patients and outcome events to ensure statistical power. Showing non-significance in clinical outcomes between the 2 treatments is easier than identifying statistically significant differences in comparative effectiveness research.[5] This may explain why many previous studies, including the study of Kim *et al.*, have shown no significant difference in risk of HCC among drugs.[1,6–8]

Collectively, it is important to note that all the studies that compared the risk of HCC between TDF and ETV therapies have indicated one direction favoring TDF or no direction. No study has shown the opposite direction of favoring ETV over TDF.[6–8] Even the study by Kim *et al.* also indicated a lower risk of HCC with TDF in patients with cirrhosis (hazard ratio 0.85; HCC incidence at 5 years of treatment, 16.0% with TDF *vs.* 20.9% with ETV), although the difference was not statistically significant. A meta-analysis consisting of 7 studies (3,698 patients) reported a lower incidence of HCC in patients with TDF than in those with ETV.[9] Recently, another large historical cohort study from Hong Kong showed a significantly lower risk of HCC in TDF than in ETV.[10]

Given that a randomized clinical trial, which is the optimum for this topic, cannot be conducted in the future, we have to depend heavily on the results of observational studies. Accordingly, caution is required in interpreting the results from observational studies, considering whether they have sufficient numbers of patients and outcome events, with high internal validity in study design and analysis.

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.

Supplementary data

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Reply to: "Comparison of risk of hepatocellular carcinoma between tenofovir and entecavir: One direction or no direction"

To the Editor:

First of all, we greatly appreciate the letter from Choi *et al.*[1] regarding our study,[2] where we concluded that the risk of hepatocellular carcinoma (HCC) was not statistically different between patients treated with entecavir (ETV) and those treated with tenofovir disoproxil fumarate (TDF) for chronic hepatitis B virus (HBV) infection. Our conclusion seems to contradict the earlier publication by Choi *et al.*,[3] which indicates a significantly lower risk of HCC among the TDF group compared to the ETV group. Indeed, since the publication of the study by Choi *et al.*,[3] the controversy surrounding which antiviral agent is better in terms of reducing HCC risk has become heated. Most recently, in the International Liver Congress™, Vienna, Austria in April 2019, 2 studies based upon cohorts from the Republic of Korea and from the United States of America were published, both of which indicate that the risk of HCC is not statistically different between the 2 treatment groups.[4,5] However, simultaneously, Yip *et al.*[6] showed that the 5-year cumulative incidence of HCC was lower in the TDF group compared to the ETV group (1.2% *vs.* 2.3%).

As indicated by Choi *et al.*,[1] patients with decompensated cirrhosis were not included in our study. We also acknowledge that decompensated cirrhosis is a well-known risk factor of HCC development. However, the major end point of this study

is to analyze the efficacy of antiviral agents in terms of reducing the risk of hepatocarcinogenesis. Death or liver transplantation caused by the deterioration of liver function in patients with decompensated cirrhosis is more likely to occur in earlier courses before *de novo* hepatocarcinogenesis. Therefore, whether inclusion of the whole spectrum of patients with chronic HBV infection, regardless of their baseline liver function, increases the scientific validity of studies remains to be determined. Importantly, when we compared the risk of HCC development between 2 groups among a study population including patients with decompensated cirrhosis, a similar outcome between the 2 treatment groups was consistently maintained ($p = 0.289$).

In terms of the number of baseline variables for adjustment in our study, the addition of serum HBV-DNA and/or alanine aminotransferase levels is not likely to lead to the different results, since both ETV and TDF are the recommended antiviral agents with high genetic barriers.[7] In addition, as we excluded patients with decompensated cirrhosis, the range of prothrombin time-international normalization ratio (PT-INR) was very narrow in our study population. Overall, Lee *et al.*[4] showed similar results between the 2 treatment groups, which were derived from the statistical analyses incorporating the baseline serum HBV-DNA, alanine aminotransferase, and PT-INR as well as other potential parameters.

As recently discussed by Wong *et al.*,[8] Kaplan-Meier curves of the cumulative probability of HCC development in Choi *et al.*'s article[3] have somewhat specific patterns, and moreover the patterns are quite different between the nationwide cohort and the hospital cohort. In the former, the probability of HCC development among the TDF group was extremely low 2 years after enrollment. Furthermore, in the latter, 2 Kaplan-Meier curves remain almost parallel between the time point of 16 months and the last observation. Therefore, such results should be interpreted with caution.

We also recognize that no study has shown the opposite direction of favoring ETV over TDF.[1,9–11] However, it does not indicate the potential advantage of TDF over ETV among treatment-naïve patients. Actually, the major purpose of such academic approaches is to analyze the efficacy by antiviral agents against hepatocarcinogenesis, which can guide the real-life practice among physicians, not to recommend "only one" antiviral agent over the others. In a similar context, not only the adverse effects of long-term maintenance of antiviral agents, but also other potential factors associated with hepatocarcinogenesis should be considered comprehensively to improve overall prognosis.[12,13]

In summary, there is insufficient evidence to draw a robust and universal conclusion in favor of any specific antiviral agent for treatment-naïve patients with chronic HBV infection in real-life practice. However, since the residual risk of HCC development remains despite long-term oral antiviral therapy, delicate surveillance for detection of early stage HCC is required.

Conflict of interest

Dr. Kim reports personal fees from Yuhan Pharmaceuticals and from Bristol-Myers Squibb, outside the submitted work.

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

Supplementary data

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