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Is Tenofovir Superior to Entecavir in Reducing the Risk of Hepatocellular Carcinoma in Chronic Hepatitis B? The Controversy Continues

See "Tenofovir is associated with lower risk of hepatocellular carcinoma than entecavir in patients with chronic HBV infection in China," by Yip TC-F, Wond VW-S, Chan HL-Y, et al, on page 215.

The article by Yip et al[1] published in this issue of *Gastroenterology* fuels the discussion on whether different nucleos(t)ide analogues may modulate the risk of hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB). This large retrospective territory-wide cohort study that included 29,350 patients with CHB who started entecavir (ETV) or tenofovir disoproxil fumarate (TDF) in Hong Kong between 2008 and 2018 has several strengths, such as a large sample size, relevant good follow-up, sophisticated statistical analysis, baseline assessment of liver disease severity and all major virologic variables, 1-year virologic and biochemical responses and determination of several HCC risk scores. In contrast, study findings must be taken with caution for several reasons. The 2 groups differed significantly in several well-known strong baseline HCC risk factors; the TDF-treated patients were younger, more frequently hepatitis B e antigen positive, and less frequently male, cirrhotic, and diabetic. Only 4.5% of 29,350 patients and particularly only 1% of 3860 patients with cirrhosis received TDF as a likely consequence of the fact that this drug became available in Hong Kong years after ETV. In addition, the number of TDF-treated patients who developed HCC was very limited: only 8 of 1394 HCCs developed in TDF-treated patients (6 patients with and 2 without baseline cirrhosis), questioning the robustness of a comparative analysis with so few events. The cumulative HCC incidence in this study started to diverge very early, immediately after week 48 (but HCC diagnosed within the first 48 weeks were excluded), which is more in line with different baseline HCC risks between the 2 groups rather than with a usually more delayed different drug effect on the HCC risk.

To adjust for significant differences in baseline characteristics and HCC risk factors between the 2 groups, Yip et al[1] used several statistical tools such as multivariable adjustment, propensity score (PS) weighting and matching, inverse probability of treatment weighting, and competitive risk analysis. In 1200 TDF-treated patients finally matched with ETV-treated patients, TDF was associated with significantly lower HCC risk after PS weighting and 1:5 matching (weighted subdistribution hazard ratio [HR], 0.36 and 0.39; $P \leq .016$). These findings were

confirmed by other subanalyses. However, sophisticated statistical methods cannot replace randomization, because they cannot completely adjust for all the differences in HCC risk factors. Even if an excellent balance can be achieved by PS, the matching will be only for identified and available rather than all possible confounders. In fact, the exact phase of chronic HBV infection and the appropriate treatment indication represent 2 related HCC risk factors[2] that cannot be accurately assessed in such territory-wide studies using code based diagnosis extracted from large databases and therefore cannot be considered in any matching method.

The possible mechanisms explaining the lower HCC risk in patients with CHB treated with TDF are unclear. It has been suggested that TDF, but not ETV, may activate the interferon lambda 3 pathway.[3] Interestingly, in the PS-matched cohort of the current study, virologic response rate at year 1 was significantly lower with ETV than TDF (69.7% vs 77.6%; $P < .001$), although the biochemical response rate was higher with ETV (71% vs 59%; $P < .001$). This finding is unexpected, because a virologic response is usually the major driver of biochemical response. The activation of the interferon lambda 3 pathway by TDF could justify, at least partly, the suboptimal biochemical response in TDF patients, as the persistence of mildly elevated alanine aminotransferase in patients with suppressed HBV replication could play some role in reducing HCC development, for example, by nonspecific killing or deaths of hepatocytes committed to neoplastic transformation. In contrast, observations even from the same group that elevated on-therapy alanine aminotransferase is associated with higher HCC risk complicate the interpretation of such findings.[4]

The results of the Hong Kong study are in line with the initial report from South Korea by Choi et al,[5] suggesting a lower HCC risk with TDF (adjusted HR, 0.68), but 2 large well-performed independent studies again from South Korea failed to confirm these findings.[6,7] Kim et al[6] reported that the annual HCC incidence did not differ between 1484 ETV-treated and 1413 TDF-treated patients (1.92 vs 1.69 per 100 person-years); by multivariable (adjusted HR, 0.975; $P = .852$) or PS-matched and ITPW analyses. Similar findings were reported by Lee et al[7] in a study enrolling 7015 consecutive patients with CHB, both in the entire cohort (PS-matching model HR, 1.03; $P = .880$) and in the subgroups of chronic hepatitis and cirrhotic patients. A third recently published study from a large international consortium of CHB also did not show any significant difference in the 5-year HCC risk between 520 paired matched patients treated with TDF or ETV.[8]

In addition to these 5 recently fully published studies, several as yet unpublished reports have addressed the same topic with contrasting results. In the PAGE-B cohort, which included approximately 2000 Caucasian patients, the 5-year HCC risk was 5.4% in ETV-treated and 6.0% TDF-treated patients (adjusted HR, 1.00; 95% confidence interval, 0.70–1.42).[9] In a French cohort including 2658 patients, the annual HCC risk was also not significantly different between ETV-treated and TDF-treated patients (0.91 vs 0.88 per 100 person-years; adjusted HR, 1.41; 95% confidence interval, 0.65–3.03).[10] At variance, a recent US study demonstrated that, after adjustment of baseline variables and PS weighting, TDF (6145 patients) was associated with significantly decreased risk of HCC compared with ETV therapy (4060 patients) (HR, 0.56; 95% confidence interval, 0.37–0.86).[11]

In summary, whether patients treated with TDF have a lower risk of HCC compared with those treated with ETV remains unsettled, because different studies, even from the same country, reached opposite conclusions.[12,13] The only exception is Europe, where 2 large independent studies reported no difference in the HCC risk between the 2 agents. To improve the quality of the data and subsequently the validity of the results, carefully collected individual data from large cohorts of homogeneous and clinically relevant subpopulations, such as compensated cirrhotics or patients with different stages of disease severity or hepatitis B e antigen profiles, should be analyzed. Thus, investigators are encouraged to merge their cohorts, because only careful collaborative efforts could unravel this interesting clinical issue.

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Does Pancreatic Cyst Stability Justify Stopping Intraductal Papillary Mucinous Neoplasm Surveillance?

See "Long-term risk of malignancy in branch-duct intraductal papillary mucinous neoplasms," by Oyama H, Tada M, Takagi K, et al, on page 226.

Pancreatic cyst surveillance of presumed branch duct-intraductal papillary mucinous neoplasms (BD-IPMN) represents an opportunity for early detection in pancreatic cancer.[1] Owing to the large numbers of asymptomatic pancreatic cysts and their overall very low risk of malignancy in the general population (relative to the numbers of actual pancreatic cancer), several tailored guidelines for surveillance based on these cysts' calculated risk of malignancy and patients' ability to undergo surgery have been proposed.[2,3] Although the decision to stop surveillance is multifactorial, including patient's life expectancy, preference, and tolerance for surgery, perhaps the most controversial item from the recent American Gastroenterological Association (AGA) clinical guidelines is the recommendation to stop surveillance if a pancreatic cyst has remained stable morphologically for >5 years.[4]

The rationale for the AGA recommendation stems from the overall very low risk of malignant progression and the assumption that the majority of pancreatic malignancy and mortality related to neoplastic cysts occur within the first 5 years of cyst discovery.[3] Since the publication of the AGA guidelines, multiple large surveillance studies of presumed BD-IPMN, with follow-up of >5 years have been published. Overall, these studies support a very high disease-specific-5 year survival for patients with low risk BD-IPMNs (without worrisome features [WF]) in the realm of 96%–98%, the persistent and often late (after 5 years) risk of developing WFs and even high-risk stigmata in otherwise low-risk IPMNs (about 5%), the late persistence of the risk of cancer (0%–4%) after 5 and 10 years of surveillance, and the potential value of using baseline cyst size or cyst rate of growth to predict progression of morphology and cancer in the setting of IPMN.[5–14]

However, the issue of stopping surveillance after pancreatic cyst stability during the initial 5 years has been more difficult to study. Even defining cyst stability is challenging, and varies from study to study. In addition to the lack of a uniform consensus about how cyst size is measured, definitions of cyst stability vary from a 20% increase in cyst size, to a rate of growth of >2 mm/yr, to the development of new WFs.[13] Of 412 patients with presumed BD-IPMN radiographic stability over 5 years of surveillance, 19% still had evidence of future growth and 1% developed carcinoma, with the observed rate of cancer development of nearly 6 times greater than what would be expected in the general population.[11] The term "trivial BD-IPMN" was recently used in a separate study, to define 378 patients