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Review

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Use of tenofovir disoproxil fumarate is associated with a lower risk of hepatocellular carcinoma than entecavir in patients with chronic hepatitis B

Won-Mook Choi, Jonggi Choi

Department of Gastroenterology, Liver Center, Asan Medical Center, University of College of Medicine, Seoul 05505, Korea.

Correspondence to: Prof. Jonggi Choi, Department of Gastroenterology, Liver Center, Asan Medical Center, University of College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea. E-mail: j.choi@amc.seoul.kr

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Abstract

In patients with chronic hepatitis B (CHB), entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are equally recommended as first-line treatment by the international guidelines. These two drugs have shown similar short and intermediate clinical outcomes, including virologic, biochemical, and histologic responses. However, there is considerable controversy as to whether ETV and TDF differ in reducing the risk of hepatocellular carcinoma (HCC) in patients with CHB despite many observational studies and meta-analyses being published. In this review, we summarize recent evidence comparing the preventive effects of these two drugs against HCC from the perspective that TDF is associated with a lower risk of HCC compared with ETV in patients with CHB.

Keywords: Hepatocellular carcinoma, hepatitis b virus, tenofovir disoproxil fumarate, entecavir, prevention

INTRODUCTION

Chronic hepatitis B (CHB) is one of the most common causes of chronic liver disease, with over 250 million people infected worldwide, accounting for 60% of hepatocellular carcinoma (HCC) cases in Asia and Africa and 20% of cases in the West[1-5]. Long-term nucleos(t)ide analog therapy reduces the risk of HCC by suppressing the replication of HBV, a well-known risk factor for HCC[6,7]. Considering their high antiviral efficacy and low resistance rate, entecavir (ETV) and tenofovir-based regimens including tenofovir

alafenamide and tenofovir disoproxil fumarate (TDF) have been equally recommended as first-line treatments for CHB by international guidelines[7-10]. ETV and TDF have shown comparable efficacy in viral suppression and biochemical response[9]. Both treatments have also been expected to be similarly effective in preventing the incidence of HCC, decompensation, and death[11,12]. Thus far, several observational studies have reported the incidence of HCC between the two treatments as secondary outcomes, not as a primary outcome for direct comparison. In 2018, Choi *et al.*[13] reported that TDF treatment was associated with a lower risk of HCC compared with ETV in a nationwide cohort and hospital cohort study. Since then, several studies have shown the superiority of TDF over ETV in preventing HCC[14,15], whereas other studies failed to find a statistical difference between the two drugs[16-18]. This debate has been extended to the meta-analyses. Eleven meta-analyses were published between December 2019 and June 2021.

In this review, we summarize recent evidence comparing the effectiveness of these two treatments from the perspective that TDF may be superior to ETV in preventing HCC development.

OBSERVATIONAL STUDIES

Studies showing the superiority of TDF in secondary prevention of HCC

The study by Choi *et al.*[13] using the nationwide cohort and the large-scale single-center validation cohort was the first to find that TDF showed a significantly lower risk of HCC than ETV. This study of 24,156 and 2701 treatment-naïve patients in the nationwide cohort and the hospital validation cohort showed that TDF conferred 34% and 32% reductions in the risk of HCC by multivariable analyses, respectively[13]. Of note, virological responses [85.2% (TDF) *vs.* 78.7% (ETV); $P < 0.001$] and alanine aminotransferase (ALT) normalization rates [44.3% (TDF) *vs.* 38.7% (ETV); $P = 0.002$] at one year were significantly higher in TDF treatment compared with ETV treatment[13].

Another study of 29,350 treatment-naïve patients with CHB from Hong Kong using a large administrative database demonstrated that TDF treatment showed a consistently lower risk of HCC [adjusted hazard ratio (aHR) = 0.36; 95% confidence interval (CI): 0.16-0.80; $P = 0.013$] than ETV treatment across all of the sophisticated statistical analyses including multivariable, propensity score (PS)-matching, PS-weighting, and competing risk analyses. In addition, patients treated with TDF showed a significantly higher virological response at one year compared with those treated with ETV (77.6% *vs.* 69.7%, respectively)[14].

A multicenter retrospective study of 1560 cirrhotic patients from Taiwan reported that TDF significantly decreased the risk of HCC compared with ETV (aHR = 0.67; 95%CI: 0.48-0.93; $P = 0.002$), which was consistently observed in PS-matching analysis and PS-weighting analysis[19]. However, the lower risk of HCC in the TDF group was not observed in the subgroup analysis of patients with compensated cirrhosis at baseline to further exclude patients with decompensated cirrhosis or patients who were enrolled after 2011 to minimize the follow-up duration between the two groups[19].

Another single-center study including 404 treatment-naïve patients with CHB from Korea observed that TDF treatment was associated with a significantly lower risk of HCC compared with ETV (aHR = 0.31; 95%CI: 0.12-0.79; $P = 0.014$) in multivariable analysis, which was consistently observed in the PS-matching analysis[15]. In this study, statistical significance was not maintained when sustained virological suppression was adjusted in the PS-matching analysis[15]. However, it may not be statistically appropriate to include sustained virological response as a PS-matching variable because it cannot be measured at baseline.

Another western study presented at the International Digestive Disease Forum 2020 analyzed the United States administrative database, comparing ETV and TDF for the risk of HCC development in treatment-

naïve patients with CHB[20]. In this study of 158,272 patients with CHB, the absolute rate of HCC in the TDF group was approximately half that in ETV group. The lower risk of HCC in the TDF group compared with the ETV group (aHR = 0.56; 95% CI: 0.37-0.86) was persistently observed in multivariable analysis after adjustment for age group, sex, baseline health conditions, and PS weighting[20].

Studies showing the superiority of TDF in tertiary prevention of HCC

Regarding the tertiary prevention of HCC after curative treatment, there are a few studies comparing the effectiveness of ETV and TDF in preventing HCC recurrence. A Chinese study including 233 patients with HBV-related HCC who underwent liver resections observed that TDF treatment was associated with a significantly longer disease-free survival compared with ETV (33 months *vs.* 24 months, respectively; $P < 0.001$)[21]. Another study from China including 479 patients with HBV-related HCC confirmed this finding that TDF treatment was superior to non-TDF treatment including ETV (aHR = 0.67; 95%CI: 0.48-0.93; $P = 0.04$) in preventing HCC recurrence after curative resection[22].

Choi *et al.*[23] conducted a retrospective single-center study of 1695 patients with HBV-related HCC with Barcelona Clinic Liver Cancer stage 0 or A who received curative resection, showing that TDF treatment was associated with a significantly lower risk of HCC recurrence (aHR = 0.82; 95%CI: 0.68-0.98; $P = 0.03$) and death or liver transplantation (adjusted HR = 0.62; 95%CI: 0.44-0.88; $P = 0.01$) in multivariable analysis compared with ETV, which was maintained in PS-matching analysis. Intriguingly, the preventive effect of TDF was more prominent in preventing late recurrence (≥ 2 years after liver resection; aHR = 0.68) than for preventing early recurrence (< 2 years liver after resection; aHR = 0.79)[23], suggesting that TDF treatment might more effectively prevent the development of *de novo* HCC than ETV after curative resection[24,25].

META-ANALYSES

In contrast to the above-mentioned studies, many studies failed to show a significant difference between the two drugs for preventing HCC occurrence[16-18,26-32]. Of note, none have reported a lower risk of HCC with ETV than TDF. This controversy has motivated many to conduct systematic reviews and meta-analyses. Eleven meta-analyses were published between December 2019 and June 2021 on this controversial issue. The results of the meta-analyses published so far are summarized in Table 1. Although the studies and patients included in the 11 meta-analyses were slightly different, most of the meta-analyses except for two (Tseng *et al.*[33] and Yuan *et al.*[34]) reported that TDF was superior to ETV in preventing HBV-associated HCC when the adjusted HR was pooled. Most meta-analyses performed subgroup analyses and/or meta-regression to address between-study heterogeneity. Three major issues were raised during the process of explaining between-study heterogeneity as follows: (1) sample size *vs.* study setting (i.e., clinical cohort, administrative database, or electronic health record database); (2) cirrhotic subgroup and whether the study included patients with decompensated cirrhosis or not; and (3) difference in follow-up duration between the two drugs.

First issue: sample size *vs.* study setting

In the meta-analysis by Choi *et al.*[35], sample size was one of the most important factors for explaining the between-study heterogeneity in mete-regression analysis. While studies with a larger number of patients showed superiority of TDF in reducing the risk of HCC compared with ETV, studies with a smaller number of patients did not. Another meta-analysis by Tseng *et al.*[33] addressed this issue by observing the differences in the study setting. TDF showed a similar risk for HCC among hospital-based cohort studies (HR = 1.03; 95%CI: 0.88-1.21), whereas TDF was associated with a lower HCC risk among studies based on the administrative claims database (aHR = 0.67; 95%CI: 0.59-0.76)[33]. Tseng *et al.*[33] explained these discrepant results between clinical cohorts and administrative database studies by the difference in residual

Table 1. Summary of meta-analyses comparing the risk of HCC between ETV and TDF

Authors	No. of studies	No. of patients	Unadjusted HR (95%CI)	Adjusted HR (95%CI)	Explanation for heterogeneity
Zhang *et al.*[51]	7	3698	0.66 (0.49-0.89)[a]	NA	No
Li *et al.*[40]	32	78,136	0.87 (0.73-1.04)[a]	NA	Subgroup analyses
Gu *et al.*[37]	11	70,864	0.75 (0.65-0.87)	0.71 (0.63-0.79)	Subgroup analyses
Wang *et al.*[52]	8	4814	0.66 (0.41-1.05)[a]	NA	No
Dave *et al.*[53]	14	69,336	0.66 (0.41-1.05)[a]	0.79 (0.63-0.99)	Meta-regression
Choi *et al.*[35]	15	61,787	0.80 (0.69-0.93)	0.75 (0.58-0.97)	Meta-regression
Liu *et al.*[54]	7	35,785	NA	0.75 (0.58-0.96)	No
Tseng *et al.*[33]	15	88,141	0.75 (0.54-1.03)	0.88 (0.73-1.07)	Subgroup analyses
Cheung *et al.*[38]	13	85,008	NA	0.81 (0.67-0.99)	Subgroup analyses
Yuan *et al.*[34]	13	80,202	0.75 (0.60-0.95)	0.86 (0.72-1.04)	Subgroup analyses
Jeong *et al.*[39]	16	50,595	0.63 (0.43-0.93)[a]	0.74 (0.63-0.87)	Subgroup analyses

[a]These meta-analyses reported risk ratio or rate ratio instead of HR. CI: Confidence interval; ETV: entecavir; HCC: hepatocellular carcinoma; HR: hazard ratio; NA: not applicable; TDF: tenofovir disoproxil fumarate.

confounding as the information contained in administrative databases is less precise and prone to errors because of inaccurate coding. However, this may be an overly simplified explanation. Determining the optimal sample size for a clinical study is critical to assure an adequate power to detect a clinical significance. To achieve a power of 0.8 for a type I error level of 0.05 with an assumed HR of 0.88 as reported in Tseng *et al.*[33], 36,364 patients would be required. Thus, studies that concluded that HCC risks were similar between the two drugs are subject to a type II error. Showing non-significance in the outcome between the two drugs is a lot easier than finding significant differences in comparative effectiveness research[36]. Considering that retrospective studies, particularly with a small sample size, entail numerous confounding factors, simply pooling the HR in a meta-analysis is part of the solution for addressing the conflict issue, but it is certainly not the complete solution.

Second issue: presence and stage of cirrhosis

Subgroup analyses were conducted in most of the meta-analyses to explain the between-study heterogeneity. In a subgroup analysis based on cirrhosis status, TDF was consistently associated with a lower risk of HCC compared with ETV in CHB patients with cirrhosis[34,35,37-39]. Moreover, another important determinant of the between-study heterogeneity was whether the study included patients with decompensated cirrhosis or not as shown in a meta-regression analysis by Choi *et al.*[35]. TDF showed a significantly lower HCC risk over ETV (HR = 0.69; 95%CI: 0.55-0.85; $P < 0.001$) in studies including patients with decompensated cirrhosis, whereas no difference between the two drugs (HR = 0.90; 95%CI: 0.76-1.06; $P = 0.20$) was found in studies excluding those patients[35]. In Korea where the most studies regarding this issue were performed, the landmark study by Choi *et al.*[13] that showed the superiority of TDF included patients with decompensated cirrhosis, whereas the other studies with a relatively large sample size showing similar risk of HCC between the two drugs did not, which may explain the inconsistent results among studies[16,17]. It is well-known that patients with cirrhosis, especially decompensated cirrhosis, have a very high risk of developing HCC. Considering that high case numbers prevent the occurrence of a type II error and facilitate statistically meaningful conclusions being made, the difference in effectiveness between the two drugs in cirrhotic subgroup or studies including patients with decompensated cirrhosis could represent a better preventive effect of TDF.

Third issue: differences in the follow-up time

Because ETV was introduced earlier than TDF, ETV-treated patients had longer follow-up durations in most studies. In the study by Lee *et al.*[17], for example, the median follow-up duration was longer in patients treated with ETV than in those treated with TDF (60 months *vs.* 36.4 months, respectively). The difference in the follow-up duration due to the asynchronous introduction of the two treatments may cause a bias in either direction. Previous meta-analyses by Tseng *et al.*[33] and Li *et al.*[40] also noticed this point, and they performed subgroup analyses based on follow-up duration. In studies with a follow-up duration of ETV that was longer than TDF by more than one year, TDF was significantly associated with a lower risk of HCC (aHR = 0.69; 95%CI: 0.61-0.79). However, there was no difference in the risk of HCC between the two treatments in studies with a minimal disparity of less than one year in the follow-up duration (aHR = 0.88; 95%CI: 0.70-1.11)[33]. The patient warehousing phenomenon, which indicates postponing treatment until a new effective drug becomes available, may have contributed to the bias toward prescribing ETV to sicker and older patients before TDF became available. However, it should be noted that TDF consistently showed a superiority over ETV (HR = 0.75; 95%CI: 0.58-0.97) in pooled analysis of PS-matched cohorts from available studies in which the baseline characteristics were well balanced[35].

Furthermore, patients with favorable outcomes such as HBeAg loss, HBsAg loss, and fibrosis/cirrhosis regression are more likely to be enriched in the longer-term follow-up cohort[41,42], which results in attrition bias acting in favor of ETV. In addition, it is well-known that the preventive effect of antiviral treatment against HCC becomes increasingly evident over time[11,43,44]. Thus, it is unlikely that a longer follow-up duration of ETV may be biased in favor of TDF.

From a statistical perspective, all published studies calculated HR with a Cox proportional hazards model, which means that the proportional hazard assumption was satisfied in all studies and the HR comparing TDF and ETV was constant with respect to time. This implies that the issue of the difference in the follow-up time between the two drugs may not be statistically important.

PLAUSIBLE EXPLANATIONS FOR THE SUPERIORITY OF TDF

The mechanism underlying the reduced HCC risk associated with TDF over ETV is unclear. It has been postulated that antiviral treatment reduces the HCC risk by modifying three components on a different time scale[45]. Liver injury or inflammation are the first to be affected as antiviral treatment suppresses viral replication. Second, regression of fibrosis/cirrhosis due to long-term antiviral treatment may substantially reduce the risk of HCC. Lastly, the risk of HCC may further decrease when antiviral treatment prevents the formation of cccDNA and subsequent host-genome integration[45]. Based on this postulation, several plausible explanations could be noted. TDF has a higher antiviral potency, which may affect all of the subsequent modifiable components. In a study by Choi *et al.*[13], at one year of treatment, TDF treatment resulted in higher rates of virological response and ALT normalization. Yip *et al.*[14] also observed a higher rate of virological response of TDF compared with ETV at one year of treatment. This was consistent with the findings of recent meta-analyses, which found that the virological response was higher with TDF compared with ETV[37,46]. In a small randomized controlled trial comparing the efficacy of TDF and ETV, patients treated with TDF had a greater reduction in their HBsAg level than those treated with ETV[47]. Moreover, Papatheodoridis *et al.*[18] found more frequent elastographic reversion of cirrhosis (liver stiffness measurements of ≥ 12 kPa) in TDF compared with ETV (73.8% *vs.* 61.5%; $P = 0.038$) after five years of treatment despite similar rates of HCC development between the two treatments. This may suggest that TDF is better at modifying the second modifiable component (i.e., fibrosis or cirrhosis). In addition, a translational research study found a higher interferon lambda-3 level, which had a potent antitumor activity against HCC[48,49], in patients treated with TDF compared with those treated with ETV[50].

CONCLUSION

Since the study by Choi *et al.*[13] first reported a better preventive effect of TDF than ETV against HCC, many studies have shown no difference between the two drugs, an issue that has become a matter of contention in the field of hepatology. Nevertheless, all of the studies comparing the risk of HCC between ETV and TDF were either neutral or in favor of TDF. No study was in favor of ETV over TDF. In line with observational studies showing one direction favoring TDF or no direction, most meta-analyses published thus far have also reported the superiority of TDF over ETV in preventing HCC. However, a large degree of uncertainty remains for this issue due to a lack of randomized clinical trials comparing the preventive efficacy of ETV and TDF against HCC occurrence. Bias remains in many observational studies due to a lack of some confounding factors such as presence of comorbid diseases and family history of HCC. Considering the inconsistent methodologies of the previous observational studies, simply pooling the estimates in a meta-analysis is not a definitive answer to this issue. Moreover, a randomized clinical trial would not be feasible in the near future given the need for a large number of patients with a sufficient length of follow-up time. Thus, an alternative approach such as an individual patient data meta-analysis, which allows for adjusting bias with consistent methodologies across all datasets, should be taken into consideration. This would provide a more robust estimate of HCC risk between ETV and TDF in patients with CHB and help to identify the subgroup of patients who will have more benefit from TDF than ETV.

DECLARATIONS

Authors' contributions

Wrote the entire manuscript and designed figure and table: Choi WM
Overviewed and edited the entire manuscript: Choi J

Availability of data and materials

Not applicable.

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Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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