Comparison of the Efficacy of Entecavir and Tenofovir in Reducing Hepatocellular Carcinoma Risk in Chronic Hepatitis B Patients: A Real-Life Study in Turkey

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ABSTRACT

Background: *It is controversial whether entecavir or tenofovir differs in reducing hepatocellular carcinoma (HCC) risk. We aimed to compare the efficacy of entecavir and tenofovir in reducing HCC risk in chronic hepatitis B (CHB) patients.*

Methods: *This retrospective study included 607 nucleos(t)ide naive CHB patients who had received entecavir or tenofovir. Patients who developed HCC during the first 12 months of therapy were excluded. Cumulative HCC incidences at years 2, 3, 4, 5 and 10 were compared between entecavir and tenofovir groups. Factors associated with HCC were determined by univariate and multivariate analyses.*

Results: *Nineteen (3.1%) patients developed HCC, 12 (4.8%) in entecavir group and 7 (1.9%) in tenofovir group (P = .045). In the entire cohort, cumulative HCC incidences at years 2, 3, 4, 5 and 10 were 1.8%, 2.9%, 4.4%, 5.2% and 9.9% in entecavir group, and 0.6%, 2.4%, 2.4%, 2.4% and 3.7% in tenofovir group, respectively (log-rank P = .130). In multivariate analysis, age ≥50 years, cirrhosis, decompensated cirrhosis, high GGT and low platelet levels were associated with HCC in the entire cohort. In advanced fibrosis/cirrhosis cohort, cumulative HCC incidences at years 2, 3, 4, 5 and 10 were 4.6%, 7.1%, 8.6%, 12.1% and 15.5% in entecavir group, and 1.8%, 5.6%, 5.6%, 5.6% and 8.5% in tenofovir group, respectively (log-rank P = .267). In multivariate analysis, age ≥50 years, decompensated cirrhosis, high GGT and low platelet levels were associated with HCC in the advanced fibrosis/cirrhosis cohort.*

Conclusion: *Entecavir and tenofovir are similarly effective in reducing HCC risk in CHB patients.*

INTRODUCTION

Chronic hepatitis B virus (HBV) infection is one of the most common causes of cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality. HBV related cirrhosis and HCC are among the most common indications for liver transplantation.[1]

In chronic hepatitis B (CHB), persistant HBV replication is the most important risk factor for progression to cirrhosis and HCC development.[2] Therefore, the goal of CHB therapy is maintained suppression of HBV replication.[1,3] Lamivudin was shown to reduce disease progression and HCC development in patients with advanced disease compared to untreated controls,[4] and was also shown to be associated with regression of fibrosis and cirrhosis.[5]

Currently, entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide fumarate (TAF) are the first-line therapies in CHB due to high resistance rates in lamivudin-treated patients.[1,3] At long-term follow-up, therapy with ETV or TDF results in suppression of HBV replication in most patients, and even reversal of fibrosis and cirrhosis.[1,3,6,7] HCC risk also decreases with the use of these drugs.[8,9] However, HCC still develops and remains the most important risk factor for mortality in patients under antiviral therapy.[1,10]

Although ETV and TDF are similarly effective in achieving virological suppression, there is a controversy between studies that compared the efficacy of ETV and TDF in reducing HCC risk. Some did not show a difference between ETV and TDF,[11-14] whereas others showed that

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TDF was superior to ETV.[15,16] Moreover, all these studies were performed in Asian countries.

In the present study, we aimed to compare the efficacy of ETV and TDF in reducing HCC risk in Turkish CHB patients. We also aimed to evaluate risk factors for HCC in CHB patients.

MATERIALS AND METHODS

We retrospectively reviewed the data of CHB patients who were admitted to Gastroenterology Outpatient Clinics of Haydarpaşa Numune and Ümraniye Training and Research Hospitals between January 2007 and December 2018. The study included nucleos(t)ide naive patients if they had received ETV or TDF for at least 12 months. Patients who developed HCC prior to therapy or during the first 12 months of therapy, had coinfection with hepatitis D virus, hepatitis C virus or human immunodeficiency virus, or had a history of liver transplantation were excluded.

Baseline laboratory data [HBeAg status, serum HBV DNA, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), albumin, bilirubin, prothrombin time (PT), international normalized ratio (INR), alpha-fetoprotein (AFP) levels and complete blood count], presence of diabetes mellitus (DM), liver biopsy results if available and results of imaging studies [ultrasonography (USG), computerized tomography (CT) and magnetic resonance imaging (MRI)] were recorded. Results of laboratory tests and imaging studies at follow-up were also recorded.

CHB was diagnosed if patients had HBsAg positivity for at least 6 months. Therapy was started according to reimbursement criteria of the Social Security Institution of Turkey. The criteria to start therapy were as follows: (1) serum HBV DNA positivity regardless of serum ALT levels and HBeAg status in patients with clinically proven cirrhosis and (2) HBV DNA ≥ 2000 IU/mL and histological activity index (HAI) ≥ 6 or fibrosis ≥ 2 on liver biopsy regardless of serum ALT levels and HBeAg status in noncirrhotic patients. By the year 2011, liver biopsy was not mandatory in both HBeAg positive and negative noncirrhotic patients if HBV DNA levels were ≥ 20 000 IU/mL and serum ALT levels were ≥ 2 × upper limit of normal for at least 6 months.

The severity of liver disease was defined biochemically, histologically, endoscopically and radiologically. The presence of hypoalbuminaemia, hyperbilirubinemia, and prolonged PT and INR on liver biochemistry, and/or stage 5-6 fibrosis (Ishak) on liver biopsy were defined as cirrhosis. The presence of esophagogastric varices on endoscopy, and/or splenomegaly (with thrombocytopenia) and elevated portal vein diameter plus at least one of the following on imaging studies were also defined as cirrhosis: (1) nodular appearance in liver parenchyma, (2) irregularity on liver surface and (3) right lobe atrophy with a caudate lobe or left lobe hypertrophy. History of variceal bleeding or hepatic encephalopathy, or presence of ascites were further defined as decompensated cirrhosis. Biochemical, histological, radiological and endoscopical results incompatible with cirrhosis were defined as noncirrhosis. Stage 4 fibrosis (Ishak) was defined as advanced fibrosis.

Serum HBV DNA levels were measured by polymerase chain reaction assays of various manufacturers depending on time points in each center. Because the lower detection limit of PCR assays varied between various manufacturers, serum HBV DNA level <80 IU/mL was defined as HBV DNA negativity. Serum HBV DNA negativity, which was once achieved and then maintained throughout the course of therapy, was defined as maintained virological response (MVR). A decrease in serum HBV DNA ≥1 log IU/mL but detectable HBV DNA after month 12 of therapy was defined as a partial virological response. An increase in serum HBV DNA ≥1 log IU/mL compared to the nadir or reappearance of serum HBV DNA when negative was defined as a breakthrough. An increased serum ALT with accompanying virological breakthrough was defined as hepatitis flare. Serum ALT level ≤42 U/L was defined as ALT normalization.

Patients had undergone abdominal USG every 6-12 months for HCC surveillance. Serum HBV DNA, liver chemistries and serum AFP were measured every 3-6 months. When any new lesion was detected on USG or serum AFP increased in the absence of any lesion on USG, patients then underwent triphasic CT or dynamic MRI. HCC was diagnosed if the lesion was hypervascular in the arterial phase with washout in the portal venous and/or delayed phases on CT or MRI according to the European Association for the Study of the Liver (EASL) and American Association for the Study of the Liver Diseases (AASLD) guidelines.[17,18]

Follow-up was the time interval between the start of therapy and HCC diagnosis or the date of last available imaging in the absence of HCC.

Statistical Analysis

Baseline characteristics were compared between ETV and TDF groups and between non-HCC and HCC groups

in both the entire and advanced fibrosis/cirrhosis cohorts. Continuous variables were presented as mean ± SD and categorical variables as number (%). Student's *t*-test and Mann–Whitney *U* test were performed when comparing quantitative variables, and Chi-squared test and Fisher's exact test when comparing the qualitative variables between groups. Cumulative HCC incidences were estimated using Kaplan–Meier method. Factors associated with HCC were determined by univariate and multivariate analyses in both cohorts. Logistic regression analysis was performed in multivariate analysis and odds ratios were calculated with 95% confidence intervals. A $P < .05$ was considered significant. Statistical analyses were performed using SPSS v.23.0 (IBM Corp.; Armonk, NY, USA) for Windows. The study was approved by the local ethics committee of Haydarpaşa Numune Training and Research Hospital.

RESULTS

The study included 607 Caucasian patients with a mean age of 44.45 ± 13.44 years. Of them, 397 (65.4%) were male, 148 (24.4%) were HBeAg positive, 128 (21.1%) had compensated cirrhosis and 37 (6.1%) had decompensated cirrhosis. The mean HBV DNA level was 5.98 ± 1.63 log IU/mL. In total, 248 (40.9%) patients received ETV and 359 (59.1%) received TDF. The proportion of male gender and proportion of patients with compensated cirrhosis, decompensated cirrhosis and DM were significantly higher in the ETV group, whereas the mean platelet level was significantly higher in the TDF group. Baseline characteristics of the patient are shown in Table 1.

Virological Responses and HCC Occurrence in the Entire Cohort

In the entire cohort, mean follow-up durations in ETV and TDF groups were 58.58 ± 37.90 and 46.96 ± 29.37 months, respectively ($P < .001$). HBV DNA was negative in 492 (81.1%) and ALT was normal in 516 (85.0%) patients at month 12, and MVR was achieved in 525 (86.5%) patients. There were no significant differences between ETV and TDF groups with respect to HBV DNA negativity and normal ALT rates at month 12, and MVR rates (85.1% vs. 86.4%, 87.0% vs. 85.3%, and 87.0% vs. 86.4%, respectively) ($P = .665$, $P = .537$, and $P = .805$, respectively). Hepatitis flare occurred in 20 (3.3%) patients, 10 (4.0%) in the ETV group and 10 (2.8%) in the TDF group throughout the course of therapy ($P = .392$).

Nineteen (3.1%) patients developed HCC, 12 (4.8%) in ETV group and 7 (1.9%) in TDF group ($P = .045$). Cumulative HCC incidences at years 2, 3, 4, 5 and 10 were 1.1%, 2.6%, 3.3%, 3.7% and 7.0%, respectively. Cumulative HCC incidences at years 2, 3, 4, 5, and 10 were 1.8%, 2.9%, 4.4%, 5.2% and 9.9% in ETV group, respectively; whereas they were 0.6%, 2.4%, 2.4%, 2.4% and 3.7% in TDF group, respectively (log-rank $P = .130$) (Figure 1).

Comparison of variables between patients with non-HCC and HCC in the entire cohort are shown in Table 2. In univariate analysis, age ≥50 years, DM, cirrhosis, decompensated cirrhosis, high ALP, GGT and AFP levels, prolonged INR, and low albumin and platelet levels at baseline were significantly associated with HCC. In multivariate analysis, age ≥50 years (OR 3.98; 95% CI, 1.21-13.08), cirrhosis (OR 10.84; 95% CI, 2.99-39.20), decompensated cirrhosis (OR 3.60; 95% CI, 1.12-11.63), high GGT (OR 1.006; 95% CI, 1.001-1.011) and low platelet levels (OR 0.98; 95% CI, 0.96-0.99) at baseline were significantly associated with HCC. The use of ETV or TDF was not associated with HCC in the entire cohort (Table 3).

Virological Responses and HCC Occurrence in the Advanced Fibrosis/Cirrhosis Cohort

In the advanced fibrosis/cirrhosis cohort, mean follow-up durations in ETV and TDF groups were 59.71 ± 38.13 and 51.18 ± 31.64 months, respectively ($P = .075$). HBV DNA was negative in 177 (80.5%) and ALT was normal in 182 (82.7%) patients at month 12, and MVR was achieved in 194 (88.2%) patients. There were no significant differences between ETV and TDF groups with respect to HBV DNA negativity and normal ALT rates at month 12 (92.2% vs. 84.7% and 87.1% vs. 79.7%) ($P = .101$ and $P = .142$, respectively). MVR was achieved in 94.1% and 83.9% of patients in ETV and TDF groups, respectively ($P = .018$). Hepatitis flare occurred in 7 (3.2%) patients, 2 (2.0%) in ETV group, and 5 (4.2%) in the TDF group throughout the course of therapy ($P = .456$).

Sixteen (7.3%) patients developed HCC, 10 (9.8%) in ETV group and 6 (5.1%) in TDF group ($P = .179$). Cumulative HCC incidences at years 2, 3, 4, 5 and 10 were 3.1%, 6.3%, 7.9%, 8.8% and 12.2%, respectively. Cumulative HCC incidences at years 2, 3, 4, 5 and 10 were 4.6%, 7.1%, 8.6%, 12.1% and 15.5% in ETV group, respectively; whereas they were 1.8%, 5.6%, 5.6%, 5.6% and 8.5% in TDF group, respectively (log-rank $P = .267$) (Figure 2).

Comparison of variables between patients with non-HCC and HCC in advanced fibrosis/cirrhosis cohort are shown in Table 4. In univariate analysis, age ≥50 years,

Table 1. Baseline Characteristics of Patients in the Entire Cohort

	All Patients (*n* = 607)	ETV (*n* = 248)	TDF (*n* = 359)	*P*
Age, years	44.45 ± 13.44	45.54 ± 13.69	43.69 ± 13.22	.097
Gender, male (%)	397 (65.4%)	178 (71.8%)	219 (61.0%)	.006
HBeAg positivity,* n (%)	148 (24.4%)	52 (21.1%)	96 (26.7%)	.109
HBV DNA (log IU/mL)	5.98 ± 1.63	5.93 ± 1.68	6.01 ± 1.57	.553
Creatinine (mg/dL)	0.81 ± 0.19	0.85 ± 0.25	0.79 ± 0.13	<.001
AST (IU/L)	72.59 ± 112.07	75.90 ± 131.90	70.25 ± 95.72	.545
ALT (IU/L)	108.61 ± 153.83	110.00 ± 165.88	107.63 ± 145.01	.853
ALP (IU/L)	86.39 ± 42.42	87.77 ± 31.73	83.26 ± 30.42	.095
GGT (IU/L)	53.22 ± 64.98	58.56 ± 71.05	49.48 ± 60.22	.111
Albumin (g/dL)	4.04 ± 0.53	3.99 ± 0.57	4.07 ± 0.49	.070
Bilirubin (mg/dL)	1.13 ± 2.20	1.03 ± 1.33	1.20 ± 2.63	.386
Protrombin time (s)	14.26 ± 2.43	14.43 ± 2.70	14.16 ± 2.26	.271
INR	1.10 ± 0.19	1.12 ± 0.19	1.09 ± 0.19	.068
AFP (ng/mL)	6.63 ± 13.83	7.95 ± 18.08	5.69 ± 9.72	.075
Platelet (×1000/mm^3)	192.09 ± 67.47	180.00 ± 66.86	200.49 ± 66.71	<.001
Diabetes mellitus, n (%)	91 (15.0%)	51 (20.6%)	40 (11.1%)	.001
Severity of liver disease, n (%)				
Noncirrhosis	442 (72.8%)	159 (64.1%)	283 (78.8%)	<.001
Cirrhosis	165 (27.2%)	89 (35.9%)	76 (21.2%)	
Compensated cirrhosis	128 (21.1%)	63 (25.4%)	65 (18.1%)	
Decompensated cirrhosis	37 (6.1%)	26 (10.5%)	11 (3.1%)	
Follow-up, months	51.71 ± 33.58	58.58 ± 37.90	46.96 ± 29.37	<.001

ETV, entecavir; TDF, tenofovir disoproxil fumarate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; INR, international normalized ratio; AFP, alpha-fetoprotein.
*Not available in 1 patient in the ETV cohort.

decompensated cirrhosis, high ALP, GGT and AFP levels, and low albumin and platelet levels at baseline were significantly associated with HCC. In multivariate analysis, age ≥50 years (OR 3.88; 95% CI, 1.04-14.47), decompensated cirrhosis (OR 3.56; 95% CI, 1.14-11.11), high GGT (OR 1.008; 95% CI, 1.001-1.016) and low platelet levels (OR 0.98; 95% CI, 0.97-1.00) at baseline were significantly associated with HCC. The use of ETV or TDF was not associated with HCC in the advanced fibrosis/cirrhosis cohort (Table 5).

Safety and Treatment Modification

In the entire cohort, TDF was substituted by TAF in 13 patients (7 osteoporosis, 4 hypophosphatemia and 2 impaired renal function) and by ETV in 2 patients (1 osteoporosis and 1 impaired renal function) due to adverse events (totally 4.2%). Serum HBV DNA was negative in all patients at the date of treatment modification in the TDF group. Treatment was not modified due to adverse events in any patient in the ETV group.

In the entire cohort, ETV was substituted by TDF in 7 patients due to suboptimal virological responses (4 antiviral resistance and 3 partial virological response) (2.8%). ETV was added on TDF in 2 patients due to partial virological response (0.6%).

DISCUSSION

In the present study, cumulative HCC incidences at years 2, 3, 4, 5 and 10 in ETV-treated patients were slightly higher than those in TDF-treated patients in both the entire cohort and the advanced fibrosis/cirrhosis cohort. However, ETV-treated patients were older and had more severe liver disease than TDF-treated patients. In the multivariate analyses, we did not find any difference between ETV and TDF groups in terms of HCC risk in

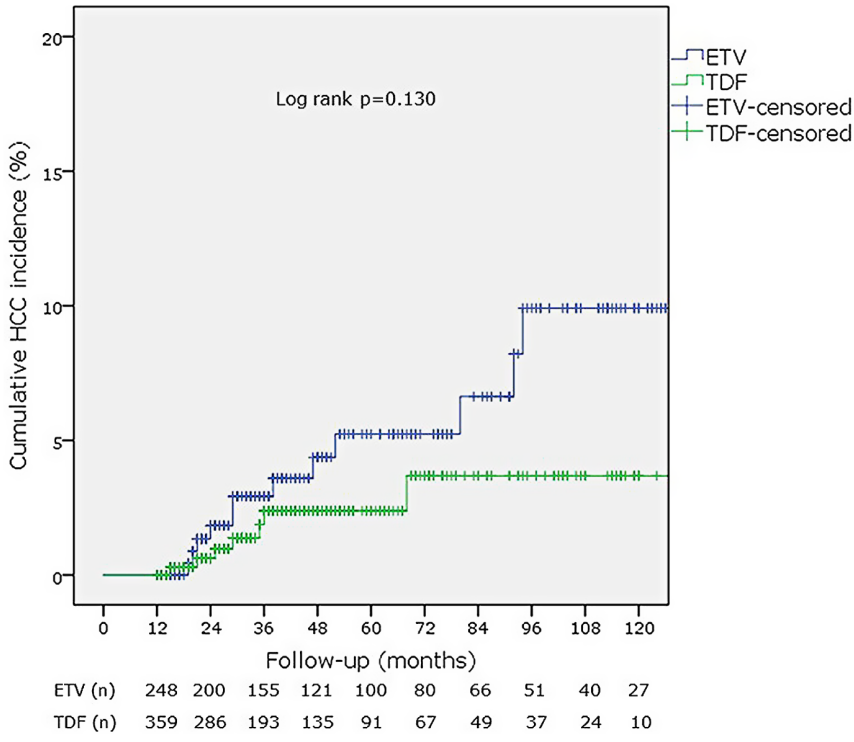

Figure 1. Cumulative HCC incidences in the entire cohort.

both the entire cohort and the advanced fibrosis/cirrhosis cohort. Age ≥50 years, cirrhosis, decompensated cirrhosis, high GGT and low platelet levels were significantly associated with HCC in the entire cohort, whereas age ≥50 years, decompensated cirrhosis and high GGT levels were significantly associated with HCC in the advanced fibrosis/cirrhosis cohort in the multivariate analyses.

Our results were in concordance with the study of Hsu et al. In that study, ETV-treated patients developed HCC more frequently than TDF-treated patients in unadjusted analysis; however, there was no difference between these 2 drugs in terms of HCC risk after multivariate analysis and PS matched analysis in both noncirrhotic and cirrhotic patients.[11] Similarly, other studies showed that TDF was not associated with lower HCC risk in both cirrhotic and noncirrhotic patients.[12-14]

One of the most striking point in the above studies was similar virological response rates in ETV and TDF groups.[11,13,14] This supports the notion that the similar efficacy of ETV and TDF in reducing HCC risk is related to their similar efficacy in suppressing HBV replication, and thus the resolution of hepatic inflammation and regression of fibrosis. In the present study, ETV and TDF showed similar efficacies in terms of virological and biochemical responses at month 12 in both cohorts. MVR rates were higher in the ETV group in the advanced fibrosis/cirrhosis cohort. However, it was due to a higher proportion of incompliant patients in the TDF group and did not result in hepatitis flare in most of them. Moreover, they rapidly became negative after the reinstitution of therapy. In a metaanalysis, ETV was similar to TDF and more effective than lamivudin in terms of virological and biochemical responses. Corresponding results were also seen in HCC risk.[19]

In contrast, Choi et al. showed TDF superior to ETV in reducing HCC risk in the Korean nationwide cohort and hospital cohort. Annual HCC incidences were lower in TDF-treated patients than those in ETV-treated patients in both cohorts. In multivariate analysis, TDF was associated with lower HCC risk.[15] In a nationwide Chinese study, TDF was associated with lower HCC risk than ETV.[16] In contrast to other studies which demonstrated no difference between ETV and TDF in terms of HCC risk, virological response rates were higher in the TDF group than the ETV group in both studies. However, it was not associated with lower HCC risk.[15,16] In a metaanalysis by Zhang Z et al., HCC risk was lower in TDF-treated patients in comparison to ETV-treated patients.[20]

Table 2. Comparison of Variables Between Patients with Non-HCC and HCC in the Entire Cohort

	Non-HCC (*n* = 588)	HCC (*n* = 19)	*P*
Age, years	43.98 ± 13.17	58.90 ± 13.85	<.001
Age ≥ 50 years, n (%)	191 (32.5%)	15 (78.9%)	<.001
Gender, male (%)	382 (65.0%)	15 (78.9%)	.326
HBeAg positivity*, n (%)	144 (24.5%)	4 (22.2%)	1.000
HBV DNA (log IU/mL)	5.98 ± 1.64	6.01 ± 1.21	.935
HBV DNA ≥6 log IU/mL, n (%)	333 (56.6%)	10 (52.6%)	.729
ETV, n (%)	236 (40.1%)	12 (63.2%)	.045
TDF, n (%)	352 (59.9%)	7 (36.8%)	
Creatinine (mg/dL)	0.81 ± 0.19	0.76 ± 0.17	.251
AST (IU/L)	71.78 ± 111.67	97.37 ± 124.19	.328
ALT (IU/L)	109.03 ± 155.02	95.89 ± 114.08	.715
ALP (IU/L)	84.06 ± 30.28	116.44 ± 36.71	<.001
GGT (IU/L)	50.88 ± 60.98	120.56 ± 121.96	<.001
Albumin (g/dL)	4.06 ± 0.51	3.53 ± 0.65	<.001
Bilirubin (mg/dL)	1.12 ± 2.22	1.43 ± 1.63	.561
Protrombin time (s)	14.22 ± 2.45	15.47 ± 1.65	.081
INR	1.10 ± 0.19	1.20 ± 0.19	.034
AFP (ng/mL)	5.91 ± 12.49	29.06 ± 28.85	<.001
Platelet (×1000/mm^3)	194.78 ± 66.44	110.79 ± 44.76	<.001
Diabetes mellitus, n (%)	84 (14.3%)	7 (36.8%)	.007
Severity of liver disease, n (%)			
Noncirrhosis	437 (74.3%)	5 (26.3%)	<.001
Cirrhosis	151 (25.7%)	14 (73.7%)	
Compensated cirrhosis	121 (20.6%)	7 (36.8%)	
Decompensated cirrhosis	30 (5.1%)	7 (36.8%)	
HBV DNA negativity at month 12,** n (%)	476 (85.9%)	16 (84.2%)	.741
Normal ALT at month 12,*** n (%)	501 (86.2%)	15 (78.9%)	.323
MVR,**** n (%)	510 (86.9%)	15 (78.9%)	.317
Flare,**** n (%)	19 (3.2%)	1 (5.3%)	.477

HCC, hepatocellular carcinoma; ETV, entecavir; TDF, tenofovir disoproxil fumarate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; INR, international normalized ratio; AFP, alpha-fetoprotein; MVR, maintained virological response. *Not available in 1 patient in HCC group. **Not available in 34 patients in the non-HCC group. ***Not available in 7 patients in the non-HCC group. ****Not available in 1 patient in the non-HCC group.

In these studies, the association of TDF with lower HCC risk was attributed to immunological features of nucleotide analogs in addition to its more potent antiviral activity.[15,16,20] Murata et al.[21] showed that nucleotide analogs, but not nucleoside analogs, induced serum interferon-lambda3 levels. However, the antitumor activity of interferon-lambda3 against HCC was not shown in humans.[22,23] Choi et al.[15] also emphasized the carcinogenic effect of ETV in mice and rats. However, this was shown when ETV was administered in higher doses than that used in CHB patients. Nevertheless, the latter hypothesis should not be overlooked because patients in the ETV group continued to develop HCC throughout 10 years, whereas those in the TDF group showed a more stable course with respect to HCC development after the first 3 years in the present study.

Table 3. Factors Associated with HCC in the Entire Cohort

	Univariate Analysis*			Multivariate Analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Age ≥50 years	7.79	2.55-23.80	<.001	3.98	1.21-13.08	.023
TDF vs. ETV	0.39	0.15-1.00	.050	0.66	0.24-1.80	.414
Diabetes mellitus	3.50	1.34-9.14	.011	1.95	0.69-5.51	.205
Cirrhosis	8.10	2.87-22.90	<.001	10.84	2.99-39.20	<.001
Decompensated cirrhosis	20.41	6.10-66.60	<.001	3.60	1.12-11.63	.031
ALP	1.02	1.01-1.04	<.001	1.01	0.99-1.03	.374
GGT	1.007	1.002-1.011	.002	1.006	1.001-1.011	.010
Albumin	0.25	0.13-0.49	<.001	0.68	0.20-2.35	.538
INR	4.73	1.02-22.02	.047	0.14	0.00-8.73	.350
AFP	1.04	1.02-1.05	<.001	1.02	0.99-1.04	.117
Platelet	0.98	0.97-0.99	<.001	0.98	0.96-0.99	.040

HCC, hepatocellular carcinoma; ETV, entecavir; TDF, tenofovir disoproxil fumarate; ALP, alkaline phosphatase, GGT: gamma-glutamyl transferase; INR, international normalized ratio; AFP, alpha-fetoprotein.
* Only factors significantly associated with HCC development are presented.

Furthermore, the 11.7% treatment modification rate in ETV-treated patients in comparison to 0.2% in TDF-treated patients in the study by Choi et al. is unexpectedly high. Although TDF was still associated with lower HCC risk after excluding these patients, such a high modification rate in the ETV group might impair unbiased comparison.[15] In these studies, the presence of cirrhosis was determined according to International Classification

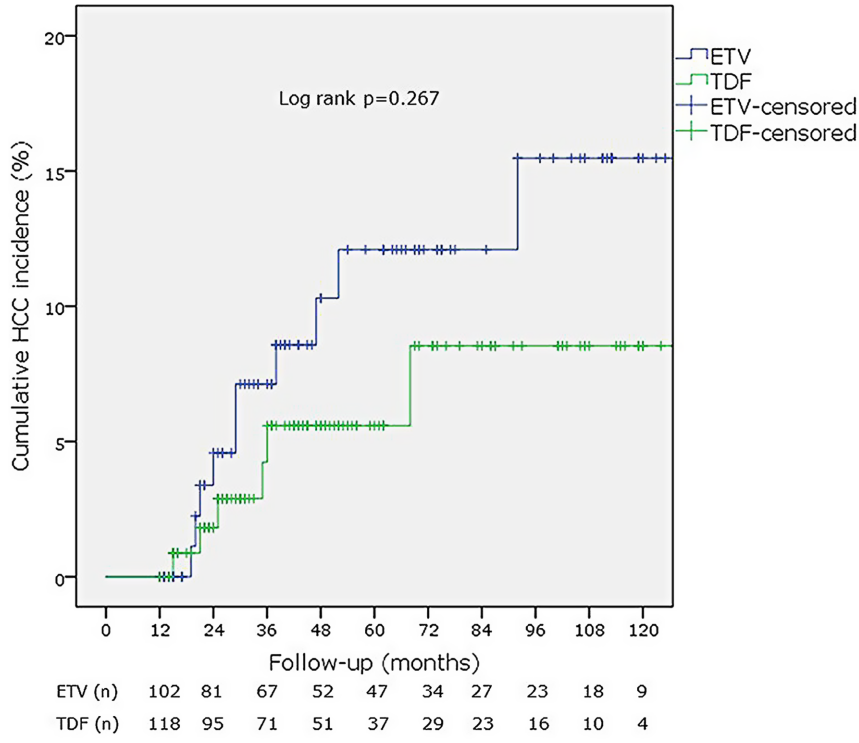

Figure 2. Cumulative HCC incidences in the advanced fibrosis/cirrhosis cohort.

Table 4. Comparison of Variables Between Patients with Non-HCC and HCC in the Advanced Fibrosis/Cirrhosis Cohort

	Non-HCC (*n* = 204)	HCC (*n* = 16)	*P*
Age, years	49.26 ± 12.69	60.82 ± 13.74	.001
Age ≥50 years, n (%)	98 (48.0%)	13 (81.3%)	.011
Gender, male (%)	149 (73.0%)	12 (75.0%)	1.000
HBeAg positivity,* n (%)	46 (22.5%)	3 (20.0%)	1.000
HBV DNA (log IU/mL)	5.96 ± 1.71	6.03 ± 1.31	.863
HBV DNA ≥6 log IU/mL, n (%)	126 (61.8%)	9 (56.3%)	.663
ETV, n (%)	92 (45.1%)	10 (62.5%)	.179
TDF, n (%)	112 (54.9%)	6 (37.5%)	
Creatinine (mg/dL)	0.82 ± 0.18	0.79 ± 0.15	.538
AST (IU/L)	77.37 ± 91.68	108.75 ± 132.72	.206
ALT (IU/L)	104.19 ± 153.22	103.31 ± 123.04	.982
ALP (IU/L)	94.33 ± 34.54	122.13 ± 37.47	.003
GGT (IU/L)	67.75 ± 59.03	128.73 ± 132.65	.098
Albumin (g/dL)	3.81 ± 0.60	3.38 ± 0.47	.006
Bilirubin (mg/dL)	1.30 ± 2.62	1.56 ± 1.69	.698
Protrombin time (s)	15.15 ± 2.89	15.72 ± 1.67	.542
INR	1.17 ± 0.23	1.24 ± 0.19	.295
AFP (ng/mL)	9.32 ± 17.09	30.76 ± 30.77	.028
Platelet (×1000/mm^3)	153.55 ± 66.60	96.63 ± 30.09	<.001
Diabetes mellitus, n (%)	45 (22.1%)	7 (43.8%)	.049
Severity of liver disease, n (%)			
F4/compensated cirrhosis	174 (85.3%)	9 (56.2%)	.100
Decompensated cirrhosis	30 (14.7%)	7 (43.8%)	
HBV DNA negativity at month 12,** n (%)	164 (88.6%)	13 (81.3%)	.414
Normal ALT at month 12,*** n (%)	169 (83.3%)	13 (81.3%)	.738
MVR,*** n (%)	181 (89.2%)	13 (81.3%)	.403
Flare,*** n (%)	6 (3.0%)	1 (6.3%)	.417

HCC, hepatocellular carcinoma; ETV, entecavir; TDF, tenofovir disoproxil fumarate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; INR, international normalized ratio; AFP, alpha-fetoprotein; MVR, maintained virological response. *Not available in 1 patient in the HCC group. **Not available in 19 patients in the non-HCC group. ***Not available in 1 patients in the non-HCC group.

of Diseases (ICD) codes and diagnosis of cirrhosis was made depending upon clinical and radiological findings.[15,16] However, early cirrhosis may also be present in liver biopsies in the absence of clinical and radiological findings of cirrhosis. So, the proportion of patients with cirrhosis might be underestimated in any treatment groups.

All these studies were performed in Asian countries, where almost all CHB patients were infected with genotype B and C.[24] In Korea, more than 98% of patients were infected with genotype C, which is associated with higher HCC risk than others.[12,24] Hsu et al. included patients from the USA; however, 88.2% of them were Asian immigrants.[11]

In a nationwide US study excluding Asian patients by Su et al.,[25] HCC risk was not different between ETV and TDF groups. However, 12.8 and 8.8% of them had HCV and HIV coinfections, respectively. In a study by Papatheodoridis GV et al.,[26] ETV or TDF did not differ in terms of HCC risk in Caucasian patients. However, they

Table 5. Factors Associated with HCC in the Advanced Fibrosis/Cirrhosis Cohort

	Univariate Analysis*			Multivariate Analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Age ≥50 years	4.69	1.30-16.94	.018	3.88	1.04-14.47	.043
Decompensated cirrhosis	13.50	6.17-29.41	<.001	3.56	1.14-11.11	.029
ALP	1.02	1.01-1.03	.005	1.01	0.99-1.03	.222
GGT	1.008	1.002-1.013	.005	1.008	1.001-1.016	.035
Albumin	0.35	0.16-0.76	.008	0.71	0.22-2.33	.575
AFP	1.03	1.01-1.05	.002	1.01	0.99-1.04	.299
Platelet	0.98	0.97-0.99	.001	0.98	0.97-1.00	.053

HCC, hepatocellular carcinoma; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; AFP, alpha-fetoprotein.
*Only factors significantly associated with HCC development are presented.

included patients from Europe, where genotype A and D predominate.[24]

In Turkey, nearly all CHB patients are infected with genotype D.[27] In a multicenter study performed in Turkey, Idilman et al.[28] showed that ETV and TDF were not different in terms of reducing HCC risk. HCC incidence was higher in that study in comparison to ours. This seems due to the higher proportion of cirrhosis and exclusion of patients who developed HCC within only 6 of therapy. Twelve of 19 patients developed HCC within 12 months of therapy in that study.

In these studies, older age and cirrhosis were invariably associated with HCC. However, HCC incidence varied according to the frequency of cirrhosis.[11-14,25,26,28] This seems due to the discrepancy between these studies in terms of study design. Some of these studies excluded patients with decompensated cirrhosis, which is the most important risk factor for HCC.[12-14] Some excluded patients who developed HCC within only 6 months of therapy[12,13,16,25,28] and one even included all patients who developed HCC after the start of therapy.[26] However, particularly cirrhotic patients who develop HCC within 12 months of therapy may already have undiagnosed HCC at the start of therapy.[26] In 2 studies, a substantial proportion of patients were antiviral therapy experienced.[25,26]

This is the first study comparing the efficacy of ETV and TDF on reducing HCC risk in Turkey, where HBV genotype D predominates. Almost all patients underwent liver biopsy except those with clinically and radiologically proven cirrhosis. Because F4 fibrosis also corresponds to advanced disease, these patients were included in the subgroup analysis along with cirrhotics. Since TDF was approved earlier for CHB treatment in Turkey than in the Asian region, follow-up time was longer in TDF-treated patients. We also included patients with decompensated cirrhosis and excluded those who developed HCC within 12 months after therapy.

There are also some limitations of the present study. ETV and TDF-treated patients had different baseline characteristics. The study population was small and number of patients who developed HCC was low. Comprehensive data about comorbid medical conditions (besides DM), medications used, smoking and alcohol drinking habits, family history of HCC, body mass index and quantitative HBsAg levels were lacking due to retrospective design of the study. All these factors may be confounding factors for the development of HCC.

In conclusion, ETV and TDF were similarly effective in reducing HCC risk in the present study. Also, there was no difference between the 2 drugs in terms of virological response. Similar HCC risk reduction with ETV and TDF seems related to similar efficacies of them in suppressing viral replication. Age ≥50 years, cirrhosis, decompensated cirrhosis, high GGT and low platelet levels in the entire cohort, and age ≥50 years, decompensated cirrhosis and high GGT levels in the advanced fibrosis/cirrhosis cohort were independent risk factors for HCC development.

Ethics Committee Approval: Ethics committee approval was received for this study from the Haydarpaşa Numune Training and Research Hospital, Clinical Research Ethics Committee, No: HNEAH-KAEK 2017/KK/138.

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REFERENCES

1. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370-398. [CrossRef].
2. Chen CJ, Yang HI, Iloeje UH, REVEAL-HBV Study Group. Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. Hepatology. 2009;49(5)(suppl):S72-S84. [CrossRef].
3. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560-1599. [CrossRef].
4. Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med. 2004;351(15):1521-1531. [CrossRef].
5. Dienstag JL, Goldin RD, Heathcote EJ, et al. Histological outcome during long-term lamivudine therapy. Gastroenterology. 2003;124(1):105-117. [CrossRef].
6. Chang TT, Liaw YF, Wu SS, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. Hepatology. 2010;52(3):886-893. [CrossRef].
7. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet. 2013;381(9865):468-475. [CrossRef].
8. Hosaka T, Suzuki F, Kobayashi M, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. Hepatology. 2013;58(1):98-107. [CrossRef].
9. Kim WR, Loomba R, Berg T, et al. Impact of long-term tenofovir disoproxil fumarate on incidence of hepatocellular carcinoma in patients with chronic hepatitis B. Cancer. 2015;121(20):3631-3638. [CrossRef].
10. Papatheodoridis GV, Sypsa V, Dalekos G, et al. Eight-year survival in chronic hepatitis B patients under long-term entecavir or tenofovir therapy is similar to the general population. J Hepatol. 2018;68(6):1129-1136. [CrossRef]. Epub 2018 Feb 8.
11. Hsu YC, Wong GL, Chen CH, et al. Tenofovir Versus entecavir for hepatocellular carcinoma prevention in an international Consortium of Chronic Hepatitis B. Am J Gastroenterol. 2020;115(2):271-280. [CrossRef].
12. Kim SU, Seo YS, Lee HA, et al. A multicenter study of entecavir vs. tenofovir on prognosis of treatment-naïve chronic hepatitis B in South Korea. J Hepatol. 2019;71(3):456-464. [CrossRef].
13. Lee SW, Kwon JH, Lee HL, et al. Comparison of tenofovir and entecavir on the risk of hepatocellular carcinoma and mortality in treatment-naïve patients with chronic hepatitis B in Korea: a large-scale, propensity score analysis. Gut. 2020;69(7):1301-1308. [CrossRef]. [CrossRef]
14. Kim BG, Park NH, Lee SB, et al. Mortality, liver transplantation, and hepatic complications in patients with treatment-naïve chronic hepatitis B treated with entecavir vs tenofovir. J Viral Hepat. 2018;25(12):1565-1575. [CrossRef].
15. Choi J, Kim HJ, Lee J, Ko MJ, Lim YS. Risk of hepatocellular carcinoma in patients treated With entecavir vs tenofovir for chronic hepatitis B. A Korean nationwide cohort study. JAMA Oncol;2019;5(1):30-36. [CrossRef].
16.Yip TC, Wong VW, Chan HL et al. Tenofovir is associated With lower risk of hepatocellular carcinoma Than entecavir in patients With chronic HBV infection in China. Gastroenterology. 2020;158(1):215-225.e6. [CrossRef].
17. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182-236. [CrossRef]. Epub 2018 Apr 5.
18. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68(2):723-750. [CrossRef].
19. Wang X, Liu X, Dang Z, et al. Nucleos(t)ide analogues for reducing hepatocellular carcinoma in chronic hepatitis B patients: A systematic review and meta-analysis. Gut Liver. 2020;14(2):232-247. [CrossRef].
20. Zhang Z, Zhou Y, Yang J, Hu K, Huang Y. The effectiveness of TDF versus ETV on incidence of HCC in CHB patients: a meta analysis. BMC Cancer. 2019;19(1):511. [CrossRef].
21. Murata K, Asano M, Matsumoto A, et al. Induction of IFN-λ3 as an additional effect of nucleotide, not nucleoside, analogues: a new potential target for HBV infection. Gut. 2018;67(2):362-371. [CrossRef].
22. Abushahba W, Balan M, Castaneda I, et al. Antitumor activity of type I and type III interferons in BNL hepatoma model. Cancer Immunol Immunother. 2010;59(7):1059-1071. [CrossRef].
23. Sato A, Ohtsuki M, Hata M, Kobayashi E, Murakami T. Antitumor activity of IFN-lambda in murine tumor models. J Immunol. 2006;176(12):7686-7694. [CrossRef].
24. Sunbul M. Hepatitis B virus genotypes: global distribution and clinical importance. World J Gastroenterol. 2014;20(18):5427-5434. [CrossRef].
25. Su F, Ioannou GN, Berry K. No difference in hepatocellular carcinoma risk between chronic hepatitis B patients treated with entecavir versus tenofovir. Gut. 2020 March 30. pii: [CrossRef]. [CrossRef].
26. Papatheodoridis GV, Dalekos GN, Yurdaydın C, et al. Incidence and predictors of hepatocellular carcinoma in Caucasian chronic hepatitis B patients receiving entecavir or tenofovir. J Hepatol. 2015;62(2):363-370. [CrossRef]. Epub 2014 Sep 6.
27. Bozdayı AM, Aslan N, Bozdayı G, et al. Molecular epidemiology of hepatitis B, C and D viruses in Turkish patients. Arch Virol. 2004;149(11):2115-2129. [CrossRef].
28. Idilman R, Günşar F, Koruk M, et al. Long-term entecavir or tenofovir disoproxil fumarate therapy in treatment-naive chronic hepatitis B patients in the real-world setting. J Viral Hepat. 2015;22(5):504-510. [CrossRef].