Editorial Commentary

Is tenofovir disoproxil fumarate superior to entecavir for prevention of hepatocellular carcinoma in patients with chronic hepatitis B?

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Chronic hepatitis B (CHB) remains a major global health problem with approximately 258 million infected individuals (1). Hepatocellular carcinoma (HCC) is one of the major and most deadly consequences of CHB. Especially cirrhotic patients are at risk of HCC. All previous studies have also revealed a consistent association between higher hepatitis B virus (HBV) DNA levels and increased HCC risk. Suppressing HBV DNA levels with antiviral therapy lowers the risk of HCC (2). Current guidelines recommend treatment with a nucleos(t)ide analogue (NA) for CHB in selected patients. The indication for such treatment is mainly based on factors such as degree of liver fibrosis, transaminase levels and HBV DNA levels. Tenofovir disoproxil (TDF) and entecavir (ETV) are currently recommended as first-line antiviral therapy based on their high efficacy to suppress HBV DNA and low risk of antiviral resistance (3,4). In case of previous lamivudine therapy there is a significant risk of resistance with subsequent ETV, which is not observed with TDF. Conversely, TDF can decrease renal function and may increase the risk of osteoporosis, which is not the case with ETV. An alternative to TDF (although at notably increased costs) is tenofovir alafenamide (TAF). Whether TDF or ETV is superior in reducing HCC risk remains a matter of vigorous debate.

A recent meta-analysis by Choi *et al.* published in the *Journal of Hepatology* (5) reported a significantly lower HCC risk with TDF than with ETV. The key strength of this study compared to previous meta-analyses is that the authors used individual patient data of more than 42,000 CHB patients, extracted from 11 participating cohorts from Taiwan, Korea and Hong Kong. Of note, 9 other cohorts were also identified by their literature search but did not agree to participate. All patients had to be treatment-naïve, without concomitant coinfections such as hepatitis C virus, hepatitis D virus or HIV, and without HCC or any other malignancy prior to the initiation of TDF or ETV. Additionally, patients were required to have completed ≥1 year of therapy. The vast majority of patients received ETV as therapy. Patients receiving ETV were older with longer follow-up, were more frequently cirrhotic and HBeAg negative, and had more often concomitant metabolic dysfunction. To account for these confounding factors, the authors applied various state of the art statistical methods, including multivariable Cox regression, propensity score matching, propensity score weighting and sensitivity analyses across clinically relevant subgroups. In their analysis of the overall cohort, the authors found a significantly lower risk (adjusted hazard ratio 0.77) of HCC in the TDF group than in the ETV group after adjustment for the aforementioned potential confounders (5). The effect estimates were generally consistent across various

subgroups, although statistical significance was often not obtained. The results from this large study by a respected group of investigators provides potentially important guidance for the choice of first-line NA treatment in Asian patients with CHB.

The findings reported in the current study are consistent with the result of several previous meta-analyses on primary prevention of HCC (6-9) and are also consistent with some studies performed in patients who have undergone potentially curative treatment of HBV-associated HCC. In this population, TDF treatment has been associated with a reduced risk of HCC recurrence (10). However, other meta-analyses provided contradictory results claiming there is no significant difference in risk of primary HCC in patients receiving TDF or ETV (11,12). It is important to note that all studies on this topic are non-interventional by design, as randomized controlled trials with sufficient power to address this topic are lacking.

Given the heterogeneous results obtained with previous studies, important questions that remain pertain to potential causes of these discrepancies, how these differences should influence our interpretation of the findings and whether the findings reported by Choi *et al.* are applicable to the entire CHB population.

Firstly, differences in methodology and the included patient populations may partially account for the conflicting results. Choi *et al.* (5) performed an individual patient data meta-analysis, aligning inclusion criteria, dataset variables and statistical methodologies across all patients, optimizing precision of their estimates. However, there remains a risk of residual confounding and limitations related to differences in follow-up duration across treatment arms. These issues are related to the fact that TDF was more recently introduced for HBV treatment than ETV in the countries where the patients were enrolled. As a result, the majority of patients included in this study received ETV and the follow-up duration was shorter in TDF treated patients. When Choi *et al.* (5) attempted to adjust for this by excluding patients enrolled before 2011, TDF was still associated with reduced HCC risk, but statistical significance was lost. The influence of differences in follow-up duration was also apparent in the meta-analysis performed by Tseng *et al.* (11), suggesting this may be an important confounding factor.

The longer availability of ETV has also resulted in other important differences across treatment groups—patients treated with ETV were more likely to have site-defined cirrhosis and more often had metabolic dysfunction, both of which are risk factors for HCC (13). Although the authors attempted to adjust for these differences, metabolic dysfunction is not systematically screened for in CHB patients, and underreporting is probably high (and more likely to affect ETV treated patients). Since ETV is more likely to be prescribed to elderly patients and those at increased metabolic risk, such underreporting and failure to account for this in multivariable analysis could disadvantage ETV in any comparison with TDF.

Finally, the mechanism behind the difference in reducing HCC risk between the two regimens remains unclear. In previous studies, it was suggested that HBV DNA levels were more adequately suppressed in patients treated with TDF versus ETV (5). Since HBV DNA suppression halts progressive necroinflammation and fibrosis in most patients, this might explain some of the benefits observed with TDF (3). Complete viral suppression has been associated with a reduced risk of HCC, especially among patients with advanced fibrosis (14). Since degree of viral suppression was not analyzed in this study, we cannot infer whether the reported differences in HCC incidence across treatment groups are related to drug class, or differences in the degree of viral suppression during the treatment period.

Nevertheless, despite these potential issues and heterogeneity across meta-analyses, it is important to note that as far as HCC incidence is concerned, all major studies on this topic have either favoured TDF or provided neutral results, whereas none of the studies favoured ETV.

Should these findings influence our choice of antiviral therapy in our CHB patients? One group in whom these findings cannot currently be applied are non-Asian patients; this subgroup was not included in the study by Choi *et al.*, and a study performed in Caucasians did not show a difference in HCC risk for ETV and TDF (15). Furthermore, it is important to note that in general the vast majority of CHB patients treated with ETV and TDF have a very low risk of HCC, regardless of the type of antiviral therapy. The potential benefit of TDF over ETV is therefore probably limited to the subgroup of patients with a substantially increased risk of HCC, e.g., those with elevated PAGE-B scores. Unfortunately, careful subgroup analyses focusing on these groups have not yet been performed. Furthermore, recent studies have shown that TDF therapy is associated with an excess risk of developing adverse renal and bone events. These risks should be balanced with the potential benefits associated with regards to HCC risk reduction, particularly among patients at low

predicted risk of HCC and those at high risk of osteoporosis and/or renal insufficiency. Since all studies on this topic did not enroll patients treated with TAF, it is unclear whether the benefits attributed to TDF can also be applied to this agent.

In conclusion, Choi *et al*. aimed to answer the controversial question as to which antiviral should be preferred to reduce the risk of HCC in a patient with CHB. Based on previous studies and the compelling results provided by the current report, TDF could be preferred in Asian patients in whom these potential benefits are not counterbalanced by the increased risk of renal and/or bone disease associated with TDF treatment. Whether these findings are applicable to non-Asian patients, and patients at low predicted risk of HCC, remains to be determined.

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Footnote

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