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Tenofovir disoproxil fumarate is not associated with a lower risk of hepatocellular carcinoma compared to entecavir in patients with chronic hepatitis B

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Abstract

A paper published several years ago suggested that tenofovir disoproxil fumarate (TDF) was superior to entecavir (ETV) for reducing the risk of hepatocellular carcinoma (HCC). Since then, many observational studies have been conducted comparing TDF and ETV. Many studies in Asia demonstrated similar HCC risks between ETV and TDF groups. Similarly, recent studies involving Caucasian and European did not observe any differences in HCC risk between these groups. In this article, we briefly review studies that compared the incidence rates of HCC between ETV and TDF and discuss potential reasons for the discrepant results.

Keywords: Hepatitis B, entecavir, tenofovir, hepatocellular carcinoma

INTRODUCTION

Hepatitis B virus (HBV) infection is a major cause of chronic liver disease worldwide. In the present era of potent antiviral therapy, entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are used to suppress HBV replication and prevent disease progression[1,2]. Although both antiviral agents reduce the hepatocellular carcinoma (HCC) risk compared to no antiviral treatment, it is not clear whether TDF is

superior to ETV in terms of reducing the HCC risk in patients with chronic hepatitis B (CHB). No randomized clinical trials have yet been conducted on this topic. Instead, several observational studies have compared the effects of TDF and ETV in terms of the risk of HCC development. The studies, which have generated strong interest in this topic, are summarized in this article [Table 1].

Studies showing the superiority of TDF

Choi *et al.*[3] were the first to suggest that TDF is superior to ETV for reducing the risk of HCC development. Choi *et al.*[4] analysed two retrospective cohorts based on a large administrative data set (24,156 patients with CHB) and a tertiary hospital-based cohort (2701 patients with CHB). The risk for HCC was 39% lower in the TDF group compared to the ETV group [hazard ratio (HR) = 0.61; 95% confidence interval (CI): 0.53-0.70]. The difference remained statistically significant after adjustment for covariates. Patient's compliance to antivirals and surveillance may differently affect the risk for HCC development. In addition, patients in the ETV group had greater primary exposure to lamivudine compared to the TDF group patients. Moreover, treatment was switched more frequently for the patients in the ETV group (12%) compared to the TDF group (0.2%).

Recently, the same group of researchers again reported a significantly lower risk of HCC in TDF compared to ETV (HR = 0.80; 95%CI: 0.69-0.93)[5]. This systematic review and meta-analysis included 15 studies (16,101 patients with TDF and 45,686 with ETV). Meta-regression analyses were used to explain between-study heterogeneity and the conflicting results of the included reports. Between-study heterogeneity in this meta-analysis was explained by differences in sample sizes, the ages of the participants, the proportions of patients with cirrhosis, and the inclusion criteria (e.g., inclusion of decompensated cirrhosis).

Another study, conducted in Hong Kong, demonstrated similar results. Yip *et al.*[6] observed a lower risk of HCC development with TDF than ETV treatment in 29,350 treatment-naïve CHB patients (1309 patients with TDF and 28,041 with ETV). To minimize selection bias, the researchers used various statistical methods, including propensity score matching and weighting, inverse probability of treatment weighting, and competitive risk analysis. There was a lower incidence of HCC among TDF than ETV patients after propensity score weighting (HR = 0.36; 95%CI: 0.16-0.80; P = 0.013) and 1:5 matching (HR = 0.39; 95%CI: 0.18-0.84; P = 0.016). However, the effects of confounders could not be eliminated despite the application of propensity score weighting and competitive risk analysis. In addition, as ETV was approved by the Food and Drug Administration prior to TDF, the TDF group included fewer patients and had a shorter follow-up period.

Studies showing no difference between ETV and TDF

In contrast, three studies from South Korea did not observe any differences in the risk of HCC development between TDF and ETV groups[7-9]. Most studies related to this topic has been conducted in East Asia.

Our group reported that the annual incidence of HCC did not differ between ETV-treated (n = 1484) and TDF-treated (n = 1413) patients (1.92 and 1.69/100 person-years, respectively; adjusted HR = 0.975)[7]. In that study, treatment-naïve CHB patients were recruited from four teaching hospitals and received either ETV or TDF as a first-line antiviral drug. Statistical methods yielded similar results in both propensity score-matching (HR = 1.021; P = 0.884) and inverse probability of treatment weighting analyses (HR = 0.998; P = 0.988). Long-term use of ETV did not increase the risk of HCC development.

Lee *et al.*[8] reported similar results for 7015 CHB patients. No differences were observed in the incidence of HCC between TDF and ETV groups (HR = 1.030; 95%CI: 0.703-1.509; P = 0.880 for the propensity score

Table 1. The summary of studies which were reviewed in this commentary

Authors	Country	Study design	Number of patients	HR (TDF *vs.* ETV)	95%CI
Choi *et al.*[4]	South Korea	Retrospective	24,156 patients with CHB (administrative data) and 2701 patients with CHB (a tertiary hospital-based cohort)	0.61*	0.53-0.70
Choi *et al.*[5]	South Korea	Meta-analysis	16,101 patients with TDF and 45,686 patients with ETV	0.80*	0.69-0.93
Yip *et al.*[6]	Hong Kong	Retrospective	29,350 treatment-naïve CHB patients (1309 patients with TDF and 28,041 with ETV)	0.36* (PS matching) 0.39* (1:5 matching)	0.16-0.80 0.18-1.84
Kim *et al.*[7]	South Korea	Retrospective	TDF (n = 1413) and ETV (n = 1484)	1.021 (PS matching) 0.998 (IPTW)	
Lee *et al.*[8]	South Korea	Retrospective	TDF (n = 1439) and ETV (n = 1583)	1.03	0.703-1.509
Oh *et al.*[9]	South Korea	Retrospective	TDF (n = 807) and ETV (n = 753)	1.26	0.81-1.97
Tseng *et al.*[10]	Taiwan	Meta-analysis	520 matched pairs of patients with TDF or ETV	1.03	0.88-1.21
Papatheodoridis *et al.*[11]	Caucasian	Retrospective	TDF (n = 1163) and ETV (n = 772)	1.17	0.70-1.97
PoI[12]	European	Retrospective	1800 patients (986 patients with TDF and 814 with ETV)	1.24 (IPW analysis) 1.06 (Univariable) 1.51 (Multivariable)	0.49-3.13 0.45-2.52 1.51-3.92

*TDF had lower risk of HCC development compared to ETV. HR: Hazard ratio; 95%CI: 95% confidence interval; CHB: chronic hepatitis B; ETV: entecavir; TDF: tenofovir disoproxil fumarate; PS: propensity matching; IPTW: inverse probability of treatment weighting.

model) or in the subgroup of cirrhotic patients. Similarly, no differences were observed in the rates of all-cause mortality or liver transplantation between TDF-treated and ETV-treated patients in the entire cohort (HR = 1.090; 95%CI: 0.622-1.911; P = 0.763 for the propensity score model), or in the subgroup of CHB patients with cirrhosis.

Oh *et al.*[9] analysed data from 1560 treatment-naïve CHB. HCC was developed in 4.5% and 5.6% of ETV-treated (n = 753) and TDF-treated (n = 807) patients, respectively. There was no difference between the ETV and TDF groups (HR = 1.26; 95%CI: 0.81-1.97; P = 0.303). The cumulative incidence rates of HCC at 2, 3, 4, and 5 years were 1.3%, 3.2%, 4.0%, and 4.5% in the ETV group and 2.2%, 3.8%, 5.2%, and 5.5% in the TDF group, respectively. The differences in incidence rates between the groups remained statistically insignificant after propensity score matching.

Tseng *et al.*[10] included 31 studies and 119,053 patients in their systematic review and meta-analysis. The 5-year cumulative incidence rates of HCC were 5.97% (95%CI: 5.81-6.13) for ETV and 3.06% (95%CI: 2.86-3.26) for TDF in studies with unmatched populations (P < 0.0001). However, in studies matched by propensity scores, the 5-year cumulative incidence rates of HCC were 3.44% (95%CI: 3.08-3.80) for ETV and 3.39% (95%CI: 2.94-3.83) for TDF (P = 0.87). After adjustment for covariates in 14 comparative studies, the risk of HCC development was similar between TDF-treated and ETV-treated patients (adjusted HR = 0.88; 95%CI: 0.73-1.07; P = 0.20).

The data from Caucasian and European did not show any differences in the risk of HCC between ETV and TDF groups[11,12]. The 5-year cumulative incidence rates of HCC were not statistically different between CHB patients treated with ETV (n = 772) and TDF (n = 1163), at 5.4% and 6.0%, respectively (P = 0.321)[11]. In multivariate analyses, HCC risk was similar between the ETV and TDF groups (HR = 1.17; 95%CI: 0.70-1.97; P = 0.549) after adjustment for risk factors (age, smoking status, diabetes, alanine aminotransferase level, hepatitis B e-antigen level, antiviral therapy before ETV/TDF, and cirrhosis). European data also revealed a similar risk of HCC development between ETV- and TDF-treated patients with CHB (HR = 1.24; 95%CI: 0.49-3.13 in inverse probability weighting analysis, HR = 1.51; 95%CI: 0.58-3.92 in multivariate analysis)[12].

For the purpose of secondary prevention, the risks of HCC development between ETV and TDF are still controversial. TDF was associated with a lower risk of HCC recurrence after curative hepatectomy for HBV-related HCC[3]. Contrarily, ETV and TDF treatment did not show differ in terms of HCC recurrence after hepatic resection or radiofrequency ablation (HR = 0.932; P = 0.622)[13].

The reason for the discrepancies among studies is not clear. However, there are several possibilities[14]. First, many studies claiming superiority of TDF analysed big data, which may have imbalanced the HCC risk factors despite statistical matching. Second, patients with severe chronic liver disease tended to first receive ETV because it was approved earlier than TDF. Also, TDF may be toxic to bones and kidneys, biasing initial patient selection. Third, the meta-analysis included studies that lacked statistical significance or had very small numbers of patients. Fourth, interferon-lambda was suggested to mediate the anti-tumour effect of TDF, but there is no definitive *in vitro* or *in vivo* evidence that ETV is more carcinogenic than TDF. Lastly, TDF seemed to be associated with more frequent "elastographic reversion" of cirrhosis at year 5[15], but further studies are needed for validation

CONCLUSION

It is not clear whether TDF is superior to ETV for HCC prevention. Most observational studies have demonstrated similar HCC risk levels between ETV and TDF. Our published data also support the view that there is no difference between ETV and TDF in terms of the risk of HCC development. Because it is challenging to perform a prospective, randomized study to compare HCC risk between ETV and TDF, further well-designed comparisons are needed to confirm the best treatment for patients with CHB.

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Authors' contributions

Writing: Lee HW, Kim SU
Supervision: Kim SU

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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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