References

[1] Bruix J, Chan SL, Galle PR, Rimassa L, Sangro B. Systemic treatment of hepatocellular carcinoma: an EASL position paper. J Hepatol 2021;75:960–974. https://doi.org/10.1016/j.jhep.2021.07.004.
[2] Dai CY, Yeh ML, Yu ML. An EASL position paper for systemic treatment of hepatocellular carcinoma: go forward courageously. J Hepatol 2022;76:478–480. https://doi.org/10.1016/j.jhep.2021.08.023.
[3] Sangro B, Bruix J, Chan SL, Galle PR, Rimassa L. Reply to: "An EASL position paper for systemic treatment of hepatocellular carcinoma: go forward courageously". J Hepatol 2022;76:480–481. https://doi.org/10.1016/j.jhep.2021.10.021.
[4] Sangro B, Gomez-Martin C, de la Mata M, Iñarrairaegui M, Garralda E, Barrera P, et al. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. J Hepatol 2013;59:81–88. https://doi.org/10.1016/j.jhep.2013.02.022.

Mathias Jachs[1]
Bernhard Scheiner[1,2]
Matthias Pinter[1,2,*]
[1]*Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria*
[2]*Liver Cancer (HCC) Study Group Vienna, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria*
[*]Corresponding author. Address: Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria; Tel.: +43 1 40400 47440, fax: +43 1 40400 47350.
E-mail address: matthias.pinter@meduniwien.ac.at (M. Pinter)

Is it safe to treat chronic hepatitis C patients with decompensated cirrhosis with PI-based DAAs?

To the Editor:

We read the recent study published by Torgerson and colleagues with great interest.[1] In this large Veteran Affairs cohort study, the authors conclude that protease inhibitor (PI) direct-acting antivirals (DAAs) are safe and do not increase the risk of hepatic decompensation compared to non-PI DAAs. We would like to highlight several considerations before these findings can be applied to clinical practice.

First, we noted in the methods section that patients with decompensated cirrhosis were not included in this study, but in the patient flow diagram, there was no mention as to how many patients were excluded from the original cohort due to having decompensated cirrhosis or having a history of decompensated cirrhosis.

Second, we noted that about 22% of the included cohort (15,568/71,391) were excluded owing to unknown baseline status or because they may have been at a higher risk of aminotransferase elevations or hepatic decompensation with PI-based DAAs (namely those with acute liver injury within 2 years of study index, those with hepatocellular carcinoma, and those with missing lab data). However, since many of these patients are no longer considered as being at high risk of decompensation following PI-based DAA treatment, as shown in prior studies,[2] this exclusion limits the generalizability of the findings beyond currently approved treatment indications.[3]

Additionally, some patients in the "high-risk" group in this study may not even have cirrhosis because FIB-4 >3.25 indicates stage 3-4 fibrosis. Given the recent study which questioned the performance of FIB-4 to rule-in the presence of cirrhosis among patients with HCV,[4] we suggest that the diagnosis of cirrhosis should be refined using radiological or histological evidence of cirrhosis, or liver stiffness measurement.

Furthermore, patients with cirrhosis were not stratified based on Child-Pugh class. The risk of hepatic decompensation is higher in those with clinically significant portal hypertension as measured by liver stiffness measurement [5] or other measures. While matching was done for model for end-stage liver disease (MELD) score, the results were largely driven by patients with a low MELD score (70% had MELD <10, and only <2% of the total cohort had an MELD ≥15), in whom the risk of hepatic decompensation was likely to be low. Together, these characteristics suggest that the overall study population had a low baseline risk of developing the adverse outcomes of interest. This is an important consideration before concluding the safety of PI-based DAAs among high-risk patients with cirrhosis.

Lastly, we found the reported sustained virologic response (SVR) rates potentially misleading. Although the authors noted in Table 4's footnote that the SVR rates were calculated only for those tested for SVR, we would like to clarify the patient selection for SVR testing, specifically, whether all patients with HCV treatment interrupted due to acute liver injury were offered an SVR test, despite incomplete treatment. This is important clinical information as about 30% of patients did not undergo SVR testing.

Nonetheless, we would like to congratulate the authors as the current study validates the real-world tolerability of PI-based DAAs and the current EASL guidelines.[4] However, as highlighted by the author, more studies are needed to better examine the impact of PI-based DAAs on the risk of hepatic decompensation among patients with prior or current decompensated cirrhosis.

Financial support

No external funding to disclose.

Conflict of interest

WYJ: Invited speaker: Gilead. MHN: Research support: Pfizer, Enanta, Gilead, Exact Sciences, Vir Biotech, Helio Health, National Cancer Institute, Glycotest, B.K. Kee Foundation; Consulting and/

Received 21 December 2021; accepted 23 December 2021; available online 21 January 2022
https://doi.org/10.1016/j.jhep.2021.12.037

or Advisory Board: Intercept, Exact Science, Gilead, GSK, Eli Lilly, Laboratory of Advanced Medicine, Janssen.

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

Authors' contributions

Guarantor of article: Mindie H. Nguyen. Specific author contributions: Study design, data collection, data analysis, data interpretation, and drafting of the article: All authors. Study concept and study supervision: Mindie H. Nguyen.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.12.037.

References

[1] Torgersen J, Newcomb CW, Carbonari DM, Rentsch CT, Park LS, Mezochow A, et al. Protease inhibitor-based direct-acting antivirals are associated with increased risk of aminotransferase elevations but not hepatic dysfunction or decompensation. J Hepatol 2021;75(6):1312–1322. https://doi.org/10.1016/j.jhep.2021.07.021.

[2] Gane E, Poordad F, Zadeikis N, Valdes J, Lin CW, Liu W, et al. Safety and pharmacokinetics of glecaprevir/pibrentasvir in adults with chronic genotype 1-6 hepatitis C virus infections and compensated liver disease. Clin Infect Dis 2019;69(10):1657–1664. https://doi.org/10.1093/cid/ciz022.

[3] Saleem N, Miller LS, Dadabhai AS, Cartwright EJ. Using vibration controlled transient elastography and FIB-4 to assess liver cirrhosis in a hepatitis C virus infected population. Medicine (Baltimore) 2021;100(23):e26200. https://doi.org/10.1097/MD.0000000000026200.

[4] EASL recommendations on treatment of hepatitis C: final update of the series. J Hepatol 2020;73(5):1170–1218. https://doi.org/10.1016/j.jhep.2020.08.018.

[5] Pons M, Augustin S, Scheiner B, Guillaume M, Rosselli M, Rodrigues SG, et al. Non-invasive diagnosis of portal hypertension in patients with compensated advanced chronic liver disease. Am J Gastroenterol 2021;116(4):723–732. https://doi.org/10.14309/ajg.0000000000000994.

Yu Jun Wong[1,2]
Mindie H. Nguyen[3,4,*]
[1]*Department of Gastroenterology and Hepatology, Changi General Hospital, Singapore*
[2]*Duke-NUS Medical School, Singapore*
[3]*Division of Gastroenterology and Hepatology, Department of Medicine, Stanford University Medical Center, Palo Alto, California, USA*
[4]*Department of Epidemiology and Population Health, Stanford University Medical Center, Palo Alto, California, USA*
[*]Corresponding author. Address: Division of Gastroenterology and Hepatology, Department of Medicine, Stanford University Medical Center, 780 Welch Road, Rm CJ250K, Palo Alto, CA 94304-1509, USA.
E-mail addresses: wongyujun1985@gmail.com (Y.J. Wong), mindiehn@stanford.edu (M.H. Nguyen)

Reply to: "Is it safe to treat chronic hepatitis C patients with decompensated cirrhosis with PI-based DAAs?"

To the Editor:

We thank Drs. Wong and Nguyen for their interest in our study.[1] They raise several considerations and provide an opportunity to clarify some of the aspects of our article.

We agree with Drs. Wong and Nguyen that our study's findings should not be generalized beyond the FDA-approved treatment indications for direct-acting antivirals (DAAs). Indeed, our study was never designed to address the question of whether it is safe to treat chronic HCV-infected patients who have decompensated cirrhosis with protease inhibitor (PI)-based DAA regimens. Since PI-based DAAs are currently contraindicated for use among patients with decompensated cirrhosis, these patients were excluded from our analyses.[2,3] Patients with prevalent acute liver injury (ALI) outcomes, including hepatic decompensation, within 2 years prior to DAA initiation were excluded from the analysis (n = 6,794 in Fig. 1)[4] to ensure that incident ALI events following DAA initiation could be ascertained and attributed to the PI or non-PI cohorts. This included 837 patients who were excluded due to a recent history of hepatic decompensation.

Although some of the exclusions we implemented may affect the generalizability of our study, these exclusions increased our study's internal validity. We required at least 2 years in the VA system prior to DAA initiation to ensure we could adequately ascertain the variables that influence clinicians' decisions to prescribe PI *vs.* non-PI-based DAA therapy and which might affect risk of ALI. We excluded patients with prevalent ALI to enable determination of the risk of incident ALI events, decreasing the potential for erroneous attribution of prevalent ALI events to the exposure under evaluation in this real-world cohort.

The FIB-4 index was employed in our study to identify patients with advanced hepatic fibrosis/cirrhosis, a stratification approach now recommended in the simplified pretreatment evaluation by the American Association for the Study of Liver Diseases and the Infectious Disease Society of America.[3] Since cirrhosis is a clinically silent disease process, requiring radiologic or histologic evidence to ascertain its presence may not be practical since: i) not all patients undergo liver biopsy or radiographic imaging prior to DAA initiation, and ii) ultrasound, the most commonly utilized radiographic modality, is insensitive for the diagnosis of cirrhosis.[5] Transient elastography, while ideal for point-of-care assessment of fibrosis, was not widely available in the VA during the course of the study period.

Drs. Wong and Nguyen noted that patients with cirrhosis in our study were not stratified by Child-Pugh class. We elected not

Received 16 February 2022; accepted 18 February 2022; available online 10 March 2022
https://doi.org/10.1016/j.jhep.2022.02.025