 6/2015 within a nationwide quality assurance program were included. An interval cancer was defined as colorectal cancer diagnosed at least 6 month after screening colonoscopy and the scheduled time of surveillance colonoscopy.

Results: 146,894 colonoscopies were included (50.8% women, median age 60 years) of which 19% were classified as high risk. During a median follow up of 36.9 month, 114 interval cancers were identified. Patients with high-risk lesions had significantly higher incidence rates of interval cancers than those in the low-risk group (HR 1.77 [1.18–2.66]; p = 0.006). Other factors associated with interval cancer were older age (HR per 10 years 1.87 [1.52–2.29]; p < 0.001) and adenoma detection rate ≤20% (HR 0.65 [0.44–0.95]; p = 0.025). Interestingly, there was no association with female sex.

Conclusion: High-risk lesions are a stronger predictor for the occurrence of interval cancer than poor adenoma detection rate. In contrast to previous studies there was no association with female sex.

Disclosure: Nothing to disclose

TUESDAY, OCTOBER 23, 2018   15:45–17:15

Artificial intelligence: The rise of the machines – Room N2_____

OP249 AUTOMATIC DETECTION OF EARLY GASTRIC CANCER IN ENDOSCOPIC IMAGES USING A TRANSFERRING CONVOLUTIONAL NEURAL NETWORK

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Introduction: Early detection of gastric cancer is difficult even for well-trained endoscopists, therefore machine learning is expected to be useful for reducing misdetection and interobserver variability in endoscopic diagnosis. Dramatic changes in detection accuracy in machine learning have been occurring since the upsurge in the utility of convolutional neural network (CNN). Although many results have been reported, there are relatively few effective methods to automatically detect early gastric cancer with small morphological features, which implies that automatic detection methods can be extremely difficult to construct. Additionally, it is well-known that CNN-based methods require the preparation of a large number of annotated datasets. Automatic detection scheme with high efficient learning which can achieve high accuracy is required.

Aims and Methods: In this study, we proposed a CNN-based automatic detection scheme to assist endoscopic image diagnosis for early gastric cancer with efficient learning system. We used one hundred non-magnifying endoscopic images of early gastric cancer which were segmented and annotated into 2 classes (cancer area and normal area) for learning. We also used 698 noncancerous images for learning. The images are 24-bit full-color images of size 1000 × 870 pixels extracted from the endoscopic video taken under white light (GIF-H290Z or GIF TYPE H260Z, Olympus Optical, Tokyo, Japan) and a standard video endoscope system (EVIS LUCERA ELITE, Olympus Optical). We obtained detailed texture information based on randomly cropped small images derived from cancer images and normal images of the learning data. The information was utilized to perform a transfer learning for tuning CNN-based prediction scheme. Validation was conducted with the 4,653 cancer small images and 4,997 normal small images, which were randomly cropped from cancer area and normal area of 128 gastric cancer images, not used as the learning data. Detection of early gastric cancer on the full size endoscopic images was performed in each blocks where the image was divided into 90 blocks. The detection results were shown as a color heat map, showing the likelihood of cancerous area. The detection accuracy was evaluated by counting the number of images when at least one block matches the ground truth.

Results: The sensitivity, specificity, and accuracy of our trained CNN-based prediction scheme for 4,653 cancer images and 4,997 normal images was 80.0%, 94.8%, and 87.6%. Automatic detection of early gastric cancer for full size endoscopic images were successfully done with showing detected cancerous area as pseudo colored heatmap, and detection success was accomplished in a total of 106 images (82.8%) out of 128 cancer images. Conversely, a total of 491 images (70.3%) out of 698 normal images were correctly predicted as "normal." The processing time was 4 ms per image, except for the time required to input/output the image.

Conclusion: Our preliminary CNN-based prediction scheme achieved high accuracy in early gastric cancer detection from the small amount of learning datasets. Automatic detection of early gastric cancer may offer sufficient assistance to endoscopists in decision making.

Disclosure: Nothing to disclose

OP250 CAN ARTIFICIAL INTELLIGENCE USING CONVOLUTIONAL NEURAL NETWORKS DIAGNOSE ESOPHAGEAL CANCER

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Introduction: Esophageal cancer is the eighth most common cancer worldwide, and the sixth cause of death. Patients are usually diagnosed at an advanced stage when it is often too late for effective treatment, thus it is important to detect in early stage. In recent years, artificial intelligence (AI) using deep learning has made remarkable progress in various medical fields, however, there is no report about the diagnosis of esophageal cancer. Here, we demonstrate the diagnostic ability of AI to detect esophageal cancer including squamous cell carcinoma (SCC) and adenocarcinoma.

Aims and Methods: We collected 8428 training images of esophageal cancer lesions that were histologically proven to be SCC or adenocarcinoma in 384 patients in Cancer Institute Hospital, Tokyo, Japan from 2014 to 2017. The training esophageal cancer images included 397 lesions of esophageal SCCs (ESCCs) which consisted of 332 lesions of superficial cancer and 65 lesions of advanced cancer. A total of 32 lesions of esophageal adenocarcinomas (EACs) were also included for training and consisted of 19 lesions of superficial cancers and 13 lesions of advanced cancers. With these training images, we developed deep learning through convolutional neural networks (CNNs). We also prepared 1118 test images in 47 patients with 49 esophageal cancers, including 41 ESCCs and 8 EACs, (169 images of esophageal cancer and 376 images without cancer)- and 50 patients without esophageal cancer (573 images of the non-cancerous part of the esophagus) to evaluate the diagnostic accuracy. All cases of esophageal cancer were confirmed to have no other cancer using WLI, NBI, iodine staining, and follow-up endoscopy after the treatment.

Results: The CNN took 27 seconds to analyze 1118 test images and correctly detected esophageal cancer cases with a sensitivity of 98% (48/49). CNN could detect all 7 small cancer lesions less than 10 mm in size. In contrast the CNN misdetected 42 non-cancerous lesions, which caused low positive predictive value (54%). However, the PPV of NBI with magnification was reported to be 45% in experienced endoscopists and 35% in less experienced endoscopists, which was not so different from our outcomes. The misdetected lesions included scars of endoscopic resection and esophagogastric junction. This can be corrected by deep learning about each normal structure and benign lesion, which will surely reduce false positives and improve the PPV significantly. Each image of esophageal cancer, whether taken with WLI or with NBI, was separately diagnosed as either superficial or advanced cancer by the CNN. The accuracy in diagnosis was quite high for both imaging modalities. The diagnostic accuracy was 99% (142/143) for superficial cancer and 92% (23/25) for advanced cancer. The accuracy in diagnosis for ESCC and EAC was 99% (146/147) and 90% (19/21), respectively. In addition, the CNN could detect all 5 esophageal cancers in the video of endoscopic screening in 5 cases.

Conclusion: AI-based diagnostic systems developed by deep learning demonstrated high diagnostic accuracy with high sensitivity to detect esophageal cancer with surprising efficiency. For the first step, we analyzed only still images and we think this system is useful for rechecking the stored images after EGD. In addition, we succeeded demonstrating the usefulness of the CNN system for videos, which could help identify esophageal cancer during EGD in real time. We believe the AI-based diagnostic system will support us in detecting esophageal cancers and allow early detection of esophageal cancer in daily clinical practice in the near future.

Disclosure: Nothing to disclose

OP251   THE ARGOS PROJECT: FIRST RESULTS OF A DEEP LEARNING ALGORITHM FOR THE DETECTION OF BARRETT NEOPLASIA

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Introduction: Early neoplasia in Barrett's esophagus (BE) is difficult to detect during surveillance endoscopies. This is partly because of its subtle appearance and partly because most endoscopists rarely encounter early BE neoplasia and therefore are unfamiliar with its endoscopic appearance. Computer- aided detection (CAD) systems might be able to assist endoscopists real-time in the detection of early BE neoplasia, thereby improving efficacy of BE surveillance. Recently, several *deep learning techniques* using Transfer Learning in Convolutional Neural Networks (CNNs) have shown promising results in other fields. CAD systems using deep learning techniques allow for faster execution time than the conventional clinically inspired algorithms, which will be essential for real-time operation.

The aim of this study was to evaluate feasibility of a deep learning algorithm for detection of BE neoplasia using high-quality endoscopic images.

Aims and Methods: Endoscopic overview images of 40 subtle early neoplastic BE lesions and 20 non-dysplastic BE patients were prospectively collected in White Light Endoscopy (WLE) in three tertiary referral centers. To establish a ground truth for detection and delineation, 6 international BE experts delineated all neoplastic images using a proprietary online delineation module.

The area ≥4 experts delineated was labelled as *the sweet spot*. The area with at least 1 expert delineation was labelled as the *soft spot*. Positive samples were extracted from the sweet spot of the neoplastic images, while negatives samples were taken from the area outside of the soft spot and from the NDBE images. The deep learning algorithm was trained using transfer learning on a Resnet50 model pre-trained on ImageNet. The images were divided in blocks of 128 x 128 pixels that were used as input to the CNN. Based on their location, each image block was then classified as neoplastic or non-neoplastic separately and aggregated to obtain a segmentation mask. For each detected neoplastic image, the algorithm produced 2 separate delineations: A complete delineation of the neoplastic area and a 'red-flag' indication of only the most suspicious part of the lesion.

Outcome parameters: 1) Detection scores: Diagnostic accuracy of the algorithm per image in terms of accuracy, sensitivity, specificity, NPV and PPV; 2) Localization scores: Percentage of recognized neoplastic images where the delineation of the algorithm detected the soft spot and sweet spot; 3) Red-flag indication: Percentage of recognized neoplastic images where the algorithm red-flagged the soft spot and sweet spot.

Performance was evaluated using 4-fold cross-validation.

Results: Accuracy, sensitivity, specificity, NPV and PPV for detection per image were 92%, 95%, 85%, 93% and 90%, respectively. On the detected neoplastic images, the algorithm identified both the soft- and sweet spot to be neoplastic in all cases (100%). On these images the algorithm furthermore red-flagged the soft spot and sweet spot to be neoplastic in 97% and 87%, respectively.

Conclusion: Detection scores of the first version of this deep learning algorithm were high. On all detected images, the algorithm recognized the location of the neoplastic lesion. These results are promising and show feasibility of computer-aided detection as a red-flag detection technique in BE surveillance. Future steps will focus on further development of the algorithm towards video- and real-time analyses.

Disclosure: Nothing to disclose

OP252   NOVEL COMPUTER-ASSISTED SYSTEM FOR THE DETECTION AND CLASSIFICATION OF COLORECTAL POLYPS USING ARTIFICIAL INTELLIGENCE

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Introduction: Recently the American Society for Gastrointestinal Endoscopy (ASGE) addressed the ''resect and discard'' strategy, which suggests that diminutive polyps can be resected and discarded without submitting pathological assessment, when it is estimated not as adenomatous polyps with high confidence. This strategy can reduce the physician's burden, complications caused by biopsy, and medical costs. However, endoscopists need specific training until they can precisely detect and classify colorectal polyps, and in this regard computer-assisted diagnose (CAD) system may be of help. Previous studies have suggested promising application of artificial intelligence (AI), using deep learning in object recognition.

Aims and Methods: We aimed to construct a CAD using deep learning method that can accurately identify and classify CP in stored colonoscopy images. A deep convolutional neural network (CNN) architecture called Single Shot MultiBox Detector was utilized to develop and validate the CAD system in the present study. We trained the CNN using 16,418 images: 4,752 of CP and 4,013 of normal colorectums, and subsequently validated the performance of the trained CNN in 7,077 colonoscopy images, including 1,172 CP images from 309 various types of CP. Diagnostic speed and yields for the detection and classification of CP were evaluated as a measure of performance of the trained CNN.

Results: he processing speed of the CNN was 20 ms per frame. The trained CNN identified 1,247 CP with a sensitivity of 92% and a positive predictive value (PPV) of 86%. Among the correctly detected polyps, 83% of the CP were accurately classified, and furthermore, 97% of adenomas were precisely identified.

Conclusion: ur CNN showed robust performance to detect and classify CP through colonoscopy images, highlighting its high potential for future application as a CAD system of CP during colonoscopy.

Disclosure: T. Tada and K. Aoyama are employed by AI Medical Service Inc.

OP253   COMPUTERIZED IMAGE ANALYSIS MAY PREDICT DELAYED BLEEDING AFTER COLONIC ENDOSCOPIC MUCOSAL RESECTION

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Introduction: Clinically significant post-endoscopic bleeding (CSPEB) is the most common complication following colonic endoscopic mucosal resection (EMR). Current prediction tools are based on peri-procedural patient and lesion characteristics and do not account for the post-EMR mucosal defect appearance. We hypothesized that CSPEB may be predicted by analyzing the morphometric characteristics of blood vessels within the post-EMR mucosal defect. Our aim was to create a tool that will allow real-time identification of high-risk patients, which may benefit from prophylactic treatment and close monitoring.

Aims and Methods: Patients from the Australian prospective EMR cohort (ACE) were assigned to 2 groups based on presence or absence of CSPEB. The groups were matched in a 1:1 ratio for the clinical variables known to be associated with CSPEB (Age, aspirin use, lesion location in the colon, lesion size, histological subtype and intraprocedural bleeding). Standard EMR was performed, detailed patient lesion and procedural characteristics were recorded and meticulous photo-documentation prior to, during and after the procedure was obtained. A telephone interview was conducted 14 days after the procedure as part of the ACE study protocol, to record adverse events.

Computerized morphometric analysis was used to quantify various morphological characteristics of the blood vessels within the post-EMR mucosal defect. Multivariate Discriminant Regression Analysis and neural network were used as prediction models.

Results: Over the course of 6 years, until 2015, 1332 colonic lateral spreading lesions (LSL) >20 mm underwent EMR at Westmead hospital as part of the ACE study. 88/1332 (6.6%) had CSPEB. 43 cases and 43 matched controls with high quality images of the post EMR mucosal defect were selected for the analysis (median lesion size 40 mm (IQR 30-51.25)). Out of 30 blood vessel characteristics, 5 morphometric characteristics were independently associated with CSPEB (table 1).

Discriminant analysis using the 5 independent predictors yielded 86% sensitivity and 76.7% specificity in correctly identifying patients at risk of CSPEB. A Neural Network (NNET) classifier using the same independent predictors was trained on 60 subjects (30 controls and 30 cases) and subsequently tested on 26 subjects (13 controls and 13 cases). Training and testing subjects were chosen by computer randomization. The validated NNET algorithm yielded a sensitivity of 100% and a specificity of 76.9% for correctly identifying patients at risk of CSPEB.

Conclusion: Morphological characteristics of blood vessels in post-EMR defects can be used to predict delayed bleeding following colonic EMR. Future applications may include real-time computerized image analysis of blood vessels, which may assist in clinical decision-making regarding high-risk patients.

Independent morphometric variables:	Variable description	Multivariate means- Control group	Multivariate means- CSPEB group	P value
1. Diamax	Maximal diameter- maximal diameter of blood vessels	69.03	113.07	p < 0.001
2. Radmin	Minimal radius- minimal radius of blood vessels	3.28	5.09	p = 0.002
3. Perim	Perimeter-length of blood vessels outline	193.86	337.82	p < 0.001
4. Perim2	Perimeter 2-chain code length of outline (including holes, if any exist)	220.68	351.83	p < 0.002
5. FD	Fractal Dimension- complexity of blood vessel contour	1.10	1.11	p = 0.005

[Table 1- Morphometric variables independently associated with CSPEB]
Disclosure: Nothing to disclose

OP254   NOVEL COMPUTER-AIDED DIAGNOSIS SYSTEM USING CONVOLUTIONAL NEURAL NETWORKS FOR ENDOSCOPIC DISEASE ACTIVITY IN PATIENTS WITH ULCERATIVE COLITIS

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Introduction: Endoscopic findings for patients with Ulcerative Colitis (UC) are important to evaluate the extent and severity of the disease, as well as to determine the management of UC. However, since endoscopic diagnosis is an observer-dependent method, a certain period of training time is necessary for endoscopists to acquire sufficient ability to accurately evaluate the inflammatory disease activity. Inter-observer variability is known to exist in endoscopic diagnosis. An image recognition system with artificial intelligence (AI) has great potential to support physicians' clinical practices by providing objective and specialist-level diagnoses in the field of gastrointestinal endoscopy (1), including in the diagnosis of UC.
Aims and Methods: In this study, we constructed a computer-assisted diagnosis (CAD) system with a convolutional neural network (CNN) and evaluated its performance with a large dataset of endoscopic images from UC patients.
A retrospective review was performed of patients with UC who underwent colonoscopy at a single center in Japan from October 2006 to June 2017. A CNN-based CAD system, constructed based on GoogLeNet architecture, was trained with 26,304 colonoscopy images from 841 UC patients that were tagged with both anatomical locations and Mayo endoscopic scores (Mayo 0, Mayo 1, and Mayo 2-3). The performance of the CNN to identify mucosal healing state (Mayo endoscopic score 0 or 1) was evaluated in an independent test set of 4,589 images from 117 UC patients by using receiver operating characteristic (ROC) curves and calculating the area under the receiver operating characteristic curves (AUROCs). Additionally, AUROCs in each location of the colorectum (right-sided colon, left-sided colon, and rectum) were evaluated.
Results: Of the 4,589 images, 65% (1237 of 1890 images) of the Mayo 0 images, 56% (1295 of 2293 images) of the Mayo 1 images, and 51% (206 of 406 images) of the Mayo 2-3 images were correctly classified as each class of Mayo scores by the CNN-based CAD system. ROC curves of the CNN-based CAD system showed high performance with an AUROC value of 0.95 to identify Mayo endoscopic score 0 or 1 vs. 2 or 3. The performance of the CNN was better in right-sided colon and left sided-colon than in rectum (AUROC = 0.96, 0.97, and 0.88, respectively).
Conclusion: The CNN-based CAD system showed robust performance in identifying endoscopic inflammation severity in patients with UC, highlighting its capacity to support immature endoscopists and reduce inter-observer variability.
Disclosure: The authors declare no conflict of interest. T. Tada and K. Aoyama are employed by AI Medical Service Inc.

Reference

1. Shichijo S, Nomura S, Aoyama K, et al. Application of Convolutional Neural Networks in the Diagnosis of Helicobacter pylori Infection Based on Endoscopic Images. *EBioMedicine*. 2017 Nov; 25: 106–111.

OP255   ENDOGENOUS GLP-1 AFFECTS CENTRAL REGULATION OF APPETITE IN HEALTHY LEAN MALES

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Introduction: Exogenous infusion of glucagon-like peptide-1 (GLP-1) triggers appetite responses and can affect brain activity in areas involved in the regulation of appetite, including hypothalamic and reward-related brain regions. In contrast, the physiological role of endogenous GLP-1 in the central regulation of appetite has hardly been investigated.
Aims and Methods: The study was performed as randomized, cross-over trial. 12 healthy lean male subjects received an intragastric glucose (ig-gluc) load with or without intravenous (iv) exendin9-39 (ex9-39; specific GLP-1 receptor antagonist). Functional magnetic resonance imaging was used to investigate the effect of endogenous GLP-1 on resting state functional connectivity (rsFC) between homeostatic and reward-related brain regions. Visual analogue scales were used to rate appetite-related sensations. Blood samples were collected for insulin and glucose measurements.
Results: The main findings can be summarized as follow: i) after iv-ex9-39/ig-gluc a significantly higher rsFC was found relative to ig-gluc between the hypothalamus and the left lateral orbitofrontal cortex (OFC) as well as the left amygdala (p ≤ 0.001, respectively); ii) after iv-ex9-39/ig-gluc a significantly higher rsFC was found relative to ig-gluc between the right nucleus accumbens and the right lateral OFC (p < 0.001); iii) after iv-ex9-39/ig-gluc a significantly lower rsFC was found relative to ig-gluc between the midbrain (VTA) and the right caudate nucleus (p = 0.001); iv) ig-gluc significantly decreased prospective food consumption and increased fullness sensations compared to the pre-infusion baseline (p = 0.028 and p = 0.019, respectively), these effects were not present in the iv-ex9-39/ig-gluc condition v) after iv-ex9-39/ig-gluc an attenuated increase in plasma insulin concentrations was found relative to ig-gluc (p = 0.012).
Conclusion: In conclusion, this trial in healthy lean individuals indicates that glucose-induced endogenous GLP-1 release affects central regulation of appetite by modulating rsFC in homeostatic and reward-related brain regions in a GLP-1 receptor-mediated fashion.
Disclosure: Nothing to disclose

OP256   ENDOSCOPIC SLEEVE GASTROPLASTY (ESG): A METABOLIC PROCEDURE?

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Introduction: Morbid obesity is a worldwide major health problem that carries enormous socio-economic costs and a high incidence of comorbidities such as hypertension, diabetes mellitus (DM), and dyslipidemia[1]. Bariatric surgery is the only proven effective treatment; however, treatment rates remain low, because of poor patient acceptance, high costs, and non-negligible risks of complications. Any alternative treatment that could cure, control or even improve the morbidity of obesity and related diseases would have a tremendous medical, social and economic impact. Endoscopic sleeve gastroplasty (ESG) is an incisionless procedure suitable for widespread clinical adoptionshown to be effective to induce weight loss up to 24 months in moderately obese patients[2]. Currently, few data are available concerning the effects of ESG on comorbidities related to morbid obesity[3].
Aims and Methods: The aim of this study is to evaluate the impact of ESG on comorbidities due to morbid obesity (diabetes, hypertension, gastro-esophageal reflux, sleep apnea) at 6 months follow-up.
Between October 2016 and April 2018, 92 patients underwent ESG in 2 expert centers.
ESG was performed by the application of 4 to 6 full-thickness sutures using the OverStitch suturing platform. Patients mean % of excess weight loss (%EWL), clinical outcomes and medication use were assessed. Quality of life (QOL) was evaluated with the GIQLI and the BAROS questionnaires.
Results: 24 patients (26%) had a mean follow-up of at least 6 months and 15 (62.5%) presented at least 1 comorbid condition at inclusion. At 6 months %EWL was 29.95 ± 20.26 and 13 patients (86.6%), reduced (60%) or suspended (53.3%) pre-operative medications (p < 0.001) (Table 1.). No correlation was

found between weight loss and improvement or suspension of medications with the exception of diabetic patients in whom a greater weight loss resulted in a reduction of oral antidiabetics or insulin use (Pearson 0.746, p = 0.04; Spearman 0.737, p = 0.03).

Mean GIQLI score improved from 105.4 ± 17.2 (p = 0.06) to 113.4 ± 16.84 and mean BAROS score from 0.9 ± 0.9 to 1.3 ± 1 (p = 0.13).

Conclusion: ESG is a safe and effective bariatric endoscopic procedure that resulted in a positive impact onboth metabolic diseases and quality of life. Thus, ESG could provide a unique opportunity to reach a greater number of obese patients, earlier in their disease or at a younger age presenting with metabolic comorbid conditions. Larger studies are needed to confirm these preliminary encouraging results.

Disclosure: Nothing to disclose

References

1. Lopes EC, Heineck I, Athaydes G, et al. Is Bariatric Surgery Effective in Reducing Comorbidities and Drug Costs? A Systematic Review and Meta-Analysis. *Obesity Surgery* 2015; 25: 1741–1749.
2. Abu Dayyeh BK, Rajan E, Gostout CJ. Endoscopic sleeve gastroplasty: A potential endoscopic alternative to surgical sleeve gastrectomy for treatment of obesity. *Gastrointest Endosc* 2013; 78: 530–535.
3. Sharaiha RZ, Kumta NA, Saumoy M, et al. Endoscopic Sleeve Gastroplasty Significantly Reduces Body Mass Index and Metabolic Complications in Obese Patients. *Clin Gastroenterol Hepatol* 2017; 15: 504–510.

OP257 SAFETY, TOLERABILITY AND EFFICACY OF A NOVEL SELF-USE BIODEGRADABLE DEVICE FOR OBESITY

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Introduction: Obesity is a complex, chronic medical condition with a major negative impact on human health including type-2 diabetes mellitus (T2DM), hypertension and cardiovascular disease. The objective of the current study was to investigate the safety, tolerability and efficacy of an orally taken biodegradable device (Epitomee Device, Epitomee Medical, Caesarea, Israel) for induction of weight loss, and improvement of glycemic control and blood pressure levels in high-risk patients. The technology is based on absorbent pharmaceuticals polymers and bonding materials that self-expand in the stomach to create a pH sensitive super absorbent scaffold that stimulates gastric mechanoreceptors and activates early satiety signaling.

Aims and Methods: This was a prospective, 12-week twice daily use of the encapsulated device in patients with BMI of 27-40 kg/m^2 and controlled hypertension and/or dyslipidemia conducted at the Assaf Harofeh Medical Center from June 2014 through August 2017. Life interventional program, hypocaloric diet and increased physical activity were instructed. Weight, vital signs, laboratory tests and post treatment endoscopies were performed. Efficacy endpoints were the percent change in total body loss (TBL) and proportion of participants with at least 5% TBL at week 12 as well as changes in cardio-metabolic markers. Safety assessments included evaluation of treatment-associated adverse events, vital signs, laboratory and endoscopic findings.

Results: 52 subjects completed 12 weeks of treatment with a clinically significant mean percentage TBL of $4.52 \pm 2.97\%$ (p < 0.001) and mean excess weight loss of $21.86 \pm 16.15\%$ (p < 0.001). Of these, 42% achieved significant weight loss of more than 5% TBL and approximately third reduced their baseline weight more than 8%. Average patients' BMI declined from 33 to 31 and waist circumference reduced by -4.41 $\pm$ 3.34 cm (p < 0.001). In hyperlipidemic (n = 9) or pre-diabetic patients (fasting glucose > 100; n = 12) there was significant improvement in triglycerides (254.11 ± 57.43 vs. 161.78 ± 46.60) (p = 0.0076) and fasting glucose (104.92 ± 3.26 vs. 99.20 ± 7.73), (p = 0.04), respectively. 80% of hypertensive patients became normalized at week 12 with an average systolic BP reduced from 147 to 126 mmHg and diastolic BP improved from 96 to 74 mmHg (p < 0.02). In 50% or prediabetic patients, fasting glucose was reduced from 104.0 ± 3.2 to 92.8 ± 7 (small sample size to calculate p value) and in 44% of the prediabetic patients with HbA1C% > 5.7 (n = 9), HbA1C% was reduced from 6.03 ± 0.21 to 5.60 ± 0.21 (small sample size to calculate p value) There was no device related serious adverse event (AE). All device related AEs were mild and transient and most were headache, bloating, nausea, constipation. Endoscopy in 26 enrolled subjects, 12 weeks after the device ingestion, revealed mild non-clinical gastritis/duodenitis without erosions in very few patients (n = 5).

Conclusion: 12 weeks of treatment with the orally taken biodegradable Epitomee Device resulted in meaningful weight loss, accompanied by improvement in several cardio-metabolic parameters including waist circumference, triglycerides, fasting glucose levels and blood pressure. The novel device was well tolerated and has a favorable safety profile without related SAE. Long-term randomized controlled trials are in progress.

Disclosure: E.B. has participated on advisory board and was consultant for Epitomee Medical.

OP258 EFFICACY OF A TAILORED *HELICOBACTER PYLORI* ERADICATION THERAPY BASED ON BODY WEIGHT IN OBESE PATIENTS

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Introduction: The clinical management of *Helicobacter Pylori* (HP) infection in obese patients is complicated due to the lower eradication rates with standard therapeutic therapy. Body Mass Index (BMI) is an independent risk factor. Although the cause of this poor eradication remain to be elucidated, the physiological changes that obesity produce may lead to sub-therapeutic antibiotics concentrations and the current paradigm "one dose fits all" may be changed. The impact of these changes depends upon patient characteristics (degree obesity, underlying organ function) and the chemical properties of the antibiotic (hydrophilic or lipophilic). For most drugs, the interaction between drug pharmacokinetics/pharmacodynamics and BMI is complex and there is a lack of consensus formula that should be used for dosage calculation.

Aims and Methods: To evaluate the HP eradication of a tailored Quadruple Concomitant regimen based on body weight compared to standard Quadruple Concomitant therapy in obese patients undergoing bariatric surgery.

This prospective, open-label study included 104 obese patients undergoing bariatric surgery. Upper endoscopy and HP assessment by histology was performed at baseline and the post-treatment status was assessed by C13 Urea Breath Test, 6-8 weeks after the end of therapy. All patients were treated 14 days with a Quadruple Concomitant therapy with a proton pump inhibitor, amoxicillin, clarithromycin and metronidazole. 51 obese patients received a tailored regimen based on the body weight. Lipophilic antibiotics (metronidazole and clarithromycin) were adjusted according with the Total Body Weight until their maximal doses. Amoxicilin (hydrophilic drug) was adjusted with the Adjusted Body Weight (Ideal Body Weight according to the modified Devine formula and a weight correction factor of 0.3) until their maximal dose. Simultaneously, 53 obese patients, received the standard Quadruple Concomitant therapy with a proton pump inhibitor BID, clarithromycin 500 mg BID, amoxicillin 1000 mg BID and metronidazole 500 mg BID.

Results: Per-protocol and intention-to-treat eradication after the tailored body weight regimen were 90% (95% CI 77-96) and 86% (95% CI 73-93) whereas in the standard treatment obese group were 67% per-protocol (95% CI 53-78) and 66% (95% CI 52-77) by intention to treat. HP eradication in obese patients with the tailored body weight regimen were significantly higher than the control obese group. p < 0.001 Per-protocol and p < 0.05 Intention-to-treat. The distribution of age, gender, smoking and diabetes did not differ significantly between the 2 groups. 3 patients discontinued the treatment due to adverse events

Conclusion: A tailored Quadruple Concomitant regimen based on body weight in obese patients undergoing bariatric surgery is significantly more effective than than standard Quadruple Concomitant therapy. A tailored eradication treatment with the antibiotics adjusted according to the body weight could be considered as a new strategy for obese patients.

Disclosure: Nothing to disclose

OP259 EFFECTS OF DIETARY FIBRES ON INDOMETHACIN-INDUCED INTESTINAL PERMEABILITY IN ELDERLY: A RANDOMISED PLACEBO CONTROLLED PARALLEL CLINICAL TRIAL

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Introduction: The global population of elderly (> 65 years) is increasing and will have a major impact on health-care systems (1, 2) due to an increased incidence of age-related diseases. Gastrointestinal (GI) symptoms are common among the elderly and approximately 60% are estimated to be affected (3, 4). The elevated pharmaceutical load in elderly is of potential harm to the intestine and it is known that long-term use of non-steroid anti-inflammatory drugs (NSAID), commonly used for pain management among elderly, can cause gastric ulceration, enteropathy (5, 6) and increased intestinal permeability (7). A deteriorated barrier function is associated with increased psychological distress in elderly with GI symptoms (8), and many diseases of inflammatory character such as inflammatory bowel disease (9). We have previously shown that specific dietary fibres attenuate stress-induced hyperpermeability *ex vivo* in ileal tissues from patients with Crohn's disease (9). However, the potential of dietary fibres to strengthen the intestinal barrier function *in vivo* in elderly individuals is, to our knowledge, not known.

Aims and Methods: We performed a placebo-controlled parallel clinical trial to investigate whether 6 weeks of oral supplementation of wheat-endosperm derived

arabinoxylan or oat β-glucan could strengthen the intestinal barrier function of elderly individuals and reduce indomethacin (NSAID)-induced gut permeability. Furthermore, inflammatory/oxidative status and self-reported health was evaluated after dietary fibre intervention.

All qualified subjects (n = 49) participated in a 3-arm study design. Each arm consisted of 6 weeks of intervention with arabinoxylan, oat β-glucan or placebo (maltodextrin). Primary outcome was set to changes in indomethacin-induced intestinal permeability before and after intervention as assessed by an *in vivo* multi sugar test. Secondary outcomes were set to changes in: systemic inflammatory/oxidative status and self-reported health. Blood was collected during the beginning and end of the study. Dietary intake was estimated using a food frequency questionnaire (FFQ).

Results: Indomethacin was found to significantly increase gastroduodenal and small intestinal permeability in all 3 intervention arms while colonic permeability was significantly increased in one of the intervention arms. No significant effects on the primary parameters (intestinal permeability) or secondary parameters (inflammatory/oxidative levels in blood plasma and self-reported health) were observed after intervention with either dietary fibre, compared to placebo. Intervention with arabinoxylan demonstrated a significant decrease in symptoms of diarrhoea within the intervention arm after stratification for GI symptoms, however these results did not reach significance when compared to placebo. FFQ analysis revealed that 85% of all 49 elderly participants had an insufficient fibre intake, accounting only for a median of 64.6% (IQR 50.6–83.8%) of the Nordic Nutrition Recommendations (NNR).

Conclusion: Our data show that supplementation of arabinoxylan or oat β-glucan was not able to attenuate indomethacin-induced intestinal permeability. However, our results also show that dietary fibre intake among elderly was below the NNR levels. This emphasises the importance to further investigate the effect of dietary fibres on gut health and barrier function in elderly for the development of appropriate dietary guidelines regarding supplementation of dietary fibres.

Disclosure: The EU 7th framework programme FibeBiotics financed this study. Bioactor (Netherlands) and Swedish Oat Fiber (Sweden) provided the study supplement arabinoxylan and oat β-glucan, respectively, but had no involvement in the design, analysis or interpretation of the results in this study.

References

1. Cohen JE. Human population: the next half century. *Science*. 2003.
2. Dennison C, et al. The health-related quality of life and economic burden of constipation. *Pharmacoeconomics*. 2005.
3. Chaplin A, et al. Prevalence of lower gastrointestinal symptoms and associated consultation behaviour in a British elderly population determined by face-to-face interview. *Br J Gen Pract*. 2000.
4. Zuchelli T, et al. Gastrointestinal issues in the older female patient. *Gastroenterol Clin North Am*. 2011.
5. Lagerin A, et al. Extent and quality of drug use in community-dwelling people aged >/= 75 years: A Swedish nationwide register-based study. *Scand J Public Health*. 2017.
6. Bjarnason I, et al. Effect of non-steroidal anti-inflammatory drugs and prostaglandins on the permeability of the human small intestine. *Gut*. 1986.
7. van Wijck K, et al. Novel multi-sugar assay for site-specific gastrointestinal permeability analysis: a randomized controlled crossover trial. *Clin Nutr*. 2013.
8. Ganda Mall JP, et al. Are self-reported gastrointestinal symptoms among older adults associated with increased intestinal permeability and psychological distress? *BMC Geriatr*. 2018.
9. Ganda Mall JP, et al. A beta-Glucan-Based Dietary Fiber Reduces Mast Cell-Induced Hyperpermeability in Ileum From Patients With Crohn's Disease and Control Subjects. *Inflamm Bowel Dis*. 2017.

OP260 PERCUTANEOUS TRANSESOPHAGEAL GASTROTUBING (PTEG) AS THE SUITABLE PROCEDURE FOR THE PATIENTS THAT PERCUTANEOUS ENDOSCOPIC GASTROSTOMY (PEG) INSERTION IS CONTRAINDICATED

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Introduction: Percutaneous transesophageal gastrotubing (PTEG) was developed as an alternative route to access the gastrointestinal tract for the patients that Percutaneous Endoscopic Gastrostomy was contraindicated with conditions such as prior gastrectomy, gastric anterior wall malignancies, or massive ascites. PTEG will be an ideal method for tube feeding and decompression.

Aims and Methods: The aim of this study is to evaluate the clinical usefulness of PTEG for the patients who need tube feeding or decompression from gastrointestinal tract. A rupture-free balloon (RFB) catheter is inserted into the upper esophagus. Percutaneous balloon puncture with a specialized needle is then performed from the left side of patient's neck under ultrasonographic control. A guide wire is inserted through the needle into the RFB, followed by a dilator and sheath. A placement tube is then inserted through the sheath, and the sheath is removed. Double Balloons equipped over tube type RFB were used instead of primary RFB in 25 cases that the puncture needle is punctured into the over tube trough the balloon. We perform PTEG in a total of 172 patients (109 men and 63 women, mean age 71.2 years) in whom PEG was not feasible. PTEG was performed for nutrition in 97 patients and for decompression in 75.

Results: Satisfactory results were achieved in all 172 patients. Median follow-up was 305.0 days in those who received nutrition and 66.0 days in patients who received decompression. All patients were free from nasal tube prior insertion. 6 of 97 patients for nutrition were able to be freed from tube feeding due to PTEG tube feeding support, oral ingestion could be achieved in 44.0% and home care could achieved in 66.0% of decompression group patients. Major complications were bleeding in 2 patients required blood transfusion and 1 patient had tracheal penetration, which was managed conservatively. Other complications were minor oozing bleeding in 12 patients that did not require blood transfusion, subcutaneous emphysema in 2 patients, which were managed conservatively. No patient required surgical treatment or died after PTEG.

Conclusion: PTEG is safe and useful for long-term nutrition and/or decompression for the patient who is contraindicated to PEG. PTEG is an only procedure to be free from a nasal tube especially for the patients with carcinomatous peritonitis. PTEG is a suitable procedure of the patients having an eating disorder and/or the malignant disease as tubal feeding and palliative care.

Disclosure: Nothing to disclose

OP261 PMCA PUMP DYSFUNCTION CAUSES CA²⁺ OVERLOAD AND PANCREATIC DUCTAL EPITHELIAL CELL DAMAGE IN CYSTIC FIBROSIS

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Introduction: The cystic fibrosis transmembrane conductance regulator (CFTR) has a major role in pancreatic ductal secretion and its genetic defects damage the pancreas. It is known that intracellular Ca^{2+} homeostasis is disturbed in bronchial epithelial cells in cystic fibrosis (CF), but the connection of CFTR and the intracellular Ca^{2+} signaling has never been suggested in pancreatic damage in CF before.

Aims and Methods: Our aim was to characterize the Ca^{2+} homeostasis of CFTR-deficient PDEC.

Wild type (WT) and CFTR knockout (KO) mouse pancreatic ductal (PDEC) and acinar cells (PAC), human CF pancreatic cell line (CFPAC-1) and human pancreatic organoids generated from induced pluripotent stem cells (IPSC) of controls and CF patients were used in the study. Intracellular Ca^{2+} levels, mitochondrial membrane potential ($\Delta\Psi_m$) and mitochondrial morphology was assessed using fluorescent probes and transmission electron microscopy, respectively. Immunofluorescent staining and quantitative PCR measurements were performed to detect changes of protein expressions. Protein ligation assay (PLA) was performed to detect contact between proteins.

Results: The plateau phase of the agonist-induced Ca^{2+} signal was significantly elevated in CFTR KO PDEC caused by decreased function of the plasma membrane Ca^{2+} pump (PMCA). Functional inhibition of CFTR had no effect on the PMCA activity. Whereas native CFPAC-1 cells, CF human organoids and murine PDEC treated with siCFTR showed similarly impaired PMCA activity. On the other hand, different strategies to restore the CFTR expression, such as Sendai virus mediated gene delivery in CFPAC-1, or VX-809 treatment of CF organoids completely restored PMCA function. As a downstream consequence, sustained $[Ca^{2+}]_i$ elevation decreased $\Delta\Psi_m$ and released cytochrome c in CFTR KO PDEC without significant alteration of mitochondrial morphology. Immunostaining revealed the colocalisation of PMCA4 and CFTR on the apical membrane of polarized, primary PDEC and PLA confirmed the intimate proximity of the proteins. Calmodulin, a possible link among CFTR and other proteins, showed plasma membrane localization in WT PDEC, which was shifted to the cytosol of CFTR KO cells.

Conclusion: Impaired expression of the CFTR leads to disturbed Ca^{2+} homeostasis and mitochondrial damage in primary PDEC due to the decreased activity of PMCA. These changes can contribute to the pancreatic damage seen in cystic fibrosis.

Disclosure: Nothing to disclose

OP262 HIGH-FAT DIET AND ANTIBIOTICS INCREASE PATHOBIOME-ASSOCIATED MORTALITY IN EXPERIMENTAL NECROTIZING PANCREATITIS

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Introduction: Acute pancreatitis is a complex gastro-intestinal disorder with severe complications in around 20-30% of the patients. Intestinal micro-organisms, collectively called the gut microbiome, are thought to drive the key processes in pancreatitis disease progression, such as bacterial translocation and increased systematic immune response. A western, high-fat (HF) diet and antibiotics are known to cause alterations in the microbiome composition and function. We hypothesize that severe dysregulation of the gut microbiome attenuates severity and drives mortality in experimental necrotizing pancreatitis.

Aims and Methods: The aim of the experiment was to demonstrate the role of the microbiome in an experimental mouse model of necrotizing pancreatitis. Pancreatitis was induced by retrograde infusion of 4% sodium taurocholate in the pancreatic duct of 12 week old C57BL/6 mice.[1] Serum amylase was measured to confirm induction of pancreatitis. A group of mice received 2 doses of meropenem (i.p. 100 mg/kg b.w.) prior to the procedure. Other mice were additionally fed a diet for 3 weeks that contained 60% poly unsaturated fatty acids (HF/ antibiotic group). Control groups of mice were fed a normal diet (chow) and underwent either sodium taurocholate or saline infusion (sham group). The surviving mice were sacrificed 48 hours after the procedure and blood and tissues were collected. Severity of pancreatitis was evaluated by morbidity score (rated 1 to 5) and histology severity score of pancreatic tissue. Bacterial dissemination was determined by blood culture on selective CNA and MacConkey media plates.

Results: Preliminary results show that all mice that were treated with 4% sodium taurocholate developed severe necrotizing pancreatitis, with mean serum amylase levels of 50,865 U/l after 24 hours. The sham-operated group showed only slight hyperamylasemia (mean 3,915 U/l) and mild pancreatic oedema. Mortality was increased in mice that received HF-diet and meropenem (60%, 3 out of 5) or meropenem alone (29%, 5 out of 17) as compared to the chow group, with average morbidity scores of respectively 4, 3 and 2. There was no mortality amongst the chow or sham group. Histology severity scores of the pancreas were increased in the HF/antibiotic and antibiotic alone groups. Blood cultures showed grow of mainly gram positive bacteria (CNA media). Bacterial load in blood was increased in the meropenem group (1.6×10^6 CFU/ml) as compared to the chow group (3×10^3 CFU/ml). No bacterial growth was observed in the sham group.

Conclusion: We are showing that exposure to factors that are known to cause dysregulation of the intestinal microbiota, such as broad-spectrum antibiotics and western diet, induces early mortality in experimental pancreatitis. Although preliminary, the data suggests that increased gut-derived bacterial dissemination is the main driver of mortality in this model. Validation through additional experiments has to confirm this and explain the underlying mechanisms. This novel model of microbiome-driven mortality in acute pancreatitis may enable us to investigate novel treatment approaches such as fecal microbiota transplantation.

Disclosure: Nothing to disclose

Reference

1. Laukkarinen, J. M., et al. (2007). "A mouse model of acute biliary pancreatitis induced by retrograde pancreatic duct infusion of Na-taurocholate." *Gut* 56(11): 1590–1598.

OP263 GENETIC INHIBITION OF CYCLOPHILIN D PROTECTS AGAINST BILE ACID OR ETHANOL AND FATTY ACID INDUCED PANCREATIC DUCTAL EPITHELIAL CELL DAMAGE IN MICE

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Introduction: Mitochondrial dysfunction is a hallmark of several disease pathogenesis including acute pancreatitis (AP). Our previous results suggest that mitochondrial damage is crucial in bile acid induced inhibition of pancreatic ductal HCO_3^- secretion, however the details of mitochondrial function and dysfunction in pancreatic ductal epithial cells (PDEC) is not known yet. Cyclophilin D (Cyp D) has a crucial role in the opening of the mitochondrial transition pore (mPTP) which could be a target to avoid mitochondrial Ca^{2+} overload and cell death.

Aims and Methods: The aim of our study was to study the effect of the genetic inhibiton of Cyp D in the pancreatic ductal epithelial cells.
Wild type (WT) and Cyp D knock out (KO) mouse pancreatic ducts were isolated by microdissection. Mitochondrial membrane potential ($\Delta\psi_m$) was measured by confocal microscopy and pancreatic ductal HCO_3^- secretion by microfluorometry. Functionally active mitochondria in the pancreatic ducts were detected by immunofluorescence microscopy using TOMM20 mitochondrial marker.

Results: The genetic knock out of cyclophilin D significantly reduced the loss of $\Delta\psi_m$ and protected pancreatic ductal HCO_3^- secretion during the administration of 500μM chenodeoxycholic acid or 100mM ethanol (EtOH) and 200μM palmitoleic acid (PA) treatment. Immunfluorescence meaurements revealed a significant difference in the amount of the newly synthetized mitochondrial preproteins between the CDC and the EtOH+PA treated WT and Cyp D KO groups.

Conclusion: Our results suggest that mitochondrial function has a central role in the function of PDEC presumably by providing ATP for fluid and ion secretion. On the other hand the opening of MPTP seems to be crucial in the bile acid induced toxicity offering a potential therapeutic target in AP.

Disclosure: Nothing to disclose

OP264 NNOS INHIBITION RELIEVES PAIN IN CHRONIC PANCREATITIS

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Introduction: Abdominal pain is the most unpleasant and the most frequent symptom in human chronic pancreatitis (CP). In the presen study, we aimed to perform a detailed analysis of the neuropeptide content of intrapancreatic nerves in human CP and at identifying novel analgesic-therapeutic targets.

Aims and Methods: Intrapancreatic nerves in human CP (n = 23), pancreatic cancer (n = 19) and normal human pancreas (NP, n = 10) specimens were immunohistochemically stained against the nociceptive neuropeptides substance P (SP), calcitonin-gene-related-peptide (CGRP), vasoactive intestinal peptide (VIP), and neuronal nitric oxide synthase (nNOS). The proportion of nerve fibers that contain these neuropeptides was quatified for each nerve and compared between these three entities. Mouse dorsal root ganglia (DRG) neurons were treated with tissue extracts from human CP-, PCa- and NP-specimens, and the sprouting of neurites that contain these neuropeptides was compared. Specific inhibitors were applied to genetically engineered mouse models of PCa (e.g. KPC and KC mice), of CP (Ptf1a-Cre;Atg5lox/lox mice), and to mice with cerulein-induced CP, and their pain-associated behavior was compared.

Results: Human CP and NP specimens contained comparable amounts, and PCa specimens rather lowered amounts of intra-neural SP, CGRP, VIP and nNOS. However, CP patients with increasing pain severity exhibited higher amounts of nNOS in their pancreatic nerves. Treatment of mouse DRG neurons with CP tissue extracts led to specific enrichment of nNOS-containing neurites ex vivo. The density of nNOS-containing neurites was enhanced upon neutralization of brain-derived-neurotrophic factor (BDNF) in the human CP extracts, and accordingly also in BDNF-knockout mice. Administration of the specific nNOS inhibitor NPLA ameliorated the abdominal mechanosensitivity of mice with the painful cerulein-induced CP. However, KPC mice or Ptf1a-Cre;Atg5lox/lox mice with rather painless CP did not show any change in their abdominal mechanosensitiviy upon NPLA treatment.

Conclusion: Inhibiting nNOS via specific agents may represent a novel mode of analgesic therapy for pain due to CP, which needs to be tested in clinical studies.

Disclosure: This abstract has also been submitted for presentation at the 2018 meeting of the European Pancreatic Club.

OP265 PERICYTES ENHANCE NEUROGENESIS IN PANCREATIC CANCER

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Introduction: Pancreatic cancer (PCa) exhibits an unparalled degree of neural invasion and neurogenesis. In our recent analyses, we could show that neurogenesis and neural invasion in PCa correlate with angiogenesis. Pericytes are perivascular cells that critically regulate vessel permeability and metastasis in cancer. Here, we dissected the potential role of pericytes in PCa-associated neurogenesis.

Aims and Methods: The proportion of pericyte-covered vessel area (pericyte coverage index) and the proportion of pericyte-covered vessels (pericyte-covered cells/PCV) was histologically and automatically quantified in human PCa (n = 39) and normal pancreas (NP, n = 30) sections after immunostaining with the pericyte markers $CD146^+$ and αSMA^+. Th results were correlated with the nerve and vessel density, and the rate of neural invasion on each section. In a

cross-species analysis, we compared the pericyte coverage in KPC mice in comparison with wildtype mice. To investiage the interactions between angiogenesis and neurogenesis *in vitro*, we developed a 3D heterotypic co-culture system with mouse dorsal root ganglia (DRG), PCa cells and pericytes, and determined the neurite density of DRG neurons. In a transcriptomic analysis, we compared the transcription profile of pericytes that were stimulated with PCa cell supernatants and compared this to unstimulated pericytes.

Results: In human PCa tissues, PCV and PCI were increased around $CD146^+$ microcapillaries when compared to NP ($PCV_{PDAC} = 38.8 \pm 3.4\%$, vs. $PCV_{NP} = 23.4 \pm 3.7\%$, p = 0.0049; $PCI_{PDAC} = 19.6 \pm 2.2\%$ vs. $PCI_{NP} = 11.3 \pm 2.3\%$, p = 0.018). Similarly, PCV & PCI were higher around macrocapillaries-associated pericytes (αSMA^+/CD31-stained areas), when compared to NP. In KrasG12D-based mouse PCa models, there was a very similar increase in PCV and PCI, especially in the KC, but also in the KPC model (p = 0.0105). There was no correlation between PCI, PCV and nerve density or neural invasion. In 3D co-cultures, DRG exhibited enhanced neurite density upon co-culture with both PCa cells and pericytes. PCa-cell-stimulated pericytes upregulated the expression of multiple molecules in metabolic and pro-inflammatory pathways.

Conclusion: Increased pericyte coverage is one of the typical alterations in the PCa microenvironment. Activated pericytes also seem to contribute to PCa-associated neurogenesis.

Disclosure: This abstract has also been submitted for presentation at the 2018 meeting of the European Pancreatic Club.

OP266 HIGH EXPRESSION OF SERUM EXOSOMAL MIR-21-5P IN TYPE 1 AUTOIMMUNE PANCREATITIS

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Introduction: Type 1 autoimmune pancreatitis (AIP) is now accepted as a new clinical entity of pancreatic disorder that is characterized by diffuse irregular narrowing of the main pancreatic duct, lymphoplasmacytic infiltration with fibrosis, Th-2-balanced inflammation, and high serum levels of IgG or IgG4. Since the fibroinflammatory process of AIP responds to immunosuppressants, abnormal immune systems are considered to be involved in the development of AIP. However, the investigation of the complex pathogenetic mechanisms underlying this disease remains to be elucidated.

Exosomes are small extracellular vesicles secreted by myriad of cell populations into body fluids, playing a pivotal role in cell-to-cell communications. These vesicles convey nucleic acids, including microRNA, and proteins derived from the cells which they are secreted to recipient cells. Exosomes not only maintain immune homeostasis but are also involved in the pathophysiology of various diseases such as cancer and autoimmunity. However, it has not been addressed the correlation between disease exosomes and the pathogenesis in type 1 autoimmune pancreatitis (AIP). To clarify it, we performed microRNA (miRNA) screening of serum-derived exosomes in patients with type 1 AIP.

Aims and Methods: We comprehensively analyzed the miRNA expression derived from serum exosomes using microarrays in patients with type 1 AIP (n = 10) in comparison to that in healthy adults (n = 10). Differences in signals of higher than 3 times or lower than 1/3 were regarded as represent significant differences in expression. The expression of miRNAs selected by microarrays were also analyzed by quantitative reverse-transcription polymerase chain reaction (qRT-PCR).

Results: In analysis of microarrays, the signals of 8 miRNAs (miR-659-3p, -27a-3p, -99a-5p, -21-5p, -205-5p, -100-5p -29c 3p, and -125b-1-3p) were higher, and the signals of 2 miRNAs (miR-4252 and -5004-5p) were lower in patients with type 1 AIP, respectively, than in healthy adults. Quantitative reverse-transcription polymerase chain reaction (qRT-PCR) revealed that exosomal miR-21-5p was significantly upregulated in patients with type 1 AIP (n = 10) compared with that in healthy adults (n = 10) (p = 0.04). qRT-PCR analysis also revealed that miR-21-5p expression was upregulated in patients with type 1 AIP compared with that in patients with chronic pancreatitis (n = 10); however, this difference was not significant (p = 0.05).

Conclusion: Alterations in the expression of miRNA contained in exosomes is considered to play a role in the initiation or modulation of the pathophysiology of several diseases. The present study suggests that dampening of gene expression by miR-21 may be involved in the pathophysiology of type 1 AIP.

Disclosure: Nothing to disclose

References

1. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas.* 2011; 40: 352–8.
2. Biological properties of extracellular vesicles and their physiological functions. J Extracell Vesicles. 2015;4:27066. Diversifying microRNA sequence and function. *Nat Rev Mol Cell Biol.* 2013; 14: 475–88.

VC01 ENDOSCOPIC APPENDICEAL FECALITH EXTRACTION BY NOTES TECHNIQUE

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Introduction: A 74-year-old man had a 2-weeks history of repeated right lower abdominal pain. Colonoscopy revealed a 10-mm subepithelial lesion near the appendiceal orifice. The lesion could be pushed by a biopsy forcep and was found to have a hard consistency. It was well defined and appeared heterogeneous echotexture in endoscopic ultrasongraphy. Contrast-enhanced computed tomography showed a $8 \times 10mm$ high density mass in the cecum. Chronic appendicitis caused by appendiceal fecalith obstruction was suspected.

Aims and Methods: After endoscopic retrograde appendicitis therapy (ERAT) failed, a endoscopic treatment was still requested by patient. Therefore, the endoscopic appendiceal fecalith extraction was attempted.

Results: First, along the marker dots, the anal side mucosa of the lesion was incised using the flush-knife. Then, a metal clip with dental floss bited the incised mucosa, and another metal clip was used to fix the pull line to the opposite side of cecal wall. So, a pulley-like traction device was structured to expose the subepithelial lays adequately. After the full-thickness resection of cecum and appendix, a fecalith was exposed in the appendix lumen and was taken out by a snare soon. After careful hemostasis, the cecum and appendix defect were closed by metallic clips partly, and the residual defect was unclosed to form a artificial fistula (arrow) from appendix to cecum for internal drainage. The patient experienced no procedure related adverse events.

Conclusion: This novel NOTES technique provides another choice for management of the subepithelial lesion-like appendiceal fecaliths.

Disclosure: Nothing to disclose

VC02 JEJUNAL DIVERTICULUM: A RARE CAUSE OF LIFE-THREATENING MIDGUT BLEEDING SUCCESSFULLY TREATED BY DOUBLE-BALLOON ENTEROSCOPY (DBE) (WITH VIDEO)

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Introduction: Small bowel diverticula are a rare cause of gastrointestinal (GI) bleeding. Their pathogenesis is still unclear and can be found in up to 1-2% of the general population. Although these lesions are usually asymptomatic, midgut bleeding from diverticula in the jejunum or ileum could lead to a life-threatening situation, warranting emergency invasive therapy and often abdominal surgery.

Aims and Methods: Our aim was to demonstrate the usefulness of the double-balloon enteroscopy (DBE) in the setting of an acute, severe small bowel diverticular bleed.

A 79-year-old woman with hypertension and type II diabetes mellitus was referred to our institution with melaena and severe anaemia requiring urgent, repeat blood transfusions. Bi-directional conventional endoscopy did not reveal the cause of bleeding. Small bowel capsule endoscopy (SBCE) showed multiple diverticula within the jejunum and ileum. Emergency computed tomography (CT) mesenteric angiography demonstrated a faint 'blush' at one of the jejunal lesions.

Results: Once the patient was haemodynamically stable, emergency anterograde DBE was performed under general anaesthesia (GA) in our main operating theatres. The enteroscope was inserted into the jejunum, approximately 1.5 meters post-pylorus. The culprit cause of the bleeding was identified within a large (5cm orifice) diverticulum, where a large, adherent, pulsating blood clot was seen. In the first instance, peri-lesion, quadrantic injection of a total of 20mLs of adrenaline solution (1 in 10,000 dilution) was performed. The clot was then cautiously removed with a long endoclip to reveal the actively bleeding vessel which was then promptly clipped. A total of 3 clips were placed for effective haemostasis and a submucosal tattoo was placed adjacent to the bleeding point for future reference. The patient remained stable after the procedure and did not require any further blood transfusion.

Conclusion: DBE facilitated endotherapy is a precise, safe and minimally invasive approach to the effective management of severe bleeding caused by small bowel diverticula.

Disclosure: Dr Despott receives research support from Aquilant Medical and Fujifilm. Dr. Hayashi has received honoraria from Fujifilm Corp. All other authors disclosed no financial relationships relevant to this publication.

VC03 FIRST REPORT OF A COMBINED RESECTION TECHNIQUE USING A NOVEL NON-THERMAL, AUTOMATED MECHANICAL RESECTION SYSTEM OF A GIANT, FIBROTIC, CIRCUMFERENTIAL LESION INVOLVING THE WHOLE DUODENAL BULB (WITH VIDEO)

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Introduction: Incidental duodenal non-ampullary lesions are found at upper gastrointestinal (GI) endoscopy in 1-5% of cases. Endoscopic resection of duodenal lesions carries a higher risk of bleeding due to the rich vascularity and exposure to bile and pancreatic enzymes. The risk of perforation is also intrinsically increased due to thin nature of the duodenal wall. In addition, endoscopic resection of fibrotic duodenal lesions can be extremely challenging (even in expert hands) and carries high failure and complication rates, often warranting extensive surgical management. To date, there is no widely accepted optimal management strategy for duodenal lesions and conservative management with endoscopic surveillance is frequently adopted. Although at diagnosis, duodenal adenomas are most often benign, they retain an intrinsic risk of malignant transformation.

Aims and Methods: Our aim was to use a novel, combined endoscopic approach for the management of an otherwise unresectable giant, fibrotic, circumferential lesion involving the whole duodenal bulb.
A 72-year-old woman with hypertension presented with anaemia and melaena. An upper GI endoscopy revealed a 7cm circumferential lesion (Paris 0-IIa, 0-IIb) laterally spreading tumour (LST) involving the entire duodenal bulb. Histolopathological analysis of biopsies taken at another institution, were in keeping with a tubulovillous adenoma with low-grade dysplasia. Invasion of the muscularis propria was excluded by endoscopic ultrasound (EUS).

Results: A first resection attempt through a combination of wide-field endoscopic mucosal resection (EMR) and saline-immersion therapeutic endoscopy (SITE) hybrid-EMR techniques allowed only resection of less that 10% of the lesion, due to severe fibrosis. Delayed bleeding 24 hours post-resection was successfully treated endoscopically. 6 weeks later, a planned second attempt at endoscopic resection was performed under general anaesthesia. The lesion was initially injected with adrenaline solution (1 in 10,000 dilution). A combination of the use of a novel, non-thermal, automated-mechanical-suction-resection system with cold snaring allowed us to achieve 50% resection of the lesion in less than 2 hours. Mild, self-limiting, intra-procedural oozing did not require further endotherapy and no major immediate or delayed adverse events occurred. Completion of the resection using the same technique is planned to be performed shortly.

Conclusion: To the best of our knowledge, this is the first report of a resection technique using a novel non-thermal, automated-mechanical-suction-resection system for a giant duodenal adenoma. In our opinion, this novel salvage endoscopic technique appears to be a safe and effective, minimally invasive alternative to major surgery and warrants further study.

Disclosure: Dr Despott receives research support from Aquilant Medical and Fujifilm. Dr. Hayashi has received honoraria from Fujifilm Corp. All other authors disclosed no financial relationships relevant to this publication.

VC04 UNDERWATER PANCREATOSCOPY THROUGH THE DUCT OF SANTORINI: DIRECT VISUAL GUIDED BIOPSIES OF AN INTESTINAL-TYPE IPMN

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Introduction: Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are potentially malignant intraductal epithelial neoplasms that are grossly visible and are composed of mucin-producing columnar cells. The lesions show papillary proliferation, cyst formation, and varying degrees of cellular atypia [1,2]. IPMNs may involve the main pancreatic duct and/or the branch ducts, carring a risk of malignancy from 15%-60% [3]. The approach to the diagnosis of pancreatic cystic neoplasms typically starts with cross-sectional imaging as abdominal MRI or CT-scan [4]. Endoscopic ultrasound with fine-needle aspiration aid to confirm a diagnosis or to assess for malignant features. Pancreatoscopy and intraductal ultrasonography can lead to the final diagnosis [5]

Aims and Methods: We present an interesting case of an IPMN diagnosis through peroral Santoriniscopy with target biopsies.

Results: A 72 year-old male was admitted due to severe abdominal pain. The laboratory work-up reveled high levels of bilirubin, gamma-glutamyl transpeptidase and alkaline phosphatase. An abdominal MRI revealed a suspect IPMN with significant ectasia of both the main and the branch pancreatic ducts. Endoscopic ultrasound confirmed the suspect of IPMN showing a significant amount of mucus trough the minor papilla. A peroral Santoriniscopy using the SpyGlass System (Boston Scientific, Massachusetts, USA) showed a frond-like projections from the epithelial lining and biopsies were taken using SpyBite forceps (Boston Scientific, Massachusetts, USA). Histology of the intraductal

biopsies demonstrated severely atypical cells compatible with the diagnosis of malignancy. The patient was subsequently referred to the surgical oncology department and underwent a total pancreatectomy. Final pathology demonstrated an intestinal-type IPMN with associated invasive colloid carcinoma, rich in mucin. All lymph nodes were negative for malignancy.

Conclusion: Spyglass pancreatoscopy can allow direct endoscopic visualization of the pancreatobiliary ducts, and ductal lesions can be directly biopsied. In our case, the pancreatoscopy, allowed the diagnosis to be made before progression to invasive cancer and the subsequent surgery.

Disclosure: Nothing to disclose

References

1. Longnecker DS, Adsay NV, Fernandez-del Castillo C, et al. Histopathological diagnosis of pancreatic intraepithelial neoplasia and intraducta papillary-mucinous neoplasms: interobserver agreement. *Pancreas* 2005; 31: 344–349.
2. Hruban RH, Takaori K, Klimstra DS, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *AM J Surg Pathol* 2004; 28: 977–987.
3. Tanaka M, Fernandez-del castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology*. 2012; 12: 183–197.
4. Wakabayashi T, Kawaura Y, Morimoto H, et al. Clinical management of intraductal papillary mucinous tumors of the pancreas based on imaging findings. *Pancreas* 2001; 22: 370–377.
5. Arnelo U, Siiki A, Swahn F, et al. Single-operator pancreatoscopy in helpful in the evaluation of suspected intraductal papillary mucinous neoplasm (IPMN). *Pancreatology* 2014; 14: 510–514.

VC05 ENDOSCOPIC TREATMENT OF A DIVERTICULAR OESOPHAGEAL DUPLICATION

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Introduction: Oesophageal duplications, accounts for 15% of all digestive tract duplications. They are rare congenital malformations, presenting as cystic, tubular or diverticular, which is the rarest of the 3.
Oesophageal duplications can remain asymptomatic for decades, and clinical manifestations can occur at any moment.

Aims and Methods: We present the case of a 24-year-old man with an oesophageal duplication, who received successful endoscopic treatment.
The young patient, with mental retardation, had a history of dysphagia since the childhood. Dysphagia worsened recently, and was associated with regurgitation and abdominal pain. For this reason, he underwent barium oesophagram and esophagogastroduodenoscopy (EGD) that showed a paraesophageal diverticulum, on the right side of the mid oesophagus, suggestive for diverticular oesophageal duplication.
Open surgery was attempted in another centre, but eventually the diverticulum was not excised, being the resection considered too dangerous.
The patient was thus referred to our Unit.
Preliminary EGD confirmed the presence of a diverticulum of the middle tract of the oesophagus, extended for 70 mm, and starting at 35 cm from the upper incisors. A cap-assisted septotomy was performed, similarly to the treatment usually deserved to Zenker's diverticulum. The endoscopic procedure was done with the patient supine, under general anaesthesia with endotracheal intubation. The septum between the original oesophageal lumen and the diverticulum was carefully cut with a needle-knife (KD-10Q-11, Olympus, Japan) and Endo-cut current (VIO 300D, ERBE, Tubingen, Germany).
Occasional bleedings at the site of incision were stopped by using haemostatic forceps on the visible vessels.
At the end of the procedure, endoscopic clips were placed at the base of incision, to prevent bleeding and perforation.

Results: Post-operative course was uneventful. A water-soluble contrast study on first post-operative day confirmed the absence of leakages or stasis into the diverticulum. Contrast quickly passed through the oesophagus and the oesophago-gastric junction into the stomach. On second post-operative day the patient started oral feeding and, 2 days later, he was discharged.
1 month after the treatment he is in good clinical conditions, having normal diet, without dysphagia or regurgitation.

Conclusion: To our knowledge, this is the first report of a completely endoscopic treatment of diverticular oesophageal duplication. The procedure was relatively easy and extremely rapid. Recovery after the operation was very quick, with an early oral feeding. This procedure should probably be considered as first line therapy of this rare disorder.

Disclosure: Nothing to disclose

VC06   INTRALUMINAL SUBMUCOSAL MYOTOMY FOR TREATMENT OF MID-OESOPHAGEAL DIVERTICULAE ASSOCIATED WITH OESOPHAGEAL MOTILITY DISORDERS

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Introduction: Thoracic diverticulae can be categorised according to their location; 1) mid-oesophageal, 2) epiphrenic.They are thought to arise either as a result of inflammation or in association with spastic motility disorders such as achalasia. Effective endoscopic therapy for thoracic diverticulae is yet to be described.

Aims and Methods: This video describes 2 cases of the use of a novel technique of intraluminal submucosal myotomy (ISM) for patients with symptomatic epiphrenic diverticulae associated with spastic oesophageal motility disorders.

Results: This video describes 2 cases showing the technique of ISM.

Case: 1–39-year-old female with a 2-year history of worsening dysphagia, chest and regurgitation of food. After a failed surgical diverticulotomy the patient was diagnosed with hypertensive peristalsis on manometry. She initially underwent a POEM procedure with some symptom resolution but developed dysphagia due to stenosis at the site of the diverticulum. An ISM was performed. The patient is symptom free at 6 months.

Case 2: 64-year-old female with a 12-month history of chest pain and regurgitation of food. Manometric assessment confirmed diffuse oesophageal spasm and was found to have a large diverticulum on endoscopic examination. She also underwent a POEM procedure initially and subsequently underwent ISM four weeks later. The patient is symptom free at 4 months.

Conclusion: ISM is an effective and safe new novel technique for treatment of epiphrenic diverticulae associated with spastic oesophageal motility disorders.

Disclosure: Nothing to disclose

References

1. Thomas ML, Anthony AA, Fosh BG, Finch JG, Maddern GJ. Oesophageal diverticula. *Br J Surg*. 2001 May; 88(5): 629–42.
2. D'Ugo D, Cardillo G, Granone P, Coppola R, Margaritora S, Picciocchi A. 2. Esophageal diverticula. Physiopathological basis for surgical management. *Eur J Cardiothorac Surg*. 1992; 6(6): 330–4.

VC07   A COMBINATION OF ENDOSCOPIC TECHNIQUES FOR MANAGEMENT OF BURIED BUMPER SYNDROME

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Introduction: Buried bumper syndrome (BBS) is a rare, long-term complication of percutaneous endoscopic gastrostomy (PEG) placement, occurring in 2-6% of cases. BBS is thought to occur due to prolonged compression of the tissue between the external and internal fixators, leading to 'burying' of the PEG bumper into the gastric wall. Consequences of BBS include tube obstruction and more rarely bleeding, abscess formation, and perforation. Several endoscopic techniques are described for the management of BBS and these may be complimentary when used in combination.

Aims and Methods: A 32-year-old woman with diabetes, chronic kidney disease, a history of hypoglycaemic brain injury and gastroparesis, requiring a venting PEG, presented with abdominal pain. PEG tube obstruction led to the suspicion of BBS and abdominal computerised tomography confirmed this.

Results: At upper gastrointestinal endoscopy under general anaesthesia, the internal bumper was found to be completely buried by granulation and fibrotic tissue. A 2.5mm ball-tip, needle-type, irrigation knife was initially used to partially dissect the overgrown gastric tissue in order to achieve insertion of a biopsy forceps through the external aspect of the PEG tube and through the dissected orifice. This maneuver opened a track in the overgrown tissue for insertion of a sphincterotome mounted on a guide wire through the external PEG tube. The sphincterotome was then flexed completely and several radial incisions on the overgrown tissue were performed using external traction on the sphincterotome. Finally, a 6mm endoscopic balloon dilator was passed through the scope and pulled into the PEG tube by the biopsy forceps inserted through the external end of the tube. The balloon was then fully inflated within the PEG tube and traction was applied to the balloon and endoscope for release of the buried bumper and PEG tube remnant from the dissected overgrown tissue into the stomach. The dissected orifice was then closed using endoscopic clips. The procedure was performed under antibiotic prophylaxis.

Conclusion: To the best of our knowledge, this is the first use of a complementary, multimodality endoscopic approach for the effective, minimally invasive, safe management of BBS.

Disclosure: Dr Despott receives research support from Aquilant Medical and Fujifilm. All other authors disclosed no financial relationships relevant to this publication.

VC08   THE BRIDGING METHOD ASSOCIATED WITH A PERCUTANEOUS DRAINAGE OF THE LATERAL LIVER PART IN THE SAME OPERATIVE TIME

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Introduction: Biliary drainage of hilary complex malignant stenosis of the liver, after Whipple surgery is always challenging. We report a case of biliary drainage with combination of EUS drainage and bridge technique, associated with percutaneous drainage.

Aims and Methods: A 73-year-old man had undergone a pancreaticoduodenectomy for an ampullary degenerative tumour. He later developed liver metastases and begun chemotherapy. Finally he suffered from jaundice because of a recurrence in the biliary digestive anastomosis. A 4-step drainage was carried in our institution. The first one consisted of a transgastric EUS-guided puncture of the left-side bile duct with a 19-gauge needle (EchoTip® Ultra 19-A, Cook Medical). Then, the second step was the insertion of a 0.035–inch guidewire, which was positioned in the right biliary tree (Segment VII and VIII) crossing the bile bifurcation. After crossing the hilum with a 6-Fr cystotome (Endo-Flex® company, Voerde, Germany), and a dilation with a 4-mm balloon, a non-covered self-expandable metal stent (Wallflex[TM] Biliary stent, Boston Scientific) placed communicating the right and left biliary ducts. Finally, the third step was to perform hepaticogastrostomy, inserting a second stent (GIOBOR[TM] Biliary Stent, Taewoong Medical), partially covered, from the left biliary duct, to the stomach. The fourth step was to carry out a puncture with a Neff needle because of an absence of lateral liver drainage; a guidewire was, then, inserted in the bile duct to jejunal limb. This was then replaced by an Amplatz (after insertion of a catheter) and dilated with a 6-mm biliary balloon. An 8-mm biliary stent (Zilver® Self-Expending Stent, Cook Medical) was placed into the jejunal limb. An 8,5-Fr external drain was left in place for 4 days.

Results: No biliary complication occurred and the patient could have chemotherapy again. He died 4 months later due to progression of the disease.

Conclusion: The bridge technique performed by EUS, associated in the same session to percutaneous drainage can be an alternative, to drain complex hilary malignant stenosis.

Disclosure: Nothing to disclose

VC09   A CASE OF A BILIARY CAST SYNDROME MIMICKING INTRAHEPATIC CHOLANGIOCARCINOMA

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Introduction: Biliary cast syndrome (BCS) is an uncommon complication described in orthotopic liver transplant recipient characterized by molded intrabiliary black material and secondary biliary obstruction. Cholangiographic features of BCS are poorly known by endoscopists and hepatologists.

Aims and Methods: We describe here a particular presentation of BCS in which the follow-up gave the diagnosis.

We report a video-illustrated case of a BCS and its endoscopic management.

Results: A 56-year-old male with a history of hypertension and liver transplantation for hepatocarcinoma with cirrhosis of mixed origin (Hepatitis C and alcohol) 10 years ago, presented with cholestasis associated to a 16mm lesion suspended in the VIII biliary segment. An endoscopic retrograde cholangiopancreatography (ERCP) allowed to extract lithiasis fragments after biliary sphincterotomy and to brush segment VIII for cytology sampling, which was negative for cholangiocarcinoma. An Echoendoscopy (EUS) with Fine needle aspiration (FNA) disclosed inflammatory tissue with no neoplastic cells. Knowing the negative balance and the general condition of the patient, decision was made to follow the patient by magnetic resonance cholangiopancreatography (MRCP). A discrete increase in the size of segment VIII lesions and changes in its characteristics on the MRCP made 6 months later led to the decision to perform a cholangioscopy to obtain histological evidence before a possible surgical treatment. The cholangioscopic picture was in favour of intrahepatic biliary neoplasia (villous aspect of the mucosa) with upstream intrahepatic black stone. Several biopsies done under direct visualization was performed and showed chronic cholangiopathy with no sign of associated malignancy.

Due to all the previous negative results and the good condition of the patient, the decision was taken not to resect the lesion and to follow him by MRCP every 6 months.

After 2 years, he developed a septic cholangitis episode and increased cholestasis. MRCP showed necrotic saccular dilatation of the right intrahepatic bile duct at the former segment VIII lesion site, associated with distal migration of material at the choledoco-choledochal anastomosis. By ERCP, we obtained complete removal of the material which was compatible with cast in 2 sessions, with temporary plastic stents placement to ensure optimal biliary drainage in between. The evolution of the patient was rapidly favorable both clinically and biologically. At 3 months of follow-up, there was no recurrence of cholangitis or cholestasis.

Conclusion: This case illustrates a rare presentation of tardive intrahepatic BCS initially mimicking an intrahepatic cholangiocarcinoma 10 years after liver transplantation. The follow-up of the patient gave the clue, and highlights ERCP management of BCS

Disclosure: Nothing to disclose

VC10   RECTAL BAND LIGATION FOR THE TREATMENT OF RADIATION PROCTITIS (WITH VIDEO)

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Introduction: Radiation proctitis (RP) is a complication occurring in 5% to 20% of patients undergoing pelvic radiotherapy (RT). Argon Plasma Coagulation (APC) is the endoscopic treatment of choice for CRP, as it is considered to be effective and well-tolerated.

Aims and Methods: 3 patients (74, 82 and 60 yrs) with a history of pelvic neoplasia underwent lower endoscopy that showed presence of haemorrhagic chronic radiation proctitis (RP). All 3 patients received treatment with rectal band ligation (RBL). We report 3 cases of patients with a history of pelvic neoplasia who developed RP following RT, who have been successfully treated with rectal band ligation (RBL).

Results: The procedures were well tolerated and no pain was referred during the RBL nor during the following days. 1 patient presented tenesmus, resolved by conservative treatment with topical drugs. During follow-up the 3 patients were asymptomatic and not further episodes of rectorrhagia were reported.

Conclusion: RBL is effective, safe and fast, and offers an alternative treatment for radiation proctitis, especially in the case of extensive disease.

Disclosure: Nothing to disclose

WEDNESDAY, OCTOBER 24, 2018   08:30–10:00
New insights in the diagnosis of pancreatic cyst lesions – Room F1

OP267   EFFECT OF ASPIRIN, ACE INHIBITORS/SARTANS AND STATINS USE ON THE PROGRESSION OF BD-IPMN IN FOLLOW UP: A MULTICENTER STUDY

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Introduction: Aspirin (ASA), Ace Inibitors/Sartans (ACEI/ARB) and Statins (STAT) inhibit tumoral growth in several clinical and preclinical models, including pancreatic cancer (PDAC). These drugs might, therefore, slow the progression of PDAC precursor lesions, such as IPMNs, but this has been poorly investigated.

Aims and Methods: to evaluate the possible effect of ASA, ACEI/ARB and STAT used for cardiovascular prevention on the progression of BD-IPMN in follow-up (FU).
Multicenter, retrospective study on a cohort of BD-IPMN without indication for surgery (asymptomatic, no mural nodules, main pancreatic duct (MPD) diameter < 5 mm, cyst diameter < 4 cm) undergoing radiological follow up according to current guidelines. Clinical and radiological characteristics were collected and the possible association between the use the drugs of interest and progression analyzed. Progression was defined as dimensional if cyst size increased > 2 mm or new cysts appeared and clinically relevant if changes representing an absolute or relative indication for surgery appeared. Users and non-users of the drugs of interest were compared.

Results: From 878 IPMN patients from a multicenter prospectively collected database, 517 patients (2002-2017), fulfilled criteria for inclusion: 58.8% from Karolinska University Hospital, 17.3% from San Raffaele Scientific Institute and 23.9% from Sant'Andrea Hospital. Mean age was 65.8 years (64.8–66.8), 37.9% were male; the mean cyst diameter at start of FU was 17.2 mm (16.5–18.1). 53.6% underwent progression during a mean FU of 39 months, 50.1% dimensional, 3% clinically relevant progression.
The rate of dimensional (52.2% vs 49.2%; p = 0.5) and of clinically relevant progression (2.5% vs 4.0%; p = 0.4) were not different among ASA users and no-users The same outcome was shown for patients treated with STAT, compared to untreated patients (respectively 47.4% vs 51.5%, p = 0.3; 2.6% vs 3.9%, p = 0.4), for patients who had been treated with ACE/ARB compared to patients who hadn't, (52.5% vs 48.9%, p = 0.4; 4.9% vs 2.6%, p = 0.1), and for patients who had been treated with a combination of the 3 drugs compared to untreated ones (respectively 47.5% vs 50.4%, p = 0.6; 1.7% vs 3.5%, p = 0.4).

Conclusion: The use of ASA, ACEI/ARB and STAT is not associated with statistically significant lower rate of progression in BD-IPMN during FU. Further analyses for subgroups of patients, cyst features and drugs dosage or length of use are ongoing.

Disclosure: Abstract previously presented at the EPC meeting

OP268   REDUCING PANCREATIC CYST SURVEILLANCE: DEVELOPMENT OF THE DUTCH AMERICAN RISK STRATIFICATION TOOL (DART-I) TO IDENTIFY IPMN WITH LOW RISK TO PROGRESS AND FULFILL RESECTION CRITERIA

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Introduction: Neoplastic pancreatic cystic lesions are discovered with increasing frequency, with the most prevalent being the intraductal papillary mucinous neoplasm (IPMN). Most IPMNs will never evolve into malignancy, but because risk stratifying tools are lacking, the majority of cysts currently undergo redundant lifelong surveillance.

Aims and Methods: We aimed to develop a score chart to identify IPMN with low risk to progress and fulfill the resection criteria according to the 2012 international Fukuoka guidelines. We retrospectively reviewed the prospectively-maintained databases of three international academic institutions, containing patients with a pancreatic cystic lesion identified in the period 2003-2013. Patients were included if they had a presumed IPMN on imaging, without worrisome features or high-risk stigmata at baseline, as defined by the 2012 international Fukuoka guidelines, and were followed ≥12 months. Fulfilling resection criteria was

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Abstract No: OP268
Table 1: Patient and cyst characteristics and final multivariable logistic regression model.

	Total (N = 876)	No progression (n = 760)	Progression (n = 116)	Coefficient	Hazard ratio (95% CI)	P-value
Center, Erasmus UMC	80 (9.1)	66 (8.7)	14 (12.1)	–	–	–
Columbia UMC	483 (55.1)	410 (53.9)	73 (62.9)	–	–	–
Mayo Clinic	313 (35.7)	284 (37.4)	29 (25)	–	–	–
Age, mean (SD), y	66 (11.2)	65 (10.9)	67 (12.8)	NA	NA	NA
Male gender	322 (36.8)	272 (35.8)	50 (43.1)	–	–	–
Diabetes mellitus	192 (21.9)	158 (20.8)	34 (29.3)	NA	NA	NA
BMI, mean (SD)	27 (4.9)	27 (4.8)	27 (5.3)	NA	NA	NA
Smoking ever	343 (39.2)	289 (38.0)	54 (46.6)	0.3308	1.39 (0.96-2.02)	0.082
Alcohol ever	373 (42.6)	320 (42.1)	53 (45.7)	–	–	–
Location dominant cyst, Head	381 (43.5)	329 (43.3)	52 (44.8)	–	–	–
Body	313 (35.7)	274 (36.1)	39 (33.6)	–	–	–
Tail	179 (20.4)	154 (20.3)	25 (21.6)	–	–	–
Multifocality	336 (38.4)	281 (37.0)	55 (47.4)	0.3930	1.48 (1.01-2.17)	< 0.001
Largest diameter, mean (SD), mm	12 (6.4)	11 (5.9)	17 (6.7)	0.1095	1.12 (1.08-1.15)	0.043

Values presented as n (%) unless otherwise indicated; NA, not available because not part of final prediction model

defined as developing any of the following: jaundice, an enhancing solid component, main pancreatic duct ≥5 mm, cyst size ≥3 cm, non-enhancing mural nodule, abrupt change in caliber of pancreatic duct with distal pancreatic atrophy, and cytology suspect or positive for malignancy.

We developed a multivariable prediction model using Cox-proportional hazard regression analysis with stepwise backward selection. An internal-external validation was performed within the subcohort of each of the three participating centers. The Dutch American Risk stratification Tool (DART-I) was developed to identify patients with low risk to progress and fulfill the resection criteria.

Results: A total of 876 patients with presumed IPMN were included (mean age 66 years, 37% male, 74% Caucasian). After a mean follow-up of 50 months (range 12-157) and a total follow-up of 3,651 person-years, 116 patients progressed to fulfill resection criteria. Age, history of diabetes, BMI, smoking, cyst size, and cyst multifocality were analyzed as predictors. The final model included cyst size (HR 1.12, 95% CI 1.08–1.15), cyst multifocality (HR 1.48, 95% CI 1.01–2.17), and smoking (1.39, 95% CI 0.96–2.02) and had a moderate discriminative ability. The C-statistics in the respective subcohorts were 0.691 (Columbia UMC), 0.718 (Mayo Clinic), and 0.6115 (Erasmus UMC). When using the DART-I, a patient with unifocal IPMN < 10 mm and without a history of smoking has a predicted 3-year risk of 1-2% and 5-year risk of 2-5% to progress and fulfill resection criteria.

Conclusion: In radiologically presumed IPMNs without worrisome features or high-risk stigmata, the DART-I score chart successfully identifies lesions with low risk to progress and fulfill resection criteria. When validated, this model may be used to explore strategies that will reduce unnecessary surveillance.

Disclosure: Nothing to disclose

WEDNESDAY, OCTOBER 24, 2018   08:30–10:00
Management of superficial gastric cancer – Room F2_____

OP269   ATROPHIC GASTRITIS IN ALL-CAUSE UPPER GASTROINTESTINAL ENDOSCOPY AT A TERTIARY ENDOSCOPIC CENTER: SEVERITY ACCORDING TO THE OLGA STAGING SYSTEM

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Introduction: Chronic atrophic gastritis (CAG), especially when extensive, *H. pylori*-related and intestinal metaplasia-associated, is a recognized precursor of gastric cancer. Although generally distinguished between *H. pylori*- and auto-immune-induced, the first associated with intestinal gastric cancer (GC) and the latter also with carcinoid tumors, there is epidemiological evidence that autoimmunity, with development of anti-parietal cell antibodies (APCA) may be triggered by *H. pylori* infection.

Aims and Methods: The aim of the present study was to establish the incidence of CAG, the frequency of this condition in different age groups, and to explore the distribution and severity of gastric lesions as classified according to the Operative link for gastritis assessment (OLGA system).

Records of all esophago-gastroduodenoscopies performed for all causes at our Endoscopy unit between January 2015 and January 2018 were retrieved. At our center, the performance of mucosal biopsies according to the Sydney protocol (2 samples from the antrum, 1 sample from the incisura angularis, and 2 samples from gastric body), constitutes the standard practice, and since 2015, all cases are uniformly reported using the OLGA system, which grades the GC risk according to both the topography and the severity of gastric atrophy. For the purposes of the study, repeat endoscopy, age below 18 years and previous esophageal or gastric surgery, esophagogastric endomucosal resection or sub-mucosal dissection were excluded.

Results: A total of 3650 (F = 2133, mean age = 58.5 ± 16.4) were included in the study. OLGA stages 0, I, II, III, and IV were respectively found in 69.8%, 21.1%, 6.8 % 2.1%, and 0.2%. In particular, atrophy limited to the antrum (A1/A2/A3 C0), to the body (A0 C1/C2/C3), or affecting both antrum and body (all grades of A and C) were 793, 152, and 149, respectively. Enterochromafin cell hyperplasia, was found in 52/152 and in 31/149 patients with atrophy of the body of both antrum and body, respectively, while they were absent in patients with antrum atrophy only. Overall prevalence of *H. pylori* infection was 16.3%; of 594 patients in whom *H. pylori* infection was documented, 61.6% had no atrophy, whereas atrophy of the antrum only was significantly more frequent (29.5%) than mixed body and antrum atrophy as well as atrophy of the body only (5.6% and 3.4%, respectively; p < 0.001). Overall, gastric cancer was diagnosed in 15/3650 (0.4%) patients, 14 cases of adenocarcinoma and carcinoid tumor in 1. Tumor cases arose in patients without atrophy, with atrophy of the antrum only, with atrophy of the body only, and with mixed antrum and body atrophy in 7 (0.3%), 5 (0.6%), 2 (2.3%), and 1 (0.6%), respectively.

Conclusion: The overall low prevalence of *H. pylori* infection observed is in correspondence with a large group of patients with no atrophy, which probably represents early diagnosis and eradication of infection in our population, before more advanced stages of atrophy ensue. Survelliance endoscopy is warranted in more severe stages of CAG, although gastric cancer in the absence of CAG reflects the importance of other pathways leading to neoplasm development.

Disclosure: Nothing to disclose

OP270   IN ATROPHIC GASTRITIS 3-YEARS ENDOSCOPIC SURVEILLANCE ACCORDING TO MAPS (MANAGEMENT OF PRECANCEROUS CONDITIONS AND LESIONS IN THE STOMACH) GUIDELINES SEEMS SATISFACTORY TO EARLY DETECT POTENTIAL NEOPLASTIC LESIONS

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Introduction: Atrophic gastritis (AG) is associated with gastric cancer (GC) and type I gastric carcinoid (TIGC). Current European MAPS guidelines (1), recommend for AG patients with extensive atrophy and/or intestinal metaplasia endoscopic follow-up every 3-years after diagnosis. OLGA/OLGIM (operative link on gastric atrophy/metaplasia) assessment was proposed for staging of gastritis and stratifying neoplastic risk (2,3). Prospective studies evaluating whether 3-years follow-up interval is appropriate in terms of early detection of gastric neoplastic lesions are lacking.

Aims and Methods: This study aimed to evaluate the occurrence of gastric neoplastic and preneoplastic lesions and changes of OLGA/OLGIM scores in AG patients at 3-years endoscopic-histological follow-up.

A total of 80 consecutive, newly diagnosed AG patients (77.5% F, median age 64.5 (29-87) years) followed-up 3 years after diagnosis were included. Each patient underwent gastroscopy with biopsies (Sydney System) at baseline and at 3-years follow-up. Among them, 25 (31.1%) were cured from *H. pylori*. At baseline OLGA scores 0, I, II, III, IV were observed in 0, 9 (11.3%), 58 (72.5%), 10 (12.5%), 3 (3.7%) patients, respectively; OLGIM scores 0, I, II, III, IV were observed in 11 (13.8%), 22 (27.5%), 43 (53.7%), 4 (5%), 0 patients, respectively.

Extensive atrophy/intestinal metaplasia was present in 21 (26.3%) patients. At baseline 7 (8.7%) patients presented polypoid neoplastic lesions, all removed by snare polypectomy: 3 low-grade dysplasia (LGD) adenomas and 4 TIGC. The number of gastroscopies needed to be performed (NNS) to detect 1 case of gastric neoplastic lesion was expressed as the number of 3-years surveillance endoscopies by the number of detected neoplastic lesions.

Results: At 3-years follow-up overall 6 (7.5%) neoplastic lesions were detected: 2 (2.5%) LGD adenomas in 2 patients, 4 (5%) carcinoids in 4 patients (in 2 of them recurrent), no GC. The NNS was 13.3.

OLGA and OLGIM scores were unchanged, increased and decreased in 58 (72.5%) and 49 (61.2%), 9 (11.3%) and 15 (18.8%), and 13 (16.2%) and 16 (20%) patients, respectively.

The occurrence of gastric neoplastic lesions in patients with or without extensive atrophy/intestinal metaplasia was not different (p = 0.943 by chi-square test). When only the 21 (26.3%) patients with extensive atrophy/intestinal metaplasia at baseline would have been considered eligible for surveillance, at 3-years follow-up only 1 LGD adenoma would have been detected, as the other neoplastic lesions 4 TIGC and the other LGD adenoma occurred in patients without extensive atrophy/intestinal metaplasia at baseline.

Conclusion: In AG patients, the 3-years endoscopic surveillance as proposed by MAPS seems satisfactory to early detect potential gastric neoplastic lesions. An increase of OLGA/OLGIM scores is observed in a low proportion of patients (10% and 18%). Extensive atrophy/intestinal metaplasia as eligibility criteria to offer surveillance in AG patients may be restrictive.

Disclosure: Nothing to disclose

References

1. Dinis-Ribeiro M, et al. *Endoscopy* 2012; 44: 74–94.
2. Capelle LG, et al. *Gastrointest Endosc.* 2010; 71: 1150–8.
3. Rugge M, et al. *World J Gastroenterol* 2011 Nov 7; 17(41): 4596–601.

OP271   CLINICAL OUTCOMES OF EARLY GASTRIC CANCER BEYOND EXPANDED CRITERIA AFTER ENDOSCOPIC RESECTION

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Introduction: We aimed to determine the clinical outcomes of early gastric cancer (EGC) beyond expanded criteria after endoscopic resection according to the pathological extent.

Aims and Methods: A total of 288 patients with 289 lesions beyond expanded criteria of endoscopic submucosal dissection (ESD) for EGC were analyzed between 2005 and 2016, and classified into 2 groups according to additional treatment; observation (n = 175 patients, 175 lesions) and surgery (n = 113 patients, 114 lesions).

Results: Depth of tumor invasion was deeper, and tumor-positive vertical margin, lymphatic and venous invasion were more common in the surgery group compared with the observation group (p < 0.001). Residual, synchronous and metachronous tumor were more common in the observation group, but regional

lymph node (LN) and distant metastasis did not differ between the groups. Overall survival (OS) and 5-year disease-specific survival did not differ between the groups (88.6 vs 93.8%; p = 0.259, 98.2 vs 100%; p = 0.484), but 5-year disease-free survival was lower in the observation group (73.5 vs 97.9%; p < 0.001). On multivariate analysis, presence of ulcer, large tumor size, tumor-positive lateral and vertical margin were risk factors of residual tumor over T2 and lymphatic and venous invasion were risk factors of regional LN metastasis.

Conclusion: In patients with the pathology beyond expanded criteria of ESD for EGC with ulcer, large tumor size, tumor-positive lateral and vertical margin, lymphatic and venous invasion, additional surgical resection should be considered for the risk of residual tumor or LN metastasis.

Disclosure: Nothing to disclose

OP272   LOWER RISK OF ATROPHIC GASTRITIS IN MALT LYMPHOMA DESPITE H. PYLORI INFECTION

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Introduction: Atrophic gastritis and intestinal metaplasia are sequential consequences of chronic *H. pylori* infection. *H. pylori* infection is a well-known risk factor for gastric adenocarcinoma and MALT lymphoma of the stomach. Atrophic gastritis and intestinal metaplasia increase the risk of gastric adenocarcinoma development. The relationship between gastric MALT lymphoma and atrophic gastritis-intestinal metaplasia has not been on the spot of interest. We here investigated the clinical characteristics of gastric MALT lymphoma and co-presence of atrophic gastritis and intestinal metaplasia.

Aims and Methods: Study was conducted by review of the electronic medical record of patients who were diagnosed with gastric MALT lymphoma at an academic institute, the Yeouido St. Mary's Hospital, Seoul, Korea, from January 2001 to Mar 2018. Clinical characteristics and pathologic backgrounds including *H. pylori* infection positivity, atrophic gastritis and intestinal metaplasia were investigated.

Results: A total of 47 subjects were enrolled consecutively during the study period and analyzed retrospectively. The mean age was 57.19–year-old (range 36 ∼ 85). The male to female ratio was 1.19 (25/21). Endoscopic appearances varied; thirteen subjects presented ulcerative mass (28.26%), 12 (26.09%) flat atrophic patch of discoloration, 16 (34.78%) erosive patches, 2 (4.35%) multiple polypoid lesions and 3 (6.52%) subepithelial tumor-like appearance. *H. pylori* infection was proved in 82.6 % (38/46). On histologic examination, background atrophic gastritis-intestinal metaplasia was accompanied by 28.26% (13/46). Serum pepsinogen I and II, as a serological marker for atrophy, was evaluated in 17 subjects. Only 5 of 17 (29.41%) showed compatible with atrophic gastritis (pepsinogen I/II ratio of less than 3).

Conclusion: The background mucosa of gastric MALT lymphoma differs from that of gastric adenocarcinoma in terms of atrophic gastritis-intestinal metaplasia. Less than 30% of gastric MALT lymphoma accompanied background atrophic gastritis. Age can be a confounding factor. We will precede the age-matched comparison between patients with gastric adenocarcinoma and MALT lymphoma.

Disclosure: Nothing to disclose

WEDNESDAY, OCTOBER 24, 2018   08:30–10:00
The broad spectrum of IBD management – Room G_____

OP273   EARLY VERSUS LATE INTERVENTION WITH ANTI-TNFα-ANTIBODIES IN CROHN'S DISEASE: EFFECT ON MUCOSAL HEALING, DEVELOPMENT OF STRICTURES AND NEED FOR RESECTIVE SURGERY. A RETROSPECTIVE COHORT ANALYSIS

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Introduction: Anti-TNFα-antibody therapy is one of the most potent treatments in Crohn's disease (CD) for active disease as well as in maintenance therapy, and it might alter the course of disease by preventing irreversible bowel damage and further associated complications. Therefore, since its introduction, anti-TNFα-antibodies (TNF-inhibitors) have been used by gastroenterologists progressively earlier in the course of the disease.

Aims and Methods: We aimed to assess the effect of early intervention of TNF-inhibitors in CD patients of the Munich IBD Center on mucosal healing, clinical remission, development of strictures and need for surgery as compared to late intervention within an observation period of 2 years. Early intervention was defined as introduction of TNF-inhibitors within 24 months after first diagnosis of CD and late intervention was defined as introduction after 24 months. In this retrospective cohort analysis we included data from 242 patients from 2007 to 2015 who had received either infliximab (IFX) or adalimumab (ADA) for at least 2 years. Chi2 and T-tests were used for statistical analysis to assess the rates of

mucosal healing, clinical remission, stricturing disease and need for resective surgery within 2 years after the introduction of TNF-inhibitors. Endoscopic findings of the last ileocolonoscopy before and the first ileocolonoscopy after introduction of TNF-inhibitors provided data on mucosal healing and strictures. Clinical remission was defined as CDAI score of less than 150 points.

Results: 90 patients had received early treatment with TNF-inhibitors and were assigned to the early intervention group: 45.8% received IFX, 10.7% ADA and 43.5% where switched from IFX to ADA or vice versa. 152 patients met criteria for the late intervention group: 60.0% received IFX, 3.8% ADA and 35.7% were switched. Both groups were comparable to sex, genetic susceptibility (NOD2/CARD15), extraintestinal manifestations, presence of bowel strictures and disease activity at the time of introduction. Patients of the early intervention group were younger at start of TNF-inhibitors (26 vs. 32 years; p = 0.001) and more often showed upper GI- manifestations (23% vs. 5%; p < 0.001). The early intervention group had received less corticosteroids (p = 0.014), 5-ASA (p < 0.001), azathioprine (p < 0.001) and methotrexate (p = 0.057).

Within an observation period of 2 years, patients of the early intervention group not only achieved higher mucosal healing rates than patients of the late intervention group (47.5% vs. 25.0%; p = 0.005), they also developed significantly less bowel strictures (10.2% vs. 28.4%; p = 0.008). The combination of absence of mucosal healing and presence of strictures was found significantly more often in the late intervention group (79.5% vs. 53.3%; p = 0.001).

Clinical remission rates 24 months after the introduction of TNF-inhibitors did not differ between the 2 groups. (89.4% vs. 87.9%, p = 0.737).

Within 2 years after introduction, less patients in the early intervention group underwent surgery, however the difference was not significant (17.8% vs. 26.9%, n = 16 vs. n = 41, p = 0,103), possibly due to the small size of the group and the short observation period of only 2 years.

Conclusion: In Crohn's disease, early introduction of TNF-inhibitors within 2 years after diagnosis is associated with higher rates of mucosal healing and lower rates of complications such as bowel strictures when compared to late intervention. It may also reduce the risk of the need for surgery. We conclude that anti-TNFα-antibody therapy could alter the course of disease and prevent irreversible bowel damage.

Disclosure: Thomas Ochsenkühn has received lecture fees, unrestricted travel grants and honoraria for advice from Abbvie, Biogen, Celltrion, Janssen, MSD, Mundiphama, R-Biopharm, Sandoz, Shields, Shire, Stada, and Takeda. Stephanie Howaldt has received lecture fees, unrestricted travel grants and honoraria for advice from Biogen, Janssen, MSD, Mundiphama, Shield, r-Biopharm, Pfizer and Takeda. Fabian Schnitzler has received honoraria from Abbvie and MSD.

OP274   POST-COLONOSCOPY COLORECTAL CANCER RATES IN IBD ARE HIGH AND VARY BY NHS TRUST IN ENGLAND

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Introduction: Colorectal cancer (CRC) risk is increased in those with inflammatory bowel disease (IBD). Guidelines advocate surveillance colonoscopy for patients with longstanding IBD. Post-colonoscopy colorectal cancer (PCCRC) is a key quality indicator of colonoscopy. There is limited data exploring the rate of PCCRC in those with IBD and potential risk factors associated with IBD-related PCCRC.

This study explored national and individual hospital rates of IBD-related PCCRC in England since 2006. Further analysis explored potential associations with IBD-related PCCRC in order to inform future quality improvement interventions.

Aims and Methods: We identified all those who had undergone a colonoscopy between 1/1/2006 and 31/12/2012 and developed a CRC before 31/12/2015 using linked national Hospital Episode Statistics and National Cancer Registration and Analysis Service data. IBD cases were identified by relevant ICD-10 codes. Using international consensus guidelines.[1,2] The rate of PCCRC within 3 years (PCCRC-3yr) was calculated as the number of false negative colonoscopies (within 6-36 months of CRC) divided by the sum of the true positive (within 6 months of CRC) and false negative colonoscopies. The IBD-associated PCCRC-3yr rate in each NHS hospital trust in England was ranked and trusts were separated into quintiles. Factors associated with IBD-related PCCRC were investigated.

Results: Between 2006 and 2012 we identified 7781 PCCRC, 800 (10%) with a diagnosis of IBD. Nationally, the IBD-PCCRC-3yr rate was 35%, and varied between hospital trusts with those in the lowest quintile having a mean, unadjusted rate of 19% (SD +/- 7%) compared to 52% (SD +/- 7%) in the highest

quintile. PCCRC cases were younger at diagnosis (60yrs compared to 66yrs), were less likely to have diverticular disease (10% compared to 16%), and had undergone more previous colonoscopies when compared to detected cases (within 6 months of colonoscopy). There was no significant difference for sex, bowel location, deprivation score, or metachronous tumours.

Conclusion: PCCRC-3yr in those with IBD is high, and accounted for 10% of all PCCRC-3yr in England between 2006 and 2012. There is a wide variation in the unadjusted rates between NHS trusts in England that is unlikely to be explained by natural variation. There is an urgent need to investigate avoidable reasons for cancers in those with IBD to optimise surveillance and prevention of CRC in IBD.

Disclosure: Nothing to disclose

Reference

1. Morris EJA et al. Gut 2014; 64: 1248–56. 2 Beintaris I et al. *UEG J* 2017; 5: PO436.

OP275 VEDOLIZUMAB TROUGH LEVELS AND HISTOLOGICAL HEALING IN ULCERATIVE COLITIS

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Introduction: Histological healing may be the ultimate therapeutic goal in ulcerative colitis (UC). Higher vedolizumab trough levels during induction treatment have been associated with better outcomes in UC patients. The association between vedolizumab trough levels and histological healing during maintenance therapy in UC is unknown.

Aims and Methods: In this single-center, retrospective cohort study, we aimed to investigate the association between vedolizumab trough levels and histological healing during maintenance therapy in UC, and to identify potential factors associated with histological healing. Between June 2014 and March 2018, all consecutive patients with moderate-to-severe UC on vedolizumab maintenance therapy who had a histological evaluation and underwent therapeutic drug monitoring within 3 months of this evaluation, were included. Per event analysis was performed. Histological healing was defined as Nancy histological index $\leq$ 1. Pathologists were blinded to the results of the therapeutic drug monitoring.

Results: 35 histological samples from 31 patients (n = 27 with 1 histological sample; n = 4 with 2 histological samples) were analyzed. Mean (standard deviation) time between histological evaluation and therapeutic drug monitoring was 11.1 (35.1) days. Histological healing was found in 18/35 (51.4%) of assessments (n = 15 with Nancy histologic index of 0; n = 3 with Nancy histological index of 1). Median (interquartile range) serum vedolizumab trough levels were higher in the group with histological healing compared with the group without histological healing (31.5 (25-49.1) µg/mL vs. 15 (9-26.6) µg/mL; p = 0.02). The higher vedolizumab trough levels were associated with higher rates of histological healing (p = 0.04; Table 1). A cut-off vedolizumab trough level of 25 µg/mL predicted histological healing with a sensitivity, specificity, accuracy, positive predictive value and negative predictive value of 77%, 71%, 74%, 74% and 75%, respectively, leading to an area under the receiver operating curve of 0.62 (95% confidence interval 0.58–0.92; p = 0.004). Vedolizumab trough levels higher than 25 µg/mL were associated with histological healing on bivariate analysis (odds ratio 8.4; 95% confidence interval 1.8–38.6; p = 0.006).

Conclusion: This is the first study looking at the association between vedolizumab trough levels and histological healing in UC. Histological healing rates were significantly greater in patients with the highest vedolizumab trough levels during maintenance therapy in UC. A vedolizumab trough level threshold of 25 µg/mL was found most optimal to predict histological healing.

Quartile	Vedolizumab trough level	Number of samples, n	Histological healing (Nancy histological index ≤ 1), n (%)
1	≤8.75	4	1 (25)
2	>8.75 − ≤18.5	9	2 (22.2)
3	>18.5 − ≤33	11	6 (54.5)
4	>33	11	9 (81.8)

[Rates of histological healing by vedolizumab trough level quartiles during maintenance therapy in UC patients.]

Disclosure: Silvio Danese has served as a speaker, a consultant and an advisory board member for Abbvie, Ferring, Hospira, Johnson & Johnson, Merck, Millennium Takeda, Mundipharma, Pfizer, Tigenix, UCB Pharma and Vifor. Laurent Peyrin-Biroulet received consulting fees from Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Pharmacosmos, BMS, UCB-pharma, Hospira, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, Pfizer, HAC-Pharma, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis, and lecture fees from Merck, Abbvie, Takeda, Janssen, Ferring, Norgine, Tillots, Vifor, Mitsubishi, HAC-pharma. The other authors declare no conflicts of interest.

OP276 POSITIVE HISTOLOGIC MARGINS IS A RISK FACTOR OF RECURRENCE AFTER ILEOCAECAL RESECTION IN CROHN'S DISEASE

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Introduction: Surgical resection is not curative in Crohn's disease (CD) and recurrence after surgery is a common situation. The identification of patients at high risk of recurrence remains disappointing in clinical practice. The impact of residual microscopic disease on margins on the risk of recurrence after ileocaecal resection is still subject to debate.

Aims and Methods: All patients who underwent ileocaecal resection between January 1982 and December 2016 were prospectively identified. Demographic data, clinical, surgical and histological variables were retrospectively collected. Positive histologic margin was defined by the presence of acute inflammatory lesions on margins: erosion, ulceration, chorion infiltration by neutrophils poly-nuclears, cryptic abscesses or cryptitis.

Results: 125 patients were included, with a median follow-up of 8 years (Interquartile Range (IQR), 4.3–15.2). Half (49.6%, n = 62) were women, and the median age at surgery was 33 years (24–42). 56 (44.8%) had positive inflammatory margins. Five years after surgery, respectively 29 (51%) and 23 (34%) patients with positive and negative margins had clinical recurrence (p = 0.034). At the end of the follow-up, respectively 60% (n = 34) and 47% (n = 33) patients had clinical recurrence (p = 0.07). CD-related hospitalizations were observed in respectively 37.5% (n = 21) and 18.8% (n = 13) with positive and negative margins (p = 0.02). 14 patients (25%) with positive intestinal margins were reoperated at the end of the follow-up compared to 5 patients (7%) with negative margins (p = 0.04). Multivariate analysis confirmed that positive intestinal margin was independently associated with CD-related hospitalization (Odds Ratio (OR), 2.5 (CI95%, 1.1–5.5), p = 0.03) and surgical recurrence (OR, 4 (95% CI, 1.3–12.5), p = 0.01).

Conclusion: Positive histologic margin, as defined by the presence of erosion, ulceration, chorion infiltration by neutrophils polynuclears, cryptic abscesses or cryptitis, was associated with an increased risk of clinical and surgical recurrence after ileocaecal resection for Crohn's disease.

Disclosure: Nothing to disclose

OP277 EFFECTIVENESS AND SAFETY OF VEDOLIZUMAB IN INFLAMMATORY BOWEL DISEASES

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Introduction: Scarce information on the effectiveness and safety of vedolizumab (VDZ) in inflammatory bowel disease (IBD) in clinical practice is available.

Aims and Methods: We aimed to evaluate the effectiveness and safety of VDZ in IBD. Patients of the ENEIDA registry with active IBD that received VDZ were included. Response was defined based on Harvey-Bradshaw index (HBI) in Crohn's disease (CD) and Partial Mayo Score (PMS) in ulcerative colitis (UC). Variables associated with short-term remission (week 14) were identified by logistic regression analysis. Kaplan-Meier curves and Cox model were used to evaluate the long-term durability of VDZ treatment.

Results: 521 patients were included. 93% of them had been exposed to prior anti-TNF agents. At week 14, 62% had response (47% remission). In the multivariate analysis, CD (vs UC) [Odds ratio (OR) = 0.3, 95% confidence interval (95% CI) = 0.3–0.9], higher C-reactive protein (CRP) (mg/dL) at baseline [OR = 0.9 (95% CI = 0.8–0.9)], previous intestinal resection [OR = 0.4 (95% CI = 0.3–0.9)] and mild (vs severe) disease at baseline [OR = 8 (95% CI = 4-16)] were associated with impaired response to VDZ treatment. 316 patients (62%) had endoscopic assessment at baseline; endoscopic activity was not predictive factor for clinical remission at week 14. 307 patients (achieving at least response after induction) were included in the long-term analysis. 79 patients discontinued VDZ (70% loss of efficacy and 10% partial response) after a median of 13 months; discontinuation rate was 22% per patient-year. The proportion of patients remaining on VDZ was 81% at 12 months, 60% at 24 months and 38% at 36 months. To have CD (vs UC) [Hazard ratio (HR) = 1.8 (95%CI = 1.1–3)] and higher CRP (mg/dL) at week 14 [HR = 1.05 (95%CI = 1.01–1.1)] were predictors of VDZ discontinuation. 94 patients lost response during follow-up (incidence rate 37% per patient-year). CD (vs. UC) [HR = 1.9 (95%CI = 1.2–2.9)] and higher CRP (mg/dL) at week 14 [HR = 1.04 (95%CI = 1.008–1.09)] were significantly associated with loss of response. 7% of patients had adverse events after 527 patient-years of exposure, leading to the treatment discontinuation in 3% of patients (table 1).

Conclusion: Over 60% of IBD patients respond to VDZ treatment, even in a refractory cohort. A relevant proportion of patients discontinue the treatment over time, mainly due to loss of response. CD and disease burden impair both short and long-term response. VDZ seems to be safe in clinical practice.

Adverse events	N	Event rate per 100 patient-years
Infections	14	2.6
Sinopulmonary	6	1.3
Gastrointestinal	3	0.5
Conjunctivitis	1	0.2
Chickenpox	1	0.2
Herpes-zoster reactivation	1	0.2
Osteomyelitis	1	0.2
Otitis	1	0.2
Skin reactions	6	1.3
Infusional reactions	5	0.9
Heart failure	3	0.5
Bowel perforation	2	0.4
Deaths	2	0.4
Dizziness	2	0.4
Headache	2	0.4
Worsening of perianal disease	2	0.4
Arthralgias	1	0.2
Colon cancer	1	0.2
Fever of unknown cause	1	0.2
Neurological symptoms	1	0.2

[Table 1. Adverse events during vedolizumab treatment.]

OP278 CLINICAL RESPONSE TO TREATMENT, DISEASE PHENOTYPE AND SEROLOGY COMBINED ARE STRONG PREDICTORS OF THE NEED FOR SURGERY IN CHILDREN WITH CROHN'S DISEASE TWO YEARS AFTER DIAGNOSIS: RESULTS FROM THE PROSPECTIVE MULTICENTRE GROWTH STUDY

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Introduction: The ability to predict high-risk Crohn's disease (CD) at diagnosis would enable physicians to intensify treatment earlier and only in those at risk of severe outcomes, thus limiting the need for intensification of treatment for

patients at low risk. We attempted to develop a model to detect patients at risk for early surgery, defined as requiring surgery within 2 years from diagnosis.

Aims and Methods: A prospective multicentre inception cohort of newly diagnosed children with CD was established, with progress followed to 2 years post-diagnosis. Phenotypic characteristics, measures of disease severity and inflammation, as well as serological markers were measured at baseline and week 12, and follow-up data were collected at 8, 12, 26, 52, 78, and 104 weeks. Patients undergoing surgery for disease related complications were recorded. Chi-square automatic interaction detection (CHAID) algorithm was used to develop a model with predictors for early surgical complications.

Results: A total of 285 patients had data collected with 31(10.9%) needing surgery within 2 years. Multivariate analysis identified stricturing disease at baseline (OR 5.26, 95% CI 2.02–13.67 (p = 0.001)), and Paediatric Crohn's Disease Activity Index (PCDAI) > 10 (OR 1.03, 95% CI 1.00–1.07 (p = 0.005)), together with low C-reactive protein (CRP) (OR 0.82, 95% CI 0.70–0.98, (p = 0.025)) at week 12 to be key predictors of the risk for surgery within 2 years. Achieving clinical remission by week 12 modulated the risk for surgery even if stricturing disease was present at diagnosis, while immunomodulators only reduced risk for patients that achieved clinical remission. In our CHAID model, a patient without stricturing disease, PCDAI of < 10 at 12 weeks and no immunosuppression therapy has a 0.8% chance of surgery. In contrast, a patient without stricturing disease, PCDAI of > 10 at 12 weeks, and anti-OmpC positive has a 38% risk of surgery at follow-up.

Conclusion: A risk stratified algorithm using PCDAI at 12 weeks, OmpC status, behavioural phenotype and use of immunosuppression, can categorise patients into high and low-risk groups for surgery at follow-up. This data can be incorporated into management plans that personalise treatment strategies soon after diagnosis.

Disclosure: Nothing to disclose

WEDNESDAY, OCTOBER 24, 2018   08:30–10:00
The truth is under the microscope – Room 1.61/1.62_____

OP279 FACTORS ASSOCIATED WITH PATHOLOGICAL COMPLETE RESPONSE AFTER NEOADJUVANT CHEMORADIOTHERAPY IN PATIENTS WITH OESOPHAGEAL CANCER: RESULTS FROM A NATIONWIDE STUDY

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Introduction: Over the last decade neoadjuvant chemoradiotherapy (nCRT), preferably the CROSS regimen (carboplatin/paclitaxel + 41.4 Gy radiotherapy), has become standard of care for resectable oesophageal cancer in The Netherlands. About 20% to 50% of the patients achieve a pathological complete response (pCR) after nCRT. A pCR is associated with improved survival and the role of surgery is questioned in these patients.

Aims and Methods: The aim of this population-based cohort study was to investigate factors associated with pCR after nCRT and surgery.

All oesophageal cancer patients treated with nCRT followed by oesophagectomy in the period 2009-2015 were identified from the Nationwide Netherlands Cancer Registry. Patients with unknown tumour response were excluded. Pathological tumour response was categorized as pCR (ypT0N0) and non-pCR (ypT0N+, ypT1-4N0 and ypT1-4N+). The 3-year survival rates were compared with log-rank analysis. Univariable and multivariable logistic regression models were used to investigate the association between clinicopathological variables and pCR. The effect of chemotherapy schedule and radiotherapy dose on pCR were analysed in a subgroup of patients from whom details on neoadjuvant treatment were available. Multivariable Cox regression on overall survival within the group of patients with pCR was performed.

Results: A total of 3533 patients were included and 841 patients (24%) had a pCR (19% in adenocarcinoma and 41% in squamous cell carcinoma). Patients with pCR had higher 3-year survival rate compared to non-pCR patients (68% vs. 48%, p < 0.001). In the non-pCR group, ypT1-4N+ patients had the lowest 3-year survival rate, followed by ypT0N+ and ypT1-4N0 (respectively, 30%, 52% and 60%, p < 0.001). In multivariable analysis age above 70 years (OR 1.2, 95% CI 1.0–1.5), squamous cell histology (OR 3.0, 95% CI 2.6–3.6), cT1-2 (OR 1.2, 95% CI 1.0–1.5), cN+ (OR 0.74, 95% CI 0.6–0.9) and cNx (OR 0.3, 95% CI 0.1–0.7) were associated with higher or lower chance of pCR. In subgroup analysis (N = 668), completion of the CROSS chemotherapy cycles (complete vs. incomplete, p = 0.86) and radiotherapy dose (41.4 Gy vs. > 41.4 Gy, p = 0.22) were not associated with pCR. Factors inversely associated with overall survival in patients who achieved pCR were: age above 70 years (HR 1.4, 95% CI 1.0–1.7) and less than 10 dissected lymph nodes (HR 1.4, 95% CI 1.1–1.9).

Conclusion: Pathological tumour response is not only determined by treatment-related (e.g. number of dissected lymph nodes) factors, but also by patient-related (e.g. age) and tumour-related (e.g. histology and clinical stage) factors.

Completing recommended chemotherapy and/or radiotherapy schedules was not related to pCR in our series.

Disclosure: Nothing to disclose

OP281 MICROSCOPIC POSITIVE TUMOR MARGIN DOES NOT INCREASE THE RATE OF RECURRENCE IN ENDOSCOPIC RESECTED GASTRIC MESENCHYMAL TUMORS COMPARED TO NEGATIVE TUMOR MARGIN

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Introduction: The endoscopic resection of Gastrointestinal Mesenchymal Tumors (GIMTs) is widely accepted due to its minimal-invasiveness. However, a major concern for endoscopic resection is its high rate of positive microscopic margin which was thought to be related with a higher risk of recurrence. We herein designed this study to examine the impact of R1 endoscopic resection for prognosis of GIMT, featuring a large retrospectively maintained endoscopic resection cohort with long follow up and specimen reevaluation by a single pathologist with expertise on GIMT.

Aims and Methods: This study aimed to find out whether the positive margin affects the recurrence rate of gastric GIMT and the factors associated with positive margin. The patients with gastric GIMTs were recruited in the pretrospectively cohort from January 2008 to December 2013. Indications for endoscopic resection are as follows: (1) GIST or suspected GIST > 2cm in size or < 2cm but with rapid growth or high-risk features (e.g. nuclear atypia, high mitotic rate, heterogeneous echogenicity); (2) non-GIST mesenchymal tumors > 2-3cm in size, with rapid growth or high risk features; (3) symptomatic gastric submucosal lesions; (4) undiagnosed gastric submucosal lesions in young patients for whom the risk of resection might be outweighed by the benefit of avoiding life-long surveillance of these lesions (after careful discussion and informed consent). Clinical and pathological features, endoscopic, and follow-up data were collected and analyzed.

Results: 777 patients were included in the study. All tumors were removed along pseudocapsule without macroscopic residual (ER0) and the median tumor size was 15.2 mm (range 3-100 mm). Pathological evaluation revealed 371(47.7%) gastrointestinal stromal tumors (GISTs). The rate of microscopic R1 resection rate was 47.0% (443/777). On stepwise multivariate analysis, a significantly increased incidence of R1 resection was recorded in the GISTs (OR 11.13, 95% CI 3.00–41.37). In the subgroup analysis of GIST, the univariate analysis revealed that EFTR achieved a higher rate of R0 resection (OR 0.56, 95% CI 0.31–1.00) while it was proved insignificant on stepwise multivariate analysis. Local recurrence occurred in 2 patients during a mean follow-up time of 34.2 months. The recurrence rate of R0 and R1 groups was statistically insignificant (p = 0.841).

Conclusion: Endoscopic resection is a feasible option for the resection of gastric GIMT and has minimal risk of recurrence after a mean follow-up of 34.2 months. The rate of R1 resection is high but is not related to a high rate of recurrence compared to R0 resection. The ER0 resection is sufficient for gastric GIMT.

Disclosure: Nothing to disclose

OP282 RISK STRATIFICATION OF SYMPTOMATIC PATIENTS SUSPECTED OF COLORECTAL CANCER USING FAECAL BIOMARKERS (FAECAL IMMUNOCHEMICAL TEST AND FAECAL CALPROTECTIN) AND URINARY VOLATILE ORGANIC COMPOUNDS

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Introduction: Colorectal cancer (CRC) is the second most common cause of cancer-related deaths. Clinical presentation varies with an overlap with benign colorectal pathologies. Hence the dilemma for the clinician is to distinguish those with significant versus non-significant pathology without recourse to invasive and costly investigations.

Aims and Methods: We undertook a diagnostic accuracy study of CRC using faecal immunochemical test for haemoglobin (FIT), faecal calprotectin (FCP)

and urinary volatile organic compounds (VOCs) in patients presenting with lower gastrointestinal symptoms.

In this prospective single-centre cohort study 1016 symptomatic patients with suspected CRC referred by general practicioners to secondary care were recruited. A total of 562 patients, who returned stool samples for FIT and FCP as well as urine samples for urinary VOC measurements and completed colonic investigations, were included in the final statistical analysis. Quantitative FIT was performed on automated HM-JACKarc analyser and FCP was measured using the EliA Calprotectin fluoroimmunoassay on the automated ThermoFisher ImmunoCap 250 analyser. A commercial gas analysis instrument (Lonestar Field Asymmetric Ion Mobility Spectrometry (FAIMS), Owlstone Medical, Cambridge, UK), based on ion mobility spectroscopy (IMS), was utilised to analyse VOCs emanating from urine samples. Various statistical parameters were calculated for each clinical group with 95% confidence intervals (CIs).

Results: The sensitivity and specificity for CRC using FIT were 0.80 (CI: 0.66–0.93) and 0.93 (CI: 0.91–0.95) respectively. The negative predictive value (NPV) was 0.99 (CI: 0.98–1.0). Using urinary VOCs the sensitivity and specificity were 0.63 (CI: 0.46–0.79) and 0.63 (CI: 0.59–0.67) respectively and the NPV was 0.96 (CI: 0.94–0.98). However, for those with FIT negative CRC (false negatives), adding urinary VOCs resulted in sensitivity of 0.97 (CI: 0.90–1.0) and specificity of 0.72 (CI: 0.68–0.76) with NPV of 1.0 (CI: 0.99–1.0).

Conclusion: Faecal biomarkers are useful in excluding CRC patients in symptomatic population with NPV of 99% for FIT. The addition of urinary VOCs shows promise as a second stage test improving FIT performance with NPV of 100% for CRC. It is envisaged that both these non-invasive tests (FIT and urinary VOCs) can be requested within primary care and analysed within a central laboratory at low cost to guide secondary care referral patterns.

Disclosure: RPA has provided educational lectures on behalf of Alpha Labs Ltd. & Thermo Fisher Scientific Ltd. CT has provided educational lectures on behalf of Thermo Fisher Scientific Ltd. All remaining authors disclose no conflicts of interest.

References

1. Mowat C, Digby J, Strachan JA, et al. Faecal haemoglobin and faecal calprotectin as indicators of bowel disease in patients presenting to primary care with bowel symptoms. *Gut.* 2016; 65(9): 1463–9.
2. Arasaradnam RP, McFarlane MJ, Ryan-Fisher C, et al. Detection of colorectal cancer (CRC) by urinary volatile organic compound analysis. *PLoS One.* 2014; 9(9): e108750.

OP283 CLINICOPATHOLOGICAL STUDY OF LATERALLY SPREADING TUMORS OF THE COLORECTUM

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Introduction: Laterally spreading tumors (LSTs) of the colorectum are classified into the following four subtypes according to their morphology ; granular homogeneous type (LST-GH), granular nodular mixed type (LST-GM), non-granular flat-elevated type (LST-NGF), and non-granular pseudo-depressed type (LST-NGPD). Clinical features of each subtype of LSTs have not been fully evaluated.

Aims and Methods: The aims of this study was to clarify the clinicopathological features of colorectal LSTs focusing on their subtypes. We reviewed clinical charts and surgical pathology files of 6243 endoscopically resected specimens during January 2007 and December 2017 at our institution. A total of 490 LSTs were detected. We examined the clinical features (mean age, male to female ratio, size, location, Incidence of concomitant carcinoma) according to their subtypes.

Results: Of these 490 lesions, a total of 180 (36.7%) were LST-GH, 43 (8.8%) LST-GM, 233 (47.6%) LST-NGF, and 34 (6.9%) LST-NGPD. Mean age of patients with each subtype was 68.6 years old for LST-GH, 67.0 for LST-GM, 67.2 for LST-NGF, and 66.8 for LST-NGPD. Male to female ratio (M/F) was 1.31 for LST-GH, 1.87 for LST-GM, 1.84 for LST-NGF, and 1.62 for LST-NGPD. Mean size of LST-GH (20.8mm) and LST-GM (25.1mm) were significantly larger than that of LST-NGF (16.7mm) and LST-NGPD (15.3mm). All subtypes were located predominantly in the proximal colon.

Incidences of concomitant carcinomas in LST-GH, LST-GM, LST-NGF, and LST-NGPD were 17.8% (32 out of 180), 44.2% (19 out of 43), 15.9% (37 out of 233), and 52.9% (18 out of 34), respectively. Incidences of concomitant submucosal carcinomas in LST-GH, LST-GM, LST-NGF, and LST-NGPD were 0% (0 out of 180), 14.0% (6 out of 43), 2.1% (5 out of 233), and 20.6% (7 out of 34), respectively.

Conclusion: Each subtype of LSTs has distinct clinical features. LST-GM and LST-NGPD have higher malignant potentials than other subtypes. Especially LST-NGPD has the highest risk of invasive carcinoma regardless of its size. Therefore we should carefully detect these lesions and choose appropriate treatment according to the subtypes.

Disclosure: Nothing to disclose

OP284 CLINICAL, ENDOSCOPIC AND MOLECULAR BIOMARKERS IN PREDICTING METACHRONOUS ADVANCED LESIONS FROM POPULATION-BASED SCREENING FOR COLORECTAL CANCER (CRC)

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Introduction: Many factors associated with the development and recurrence of colon lesions has been described. The clinical guidelines follow up recommendations are based on the size, number and pathologic characteristics of the removed lesions in baseline colonoscopy, although, genetic clinical factors could also have influence over time. Identifying predictors of metachronous lesions would provide a better risk stratification and improve the efficiency of surveillance programs.

Aims and Methods: We aimed to determine predictive factors of metachronous lesions at 3 years in individuals with advanced adenomas (high-grade dysplasia, villous component or ≥ 10 mm) and/or multiplicity ≥ 3 polyps in baseline screening colonoscopy. Analysis of all cases with advanced polyps and/or multiplicity from population-based screening for colorectal cancer (CRC) of Barcelona representative area (CiutatVella-SantMartí) detected at the first round of baseline colonoscopy (2010-2011) with surveillance colonoscopy at 3 years. Epidemiological and clinical information/data of all individuals were collected, and molecular study was performed in baseline polyps, including immunochemistry expression of p53, MLH1, CDX2, Keratin 20, Keratin 7, KI 67 and β-catenin proteins, as well as mutations in KRAS, NRAS and BRAF genes. For the statistical study, a bivariate analysis and logistic regression was performed.

Results: 518 cases with a complete colonoscopy at 3 years were included. 66.2% were men with a mean age of 64 years. 51.8% had hypertension, 15% Diabetes, 46.5% dyslipidemia, 12.3% chronic obstructive pulmonary disease, 70.6%, exposure to tobacco 45.8% were overweight and 34.7% were obese. Regarding the surveillance colonoscopy, it was normal or with low-risk polyps in 420 cases (80.1%); in 98 cases (18.9%) advanced and/or multiplicity lesions were identified: 73 advanced adenomas in 59 cases (11.4%), ≥ 3 adenomas in 62 cases (11.9%), ≥ 3 adenomas and/or serrated in 71 cases (13.7%). The immunohistochemical study of cytokeratin (CK) 7 and 20, KI 67, β-catenin, p53, MLH1 and CDX2 was performed in 460 cases and included localization of expression and the intensity of staining. Among individuals with advanced adenoma at 3 years, none had loss of expression of MLH1 or CDX2; in 7 cases (1.5%) loss of expression of p53 was observed, Ki 67 nuclear expression was observed in 1.8% and B-catenin in 46.9%, CK7cytoplasmatic reaction in 9.4% and CK 20 in 85.5%, without differences regarding intensity of staining in COR curve. Regarding mutations, we identify 144 (32%) polyps mutation in KRAS gen, in 27 (5.9%) polyps with NRAS mutation distributed more frequently in codons 12-13, 59-61 and 117-146. BRAF mutation was identified in 32 cases (7.1%) mainly distributed in codon 600. None of these mutations were associated statistically significantly with metachronous lesions. The presence of ≥ 3 polyps in the basal colonoscopy was the only independent predictor of advanced lesion to the surveillance colonoscopy (p = 0.001).

Conclusion: The multiplicity in baseline colonoscopy seems to be the most important factor to identify population at risk of advanced metachronous polyps. We could not demonstrate usefulness of molecular biomarkers in predicting metachronous advanced lesions in individuals with intermediate or high-risk polyps. Increasing the surveillance interval after a complete resection of lesions could be a strategy, maintaining the surveillance at 3 years in case of multiplicity in the baseline colonoscopy. More studies are needed to improve stratificationof thethe risk of metachrony.

Disclosure: Nothing to disclose

WEDNESDAY, OCTOBER 24, 2018   08:30–10:00
Upper GI sensitivity and symptom generation – Room N1_____

OP285 GENETIC VARIATION IS ASSOCIATED WITH WORSE AFFECT SCORES, HIGHER SYMPTOM BURDEN, AND MUCOSAL INJURY IN PATIENTS WITH ESOPHAGEAL SYMPTOMS

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Introduction: Genetic variation has been linked to increased symptom burden with esophageal symptoms and functional gastrointestinal (GI) disorders through centrally mediated mechanisms. We evaluated relationships between symptom burden and SNPs in GNB3 (G-protein-coupled receptor in the brain-gut axis), ADRB2 (mediator of stress response), ADAMTS17 (extracellular matrix protein involved cellular junction permeability), SGK1 (treatment response to venlafaxine and susceptibility to anxiety), and FAAH (neuroendocrine regulation, associated with anxiety, IBS, depression), in an enriched population with esophageal symptoms.

Aims and Methods: Consecutive subjects with esophageal symptoms presenting for clinical evaluation or esophageal physiologic testing at a tertiary care center were identified for inclusion. Patients with major esophageal motor disorders and prior foregut surgery were excluded. Subjects provided sputum samples for genotyping and completed a symptom questionnaire that included GERDQ, short-form health survey-36 (SF-36), Beck Anxiety and Depression Inventories (BAI and BDI), esophageal symptom surveys and 10 cm visual analog scales (VAS) rating symptom bother and severity. We used thresholds for symptoms scores derived using receiver operating characteristic analysis to compare frequency of minor alleles between high and low symptom burden. 6 selected SNPs from GNβ3, 2 from ADRB2 and 1 each from ADAMTS17, SGK1, and FAAH were assessed. Data were compared to healthy volunteer controls with no esophageal symptoms or anti-reflux therapy.

Results: Sputum from 237 study subjects (54.3 ± 1.0 yrs, 64.3% F) and 67 controls (49.3 ± 2.0 yrs, 66.7%) had sufficient genetic material for genotyping, and adequate clinical data for analysis. Compared to controls, study subjects had higher GI symptom scores, BDI, and BAI scores, lower total and physical health SF-36 scores, ($p \leq 0.02$), but similar mental health SF-36 and GERDQ scores ($p \geq 0.10$). There was a non-significant increase in minor allele frequency in ADAMTS17 and FAAH in subjects compared to controls (51% to 16.7%, $p = 0.1$ and 35% to 15%, $p = 0.2$, respectively); other SNPs were distributed similarly between subjects and controls. Minor alleles in 3 SNPs in GNβ3 (Rs 5446, Rs 5443, and Rs 2301339) were associated with higher symptom severity ($p \leq 0.03$). Rs5446 and Rs5443 had worse mental SF36 scores ($p = 0.04$), Rs 2301339 also trended towards significance ($p = 0.06$). BDI was higher in two GNβ3 SNPs (Rs5445 and Rs2301338) ($p \leq 0.01$); BAI was higher in the ADRB2 SNP Rs1042713 ($p = 0.05$). Using previously derived cutoffs to separate high from low symptom or inventory scores, subjects with high symptom severity were more likely to have a minor allele in ADRB2 SNP Rs1042713 ($p = 0.045$), and GNβ3 SNPs (Rs 5446, Rs 5443, and Rs 2301339) ($p \leq 0.03$). Perceptive symptoms (heartburn, chest pain) were associated with a minor allele in ADRB2 SNP Rs1042713 (64% to 43% $p = 0.04$). Subjects with minor alleles in three GNβ3 SNPs were more likely to have evidence of esophageal mucosal injury on endoscopy compared to major alleles only (Rs 5446: 63% vs. 37%, $p = 0.04$, Rs5443 62% vs 38%, $p = 0.04$, Rs2301339: 62% vs. 38%, $p = 0.03$, respectively). This same subset of patients had worse symptom bother (VAS 6.5 ± 0.3 vs 5.4 ± 0.3, $p = 0.02$) and severity (VAS 6.2 ± 0.3 vs 4.7 ± 0.3, $p < 0.01$), but GERD phenotypes and acid burden were not predicted by these SNPs.

Conclusion: Genetic variation in GNβ3 and ADRB2 can explain increased esophageal symptom burden, abnormal affect and more importantly, likelihood of esophageal mucosal injury in patients with esophageal symptoms.

Disclosure: Nothing to disclose

OP286 GASTRIC TRPA1 STIMULATION BY ALLICIN-CONTAINING GARLIC POWDER INDUCES SPECIFIC EPIGASTRIC SYMPTOMS THAT DIFFER FROM SYMPTOMS INDUCED BY TRPV1 STIMULATION AND GASTRIC DISTENSION

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Introduction: Gastric distension and chemical stimulation of the TRPV1 receptor with capsaicin elicit specific and distinct epigastric symptoms. TRPA1 is another excitatory ion channel which is involved in sensory processes including thermal (cold) nociception, and inflammatory pain. Allicin in garlic is a strong activator of the TRPA1 channel.

Aims and Methods: We aimed to characterize the sensations induced by intragastric application of allicin-containing garlic powder and to compare the quality of sensations with capsaicin and distension induced perception. Initially the allicin content of a commercially available garlic powder was determined by HPLC (0.5%) and the stability of allicin for at least 60 minutes after dilution of the powder was confirmed *in vitro*. After a dose finding trial 2 g garlic powder ($\triangleq 10$ mg allicin) dissolved in 10 mL H_2O, was determined to induce moderate but consistent sensations. A 3-luminal tube with a barostat balloon was placed into the proximal stomach and was used for double blind, random infusion of garlic solution or placebo and for stepwise gastric distension. 7 healthy volunteers were studied. Symptoms were recorded with a graded symptom questionnaire evaluating 7 symptoms (5 grades per question). Symptom recording was performed after the garlic/placebo bolus for 15 minutes and during graded barostat-balloon distensions. Additionally, 25 healthy subjects received a capsule containing 0.75 mg capsaicin and symptoms were recorded every 5 minutes for 45 minutes thereafter. Symptom scores were recorded and areas under the curves were calculated. A p-value < 0.01 was considered significant in view of multiple comparisons.

Results: Bolus injection of garlic caused immediate epigastric symptoms, mean aggregate symptom scores (AUC in 15 minutes) were 106 ± 49 vs. 35 ± 30 after placebo ($p = 0.01$). Garlic induced significant epigastric pressure, stinging, and warmth ($p < 0.01$ vs. placebo), while the symptoms cramps, satiety, nausea and pain were not significantly different from placebo ($p > 0.05$). After capsaicin ingestion warmth and stinging were the most intense symptoms overall, but the difference to other symptoms was significant only compared to pain and cramps ($p < 0.01$). During balloon distension epigastric pressure was significantly more intense than all other evaluated qualities of sensations ($p < 0.001$), while warmth was significantly less intense than all other evaluated qualities of sensations ($p < 0.01$).

Conclusion: Garlic powder containing allicin induces immediate epigastric symptoms of pressure, stinging and warmth. Gastric TRPA1 stimulation by allicin induces specific epigastric symptoms that differ from symptoms induced by TRPV1 stimulation and mechanical distension. TRPA1 is a receptor that is involved in gastric sensation.

Disclosure: Nothing to disclose

OP287 THE INCREASE OF EFFECTOR MEMORY T-CELLS IN SMALL INTESTINE OF FUNCTIONAL GASTROINTESTINAL DISORDER (FGID) PATIENTS RELATING TO GUT BACTERIA AND SYMPTOM GENERATION

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Introduction: Minimal inflammation has been reported in functional gastrointestinal disorders (FGID), but the causes of immune activation are largely unknown. Alterations of the stool microbiota have been reported in FGID patients, suggesting specific microbe-host interactions might be a key driver of immune activation. However, these relationships are virtually unexplored in the small intestine. Thus, we aimed to characterise the links between alterations in immune function, the duodenal mucosa-associated microbiome (d-MAM), and gastrointestinal symptoms in FGID patients.

Aims and Methods: 148 patients undergoing endoscopy were recruited in total. GI symptoms were assessed by a standardised questionnaire (SAGIS). Based on all clinical data, the cohort was divided into FGID (n = 88) and non-FGID control patients (n = 60) without relevant structural abnormalities; controls including a positive FOBT and/or iron deficiency anaemia test. Peripheral Blood Mononuclear cells (PBMCs) were isolated from peripheral blood using Ficoll density gradient centrifugation. Lamina propria (LP) cells were isolated from duodenal biopsies by collagenase. T-cells in PBMCs and lamina propria were analysed by flow cytometry. Genomic DNA was extracted from duodenal biopsies obtained using our patented aseptic device (MTW, Germany), and used to produce bar-coded PCR amplicons of the bacterial 16S rRNA gene, which were sequenced using Illumina MiSeq technology. Bioinformatics analyses were performed using QIIME and Calypso with statistical significance assessed by T-test or Spearman correlation.

Results: There was a significant increase of CD4 gut-homing T-cells in peripheral blood of FGID patients vs controls ($p < 0.015$). However, the increase of peripheral CD4 gut-homing T-cells does not lead to an increase of this population in the duodenal LP. Instead, there was positive correlation between effector memory T-cells (T_{EM}-cells) in LP with both peripheral CD4 ($r = 0.43$, $p < 0.005$) and CD8 ($r = 0.33$, $p < 0.037$) gut-homing T-cells. The T_{EM}-cell number in the LP was also strongly and positively correlated with the intensity of GI symptoms ($r = 0.44$, $p < 0.0001$) and a positive correlation between T_{EM}-cells number and the relative abundance of a specific member of the d-MAM assigned to the genus *Neisseria* ($r = 0.34$, $p < 0.04$) was also found. Negative correlations were observed between T_{EM}-cell number in LP and the relative abundance of specific members of the d-MAM assigned to *Streptococcus* ($r = -0.40$, $p < 0.01$), *Prevotella* ($r = -0.39$, $p < 0.02$), and *Selenomonas*, ($r = -0.39$, $p < 0.02$). Interestingly, patients with more severe symptoms showed lower numbers of both CD4 and CD8 gut-homing T-cells in the mucosa ($p < 0.0001$), as well as a reduction in their d-MAM alpha diversity (within sample) (Chao1 metric; $r = 0.37$, $p < 0.02$). There was also a direct correlation between proportion of LP gut homing T-cells and d-MAM diversity ($p < 0.035$).

Conclusion: The increase of gut-homing T-cells in peripheral blood, and T_{EM}-cells in duodenal LP, are positively correlated to symptom severity in FGID patients. In contrast, patients with the higher symptom severity had lower numbers of gut-homing T-cells in the mucosa and this was associated with lower bacterial diversity. The observed changes in T_{EM}-cells in duodenal LP were also linked to changes in the relative abundance of specific bacterial lineages assigned to *Neisseria* (positively), *Streptococcus*, *Prevotella* and *Selenomonas* (negatively), providing new insights into specific microbe-host interactions affecting FGID pathophysiology and its manifestations.

Disclosure: Nothing to disclose

OP288 EVIDENCE OF A DYSREGULATED STRESS HORMONE RESPONSE RELATED TO NLRP6 INFLAMMASOME ACTIVATION IN PATIENTS WITH FUNCTIONAL DYSPEPSIA

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Introduction: Functional dyspepsia (FD) affects 15% of the population and is characterised by recurring upper gastrointestinal (GI) symptoms in the absence of structural abnormalities identifiable by routine diagnostic practice. Recent evidence has implicated subtle changes in immune cell populations, namely eosinophils and mast cells in the pathophysiology of FD. Psychological stress is a key factor associated with the onset of FD and is a trigger of symptom exacerbations, however the biological mechanisms through which stress may lead to FD have not yet been defined. Recent pre-clinical work has identified that the primary stress hormone corticotrophin releasing hormone (CRH) may regulate expression of the innate immune protein NLRP6. NLRP6 in turn, regulates the release of IL-18, which is potently chemotactic for eosinophils and mast cells. We hypothesised that stress hormone levels are altered in patients with FD and that this leads to alterations in GI mucosal homeostasis and immune cell recruitment.

Aims and Methods: Our aims were to examine stress hormone levels in patients with FD compared to healthy subjects and correlate with activation of NLRP6 in these patients. FD patients were identified by Rome III criteria; asymptomatic individuals were recruited as controls. Psychological stress was measured using the Hospital Anxiety and Depression Scale (HADS) questionnaire. Serum CRH levels were measured by ELISA. Pinch biopsies were collected from the duodenum of FD patients and non-FD controls. Biopsies were either formalin fixed and stained immunohistochemically for NLRP6 or RNA was extracted from enriched epithelial cell preparations for qPCR analysis.

Results: Overall, there was no difference in HADS score between FD and non-FD cohorts (n = 10, p = 0.25). However, levels of CRH were significantly reduced in both duodenal tissue (n = 6, p = 0.001) and serum (n = 10, p = 0.013) of FD patients compared to non-FD controls. HADS positively correlated with serum CRH in controls but not in patients with FD. Duodenal NLRP6 was significantly increased in patients with FD compared to non-FD controls (n = 6, p = 0.007) and epithelial expression of NLRP6 was positively correlated with expression of IL-18, which was elevated at the gene level (r = 0.95, p = 0.015) in FD patients compared to non-FD controls. Overall, there was no difference in the number of CD117+ mast cells between patients with FD and controls (n = 9, p = 0.45), however post-hoc analysis revealed a significant increase in mast cell numbers between patients with epigastric pain syndrome (EPS) compared to patients with post-prandial distress syndrome (PDS) symptoms (n = 3 per group, p = 0.04).

Conclusion: This study has identified 2 novel pathological features of FD, (decreased CRH and increased NLRP6) and suggests a dysregulation in the hormonal stress response disrupts GI mucosal homeostasis in patients with FD. Additionally, our data indicates that EPS and PDS subtypes of FD may be symptomatically and immunologically distinct, confirming the heterogeneity of FD.

Disclosure: Nothing to disclose

OP289 EXPLORATORY STUDY: COGNITIVE RESTRAINT ASSOCIATED WITH BASELINE VAGAL TONE AND POSTPRANDIAL RESPONSE TO INTEROCEPTIVE STIMULUS IN HEALTHY LEAN ADULTS

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Introduction: The vagus nerve carries sensorimotor information between the brain and gastrointestinal (GI) tract. Vagal tone plays an important role in the regulation of appetite[1] and is associated with a range of positive health behaviours. Upon consumption of a meal, internal afferent signals are conveyed to the brainstem depending on the size and nutrient composition of the meal. These are integrated with external sensory information before descending and modulatory pathways elicit an efferent motor response, accompanied by changes in appetite-related sensations. Differences in vagal tone may moderate periprandial responses to interoceptive and exteroceptive stimuli and influence eating behaviour. Previously, an interaction between intragastric infusion of fatty-acid (FA)

and negative mood induction has been reported to effect behavioural and neural responses in healthy lean subjects[2].

Aims and Methods: The aim of this pilot study was to investigate the relationship between vagal tone and eating behaviour and the effect of the putative interaction between FA and negative mood on appetite-related sensations and food consumption. 10 healthy subjects (3 male, median [range] age 29 [22-52] BMI 22.5 [19.4–24.0]) completed the Three-Factor Eating Questionnaire (TFEQ) and 4 visits in a 2x2 crossover design. Cardiac vagal tone (CVT), affective state and appetite-related sensations were assessed at baseline and following intragastric infusion of 250 ml 0.05 mol/L C-12 fatty-acid ("fat" condition vs saline). At 3 min pre-infusion (-3 min), negative mood induction ("sad" condition vs neutral) began, up to 30min post-infusion (PI). Subjects were offered an ad libitum buffet and instructed to eat until comfortably full (40-70min PI). Spearman's ρ was calculated for baseline CVT against TFEQ scores for cognitive restraint (CR), emotional eating (EE) and unrestrained eating (UE) and the main effect of "fat*sad" was tested with ANOVA including "condition" as a within-subject variable for the following (compared to -3min baseline): Δ CVT, Δ fullness (1-100 visual analogue scale, VAS), Δ arousal (1-9 self-assessment mannikin, SAM) and Δ negative mood (1-9 SAM) at 20min PI controlling for baseline values; and total energy (kcal) and total fat (g) consumed at 40-70min PI controlling for baseline hunger rating.

Results: Baseline CVT (median: 14.12 LVS, range: 2.9–26.8) was negatively correlated with TFEQ-CR (r = -0.74, p = 0.013) but not UE (r = -0.25, p = 0.51) or EE (r = -0.01 p = 0.98). The effect of "fat" on Δ CVT (20min vs -3min PI) was significant (F(1) = 11.03, p = 0.003) and the interaction term approached significance (F(1) = 3.14, p = 0.09). Controlling for baseline ratings, there was no significant effect of either "fat", "sad" or "fat*sad" on Δ fullness, Δ arousal or Δ negative mood. Baseline hunger had a significant effect on the amount of fat consumed (F(1) = 4.86, p = 0.04), but here was no significant effect of condition or interaction on total energy or fat consumption.

Conclusion: Relatively high baseline CVT and the strong correlation with CR in this lean sample supports the association between vagal tone and positive cognitive restraint. Small sample size, low dose and volume of fatty-acid infused, and subtlety of the mood induction could account for the limited effect of the experimental interventions on subjective ratings and food consumption. However, this exploratory study suggests that CVT could be a non-invasive biomarker of subconscious physiological responses. Future work will investigate the role of circulating gut peptides and the relationship between vagal tone and GI motility.

Disclosure: Nothing to disclose

References

1. Browning KN, Verheijden S, Boeckxstaens GE. The Vagus Nerve in Appetite Regulation, Mood, and Intestinal Inflammation. *Gastroenterology* 2017; 152: 730–744.
2. Van Oudenhove L, McKie S, Lassman D, et al. Fatty acid-induced gut-brain signaling attenuates neural and behavioral effects of sad emotion in humans. *The Journal of Clinical Investigation* 2011; 121: 3094–3099.

OP290 RANDOMIZED CONTROLLED TRIAL: THE EFFECT OF TRANSCUTANEOUS VAGAL NERVE STIMULATION ON REVERSING ACID – INDUCED OESOPHAGEAL HYPERSENSITIVITY IN HUMANS

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Introduction: Accumulating evidence suggests that the vagus nerve exerts an anti-nociceptive effect in the viscera. Visceral pain hypersensitivity is a key pathophysiological mechanism of number of common disorders including subtypes of gastro-oesophageal reflux disease (GORD).

Pain hypersensitivity is an exaggerated response to an injury that may persist despite the cessation of the injury. We have previously demonstrated that Transcutaneous Vagal Nerve Stimulation (tVNS) prevents the development of experimental acid-induced oesophageal pain hypersensitivity when applied at the same time with the injury-causing agent (acid) (Farmer AD et al, DDW 2017). However, in patients, the exact onset of the injury is unpredictable, thus a therapeutic intervention would preferably be able to reverse an already established hypersensitivity.

Aims and Methods: Our aim was to determine whether electrical stimulation of the auricular branch of the vagus nerve can reverse an established experimental hypersensitivity in a validated model of acid induced oesophageal pain hypersensitivity due to central sensitisation in healthy subjects.

In a prospective randomised sham-controlled crossover trial in 24 healthy participants (12 male, mean age 26.4 ± 6.24 years), we measured electrical pain tolerance thresholds (PT) in the proximal oesophagus, at the start of the experiment (T0), following that, we infused 240 ml of 0.15M hydrochloric acid in the distal oesophagus (T0-T30). After that, we allowed participants to rest for 30 min and

then measured PT for the second time (T60). Only participants with PT drop of $\geq$6 mA (milliamp) measured at (T60) were considered to be sensitizers and therefore recruited. After that, participants were randomized in a blinded crossover design to receive either transcutaneous auricular electrical vagal nerve stimulation (tVNS) (pulse width: 250 μs, 25 Hz, cycle: 30s on, 30 s off), or sham stimulation with the same parameters, for 30 minutes (T60-T90). PTs were measured both, immediately (T90) and 30 min after the end of active/sham stimulation (T120). PTs were analysed using a general linear model for repeated measures with PTs as dependent variables, active/sham as factor and the difference in the initial degree of sensitisation between visits as a covariate (IBS SPSS 23, USA). **Results:** 18 participants (8 male, mean age 26 ± 6.3 years) sensitised and were included. When compared to sham, tVNS significantly increased PT at the end of the stimulation; 19.4mA ($\pm$21) vs. 2.7 mA ($\pm$12.1), p = 0.01, 95% CI [4.16–27.96]. The effect of tVNS on PT remained significant 30 min after the end of stimulation; 22.5 ($\pm$23.8) vs. 7.69 ($\pm$18.44), p = 0.049, 95% CI [0.079–29.77].

Conclusion: Our results suggest that tVNS reverses experimental acid-induced oesophageal pain hypersensitivity in healthy participants. Future studies are warranted to replicate this effect in patients with reflux hypersensitivity and other disorders where pain hypersensitivity is suspected.

Disclosure: Nothing to disclose

WEDNESDAY, OCTOBER 24, 2018   08:30–10:00
CRC in young adults and genetically predisposed patients – Room L7

OP291 THE OLD VERSUS THE NEW: WHAT IS DIFFERENT IN COLORECTAL CANCER?

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Introduction: Colorectal cancer (CRC) is the third most common cancer in the United States and the second leading cause of all cancer-related deaths. Although the incidence has been decreasing for adults ($\geq$50), it has been on the rise for adults younger than 50.

Aims and Methods: We aim to identify potential risk factors in CRC occurrence in young adults. A population-based study using a national database, Explorys, was used to identify all CRC cases from Jan 2012 to Dec 2016. Subgroups were stratified based on age (25-49 years vs. $\geq$50 years). Demographics, comorbidities, and symptom profiles were recorded and compared between both age groups. Furthermore, the younger group was also compared with a control group consisting of individuals aged 25-49 years without a diagnosis of CRC. 20 data points for CRC related factors were analyzed to identify potential risk factors specific to early-onset CRC. Odds ratio and p-value calculations were performed and reported using social sciences statistical software.

Results: 68,860 patients were identified with CRC, of which 5,710 (8.3%) were younger than 50 years of age. Early-onset CRC demonstrated a significantly higher incidence in African-Americans, family history (FH) of cancer, FH of GI specific malignancy, FH of colonic polyps, obesity (BMI$\geq$30), presenting symptoms of abdominal pain, rectal pain, rectal bleeding, colitis and altered bowel function as compared to patients $\geq$50 years with diagnosis of CRC. Additionally, early-onset CRC significantly had higher rates of FH of cancer,

GI cancer, colonic polyps, colitis, obesity, and symptoms of abdominal pain, rectal pain, rectal bleeding, weight loss and altered bowel function when compared to the control group.

Conclusion: The rise of CRC in the younger population remains concerning. Identifying risk factors for early-onset CRC is necessary to optimize guidelines for early screening. Pending further investigation, these risk factors should lower the threshold of suspicion for early CRC and potentially early CRC screening especially in patients 40-49 years of age.

Disclosure: Nothing to disclose

OP292 INCREASING INCIDENCE OF COLORECTAL CANCER IN YOUNG ADULTS IN EUROPE

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Introduction: In the North American population, colorectal cancer (CRC) incidence for individuals older than 50 years steadily declines, but an opposite trend has been suggested among young adults. In Europe, trends in CRC incidence among younger individuals are lacking.

Aims and Methods: The aim of this study was to analyze trends in incidence rates of young adults with CRC in the European Union over the last 25 years.

Abstract No: OP291
Table 1: Odds Ratio of Early-Onset CRC vs. Later-Onset CRC and the Control Cohort

Factors	Early-Onset CRC	Later-Onset CRC	Odds Ratio (95% CI)	p-value	Control	Odds Ratio (95% CI)	p-value
Male	2800	32320	0.91 (0.87-0.96)	0.0011	4931130	1.34 (1.27-1.41)	0.0001
Female	2910	30690	1.09 (1.04-1.16)	0.0011	6869290	0.75 (0.71-0.79)	0.0001
Caucasian	3880	52330	0.43 (0.41-0.46)	0.0001	6947160	1.48 (1.4-1.57)	0.0001
African-American	860	8260	1.18 (1.09-1.27)	0.0001	1462790	1.25 (1.17-1.35)	0.0001
Asian	110	1380	0.88 (0.72-1.07)	0.1905	258990	0.88 (0.72-1.06)	0.1668
Abdominal Pain	3060	24490	1.82 (1.72-1.92)	0.0001	2317490	4.73 (4.49-4.49)	0.0001
Rectal Pain	170	1260	1.5 (1.28-1.77)	0.0001	48200	7.48 (6.42-8.72)	0.0001
Altered Bowel Function	1440	14610	1.12 (1.05-1.19)	0.0005	680420	5.51 (5.19-5.85)	0.0001
Rectal Bleeding	790	7960	1.11 (1.03-1.20)	0.0091	190310	9.83 (9.12-10.6)	0.0001
Weight Loss	490	7800	0.66 (0.6-0.73)	0.0001	147250	7.43 (6.77-8.15)	0.0001
Family History of Cancer	1360	9400	1.78 (1.67-1.90)	0.0001	308120	11.66 (10.97-12.39)	0.0001
Family History of GI Malignancy	840	4300	2.36 (2.18-2.55)	0.0001	70560	28.67 (26.64-30.86)	0.0001
Family History of Polyps	60	470	1.41 (1.08-1.85)	0.0121	15350	8.15 (6.31-10.52)	0.0001
Tobacco Use	3600	42360	0.83 (0.79-0.88)	0.0001	4838172	2.46 (2.33-2.59)	0.0001
Alcohol Use	2000	24850	0.83 (0.78-0.88)	0.0001	2832100	1.71 (1.62-1.8)	0.0001
Colitis	710	7270	1.09 (1.00-1.18)	0.043	395260	4.1 (3.79-4.43)	0.0001
BMI $>=30$	3510	36770	1.14 (1.08-1.20)	0.0001	4202120	2.88 (2.74-3.04)	0.0001
Hypertension	1710	41740	0.22 (0.21-0.23)	0.0001	1534060	2.86 (2.7-3.03)	0.0001
Hyperlipidemia	1090	33960	0.20 (0.19-0.22)	0.0001	1062040	2.39 (2.23-2.55)	0.0001
Polyp History	630	8970	0.75 (0.69-0.81)	0.0001	155640	9.28 (8.54-10.08)	0.0001

Data on age-related incidence of CRC were retrieved from national European cancer registries with a data time-frame of at least 10 years, ranging from 1990 until 2016. Young adults, defined as people between 20 to 49 years of age, with confirmed colon or rectal cancer were included. 5-year incidence and mortality rates were collected, expressed per 100.000 person-years and corrected for age and population numbers. Trends were calculated using a Joinpoint regression analysis, and expressed as annual percent change (APC) with a 95% confidence.

Results: Data from 20 European countries were included. In adults aged 20 to 39 years of age, the overall CRC incidence rate increased by 4.9% (95% CI: 3.9–5.9) annually since 2005. For colon cancer, incidence rate increased in men by 2.2% (95% CI: 1.4–3.0) per year from 1990-2010 and with an even higher increase of 7.3% (95% CI: 2.3–12.5) per year from 2010-2016. In women the incidence rate increased by 1.5% (95% CI: 0.4–2.7) per year from 1990-2008 and increased even more by 8.9% (95% CI: 4.8–13.2) per year from 2008-2016. Incidence rate of rectal cancer increased for both men and women, respectively 2.4% (95% CI: 1.9–3.0) and 2.0% (95% CI: 1.2–2.8) per year.

In adults aged 40 to 49 years, the overall CRC incidence rate increased by 1.2% (95% CI: 0.6–1.8) per year from 2002. The incidence rate of colon cancer increased in men by 0.5% (95% CI: 0.1–0.8) per year, and also in women by 0.5% (95% CI: 0.0–1.0) per year. Incidence rate of rectal cancer in men decreased by 3.9% (95% CI:-7.1– -0.7) from 1990-1997, and then increased from 1997-2016 by 1.6% (95% CI: 0.8–2.3). Rectal cancer in women increased by 8.3% (95% CI: 4.7–12.0) per year in 1990-1996, and remained stable from 1996-2016.

The overall age adjusted mortality rates for CRC did not show a significant trend in adults 20 to 39 years of age. However, mortality rates in adults 40 to 49 years of age decreased by 3.8% (95% CI: -4.4– -3.2) per year from 1990-2006, and remaind stable from 2006-2016.

Conclusion: There is an increased incidence rate in CRC in young adults in Europe. The cause for this trend is still unknown. Awareness and future studies to elucidate causes for this trend are needed and may help to set up screening strategies to prevent and detect these cancers at an early and curable stage.

Disclosure: Nothing to disclose

OP293　SCREENING FOR COLORECTAL CANCER BASED ON POLYGENIC RISK AND FAMILY HISTORY

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Introduction: There is a growing body of evidence that common, low-risk genetic variants play a significant role in colorectal cancer (CRC) risk due to their relatively high prevalence in the population. When combined with family history, they have been shown to improve risk stratification of the general population. We aimed to investigate the impact of risk-based screening (RBS) for CRC, and compare it, in terms of effectiveness and cost-effectiveness, to uniform biennial screening.

Aims and Methods: We used the Microsimulation Screening Analysis-Colon (MISCAN-Colon) to model the effects and costs of screening for CRC in a risk stratified Australian population aged 40-74 years. Individuals were placed into 1 of 5 risk groups based on relative risk (very low, low, average, high, very high) which was determined by their polygenic risk profile and family history of CRC. Screening strategies varied by start age (40, 46, 50, 54 or 60), test (no screening, faecal immunochemical test (FIT) and colonoscopy (COL)) and interval (annual, biennial or triennial FIT, and 5- or 10-yearly COL).

We then assessed 6 screening scenarios – no screening, uniform biennial FIT screening for individuals aged 50-74 years and 4 RBS scenarios (R1-4). RBS scenarios increased in complexity: in R1 we modified screening start age, while in R2 we modified start age and interval and in R3 and R4 we also modified screening tests. Screening stop age was 74 years for all scenarios. In a sensitivity analysis we included costs for obtaining risk profile which included polygenic testing.

Results: Without screening, 78.7 CRC cases per 1,000 40-year olds were clinically detected over the 50-year follow-up period. This scenario resulted in 26.6 CRC deaths, yielded 23,723 QALYs and cost AU$2.14 million. Compared to no screening, uniform screening resulted in lower CRC incidence (66.8 cases) and mortality (19.6) and an increased yield in QALYs (23,755 QALYs) and costs ($2.20 million). The RBS strategies resulted in similar CRC incidence and mortality to uniform screening, with the most intensive strategy (R4) having the lowest incidence and mortality. QALYs and costs increased slightly in the RBS scenarios with R4 having the highest yield and costs.

The average cost-effectiveness ratio (ACER) of uniform screening compared to no screening was $2,149 per QALY gained. However, when we considered all strategies, R2, where screening start age and interval were modified, demonstrated cost-effectiveness with an ACER of $1,546 per QALYs gained compared

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to no screening with R1 and uniform screening being dominated by R2 and R3 extendedly dominated by R4 (ICER $15,190). R4, where screening start age and interval were modified, and those at highest risk were offered 5-yearly COL, was also cost-effective with an ICER of $10,989 compared to R2. When costs for obtaining risk profile were included, only uniform screening was deemed to be cost-effective.

Conclusion: Our results indicate that RBS determined by common genetic variants and family history is cost-effective, however, overall the gains are small. If, in addition to an earlier start age of screening, individuals at highest risk are offered 5-yearly COL instead of FIT (R4), benefits are expected to be largest. Including costs for obtaining risk profile significantly alters the results, with only uniform screening being cost-effective. The benefits of RBS may alter as new variants are discovered.

Disclosure: Nothing to disclose

OP294　YIELD OF LYNCH SYNDROME SURVEILLANCE FOR INDIVIDUAL MMR GENES

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Introduction: Lynch syndrome (LS) is the most common hereditary cause of colorectal cancer (CRC) and is caused by germline mutations in the MMR genes *MLH1, MSH2, MSH6* or *PMS2*. Although different genes may result in different CRC risk, all LS patients are currently offered the same surveillance interval regardless of the gene involved. Therefore, we aimed to assess the yield of LS surveillance for each individual MMR gene carrier group.

Aims and Methods: All patients diagnosed with LS in our center and participating in LS surveillance were included. Patients who had developed CRC before the identification of a MMR mutation were excluded. Data on age, gender, MMR gene involved, number of colonoscopies performed, interval between colonoscopies, and findings at each examination including histopathology were collected. Adenomas were considered advanced in case of a villous component, high-grade dysplasia and/or ≥10mm in size. We compared the development of (advanced) adenomas and CRC between patients with *MLH1, MSH2, MSH6* and *PMS2* mutations.

Results: A total of 314 LS carriers were included. Colonoscopy data were available for 264 (84%) patients from 113 different families (38% male, median age at time of first colonoscopy was 44 years (IQR 35-56 years, range 20-80 years)). Of these patients, 55 had a *MLH1*, 44 a *MSH2*, 143 a *MSH6* and 22 a *PMS2* mutation. Median follow-up time was 6 years (IQR 2-10 years). At first colonoscopy, adenomas were found in 70 (27%), advanced adenomas in 33 (13%) and CRC in 8 patients (age range 46-69 years, 3 *MLH1*, 1 *MSH2* and 4 *MSH6* mutation carriers). A total of 916 follow-up colonoscopies were performed in 220 patients. CRC was found in 9 patients, 4 in *MLH1* mutation carriers and 5 in *MSH2* mutation carriers. No CRC was found in *MSH6* or *PMS2* mutation carriers. There were no significant differences in the number of colonoscopies with adenomas or advanced adenomas between the different gene mutation carrier groups. In total, 264 adenomas were found in 103 different patients (47% of the patients). Mean number of adenomas per procedure (MAP) was 0.28. Mean number of adenomas per positive procedure (MAP+) was 1.38. There were also no significant differences in MAP or MAP+ between the different gene mutation carrier groups. Median time of adenoma development (calculated as the time since the last adenoma identified or since the first colonoscopy in case no previous adenomas were found) was 3 years (IQR 2-6 years). There were no significant differences in time to development of an adenoma or advanced adenoma between the groups adjusted for age and gender. In *MLH1* and *MSH2* mutation carriers advanced neoplasia (advanced adenoma or colorectal carcinoma) was found in shorter follow-up time than in *MSH6* mutation carriers. 6 patients died during LS surveillance. Only 1 patient died from CRC, which was diagnosed at the first colonoscopy. In total 3/6 patients died from pancreatic cancer (1 MSH6 and 2 MSH2 mutation carriers).

Conclusion: Since no CRC was found during follow-up in *MSH6* and *PMS2* mutation carriers and advanced neoplasia was found in shorter follow-up time in *MLH1* and *MSH2* mutation carriers, the colonoscopy interval in *MSH6* and *PMS2* mutation carriers might be less stringent than for *MLH1* and *MSH2* mutation carriers.

Disclosure: Nothing to disclose

OP295 HIGH-DEFINITION WHITE-LIGHT COLONOSCOPY VERSUS CHROMOENDOSCOPY FOR SURVEILLANCE OF LYNCH SYNDROME. A MULTICENTER, RANDOMIZED AND CONTROLLED STUDY (ENDOLYNCH STUDY)

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Introduction: Adenomas in Lynch syndrome have an accelerated progression to colorectal cancer which might occur despite a regular follow-up. Despite low evidence, clinical guidelines recommend using high-definition technology and pan-chromoendoscopy (CE) for colonoscopy surveillance in Lynch syndrome.
Aims and Methods: We hypothesized that high-definition white-light endoscopy (WLE) could be equally effective than CE for detection of adenomas in patients with LS. We conducted a multicenter randomized controlled study with endoscopists with high ADR (39%-61% in screening colonoscopies), devoted to high-risk conditions of colorectal cancer. Patients with confirmed mismatch repair mutation were prospectively randomized 1:1 to WLE or CE. The main outcome was the adenoma detection rate (ADR). 122 subjects in each group were required to demonstrate non-inferiority of WLE versus CE as reference group (non- inferiority margin of 15%; power 80%; drop-out 10%; significance level of .025).
Results: 256 patients were included in 14 Spanish centers (26 endoscopists). Patient baseline characteristics are shown in the table. The ADR for WLE versus CE were 28.1% (95% confidence interval 21.1%-36.4%) versus 34.4% (26.4%-43.3%) respectively (p = 0.281). The detection rate of lesions in WLE versus CE group were as follow: total polyps 50.0% (41.5%-58.5%) versus 57.7% (58.6%-74.7%) (p = 0.004), serrated lesions 23.4% (16.9%-31.4%) versus 37.5% (29.5%-46.1%) (p = 0.015), proximal serrated lesions 10.2% (6.0%-16.6%) versus 11.7% (7.0%-18.4%) (p = 0.689), sessile serrated lesions 5.5% (2.4%-10.8%) versus 3.9% (1.6%-8.8%) (p = 0.554) and advanced adenomas 7.8% (4.3%-13.7%) versus 3.9% (1.6%-3.9%) (p = 0.183) respectively. The mean (± standard deviation) of lesions per patient for WLE versus CE were as follow: adenomas 1.04 (1.37) versus 0.86 (1.04) (p = 0.670), polyps 2.36 (1.77) versus 2.67 (2.29) (p = 0.004), serrated lesions 0.67 (0.89) versus 1.04 (1.38) (p = 0.004), proximal serrated lesions 0.25 (0.56) versus 0.25 (0.61) (p = 0.426), sessile serrated lesions 0.10 (0.31) versus 0.11 (0.67) (p = 0.660) respectively. The previous colonoscopy was performed with standard definition white-light with adequate bowel preparation. The total procedural time and withdrawal time (mean ± standard deviation; in minutes) were superior in the CE arm: 22.42 ± 8.72 versus 30.67 ± 12.84 (p < 0.001) and 13.5 ± 5.63 versus 18.37 ± 7.57 (p < 0.001) respectively.
Conclusion: In a scenario with expert endoscopists, high-definition WLE is an optimal and efficient endoscopic technique for surveillance of Lynch syndrome patients. CE prolonged the procedural time without increasing detection of relevant lesions.

	WLE n = 128	CE n = 128	p
Female sex (%)	55.5	64.1	0.161
Age -years- (standard deviation)	47.6 (13.6)	46.7 (14.3)	0.616
History of colorectal cancer (%)	21.9	20.3	0.759
History of extracolonic cancers (%)	20.3	21.1	0.877
MLH1 (%)	26.8	30.5	0.514
MSH2 (%)	44.1	39.1	0.415
MSH6 (%)	18.9	25.8	0.187
PMS2 (%)	9.4	3.9	0.076
Epcam (%)	0.8	0.8	0.996
Previous surveillance colonoscopies (%)	90.6	86.7	0.324
Elapsed time since last colonoscopy -months- (standard deviation)	16.7 (7.0)	17.8 (13.5)	0.425

[Patient baseline characteristics]

Disclosure: Nothing to disclose

Reference

1. Kamiński MF, Hassan C, Bisschops R, et al. Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2014; 46(5): 435–49.

OP296 RESULTS OF THE DANISH POLYPOSIS REGISTRY – FOCUS ON COLORECTAL CANCER IN THE 20TH CENTURY

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Introduction: Familial adenomatous polyposis (FAP) is an autosomal dominant disorder that predisposes to colorectal cancer (CRC). It is recommended that patients with FAP are monitored in national databases. The Danish Polyposis Registry is a nationwide, complete registry of FAP patients established in 1977 The aims of this study were to assess the current incidence and prevalence of colorectal cancer in FAP patients, the choice of surgical treatment, and finally to compare the course of disease for probands and call-up patients.
Aims and Methods: The annual incidence rate was calculated by diving number of newly diagnosed cases with the mean population for that year (Statistics Denmark), while the prevalence was calculated by dividing the number of FAP patients with the total population by end of the year (Statistics Denmark). The complete number of CRC was extracted from Nordcan. Probands were defined as patients diagnosed due to bowel symptoms and without any knowledge of hereditary bowel disease. Call-up patients were defined as screen detected patients diagnosed at prophylactic examination due to FAP diagnosis in first degree relatives.
Results: By the end of 2017, the Danish Polyposis Registry comprised 221 families with 722 affected individuals, including 610 with histologically verified FAP (309 probands and 311 call-ups). The annual incidence of FAP was 0.13/100,000, while the prevalence by the end of 2017 was 6.04/100,000. During 1999-2017, the proportion of FAP related CRC (n = 34), constituted only 0.05% of the all cases of CRC (n = 72,218) in Denmark. 198 (32%) patients had CRC when diagnosed with FAP. The rate of CRC at the time of the FAP diagnosis was significantly higher in probands compared to call-ups (62% vs. 2%, p < 0.0001). Of 610 patients with complete follow-up, 198 (32%) had CRC. Dukes classification was known in 154 patients; 26 (17%) were stage A, 42 (27%) stage B, and 86 (56%) stage C. Colectomy was the preferred surgical modality in 78%, rising from 52% before 1975, to 89% since 2002. The use of colectomy was significantly higher in call-ups (249/249) compared to probands (188/260) (100% vs. 73%, p < 0.0001). Of 295 patients with a known cause of death, 195 (66%) died of CRC, 37 from another malignant disease (13%), while 65 (22%) died from a non-malignant disease.
Conclusion: The Danish Polyposis Registry enables close monitoring of the rate of CRC and quality measurements as the rate of colectomy.
Disclosure: Nothing to disclose

WEDNESDAY, OCTOBER 24, 2018   08:30–10:00

From microbiota to immune mechanisms in CRC carcinogenesis – Room L8

OP297 PROFILES OF BACTERIA-DERIVED EXTRACELLULAR VESICLES IN STOOL, SERUM AND URINE IN PATIENTS WITH COLORECTAL CANCER: A PRELIMINARY STUDY

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Introduction: Alternations of gut microbiota is well-known in colorectal carcinogenesis. Gut microbiota-derived extracellular vesicles (EVs) are widely distributed throughout the body including the blood and urine. In this study, we investigated profiles of bacteria-derived EVs in stool, blood and urine, and evaluated whether they can be a useful marker for the metagenomic analysis of colorectal cancer (CRC).
Aims and Methods: This study incorporated 50 healthy controls and 14 patients with CRC. Information on anthropometric variables, location of tumor, cancer stage, and smoking and drinking habits were collected in patients with CRC. Additionally, we analyzed and compared the bacteria-derived EVs of the study subjects by using 16S ribosomal RNA gene sequencing of their stool, blood and urine samples, which allowed us to identify over 3,200 operational taxonomic units corresponding to gut microbiota reported in previous studies.

Results: In stool, non-EV bacterial microbiome, microbial diversity was significantly increased in CRC patients (Shannon index, p = 0.006); relative abundance of phylum Proteobacteria was decreased (FDR q = 0.003) and abundance of phylum Bacteroidetes was increased (q = 0.023) in CRC patients; abundances of families Rikenellaceae and Porphyromonadaceae were significantly different between controls and CRC patients (q < 0.05). In stool bacteria-derived EVs, microbial diversity was not different between controls and CRC patients (Shannon index, p > 0.05); relative abundances of family Comamonadaceae was significantly increased in CRC patients (q < 0.001). In urine bacteria-derived EVs, abundances of phylum Bacteroidetes (q = 0.003) was increased, whereas abundances of Fusobacteria was decreased (q = 0.005); abundances of families Pseudomonadaceae, Rhodocyclaceae, Comamonadaceae, and Oxalobacteraceae were different between the 2 groups (q < 0.01). In serum bacteria-derived EVs, abundances of phyla Proteobacteria and Bacteroidetes were increased (q < 0.001) and abundances of family Comamonadaceae was increased (q = 0.002).

Conclusion: In stool, EV-derived microbiome shows a distinct profile comparing to non-EV bacterial microbiome. These results suggest that some of the bacteria-derived EVs such as Comamonadaceae in stool, blood or urine may play a role in colorectal carcinogenesis and they might be surrogate markers for the diagnosis of CRC. Further studies are necessary to clarify this issue.

Disclosure: Nothing to disclose

OP298 *FUSOBACTERIUM NUCLEATUM* PROMOTE METASTASIS OF COLORECTAL CANCER

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Introduction: *Fusobacterium nucleatum* (*F. nucleatum*) is among the most prevalent bacterial species in colorectal cancer (CRC) tissues and play an important role in colorectal carcinogenesis [1, 2]. A recent study reported *Fusobacterium* strains were consistently detected in primary tumors and paired metastases, suggesting that *Fusobacterium* might travels with the primary tumor cells to distant sites, as part of metastatic tissue colonization [3]. However, whether *F. nucleatum* could drive the metastasis of colorectal cancer is remained to be clarified. We aimed to clarified the role of *F. nucleatum* in metastasis of colorectal cancer.

Aims and Methods: The abundance of *F. nucleatum* in fecal samples from CRC patients and healthy people were detected by quantitative real-time PCR. Colorectal cancer cell lines were incubated with *F. nucleatum* or phosphate buffer saline (PBS control) and analyzed migration and invasion by transwell and wound healing assays. Cells were incubated with *F. nucleatum* or PBS and injected into tail vein of nude mice and metastasized nodules in the lungs were counted. The relative expression of matrix metalloproteinases (MMPs) were analyzed by quantitative real-time PCR and western blot.

Results: The relative abundance of *F. nucleatum* was increased in fecal samples of colorectal patients compared with healthy people (N = 30, T = 37). Furthermore, the abundance of *F. nucleatum* in fecal samples from CRC patients with lymph nodes metastasis was more than patients without metastasis. *F. nucleatum* co-culture promote CRC cells migration and invasion *in vitro*. Similarly, injection of CRC cells infected with *F. nucleatum*. We found MMPs (MMP-1, MMP-3, MMP-7, MMP-9, MMP-12) were significantly upregulated in CRC cells incubated with *F. nucleatum* vs. PBS.

Conclusion: Our research firstly provided novel evidence that *F. nucleatum* promote metastasis of colorectal cancer, suggesting tumor microbiota are essential components of the cancer micro-eviroment.

Disclosure: Nothing to disclose

References

1. Yu, J., Q. Feng, etc, Metagenomic analysis of faecal microbiome as a tool towards targeted non-invasive biomarkers for colorectal cancer. *Gut*, 2017. 66(1): 70–78.
2. Yang, Y., W. Weng, ect, Fusobacterium nucleatum Increases Proliferation of Colorectal Cancer Cells and Tumor Development in Mice by Activating TLR4 Signaling to NFkappaB, Upregulating Expression of microRNA-21. *Gastroenterology*, 2016.
3. Bullman, S., C.S. Pedamallu, etc, Analysis of Fusobacterium persistence and antibiotic response in colorectal cancer. *Science*, 2017. 358(6369): 1443–1448.

OP299 CONCOMITANT REDUCTION OF CD4CD8AA LYMPHOCYTES IN BLOOD AND OF FAECALIBACTERIUM PRAUSNITZII IN INTESTINAL MICROBIOTA IN PATIENTS WITH COLORECTAL CANCER

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Introduction: Changes in the intestinal microbiota composition, with potential contribution in carcinogenesis, have been reported in patients with colorectal cancer (CRC). In particular, a decrease in the *Faecalibacterium prausnitzii* (*F. prausnitzii*) population has been identified. A CD4/CD8aa double positive lymphocyte population (CD4CD8aa) has been identified in human colonic mucosa and peripheral blood. This population has a phenotype and a cytokinic profile common to regulatory Treg lymphocytes and has a TCR repertoire with specificity for *F. prausnitzii*. Their serum concentrations are significantly reduced in patients with chronic inflammatory bowel disease (IBD).

Aims and Methods: The objectives of this work were: 1) to detect dysbiosis in the fecal microbiota of patients with CRC by metagenomic analysis 2) to investigate changes in the levels of CD4CD8aa circulating lymphocytes specific for *F. prausnitzii*. Patients with CRC without IBD and control subjects were included prospectively. None had received antibiotics in the previous month or any anti-tumor treatment. A stool sample was collected for each participant, immediately frozen at -80°C until analysis. The CD4CD8aa population was identified and quantified on fresh whole blood by flow cytometry with anti-CD3, anti-CD4 and anti-CD8a co-labelling.

Results: 21 patients with CRC (mean age 66 years [extremes 44-79], mean body mass index 25.2 kg/m^2, right colon cancer n = 7, left colon cancer n = 7, rectal cancer n = 6) and 20 controls subjects (mean age 66 years [extremes 46-79], mean body mass index 26.4 kg/m^2) were included. Fecal microbiome diversity was not different between the 2 groups (Permanova, Bray-Curtis distance, p = 0.086). The mean relative abundance of *F. prausnitzii* was significantly decreased in CRC patients compared with controls (0.018 +/- 0.015 versus 0.043 +/- 0.030, respectively, p = 0.01). 2 other bacterial species were also decreased in CRC patients compared with controls: *Eubacterium hallii* and *Eubacterium siraeum*. The mean absolute count of CD4CD8aa in the blood among CD3 + was significantly lower in patients compared with control subjects (2.21 +/-5.47 versus 1.50 +/-1.4, respectively, p = 0.04). There was a non-statistically significant decrease in mean absolute count of CD4CD8aa among CD4 + (3.10 +/-7.16 versus 2.25 +/- 2.10, p = 0.07).

Conclusion: This work 1) objectives in metagenomic analysis the presence of fecal microbiota dysbiosis in patients with CRC, 2) shows a concomitant decrease in the frequency of the CD4CD8aa regulatory lymphocyte population among circulating T cells and the *F. prausnitzii* population in the fecal microbiota of these patients. This dysbiosis and this modification of the regulatory lymphocyte population could be involved in colonic carcinogenesis.

Disclosure: This work has been supported by Biocodex (research grant) and the SNFGE Robert Tournut grant.

OP300 ROLE OF INFLAMATORY RESPONSE, INSULIN RESISTANCE AND ENVIRONMENTAL FACTORS IN NON-FILIATED ATTENUATED POLYPOSIS

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Introduction: In the majority of patients with multiple colonic polyps, no genetic or other causes are found for their pathology. The presence of an increased inflammatory response in the context of a metabolic syndrome could predispose to this condition.

Aims and Methods: The aim of this study is to analyze the presence of inflammatory cytokines and levels of glucose, insulin and C-reactive protein (CRP) in serum of patients with multiple colonic polyps and compare it with healthy patients' serum. Factors such as smoking and the presence of Diabetes Mellitus (DM) are also analyzed. 83 patients with 10 or more adenomatous or serrated polyps from the EPIPOLIP multicenter project, in which 22 hospitals participated, were included. Individuals with hyperplastic rectosigmoid polyps as the only alteration were excluded. In turn, 53 individuals with normal colonoscopy from the CCR screening program of the Valencian Community were included as controls. Glucose, C-reactive protein and basal insulin were determined. Quantification of IL-2, IL-4, IL-6, IL-10, IL-11, IL-17A and IL-23 cytokines levels in serum was performed by enzyme-linked immunosorbent assay (ELISA) and Data analysis was performed using the SPSS statistical analysis tool.

Results: The mean age of diagnosis in both groups was 60 years. We included 71 men (86%) and 12 women (14%) in the case group and 43 (81%) men and 10

(19%) women in the control group. We found a significant increase of IL-2, IL-4, IL-6, IL-17A and IL-23 in the serum of patients with polyposis compared to controls (p = 0.001, p = 0.001, p = 0.001, p = 0.001, p = 0.014 respectively). We did not detect significant differences of IL-11 and IL-10 between both groups (p = 0.164, p = 0.4). A significant increase of CRP was found in the group of patients with polyposis; however, the HOMA index did not present significant differences. We found a significantly higher number of smokers in the group of patients with polyposis than the control group (67% vs 16%, p = 0.001) respectively. Also, a significantly higher percentage of cases had DM (11% vs. 5%, p = 0.01). 24% of individuals with polyposis developed CC.

Conclusion: The high concentration of CRP and presence of high levels of IL-2, IL-4, IL-6, IL-23 and IL-17A in the group of patients with polyposis indicates the presence of an inflammatory response in these patients. Signaling by IL-23/IL-17A axis along with other cytokines and other factors such as tobacco consumption and DM may be playing an important role in the development of polyposis in these patients.

Disclosure: Nothing to disclose

OP301 COMBINED LOW DENSITIES OF FOXP3^{+} AND CD3^{+} TUMOR-INFILTRATING LYMPHOCYTES FOR THE INTRA-STAGE II IDENTIFICATION OF COLORECTAL CANCERS WITH THE HIGHEST RISK OF PROGRESSION

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Introduction: The densities of CD3^{+} and CD8^{+} tumor-infiltrating lymphocytes (TILs) in association with TNM-staging may modify prognostic estimates of non-metastatic colorectal cancer (CRC), potentially leading to an innovative Immunoscore forecasting system. FoxP3^{+}TILs, not included in the Immunoscore, may as well impact on CRC prognosis. Implementing the immune classification of CRC, we compared the prognostic weight of CD3^{+}, FoxP3^{+}TILs, and TNM classifiers for predicting the outcome of patients with stage II and III CRC.

Aims and Methods: The surface covered by FoxP3^{+} and CD3^{+}TILs at the invasive front of 413 stage II-III CRC and TNM classifiers were first challenged by classification and regression tree analysis (CART) by recursive partitioning to identify independent prognostic factors. Significant prognostic factors and their interactions were then re-assessed by logistic regression and Cox modeling, also in a validation set of 215 stage II CRCs.

Results: In the trial set, recursive partitioning recognized an influence of TILs on recurrence risk only within the decisional tree of stage II. Low-FoxP3^{+}TIL densities ranked first (OR 5.20; 95% CI, 2.26–11.9; p < 0.001), and low-CD3^{+}TILs further stratified the risk (OR, 4.46; 95% CI, 1.58–12.6; p < 0.001) of low-FoxP3^{+} patients. Linear regression analysis showed no correlation (p = 0.26) between the density of FoxP3^{+} TILs and that of CD3^{+} cells. At standard multivariate analysis, TILs interacted with stage (FoxP3^{+}, p = 0.06; CD3^{+}, p = 0.02) and MS-instability (FoxP3^{+}; p = 0.02). In stage II MS-stable cancers, concomitant low-FoxP3^{+}/low-CD3^{+}TILs identified patients with the highest risk of progression in the trial (HR 7.24; 95% CI, 3.41–15.4; p < 0.001), and in the validation (HR 15.16; 95% CI, 3.43–66.9; p < 0.001) sets. At ROC curve analysis of the trial set, TIL densities identified recurrences in stage II MSS CRCs with an AUC of 0.75 for FoxP3^{+} TILs, and of 0.71 for CD3^{+} cells. In the validation set, the AUCs were superimposable to those of the trial set (0.77 for FoxP3^{+}, and 0.71 for CD3^{+} TILs). In pooled stage II analysis, patients with concomitant low-TILs had the poorest survival, irrespectively of allocation to adjuvant therapy (43.5%) or to surveillance (45.5%; p = 1.0).

Conclusion: Combined assessment of independent FoxP3^{+}-CD3^{+}TILs accurately forecast the outcome of stage II microsatellite-stable CRC patients, eventually outplayed by nodal invasion. By contributing to improved stratification of the recurrence risk, TIL assessment may clarify what patients would benefit from adjuvant chemotherapy in stage II CRC. Combinations of the measurements of two independent TIL populations can be inspected for determining refined thresholds at which their prognostic (and predictive) value is maximized. The foretelling power of TILs warrants refinement using data from randomized controlled trials, to establish interactions with TNM and the with post-surgical treatments.

Disclosure: Nothing to disclose

OP302 RNASEH2-GUIDED RIBONUCLEOTIDE EXCISION REPAIR PREVENTS INTESTINAL TUMORIGENESIS

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Introduction: Insufficient repair of DNA lesions results in the acquisition of somatic mutations and displays the driving force in cancerogenesis. Ribonucleotide incorporation by eukaryotic DNA polymerases occurs during every round of genome duplication and represents by far the most frequent type of naturally occurring DNA lesions. RNAse H2 removes misincorporated ribonucleotides from genomic DNA in a process termed ribonucleotide excision repair (RER). Whether intestinal epithelial proliferation requires RER and whether abrogation of RER is involved in the etiology of cancerogenesis at all is unknown.

Aims and Methods: Mice with an epithelial specific deletion of RNase H2 subunit b (H2b$^{\Delta IEC}$) and co-deletion of the tumor suppressor p53 (H2b/p53$^{\Delta IEC}$) were generated and phenotyped at young and old age. RNA sequencing was performed in isolated epithelial cells and intestinal organoids. Mutational signature of spontaneous tumors from H2b/p53$^{\Delta IEC}$ mice were characterized using exome sequencing. Association of tumor RNase H2 expression and patient survival was assessed in transcriptome data from 467 CRC patients.

Results: H2b$^{\Delta IEC}$ mice display chronic epithelial DNA damage and develop a p53-dependent proliferative exhaustion of the intestinal stem cell compartment. H2b/p53$^{\Delta IEC}$ mice have restored epithelial proliferation and spontaneously develop small intestinal carcinomas. Resulting tumors display a distinct mutational signature characterized by T > G base substitutions at GpTpG trinucleotides. Transcriptome data from human colorectal cancer patients indicate that reduced RNase H2 expression is associated with poor survival in CRC.

Conclusion: We propose a hitherto unappreciated role for RNase H2 as a tumor suppressor gene in CRC. Our mouse model provides a novel tool to study the impact of abrogated RER on intestinal carcinogenesis.

Disclosure: Nothing to disclose

WEDNESDAY, OCTOBER 24, 2018   10:30–12:00
IBD clinical trials II – Room E2

OP303 EFFICACY AND SAFETY OF MIRIKIZUMAB (LY3074828) IN PATIENTS WITH MODERATE-TO-SEVERE ULCERATIVE COLITIS IN A PHASE 2 STUDY

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Introduction: The cytokine IL-23 is involved in inflammatory bowel disease pathogenesis. A Phase 2, multi-centre, randomised, double-blind, placebo (pbo)-controlled trial (NCT02589665) of mirikizumab (miri; IL-23p19 antibody) was conducted to evaluate miri's efficacy and safety in patients with moderate-to-severe ulcerative colitis (UC). The primary objective was to evaluate superiority of miri to pbo in inducing clinical remission at wk 12. Other objectives included clinical response, safety, and adjunctive inflammatory markers [faecal calprotectin (fCLP), serum C-reactive protein (CRP)]. The ongoing study's completed induction phase results are reported here (presented at DDW 2018).

Abstract No: OP303
Table 1.

Treatment Groups

Mean (SD), unless otherwise indicated	Pbo (N = 63)	Miri 50 mg (N = 63)	Miri 200 mg (N = 62)	Miri 600 mg (N = 61)	Miri All (N = 186)
Baseline Characteristics at Week 0					
Age, years	42.6 (13.5)	41.8 (14.1)	43.4 (14.7)	42.4 (13.4)	42.5 (14.0)
Male, n (%)	36 (57.1)	38 (60.3)	37 (59.7)	38 (62.3)	113 (60.8)
Weight, kg	74.1 (16.9)	77.0 (17.2)	75.6 (17.3)	73.0 (15.1)	75.2 (16.6)
Modified Mayo Score	6.65 (1.18)	6.58 (1.34)	6.39 (1.38)	6.53 (1.26)	Not calculated
Faecal calprotectin, mg/kg	2264 (3425)	2972 (3868)	2067 (2964)	3215 (6197)	2740 (4505)
Serum CRP, mg/L	8.7 (13.4)	9.3 (12.9)	9.1 (12.9)	14.6 (25.9)	11.0 (17.1)
Week 12					
Clinical remission[2], n (%)	3 (4.8)	10 (15.9)	14 (22.6)**	7 (11.5)	31 (16.7)*
Clinical response[3], n (%)	13 (20.6)	26 (41.3)*	37 (59.7)***	30 (49.2)**	93 (50.0)***
Faecal Calprotectin, mg/kg, change from baseline	387 (5456)	−425 (3769)†	−1268 (3117)†	−2062 (7320)†	−1219 (4957)*
Serum CRP, mg/L, change from baseline	3.0 (22.2)	−2.8 (12.5)†	−4.6 (12.0)†	−9.2 (26.5)†	−5.5 (18.2)**
TEAEs, n (%)	32 (50.8)	36 (57.1)	32 (51.6)	32 (53.3)	100 (54.1)
Serious adverse events, n (%)	2 (3.2)	0 (0)	2 (3.2)	3 (5.0)	5 (2.7)
Discontinuations from study due to adverse events, n (%)	3 (4.8)	0 (0)	1 (1.6)	2 (3.3)	3 (1.6)

P-value vs. Pbo *p < 0.05; **p < 0.01; ***p < 0.001; † P value not determined [1] Exposure-based dosing- dose increased at day 29 or 57 if [Miri]$_{serum}$ < 0.5 or 2.0 mcg/mL for miri 50 mg and 200 mg, respectively. [2] Clinical remission- 9 pt Mayo subscore for rectal bleeding = 0, stool frequency = 0 or 1 with ≥ 1 point decrease from baseline, and endoscopy = 0 or 1, excluding PGA [3] Clinical response- 9-point Mayo subscore decrease ≥ 2 points and ≥ 35% change from baseline, including either decrease in rectal bleeding subscore of ≥ 1 pt or rectal bleeding score of 0 or 1, excluding PGA

Aims and Methods: Patients with moderate-to-severe UC (Mayo score of 6 to 12; endoscopic subscore ≥2) were randomized at equal ratios to receive pbo (N = 63), miri 50 mg (N = 63) or 200 mg (N = 62) with possibility of exposure-based[1] increases (2-12-fold or 1.5–3-fold, respectively, up to a 600 mg dose), or a fixed miri 600 mg (N = 61) dose intravenously at wks. 0, 4, and 8. Patients could receive oral 5-ASA or corticosteroids (≤20 mg/d prednisone equivalent), thiopurines, must have failed ≥ 1 conventional UC therapy, and could be naïve to or had prior exposure to biologics. Endoscopic videos were read centrally by experts blinded to treatment allocation and time point. Comparisons of rates of clinical remission[2] (primary outcome) and clinical response[3] were made using logistic regression analysis.
Results: Baseline characteristics were similar among treatment groups, although mean fCLP and CRP levels were higher in the miri 600 mg group. Most patients (63%) had been previously exposed to or failed biologic therapy, with 9.5% and 11.3% in the pbo and pooled miri (Miri all) groups receiving ≥ 3 biologics, respectively. At wk 12, clinical remission rates were greater (p < 0.01) in patients treated with miri 200 mg, but not miri 50 mg or miri 600 mg, versus pbo-treated patients. Clinical response rates at wk 12 were greater (p < 0.05) for all miri groups, compared to pbo group. At wk 12, fCLP and CRP levels were reduced (p < 0.05 and < 0.01, respectively) in the Miri All group versus pbo. There were similar rates of serious adverse events and treatment-emergent adverse events (TEAEs) across treatment groups.
Conclusion: Miri demonstrated efficacy in the induction treatment for patients with moderate-to-severe UC, as assessed by multiple measures. Miri treatment reduced faecal calprotectin and CRP levels across all doses compared to baseline. Overall adverse event frequencies were similar for miri and pbo-treated patients. These are the first data evaluating the efficacy of an IL-23p19 antibody in patients with UC.
[Results Table]

OP304 CORRELATION BETWEEN CLINICAL AND ENDOSCOPIC ENDPOINTS AND REMISSION PER INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE SCORE IN PATIENTS WITH CROHN'S DISEASE: DATA FROM CELEST

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Introduction: Crohn's Disease Activity Index (CDAI) remission (CDAI < 150) has been shown to correlate with Inflammatory Bowel Disease Questionnaire (IBDQ) remission (IBDQ ≥170). However, the correlation between new clinical endpoints that focus on patient-reported outcomes and quality of life is not well understood. We examined the relationship between definitions of clinical remission/endoscopic improvement and IBDQ defined remission and IBDQ changes.
Aims and Methods: In CELEST, adults with active CD (CDAI 220-450), an average daily very soft/liquid stool frequency (SF) ≥2.5 or daily abdominal pain (AP) score ≥2.0, and Simplified Endoscopic Score for CD (SES-CD) ≥6 (≥4 for those with isolated ileitis) were randomised to placebo or upadacitinib (UPA) 3, 6, 12, or 24 mg twice daily, or 24 mg once daily for 16 wks. Patients who completed wk 16 were re-randomised to receive UPA 3, 6, 12 mg BID, or 24 mg QD for 36 wks. This analysis included patients who received UPA induction treatment for 16 wks and patients who achieved clinical response to UPA at wk 16 and continued to receive UPA until wk 52. The proportion of patients who achieved clinical remission (SF≤2.8 and AP≤1.0, both not worse than baseline [BL], among patients with BL SF ≥4 or AP score ≥2) at wk 16 and 52 and endoscopic improvement (decrease in SES-CD >50% from BL or endoscopic remission, defined as SES-CD ≤4 and ≥2-point reduction from BL and no subscore >1) at wk 12/16 and 52 were analysed by IBDQ remission cut-offs (<170 or ≥170). Correlation of efficacy endpoints (yes/no) with IBDQ score at wk 16 and 52 were assessed with polychoric correlation and 2-sided Wald Chi-square test. Changes from BL in IBDQ score at wk 16 and 52 were also assessed by clinical remission or endoscopic improvement status at wk 12/16 and 52.
Results: A high correlation between clinical remission and IBDQ remission (IBDQ≥170) was observed at wk 16 and 52 (p < 0.001; **Table**). A moderate to high correlation was seen between endoscopic improvement and IBDQ remission at both time points (p < 0.001; **Table**). The mean change from BL to wk 16 and 52 in IBDQ score was numerically higher in patients who achieved clinical remission at wk 16 and 52 (70.1 and 82.0, respectively) vs those who did not (18.9 and 33.1). Similarly, patients who achieved endoscopic improvement at wk 12/16 and 52 had numerically higher mean changes from BL to wk 16 and 52 in IBDQ score (57.2 and 67.3, respectively) vs patients who did not (24.2 and 39.8).
Conclusion: In the phase 2 CELEST study of UPA in patients with CD, the new definitions of clinical remission and endoscopic improvement correlated significantly with improved quality of life.

Endpoint	Week	IBDQ ≥170 n/N (%)	IBDQ <170 n/N (%)	Polychoric correlation
Clinical remission	16	30/49 (61.2%)	12/93 (12.9%)	0.727; p<0.001
	52	27/35 (77.1%)	8/36 (22.2%)	0.760; p<0.001
Endoscopic improvement	12/16	28/54 (51.9%)	14/99 (14.1%)	0.616; p<0.001
	52	24/36 (66.7%)	12/40 (30%)	0.545; p<0.001

IBDQ, Inflammatory Bowel Disease Questionnaire; SES-CD, Simplified Endoscopic Score for Crohn's disease.
Clinical remission defined as SF≤2.8 and AP≤1.0 (both not worse than baseline)

Continued

Endpoint	Week	IBDQ ≥170 n/N (%)	IBDQ <170 n/N (%)	Polychoric correlation

Endoscopic improvement (defined as decrease in SES-CD >50% from baseline) or endoscopic remission (defined as SES-CD ≤ 4 and ≥2-point reduction vs induction baseline and no subscore >1 in any individual variable).

[Table: Correlation between clinical remission or endoscopic improvement and IBDQ remission at weeks 12/16 and 52]

OP305 TIME TO LOSS OF EFFICACY FOLLOWING TOFACITINIB INTERRUPTION IN PATIENTS WITH ULCERATIVE COLITIS: RESULTS FROM OCTAVE SUSTAIN

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Introduction: Patients with adequately controlled ulcerative colitis (UC) may have a need to stop pharmacological treatment for a range of reasons, including adverse events, to accommodate surgery or transition of care.[1] Tofacitinib is an oral, small molecule Janus kinase inhibitor that is being investigated for UC. This analysis included patients with clinical response to 8 weeks of tofacitinib treatment in OCTAVE Induction 1 & 2 (NCT01465763 & NCT01458951), who were subsequently randomised to receive placebo in the 52-week OCTAVE Sustain maintenance study (NCT01458574),[2] ie a surrogate for treatment interruption.

Aims and Methods: We aimed to evaluate time to treatment failure following treatment interruption for clinical responders to tofacitinib as induction therapy. Treatment failure was defined, based on total Mayo score, as increase ≥3 points from OCTAVE Sustain baseline total Mayo score, plus increase in rectal bleeding subscore and endoscopic subscore ≥1 point and absolute endoscopic subscore ≥2 points. Patients with treatment failure after ≥8 weeks in OCTAVE Sustain were required to discontinue the study. Dropouts due to insufficient clinical response were treated as treatment failures. Event rates for treatment failure and quartile event times were estimated based on the Kaplan-Meier method.

Results: This analysis included 174 patients who had tofacitinib induction therapy and were randomised to placebo in OCTAVE Sustain. Baseline demographics and disease characteristics were consistent with the overall study population (Table);[2] 52 patients (29.9%) were in remission at OCTAVE Sustain baseline. The cumulative proportions of patients with treatment failure over time in OCTAVE Sustain are summarised in the Table. At Week 52 of OCTAVE Sustain, 124 patients (75.3%) had treatment failure. The estimated first, second and third quartiles for time to treatment failure were 65, 135 and 371 days, respectively. Using non-responder imputation, rates of remission, mucosal healing and clinical response at Week 52 of OCTAVE Sustain in the placebo group population were 10.3%, 12.6% and 19.0%, respectively. In this placebo group, the most frequent reason for discontinuation from the study was insufficient clinical response (including worsening UC: 69.5% of patients). Subsequent retreatment with tofacitinib 10 mg twice daily in an open-label extension study recaptured remission, mucosal healing and clinical response in 40.4%, 55.4% and 75.8% of patients, respectively, by Month 2.[3]

Conclusion: For patients with initial clinical response to 8 weeks of tofacitinib induction therapy, treatment failure occurred a median of 135 days after tofacitinib interruption, ie following re-randomisation to placebo in OCTAVE Sustain.

Table. Baseline demographics and disease characteristics, summary of efficacy and safety, and time to treatment failure for the tofacitinib treatment interruption population in OCTAVE Sustain

	Tofacitinib treatment interruption population N = 174[a]
Baseline demographics and disease characteristics	
Age in years, mean (SD)	43.2 (14.0)
Male, n (%)	103 (59.2)
OCTAVE Sustain baseline total Mayo score, mean (SD)	3.2 (1.9)
Efficacy at baseline of OCTAVE Sustain, n (%)	
Remission	52 (29.9)
Mucosal healing	87 (50.0)
Clinical response	172 (98.9)
Efficacy at Week 52 of OCTAVE Sustain, n (%)	
Remission	18 (10.3)
Mucosal healing	22 (12.6)
Clinical response	33 (19.0)
Summary of safety in OCTAVE Sustain, n (%)	
AEs	132 (75.9)
SAEs	12 (6.9)
Discontinued due to AE	5 (2.9)
Discontinued due to insufficient clinical response (including worsening UC)	121 (69.5)
Estimated cumulative event rate at OCTAVE Sustain time point	**Treatment failure, n (%)[b]**
Baseline	0 (0.0)
Week 4	2 (1.2)
Week 8	45 (26.6)
Week 16	78 (46.3)
Week 24	109 (65.3)
Week 32	115 (69.1)
Week 40	120 (72.2)
Week 52	124 (75.3)
Time to event, days	
First quartile	65
Second quartile	135
Third quartile	371

[a]Patients with clinical response to 8 weeks of tofacitinib induction therapy and randomised to placebo in OCTAVE Sustain; [b]Based on N = 169 evaluable patients.
AE, adverse event; N, number of evaluable patients; n, number of patients with event; SAE, serious adverse event; SD, standard deviation; UC, ulcerative colitis.
[Table]

References

1. Pariente B, Laharie D. *Aliment Pharmacol Ther* 2014; 40: 338–53.
2. Sandborn WJ et al. *N Engl J Med* 2017; 376: 1723–36.
3. Panés J et al. *J Crohns Colitis* 2018; 12(Suppl 1): P516.

OP306 EFFICACY AND SAFETY OF USTEKINUMAB FOR CROHN'S DISEASE: RESULTS FROM IM-UNITI LONG-TERM EXTENSION THROUGH 3 YEARS

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Introduction: Ustekinumab (UST) is a fully human mAB to IL 12/23p40 approved for the treatment of moderate-to-severe active Crohn's disease (CD). The ongoing IM-UNITI long-term extension (LTE) evaluates the efficacy and safety of subcutaneous (SC) UST through approximately 5 years of treatment, with results through wk156 (efficacy assessed at wk152) reported herein.
Aims and Methods: 1281 patients (pts) entered the maintenance study, including 397 UST induction responders in the primary population (randomized to SC placebo (PBO), n = 133; UST 90mg q12w, n = 132; or UST 90mg q8w, n = 132). A 1-time dose adjustment to 90mg q8w occurred in randomized pts who met loss of response criteria between wks8 & 32. Non-randomized pts included: PBO induction responders who continued on PBO, non-responders to PBO induction who received UST 130mg IV then UST 90mg SC q12w if in clinical response at wk8, and non-responders to UST induction who received UST 90mg SC and if in clinical response at wk8 continued on q8w. All pts who completed treatment through wk44 were eligible to enter the LTE continuing on the same treatment they were on at wk44; no dose adjustment occurred in the LTE. This included 567 UST-treated pts, of which 237 were from the primary population. PBO-treated patients discontinued treatment after the study unblinding, which occurred after the Wk44 DBL. Efficacy was collected every 12wks prior to the study unblinding and then at q12w or q8w UST dosing visits.
Results: Discontinuation of study agent prior to wk156 occurred in 29.6% of 567 UST-treated pts. Table 1 presents analyses for randomized pts who entered the LTE where pts with missing data or who terminated study participation prior to wk152 are assumed not to be in response or remission at wk152, with 61.9% of q12w pts & 69.5% of q8w pts (non-dose adjusted) in remission at wk152. Among all UST-treated pts, remission rates at wk152 were 56.3% & 55.1% for q12w and q8w, respectively. In an ITT analysis of randomized pts from wk 0 of maintenance through wk152, 38% (49/129) of UST induction responder q12w pts and 43% (55/128) of q8w pts were in remission at wk152. Antibody to UST rates through wk156 remained low, occurring in 4.0% (8/202) of randomized patients continuously receiving UST (which excludes randomized PBO dose adjusters) and 4.8% (27/567) of all pts treated with UST. Safety events (per hundred patient-years) were not higher among all UST-treated pts entering the LTE compared to PBO from wk44 through wk156, including overall AE's (325.26 vs 358.8), SAEs (19.4 vs 23.11), and serious infections (4.14 vs 4.62), with 1061.6 patient-years of follow-up among UST-treated pts and 173.1 patient-years of follow-up among PBO pts. Among all UST-treated pts, there were 3 deaths (ESRD, acute MI, sepsis) between weeks 96 and 156. There were 2 non-NMSC malignancies (adenocarcinoma of the small intestine and CML) reported between wks96 and 156.
Conclusion: SC UST maintained clinical response and remission through 3 years in a substantial proportion of patients, particularly those who were naïve to TNF antagonists. UST was well-tolerated through 3 years, with no new safety signals observed.

	Continuous 90 mg UST Q12 wks (n = 84)	Continuous 90 mg UST Q8wks (n = 82)	Patients with Prior Dose-adjustment (n = 71)	All UST-treated (n = 237)
Clinical Remission (%)	61.9	69.5	47.9	60.3
Clinical Response (%)	67.9	76.8	60.6	68.8
Clinical Remission and not receiving corticosteroids at Week 152 (%)	54.8	61.0	39.4	52.3
Clinical Remission in patients refractory or intolerant to TNF-antagonists	14/32 (43.8%)	16/27 (59.3%)	14/32 (43.8%)	44/91 (48.4%)
Clinical Remission in patients naïve to TNF-antagonists	27/38 (71.1%)	28/39 (71.8%)	16/28 (57.1%)	71/105 (67.6%)

[Table 1: IM-UNITI Efficacy Assessments at Week 152 Among Randomized Patients who entered LTE]

Disclosure: This study was funded by Janssen Research & Development, Inc.

OP307 LONG-TERM SAFETY AND EFFICACY OF RISANKIZUMAB TREATMENT IN PATIENTS WITH CROHN'S DISEASE: INTERIM RESULTS OF THE ONGOING PHASE 2 OPEN-LABEL EXTENSION STUDY

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Introduction: The efficacy and safety of risankizumab (RZB), an IL-23 inhibitor, as induction and maintenance treatment in patients (pts) with moderate-to-severe Crohn's disease (CD) have been previously described.[1,2] Pts who responded to RZB in the Ph2 induction and maintenance study[2] could enrol in an open-label extension (OLE) study. Interim efficacy and safety of RZB maintenance treatment, up to 2 years, are reported from the ongoing OLE.
Aims and Methods: Pts who achieved clinical response (decrease from baseline [BL] in CD Activity Index [CDAI] ≥100) without remission (CDAI < 150) after Period 2 (week 26) or clinical response and/or remission after Period 3 (week 52) of the preceding study[1] were enrolled to receive open-label 180 mg s.c. RZB every 8 weeks for up to 216 weeks. Pts who lost clinical response or remission after completion of the preceding study were re-induced with open-label 600 mg i.v. RZB infusions at weeks 0, 4, 8. Pts could only receive subsequent 180 mg s.c. RZB maintenance treatment if they achieved response or remission following re-induction treatment. Ileocolonoscopy was performed at yearly visits. Treatment-emergent adverse events (AEs) were collected throughout the study participation for up to 15 weeks after the last dose of study drug or up to the data cut-off date of March 31, 2018. Efficacy data (clinical remission and endoscopic remission [CD Endoscopic Index of Severity (CDEIS) ≤4 or CDEIS ≤2 for pts with initial isolated ileitis]) are reported up to week 48, when all pts enrolled in the OLE had the opportunity to reach the visit date before the interim cut-off date. Non-responder imputation (NRI) was used for missing data.
Results: A total of 65 adults with CD were enrolled, including 4 pts who were re-induced. At BL of preceding study, median (range) age 34 (19-67) years and median disease duration 10 (2-38) years; 60 pts (92.3%) were previously exposed to TNF antagonists; 13 pts (20%) and 21 pts (32.3%) were receiving corticosteroids and immunomodulators, respectively, at BL of preceding study. The mean (SD) exposure to RZB was 657.2 (190.73) days (Median: 689; Range: 164-900). As of the data cut-off date, 14 (21.5%) pts have prematurely discontinued from the study. At Week 0 of the current study, 48/65 (73.9%) pts were in clinical remission and 28/65 (43.1%) pts had endoscopic remission. Clinical remission rates were sustained up to week 48 (Table). The proportion of pts with endoscopic remission increased from BL to week 48 (Table). AEs were reported for 58/65 (89.2%) pts; 18 (27.7%) pts had serious AEs. The most common AEs occurring in >10% of pts were nasopharyngitis (26.2%), fatigue (16.9%), arthralgia, and worsening CD (15.4% each). 4 serious infections in 5 pts were perianal abscess (1 pt), *Campylobacter* infection (1 pt), viral gastroenteritis (2 pts), and peritonitis (2 pts). No events of tuberculosis, malignancies, or deaths occurred in the study.

	Clinical remission n/N (%)	Endoscopic remission[a] n/N (%)
Week 0[b]	48/65 (73.8)	27/65 (41.5)
Week 8	47/65 (72.3)	
Week 16	46/65 (70.8)	
Week 32	48/65 (73.8)	
Week 48	45/65 (69.2)	35/65 (53.8)

All patients in the OLE had the opportunity to reach the week 48 visit before the cut-off date. [a]Data are from central reading [b]Visits in OLE
[Proportion of pts achieving clinical remission and endoscopic remission by visit in pts receiving open-label 180 mg SC RZB maintenance treatment (NRI)]

Conclusion: In this interim analysis, clinical and endoscopic remission was sustained in pts with CD receiving long-term open-label RZB treatment. The safety profile of RZB remains consistent with previously published safety data.[2] No new safety signals were identified.

References

1. Feagan BG et al., *Lancet*. 2017, 29; 389(10080): 1699–1709.
2. Feagan BG et al., *Gastroenterology*, 2017, 152; (5): S1310.

OP308 LONG-TERM SAFETY OF THE ANTI-MUCOSAL ADDRESSIN CELL ADHESION MOLECULE-1 (MADCAM-1) ANTIBODY SHP647 IN ULCERATIVE COLITIS: AN OPEN-LABEL EXTENSION STUDY (TURANDOT II)

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Introduction: SHP647 is a fully human IgG_2 monoclonal antibody that binds to human mucosal addressin cell adhesion molecule-1 (MAdCAM-1) to reduce lymphocyte homing to the gastrointestinal tract. In a 12-week (wk), randomized, double-blind phase 2 trial (TURANDOT; NCT01620255), SHP647 was well tolerated and superior to placebo for the induction of remission in patients with ulcerative colitis (UC).[1]

Aims and Methods: This phase 2, multicentre, 2-part, open-label (OL) extension study (TURANDOT II; NCT01771809) assessed the long-term safety and tolerability of SHP647 in patients with moderate-to-severe UC who previously completed the induction study TURANDOT I on placebo or 7.5mg, 22.5mg, 75mg or 225mg s.c. SHP647 every 4 wks and had discontinued immunosuppressants. At TURANDOT II baseline, patients were randomized to 75mg or 225mg s.c. SHP647 every 4 wks for 18 months (wks 0-72; OL period 1). Those assigned to 75mg and having relapse or no response by wk 8 could undergo dose escalation to 225mg, at the investigator's discretion. In the second OL treatment period (OL period 2), all patients received 75mg every 4 wks for a further 18 months (wks 76-144). Patients were followed up for safety 3 and 6 months after treatment cessation. Primary endpoints were adverse events (AEs), serious AEs (SAEs) and AEs leading to withdrawal. Mucosal healing (Mayo endoscopic subscore 0 or 1, centrally-read endoscopy), clinical remission (total Mayo score ≤2 with no individual subscore >1, rectal bleed subscore 0 or 1) and response (based on total Mayo score) were assessed at wk 16.

Results: In total, 331 patients were screened and randomized to 75mg (n = 165) or 225mg (n = 166). One patient was randomized to 75mg but not treated; 180 patients completed OL period 1 with 94 escalating from 75mg to 225mg, and 127 patients completed OL period 2. Table 1 shows the incidences of AEs and SAEs. 1 fatal treatment-emergent adverse event was reported, a 26-year-old woman (75mg escalated to 225mg) who died of pulmonary embolism; this was not considered drug-related. There were no reports of progressive multifocal leukoencephalopathy or lymphoproliferative disorders. Serious infections were infrequent (n = 18, 5.5%). The most reported term was gastroenteritis (n = 3, 0.9%), 1 case was considered drug-related. Overall, UC was the most frequently-reported SAE (10.0%) and the most common AE leading to treatment withdrawal (7.0%). At wk 16, the following rates of clinical response (56.1% and 57.2%), clinical remission (18.3% and 22.3%) and mucosal healing (27.4% and 29.5%) were observed in patients in the 75mg and 225mg groups, respectively. Among patients who had achieved clinical response in the induction study (75mg and 225mg groups), rates of clinical response (79.7% and 77.3%), clinical remission (30.4% and 40.0%) and mucosal healing (43.0% and 50.7%) reported at wk 16 were markedly higher. While the likelihood of completing OL period 1 was similar for patients randomized to receive 75mg (54.9%) and 225mg (54.2%), within the 75mg group the completion rate was higher for the 70 patients who did not escalate than for the 94 patients who did (81.4% vs 35.1%).

Conclusion: SHP647 was well tolerated for up to 36 months in patients with moderate-to-severe UC. Continued clinical benefit was observed in both treatment arms, supporting the efficacy of SHP647.

	SHP647 75mg (n = 164)	SHP647 225mg (n = 166)	SHP647 overall (n = 330)
On-treatment AEs, n (%)	146 (89.0)	147 (88.6)	293 (88.8)

(continued)

Continued

	SHP647 75mg (n = 164)	SHP647 225mg (n = 166)	SHP647 overall (n = 330)
SAEs, n (%)	34 (20.7)	40 (24.1)	74 (22.4)
AEs related to study drug, n (%)	58 (35.4)	61 (36.7)	119 (36.1)
AEs leading to withdrawals, n (%)	12 (7.3)	23 (13.9)	35 (10.6)

[Table 1. Primary safety endpoints in TURANDOT II]

Reference

1. Vermeire S et al. *Lancet* 2017; 390: 135–44.

WEDNESDAY, OCTOBER 24, 2018   10:30–12:00
An upper GI melange – Room K

OP309 A 3-BIOMARKER PANEL ON BIOPSIES TARGETED BY ADVANCED ENDOSCOPIC IMAGING CAN PREDICT PROGRESSION TO DYSPLASIA IN PATIENTS WITH BARRETT'S OESOPHAGUS

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Introduction: The aim of endoscopic surveillance of Barrett's oesophagus (BO) is prevention of invasive adenocarcinoma by detection of early neoplasia. However, in the absence of histologic dysplasia it is difficult to assess the risk of progression. Molecular biomarkers could aid risk stratification. The aim of this study was to assess the utility of a panel of biomarkers on a small number of biopsies in predicting neoplastic progression of BO.

Aims and Methods: In a previous prospective study in three European centres we tested 9 biomarkers on endoscopic biopsies targeted by autofluorescence imaging for diagnosis of dysplasia. The biomarker panel included p53 and cyclinA immunohistochemistry (IHC), aneuploidy and G2/tetraploidy, hypermethylation of p16, RUNX3 and HPP1, and loss of heterozygosity at 9p and 17p loci. Patients without baseline high-grade dysplasia (HGD) or intramucosal cancer (IMC) were followed up endoscopically. Logistic regression by stepwise selection approach and LASSO regularization was used to select the most predictive biomarkers to form a small panel. Fisher's exact test was used to calculate odds ratios (OR). Means and medians were compared with Mann-Whitney and Student t-test. The primary endpoint was any histologic progression (progression from non-dysplastic BO to any grade of dysplasia or progression from low-grade [LGD] to HGD/IMC. Secondary endpoints included any progression to HGD/IMC and time to progression.

Results: Out of 203 patients with BO in the original cohort, 78 were excluded due to HGD/IMC at baseline endoscopy (n = 29), LGD treated with RFA at follow

up (n = 8) and lack of follow up (n = 41). The characteristics of the 125 patients included in the analysis are shown in Table 1.

Variable	Total patient population (n = 125)	Progressors (n = 42)	Non-progressors (n = 83)	Progressors vs non-progressors comparison
M:F (ratio)	106:19 (5.58:1)	36:6 (6:1)	70:13 (5.38:1)	p > 0.05
Mean age (Range)	64.9 (35.0–83.6)	63.98 (44.16–83.58)	65.35 (35.00–82.47)	p > 0.05
Mean BO length (Range)	7.13 (2-17)	7.00 (3-14)	7.19 (2-17)	p > 0.05
Median follow-up in years (IQR)	3.85 (1.87–5.31)	1.22 (0.59–3.50)	4.24 (2.86–8.69)	p < 0.0001
Baseline histology NDBO/Indefinite dysplasia/LGD	96/10/19	24/4/14	72/6/5	p < 0.01

[Table 1. Baseline demographic, endoscopic and histopathological characteristics of patients included in the study]

Logistic regression analysis revealed that p53 and aneuploidy were the only covariates which independently predicted progression to dysplasia (Regression coefficient: 0.91 +/-0.46 and 1.39 +/-0.67, respectively). p53 had an OR for any neoplastic progression of 2.94 (CI 1.30–6.66, p < 0.01), while aneuploidy had an OR of 5.37 (CI 1.54–18.76, p < 0.01). Of the remaining biomarkers, cyclinA was a weak predictor but missed statistical significance (p = 0.08). The ORs for progression to HGD/IMC for p53 and aneuploidy were 3.77 (CI 1.53–9.29, p < 0.01) and 6.17 (CI 1.65–23.11, p < 0.01), respectively. When combined into a 2-biomarker panel with a cut-off of 1 positive biomarker, p53 and aneuploidy had OR of 3.66 (CI 1.59–8.45, p < 0.01) for any progression and 4.81 (CI 1.90–12.14, p < 0.001) for progression to HGD/IMC. Moreover, we tested whether the addition of cyclinA improved risk stratification. The 3-biomarker panel with a cut-off of 2 positive markers predicted any neoplastic progression with an OR of 7.57 (CI 1.86–30.81, p < 0.001), and progression to HGD/IMC with an OR of 12.50 (CI 3.43–45.60, p < 0.0001). Finally, among progressors, those with positive biomarker panel had significantly shorter time-to-progression compared to patients with negative biomarker panel (Median 0.42 vs 1.47 yrs, p < 0.01).

Conclusion: In conclusion, we found that a small 3-biomarker panel, comprising of p53, aneuploidy and cyclinA, on biopsies targeted by advanced imaging, is a strong predictor of neoplastic progression in patients with BO and could inform endoscopic management.

Disclosure: Prof K. Ragunath has received research support, consultancy and educational grants from Olympus.

OP310   PATIENT-DERIVED ORGANOID-BASED PREDICTION OF CONCURRENT CHEMO-RADIOTHERAPY RESPONSE IN ESOPHAGEAL CANCER

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Introduction: Information for prediction factors of concurrent chemo-radiotherapy (CCRT) response has been limited. Patents derived organoid have advantages in providing more physiologically relevant and predictive data for *in-vivo* response.

Aims and Methods: Patient-derived organoid culture was performed using tumor tissues acquired from esophageal cancer before 1st CCRT start. After 7 days cultured, same sized organoids were collected and were treated with 5-FU and 5Gy radiotherapy was provided. After 6 days, primary cultured cells were stained and fluorescent images were captured. Clinical response was assessed after 4th cycle CCRT. Clinical response was classified as complete remission (CR), partial remission (PR), and disease progression (PD).

Results: A total of 27 esophageal cancer patients were enrolled. Final success rate of patient-derived organoid culture was 78% (21/27). CCRT response in patient-derived organoids were evaluated in 21 cases. A total of 16 persons were followed up more than 4 cycles of CCRT and were analyzed. Clinical CR was observed in 10 persons and 2 persons showed clinical PR (n = 4) or PD (n = 2). Live activity was noted in less than 10% of organoids in all patients with clinical CR and was observed in 30-40% of organoids in all patients with clinical PD. Live activity was noted in less than 20-30% of organoids ls in all patients with clinical PR.

Conclusion: It takes 2 weeks to evaluate the CCRT response in organoids from tissue acquirement. High agreement between clinical response and response in organoids was observed. The evaluation of CCRT response in organoids will provide a good predictor of clinical CCRT response and precision medicine.

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Disclosure: Nothing to disclose

OP311   THE GUT MICROBIOME INFLUENCES PROGRESSION FROM METAPLASIA TO DYSPLASIA IN THE IL-1β MOUSE MODEL OF BARRETT OESOPHAGUS

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Introduction: The incidence of Oesophageal Adenocarcinoma (OAC) is increasing, with the only known precursor lesion being Barrett's Oesophagus (BO). Even though there is an association of BO and OAC with obesity and diet, little is known about the responsible mechanisms. Confounding environmental or dietary factors that are prevalent in obese patients might also influence the risk of BO progression. Changes in diet lead to alterations in the gut microbiome and such alterations could have an effect on the susceptibility to gastrointestinal neoplasia. A possible link of microbiome changes in BO and OAC needs to be analyzed in order to understand the role of the microbiome for carcinogenesis or cancer prevention and surveillance strategies.

Aims and Methods: To investigate whether the gut microbiota influences inflammation and tumor development in our mouse model, we for the first time re-derived germ-free (GF) L2-IL-1β mice (IL-1β). We further utilized changes in the diet and housing, specifically a specific-pathogen-free (SPF) and an open cage facility. Using histology and immunohistochemistry the phenotype of the mice was evaluated. The microbiome was analyzed using 16S rRNA gene sequencing followed by sequence analysis using QIIME and mothur followed by LEfSe. The PICRUSt pipeline was then used for *in silico* pathway analysis.

Results: IL-1β mice fed with a high-fat diet (HFD) with 48% fat compared to regular lab chow, or HFD matched control diet (Ctrl) showed a more severe phenotype with increased dysplasia. The HFD phenotype could be reproduced in the open cage facility, where we additionally observed an increased phenotype with HFD leading to a further acceleration compared to the SPF. Elimination of the microbiota led to a marked reduction of inflammation, metaplasia and most important dysplasia in the BE mouse model. This correlated with a reduced influx of neutrophils and immature myeloid cells into the esophagus of germ-free IL-1β mice, directly linking the gut microbiome to the inflammatory phenotype. In summary an increase of the phenotype could be observed with decreasing hygiene level.

Since the lower GI tract harbors the majority of the intestinal microbiota, we analyzed the intestinal microbiota by 16S rRNA gene amplicon sequencing of fecal samples. While only a modest reduction in microbial diversity could be observed, analysis of microbial β-diversity showed separate clustering of HFD fed IL-1β mice in comparison to all other groups, due to a unique taxonomic profile. We further observed an altered *Firmicutes* to *Bacteroidetes* ratio, correlating with similar alterations of this ratio in patients. Changes in community structure in microbiota from HFD fed IL-1β mice pointed to unique functions. PICRUSt analysis of 16S data generated a predictive metagenome with different clustering of the KEGG data in the IL-1β mice with HFD compared to Chow and Ctrl, suggesting a functional microbial high-fat associated component contributing to disease acceleration. One of the most significantly regulated pathways in the predictive KEGG analysis of the community profile was bacterial Lipopolysaccharide biosynthesis in HFD fed IL-1β mice.

Conclusion: Our results demonstrate an influence of the gut microbiome on oesophageal carcinogenesis. While the mechanisms responsible for these differences need not be investigated, studies in patients should be performed. Changes in the microbiome of BO patients could be used to identify patients at risk for progression to OAC or the microbiome could be changed by dietary or drug interventions for a more favorable outcome.

Disclosure: Nothing to disclose

OP312   LONG-TERM EFFICACY AND SAFETY OF RPC4046, AN ANTI-INTERLEUKIN-13 MONOCLONAL ANTIBODY, IN PATIENTS WITH EOSINOPHILIC ESOPHAGITIS: RESULTS FROM THE OPEN-LABEL EXTENSION OF THE HEROES STUDY

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Introduction: HEROES was a 16-wk double-blind (DB), placebo-controlled, phase 2, multicenter trial followed by a 52-wk open-label extension (OLE) in adults with active eosinophilic esophagitis (EoE) that demonstrated a statistically significant reduction in esophageal eosinophil count and improvements in EoE Endoscopic Reference Score (EREFS), EoE Histology Grade, Stage Score (EoEHSS), and patient perception of disease severity and symptoms. The objective of OLE was to characterize the effects of RPC4046 for up to 52 wks.

Aims and Methods: Patients who completed the 16-wk DB, placebo-controlled period entered OLE and received weekly doses of RPC4046 360 mg subcutaneously. Esophageal biopsies and clinical assessments occurred at OLE wks 12, 24, and 52. Outcomes included assessment of mean and peak esophageal eosinophil count, EoEHSS, EREFS, symptoms (EoE Activity Index [EEsAI]), and safety. Esophageal eosinophil counts and histology scores were determined by a central pathologist. OLE analysis was performed according to the original DB treatment assignment.

Results: In the DB period, 99 patients were randomized 1:1:1 to RPC4046 360 mg (n = 34), RPC4046 180 mg (n = 31), or placebo (n = 34). 90 patients completed the 16-wk DB period, 86 entered OLE, and 66 completed the additional 52 wks of therapy. Mean esophageal eosinophil counts (cells/hpf) in OLE remained stable in patients on RPC4046 360 mg or 180 mg prior to OLE but improved rapidly in patients on placebo prior to OLE. Similar effects by treatment group before OLE entry were seen across other outcome measures: peak eosinophil count, EREFS over all locations, and EoEHSS grade and stage. In OLE, the proportion of patients achieving symptomatic remission as determined by an EEsAI score ≤20 was 24.4% (OLE baseline), 44.4% (wk 12), 51.3% (wk 24), and 58.2% (wk 52). The most frequent adverse events (AEs) (≥10%) in OLE were upper respiratory tract infection, nasopharyngitis, oropharyngeal pain, sinusitis, and headache. Types and incidence rates of AEs in OLE were consistent with those in the DB period. The overall incidence rate of AEs/100 patient-yrs of exposure remained consistent in OLE relative to the DB period.

Conclusion: Patients who received RPC4046 360 mg or 180 mg in the DB period and received 360 mg in OLE had sustained clinical and histologic improvement of EoE disease activity through 52 wks. Patients who received placebo during the DB period and then received RPC4046 360 mg in OLE showed improvement by wk 12 that was maintained through wk 52. Generally, the overall incidence and types of AEs remained consistent with longer duration of exposure.

| Visit | Double-Blind Randomized Treatment Group | | | Total |
	Placebo (n = 29)	RPC4046 180 mg (n = 28)	RPC4046 360 mg (n = 29)	Total (N = 86)
Esophageal Eosinophil Counts				
OLE baseline, mean (SD)	88.4 (55.9)	27.1 (36.9)	25.6 (30.5)	47.3 (51.4)
OLE wk 12, mean (SD)	21.2 (21.4)	21.9 (32.3)	35.2 (43.2)	26.0 (33.6)
OLE wk 24, mean (SD)	20.4 (21.0)	24.5 (24.1)	21.1 (24.3)	22.0 (22.9)
OLE wk 52, mean (SD)	20.7 (26.8)	15.1 (23.1)	24.8 (38.1)	20.1 (29.8)
EREFS Total Score				
OLE baseline, mean (SD)	8.1 (5.1)	5.5 (3.8)	6.5 (4.4)	6.7 (4.6)
OLE wk 12, mean (SD)	5.0 (4.1)	4.3 (3.9)	4.0 (3.8)	4.4 (3.9)
OLE wk 52, mean (SD)	3.0 (3.1)	4.6 (4.4)	3.0 (2.4)	3.6 (3.5)
EoEHSS – Histology Grade Score				
OLE baseline, mean (SD)	40.9 (13.5)	21.5 (12.4)	20.0 (6.5)	27.5 (14.7)
OLE wk 12, mean (SD)	19.3 (6.7)	19.5 (10.6)	22.5 (9.4)	20.4 (9.0)
OLE wk 52, mean (SD)	19.9 (9.0)	19.5 (9.2)	21.9 (11.6)	20.4 (9.9)
EoEHSS – Histology Stage Score				
OLE baseline, mean (SD)	40.9 (12.7)	21.7 (12.6)	19.4 (7.0)	27.4 (14.7)
OLE wk 12, mean (SD)	18.9 (7.5)	19.2 (11.0)	21.8 (10.1)	20.0 (9.6)
OLE wk 52, mean (SD)	20.4 (9.9)	21.5 (10.2)	22.2 (11.2)	21.4 (10.3)

EoE = eosinophilic esophagitis; EoEHSS = EoE Histology Scoring System; EREFS = EoE Endoscopic Reference Score; OLE = open-label extension; SD = standard deviation.

[Mean Esophageal Eosinophil Counts by Visit in the Open-Label Extension (RPC4046 360 mg)]

OP313 PAN-EUROPEAN REGISTRY ON *H. PYLORI* MANAGEMENT (HP-EUREG): INTERIM ANALYSIS OF 16,600 FIRST-LINE TREATMENTS

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Introduction: The best approach for *Helicobacter pylori* management remains unclear. An audit process is essential to ensure that clinical practice is aligned with best standards of care.

Aims and Methods: Our aim was to evaluate the efficacy of most common first line treatments. International multicenter prospective non-interventional registry starting in 2013 aimed to evaluate the decisions and outcomes of *H. pylori* management by European gastroenterologists. National coordinators were selected from each country to identify a representative group of recruiters. All infected adult patients were systematically registered at an e-CRF by AEG-REDCap. *Variables included*: Patient demographics, previous eradication attempts, prescribed treatment, adverse events, and outcomes. Intention-to-treat and per-protocol analyses were interim. Data monitoring was performed to ensure the quality of the data.

Results: So far, 21,300 patients from 27 European countries have been evaluated. Average age was 49 years, 60% were women, and 18% had peptic ulcer. The majority of cases (78%, 16,614 patients) were naïve to *H. pylori* treatment. Pre-treatment resistance rates were: 24% to clarithromycin, 34% to metronidazole, and 14% to both. Drug prescription and efficacy is shown in the table. Triple therapy with amoxicillin and clarithromycin was the most commonly prescribed (45%), achieving overall < 80% eradication rate. Over 90% eradication was obtained only with 10-day bismuth quadruple therapies or 14-day concomitant treatment. Longer treatment duration, higher acid inhibition and compliance were associated with higher eradication rates in the multivariate analysis.

Conclusion: Management of *H. pylori* infection by European gastroenterologists is heterogeneous, suboptimal and frequently discrepant with current recommendations. Only quadruple therapies lasting at least 10 days are able to achieve over 90% eradication rates.

Treatment	N	% Use	ITT	(95% CI)	PP	(95% CI)
PPI + C+A	6,998	41,4%	70.7%	(74.6–76.7)	77.9%	(76.9–78.8)
PPI + C+A+M	3,285	19.8%	87.3%	(86.0–88.3)	89.4%	(88.3–90.4)
PPI + C+M	980	5.8%	74.6%	(71.3–79.6)	81.4%	(78.8–83.9)
PPI + C+A+T seq	795	5.2%	80.0%	(78.6–82.5)	93.3%	(91.5–95.0)
PPI + C+A+B	898	5.4%	86.1%	(83.3–88.9)	87.7%	(85.3–90.0)
PPI + C+A+M seq	626	4.0%	75.2%	(72.9–78.2)	82.4%	(79.4–85.3)
PPI + A+M	511	3.1%	70.5%	(67.9–74.8)	82.4%	(79.0–85.7)
PPI + A+L	378	2.3%	78.0%	(73.6–82.1)	79.5%	(75.3–83.6)
PPI + M+Tc+B s.c.	422	2.6%	89.2%	(85.8–92.3)	95.3%	(92.6–97.9)
PPI + C+A+T	142	0.9%	86.2%	(81.2–91.1)	94.4%	(90.6–98.1)
PPI + M+Tc+B	179	1.1%	77.1%	(73.1–80.0)	90.8%	(86.0–95.5)

ITT – intention to treat, PP – per-protocol, 95%CI – 95% confidence interval, PPI – proton pump inhibitor, Seq – sequential, C – clarithromycin, M – metronidazole, T – tinidazole, A – amoxicillin, L – levofloxacin, B – bismuth, Tc – tetracycline, s.c. – single capsule
[Table 1]

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OP314   STATIN USE AND GASTRIC CANCER RISK IN *H. PYLORI*-ERADICATED SUBJECTS: A TERRITORY-WIDE COHORT STUDY WITH PROPENSITY SCORE ADJUSTMENT

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Introduction: Despite successful *H. pylori* (HP) eradication, some individuals can still progress to gastric cancer (GC). Although statin has been shown to reduce the risk of gastric cancer, the results are largely confounded by the presence of HP infection. The aim of this study was to explore the potential effects of statin uses on gastric cancer development in a large cohort of HP-eradicated subjects.

Aims and Methods: This cohort study was based on the territory-wide electronic healthcare database of Hong Kong, from which all subjects prescribed with clarithromycin-based triple therapy for HP infection between 2003 and 2012 were identified. The observation period commenced from the date of HP therapy and the follow-up was censored at GC diagnosis, death or study end date (December 2015). Statin use was defined as > 30-day use during the study period. Exclusion criteria included GC diagnosed within the first year of HP therapy, prior history of GC or gastrectomy, and failure of HP eradication. The hazard ratio (HR) of GC with statin use was estimated by Cox model with propensity score adjustment for other variables (age, sex, comorbidities and other medications use).

Results: In total, 63,605 HP eradicated patients were included in analysis including 15,990 (25.1%) statin users. During a median follow-up of 7.6 (IQR: 5.1–10.3) years, 169 (0.27%) developed GC (incidence rate: 3.5 per 10,000 person-years) and the median age at gastric cancer diagnosis was 71.1 (IQR 61.6–81.8) years. The median cumulative defined daily dose (cDDD) of statin users was 432. A lower GC risk was observed in statin users (HR derived from propensity score adjustment with trimming 0.30; 95% CI 0.18–0.52) than non-users. The propensity score adjusted absolute risk difference between statin and non-statin use was 2.76 fewer gastric cancers (95% CI 1.89–3.24) per 10,000 person-years. By stratified analysis, the protective effect of statin was significant for non-cardia cancer (HR 0.27; 95% CI 0.14–0.52), but not for cardia cancer (HR 0.39; 95% CI 0.14 -

1.07). There was also a significant trend towards lower GC risk with increasing duration and dose of statin (p-trend < 0.001).

	Hazard Ratio	95% CI	P value	P trend
Duration				
Non-user	Ref	–	–	<0.001
<2 yr	0.46	0.24–0.91	0.025	
2-5 yr	0.21	0.09–0.48	<0.001	
>5 yr	0.20	0.07–0.57	0.003	
Dose				
Non-user	Ref	–	–	<0.001
<432 cDDD	0.37	0.20–0.70	0.002	
≥ 432 cDDD	0.23	0.10–0.49	<0.001	

[*Association between duration and dose of statin use and gastric cancer risk after propensity score adjustment*]

Conclusion: In this territory-wide study, statin use was associated with a significantly lower risk of GC development among HP-eradicated patients, in a duration- and dose-response manner.
Disclosure: Nothing to disclose

OP315   GENETIC CHARACTERIZATION OF ADULT PATIENTS WITH SEVERE ENTEROPATHIES REVEALS MONOGENIC DISORDER IN HALF OF CASES

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Introduction: Besides refractory celiac diseases, severe enteropathies with intestinal villous atrophy, autoimmune enteropathy (AIE) or associated with common variable immunodeficiency (CVID), remain therapeutic challenges.
Aims and Methods: Identification of genetic defect may help for targeted therapy. We used a dedicated next-generation DNA sequencing (NGS) covering all exons of 100 genes on genomic DNA from 21 adult patients referred for non-celiac enteropathy with villous atrophy (2001-2017). Complementary analysis with Whole Exome Sequencing (WES) was performed in 5 patients and their relatives.
Results: All the 21 patients (15F/6M) had chronic diarrhea, malnutrition and intestinal villous atrophy refractory to a gluten free diet. 5 patients had AIE with serum anti-AIE-75KD antibodies and 16 patients had CVID. One patient had both CVID and detectable serum anti-AIE 75KD antibodies. Monogenic intestinal disorder was identified in 10/21 (48%) patients. Targeted NGS revealed mutations in following genes: STAT-3 (n=3), CTLA-4 (n=3), ICOS (n=1), LRBA (n=1), TNFA1P (n=1) and NFKB1 (n=1). Targeted therapy was initiated in 2 patients with CTLA-4 mutations and in 1 patient with and STAT-3 mutation.
Conclusion: Genetic study of adult patients with non-celiac severe enteropathy with villous atrophy reveals monogenic disorder in half of cases with possibility of targeted therapy.
Disclosure: Nothing to disclose

OP316   EXTERNAL VALIDATION OF THE INTERNATIONAL BLEEDING RISK SCORE IN BOTH UPPER AND LOWER GI BLEEDING: AN INTERNATIONAL MULTICENTRE STUDY

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Introduction: Several risk scores have been developed for prediction of mortality in patients with upper gastrointestinal bleeding (UGIB). It would be clinically useful if a score was accurate at predicting mortality in both UGIB and lower GI bleeding (LGIB). The recently described pre-endoscopic International Bleeding Risk Score (IBRS) includes the variables: age, comorbidities (altered mental status, liver cirrhosis, disseminated malignancy, ASA-score), and blood tests (urea, albumin, creatinine) and was developed for predicting 30-day mortality in UGIB. IBRS performed well in its derivation dataset but requires external validation.

Aims and Methods: We sought to validate the IBRS in both UGIB and LGIB using international datasets. We assessed the performance of the IBRS for predicting 30-day mortality in UGIB using prospectively collected data on 3324 consecutive cases from a national Italian database, 547 consecutive cases admitted to a Spanish hospital, and retrospectively collected data on 148 consecutive patients admitted to an Israeli hospital. 2) We compared the performance of the IBRS to the AIMS65 and Admission Rockall score (ARS) using the IBRS derivation data from a recently published international study of 3012 consecutive UGIB patients. 3) We assessed the performance of the IBRS in predicting 30-day mortality in LGIB using data from a UK audit of 2340 patients.

Results: 1) Validation of IBRS in UGIB: 4019 patients were included in the validation cohorts with mean age 67 years, mean ASA-score of 2.3, and mortality 7.0%. The IBRS had an area under the receiving operator characteristic curves (AUROC) for prediction of mortality of 0.81 (95% CI: 0.78–0.83). Patients with low IBRS ($\leq$3; 34%) had a mortality rate of 1.0% whereas patients with high IBRS ($\geq$8; 15%) had a mortality rate of 25%. Performance of IBRS in each cohort is shown in table 1. 2) Comparison of IBRS with AIMS65 and ARS: IBRS had similar overall diagnostic ability for prediction of mortality as AIMS65 (AUROCs: 0.81 vs 0.79; p = 0.23), but was superior to ARS (AUROCs: 0.81 vs 0.76; p < 0.012). Classified low-risk patients using IBRS had lower mortality than those classified low-risk with AIMS65 (threshold $\leq$ 1) (1.0 vs 3.4%; p < 0.001). Although IBRS classified a higher number of patients as being at low risk of death compared with ARS (threshold $\leq$ 1) (34% vs 30%; p < 0.001), the mortality rates were similar among classified low-risk patients (1.0 vs. 1.3%). 3) Validation of IBRS in LGIB: The IBRS was also closely associated with mortality in LGIB (AUROC: 0.84 (95% CI: 0.79–0.89). Patients with IBRS$\leq$3 (55%) had a mortality rate of 0.6% whereas patients with IBRS$\geq$8 (3.3%) had a mortality rate of 18%.

Conclusion: IBRS has good performance for predicting 30-day mortality in both UGIB and LGIB. One third of UGIB patients and more than half of LGIB patients can be identified by IBRS as having very low risk of death. IBRS enables identification of a higher number of true low-risk patients than ARS, and mortality among classified low-risk patients is lower with IBRS than AIMS65. IBRS also enables early identification of patients at high risk of death which may allow targeted management to improve outcome.

Cohort (n)	n	AUROC [95% CI]	Mortality in classified low-risk patients; n(%)	Mortality in classified high-risk patients; n(%)
Development cohort	3012	0.86 [0.84–0.89]	11 (0.7)	91 (34)
Validation cohort – Italy	3324	0.80 [0.77–0.83]	14 (1.2)	100 (25)
Validation cohort – Spain	547	0.81 [0.76–0.86]	0 (0)	25 (28)
Validation cohort – Israel	148	0.91 [0.83–0.99]	0 (0)	4 (18)
Validation cohorts overall -UGIB	4019	0.81 [0.78–0.83]	14 (1.0)	129 (25)
Validation cohort – LGIB	2340	0.84 [0.80–0.89]	7 (0.6)	10 (18)

[Table 1. International bleeding risk score (IBRS) for prediction of 30-day mortality]

Disclosure: Nothing to disclose

OP317 ASSESSMENT OF MICROPLASTIC CONCENTRATIONS IN HUMAN STOOL – PRELIMINARY RESULTS OF A PROSPECTIVE STUDY

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Introduction: Microplastic is defined as plastic particles with a size of 5mm to 1µm. The world plastic production has been growing exponentially within the past years, reaching up to 300 megatons/year. Pollution causes plastic to accumulate in the sea, where it is ingested by sea animals, thus integrating plastic into the food chain. Significant amounts of microplastic have been detected in tuna, lobster and shrimp. Microplastic may harm via bioaccumulation (especially when the intestinal barrier is damaged) and can serve as a vector for toxic chemicals or pathogens. Moreover, ingested plastic may affect intestinal villi, nutritional uptake and can induce hepatic stress. Since human data is very scarce, we are the first to quantify and characterize microplastic in human stool.

Aims and Methods: In this prospective pilot study, 8 healthy participants from Finland, Italy, Japan, the Netherlands, Poland, Russia, United Kingdom and Austria were included. Exclusion criteria were: gastrointestinal disease, recent dental treatment, medical diets, alcohol abuse and intake of drugs affecting stool frequency, consistency or resorption. The participants documented daily food intake for a week before sampling ∼100g of stool. After clearing samples from liquids and natural organic solids (e.g., bacterial biomass, undigested plant matter, proteins, and fats), the remaining particles of 50-500 micrometer size were characterized using Fourier-transform infrared (FT-IR) micro-spectroscopy. The data analysis consisted of screening for 11 plastic types: PS, PU, PE, PP, PVC, PET, PA, PC, PMMA, POM and MF.

Results: Exposure to plastic was frequent among the 8 participants (age 46 ± 12 years; 37% male). In the week before sampling 21 ± 12 dishes with plastic wrapping were consumed and daily 740 ± 580ml water were drunk from plastic bottles (11% fizzy drinks). None was vegetarian and sea fish was consumed by 6 participants (2.6x/week). 3 participants used polyethylene glycol (PEG) containing tooth-paste. 5/8 samples have been analyzed so far. The analytical screening identified polystyrene (PS) and polyurethane (PU) plastics in 2 of 5 samples, while in the other samples no definite results are yet obtainable due to high residual cellulose and fat content masking the presence of microplastic.

Conclusion: Increased plastic pollution can cause plastic contamination of foods, which may affect the GI-tract. We are the first to detect presence of polystyrene and polyurethane microparticles in human stool samples. Currently, we are optimizing the stool-sample separation technique of clearing non-plastic particles to further improve quantification and characterisation of microplastic load by FT-IR micro-spectroscopy.

Disclosure: Nothing to disclose

WEDNESDAY, OCTOBER 24, 2018 10:30–12:00
How to improve diagnostic accuracy in pancreatobiliary EUS – Room N1_____

OP318 EFFICACY OF CONTRAST-ENHANCED ENDOSCOPIC ULTRASONOGRAPHY FOR LYMPHADENOPATHY: A PROSPECTIVE MULTICENTER PILOT STUDY

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Introduction: Accurate differential diagnosis of lymphadenopathy is important to determine appropriate treatment course. Endoscopic ultrasound (EUS) with Doppler function is useful to obtain detailed images of lymph nodes, although its capability for differential diagnosis remains unsatisfactory. Contrast enhanced EUS (CE-EUS) allows qualitative and quantitative evaluation based on real-time perfusion imaging. CE-EUS has potential to be able to differentiate malignant from benign lesions more accurately without any further invasive technique such as fine needle aspiration (FNA).

Aims and Methods: The aim of this study was to evaluate the efficacy of CE-EUS in differentiating malignant from benign lymphadenopathy. Patients who underwent EUS-FNA for abdominal or mediastinal lymphadenopathy around upper gastrointestinal tract were prospectively enrolled between August 2016 and March 2018 at 3 tertiary care centers. The lymphadenopathy of long axis > 10mm detected by B-mode EUS was included. The vascular (hypervascular or hypovascular) and enhancement (homogeneous or heterogeneous) patterns of lymphadenopathy were qualitatively evaluated during CE-EUS. The echo intensity change in the lymphadenopathy was quantitatively evaluated by time intensity curve (TIC) analysis with regard to the following aspects: peak intensity, time to peak, intensity gain, velocity of increase and velocity of reduction in 60 seconds. The final diagnoses were obtained by either EUS-FNA diagnosis with at least 6 months follow-up or surgical diagnosis.

Results: Consecutive 100 patients with 34 mediastinal and 66 abdominal lymphadenopathies were enrolled. The final diagnoses were 70 malignant lesions [34 malignant lymphomas, 24 adenocarcinomas, 9 other carcinomas, 2 neuroendocrine carcinomas (NECs) and 1 neuroendocrine tumor (NET)] and 30 benign lesions (18 reactive lymph nodes, 10 sarcoidosises, 1 tuberculosis and 1 nontuberculous mycobacterium infection). The vascular and enhancement patterns were classified into the three categories: hypervascular with homogeneous (23 malignant and 26 benign), hypervascular with heterogeneous (11 malignant and 2 benign) and hypovascular with heterogeneous (36 malignant and 2 benign). When the heterogeneous enhancement was defined as malignancy, the sensitivity, specificity, and accuracy of the qualitative assessment in CE-EUS were 67.1%, 86.7% and 73%, respectively. Since hypervascular with homogenous enhancement in CE-EUS had a mix of benign and malignant lesions, TIC for hypervascular with homogenous lesions was applied and showed that the velocity of reduction showed significant difference between malignant lesion than benign one (p = 0.0011). The ROC analysis of velocity of reduction for malignancy showed area under the curve of 0.77 with the optimal cut-off value of 0.149 dB/s. With this cut-off value, the sensitivity, specificity, and accuracy in velocity of reduction for malignancy in hypervascluar with homogenous lesions were 65%, 88.5% and 80.9%, respectively. The sensitivity, specificity, and accuracy

of CE-EUS for malignancy were improved to 88.6%, 76.7%, and 85%, respectively, if the qualitative and quantitative analysis were combined in CE-EUS.

Conclusion: Although the qualitative analysis in CE-EUS for mediastinal or abdominal lymphadenopathy only showed the decent diagnostic accuracy of 73%, the combined qualitative and quantitative analyses improved the diagnostic accuracy to 85%. CE-EUS with the combined qualitative and quantitative analyses for lymphadenopathy might be useful to complement regular EUS and EUS-FNA.

Disclosure: Nothing to disclose

OP319 CHANGING TREND IN EUS-GUIDED TISSUE ACQUISITION: IN MEMORIAM – FNA, BIRTH – FNB

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Introduction: Fine needle aspiration cytology (FNA) has been the preferred method of specimen evaluation for the past 25 years. Recently, fine needle biopsy (FNB) has become increasingly popular to procure histological core tissue. Although several studies have compared both methods, the impact of FNB on clinical practice is unclear.

Aims and Methods: We aimed to evaluate the impact of FNB on EUS-guided sampling of solid masses over a 4-year period. EUS-FNA using a 22 or 25G needle was the preferred technique for sampling solid mass lesions from 2014-2015 and EUS-FNB using a 22G needle from 2016-2017. Suction was not applied, stylet was not used after the first pass and fanning maneuver was adopted. Per unit policy, after establishing an onsite diagnostic adequacy by rapid evaluation (ROSE), 2 dedicated passes were performed for offsite assessment by cell block preparation. The main outcome measures were 1) Compare the median number of passes required to achieve diagnostic adequacy at ROSE, 2) Compare diagnostic yield at offsite assessment by cell block, which was defined as presence of histological tissue conducive for interpretation.

Results: Of 3020 patients who underwent EUS-guided sampling of solid masses, 2082 (68.9%) underwent FNA and 938 (31.1%) underwent FNB. Lesions were pancreatic 2154 (71.3%), subepithelial 218 (7.2%), lymph nodes 352 (11.7%) or other 296 (9.8%). The median number of passes to achieve diagnostic adequacy at ROSE was significantly lower for FNB compared to FNA (1 [IQR 1-2] vs. 2 [IQR 1-3], p < 0.001), irrespective of the lesion type. Also, the diagnostic yield for offsite assessment by cell block was significantly higher for FNB compared to FNA (92.3 vs. 71.1%, p < 0.001). On multivariable logistic regression analysis, the use of a FNB needle was associated with the need for only 1 pass to achieve diagnostic adequacy at ROSE (odds ratio (OR) 2.8, 95% CI, 2.4–3.4, p < 0.001) and for obtaining diagnostic adequacy at cell block (OR 4.4, 95% CI, 3.3–5.9, p < 0.001).

Conclusion: EUS-guided FNB should be the preferred technique for sampling solid mass lesions given its superior performance over EUS-FNA for both onsite and offsite assessment.

Disclosure: Shyam Varadarajulu and Robert Hawes are Consultants for Boston Scientific Corp. and Olympus American Inc. All other authors have no disclosures to declare.

WEDNESDAY, OCTOBER 24, 2018   10:30−12:00
Primary liver cancer – Room N2_____

OP320 SERUM AND URINE EXTRACELLULAR VESICLES CONTAIN MRNA BIOMARKERS FOR PRIMARY SCLEROSING CHOLANGITIS (PSC) AND CHOLANGIOCARCINOMA (CCA)

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Introduction: Cholangiocarcinoma (CCA) represents a heterogeneous group of biliary cancers with poor prognosis. The etiology of the majority of CCAs is unknown, but conditions such as primary sclerosing cholangitis (PSC) are risk factors. Simultaneously, PSC patients frequently (80%) present inflammatory bowel disease, mainly ulcerative colitis (UC). To date, there are not available sensitive and specific non-invasive biomarkers for the early diagnosis and monitoring of CCA, PSC and UC.

Aims and Methods: The aim of this study was to investigate the potential value of serum and urine extracellular vesicles (EVs) as carriers of mRNA biomarkers for CCA, PSC and UC.

EVs were isolated from serum and urine of CCA (n = 13 and 28), PSC (n = 8 and 7), UC (n = 8 and 12) and healthy (n = 9 and 5) individuals, using ultracentrifugation/filtration methods. The content of EVs was determined by mRNA microarray-based transcriptomics.

Results: Both serum and urine EVs showed round morphology (by transmission electron microscopy), similar size (∼180 nm diameter by nanoparticle tracking analysis) and markers (CD9, CD63 and CD81 by immunoblotting) consistent with exosomes and small-size microvesicles. The mRNA profiles of serum EVs revealed 1,091 mRNA transcripts differentially expressed (p < 0.01) in CCA vs. controls, 100 in PSC vs. controls, 87 in UC vs. controls, 1,522 in CCA vs. PSC, and 107 in PSC vs. UC. Moreover, the mRNA profiles of urine EVs revealed 963 mRNA transcripts differentially expressed (p < 0.01) in CCA vs. controls, 334 in PSC vs. controls, 386 in UC vs. controls, 263 in CCA vs. PSC, and 98 in PSC vs. UC. In serum EVs, *RCN1* and *PON1* transcripts had area under the ROC curve (AUC) values of 0.974 and 0.959 in CCA vs. controls, respectively, *MTRF1L* (AUC = 0.947) and *XKR6* (AUC = 0.936) in PSC vs. controls, *LOC441376* (AUC = 0.937) and *P4HA1* (AUC = 0.927) in UC vs. controls, *CMIP* (AUC = 1.000) and *CCNB1IP1* (AUC = 1.000) in CCA vs. PSC, and *SNORA11B* (AUC = 0.941) and *GRM3* (AUC = 0.929) in PSC vs. UC. In urine EVs, *ERRFI1* and *SF4* transcripts had AUC values of 0.986 and 0.964 in CCA vs. controls, respectively, *FASN* (AUC = 1.000) and *KHNYN* (AUC = 1.000) in PSC vs. controls, *SFRS17A* (AUC = 1.000) and *PTPRT* (AUC = 0.983) in UC vs control, *LDHA* (AUC = 0.911) and *MT1F* (AUC = 0.893) in CCA vs. PSC, and *ROGDI* (AUC = 0.976) and *AOF2* (AUC = 0.964) in PSC vs. UC.

Conclusion: Our results underscore the value of serum and urinary EV transcriptomic (mRNA) signatures as diagnostic tools for CCA, PSC and UC.

Disclosure: Nothing to disclose

OP321 PREDICTIVE VALUE OF PAGE-B SCORE IN TUNISIAN PATIENTS WITH CHRONIC HEPATITIS B UNDER ENTECAVIR

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Introduction: Nucleos(t)ical analogues appear to reduce the risk of hepatocellular carinoma (HCC) compared to untreated patients due to virosuppression. However, HCC continues to occur in treated patients with virologic remission. The most important challenge is to identify of patients requiring close monitoring of HCC undergoing treatment. For this, many scores were used and appear to have good predictability.

Aims and Methods: The aims of this study was to assess the accuracy of the PAGE-B score and to compare its predictive value with that of other conventional HCC risk prediction models such as REACH B score.

This is a retrospective study about 7 years (2011-2016) including all patients with chronic hepatitis B with or without cirrhosis undergoing entecavir (ETV) for at least 1 year. Date of inclusion was the start-up day treatment. Patients with C, HIV or D coinfection were not included. Clinical examination and biological examinations and abdominal ultrasound were performed every 6 months. PAGE-B and REACH-B scores were calculated on the inclusion date. PAGE-B was also calculated 1 year after treatment. The SPSS software was used in its 22nd version to carry out the statistics.

Results: Overall, 65 patients were included with mean age of 47 years (24-73 years). There was a male predominance with a sex ratio M/F = 3.4. 28 patients (43%) had previously received prior treatment: (Peg) interferon (n = 25) and lamivudine (n = 3). Chronic hepatitis B was in cirrhosis stage in 53% of cases (n = 35). Cirrhosis was compensated in 16 patients (45%) and hepatitis B virus was wild in 7.6% of cases (n = 5). HCC occurred in 16 patients (22%) within 5 years in an average period of 45 months (12-58 months). At 1 year of ETV, virosuppresion was obtained in 45 patients (70%) without reducing the risk of HCC (p = 0.53). In univariate analysis, predictors of HCC occurrence were: male gender (p = 0.046), older age (p = 0.05), cirrhosis (p = 10^{-3}), previous treatment (p = 0.05), initial high viral load (p = 0.047), and hyper bilirubinemia (p = 0.012). Positive HbeAg (p = 0.058) and platelet count (p = 0.055) were factors close to the meaning. In multivariate analysis, male gender, older age, platelet count, and positive HBeAg were independent predictors of HCC occurrence. The AUROCs of PAGE-B were significantly higher than those of the REACH-B (0.91 vs 0.80 at 5 years, p = 0,03). The HCC-free survival in patients with PAGE-B score≤10 was 92% vs 50% with PAGE-B>10 and 30% with PAGE-B≥17 (p < 10^{-3}). The HCC-free survival in patients without cirrhosis was 95% at 5 years vs 40% in

cirrhotic patients (p = 0.004). The HCC-free survival in patients without cirrhosis and having PAGE-B score < 10 was 100% at 5 years. AUROCs of PAGE-B calculated 1 year after of antiviral therapy was 0.932 with (95% CI, 0.872–0.992).
Conclusion: PAGE-B represents an easy-to-use and repeatable risk score for prediction of HCC in the first 5 years of ETV treatment, with a better accuracy than the REACH-B score. It also appears to be a dynamic score that can be calculated during treatment. We have shown that Tunisian patients without cirrhosis with PAGE-B score < 10 had a very low risk of developing HCC within 5 years after treatment and therefore, do not require close monitoring.
Disclosure: Nothing to disclose

OP322 DOUBLECORTIN-LIKE KINASE 1 (DCLK1) EXPRESSION CHARACTERIZES SPECIFIC SUBPOPULATIONS OF CANCER STEM CELLS (CSCS) IN HUMAN CHOLANGIOCARCINOMA (CCA) AND ITS INHIBITION EXERTS ANTI-CANCER EFFECTS

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Introduction: Cholangiocarcinoma (CCA) is a very aggressive cancer with a minimal responsiveness to chemotherapeutics. We have previously demonstrated that CCA is enriched of Cancer Stem Cells (CSCs); these features being associated with aggressiveness and drug resistance. In different solid tumours, DCLK1 has been demonstrated as a CSC marker.
Aims and Methods: The aim of our study was to evaluate *in vitro* the expression and the biological function of DCLK1 in mixed intrahepatic-CCA (iCCA) and mucin extrahepatic-CCA (eCCA). Specimens of human CCA (from surgically resected patients) were enzymatically digested, submitted to immunosorting for specific CSC markers (LGR5, CD13, CD90, EpCAM, CD133) and, primary cell cultures were prepared. DCLK1 expression was analysed in primary CCA cell cultures by RT-qPCR, Western Blot (WB), immunofluorescence (IF) and ELISA. Functional studies have been performed in immunosorted and unsorted cells by evaluating the effects of a selective DCLK1 inhibitor (LRRK2-IN-1) on cell proliferation (MTS Assay, cell population doubling time-PDT), apoptosis (Annessin-V-FITC/Propidium Iodide) and colony formation capacity (Clonogenic assay).
Results: RT-qPCR and WB analyses demonstrated an increased expression of DCLK1 in LGR5$^+$ cells of mucin-eCCA and in CD133$^+$ cells of mixed-iCCA with respect the unsorted cells (p < 0.01). DCLK1 showed similar cytoplasmic localization (IF) in LGR5$^+$, CD133$^+$ cells and unsorted cells. Very interestingly, DCLK1 was detected (ELISA) in the human serum samples of CCA patients but it was almost undetectable in healthy controls. The DCLK1 inhibitor, LRRK2-IN-1 (5µM) added for 3 days in CCA cell cultures, markedly impaired cell proliferation and increased PDT, induced apoptosis, decreased colony formation capacity and colony size in both iCCA and eCCA, in comparison with untreated control cells (p < 0.01). The analyses of dose-response curves (MTS assay) demonstrated the anti-proliferative effect of LRRK2-IN-1 is dose-dependent (2.5µM-20µM) with an IC50 of 9.61 µM in unsorted mucin-eCCA, 14.72 µM in unsorted mixed-iCCA, 4.51 µM in mucin-LGR5$^+$ and 9.61µM in mixed-CD133$^+$ cells.
Conclusion: In conclusion, DCLK1 expression characterizes specific CSC subpopulations of mixed-iCCA (CD133$^+$) and mucin-eCCA (LGR5$^+$) and, could represent a serum biomarker for CCA. DCLK1 inhibition exerts anti-neoplastic effects in primary CCA cell cultures.
Disclosure: Nothing to disclose

OP323 DIAGNOSTIC AND PROGNOSTIC VALUES OF BOTH S100 CALCIUM BINDING PROTEIN A4 (S100A4) AND GLYPICAN 3 IN THE TISSUES OF HEPATOCELLULAR CARCINOMA IN EGYPTIAN CIRRHOTIC HCV PATIENTS: A TISSUE MICROARRAY-BASED STUDY

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Introduction: S100 calcium binding protein A4 (S100A4) which is related to epithelial mesenchymal transition (EMT) is mainly involved in metastasis. Glypican-3 (GPC3) which is expressed mainly during pregnancy in fetal organs regulating morphogenesis has been known to be engaged in HCC development. This study evaluated both S100A4 and GPC3 expression in primary HCC in relation to tumor aggressiveness and diagnosis.
Aims and Methods: Tissues of 70 patients that met the inclusion criteria for hepatectomy out of 400 cases of HCC in Egyptian cirrhotic HCV patients were evaluated by immunohistochemistry (IHC) using antibodies against SA100A4 and GPC3 on the slides of tissue microarrays (TMAs) and compared with tumor-adjacent tissue (controls). All patients were followed up for survival, local recurrence and metastasis over a period of at least 6 months.
Results: GPC3 was more expressed in HCC than S100A4 when both were compared to control (79% and 21%), (p < 0.001 and p = 0.001) respectively. S100A4 was more significantly expressed in cases showing metastasis, vascular emboli, necrosis and grade III tumors (p = 0.005, p = 0.039, p = 0.025 and p = 0.014) respectively while no significant association with GPC3 expression with all these parameters (p > 0.05). GPC3 expression was associated with time of HCC recurrence (p = 0.02) while not with S100A4 (p > 0.05). The mean value of AFP was higher in both positive cases for S100A4 (p = 0.004) and GPC3 (p = 0.04). But in both S100A4 and GPC3 positive cases the overall survival time was not affected (p > 0.05). There was no relation between overall survival and both S100A4 and GPC3 (p > 0.05). The median overall survival was shorter in decompensated patients and in higher grade tumors (p = 0.012 and p = 0.046 respectively). After univariate regression analysis, the only significant independent predictor for recurrence was decompansation (OR 3.037) and the following independent predictors for metastasis were significant; S100A4 positive staining (OR 9.63) and necrosis (OR 8.33). After multivariate regression analysis, the most significant predictor for metastasis was S100A4 positive staining (OR 8.4).
Conclusion: S100A4 could be used as a prognostic marker for HCC progression as it is related to tumor metastasis, grading and vascular invasion while GPC3 is a reliable marker of HCC diagnosis.
Disclosure: Nothing to disclose

References

1. Shaker, M.K., et al., Epidemiological characteristics of hepatocellular carcinoma in Egypt: a retrospective analysis of 1313 cases. *Liver International*, 2013. 33(10): 1601–1606.
2. Cui, J.F., et al., Identification of metastasis candidate proteins among HCC cell lines by comparative proteome and biological function analysis of S100A4 in metastasis in vitro. *Proteomics*, 2006. 6(22): 5953–61.
3. Kim, J.K., et al., Targeted disruption of S100P suppresses tumor cell growth by down-regulation of cyclin D1 and CDK2 in human hepatocellular carcinoma. *Int J Oncol*, 2009. 35(6): 1257–64.
4. Feng, L.Z., et al., Correlation between expression of S100A4 and VEGF-C, and lymph node metastasis and prognosis in gastric carcinoma. *J Int Med Res*, 2011. 39(4): 1333–43.
5. Helfman, D.M., et al., The metastasis associated protein S100A4: role in tumour progression and metastasis. *Br J Cancer*, 2005. 92(11): 1955–8.
6. Rudland, P.S., et al., Prognostic significance of the metastasis-inducing protein S100A4 (p9Ka) in human breast cancer. *Cancer Res*, 2000. 60(6): 1595–603.
7. Haruyama, Y. and H. Kataoka, Glypican-3 is a prognostic factor and an immunotherapeutic target in hepatocellular carcinoma. *World J Gastroenterol*, 2016. 22(1): 275–83.

OP325 PERCUTANEOUS INJECTION OF ETHANOL AND MITOXANTRONE VERSUS RADIOFREQUENCY ABLATION IN THE TREATMENT OF HEPATOCELLULAR CARCINOMA

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Introduction: Ablation of liver tumours is currently the main treatment for patients whose cirrhosis precludes liver resection. It is worth mentioning that liver transplantation is not available in Egypt due to legal issues. Therefore, it

is important to research into safe and practical approaches in management of these patients. In a study performed in our centre, the combined percutaneous injection of ethanol and mitoxantrone (cytotoxic drug with very high affinity to liver cells), has been found to be superior to the injection of ethanol alone in the treatment of Hepatocellular Carcinoma (HCC).

Aims and Methods: Our work is aimed at comparing percutaneous combined local injection of ethanol and mitoxantrone and percutaneous radiofrequency ablation in the treatment of hepatocellular carcinoma. This study excluded patients with more than 1 focal lesion and lesions larger than 4cm. There were 124 patients in total, 64 were randomised into Group I who were treated with ethanol plus mitoxantrone, while 60 were randomised into Group II who were treated with radiofrequency ablation. Clinical assessment, laboratory evaluation and CT studies were performed to all patients at baseline and at 1, 3, 6, and 12 months post treatment. The primary endpoint was complete ablation of the focal lesion. Data were checked, entered and analysed using SPSS 14 for Windows.

Results: Complete ablation has been achieved in 81.3%, 81.3%, 76.6% and 71.9% of patients in group I at 1, 3, 6 and 12 months respectively, whereas in group II, the incidence of complete ablation was 88.3%, 88.3%, 85% and 81.7% at 1, 3, 6 and 12 months with no statistical significant difference between the two groups. Percentage of complete ablation in small tumours (<2.5cm) is higher than large tumours in both groups. Side effects and complications are significantly higher in group II.

Conclusion: Combined injection of ethanol and mitoxantrone is comparable to radiofrequency ablation with less frequent complications. Ethanol when combined with mitoxantrone, can provide a safe, effective and cheaper option for the treatment of HCC especially for small tumours.

Disclosure: Nothing to disclose

WEDNESDAY, OCTOBER 24, 2018   10:30–12:00

Diarrhea and bloating in functional bowel disorders – Room L7

OP326 EFFICACY OF PHARMACOLOGICAL THERAPIES FOR THE TREATMENT OF OPIOID-INDUCED CONSTIPATION: SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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Introduction: Opioids are increasingly prescribed in the West, and have deleterious gastrointestinal consequences. Pharmacological therapies to treat opioid-induced constipation (OIC) are available, but their relative efficacy is unclear. We performed a systematic review and network meta-analysis to address this deficit in current knowledge.

Aims and Methods: We searched MEDLINE, EMBASE, EMBASE Classic, and the Cochrane central register of controlled trials through to December 2017 to identify randomised controlled trials (RCTs) of pharmacological therapies in the treatment of adults with OIC. Trials had to report a dichotomous assessment of overall response to therapy, and data were pooled using a random effects model. Efficacy and safety of pharmacological therapies was reported as a pooled relative risk (RR) with 95% confidence intervals (CIs) to summarise the effect of each comparison tested, and ranked treatments according to their p-score.

Results: 27 eligible RCTs of pharmacological therapies, containing 9149 patients, were identified. In our primary analysis, using failure to achieve an average of ≥ 3 bowel movements (BMs) per week with an increase of ≥ 1 BM per week over baseline, or an average of ≥ 3 BMs per week, to define non-response the network meta-analysis ranked naloxone first in terms of efficacy (RR = 0.65; 95% CI 0.52 to 0.80, p = 0.84), and it was also the safest drug. When non-response to therapy was defined using failure to achieve an average of ≥ 3 bowel movements (BMs) per week, with an increase of ≥ 1 BM per week over baseline, naldemidine was ranked first (RR = 0.66; 95% CI 0.56 to 0.77, p = 0.91).

Conclusion: In network meta-analysis, naloxone and naldemidine appear to be the most efficacious treatments for OIC. Naloxone was the safest of these agents.

Disclosure: PL, NEB and ACF: none declared. DMB has acted as a consultant, advisor and speaker for Synergy, Allergen, Ironwood, AztraZeneca, Daiichi, Sankyo, Shionogi, Salix Pharmaceuticals, Medscape LLC, Medtronic and GI Health Foundation

OP327 EPIDEMIOLOGY OF DIVERTICULAR DISEASE OF THE COLON: AN ANALYSIS FROM THE INTERNATIONAL "DICA" PROSPECTIVE STUDY

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Introduction: Diverticulosis of the colon is the most frequent anatomical alteration detected during colonoscopy. The endoscopic classification called "DICA" (Diverticular Inflammation and Complication Assessment) has been recently developed in order to have an objective endoscopic description of the colon harbouring diverticula. Retrospective study found a significant relationship between severity of DICA score and clinical and demographic characteristics of people having diverticulosis/diverticular disease.

Aims and Methods: Aim of this study was to assess the clinical characteristic of the patients according to DICA classification and enrolled in a multicentre, international, prospective study.

2215 prospective patients at the first diagnosis of diverticular disease were enrolled after exclusion of radiological signs of acute diverticulitis; inflammatory bowel diseases; ischemic colitis; prior colonic resection; patients with severe liver failure (Child-Pugh C) or severe kidney failure; pregnant women; patients who are currently using or who have received any laxative agents or mesalazine or probiotics or antibiotics < 2 weeks prior to the enrollment; inability to comply with study protocol and to give informed consensus to the procedure; patients with or history of cancer, of any origin, within 5 years before enrollment; history of alcohol, drug, or chemical abuse. All patients were classified according to DICA classification.

Results: 1377 (62.15%) patients were classified as DICA 1, 599 (27.04%) as DICA 2, and 239 (10.80%) as DICA 3. Table 1 described clinical and demographic characteristics of the enrolled population. We found that the DICA 3 patients, were older, were more frequently females and smokers, had more frequently appendectomy and showed more than 1 co-morbidity than DICA 1 and DICA 2 patients. Abdominal pain and meteorism were the most frequent symptoms in those people, but DICA 3 patients were more symptomatic and with more severe expression of symptoms than DICA 1 and DICA 2 people. Moreover, fecal calprotectin showed higher levels in DICA 3 than in DICA 1 and DICA 2 patients ($p < 0.0001$).

No scheduled therapy was generally adopted for DICA 1 patients (53.7%), while it was adopted in only 26.4% and 10.9% of DICA 2 and DICA 3 patients

respectively. Finally, rifaximin, alone or in combination with mesalazine, was the most frequent scheduled therapy prescribed in DICA 1 (31.5%), DICA 2 (35.8%) and DICA 3 (41.4%) patients.

Conclusion: This prospective study seems to confirm that DICA endoscopic classification has a significant relationship with demographic, clinical and laboratory parameters in people having colonic diverticulosis detected at colonoscopy.

Disclosure: Nothing to disclose

OP328 OUTLET DYSFUNCTION IS PREVALENT IN SEVERE FUNCTIONAL BLOATING: A PROSPECTIVE, MULTICENTER, ITALIAN STUDY

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Introduction: Bloating and abdominal distension are bothersome symptoms frequently complained about by patients with functional gastrointestinal disorders (FGID). Etiology is unclear in many cases. However, recent studies provided evidence of impaired handling of gas as mechanism potentialy relevant to the symptom (1). Few data are available on defecation behavior in these patients (1).

Aims and Methods: Our aim was to study the relationship between the defecation pattern, the severity of bloating and the abdominal girth changes in FGID patients consulting for bloating as prevalent complain poorly responsive to controlled diet advise. We performed a prospective, multi-center study of patients with severe abdominal bloating (VAS score ≥ 24 on a 100-mm scale) as prevalent complain with/without visible abdominal distension. Patients were recruited at 4 gastroenterology outpatient clinics in Italy. Comorbid FGID were grouped according to Rome III criteria. All patients were prescribed a lactose-free diet augmented by NICE dietary advice for irritable bowel syndrome (IBS) for 2 weeks. A belt around the abdomen at standardized sites provided assessment of abdominal girth measurements. During the 2-week run-in period patients completed a daily diary log including abdominal bloating score (100-mm VAS), Bristol Stool Form and stool frequency. At randomization visit, all patients filled in a questionnaire on subjective improvement of bloating on a 5-point Likert scale (worse to major improvement) and a further abdominal bloating 100-mm VAS. A belt around the abdomen at standardized sites provided assessment of abdominal girth 2 hours after a meal. All patients reporting inadequate relief of bloating at the end of the run-in underwent a standardized balloon expulsion test (**BET**) scored as either successful or failed if the balloon could not be evacuated within 2 minutes (2). A straining questionnaire was also administered.

Results: 134 patients (112 female, 39.8 ± 11.9 mean age, 10 IBS-D, 14 IBS-M, 45 IBS-C, 13 IBS-U, 7 Functional Constipation, 36 Functional Bloating, 7 Functional Dyspepsia) completed the 2-week run-in period. A significant negative correlation was found between subjective adequate relief and both bloating and abdominal girth changes (r = -.56 and -.40, p < 0.001, respectively). 53 patients were non responder to modified NICE diet advise (70.9%) and proceeded to BET evaluation, with the vast majority (62%) failing the test. Multiple regression analysis showed that BET (successful or failed), as dependent variable, was significantly related to bloating severity (adjusted B 0.011 (95% CI 0.006–0.15), p < 0.0001) independently of abdominal girth changes, FGID diagnosis and straining questionnaire.

Conclusion: In this prospective, multicenter trial modified NICE diet advise was of clinical benefit in approximately 30% of FGID patients consulting for severe abdominal bloating. Disordered defecation was prevalent in the non-responders and correlated with subjective bloating perception. A biofeedback trial to improve defecation effort is ongoing to investigate the relevance of outlet dysfunction as contributing etiology to functional bloating.

Disclosure: Nothing to disclose

References

1. Malagelada JR, et al. Bloating and Abdominal Distension: Old Misconceptions and Current Knowledge. *Am J Gastroenterol.* 2017; 112: 1221–1231.
2. Chiarioni G, et al. Validation of the balloon evacuation test: reproducibility and agreement with findings from anorectal manometry and electromyography. *Clin Gastroenterol Hepatol.* 2014; 12: 2049–54.

OP329 SENSORY AFFERENT INNERVATION AND CORTICAL ACTIVATION ARE IMPORTANT PATHOPHYSIOLOGICAL FACTORS IN FECAL INCONTINENCE IN WOMEN

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Introduction: Fecal incontinence (FI) is a very prevalent health condition[1,2]. While pathophysiological aspects of pelvic biomechanics associated with FI have been extensively studied[3], neurophysiology of motor pathways and especially the role of afferent pathways involved in anorectal perception and its possible dysfunction are quite unknown.

Aims and Methods: To explore the integrity of neural motor (efferent) and sensory (afferent) anorectal pathways and the sensory cortical activation in patients with FI and sphincteric impairment.

A cohort of 80 patients with FI and sphincteric impairment were studied. Sphincter function and structure were evaluated with anorectal manometry (ARM) and endoanal ultrasound (EUS); neurophysiology was assessed by means of pudendal nerve terminal motor latency (PNTML) (efferent pathways) in a subgroup of 42 patients; in another subgroup of 38, cortical activation with sensory evoked potentials (SEP) after anal (ASEP) and rectal (RSEP) mucosa stimulation (afferent pathways) was studied. Parameters evaluated were right/left PNTML, amplitude/duration of the action potential; SEP: latency peaks p1, n1, p2, n2, and amplitudes of p1-n1, n1-p2 and p2-n2 segments (ASEP and RSEP). Neurophysiology (both efferent and afferent pathways) was also studied on a group of 19 healthy volunteers (HV) to set reference values.

Results: *a) Structure and function.* ARM: 83.8% of patients had impairment of EAS, 44.5% of the IAS, and 34.7% of both. EUS: 37.1% had injuries in the right anterior quadrant of the puborectalis, 60.57% showed tears on the EAE and 34.8% IAS disruptions. *b) Neurophysiology.* Efferent motor pathways: mean left PNTML of the patients was 2.52 ± 0.70; for HV was 2.13 ± 0.39 (p < 0.05). Right PNTML was 2.11 ± 0.34 and 2,14 ± 0.41 for patients and HV, respectively (ns). Amongst the patients, 27.78% showed motor neuropathy in at least 1 branch of the pudendal nerve. Sensory pathways (SEP): Patients showed longer RSEP (n1, p2 and n2) and ASEP (p1, p2, n2) compared to HV (p < 0.05). Overall, we found that 63.16% of patients showed ASEP parameters beyond the reference values, and 50% of them for the RSEP.

Conclusion: The prevalence of afferent sensory pathways impairment in patients with FI is significantly higher than that of the terminal motor pathways, probably having a determining role in the pathophysiology of FI. Future treatment strategies based on the stimulation of anal and rectal sensory innervation may be key in the rehabilitation of these patients.

Disclosure: Nothing to disclose

References

1. Ng KS, Sivakumaran Y, Nassar N, et al. Fecal Incontinence: Community Prevalence and Associated Factors–A Systematic Review. *Diseases of the colon and rectum.* 2015; 58(12): 1194–209.
2. Varma MG, Brown JS, Creasman JM, et al. Fecal incontinence in females older than aged 40 years: who is at risk? *Diseases of the colon and rectum.* 2006; 49(6): 841–51.
3. Townsend DC, Carrington EV, Grossi U, et al. Pathophysiology of fecal incontinence differs between men and women: a case-matched study in 200 patients. *Neurogastroenterology and motility: The official journal of the European Gastrointestinal Motility Society.* 2016.

OP330 PREVALENCE OF, AND PREDICTORS OF, A POSITIVE SEHCAT SCAN FOR BILE ACID DIARRHOEA IN GASTROENTEROLOGY OUTPATIENTS: A FOLLOW-UP STUDY

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Introduction: Despite recommendations from national guidelines, many clinicians do not perform 23-seleno-25-homo-tauro-cholic acid (SeHCAT) scanning to rule out bile acid diarrhoea (BAD) in patients with chronic diarrhoea [1]. Our previous study auditing the use of SeHCAT scan in our centre showed a yield of 51% in this patient group and identified that patients with terminal ileal (TI) Crohn's disease or TI resection were highly likely to have an abnormal SeHCAT scan [2]. As a result, we asked clinicians to use a therapeutic trial of a bile acid sequestrant in these patient groups instead of referring them for scanning, hence conserving nuclear medicine resources.

Aims and Methods: In light of changes to the referral criteria, we re-evaluated the yield of SeHCAT scanning in chronic diarrhoea patients, and examined factors predicting an abnormal retention. We retrospectively identified consecutive patients with chronic diarrhoea undergoing SeHCAT scanning at Leeds Teaching Hospitals Trust over a 5-year period from 2012 to 2016. We reviewed electronic patient records to obtain information on presenting gastrointestinal symptoms and any proposed risk factors for BAD. Patients were classified as having irritable bowel syndrome with diarrhoea (IBS-D) if they also reported abdominal pain or discomfort. BAD was categorized into 3 different subtypes (types I, II, and III), and severity (mild: 10-14.9% retention, moderate: 5-9.9%, severe: < 5%). We used a Pearson χ^2 test to assess the association between a positive SeHCAT scan and proposed risk factors for BAD.

Results: Between 2012 and 2016, 1071 patients were referred for SeHCAT scanning. As expected, indications for scanning changed between 2012 and 2016, with a significant reduction in referral of patients with TI Crohn's disease or TI resection year on year (χ^2 for trend, p < 0.001). Despite this, 457 (42.7%) patients had BAD and there was no downward trend in SeHCAT scanning during the 5-year study period (χ^2 for trend from 2012-2016, p = 0.39). This remained the case when data were compared with the previous 7-year study

period from 2005 to 2011 (χ^2 for trend from 2005-2016, p = 0.28). The proportion of patients with type II and III BAD increased from 2012 to 2016 (χ^2 for trend, p < 0.001). Overall, 51.6% had type II BAD, 36.1% type III, and 12.3% type I. BAD was mild in 31.7%, moderate in 34.4%, and severe in 33.9%. Of the 453 patients with IBS-D symptoms, 154 (33.7%) had a positive SeHCAT (Table 1), indicating type II (idiopathic) BAD. In total, 653 (61.0%) patients had no known risk factor for BAD, other than chronic diarrhoea, but 233 (35.7%) of these individuals had BAD, with 143 (61.4%) of them having moderate or severe BAD.

	All Individuals Tested (n = 1071)	No Evidence of BAD (n = 614)	Evidence of BAD (n = 457)	P value*
Mean age (SD)	48.1 (16.4)	48.0 (16.8)	48.4 (15.8)	0.68
Female (%)	710 (66.3)	414 (67.4)	296 (64.8)	0.36
No known risk factor for BAD (%)	653 (61.0)	420 (68.4)	233 (51.0)	<0.001
Bloating (%)	356 (33.4)	208 (34.0)	148 (32.5)	0.59
Abdominal pain or discomfort (%)	738 (69.2)	442 (72.3)	296 (65.1)	0.01
Symptoms compatible with IBS-D (%)	453 (42.3)	299 (48.7)	154 (33.7)	<0.001

*P value for Pearson χ^2 for comparison of categorical data, and one-way analysis of variance for comparison of age, across the three groups
[Table 1: Characteristics of Individuals with Types I, II, or III Bile Acid Malabsorption (2012-2016)]

Conclusion: Despite changes to referral criteria, with reduced testing in those with clear risk factors for BAD, the yield of SeHCAT scanning remained >40%. One-third of patients meeting criteria for IBS-D had idiopathic BAD. One-third of those without risk factors had evidence of BAD.

Disclosure: Nothing to disclose

References

1. Khalid U, Lalji A, Stafferton R, Andreyev J. Bile acid malabsorption: a forgotten diagnosis? *Clin Med* 2010; 10: 124–6.
2. Gracie DJ, Kane JS, Mumtaz S, Scarsbrook AF, Chowdhury FU, Ford AC. Prevalence of, and predictors of, bile acid malabsorption in outpatients with chronic diarrhea. *Neurogastroenterol Motil*. 2012; 24(11): 983-e538.

OP331 A PROSPECTIVE VALIDATION STUDY: 7α-HYDROXY-4-CHOLESTEN-3-ONE IS SUPERIOR TO FIBROBLAST GROWTH FACTOR-19 STIMULATED WITH A MEAL PLUS CHENODEOXYCHOLIC ACID FOR DIAGNOSING BILE ACID DIARRHOEA

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Introduction: The prevalence of Bile Acid Diarrhoea (BAD) is 1% in the general population and up to 32% in patients with diarrhoea-predominant irritable bowel syndrome (1). Availability of the diagnostic scintigraphic SeHCAT retention test is limited. 7α-hydroxy-4-cholesten-3-one (C4) is a proposed diagnostic alternative to SeHCAT (2, 3). Compared with SeHCAT, fasting Fibroblast Growth Factor-19 (FGF19) has an average diagnostic strength (4) but our pilot study suggested that the FGF19 response to a meal plus chenodeoxycholic acid (CDCA) stimulation may have diagnostic strength comparable with that of C4 (5).

Aims and Methods: We aimed to validate the biochemical tests C4 and the response in FGF19 to a meal plus CDCA with the SeHCAT test (NCT03059537). We prospectively recruited patients referred for SeHCAT at four Danish centres to compare SeHCAT, C4, and stimulated FGF19. Exclusion criteria included cirrhosis, ileal resection, active IBD, and use of laxatives or anti-diarrhoeal drugs 1 week before SeHCAT visit 1 and during the study. At SeHCAT visit 1 patients started a 6-day Bristol Stool Form (BSF) diary. At SeHCAT visit 2 we sampled fasting blood, subjects ingested 1250 mg CDCA and a solid meal (2 boiled eggs, 2 slices of toast bread, and 500 mL water). Plasma was sampled after 90, 120, and 150 minutes. We analysed FGF19 by enzyme-linked immunosorbent assay and C4 by high-performance liquid chromatography-tandem mass spectrometry. SeHCAT ≤ 10% defined BAD and SeHCAT > 10% defined idiopathic diarrhoea. Data are presented as median and interquartile ranges. Continuous variables are compared with the Mann-Whitney U-test.

Results: Of 71 subjects, 26 (9 male) had BAD and 45 (27 male) had idiopathic diarrhoea. Median age was 45 years (34-49) vs. 55 years (45-64); p < 0.01. Average stools per day was 3.9 (3.0–5.3) vs. 3.0 (2.0–4.0); p = 0.01. Average BSF was 5.9 (5.5–6.3) vs. 5.6 (5.0–6.2); p = 0.17. After the CDCA ingestion, the plasma CDCA values peaked at 90 minutes and FGF19 peaked at 150 minutes, with no significant difference in values between patients with BAD or idiopathic diarrhoea except for FGF19 at fasting; p < 0.01. Table 1 shows biochemical results and the receiver operating characteristics (ROC) analysis with predefined and proposed cut-off values.
With C4 < 15.4 ng/mL as the cut-off for a definite negative test, 40 of 71 subjects were C4-negative; 34 of these 40 (85%) were true negative. With C4 ≥ 45.1 ng/mL as the cut-off for a definite positive test 12 of 71 subjects were C4-positive, and 10 of these 12 (83%) were true positive. This diagnostic algorithm left 19 of 71 subjects with an inconclusive C4-test, of which 10 had SeHCAT ≤ 10%. A similar algorithm for fasting FGF19 with the cut-off values shown in Table 1 left 33 subjects with an inconclusive FGF19 test.

Conclusion: Stimulation with a meal plus CDCA does not increase the diagnostic yield of FGF19 for diagnosing BAD. In our population, C4 is the superior biochemical test and qualifies for a screening test. This needs further validation with the treatment response in a controlled trial.

Disclosure: Sigma-tau Rare Disease Ltd. provided CDCA (Xenbilox) without restrictions as an independent grant.

References

1. Wedlake L et al. Systematic review: the prevalence of idiopathic bile acid malabsorption as diagnosed by SeHCAT scanning in patients with diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther.* 2009; 30(7): 707–17.
2. Brydon WG et al. Serum 7 alpha-hydroxy-4-cholesten-3-one and selenohomocholyltaurine (SeHCAT) whole body retention in the assessment of bile acid induced diarrhoea. *Eur J Gastroenterol Hepatol.* 1996; 8(2): 117–23.
3. Vijayvargiya P et al. Methods for diagnosis of bile acid malabsorption in clinical practice. *Clin Gastroenterol Hepatol.* 2013; 11(10): 1232–9.
4. Pattni SS et al. Fibroblast growth factor 19 in patients with bile acid diarrhoea: a prospective comparison of FGF19 serum assay and SeHCAT retention. *Aliment Pharmacol Ther.* 2013; 38(8): 967–76.

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Table 1.

TABLE 1	SeHCAT ≤ 10% N = 26, median (IQR)	SeHCAT > 10% N = 45, median (IQR)	ROC analysis Area under the curve (95%CI)	Cutoff values for positive test	Sens./Spec. (%)	PPV/NPV (%)
Fasting C4	34 (16–65)**	7 (4–15)	0.83 (0.72–0.93)**	C4 ≥5.5, (§)	96/29	44/93
	C4 ≥15.4	77/76	65/85			
	C4 ≥45.1	38/93	83/71			
Fasting FGF19	72 (53–146)*	119 (84–240)	0.71 (0.58–0.83)*	FGF19 < 65.5	42/93	79/74
	FGF19 < 157.1	85/44	47/83			
Stimulated FGF19∆0-90min	36 (-14–104)	10 (-28–51)	0.40 (0.27–0.54)	∆FGF19 < 2.5, (§)	35/56	31/60

ROC: receiver operating characteristics; IQR: interquartile range; CI: confidence interval; FGF19: Fibroblast Growth Factor-19 (pg/mL); C4: 7α-hydroxy-4-cholesten-3-one (ng/mL); SeHCAT: 75-seleno-taurohomocholic acid abdominal retention test; PPV: positive predictive value; NPV: negative predictive value; *p < .01; **p < .0001; (§) These cut-off values were predefined.

5. Borup C et al. Chenodeoxycholic acid stimulated fibroblast growth factor 19 response – a potential biochemical test for bile acid diarrhoea. *Aliment Pharmacol Ther*. 2017; 45(11): 1433–42.

WEDNESDAY, OCTOBER 24, 2018 10:30–12:00
Microbiota in IBD – Room L8_____

OP332 EXPOSURE TO MICROBIOTA EARLY IN LIFE DETERMINES COLITIS SEVERITY IN ADULT MICE

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Introduction: The etiology of inflammatory bowel diseases (IBD) remains complex. Increasing evidence supports the view that perturbation of the immune system early in life imprints the intestine with an increased susceptibility to IBD in adulthood. However, how perturbations in host-microbial symbiosis and immunity in childhood impact the intestinal immunity later during adulthood remains enigmatic.
Aims and Methods: In this study, we explored the early time window, and the underlying mechanisms, during which microbiota impacts the IBD susceptibility later in life. Germ-free mice were colonized with microbiota before or after weaning and their susceptibility to develop colitis induced experimentally by dextran sulfate sodium was assessed at adult age. Immune responses, microbial metabolites and microbiota composition were determined during weaning and/or before colitis induction at adult age.
Results: We identified the weaning as a window of opportunity during which exposure to microbiota determines the severity of experimental colitis in adult mice. We showed that exposure to microbiota during weaning, but not later, induces an immune response that contributes to regulate the severity of colitis in adult mice. RNAseq analysis in the colon before colitis induction of GF mice exposed to microbiota before or after weaning revealed immune abnormalities associated with different type of cells. The underlying mechanisms involve microbial metabolites, such as short chain fatty acids (SCFAs), the administration of which, during weaning, ameliorates colitis severity at adult age. This protective effect of SCFAs early in life is dependent on the cross-talk between intestinal epithelial cells and regulatory T cells expressing the transcription factor RORγt (Retinoid-Acid Receptor-related Orphan Receptor gamma t).
Conclusion: Our study reveals how host-microbial symbiosis during a specific time window of opportunity early in life determines long-term susceptibility to inflammatory pathology.
Disclosure: Nothing to disclose

OP333 ULCERATIVE COLITIS PATIENTS IN LONG-TERM STABLE REMISSION RECOVER EUBIOTIC CHARACTERISTICS OF THEIR MICROBIOTA

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Introduction: Ulcerative colitis (UC) and Crohn's disease (CD) are inflammatory bowel diseases characterized by an aggressive immune response thought to be provoked by intestinal microbes. There are fewer and less consistent microbiota data for patients with UC than those with CD, but studies have found that diversity is reduced in the microbiota of UC patients, with lower levels of *Faecalibacterium prausnitzii* and *Roseburia hominis*, and that these findings may correlate with the severity of inflammation. A reduction in *Akkermansia* spp has also been found in these patients. Presence of *Fusobacterium* spp, and Enterobacteriaceae has also been associated with UC. The dysbiosis in UC can persist in periods of remission but there is no data in UC patients in long periods of stable remission.
Aims and Methods: To evaluate the microbiota in UC patients in long-term remission. A cross-sectional study was performed in 4 groups of subjects: 1) UC-L: UC patients in long-term remission ($\geq$5 years of flare-free disease, with clinical, endoscopic and histological remission at time of study); 2) UC-S: UC patients in short-term remission and high relapse rate (3 months in clinical remission at time of study and previously more than 1 relapse per year); 3) UC-F: UC patients with active disease (SCCAI > 4 at time of study) and 4) HC: healthy unrelated controls. We obtained 2 frozen stool samples from all subjects, except from the UC-F group from which we obtained 1 frozen stool sample at the beginning of the flare. Total bacteria, *F. prausnitzii, A. muciniphila, E. coli and F. nucleatum* were measured by quantitative Real Time PCR (qPCR, copies/gr stool).
Results: 112 subjects were included, 29 in UC-L group, 20 in UC-S, 39 in UC-F and 24 HC. Median age of UC patients was 39 years and in HC was 34 years, women comprised 52% of all UC and 58% of HC. *F. prausnitzii* abundance was significantly lower in the UC-S and UC-F groups compared to the UC-L group (median 7.67E+8 copies/g, 5.06E+8 copies/g vs. 4.37E+9 copies/g, respectively p < 0.05). *A. muciniphila* abundance was depleted in both UC-S and UC-F in contrast with UC-L and HC (median 0.00E+0 copies/g in UC-S and UC-F vs. 3.89E+6 copies/g in UC-L and 5.01E+9 copies/g in HC, p < 0.01). *E. coli and F. nucleatum* abundance was similar in all subjects studied.
Conclusion: UC patients in long-term, stable remission present an abundance of *A. muciniphila* and *F. prausnitzii* that is similar to healthy controls. UC patients

may be able to recover some eubiotic characteristics of their microbiota and this could become an important therapeutic end-point in UC.
Disclosure: Nothing to disclose

OP334 COMPARISON OF INTESTINAL MICROBIOTA COMPOSITION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASES DEPENDING ON THE PLACE OF RESIDENCE (URBAN OR RURAL)

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Introduction: The gut microbiota composition differs at the inter-individual level and depends on many factors as food, geographical conditions of human living, genetic factors, age, etc. It is probably the change in the composition of the intestinal microbiota which may cause activation of immune inflammation in ulcerative colitis and Crohn's disease patients.
Aims and Methods: The aim of the study was to reveal the influence of the place of residence (urban/rural) on the composition of intestinal microbiota in inflammatory bowel diseases (IBD) patients.
Materials and methods: The study included 91 patients with ulcerative colitis and Crohn's disease (22 living in rural, and 69 – in the urban area). The control group consisted of 96 healthy subjects (27 from rural and 69 from urban area). Total DNA was extracted from stool samples followed by whole genome sequencing (SOLiD 5500 W platform).
Results: The following bacteria were predominant in the samples of healthy subjects living in a rural area: *Clostridium* (3.20 ± 5.64)%, *Eubacterium* (16.86 ± 8.19)%, *Butyrivibrio* (1.46 ± 6.71)%, *Coprococcus* (8.82 ± 8.026)%, *Roseburia* (5.79 ± 4.02)%, *Faecalibacterium* (7.89 ± 4.93)%, *Ruminococcus* (12.63 ± 11.51)% and *Akkermansia* (1.46 ± 3.40)% in contrast to the group of IBD patients, living in a rural area: *Clostridium* (0.60 ± 1.80)%, *Eubacterium* (8.34 ± 8.07)%, *Butyrivibrio* (0.79 ± 2.59)%, *Coprococcus* (4.81 ± 7.83)%, *Roseburia* (3.11 ± 5.13)%, *Faecalibacterium* (3.64 ± 3.61)%, *Ruminococcus* (3.92 ± 6.03)%, *Akkermansia* (0.08 ± 0.21)%, p < 0.05. In the group of healthy urban residents following bacteria: *Clostridium* (1.99 ± 3.58)%, *Eubacterium* (13.68 ± 9.59)%, *Butyrivibrio* (1.77 ± 5.83)%, *Coprococcus* (5.95 ± 6.46)%, *Roseburia* (3.48 ± 3.75)%, *Faecalibacterium* (5.73 ± 5.58)%, *Ruminococcus* (7.31 ± 6.70)%, *Akkermansia* (2.29 ± 7.26)% were much more abundant than in IBD patients living in the cities. However the abundance of *Clostridium* (1.13 ± 3.04)%, *Eubacterium* (10.85 ± 11.44)%, *Butyrivibrio* (0.30 ± 1.08)%, *Coprococcus* (1.98 ± 2.84)%, *Roseburia* (2.15 ± 3.32)%, *Faecalibacterium* (4.69 ± 4.64)%, *Ruminococcus* (4.09 ± 7.23)%, *Akkermansia* (1.20 ± 5.98) was lower compared to urban IBD patients (p < 0.05). The abundance of *Bacteroides* genus was significantly higher in groups of both rural and urban IBD patients: (14.45 ± 18.02)% and (21.81 ± 19.11)% compared to the control group of healthy subjects living in rural and urban areas (2.73 ± 1.75)%, (9.81 ± 12.08)%, respectively, p < 0.05. The abundance of *Bacteroides vulgatus* was elevated in IBD patients both from rural (3.84 ± 4.02)% and urban areas (7.28 ± 9.57)% compared to the control group of subjects form rural (0.43 ± 0.52)% and urban areas (2.09 ± 3.46)%, p < 0.05. Comparative analysis of microbiota of IBD patients living in rural and urban areas revealed differences in the representation of only 2 genera of bacteria: the abundance of *Methanobrevibacter* (2.30 ± 6.19)% and *Catenibacterium* (1.18 ± 1.93)% was higher in rural patients compared to patients living in the cities (0.71 ± 2.72)% and (0.38 ± 0.850)%, respectively, p < 0.05).
Conclusion: Only 2 genus of bacteria – *Methanobrevibacter* and *Catenibacterium* – differed significantly between urban and rural IBD patients. The abundance of butyrate-producing bacteria with anti-inflammatory properties (*Subdoligranulum, Eubacterium, Faecalibacterium, Coprococcus, Ruminococcus,* etc.) was significantly decreased in IBD patients comparing to healthy subjects. The abundance of *B. fragilis*, which is the cause of diarrhea of different etiology, was not statistically different between the groups, but there was an increase in its relative representation in the group of urban IBD patients.
Disclosure: Nothing to disclose

OP335 DONOR MICROBIOTA AS A DETERMINANT FACTOR FOR RESPONSE TO FMT IN PATIENTS WITH ULCERATIVE COLITIS

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Introduction: Fecal microbiota transplantation (FMT) is an experimental approach for the treatment of patients with ulcerative colitis. Although there is growing evidence that FMT is effective in this disease, factors affecting its response are unknown.
Aims and Methods: To investigate which patient or donor factors are responsible for the treatment success of FMT in UC patients. This is an open labeled trial of repeated FMT for steroid resistant or dependent ulcerative colitis patients (n = 50). Demographic and laboratory findings of donor and recipient were

recorded. Fecal samples of donors and patients were analysed by 16SrRNA gene-based microbiota analysis in only 10 patients (and related donors).
Results: 16/50 (32%) of patients showed complete response and 4/50 (8%) had a partial remission to FMT. Response was mainly influenced by the taxonomic composition of the donor's microbiota. Stool of donors with a high bacterial richness (observed species remission 811 ± 74 vs no response 644 ± 168 at 15996 rps) and a high relative abundance of *Akkermansia muciniphila* ($4.2 \pm 2.1\%$ vs $0.3 \pm 0.1\%$), *Faecalibacterium prausnitzii* ($11.9 \pm 3.0\%$ vs $6.2 \pm 2.9\%$), and *Ruminococcus* spp. ($5.2 \pm 3.2\%$ vs $1.1 \pm 0.8\%$) were more likely to induce remission. Demographic data were also analysed. Multivariate analysis showed the duration of illness longer than 1 year was a negative predictive factor (0.72 (0.57–0.92) $p < 0.01$).
Conclusion: The taxonomic composition of the donor's intestinal microbiota is a major factor influencing factor for response in UC. Further artificial microbial preparations for ideal microbial match should be investigated. Duration of illness is a significant factor for success of FMT and early application of FMT in UC should be studied in further well-designed trials.
Disclosure: Nothing to disclose

OP336 LINKING MUCUS DEPLETION AND MICROBIOME ALTERATIONS IN UC TO MUCOSAL ENERGY SUPPLY

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Introduction: Mucosal ATP depletion as the consequence of reduced mitochondrial respiratory chain activity has been attributed to ulcerative colitis (UC) pathogenesis more than 30 years ago. Mucus producing goblet cells, which are highly dependent on energy supply via the oxidative phosphorylation (OXPHOS) system, are supposingly highly affected by reduced OXPHOS activity. Furthermore, reduced numbers of goblet cells and intestinal mucus depletion have been suggested as histological hallmarks of UC. Finally, mucus composition and glycosylation is able to shape the intestinal microbiota, which is frequently altered in UC patients. Nevertheless, experimental evidence linking mitochondrial dysfunction with intestinal mucus depletion and microbiome alterations are still missing.
Aims and Methods: Mucus producing HT29MTX cells as well as murine intestinal organoids are employed as *in vitro* or *ex vivo* model systems, respectively, in order to study mucin transcription, production, secretion and glycosylation upon energy metabolism modifying stimuli. *In vivo*, conplastic mice, carrying well-characterized single nucleotide polymorphisms in their mitochondrial genome, are studied on their susceptibility to various experimental colitis models. Furthermore, seahorse analyzer is used to control for mitochondrial respiration and glycolysis, while microbiome composition is analysed via 16srRNA next generation sequencing.
Results: *In vitro* stimulation of HT29MTX cells showed that mucus transcription and secretion is highly dependent on mitochondrial OXPHOS capacity. In line with this, mice with reduced mucosal ATP levels and OXPHOS activity depicted goblet cell reduction and increased susceptibility to DSS colitis, characterized by elevated DAI, MEICS and histologic scores. On the other hand, mice with increased mucosal ATP levels were protected against experimental colitis. Finally, gut microbial composition was highly dependent on mitochondrial genetics.
Conclusion: Taken together, we here describe a new pathway linking major hallmarks of UC. Mitochondrial OXPHOS activity and mucosal ATP levels in intestinal epithelial cells might be strongly underestimated factors in UC pathogenesis and therapeutic potentialities.
Disclosure: Nothing to disclose

OP337 IDENTIFICATION OF A BILE ACID PROFILE AND GUT MICROBIOME COMMUNITY STRUCTURE ASSOCIATED WITH EARLY FLARE AFTER NUTRITIONAL THERAPY IN PAEDIATRIC CROHN'S DISEASE

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Introduction: Changes in gut bacterial community structure are associated with Crohn's Disease (CD) development and response to therapy including reduced diversity, temporal instability, and shifts in abundances of many bacterial species. Bile acid (BAs) play a central role in modulating the immune response, and changes in the BA pool are also associated with gut bacterial activity. The liver synthesizes and conjugates the primary BAs while bacteria deconjugate, epimerize and dehydroxylate in the production of the secondary BAs. The predominant primary BAs are cholic acid (CA) and chenodeoxycholic acid (CDCA), and the predominant secondary BAs are lithocholic acid (LCA) and deoxycholic acid (DCA). Because the gut microbial community impacts the BA pool, it is possible that community changes could affect the BA-receptor mediated immune response.
Aims and Methods: The relationship between the gut microbiome and the BA pool, both obtained from stool samples collected at baseline, during exclusive enteral nutrition therapy (up to week 12) and then at 12-week intervals to 48 weeks follow-up, was investigated in 16 pediatric CD patients. Patient outcomes were classified as: sustained remission for >24 weeks (SR), non-sustained remission (NSR) or non-remission (NR). Taxonomic marker (16S) and metagenomic sequencing was performed on the stool samples. Taxonomic and functional assignments were made using QIIME and HUMAnN2, with diversity statistics computed using QIIME. Bile acid profiles were obtained from stool by liquid chromatography tandem mass spectrometry. Standard statistical tests were performed using R, and the relationship between microbial community structure and BA composition was inferred using a hierarchical Bayesian model (BioMiCo).
Results: 2 groups of patients were identified that differed in both BA profile and gut microbiome. The first group was associated with high amounts of the secondary bile acids LCA and DCA, and was comprised of SR, NSR and NR patients. These patients had relatively high levels of microbial alpha diversity, with *Ruminococcus obeum, R. torques, Bacteroides uniformis, B. vulgatus*, several species of *Alistipes* and *Subdoligranulum* being predominant lineages. The second group was associated with high amounts of unconjugated primary bile acids and 2 other secondary bile acids, ursodeoxycholic acid (UDCA) and hyodeoxycholic acid (HDCA). This group was comprised exclusively of NSR patients. Alpha diversity was lower in these patients, with *R. gnavus, B. plebeius, B. eggerthii, Clostridium boteae*, and *C. innocuum* being predominant lineages. A survey of bacterial BA genes within the metagenome revealed that most samples contained the bile salt hydrolase gene responsible for deconjugation. The bacterial genes responsible for conversion to secondary bile acids were much more restricted.
Conclusion: Primary BAs levels differed significantly between the SR and NSR patients. Moreover, high primary BAs were seen only in NSR patients. The presence of HDCA in the second group of patients (all NSR) is noteworthy, as HDCA has a detergent like effect leading to membrane disruption, and is suggested to induce strong cytotoxicity, apoptosis, and IL-8 synthesis. Based on these findings, we speculate that there may be a microbial community that leads to increased HDCA and impacts the ability to sustain remission.
Disclosure: Nothing to disclose