Immunotherapy for hepatocellular carcinoma in a patient with hepatitis B virus and hepatitis delta virus coinfection

To the Editor:

We read with great interest the EASL position paper on systemic treatment of hepatocellular carcinoma (HCC),[1] and the related discussion on the use of immune checkpoint inhibitors (ICIs) in patients with HBV and HDV coinfection.[2,3] Due to the lack of scientific evidence, the expert panel could not make a formal recommendation for the use of ICIs in HBV/HDV-coinfected individuals. Instead, they recommend an individualized approach that should take into account the lack of safety data as well as alternative treatment options.[1,3]

Herein, we want to share the case of a 71-year-old female patient with advanced HCC and HBV/HDV coinfection who received systemic therapy with the ICI-based combination of atezolizumab and bevacizumab. The patient was referred to our outpatient clinic after developing early intrahepatic and extrahepatic recurrence after liver resection for HCC. She had compensated liver cirrhosis (Child-Pugh stage A5) without portal hypertension (hepatic venous pressure gradient: 3 mmHg), and an Eastern Cooperative Oncology Group performance status of 1. After interdisciplinary tumor board discussion, systemic treatment with atezolizumab/bevacizumab was initiated. The patient was under antiviral treatment with lamivudine at the time of presentation. Viral load at start of atezolizumab/bevacizumab was negative for HBV and 840 copies/ml for HDV.

So far, the patient received 9 cycles of immunotherapy and underwent 2 radiological follow-up scans, both showing partial response. HBV viral load remained negative throughout the course of treatment, and HDV viral load decreased to 290 copies/ml and 170 copies/ml at month 3 and month 6, respectively. The decrease of HDV viral load may result from enhanced T cell-mediated immunity, as previously suggested in patients with chronic hepatitis C treated with the ICI tremelimumab for HCC.[4] Transaminases remained stable over time (Fig. 1). The patient experienced no treatment-related adverse events. After pretty much 6 months of treatment, the patient is still alive, in partial remission, and continues receiving treatment with atezolizumab/bevacizumab.

In summary, atezolizumab/bevacizumab induced a partial response, and was well-tolerated with no signs of a hepatitis flare in a patient with HCC and HBV/HDV coinfection.

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Conflict of interest

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

Authors' contributions

All authors contributed to the design, writing, and final review of the paper.

Supplementary data

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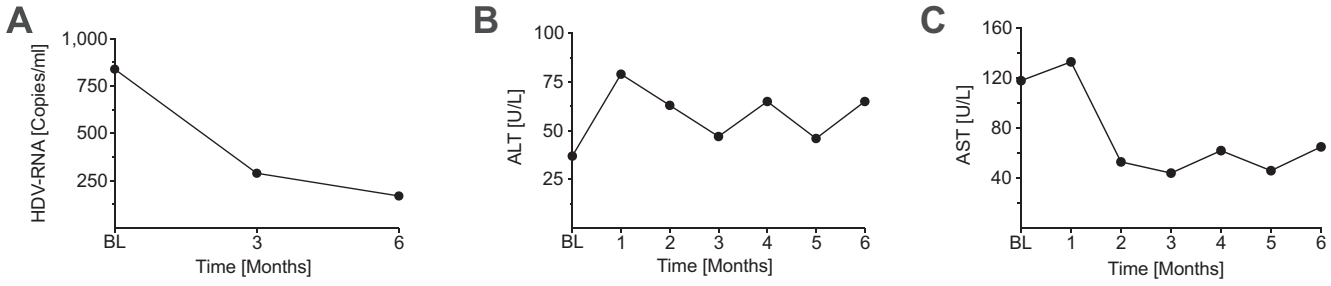

Fig. 1. Course of viral load and transaminases. Changes of (A) HDV viral load, (B) ALT, and (C) AST. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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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.

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