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Original Article

Tenofovir disoproxil fumarate: safe and effective option for managing high-viral-load chronic hepatitis B

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Abstract: Objective: This retrospective study evaluated the therapeutic effects of entecavir (ETV) versus tenofovir disoproxil fumarate (TDF) in chronic hepatitis B (CHB) patients with high viral loads. Methods: A total of 120 high-viral-load CHB patients were enrolled and assigned to two treatment groups: the ETV group (n = 56) and the TDF group (n = 64). Comparative assessments included hepatitis B virus deoxyribonucleic acid (HBV-DNA) levels, hepatitis B e antigen (HBeAg) seroconversion rates, alanine aminotransferase (ALT) normalization, clinical efficacy, safety, biological and virological responses, biochemical indicators, and treatment satisfaction. Results: The TDF group showed significantly higher HBV-DNA and HBeAg seroconversion rates, as well as ALT normalization, compared to the ETV group at both 24 and 48 weeks post-treatment (all $P < 0.05$). Additionally, the TDF group demonstrated better clinical efficacy ($P < 0.05$). While demonstrating no significant difference in the incidence of adverse reactions compared to the ETV group ($P > 0.05$). Significantly higher biological and virological response rates, as well as treatment satisfaction, were also observed in the TDF group (all $P < 0.05$). Furthermore, the TDF group exhibited superior efficacy for reducing abnormal biochemical markers ($P < 0.05$). Conclusions: These findings suggest that TDF is more effective than ETV for treating high-viral-load CHB patients.

Keywords: Entecavir, tenofovir disoproxil fumarate, chronic hepatitis B with high viral load, therapeutic effect, safety

Introduction

Chronic hepatitis B (CHB) is a progressive liver disease caused by persistent hepatitis B virus (HBV) infection lasting ≥ 6 months [1]. HBV, a hepatotropic virus, contributes to a high global morbidity and mortality rate, manifesting in either acute or chronic forms [2]. Nearly 300 million people worldwide suffer from CHB, and it leads to almost 900,000 deaths annually [3]. The high viral load subtype (HBV-DNA > 10^7 copies/mL) is particularly oncogenic, with epidemiologic studies showing a curvilinear relationship between viral load and the risk of hepatocellular carcinoma (HCC) [4, 5]. The cornerstone of CHB management is antiviral therapy, primarily consisting of interferons and nucleos(t)ide analogues (NAs). However, despite their strong antiviral effects, these treatments may cause adverse events, including fatigue, emotional disorders, nephrotoxicity, and osteomalacia [6, 7]. Therefore, further exploration of alternative treatments is essential for improving CHB therapy outcomes.

Entecavir (ETV) is an oral antiviral that can be incorporated into mitochondrial DNA (mtDNA) via mitochondrial polymerase γ, leading to mitochondrial dysfunction and morphologic changes in the host [8]. A study by Wong et al. [9] demonstrated that ETV reduced hepatic complications and mortality in cirrhotic CHB patients, suggesting its potential to prevent adverse events. Additional reports indicate that 8 weeks of ETV treatment significantly improves blood biochemistry, immunity, and virological responses in CHB patients and increases intestinal flora species abundance [10].

Tenofovir disoproxil fumarate (TDF) may also influence liver immunity, inflammation, and metabolism, potentially by the mmu-microRNA (miR)-155-5p-nuclear factor kappa-B (NF-κB) signaling pathway [11]. In a multicenter study by Hsu et al. [12], TDF was found to effectively

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reduce hepatic fibrosis in CHB, though its impact on necroinflammatory activity was statistically insignificant. Furthermore, Lim et al. [13] provided clinical evidence suggesting that TDF lowers the risk of HCC in CHB patients.

As first-line NAs, both ETV and TDF exhibit high resistance barriers and show potential in preventing HCC [14]. However, their comparative efficacy in high-viral-load CHB, especially regarding safety profiles and biochemical effects, remains underexplored. This study aims to address this gap and identify more effective therapeutic options.

Materials and methods

Case selection

This retrospective study included 120 high-viral-load CHB patients admitted between May 2022 and May 2024 at the First People's Hospital of Lin'an District. The participants were divided into two groups: 56 patients in the ETV group receiving ETV treatment, and 64 patients in the TDF group receiving TDF therapy. The study was conducted with approval from the Ethics Committee of The First People's Hospital of Lin'an District.

Inclusion criteria: 1. Diagnosed with CHB according to the diagnostic criteria [15]. 2. Hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) positive for more than 6 months. 3. High viral load status (HBV-DNA > 10^7 copies/mL) [16]. 4. First-time antiviral treatment; no previous antiviral therapy. 5. Aged 18-80 years. 6. No prior resistance to the drugs used in this study, and this was their first use of these medications. 7. Complete clinical data available.

Exclusion criteria: 1. Primary liver disease diagnosis. 2. Presence of autoimmune diseases. 3. Pregnant or lactating women. 4. Hepatitis A and/or C virus superinfection. 5. Treatment with immunomodulatory drugs in the last 6 months. 6. Drug-induced liver injury, non-alcoholic steatohepatitis, cirrhosis, etc. 7. Allergic reactions to study medications (e.g., ETV). 8. Hepatitis due to other causes. 9. Comorbid psychiatric disorders or metabolic dysfunction. 10. Prior use of immunosuppressive agents or interferon.

Intervention method

Patients in the ETV group received 0.5 mg of ETV orally once daily, while those in the TDF group received 300 mg of TDF orally once daily. Both groups were treated for 48 weeks, with each 24-week period considered one course of treatment.

Data collection and outcome measurement

(1) Seroconversion rate: HBV-DNA Seroconversion: HBV-DNA < 10^3 copies/mL. HBeAg Seroconversion: HBeAg clearance with development of anti-HBe antibodies. Alanine aminotransferase (ALT) Normalization: ALT < 40 U/L [18]. ALT was measured using a URIT automated biochemical analyzer, and HBV-DNA levels were determined using the ABI 7500 Real-Time PCR System (Applied Biosystems, USA), with a detection threshold of 10^3 copies/mL. High viral load status was defined as viral loads > 10^7 copies/mL.

(2) Biological and virological responses: Biochemical response criterion: ALT normalization. Virological response criterion: HBV-DNA < 500 IU/mL.

(3) Clinical efficacy: Effective: HBV-DNA < 10^3 IU/mL. Ineffective: HBV-DNA above limit.

(4) Safety: Treatment-emergent adverse events, including dizziness, fatigue, abdominal distension, and rash, were documented and compared between groups to determine incidence rates.

(5) Biochemical indicators: ALT, aspartate aminotransferase (AST), and total bilirubin (TBIL) levels were measured using an automated biochemical analyzer.

(6) Treatment satisfaction: Patient satisfaction was assessed using a self-designed questionnaire, scored from 0 to 3: 0 = dissatisfied; 1 = moderately satisfied; 2 = relatively satisfied; 3 = highly satisfied.

Treatment satisfaction was quantified as: Satisfaction rate = [(satisfied cases + highly satisfied cases)/total cases] × 100%.

Primary outcomes included seroconversion rates, biological and virological responses, clinical efficacy, safety, and biochemical indica-

Table 1. Comparison of baseline data

Indicator	ETV group (n = 56)	TDF group (n = 64)	χ^2/t	P
Sex (male/female)	27/29	28/36	0.240	0.624
Age (years old)	62.95 ± 9.64	63.44 ± 11.18	0.255	0.799
Disease duration (years)	1.98 ± 1.02	1.72 ± 1.05	1.371	0.173
Smoking history (without/with)	30/26	31/33	0.315	0.575
Alcoholism history (without/with)	25/31	23/41	0.943	0.332
Family medical history (without/with)	10/46	14/50	0.301	0.583

Note: ETV, entecavir; TDF, tenofovir disoproxil fumarate.

Table 2. Comparison of HBV-DNA seroconversion rate

Indicator	ETV group (n = 56)	TDF group (n = 64)	χ^2	P
4 weeks after treatment	12 (21.43)	35 (54.69)	13.870	< 0.001
12 weeks after treatment	26 (46.43)	44 (68.75)	6.122	0.013
24 weeks after treatment	42 (75.00)	61 (95.31)	10.130	0.002
48 weeks after treatment	50 (89.29)	64 (100.00)	7.218	0.007

Note: HBV-DNA, hepatitis B virus-deoxyribonucleic acid; ETV, entecavir; TDF, tenofovir disoproxil fumarate.

Table 3. Comparison of HBeAg seroconversion rate

Indicator	ETV group (n = 56)	TDF group (n = 64)	χ^2	P
4 weeks after treatment	6 (10.71)	9 (14.06)	0.306	0.580
12 weeks after treatment	16 (28.57)	27 (42.19)	2.408	0.121
24 weeks after treatment	24 (42.86)	40 (62.50)	4.630	0.031
48 weeks after treatment	28 (50.00)	45 (70.31)	5.172	0.023

Note: HBeAg, hepatitis B e antigen; ETV, entecavir; TDF, tenofovir disoproxil fumarate.

Table 4. Comparison of ALT normalization rate

Indicator	ETV group (n = 56)	TDF group (n = 64)	χ^2	P
4 weeks after treatment	11 (19.64)	13 (20.31)	0.008	0.927
12 weeks after treatment	27 (48.21)	33 (51.56)	0.134	0.714
24 weeks after treatment	33 (58.93)	49 (76.56)	4.292	0.038
48 weeks after treatment	39 (69.64)	60 (93.75)	12.020	< 0.001

Note: ALT, alanine aminotransferase; ETV, entecavir; TDF, tenofovir disoproxil fumarate.

tors. Secondary outcomes encompassed treatment satisfaction.

Statistical methods

Continuous data were expressed as mean ± SEM. Between-group comparisons were performed using independent sample t-tests, and within-group comparisons were performed using paired t-tests. Categorical data, expressed as rates (percentages), were compared between groups using the χ^2 test. Statistical analysis was conducted using SPSS 19.0, with a significance level set at $P < 0.05$.

Results

Comparison of baseline data

No significant differences were found between the ETV and TDF groups in terms of gender, age, disease duration, smoking history, alcohol consumption history, or family medical history (all $P > 0.05$). See **Table 1**.

Comparison of seroconversion rates of HBV-DNA, HBeAg, and ALT normalization

We compared HBV-DNA seroconversion, HBeAg seroconversion, and ALT normalization at various time points. At weeks 4 and 12 post-treatment, the TDF group exhibited higher HBV-DNA seroconversion rates (both $P < 0.05$), while HBeAg seroconversion and ALT normalization rates were similar between both groups (both $P > 0.05$). At weeks 24 and 48, the TDF group showed higher HBV-DNA and HBeAg seroconversion rates and superior ALT normalization compared to the ETV group (all $P < 0.05$). See **Tables 2**-**4**.

Table 5. Comparison of clinical efficacy

Indicator	ETV group (n = 56)	TDF group (n = 64)	χ^2	P
Effective	34 (60.71)	57 (89.06)	13.100	< 0.001
Ineffective	22 (39.29)	7 (10.94)		

Note: ETV, entecavir; TDF, tenofovir disoproxil fumarate.

Table 6. Comparison of safety

Indicator	ETV group (n = 56)	TDF group (n = 64)	χ^2	P
Dizziness	0 (0.00)	2 (3.13)		
Fatigue	2 (3.57)	1 (1.56)		
Abdominal distension	2 (3.57)	2 (3.13)		
Rash	4 (7.14)	0 (0.00)		
total	8 (14.29)	5 (7.81)	1.296	0.255

Note: ETV, entecavir; TDF, tenofovir disoproxil fumarate.

Table 7. Comparison of biologic and virological responses

Indicator	ETV group (n = 56)	TDF group (n = 64)	χ^2	P
Biologic response	34 (60.71)	52 (81.25)	6.203	0.013
Virological response	36 (64.29)	56 (87.50)	8.997	0.003

Note: ETV, entecavir; TDF, tenofovir disoproxil fumarate.

Comparison of clinical efficacy

The clinical efficacy rates for the ETV and TDF groups were 60.71% and 89.06%, respectively, with the TDF group showing significantly better efficacy (P < 0.05). See **Table 5**.

Comparison of safety

In the ETV group, adverse reactions included 4 cases of rash, 2 cases of fatigue, and 2 cases of abdominal distension, resulting in an overall adverse reaction rate of 14.29%. In the TDF group, 2 cases of abdominal distension, 2 cases of dizziness, and 1 case of fatigue were reported, with an overall adverse reaction rate of 7.81%. No significant difference was found between the two groups in terms of the overall incidence of adverse reactions (P > 0.05). See **Table 6**.

Comparison of biologic and virological responses

The TDF group exhibited superior biological (81.25% vs. 60.71%, P < 0.05) and virological responses (87.50% vs. 64.29%, P < 0.05) compared to the ETV group. See **Table 7**.

Comparison of biochemical indicators

No significant differences were found in the pre-treatment levels of ALT, AST, or TBIL between the two groups (all P > 0.05). However, after treatment, all biochemical markers showed a significant decline (all P< 0.05), with the TDF group showing lower levels than the ETV group (all P < 0.05). See **Figure 1**.

Comparison of overall treatment satisfaction

Patients in the TDF group reported higher satisfaction (92.19%) compared to those in the ETV group (75.00%, P< 0.05). See **Table 8**.

Discussion

Chronic hepatitis B (CHB) continues to pose a significant global health burden. Chronic infection can lead to cirrhosis and even progression to HCC, severely threatening patients' health [18]. Elevated viral load and HBeAg-positive status are well-established risk factors for disease progression, emphasizing the critical importance of effective antiviral interventions and HBeAg seroconversion in clinical management [19]. This study aims to provide an effective clinical strategy to prevent CHB progression by comparing two antiviral therapies.

Our results demonstrated superior virological outcomes with TDF compared to ETV, including significantly higher HBV-DNA seroconversion rates at weeks 4, 12, 24, and 48; and improved HBeAg seroconversion and ALT normalization at weeks 24 and 48.

These findings suggest that TDF treatment for high-viral-load CHB patients significantly enhances HBV-DNA and HBeAg seroconversion and ALT normalization, achieving effective antiviral outcomes. These results align with previous studies, such as Inoue et al. [20], which also reported TDF's advantage in promoting HBsAg seroconversion in HBeAg-positive CHB patients.

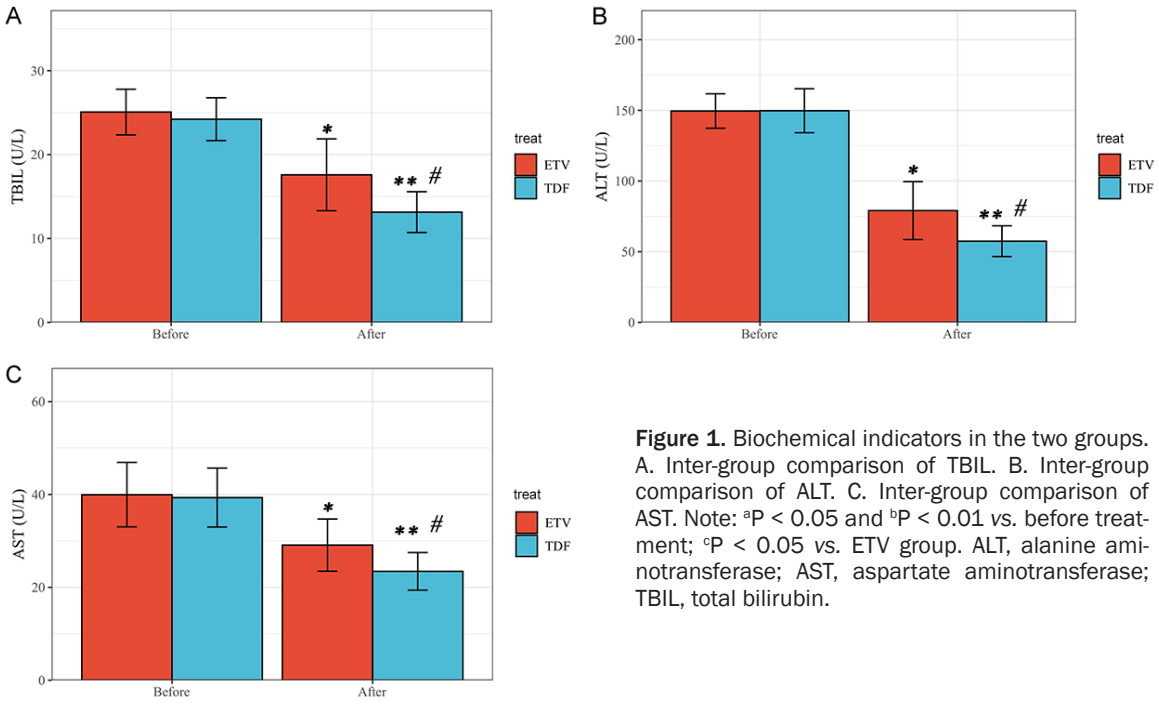

Figure 1. Biochemical indicators in the two groups. A. Inter-group comparison of TBIL. B. Inter-group comparison of ALT. C. Inter-group comparison of AST. Note: [a]P < 0.05 and [b]P < 0.01 *vs.* before treatment; [c]P < 0.05 *vs.* ETV group. ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin.

Table 8. Comparison of overall treatment satisfaction

Indicator	ETV group (n = 56)	TDF group (n = 64)	χ^2	P
Highly satisfied	17 (30.36)	27 (42.19)		
Relatively satisfied	22 (39.29)	32 (50.00)		
Moderately satisfied	11 (19.64)	5 (7.81)		
Dissatisfied	3 (5.36)	0 (0.00)		
Satisfaction	42 (75.00)	59 (92.19)	6.621	0.010

Note: ETV, entecavir; TDF, tenofovir disoproxil fumarate.

The significantly higher treatment efficacy in the TDF group (89.06%) compared to the ETV group (60.71%) indicates that TDF provides a greater therapeutic effect in high-viral-load CHB patients. Behera et al. [21] reported that TDF achieved a higher complete viral suppression rate than ETV in patients with newly diagnosed HBeAg-positive CHB, which supports our findings. Additionally, Hou et al. [22] demonstrated that TDF was more effective than adefovir dipivoxil in inhibiting the virus in CHB patients, showing lower drug resistance rates, fewer adverse events, and a higher ALT normalization rate-similar to our observations.

In terms of safety, the total incidence of adverse reactions was higher in the ETV group (14.29%) than in the TDF group (7.81%), although this difference was not statistically significant. This suggests that TDF may reduce the incidence of adverse reactions. As reported by Aladag et al. [23], TDF is safe for use in pregnant women with high viral load CHB and effectively prevents perinatal HBV transmission.

Statistically higher biological and virological response rates were observed in the TDF group compared to the ETV group, suggesting that TDF significantly improved biologic and virological responses, aiding in liver function recovery. In line with our findings, Con et al. [24] reported a significantly higher virological response in CHB patients treated with TDF compared to ETV at 48 weeks.

Our biochemical analysis further revealed that TDF-treated patients showed greater reductions in ALT, AST, and TBIL levels after treatment, indicating superior hepatoprotective effects. These results align with Liu et al. [25], who found that TDF effectively normalizes ALT, AST, and TBIL levels in CHB patients, improving liver function.

Finally, TDF treatment had a significantly higher overall treatment satisfaction rate of 92.19%

compared to 75.00% in the ETV group, further supporting its clinical uses.

This study has several limitations. The relatively small sample size may have introduced biases. A multicenter design could help mitigate this limitation and improve the generalizability of the findings. Additionally, the lack of foundational research represents a gap that could be addressed through further experimental studies to provide deeper insight into the therapeutic mechanisms of high-viral-load CHB. The absence of long-term follow-up also limits our ability to fully assess the prognostic outcomes of TDF. Future studies incorporating extended follow-up will provide a more comprehensive understanding of its long-term efficacy. We aim to address these limitations in future research to enhance the study's comprehensiveness and validity.

In summary, TDF is more effective than ETV for treating high-viral-load CHB. Specifically, it significantly improves HBV-DNA seroconversion at all treatment stages, as well as HBeAg seroconversion and ALT normalization at weeks 24 and 48. Additionally, TDF is effective in repairing liver function by improving biologic and virological response rates and reducing elevated ALT, AST, and TBIL levels. With its efficacy and safety profile, TDF also significantly increases patient treatment satisfaction. Our findings provide a valuable clinical reference for managing high-viral-load CHB.

Disclosure of conflict of interest

None.

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