Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

[3] Webb GJ, Moon AM, Barnes E, Barritt AS, Marjot T. Determining risk factors for mortality in liver transplant patients with COVID-19. Lancet Gastroenterol Hepatol 2020;5:643–644.
[4] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with covid-19 in the New York City area. JAMA 2020;323:2052–2059.
[5] Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020.
[6] **Chen G**, **Wu D**, **Guo W**, **Cao Y**, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020;130:2620–2629.
[7] **Guo H**, **Callaway JB**, Ting JP. Inflammasomes: mechanism of action, role in disease, and therapeutics. Nat Med 2015;21:677–687.
[8] Zhao C, Zhao W. NLRP3 inflammasome-A key player in antiviral responses. Front Immunol 2020;11:211.
[9] Chen IY, Moriyama M, Chang MF, Ichinohe T. Severe acute respiratory syndrome coronavirus viroporin 3a activates the NLRP3 inflammasome. Front Microbiol 2019;10:50.
[10] Shi CS, Nabar NR, Huang NN, Kehrl JH. SARS-coronavirus open reading frame-8b triggers intracellular stress pathways and activates NLRP3 inflammasomes. Cell Death Discov 2019;5:101.

Alexander Kroemer[1,*]
Khalid Khan[1]
Matthew Plassmeyer[2]
Oral Alpan[2]
M.A. Haseeb[3]
Raavi Gupta[3]
Thomas M. Fishbein[1]
[1]*MedStar Georgetown Transplant Institute, MedStar Georgetown University Hospital and the Center for Translational Transplant Medicine, Georgetown University Medical Center*
[2]*Section on Immunopathogenesis, Amerimmune*
[3]*SUNY Downstate Health Sciences University, Departments of Pathology and Cell Biology, Brooklyn, New York*
[*]Corresponding author. Address: MedStar Georgetown Transplant Institute, 3800 Reservoir Road NW, Pasquerilla Healthcare Center (PHC), 2nd Floor, Washington, DC 20007. Tel.: 202-444-3700, fax: 877-680-8193.
E-mail addresses: alexander.h.kroemer@gunet.georgetown.edu, akroemer@me.com (A. Kroemer)

SARS-CoV-2 in patients on antiviral HBV and HCV therapy in Spain

To the Editor:

The impact of SARS-CoV2 in patients with underlying chronic liver disease is still a matter of analysis within the Hepatology community.[1] We read with great interest several studies suggesting that antivirals against HCV or HBV could be evaluated as COVID-19 therapeutics. A study virtually screening usable therapeutics against SARS-CoV-2 showed that velpatasvir and ledipasvir (inhibitors of the NS5A protein of the HCV) were among the 16 candidates which gave promising binding models.[2] The polymerase of SARS-CoV-2 has been modeled and then targeted using different anti-polymerase drugs currently on the market that have been approved for use against various viruses. The structural superposition of the HCV and SARS-CoV-2 polymerase shows that the residues that bind to the drug are present in the latter, suggesting the potential use of sofosbuvir.[3,4] In addition to ribavirin and remdesivir, the HBV nucleotide analog tenofovir has appeared as a candidate drug against SARS-CoV-2 due to its tight binding to its polymerase.[4,5] However, information on COVID-19 in patients with HCV infection under active direct-acting antivirals (DAAs) or with HBV infection under tenofovir is scarce.

It is not clear if chronic HBV or HCV *per se* could impact on susceptibility to SARS-CoV-2 infection. In the preliminary report of 2 international registries, 152 cases of laboratory-confirmed COVID-19 were reported in patients with chronic liver disease (CLD). HBV and HCV accounted for 11.8% and 10.5% of the underlying causes of CLD, but there was no information regarding antiviral therapy or active disease. In a study including 5,700 patients hospitalized in New York, 0.1% of patients had HBV infection and 0.1% HCV infection, but as in the previous report, no information on the antiviral therapy status was available.[6] Due to the higher prevalence of HBV in China, we focused on the main reports from this country to study the correlation between HBV and COVID-19 diagnosis. A large hospitalized patient series from Wuhan, China, observed that 2.1% (23/1,099) of patients were HBV infected, although this was defined by the sole presence of HBsAg and no data on antiviral therapy or disease phase was provided.[7] An unpublished single-center retrospective study from China specifically analyzed the association between COVID-19 and HBV infection. This study found that 12.2% (15/123) of patients with COVID-19 had HBV infection, and reported that HBV infection was associated with a more severe course and higher mortality rate (13.3% *vs.* 2.8%), but no information on antiviral therapy was provided.[8] Finally, a recent letter suggested an inverse association between HBV and COVID-19, considering the HBV prevalence in several regions. While the HBV rates of those with COVID-19 remained between 0–1.3%, the corresponding HBV rates among the same age groups ranged from 7–11%.[9] According to these data, one might speculate about a low incidence of HCV and HBV infection in hospitalized patients with COVID-19. Nevertheless, no studies to date have reported the effect of HCV/HBV antiviral therapy on COVID-19 incidence and outcomes.

Spain has been one of the countries severely hit by the COVID-19 pandemic, with up to 239,638 reported confirmed cases so far (1 June 2020). In the most affected regions (Madrid and Catalonia) the infection rate ranged between 771–1,045 cases/100,000 habitants. The prevalence of HCV and HBV infection in these regions is 1.02% (95% CI 0.65–1.39) and 0.52% (0.26–0.77), respectively.[10]

We aimed to evaluate the incidence of SARS-CoV-2 in patients under 'active' antiviral therapy with tenofovir and DAAs

Received 17 June 2020; received in revised form 1 July 2020; accepted 6 July 2020; available online 13 July 2020
https://doi.org/10.1016/j.jhep.2020.07.007

considering the *in vitro* antiviral effect previously reported. In this multicenter study involving 12 centers in Spain (10 from Madrid and Catalonia) we have retrospectively contacted and reviewed the clinical records of 341 patients with HCV infection under DAA therapy and 1,764 patients with HBV infection under tenofovir treatment between February and May 2020. Only 1 patient under sofosbuvir/velpatasvir antiviral therapy and 8 patients under tenofovir antiviral therapy had a confirmed PCR diagnosis of SARS-CoV2. The latter would result in an overall COVID-19 infection rate of 293 cases/100,000 patients receiving active DAA therapy and 453 cases/100,000 patients under tenofovir treatment. Importantly, although 7 required hospitalization, none of the patients died due to COVID-19 disease.

The small sample size and the potential bias regarding selection of patients with HBV and HCV infection prevents us from drawing any conclusions about the incidence of COVID-19 in this cohort. However, confirmed SARS-CoV-2 infection in patients undergoing DAA or tenofovir therapy argues against the efficacy of these drugs against this virus, without excluding a partial antiviral effect. It seems clear, however, that more studies specifically analyzing the impact of the pandemic and SARS-CoV-2 on these infections and associated liver diseases are needed.

Financial support

XF: Instituto de Salud Carlos III (ISCIII) PI18/00079, Plan Estratégico Nacional contra la hepatitis C (Spanish Health Ministry), Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (grant 2017_SGR_1753) and CERCA Programme/Generalitat de Catalunya. SL: grant from Asociación Española para el Estudio del Hígado (AEEH).

Conflicts of interest

SL, XF and JGS: grant and speaker fees from Gilead, speaker fees from Abbvie. MM: speaker fees from Gilead, Abbvie, Intercept and MSD. BMM: none.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

SL, XF and JGS designated the study. SL, XF, JGS, MM and BMM reviewed the data. SL and XF drafted the letter. All authors approved the final version.

Acknowledgements

I.Fernández (H.12 Octubre), M. García-Retortillo (H. Mar), C.Fernández (H. Alcorcón), M.Diago (H.G.U.Valencia), S.Alonso (H.Gregorio-Marañón), R.M.Morillas (HGTiP), J.M.Gonzáles (H.U.Salamanca), M.Hernández (H.Puerta del Hierro), J.Cabezas (H.Valdecilla).

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.07.007.

References

[1] Moon AM, Webb GJ, Aloman C, Amstrong MJ, Cargill T, Dhanasekaran R, et al. High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: preliminary results from an International Registry. J Hepatol 2020;73(3):705–708.

[2] Chen YW, Yiu CPB, Wong KY. Prediction of the SARS-CoV-2 (2019-nCoV) 3C-like protease (3CLpro) structure: virtual screening reveals velpatasvir, ledipasvir, and other drug repurposing candidates. F1000Res 2020;9:129.

[3] Jácome R, Campillo-Balderas JA, Ponce de León S, Becerra A, Lazcano A. Sofosbuvir as a potential alternative to treat the SARS-CoV-2 epidemic. Sci Rep 2020;10:9294.

[4] Chien M, Anderson TK, Jockusch S, Tao C, Kumar S, Li X, et al. Nucleotide analogues as inhibitors of SARS-CoV-2 polymerase, a key drug target for COVID-19. J Proteome Res 2020. https://doi.org/10.1021/acs.jproteome.0c00392.

[5] Elfiky AA. Ribavirin, remdesivir, sofosbuvir, galidesivir, and tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): a molecular docking study. Life Sci 2020;253:117592.

[6] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020;10022:E1–E8.

[7] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–1720.

[8] Chen X, Jiang Q, Ma Z, Ling J, Hu W, Cao Q, et al. Clinical characteristics of hospitalized patients with SARS-CoV-2 and hepatitis B virus co-infection. medRxiv Prepr 2020. https://doi.org/10.1101/2020.03.23.20040733.

[9] Anugwom CM, Aby ES, Debes JD. Inverse association between chronic hepatitis B infection and COVID-19: immune-exhaustion or coincidence? Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa592.

[10] Rodríguez-Tajes S, Domínguez Á, Carrión JA, Buti M, Quer JC, Morillas RM, et al. Significant decrease in the prevalence of hepatitis C infection after the introduction of direct acting antivirals. J Gastroenterol Hepatol 2020:1–9. https://doi.org/10.1111/jgh.14984.

Sabela Lens[1,*]
Mireia Miquel[2]
Beatriz Mateos-Muñoz[3]
Javier García-Samaniego[4]
Xavier Forns[1]

[1]*Liver Unit, Hospital Clínic, IDIBAPS, University of Barcelona, Barcelona, Spain, CIBERehd*
[2]*Hepatology Unit, Digestive Disease Department, Parc Taulí Hospital Universitari, Institutd'Investigació i Innovació Parc Taulí I3PT, Universitat Autònoma de Barcelona, Sabadell, Spain, CIBERehd*
[3]*Hepatology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain, CIBERehd*
[4]*Liver Unit, Hospital Universitario La Paz, IdiPAZ, Madrid, CIBERehd*
[*]Corresponding author. Address: Liver Unit, Hospital Clínic, Barcelona, Spain.
E-mail address: slens@clinc.cat (S. Lens)