Editorial

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Residual risk of HCC during long-term oral nucleos(t)ide analogues (NUCs) in patients with CHB – Is one NUC better than the other?

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Antiviral therapy with oral nucleos(t)ide analogues (NUCs) is recommended by international guidelines for patients with chronic hepatitis B (CHB) who have treatment indications,[1–3] as NUCs are effective in suppressing HBV DNA and reducing the risk of hepatic events and hepatocellular carcinoma (HCC).[4,5] Entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) are the 3 recommended NUCs, with high genetic barriers to resistance as well as favorable safety profiles.[1,3,6]

In a recent issue of *Journal of Hepatology*, Kim and co-workers reported the findings of a retrospective cohort study of 2,897 patients with CHB recruited from 4 academic teaching hospitals in South Korea.[7] The authors compared the 5-year cumulative probabilities of HCC and death or liver transplantation in patients with or without compensated cirrhosis who had received ETV and TDF as the first antiviral agent. With several statistical approaches, including propensity score (PS)-matched and inverse probability of treatment weighting analyses, the authors did not demonstrate any difference in HCC incidence nor in other clinical outcomes.[7] The yearly HCC rates were approximately 4.3% and 3.4% for ETV- and TDF-treated patients with compensated cirrhosis (adjusted hazard ratio [aHR] 0.83; 95% CI 0.60–1.13; $p = 0.25$) and 0.58% and 0.76% for the corresponding patients without cirrhosis (aHR 1.60; 95% CI 0.95–2.71, $p = 0.07$).

This study adds fuel to the heated debate: is TDF better than ETV in terms of risk reduction of HCC? An earlier report from the same country reported different observations.[8] Choi and co-workers showed a significantly lower HCC risk in TDF-treated patients, compared to ETV-treated patients, in a nationwide historical population cohort study of 24,156 previously treatment-naïve patients with CHB (11,464 started with ETV, 12,692 started with TDF), as well as a hospital cohort of 2,701 patients with CHB (1,560 ETV, 1,141 TDF).[8] The authors reported a consistent HCC risk reduction with TDF treatment, with HRs ranging from 0.61–0.68 in different statistical models and cohorts. The initial publication also reported a lower risk of all-cause mortality or transplant in TDF-treated patients (HR 0.77–0.79).[8] In their updated analysis, this difference in all-cause mortality or transplant was no longer observed; whereas HRs for HCC in the full TDF cohort were changed from 0.61–0.68 relative to entecavir, which remained statistically significant.[9]

One may ask, why have data from the same country (and the patients in the report by Kim *et al.* should be a subset of those studied by Choi *et al.*) yielded such a big difference? One possibility would be difference in patient selection. First, Kim *et al.* excluded HCC in the first 6 months, whereas Choi *et al.* excluded those in the first 12 months for the hospital cohort.

Second, in Choi *et al.*'s study, but not in the Kim *et al.*'s study, patients with decompensated cirrhosis were included, a very important limitation given the well-known high risk of HCC for this population. Third, the nationwide cohort from Choi did not match ETV- and TDF-treated patients for very important baseline variables such as HBV DNA and alanine aminotransferase (ALT), well-known predictors of HCC. Fourth, the cumulative HCC curves in the Choi's paper have a specific pattern: curves start to diverge after 2 years of therapy, which would be biologically sound, but between year 2, 3 to year 4 not a single HCC occurs in the TDF-treated nationwide cohort, a very surprising finding for any HBV cohort. Additionally, in the hospital cohort where all the HCC diagnosed within the first 12 months were excluded, the cumulative incidence of HCC starts to increase immediately after 12 months, as expected, in the ETV group but only after approximately 16 months in the TDF cohort. This 3 to 4-month delay cannot be easily explained. Indeed, the 2 HCC curves remain almost parallel from this time point to the last observation time point, at year 4. These patterns were not observed in Kim's study.

This not-yet-settled controversy was recently fueled by additional studies presented at the International Liver Congress™, Vienna, Austria in April 2019. In a territory-wide cohort study in Hong Kong,[10] Yip and colleagues compared 28,041 ETV-treated patients and 1,309 TDF-treated patients. TDF was superior for preventing HCC as shown in multivariable Cox regression analysis and PS-weighted with HR ranging from 0.32–0.36 but

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not in PS-matched analysis ($p = 0.06$).[10] In order to demonstrate the minimal residual bias from unmeasured confounding, 2 negative control outcomes,[11] lung cancer and acute myocardial infarction, were adopted and illustrated the robustness of the observations.[10] However, the fact that only 8 cases of HCC occurred among the 1,309 TDF-treated patients compared to 1,386 HCC in the 28,041 ETV-treated patients, highlights the fact that the 2 populations significantly differed in terms of baseline predictors of HCC. Additionally, after PS matching the 5-year cumulative incidence of HCC was lower in the TDF compared to the ETV group (1.2% *vs.* 2.3%), but the 2 cumulative curves started to diverge immediately after week 24. This is an unexpected finding given that all the HCC diagnosed in the first 24 weeks were excluded per protocol and that liver carcinogenesis is a complex process lasting for months to years.

Different results were shown by studies performed in the US and Europe. In a multicenter US study[12] enrolling 822 patients with CHB, 407 treated with ETV and 415 treated with TDF, the aHR for HCC was similar between groups (aHR 0.70; 95% CI 0.29–1.68) in the overall population, as well as in the non-Asian and in the NUC naïve populations. The 5- and 10-year cumulative incidences of HCC did not differ between ETV- and TDF-treated patients enrolled in the PAGE-B cohort that included approximately 2,000 Caucasian patients with CHB on long-term oral therapy: 5% and 8% for ETV-treated patients and 6% and 9% for TDF-treated patients (HR for TDF *vs.* ETV adjusted for PAGE-B: 1.116; 95% CI 0.780–1.598; $p = 0.548$) (G. Papatheodoridis, personal communication).

When the rates of HCC during long-term ETV and TDF are compared, additional important issues should be considered. As ETV became commercially available many years before TDF in many countries, including Asia, patients with the most severe liver disease were preferentially treated with this drug. In addition, when TDF became available in these countries a few years later, physicians may have prioritized patients with obesity, diabetes and older age to ETV rather than TDF treatment owing to the renal and bone safety issues of the latter drug. This strategy may have concentrated patients with additional risk factors for HCC in the ETV cohorts. As sophisticated statistical methods can only minimize these important baseline confounders, the inclusion and analysis of homogeneous patient populations also stratified for presence/absence of cirrhosis remain of paramount importance.

Provided that the available studies are not concordant on this topic, is there any biological plausibility to explain why TDF may further reduce the risk of HCC in patients with CHB? Virologically, Choi *et al.* reported better virological response in the TDF-treated cohort.[8] TDF may also lead to better reduction in serum hepatitis B surface antigen (HBsAg) levels, compared to ETV.[13] Biochemically, more TDF-patients achieved ALT normalization at 1 year in Choi's cohort.[8] ALT normalization during the first year of antiviral therapy is associated with lower risk of HCC and other hepatic events in patients with CHB.[14] Immunologically, TDF and adefovir dipivoxil, both as nucleotide analogues, induced higher serum interferon lambda-3 (IFN-λ3) levels than nucleoside analogues (lamivudine and entecavir).[15] IFN-λ has potent antitumor activity in murine models of hepatoma,[16] which may partly explain the lower reported HCC risk in TDF-treated patients.

In our opinion, the observations so far are contradictory and thereby not sufficient to lead to a widespread paradigm shift in selecting TDF over ETV for treatment naïve patients. However, since the residual risk of HCC during long-term oral therapy for HBV remains the only complication affecting liver-related survival, additional observational cohorts in homogenous patients with data on liver disease severity, virologic response, and adherence to surveillance are needed.[17]

Conflict of interest

Grace Wong has served as an advisory committee member for Gilead Sciences and Janssen, and as a speaker for Abbott, Abbvie, Bristol-Myers Squibb, Echosens, Furui, Gilead Sciences, Janssen and Roche. Pietro Lampertico has served as advisor and/or speaker for BMS, Roche, Gilead Sciences, GSK, MSD, Abbvie, Janssen, Arrowhead, Alnylam, Eiger, Myr Pharma.

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

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.05.017.

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