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Similar risk of hepatocellular carcinoma during long-term entecavir or tenofovir therapy in Caucasian patients with chronic hepatitis B

To the Editor:

We read with great interest the recent article published in *Journal of Hepatology* by Papatheodoridis and his colleagues,[1] which was designed to compare the risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB) receiving entecavir (ETV) or tenofovir disoproxil fumarate (TDF) treatment. After an average follow-up of 7.1 ± 3.0 years, the authors indicated that the risk of HCC, rates of virological remission, HBsAg loss, and liver transplantation or death during ETV or TDF treatment were similar in CHB patients with or without cirrhosis. The results of this study provide important guidance value for clinical treatment of CHB, and the author's great efforts are worth encouraging. We would like to make the following comments on the basis of our experience.

First, as mentioned, patients with decompensated cirrhosis were excluded from this study. Here, we wonder why patients with decompensated cirrhosis were excluded? What is the theoretical basis for excluding patients with decompensated cirrhosis? Since previous studies have suggested that ETV and TDF are effective in patients with compensated or decompensated cirrhosis.[2,3] In this case, excluding patients with decompensated cirrhosis from this study will not accurately reflect the treatment strategies in clinical practice.

Secondly, it is obvious that the 2 survival curves in Fig. 3A,B have obvious intersection points, indicating that the data does not conform to the proportional hazards (PH) assumption.[4] Statistically, satisfying the PH assumption is an important prerequisite when using Cox proportional hazards models. The basic principle of the PH assumption is that the effect of covariates on survival rate does not change with time. However, the influence of some confounding factors on survival risk will inevitably change with time in clinical practice. Therefore, it is extremely important to test the PH assumption before constructing Cox proportional hazards models. The results of Cox proportional hazards models are meaningful only when the PH assumption is satisfied. According to the results in Fig. 3A, the HCC incidence in the 2 groups was similar within 10-year follow-up. However, beyond 10-year follow-up, the HCC incidence in the ETV group seems to be higher than that in the TDF group. In this circumstance, landmark analyses[5] are more appropriate for statistical analysis.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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

Authors' contributions

All authors drafted and approved the final manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.07.038.

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Reply to: "Similar risk of hepatocellular carcinoma during long-term entecavir or tenofovir therapy in Caucasian patients with chronic hepatitis B"

To the Editor:

We thank Wen *et al.* for their interest in our recent article, which showed that the risk of hepatocellular carcinoma (HCC) is similar during long-term (mean follow-up: 7.1 ± 3.0 years) entecavir (ETV) or tenofovir disoproxil fumarate (TDF) therapy in Caucasian patients (n = 1,935) with chronic hepatitis B, with or without compensated cirrhosis.[1]

The exclusion of patients with HBV-related decompensated cirrhosis was decided very early after the onset of the prospective annual collection of data for our PAGE-B cohort, since the main aim of the cohort was to identify patients who have no or negligible risk of HCC and can thus be safely excluded from HCC surveillance.[2] This was decided because patients with decompensated cirrhosis are definitely at high risk of HCC and must remain under HCC surveillance.[3] Thus, patients with HBV-related decompensated cirrhosis were not specifically excluded from our recent study,[1] but they have been excluded from our cohort since 2015 and it would have been unrealistic to collect information for them retrospectively just for the recent study. In any case, patients with decompensated cirrhosis represent a very small proportion of treated patients with chronic hepatitis B in Europe and the inclusion of a small number of such cases would not have had the power to change the results. In fact, in our first article published from this cohort in 2014, patients with decompensated cirrhosis represented 3.3% of the total patient population (55/1,666).[4]

A major assumption of the Cox proportional hazards model is the proportionality of the hazards (PH), implying that the covariates investigated have a constant impact on the hazard over time. Graphical methods as well as tests based on the Schoenfeld residuals[5] were used to check the PH assumption for each covariate included in the models. When we assessed the PH assumption for the type of treatment for the total sample of patients, the curves did not cross (Fig. 1 of our article)[1] and the test based on the Schoenfeld residuals was not statistically significant. Concerning Fig. 3,[1] this was provided only as a graphical representation of the cumulative incidence of HCC for patients receiving ETV or TDF according to past exposure to nucleos(t)ide analogs (NAs). Regarding the comment that the HCC incidence seems to be higher in the ETV than in the TDF group beyond 10-year follow-up when evaluated among patients naïve to NAs (Fig. 3A),[1] we would like to underline that the numbers of patients remaining at risk and the number of events (HCC) beyond 10 years of follow-up were too small in the 2 subgroups (naive or past exposure to NAs) to draw such conclusions.

In conclusion, we believe that our findings are valid for Caucasian chronic hepatitis B patients treated with ETV or TDF monotherapy, in whom there is no difference in the probability of HCC development or any other major treatment endpoint including virological and biochemical remission, HBsAg loss, liver transplantation and/or death.[1] Similar findings have been reported by another European (French) study,[6] but we understand that the issue remains unsettled for patients from East Asia, as different studies, even from the same country, reached opposite conclusions.[7]

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Conflict of interest

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

Authors' contributions

GV Papatheodoridis: Conception and design of the letter; Drafting of the manuscript; Approval of the final version of the manuscript. V Sypsa: Drafting of the manuscript; Approval of the final version of the manuscript. P Lampertico: Revision of the manuscript; Approval of the final version of the manuscript.

Supplementary data

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