Editorial Commentary

The power of prevention: how tenofovir and entecavir are changing the game in hepatocellular carcinoma

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Introduction

Individual patient data (IPD) meta-analysis by Choi *et al.* (1) compared hepatocellular carcinoma (HCC) risk between the entecavir (ETV) and tenofovir (TDF) in treatment-naïve chronic hepatitis B (CHB) patients using a multivariable Cox proportional hazards model from 11 Asian studies, totaling 42,939 patients receiving nucles(t)tide analogues (NAs) for more than one year. TDF was associated with a significantly lower HCC risk than ETV, particularly in patients with hepatitis B e antigen (HBeAg) positivity. The authors concluded, however, that a longer follow-up period may be necessary to clarify the impact disparities between therapies across the various subgroups.

Current American, European, and Asian-Pacific clinical practice guidelines recommend both ETV and TDF as first-line therapies for the treatment of CHB, particularly in NAs-naïve patients. Nonetheless, the relative HCC risk for TDF versus ETV treatment is controversial, and only two randomized controlled trials (RCTs) have demonstrated comparable efficacy, and excellent safety profiles (1). Importantly, the two RCTs involving 720 patients had the same follow-up duration (3 years).

This ambiguity has sparked intense interest and heated debate about which of these two preferred drugs is more effective at lowering the risk of HCC. Several meta-analyses produced contradictory results in this regard, with some showing concordant results and others showing no difference between these two NAs (the summary table is available at: https://cdn.amegroups.cn/static/public/hbsn-23-528-1.xlsx) (1-17).

Methodology of previous metanalyses

The heterogeneity of observational studies has hampered the majority of prior meta-analyses comparing the two NAs on HCC risk development (the summary table available at: https://cdn.amegroups.cn/static/public/hbsn-23-528-1.xlsx). *Figure 1* depicts some of the critical factors that revolve around meta-analysis study carried out in accordance with appropriate standards.

Although the meta-analyses examined were all well conducted, the type of data presented proved to be very heterogeneous. The number of patients was not always stratified by groups (TDF and ETV) but presented as "overall". The age variable was not presented consistently. They present different centrality indices (mean or median) in some cases and are absent in others. The follow-up data considered various time series (months or years). Cirrhosis, HBeAg positivity, hepatitis B virus (HBV) viremia, NAs naïve status, virologic response, and cumulative HCC incidence are all missing or incompletely presented for the majority of them. The effect size varies greatly since the

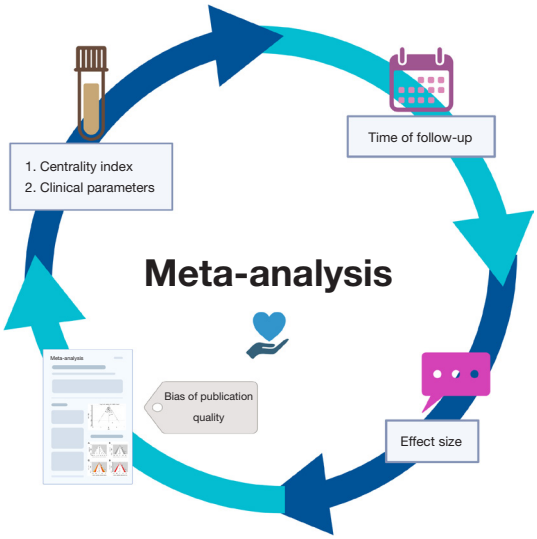

Figure 1 Some of the essential elements of a meta-analysis study conducted in accordance with appropriate standards. Created with "BioRender.com" (Agreement number: HK25ZPG7JM, Academic License).

relative risk (RR) was used in some cases and the hazard ratio (HR) in others. Only a few authors reported an unadjusted HR. Even heterogeneity's I^2 was not always reported.

Furthermore, with the exception of Jeong's paper (lack of the full text) (12), all of the meta-analyses adhere to the fundamental characteristics of a good meta-analysis. All meta-analyses are typically carried out using either "fixed effects" or "random effects" models. All authors explained different or combined uses based on different assumptions. Additionally, all authors conducted a sensitivity analysis, which is the most important part of a meta-analysis since it determines the robustness of the observed results, and subgroup analysis was used.

In terms of publication bias, Zhang *et al.* (3) and Choi *et al.* [2021] (8) used the funnel plot to test the publication bias, but did not specify the test used; Huang *et al.* (17) and Choi *et al.* [2023] (1) did not mention the bias analysis. Oh *et al.* (15), on the other hand, used an unusual test (the AS-Thomson test). Finally, all authors except Dave *et al.* (7) and Choi *et al.* (8) used the Newcastel-Ottawa scale or the Jadad scale as primary tools for assessing the quality of observational studies.

Discussion

While the majority of the observational studies were of high quality and were conducted on a national or multicenter scale using (or not) propensity score matching (PSM) to reduce selection bias and confounding factors, some studies were affected by inadequate sample size, different study designs with diverse data sets, various ethnicities, and diverse proportions of cirrhotic patients.

Notably, the different sources of search strategy among the studies may be to blame for the inclusion of some studies in the meta-analysis process. Two recent meta-analyses did not include most of the recent high-quality studies (3,6). Among studies showing no differences in the HCC risk among the two NAs, the cohort study by Kim *et al.* [2019] (18) and the retrospective study by Lee *et al.* [2020] (19) were not included in the meta-analyses by Zhang *et al.* [2019] (3), Wang *et al.* [2020] (6), and Oh *et al.* [2022] (15); the same studies were not included in the meta-analysis by Choi *et al.* [2023] (1). Besides, data from the Spanish prospective, multicenter database CIBERHEP study of Riveiro-Barciela *et al.* [2017] (20) were only included in the meta-analyses of Wang *et al.* [2020] (6), Yuan *et al.* [2021] (13), and Dave *et al.* [2021] (7). Tseng *et al.* [2020] (10), Wang *et al.* [2020] (6), Tan *et al.* [2022] (16), and Huang *et al.* [2022] (17) did not include data from Papatheodoridis *et al.*'s multicentric European PAGE-B study [2016] (21) showing similar results between ETV and TDF monotherapies.

According to Asian research, CHB patients treated with TDF have a lower cumulative incidence rate of HCC, whereas studies conducted outside of Asia found that the incidence rates of HCC are equal between TDF and ETV treatments (the summary table available at: https://cdn.amegroups.cn/static/public/hbsn-23-528-1.xlsx). These geographic disparities, may be caused by diverse demographic baseline characteristics, HBV genotypes, and healthcare systems. Age should also be considered as a potentially confounding variable, as ETV may have been chosen preferentially for older patients due to potential adverse bone effects associated with TDF or disease severity. HBV genotype C is also predominant in many Asian countries. Since patients with cirrhosis are more likely to develop HCC, the impact of antiviral treatment may be most clearly seen in studies on cirrhotic patients. Antiviral therapy, however, may be most beneficial early in the disease's course. Besides, many studies did not take into account the use of aspirin, statins, and metformin, which are well-known drugs that reduce HCC risk, or the inclusion of treatment-experienced patients.

Additionally, given the moderate to significant

heterogeneity of patient characteristics within/between studies, as well as ETV's earlier introduction than TDF in East Asia (the former in 2006, the latter in 2011), where the majority of studies have been conducted, longer follow-up periods for ETV-treated patients are more frequently available. Specifically, patients treated with TDF had a significantly lower HCC rate in studies where ETV follow-up was more than 12 months longer than TDF, whereas studies with more equal follow-up between arms found no significant difference (4,10). In the meta-analysis of Choi *et al.* [2021] (8), TDF was associated with a 23% lower HCC risk compared with ETV. On the subgroup analysis, this beneficial effect persisted in cirrhotic patients. However, there was a disparity in the follow-up periods between the 2 groups even after PSM since the ETV group had longer follow-up than the TDF group, a difference of up to 33 months. Additionally, in the PAGE-B cohort of 1,935 CHB, long-term monotherapy with ETV or TDF was associated with equivalent HCC risk during similar follow-up times (7.6 and 7.5 years, respectively) (21).

According to research conducted in Asia, particularly in Korea, the controversy surrounding the use of both NAs in the treatment of HCC stems from the arbitrary nature of significance levels, which leads to contradictory conclusions from similar datasets (22). Additionally, although high statistical power can produce statistically significant results, they are not always clinically relevant. Also, it is possible that unadjusted meta-analysis estimates can produce HRs which show that TDF decreases the risk of HCC development more than ETV because patients on ETV may have a higher risk of HCC than those on TDF. Patients with prior NAs resistance, indeed, may have been at a higher risk of HCC due to incomplete viral suppression.

In addition, subgroup analyses, which are often utilized to evaluate the effects of heterogeneity on a limited number of studies, can lead to both false-positive and false-negative results. By applying PSM or covariate-adjusted estimations, meta-analyses can decrease the influence of within-study heterogeneity. However, even when PSM and covariate adjustments are used, the resulting estimations may not always be completely accurate, particularly when significant clinical variables are not included in the analysis, as is the case when administrative claims databases are used in meta-analyses.

Regardless, utilizing IPD allows for a standard analytical approach across all studies. An IPD meta-analysis has the advantage of accounting for biases across all datasets using consistent methodologies, thereby providing a more robust estimate. Despite the obstacles involved in obtaining agreement and ethical approval from a sufficient number of studies, as well as the potential lack of versatility due to the majority of studies being conducted in East Asia, this approach would address many of the issues brought up by aggregate meta-analyses.

Ultimately, it is imperative to carefully consider the source of funding for studies, as it can have an indirect impact on the results and lead to potential bias.

Conclusions

High-quality multicenter RCTs are unlikely to be conducted to identify subgroups that benefit the most from a specific NA due to the lengthy follow-up period and large number of participants required due to the low HCC incidence in CHB patients.

Future observational studies, even if limited by their nature, could compensate for this gap if they focus on distinct subgroups such as those with cirrhosis, different ethnicities, and HBeAg seropositivity.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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