International Journal of Infectious Diseases 28 (2014) 153–159

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Comparable efficacy of tenofovir versus entecavir and predictors of response in treatment-naïve patients with chronic hepatitis B: a multicenter real-life study☆

Ayse Batirel [a,*], Ertugrul Guclu [b], Ferhat Arslan [c], Funda Kocak [d], Oguz Karabay [b], Serdar Ozer [a], Munevver Turanli [e], Ali Mert [c]

[a] Infectious Diseases and Clinical Microbiology, Kartal Dr. Lutfi Kirdar Education and Research Hospital, Semsi Denizer Cd. E-5 Karayolu Cevizli Mevkii, 34890 Kartal, Istanbul, Turkey
[b] Infectious Diseases and Clinical Microbiology, Medical Faculty, Sakarya University, Sakarya, Turkey
[c] Infectious Diseases, Medical Faculty, Istanbul Medipol University, Istanbul, Turkey
[d] Infectious Diseases and Clinical Microbiology, Basaksehir State Hospital, Istanbul, Turkey
[e] Biostatistics, Istanbul Commerce University, Istanbul, Turkey

ARTICLE INFO

Article history:
Received 7 April 2014
Received in revised form 5 August 2014
Accepted 15 September 2014

Corresponding Editor: Larry Lutwick, Kalamazoo, Michigan, USA

Keywords:
Entecavir
Tenofovir
Chronic hepatitis B
HBV
Treatment

SUMMARY

Objective: To compare responses to tenofovir (TDF) and entecavir (ETV) therapy.
Methods: This was a multicenter retrospective study including treatment-naïve patients with chronic hepatitis B (CHB) who received TDF or ETV. The primary end-points were undetectable HBV-DNA at 48 weeks and serological and biochemical responses.
Results: Out of 195 CHB patients, 90 (46%) received TDF and 105 (54%) received ETV; 72% were male, their mean age was 43 ± 12 years, and the mean duration of treatment was 30.2 ± 15.7 months. Hepatitis B e antigen (HBeAg) seropositivity was 32% in the TDF group and 34% in the ETV group. HBeAg seroconversion rates in HBeAg-positive patients were 24% in the TDF group and 39% in the ETV group; the difference was not significant ($p = 0.2$). The mean time to alanine aminotransferase (ALT) normalization and rates of ALT normalization at 3, 6, 12, 18, and 24 months were similar in the two groups ($p > 0.05$). The mean time to undetectable HBV-DNA levels in the TDF and ETV groups was 11.5 ± 8.9 and 12.9 ± 10.8 months, respectively ($p = 0.32$). A significantly greater decline in HBV-DNA levels at 12 and 18 months was observed in the TDF group ($p = 0.02$ and $p = 0.03$, respectively). Seven (7%) patients on ETV therapy had virological breakthrough ($p = 0.01$). Only one patient in each group had hepatitis B surface antigen (HBsAg) clearance. None of the patients developed decompensation or hepatocellular carcinoma during treatment.
Conclusions: The two drugs appear to have similar efficacy in CHB patients. However, 7% of patients on ETV therapy had virological breakthrough, while none of the patients on TDF therapy did.

1. Introduction

Chronic hepatitis B (CHB) is a significant health problem worldwide that may cause serious complications such as cirrhosis, liver failure, and/or hepatocellular carcinoma (HCC). Nearly 400 million people are estimated to be infected chronically with hepatitis B virus (HBV). Five-year cumulative probabilities for developing hepatic decompensation and cirrhosis are reported to be 20% and 8–20%, respectively.[1] Turkey has an intermediate endemicity for CHB (approximately 5%).

To date, sustained virological suppression to prevent HBV-related mortality has been the only achievable goal in the therapy of CHB, since rates of hepatitis B surface antigen (HBsAg) seroclearance (i.e., 'complete cure') remain very low.[2,3]

Two categories of therapeutic agents are currently available for the treatment of CHB: (1) immunomodulatory agents (interferon-alpha and pegylated interferon-alpha), and (2) oral nucleos(t)ide analogues (NAs) (lamivudine, adefovir, telbivudine, entecavir, and tenofovir). The response rate to interferons remains low, particularly

☆ This study was presented as an e-poster at APASL 2014, Brisbane, Australia.
* Corresponding author. Tel.: +90 216 4413900 ext. 1951; fax: +90 216 3520083.
E-mail address: aysebatirel@yahoo.com (A. Batirel).

http://dx.doi.org/10.1016/j.ijid.2014.09.004

for HBV genotype D, which is the most prevalent genotype in Turkey.[4,5] Furthermore, interferon tolerability is poor due to significant adverse effects.[6] The mechanism of action of NAs is the inhibition of HBV-DNA polymerase activity and therefore the suppression of HBV replication. Rates of resistance to lamivudine and adefovir have been reported to be 65–70% and 18–29% after 4–5 years of treatment.[7,8] Telbivudine caused a resistance rate of 5–25% in hepatitis B e antigen (HBeAg)-positive patients and 2.3–11% in HBeAg-negative patients.[9]

Entecavir (ETV; approved in 2005) and tenofovir disoproxil fumarate (TDF; approved in 2008) are NAs with high potency for profound and durable viral suppression and genetic barriers against resistance; these drugs are recommended for the first-line treatment of CHB in current guidelines.[1,10–12] The long-term use of these agents has resulted in no or very low resistance to date.[13,14] Although the efficacy of each has been assessed in various large-scale studies, real-life data on the comparative long-term efficacy of these drugs are very limited in the literature. Moreover, the numbers of eligible patients included in the few previously published studies directly comparing the two drugs have been quite small (patients on TDF and ETV therapy, respectively: Ceylan et al.,[15] 66 and 51 patients; Dogan et al.,[16] 65 and 29 patients; Guzelbulut et al.,[17] 20 and 24).

The aim of this retrospective study of real-life practice was to compare the cumulative virological, serological, and biochemical responses to TDF and ETV in a large group of HBeAg-positive and negative treatment-naïve patients with a high viral load, over the long-term.

2. Materials and methods

2.1. Study design and data collection

In this retrospective real-life study conducted at four centres (two universities, one tertiary education and research centre, and one state hospital in Turkey), treatment-naïve CHB patients with a high viral load ($>2 \times 10^6$ IU/ml), who received TDF (245 mg/day) or ETV (0.5 mg/day) in a compliant manner between January 2008 and October 2013, were included. The primary end-points were undetectable serum HBV-DNA levels at 48 weeks (virological response) and serological (HBeAg seroclearance/conversion in HBeAg-positive cases) and biochemical (alanine aminotransferase (ALT) normalization) responses; secondary end-points were persistence of detectable HBV-DNA and virological breakthrough.

Inclusion criteria were the following: (1) HBsAg seropositivity. (2) Pre-treatment liver biopsy consistent with CHB. (3) Pre-treatment serum HBV-DNA levels $>2 \times 10^6$ IU/ml in both HBeAg-positive and HBeAg-negative patients. (The prescription of ETV and TDF is restricted to these patients alone by the National Reimbursement Policy regulated by the Ministry of Health in Turkey.) (4) Positive or negative serology for HBeAg. (5) Serum HBV-DNA levels measured at 3–6-month intervals by PCR. (6) No prior history of receiving any treatment for CHB. (7) ETV (0.5 mg/day) or TDF (245 mg/day; the form available in Turkey) therapy for at least 1 year.

Exclusion criteria were the following: Previous use of oral antivirals or interferon-alpha for CHB treatment; co-infection with hepatitis D virus (HDV), hepatitis C virus (HCV), or HIV; non-adherence to treatment; cirrhosis; hepatic decompensation; HCC or any other malignancy; autoimmune hepatitis; illicit drug use; solid organ transplantation; pregnancy; age <18 years.

All of the patients were followed-up periodically, and CHB serology, biochemistry, and virology were investigated every 3 to 6 months. Compliance with therapy was questioned. The following data were collected from the patient records and transferred to an Excel file: age, gender, Ishak scores for pre-treatment liver biopsy samples (histological activity index (HAI) and fibrosis),[18] HBsAg, HBeAg, and hepatitis B e antibody (anti-HBe) status, serum ALT, aspartate aminotransferase (AST), and HBV-DNA levels before treatment and at months 3, 6, 12, 18, and 24 of treatment, time to ALT normalization, undetectable HBV-DNA levels, and HBeAg seroconversion (in HBeAg-positive cases), and total duration of follow-up on therapy. The data obtained were analysed and compared for virological (undetectable HBV-DNA levels), biochemical (ALT normalization), and serological (HBeAg seroconversion in HBeAg-positive patients, HBsAg seroconversion) responses to treatment with the two antiviral agents. Declines in serum HBV-DNA levels from baseline to weeks 12, 24, and 48 were compared for the two groups of patients to evaluate treatment efficacy. For HCC screening, all patients underwent abdominal ultrasonography every 6 months.

2.2. Definitions

A complete virological response was defined as complete viral suppression, shown by serum HBV-DNA levels <20 IU/ml (<100 copies/ml) at week 48.[1] A partial virological response was defined as a decrease in HBV-DNA of more than 1 $\log_{10}$ IU/ml but detectable serum HBV-DNA levels by PCR at $\geq$12 months of therapy in compliant patients.[1] Virological breakthrough was defined as a >1 $\log_{10}$ IU/ml increase in serum HBV-DNA levels from nadir on two consecutive measurements.[1]

Serological response was defined as HBeAg seroconversion (HBeAg loss and anti-HBe development) in HBeAg-positive cases.[1] Biochemical response was defined as ALT normalization (decline in ALT levels to less than the upper limit of normal) in patients with pre-treatment elevated ALT levels.[1]

Patients were considered compliant with therapy if they took their drugs once daily, regularly, without an interruption.

With regard to adverse effects, any symptom or sign, or abnormal clinical or laboratory finding that resolved after discontinuation of the drug was considered a drug-related adverse effect. An increase in serum creatinine level exceeding the upper limit of normal was considered a drug-related renal adverse effect.

2.3. Virological tests

HBsAg, HBeAg, and anti-HBe were tested with an ELISA (Architect System; Abbott Laboratories, North Chicago, IL, USA). Levels of serum HBV-DNA were tested with a PCR assay (TaqMan HBV Assay; Roche Diagnostics); the lower limit of HBV-DNA quantification was 20 IU/ml.

2.4. Ethical approval

This study was approved by the local ethics committee (Institutional Review Board of Istanbul Medipol University, Turkey).

2.5. Statistical analyses

SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Categorical variables were defined as the proportion (%) and were compared by Chi-square test or Fisher's exact test. Continuous variables were defined as the mean $\pm$ standard deviation (SD) or median (range) and were tested with the Student *t*-test or Mann–Whitney *U*-test, as appropriate. After the rates of periodic (3–6-month intervals) log decline in serum HBV-DNA levels of patients in the two groups were calculated, an independent samples *t*-test was used to test the difference. Cumulative rates of complete viral suppression were analysed by Kaplan–Meier method and were compared by log rank test.

Univariate and multivariate Cox proportional hazards regression analysis was used to identify the variables/factors determining the virological response. A p-value of <0.05 was considered to be statistically significant.

3. Results

The data of a total 210 patients with CHB who were prescribed either TDF or ETV were recorded. Among these patients, 195 (72% male, mean age 43 ± 12 years) were eligible for inclusion in the study. They were followed-up for a mean duration of 30.2 ± 15.7 (range 12–72) months. Ninety (46%) patients received TDF (mean treatment duration 27.2 ± 15.4 months) and 105 (54%) patients received ETV (mean treatment duration 33.0 ± 15.4 months).

Twenty-nine (32%) patients in the TDF group and 36 (34%) patients in the ETV group were HBeAg-positive. Patients in the two treatment groups were similar in terms of baseline parameters: age ($p = 0.65$), gender ($p = 0.06$), ratios of HBeAg positivity ($p = 0.76$), pre-treatment mean ALT ($p = 0.55$), and serum HBV-DNA levels ($p = 0.42$) (Table 1).

A pre-treatment liver biopsy was performed in 92% of patients prescribed TDF and 90% of patients prescribed ETV. Pre-treatment liver biopsy scores differed between the two groups (HAI, $p = 0.01$; fibrosis, $p = 0.03$); mean HAI scores were 7.6 ± 2.7 and 8.6 ± 2.8 and mean fibrosis scores were 2.5 ± 1.4 and 2.3 ± 1.0 for the TDF and ETV groups, respectively.

HBeAg clearance (24% in TDF vs. 44% in ETV) and seroconversion rates (24% in TDF vs. 39% in ETV) in HBeAg-positive patients in the two groups did not differ significantly ($p = 0.1$ and $p = 0.2$), although the rates were relatively higher in the ETV group. The mean time to achieve undetectable serum HBV-DNA levels in the TDF group was 11.5 ± 8.9 months, while it was 12.9 ± 10.8 months in the ETV group; the difference was not significant ($p = 0.32$).

The mean time to ALT normalization ($p = 0.1$) and rates of ALT normalization at 3, 6, 12, 18, and 24 months were similar in the two groups (Table 2).

When the decline from pre-treatment serum HBV-DNA levels at months 3, 6, 12, 18, and 24 were compared, there was no statistically significant difference between the TDF and ETV groups at months 6, 12, 18, and 24 ($p > 0.05$). However, TDF induced a significantly greater reduction in serum HBV-DNA levels at month 3 ($p = 0.047$). As most of the patients (80%) achieved a virological response by 24 months of antiviral therapy, we did not further compare log declines thereafter.

When the rates of cumulative complete viral suppression (undetectable serum HBV-DNA levels) at months 3, 6, 12, 18, and 24 were compared between the two groups, they were significantly higher at month 12 ($p = 0.02$) and month 18 ($p = 0.03$) in patients on TDF therapy (at months 12 and 18, TDF induced a significantly increased rate of undetectable serum HBV-DNA levels compared to ETV; $p = 0.02$ and $p = 0.03$, respectively) (Figure 1).

Seven (7%) patients who were on ETV therapy developed virological breakthrough, but none of the patients in the TDF group did ($p = 0.01$). These seven patients claimed that they had adhered to therapy well, but a resistance analysis could not be performed at that time. They were switched to TDF therapy. The changes in ALT and HBV-DNA levels over time in the seven patients with virological breakthrough are shown in Tables 3 and 4, respectively.

Only one patient in each group had HBsAg clearance. None of the patients in any group developed hepatic decompensation or HCC during the entire treatment period. On Cox regression analysis, none of the baseline parameters was found to be a significant predictor of the virological response (Table 5). Cumulative rates of virological, biochemical, and serological response (HBeAg loss and seroconversion) over time are illustrated in Figures 2–4.

No serious adverse effects such as lactic acidosis, severe liver problems, or increase in serum creatinine levels were seen in any of the patients in either treatment group. No adverse effects leading to discontinuation of therapy occurred during the whole treatment period. Two patients on ETV therapy experienced nausea and abdominal discomfort. One patient receiving ETV complained of fatigue and dizziness that disappeared after a few days. Three patients receiving TDF experienced nausea, one of them also had diarrhoea that resolved with symptomatic therapy. Two patients on TDF therapy developed hypophosphatemia (serum phosphate level <2.5 mg/dl), but they had no related symptoms such as fatigue or muscle weakness. Two patients receiving ETV therapy

Table 1
Comparison of baseline demographic variables, laboratory and histological parameters, and treatment responses of patients who received either tenofovir (TDF) or entecavir (ETV) therapy[a]

Characteristics	TDF ($n = 90$)	ETV ($n = 105$)	p-Value
Age, years	43.3 ± 12.9	42.0 ± 11.2	0.7
Gender, male	59.0	82.0 (78.1%)	0.06
Treatment duration, months	27.2 ± 15.4	33.0 ± 15.4	0.01
HBeAg positivity	29.0 (32.2%)	36.0 (34.3%)	0.8
Pre-treatment HBV-DNA, $\times 10^3$ IU/ml	191 613 ± 198.6	220 199 ± 101.3	0.4
Pre-treatment ALT, IU/l	116.7 ± 92.6	120.0 ± 96.6	0.6
Elevated ALT before therapy	80.0 (89.0%)	94.0 (90.0%)	0.9
Liver biopsy done	83.0 (92.0%)	94.0 (90.0%)	0.8
Baseline HAI (Ishak)	7.6 ± 2.7	8.6 ± 2.8	0.01
Baseline fibrosis (Ishak)	2.5 ± 1.4	2.3 ± 1.0	0.03
HBeAg loss	7.0 (24.0%)	16.0 (44.0%)	0.1
HBeAg seroconversion	7.0 (24.0%)	14.0 (39.0%)	0.2
Time to HBeAg seroconversion, months	12.3 ± 5.6	12.3 ± 5.8	0.9
ALT normalization	88.0 (97.8%)	104.0 (99.0%)	0.1
Time to ALT normalization, months	5.1 ± 3.6	6.3 ± 5.3	0.08
Undetectable HBV-DNA	77.0 (85.6%)	90.0 (85.7%)	0.9
Time to undetectable HBV-DNA, months	11.5 ± 8.9	12.9 ± 10.8	0. 3
Virological breakthrough	0	7.0 (6.7%)	0.01
HBsAg seroclearance	1.0 (1.1%)	1.0 (0.95%)	
HCC development	0	0	
Decompensation	0	0	

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ALT, alanine aminotransferase; HAI, histological activity index; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma.

[a] Results are given as the mean ± standard deviation, or n (%).

Table 2
Comparison of the cumulative virological responses and ALT normalization at 3, 6, 12, 18, and 24 months in patients with chronic hepatitis B who were prescribed either tenofovir (TDF) or entecavir (ETV)

	TDF (n = 90), n (%)	ETV (n = 105), n (%)	Total	p-Value
3 months				
ALT normalization	36 (40.0)	29 (27.6)	65 (33.3)	0.07
Undetectable HBV-DNA	5 (5.6)	2 (1.9)	7 (3.6)	0.2
6 months				
ALT normalization	64 (71.1)	80 (76.2)	144 (73.8)	0.4
Undetectable HBV-DNA	21 (23.6)	19 (18.1)	40 (20.6)	0.4
12 months				
ALT normalization	78 (97.5)	93 (93.9)	171 (95.5)	0.3
Undetectable HBV-DNA	62 (74.7)	59 (58.4)	121 (65.8)	0.02
18 months				
ALT normalization	61 (98.4)	85 (96.6)	146 (97.3)	0.5
Undetectable HBV-DNA	53 (82.8)	60 (67.4)	113 (73.9)	0.03
24 months				
ALT normalization	49 (98.0)	69 (98.6)	118 (98.3)	0.8
Undetectable HBV-DNA	45 (86.5)	53 (74.6)	98 (79.7)	0.1

ALT, alanine aminotransferase; HBV, hepatitis B virus.

decided to discontinue therapy after a virological response had been obtained (one of them at the end of 2 years, the other at the end of 30 months). One female patient in the TDF group discontinued therapy for a period of 13 months as she planned a pregnancy and conceived a baby. No hepatic flare was observed during the off-treatment period.

4. Discussion

The risk of developing cirrhosis and HCC is directly proportional to the viral load in patients with CHB.[2,3] Sustained suppression of serum HBV-DNA levels is one of the therapeutic goals in patients with CHB and prevents the progression of liver disease and development of complications.[19,20] The development of resistance is a significant problem with lamivudine, adefovir, and telbivudine therapies.[7–9] ETV and TDF are highly potent and safe NAs with genetic barriers to resistance, and these drugs are recommended in the first-line treatment of CHB in current guidelines.[1,11] In the present study, the two drugs induced similar virological (mean time to achieve undetectable HBV-DNA levels and rates of achieving no HBV-DNA by PCR in serum), biochemical (mean time to ALT normalization and rates of ALT normalization at 3, 6, 12, 18, and 24 months), and serological (HBeAg clearance and seroconversion rates in HBeAg-positive patients, rates of HBsAg clearance in the two groups) responses in patients with CHB. Cumulative complete viral suppression was significantly higher at months 12 and 18 in patients on TDF therapy, but not different at other time intervals during treatment with either drug. While 7% of the patients on ETV therapy had virological breakthrough, none of the patients on TDF therapy did.

In Bayesian mixed comparisons for the meta-analysis of relative efficacies of CHB treatments conducted by Woo et al., TDF was reported to be the most effective at inducing virological, biochemical, and serological responses in HBeAg-positive patients; ETV ranked second. In HBeAg-negative patients, TDF was the most

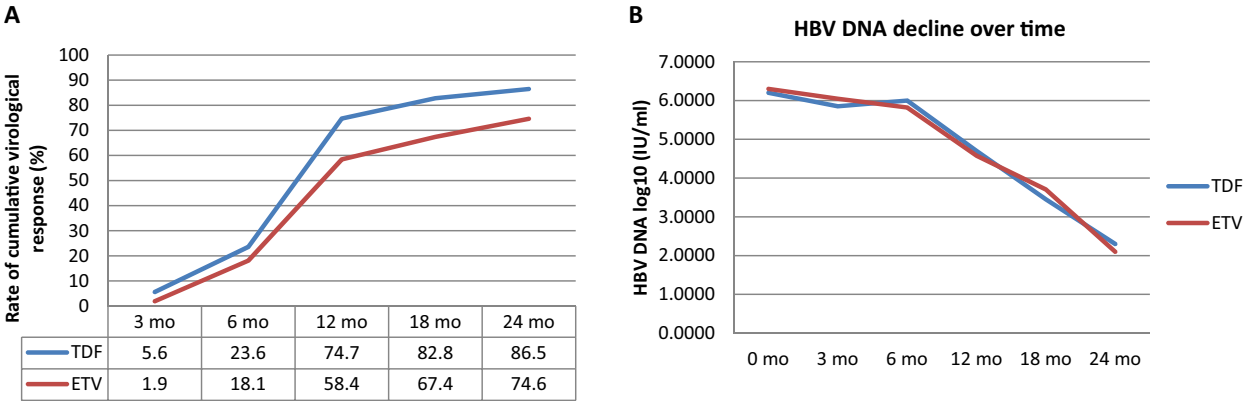

Figure 1. (a) Cumulative rates of virological response over time in patients with chronic hepatitis B who received tenofovir (TDF) or entecavir (ETV). For the comparisons of the virological response at 3, 6, 12, 18, and 24 months, the p-values are 0.047, 0.68, 0.53, 0.57, and 0.67, respectively. (b) Decline in serum HBV-DNA levels over time (3–24 months) in patients with chronic hepatitis B who received tenofovir (TDF) or entecavir (ETV). For the comparisons of HBV-DNA decline at 3, 6, 12, 18, and 24 months, the p-values are 0.07, 0.65, 0.43, 0.58, and 0.73, respectively.

Table 3
The course of ALT levels in seven patients on entecavir therapy with virological breakthrough[a]

Patient	Baseline ALT, IU/l	ALT normalization, month	Virological breakthrough, month	ALT, IU/l							
				3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
1	92	12	18[b]	85	60	57	32	67[b]	45	42	
2	120	6	24[b]	67	48	38	NA	26	96[b]	40	
3	69	6	24[b]	62	33	36	28	38	66[b]	37	
4	89	8	36[b]	NA	54	42	40	NA	39	42	87[b]
5	64	6	18[b]	54	43	46	42	79[b]	37	38	29
6	108	3	18[b]	47	37	34	38	64[b]	31		
7	140	6	18[b]	82	41	NA	42	85[b]	35	33	37

ALT, alanine aminotransferase; NA, not available.
[a] ALT normal range: 0–50 IU/l.
[b] Switch to tenofovir disoproxil fumarate therapy.

Table 4
The course of viremia in seven patients on entecavir therapy with virological breakthrough

Patient	Baseline HBV-DNA, IU/ml	Undetectable HBV-DNA, month	Virological breakthrough, month	HBV-DNA, IU/l						
				3 months	6 months	12 months	18 months	24 months	30 months	36 months
1	17×10^6	12	18[a]	772×10^3	10.3×10^3	-	815[a]	-		
2	110×10^6	12	24[a]	NA	2×10^6	-	-	11 700[a]	5930	-
3	487×10^3	6	24[a]	48×10^3	-	-	-	6850[a]		
4	1.627×10^6	6	36[a]	121×10^3	-	-	-	-	-	480 000[a]
5	1.826×10^6	6	18[a]	594	-	-	3600[a]	-	-	
6	95×10^6	12	18[a]	112×10^3	7090	-	4200[a]	-		
7	37.72×10^6	10	18[a]	5930	1300	-	6577[a]	-	-	NA

HBV, hepatitis B virus; NA, not available.
[a] Switch to tenofovir disoproxil fumarate therapy.

Table 5
Results of the Cox regression analysis to determine independent variables predictive of the virological response

Characteristics	HR (95% CI)	*p*-Value
Age	1.00 (0.99–1.02)	0.39
Gender	0.78 (0.60–1.1)	0.53
HBeAg positivity	1.56 (0.58–4.16)	0.38
Anti-HBe positivity	2.02 (0.75–5.42)	0.16
Pre-treatment HBV-DNA	1 (1–1)	0.86
Pre-treatment ALT	1.00 (0.9–1.01)	0.77
Baseline HAI (Ishak)	1.00 (0.95–1.07)	0.58
Baseline fibrosis (Ishak)	1.10 (0.95–1.3)	0.77
Therapy with TDF vs. ETV	1.10 (0.79–1.5)	0.52

HR, hazard ratio; CI, confidence interval; HBeAg, hepatitis B e antigen; anti-HBe, hepatitis B e antibody; HBV, hepatitis B virus; ALT, alanine aminotransferase; HAI, histological activity index; TDF, tenofovir; ETV, entecavir.

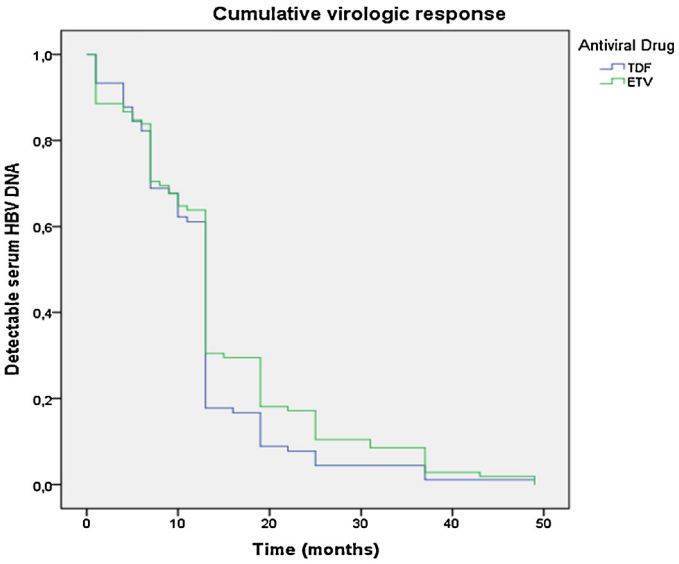

Figure 2. Cumulative probabilities of a virological response to tenofovir (TDF) and entecavir (ETV) therapy ($p = 0.72$).

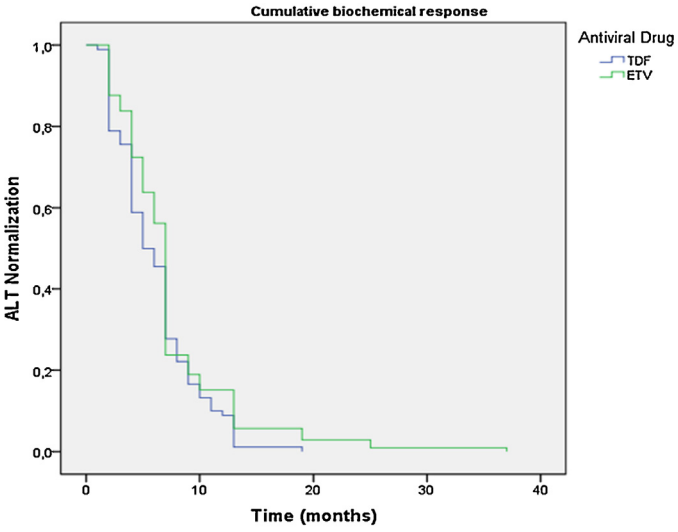

Figure 3. Cumulative probabilities of a biochemical response to tenofovir (TDF) and entecavir (ETV) therapy ($p = 0.86$).

effective antiviral agent at inducing a virological response and ranked second for biochemical response.[21] Dakin et al. reported that TDF was significantly superior to ETV regarding virological response, but comparable to ETV regarding HBeAg seroconversion after 1 year of therapy.[22] Both drugs were reported to be effective and well tolerated in compensated and decompensated cirrhotic patients.[23]

In our study, HBeAg clearance and seroconversion rates in HBeAg-positive patients were relatively higher in the ETV group, but did not differ significantly from the TDF group. Myung et al. reported the cumulative rates of HBeAg loss at 12 to 72 weeks of ETV therapy as 10.6% to 34.5%; and 3.5% to 13.2% for HBeAg seroconversion.[24] TDF therapy resulted in HBeAg loss in 24% of patients in another study.[25] In the study by Ceylan et al., HBeAg status did not predict the virological response rate, similar to the finding of our study.[15] Chang et al. reported a lower rate of HBeAg seroconversion at year 5.[26] HBeAg seroconversion occurred in only one of 29 patients in the ETV group, but none of 65 patients in the TDF group in another study.[16]

The mean time to ALT normalization and rates of ALT normalization at 3, 6, 12, 18, and 24 months were similar in the two groups in the present study. Guzelbulut et al. reported that a similar proportion of patients achieved ALT normalization on ETV or TDF therapy.[17] Chang et al. reported that ALT normalization in patients on ETV therapy was 80% at year 5.[26] Cumulative rates for biochemical response at 12, 24, 48, and 72 weeks of therapy with ETV were reported to be 40.0%, 66.2%, 84.5%, and 92.7%, respectively.[24]

The mean time to achieve undetectable HBV-DNA levels and rates of achieving negative HBV-DNA levels by PCR in serum in both groups were not significantly different. This is consistent with the results of the studies conducted by Guzelbulut et al.[17] and Dogan et al.[16] Chang et al. reported that the rate of undetectable serum HBV-DNA levels at year 5 was 94% in ETV-treated patients.[26]

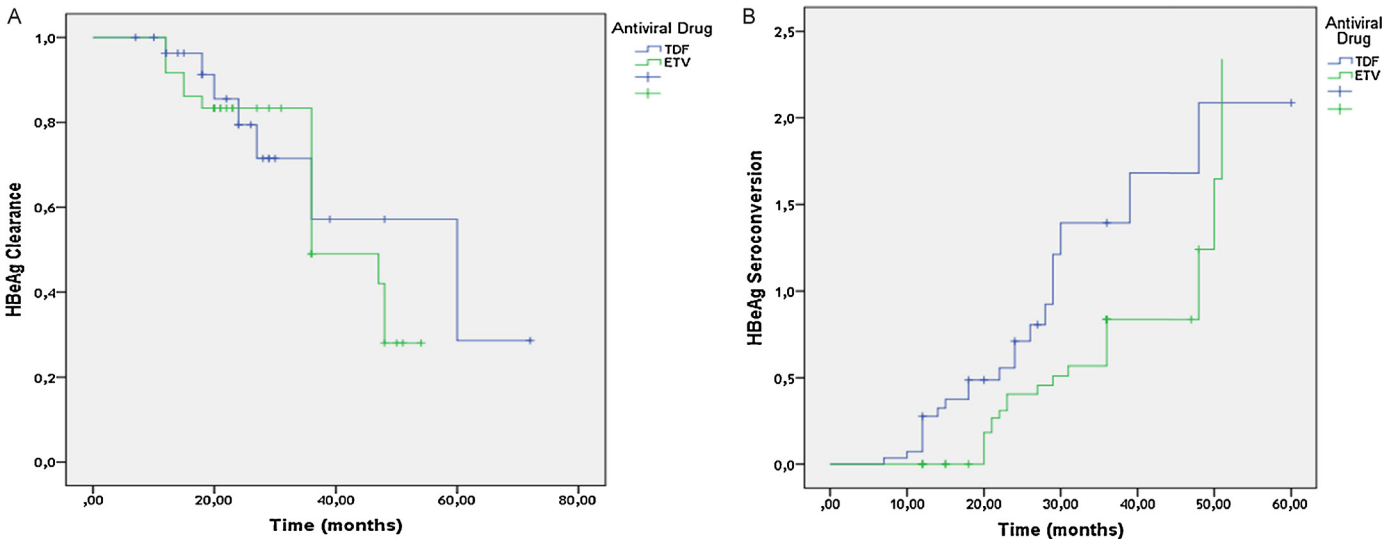

Figure 4. (a) Cumulative HBeAg clearance over time in response to tenofovir (TDF) and entecavir (ETV) therapy ($p = 0.63$). (b) Cumulative HBeAg seroconversion over time in response to tenofovir (TDF) and entecavir (ETV) therapy ($p = 0.56$).

In the present study, the declines from pre-treatment HBV-DNA levels at months 6, 9, 12, 18, and 24 were not significantly different between the TDF and ETV groups, but TDF induced a significantly greater reduction in serum HBV-DNA level at month 3. In contrast, in a recently published study, a greater decline in serum HBV-DNA levels at month 3 occurred with ETV therapy; however, the rates of decline in HBV-DNA levels at other months did not differ significantly, similar to our results.[15] Moreover, Guzelbulut et al. reported similar rates of decline in serum HBV-DNA levels with both drugs after 48 months of therapy.[17]

TDF induced a significantly more increased rate of undetectable HBV-DNA levels at months 12 and 18 compared to ETV, but the rates of undetectable HBV-DNA levels at months 3, 6, 12, 18, and 24 were similar. Myung et al. reported higher cumulative rates of virological response at 3, 6, 12, and 18 months in patients on ETV therapy than in patients on TDF therapy.[24] The difference was due to the threshold of the serum HBV-DNA level for virological response, which was set at <2000 copies/ml (approximately 400 IU/ml). In our study, a 'complete virological response' was defined as serum HBV-DNA levels <20 IU/ml (<100 copies/ml). The overall cumulative proportion of patients achieving serum HBV-DNA levels <400 copies/ml was 79% after a mean treatment duration of nearly 2 years in another study including CHB patients with prior treatment failure who were subsequently switched to TDF therapy.[25] Dogan et al. reported that either TDF or ETV therapy resulted in suppression of HBV-DNA levels in 71.3% of patients at the end of 48 weeks (66% in the present study). There was no statistical difference in the induction of undetectable levels of HBV-DNA between the ETV and TDF groups.[16] Ceylan et al. reported that TDF-treated patients had a better virological response than ETV-treated ones. ETV was more effective in reducing serum HBV-DNA levels at month 3 of antiviral therapy.[15]

Seven (7%) patients on ETV therapy developed virological breakthrough, but none of the patients in the TDF group did. While no viral breakthrough was observed in a study that included 114 naive CHB patients on ETV therapy,[27] in another study involving 258 ETV-treated patients, only five developed ETV resistance, which is less than in our study.[28] In another study which evaluated the long-term efficacy of TDF in 131 patients, virological breakthrough was not observed.[25] In the study by Chang et al., ETV resistance emerged in only one patient during 5 years of follow-up, therefore they suggested extended long-term therapy with ETV through 5 years in HBeAg-positive CHB.[26]

Only one patient in each group developed HBsAg clearance. van Bommel et al. reported HBsAg loss in 3% of 131 TDF-treated CHB patients with prior resistance to other antiviral drugs.[25] Chang et al. reported that the rate of HBsAg loss was 1.4%.[26] While none of the baseline parameters of the patients were significant predictors of the virological response in the present study, HBeAg seronegativity and a low serum HBV-DNA level at baseline were reported to be significant predictors of the virological response by Myung et al.[24]

The main limitation of our study is its retrospective design. Pre-treatment liver biopsy scores were available for most of the patients and they were different in the two groups, as the study design was retrospective. It is very difficult to convince patients to have a control biopsy performed at the end of treatment. Therefore, we could not compare the histological improvement in response to therapy to the two drugs. Moreover, the presumably ETV-resistant strains were not sequenced because the patients' health insurance companies would not pay for this and we could not obtain funding for this purpose. Nevertheless, we involved quite a large number of patients in the study. We also looked for the predictors of a response with the parameters available, but none of them was significant.

In conclusion, rates of HBeAg seroconversion in HBeAg-positive patients, ALT normalization, and serum HBV-DNA clearance were not significantly different in the two treatment groups. Moreover, the mean time to achieve undetectable serum HBV-DNA levels and ALT normalization were similar. Both drugs resulted in significant viral suppression, but the HBsAg clearance rate was very low with both drugs. Seven percent of patients on ETV therapy experienced virological breakthrough, while none of the patients on TDF therapy did. The two drugs induced comparable virological, biochemical, and serological responses in CHB patients.

Funding: None.

Conflict of interest: None to declare.

References

1. European Association for the Study of the Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. *J Hepatol* 2012;**57**: 167–85.

2. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology* 2006;**130**:678–86.
3. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006;**295**:65–73.
4. Sunbul M, Sugiyama M, Kurbanov F, Leblebicioglu H, Khan A, Elkady A. Specific mutations of basal core promoter are associated with chronic liver disease in hepatitis B virus subgenotype D1 prevalent in Turkey. *Microbiol Immunol* 2013;**57**:122–9.
5. Sonneveld MJ, Hansen BE, Piratvisuth T, Jia JD, Zeuzem S, Gane E, et al. Response-guided peginterferon therapy in hepatitis B e antigen-positive chronic hepatitis B using serum hepatitis B surface antigen levels. *Hepatology* 2013;**58**:872–80.
6. Calvaruso V, Mazza M, Almasio PL. Pegylated-interferon-alpha(2a) in clinical practice: how to manage patients suffering from side effects. *Expert Opin Drug Saf* 2011;**10**:429–35.
7. Keeffe EB, Dieterich DT, Han SH, Jacobson IM, Martin P, Schiff ER, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: an update. *Clin Gastroenterol Hepatol* 2006;**4**:936–62.
8. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology* 2006;**131**:1743–51.
9. Liaw YF, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, et al. 2-Year GLOBE trial results: telbivudine Is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology* 2009;**136**:486–95.
10. Fung J, Lai CL, Seto WK, Yuen MF. Nucleoside/nucleotide analogues in the treatment of chronic hepatitis B. *J Antimicrob Chemother* 2011;**66**:2715–25.
11. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009;**50**:661–2.
12. Liaw YF, Leung N, Kao JH, Piratvisuth T, Gane E, Han KH, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. *Hepatol Int* 2008;**2**:263–83.
13. Snow-Lampart A, Chappell B, Curtis M, Zhu Y, Myrick F, Schwalder J, et al. No resistance to tenofovir disoproxil fumarate detected after up to 144 weeks of therapy in patients monoinfected with chronic hepatitis B virus. *Hepatology* 2011;**53**:763–73.
14. Colonno RJ, Rose R, Baldick CJ, Levine S, Pokornowski K, Yu CF, et al. Entecavir resistance is rare in nucleoside naive patients with hepatitis B. *Hepatology* 2006;**44**:1656–65.
15. Ceylan B, Yardimci C, Fincanci M, Eren G, Tozalgan U, Muderrisoglu C, et al. Comparison of tenofovir and entecavir in patients with chronic HBV infection. *Eur Rev Med Pharmacol Sci* 2013;**17**:2467–73.
16. Dogan UB, Kara B, Gumurdulu Y, Soylu A, Akin MS. Comparison of the efficacy of tenofovir and entecavir for the treatment of nucleos(t)ide-naive patients with chronic hepatitis B. *Turk J Gastroenterol* 2012;**23**:247–52.
17. Guzelbulut F, Ovunc AO, Oetinkaya ZA, Senates E, Gökden Y, Salturk AG, et al. Comparison of the efficacy of entecavir and tenofovir in chronic hepatitis B. *Hepatogastroenterology* 2012;**59**:477–80.
18. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. *J Hepatol* 1995;**22**:696–9.
19. Liaw YF. Impact of therapy on the outcome of chronic hepatitis B. *Liver Int* 2013;**33**(Suppl 1):111–5.
20. Abu-Amara M, Feld JJ. Does antiviral therapy for chronic hepatitis B reduce the risk of hepatocellular carcinoma? *Semin Liver Dis* 2013;**33**:157–66.
21. Woo G, Tomlinson G, Nishikawa Y, Kowgier M, Sherman M, Wong D.F K.. et al. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. *Gastroenterology* 2010;**139**:1218–29.
22. Dakin H, Fidler C, Harper C. Mixed treatment comparison meta-analysis evaluating the relative efficacy of nucleos(t)ides for treatment of nucleos(t)ide-naive patients with chronic hepatitis B. *Value Health* 2010;**13**:934–45.
23. Miquel M, Nunez O, Trapero-Marugan M, Diaz-Sanchez A, Jimenez M, Arenas J, et al. Efficacy and safety of entecavir and/or tenofovir in hepatitis B compensated and decompensated cirrhotic patients in clinical practice. *Ann Hepatol* 2013;**12**:205–12.
24. Myung HJ, Jeong SH, Kim JW, Kim HS, Jang JH, Lee DH, et al. [Efficacy and predictors of the virologic response to entecavir therapy in nucleoside-naive patients with chronic hepatitis B]. *Korean J Hepatol* 2010;**16**:57–65.
25. van Bommel F, de Man RA, Wedemeyer H, Deterding K, Petersen J, Buggisch P, et al. Long-term efficacy of tenofovir monotherapy for hepatitis B virus-monoinfected patients after failure of nucleoside/nucleotide analogues. *Hepatology* 2010;**51**:73–80.
26. Chang TT, Lai CL, Kew Yoon S, Lee SS, Coelho HS, Carrilho FJ, et al. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. *Hepatology* 2010;**51**:422–30.
27. Lee MH, Lim SG, Jeon SJ, Kang CJ, Cho YJ, Kim SS, et al. [Clinical efficacy of entecavir therapy and factors associated with treatment response in naive chronic hepatitis B patients]. *Korean J Hepatol* 2009;**15**:446–53.
28. Yao GB, Ren H, Xu DZ, Zhou XQ, Jia JD, Wang YM, et al. [Results of 3 years of continuous entecavir treatment in nucleos(t)ide-naive chronic hepatitis B patients]. *Zhonghua Gan Zang Bing Za Zhi* 2009;**17**:881–6.