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ORIGINAL ARTICLE

Retrospective Study

Tenofovir amibufenamide *vs* tenofovir alafenamide for treating chronic hepatitis B: A real-world study

Wen-Ting Peng, Chuan Jiang, Fei-Lan Yang, Nian-Qi Zhou, Ke-Yu Chen, Jin-Qing Liu, Shi-Fang Peng, Lei Fu

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Abstract

BACKGROUND

The efficacy and safety profile of tenofovir amibufenamide (TMF) in chronic hepatitis B (CHB) patients is not well-established.

AIM

To compare the efficacy and safety of TMF and tenofovir alafenamide (TAF) over a 48-wk period in patients with CHB.

METHODS

A total of 215 subjects meeting the inclusion criteria were enrolled and divided into two groups: TMF group (n = 106) and the TAF group (n = 109). The study included a comparison of virological response (VR): Undetectable hepatitis B virus DNA levels, alanine transaminase (ALT) normalization rates, renal function parameters, and blood lipid profiles.

RESULTS

At 24 and 48 wk, VR rates for the TMF group were 53.57% and 78.57%, respectively, compared with 48.31% and 78.65% for the TAF group (P > 0.05). The VR rates were also similar in both groups among patients with low-level viremia, both hepatitis B e antigen (HBeAg)-positive and HBeAg-negative subgroups. The TMF cohort showed ALT normalization and renal safety profiles similar to the TAF group. There was a notable increase in total cholesterol levels in the TAF group (P = 0.045), which was not observed in the TMF group (P > 0.05). In patients with liver cirrhosis, both groups exhibited comparable VR and ALT normalization rates and renal safety profiles. However, the fibrosis 4 score at 48 wk showed a significant reduction in the TAF group as compared to the TMF group within the liver cirrhosis subgroup.

CONCLUSION

Our study found TMF is as effective as TAF in treating CHB and has a comparable safety profile. However, TAF may be associated with worsening lipid profiles.

Key Words: Alanine transaminase normalization; Chronic hepatitis B; Renal safety; Virological response; Blood lipid; Tenofovir

Core Tip: This is a retrospective study to compare the efficacy and safety of tenofovir amibufenamide (TMF) and tenofovir alafenamide (TAF) for 48 wk in patients with chronic hepatitis B (CHB). Our study found that TMF is as effective as TAF in treating CHB and has comparable safety profiles. In addition, TAF may cause deterioration of lipid profiles. These results suggest that TMF may be a viable alternative to TAF for CHB treatment.

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INTRODUCTION

Hepatitis B virus (HBV) infection represents a significant economic and health burden worldwide. As of 2019, over 1.5 million preventable new infections continue to occur annually, and there are approximately 296 million people living with chronic HBV infection, resulting in over 820,000 deaths annually due to liver cirrhosis and hepatocellular carcinoma (HCC)[1]. Achieving complete suppression of HBV in a safe and effective manner is crucial for preventing HBV-related adverse health events[2]. Consequently, efforts in this regard have primarily focused on antiviral treatment over the past decades. Current international guidelines recommend as first-line treatments newer antiviral agents with a high genetic barrier to HBV mutation, such as entecavir, tenofovir (TFV) disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) [3-5]. Previous studies have shown that these drugs are safe and effective in treating chronic hepatitis B (CHB). However, long-term use of TDF leads to high levels of circulating TFV, resulting in kidney and bone toxicity, particularly in aging populations[6]. TAF, a TFV prodrug, is converted into the active form of TFV diphosphate *in vivo*, similar to TDF. At a dose of ≤ 25 mg, TAF reduces the total body exposure of TFV by more than 90%[7]. The correlativity study demonstrated that TAF, with its low concentration of TFV in the circulation, reduces the drug load on the kidneys and bones, thereby improving their safety[8].

Currently, tenofovir amibufenamide (TMF) is recommended as the fourth nucleoside analog for first-line treatment of CHB in mainland China[9]. TMF, another prodrug of TFV, is produced by ProTide technology and features an additional methyl group compared to TAF. This extra methyl group may enhance TMF's stability in peripheral blood and facilitate intracellular conversion[10]. *In vitro* studies have shown that TMF has a lower EC_{50} in HepG2.2.15 cells than TAF and TDF [11]. In randomized clinical trials and prospective clinical studies with treatment durations of 48 and 96 wk, TMF was found to be similarly effective in viral suppression to TDF, but with significantly less bone and renal toxicity[12,13]. TMF was approved in June 2021 and was included in the 2021 China National Reimbursement Drug List for CHB treatment.

Due to the recent introduction of TMF in the Chinese market and the limited real-world research data for the Chinese population, there is currently a knowledge gap regarding the drug's safety and efficacy. Therefore, we conducted this clinical study to assess the safety and effectiveness of TMF in treating patients with CHB in China.

MATERIALS AND METHODS

Study design and patient selection

In this retrospective study, we enrolled a total of 587 patients aged 18 and above who had been HBsAg positive for more than 6 mo. These patients were treated at Xiangya Hospital of Central South University between July 2021 and April 2022. Patients were excluded if they met any of the following criteria: (1) Concomitant with other liver diseases, such as alcoholic liver disease, nonalcoholic fatty liver disease, autoimmune liver disease, drug-induced liver injury, hepatolenticular degeneration, or other viral infections [hepatitis A, C, and E virus or human immunodeficiency virus (HIV)]; (2) pregnant or lactating women; (3) concomitant with malignant tumors or other serious diseases affecting survival time; (4) added or changed to other antiviral drugs during treatment; and (5) patients with missing data. Of the enrolled patients, 215 were included in the final analysis and were divided into two groups based on their drug selection: The TMF group and the TAF group.

The study protocol was approved by the Medical Ethics Committee of Xiangya Hospital Central South University (approval No. 202303047).

Treatment and follow-up

During the study period, all patients received anti-HBV treatment with 25 mg of TMF (Hansoh Pharmaceuticals Co., Ltd, Jiangsu, China) or 25 mg of TAF (Gilead Sciences, Inc.) once daily immediately after diagnosis of CHB. Additionally, liver protection drugs were used according to the needs of the disease as prescribed by clinicians. Clinical results and related indicators were collected for each participant during the 48-week follow-up period. These parameters were recorded at baseline, approximately at week 24, and again at week 48.

The efficacy endpoint at week 48 was defined as the proportion of patients achieving a virological response (VR), which is characterized by a reduction in serum HBV DNA levels to less than 10 IU/mL, as measured by the real-time polymerase chain reaction method. Additionally, a pre-specified safety outcome included the percentage change in renal function markers and lipid profiles at weeks 24 and 48 in comparison with the baseline values.

Data collection

Clinical and laboratory data were collected during hospitalization, including clinical characteristics, routine blood test results [including white blood cells (WBC) and platelets (PLT)], liver function tests [including albumin, globulin, total bilirubin (TBIL), direct bilirubin (DBIL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST)], renal function tests [including serum creatinine (Cr), blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR)], HBV DNA quantification, serological biomarkers, blood lipids [including triglycerides, total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL)], serum phosphorus, alpha-fetoprotein (AFP), and liver stiffness measurement (LSM). The model for fibrosis 4 (FIB-4) score was calculated using the following formula[14]: FIB-4 = age [(year) × AST (U/L)] /[(PLT (10(9)/L) × [ALT (U/L) (1/2)]. In our study, ultrasound examinations were employed to diagnose liver cirrhosis in patients. Low-level viremia (LLV) was characterized as either persistent or intermittent detection of HBV DNA at levels below 2000 IU/mL, with a detection threshold of 10 IU/mL, following 48 wk of antiviral therapy.

Statistical analyses

The sample size for this study was calculated using G Power version 3.1.9.2 (Heinrich-Heine-Universität Düsseldorf). We predetermined the effect size f to range between 0.1 (small) and 0.4 (large), with a type I error rate (alpha) of 0.05 and a power of 0.8, considering two independent groups: TMF and TAF. Employing a one-way ANOVA model, the estimated sample size necessary varied from 84 for a large effect size to 788 for a small effect size. We ultimately recruited 215 participants for the study.

Statistical analyses were performed using SPSS for Windows, version 25.0. Continuous variables were reported as mean ± SD or median (interquartile range), while categorical variables were reported as percentages. The Student *t*-test and rank sum test were used to compare continuous variables, while the chi-squared test was used for categorical variables. All statistical tests were two-sided, and a P-value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the study population

A total of 587 patients with CHB were identified at our hospital between April 2022 and December 2021, of which 372 patients were excluded for various reasons (Figure 1). The final study population consisted of 215 patients, with 106 patients receiving TMF treatment and 109 patients receiving TAF treatment. The mean age of the study population was 40.57 ± 10.54 years, with 145 (67.74%) male patients. The mean LSM using FibroScan was 10.43 ± 3.99, and 42 (19.53%) of patients were diagnosed with cirrhosis. As shown in Table 1, there were no significant differences in baseline characteristics between the two treatment groups, including age, gender proportion, underlying disease, serum Cr, eGFR, BUN, albumin, globulin, AST, ALT, TBIL, DBIL, AFP, blood phosphorus, WBC, PLT, LSM, and FIB-4 score (all P > 0.05). These findings suggest that the two treatment groups were comparable.

Safety

During the 48-wk follow-up period, no significant drug-related adverse reactions were observed with either oral antiviral drug.

VRs

At week 48, the rate of undetectable HBV DNA (HBV DNA < 10 IU/mL) was slightly higher in the TMF treatment group (78.57%), compared to the TAF group (78.65%), although the difference was not statistically significant (Figure 2A). Similarly, the VR rates were similar in both treatment groups for patients with LLV (P > 0.05) (Figure 2B). Among the hepatitis B e antigen (HBeAg)-positive population, 74.36% of patients receiving TMF and 76.09% receiving TAF achieved HBV DNA less than 10 IU/mL (Figure 2C). In the HBeAg-negative population, 82.22% and 81.40% of patients in the TMF and TAF groups, respectively, achieved HBV DNA less than 10 IU/mL (Figure 2D).

The carrying capacity of HBV DNA decreased from 3.96 ± 2.18 to 2.13 ± 0.84 Log10 (IU/mL) in the TMF group and from 4.55 ± 2.31 to 2.35 ± 1.33 Log10 (IU/mL) in the TAF group (Figure 3A). While the TMF group showed a similar VR

Table 1 Baseline characteristics of the study population, *n* (%)

Variable	TMF group 25 mg (*n* = 106)	TAF group 25 mg (*n* = 109)	*P* value
Male	71 (66.98)	74 (67.89)	0.887
Age (yr)	40.96 ± 11.25	40.19 ± 9.84	0.707
Routine blood test			
WBC (× 10^9/L)	5.59 ± 1.64	5.59 ± 1.49	0.792
PLT (× 10^9/L)	193.97 ± 67.44	181.98 ± 68.63	0.218
Liver function			
Albumin (g/L)	45.57 ± 3.64	45.46 ± 3.59	0.746
Globulin (g/L)	29.32 ± 3.66	29.49 ± 3.70	0.617
TBIL (μmol/L)	4.55 (3.70, 5.90)	4.75 (2.20, 18.78)	0.070
DBIL (μmol/L)	2.50 (1.50, 3.90)	5.85 (4.10, 8.33)	0.152
ALT (U/L)	28.30 (20.10, 46.70)	32.40 (22.35, 49.60)	0.203
AST (U/L)	30.50 (24.90, 39.00)	30.00 (24.83, 40.80)	0.740
Kidney function			
BUN (mmol/L)	4.75 (3.99, 6.11)	4.88 (4.22, 5.70)	0.856
Creatinine (μmol/L)	79.50 (66.05, 91.00)	83.30 (73.00, 93.90)	0.177
eGFR (ml/min/1.73 m^2)	90.58 (79.84, 103.80)	97.19 (87.335, 106.38)	0.180
Viral load			
HBV DNA < 10 IU/mL	34 (32.08)	44 (40.37)	0.206
HBeAg positive	39 (36.79)	46 (42.20)	0.417
Blood lipid			
Triglycerides (mmol/L)	1.57 ± 0.82	1.65 ± 1.19	0.719
Total cholesterol (mg/dl)	4.83 ± 1.09	4.30 ± 1.54	0.173
HDL	1.18 ± 0.21	1.10 ± 0.14	0.341
LDL	3.19 ± 0.91	3.20 ± 0.94	0.877
Phosphorus (mmol/L)	1.64 ± 3.84	1.05 ± 0.44	0.958
AFP (ng/mL)	5.19 ± 8.90	5.24 ± 7.89	0.167
LSM (Kpa)	10.17 ± 4.41	10.94 ± 3.37	0.108
FIB-4 score	1.15 (0.75, 1.77)	1.27 (0.87, 2.03)	0.552
Underlying diseases			
Diabetes	5 (4.72)	6 (5.50)	0.793
Cirrhosis	23 (21.70)	19 (17.43)	0.430
Decompensated cirrhosis	4 (3.77)	4 (3.67)	0.968
Hepatocellular carcinoma	2 (1.89)	3 (2.75)	0.674
NAFLD	26 (24.53)	28 (25.69)	0.845
Treatment naïve	63 (59.43)	61 (55.96)	0.607

Data are frequency (%), median M (P25, P75), or mean ± SD deviation. TMF: Tenofovir amibufenamide; TAF: Tenofovir alafenamide; WBCs: White blood cells; PLTs: Platelets; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; DBIL: Direct bilirubin; BUN: Blood urea nitrogen; eGFR: Estimated glomerular filtration rate; P: Phosphorus; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; AFP: Alpha fetoprotein; LSM: Liver stiffness measurement; HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen; NAFLD: Nonalcoholic fatty liver disease; FIB-4: Fibrosis-4.

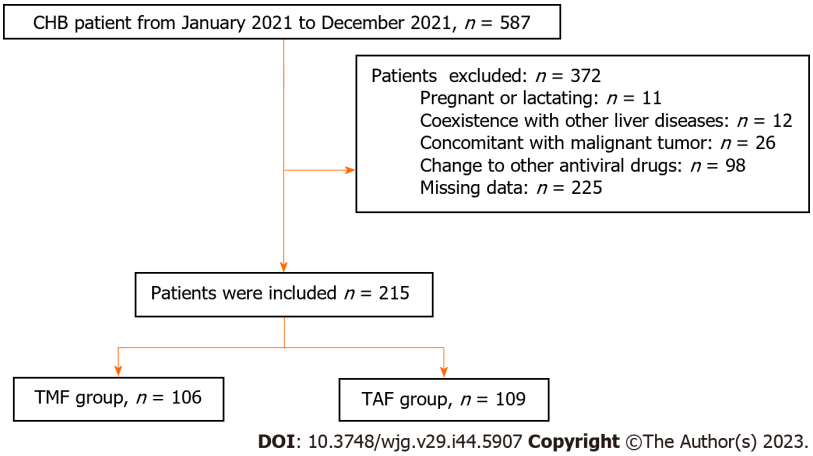

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Figure 1 Flow chart of the patient inclusion process. CHB: Chronic hepatitis B; TMF: Tenofovir amibufenamide; TAF: Tenofovir alafenamide.

within 48 wk compared with the TAF group, there was no statistical difference between the two groups (Figure 3B).

On-treatment ALT normalization

The ALT normalization rate in the TMF group was 66.04% and 78.30% at 24 and 48 wk, respectively. In the TAF group, the ALT normalization rate was 55.96% and 74.31% at 24 and 48 wk, respectively. Although the ALT normalization rate in the TAF group showed a higher trend compared to the TMF group from baseline to 48 wk, this difference did not reach statistical significance (Figure 3C). As shown in Figure 3D, both TMF and TAF groups had similar trends in ALT changes during the 48-wk period.

Changes in renal function in TMF and TAF groups

After 48 wk of treatment, Cr levels in the TMF group decreased from 79.50 (66.05, 91.00) μmol/L to 72.00 (63.00, 83.00) μmol/L, and that in the TAF group decreased from 83.30 (73.00, 93.90) μmol/L to 78.10 (61.00, 90.70) μmol/L. Meanwhile, eGFR in both groups increased slightly. However, there was no significant difference in the changes of Cr and eGFR between the two groups within 48 wk (Table 2).

Changes in blood lipids

In this study, plasma lipids consisted primarily included triglycerides, TC, LDL, and HDL. There was no significant change observed in the triglycerides, HDL, and LDL levels at 48 wk. Specifically, in the TMF group, the TC levels demonstrated a mean change of -0.23 ± 0.71 mg/dL at the 48-wk mark (P = 0.822) (Table 3). Conversely, in the TAF group, TC values exhibited a continuous rise from 4.30 ± 1.54 mg/dL at baseline to 5.2 ± 0.99 mg/dL at week 48 (P = 0.045) (Table 3).

Antiviral therapy in patients with liver cirrhosis

In our study, 23 patients in the TMF group and 19 patients in the TAF group had liver cirrhosis. The complete VR rates after 48 wk of treatment were 78.26% in the TMF group and 73.68% in the TAF group, with no significant difference between the two groups (Figure 4A). The normalization rate of ALT was similar in the two groups after 48 wk of treatment (Figure 4B). Renal safety profiles for TMF were similar to those observed for TAF at the 48-wk mark (Supplementary Table 1).

The regression of liver fibrosis was evaluated using FIB-4 scores and LSM in this study (Supplementary Table 2). Liver stiffness was measured using FibroScan. The LSM of cirrhotic patients in the TAF group decreased from baseline to the 48th week (P > 0.05). For the TMF cohort, both LSM and FIB-4 scores demonstrated a marginal increase after 48 wk of treatment; however, these differences did not reach statistical significance. In patients with liver cirrhosis, there was no significant difference between the two groups in the reduction of LSM from baseline level at the 48th week. However, the decrease in FIB-4 in patients with TAF was significantly greater than in patients with TMF [0.29 (0.06, 0.77) *vs*. -0.43 (1.16, -0.08); P = 0.001].

DISCUSSION

TFV ester prodrugs, a class of nucleotide analogs (NAs), are the first-line clinical anti-HBV drugs with potent antiviral efficacy, low resistance rates, and high safety. Various types of ester prodrugs of TFV have been designed in recent decades to improve its antiviral activity and reduce its adverse reactions[15,16].

TMF, the third commercially available TFV ester prodrug, was developed by modifying TAF through the addition of a single methyl group. It received approval from China's National Medical Products Administration for the treatment of HBV infection in 2021. Clinical trials have demonstrated that TMF possesses superior plasma stability compared to TDF

Table 2 Comparison of changes in serum creatinine and estimated glomerular filtration rate between the tenofovir amibufenamide and tenofovir alafenamide groups.

	TMF group (*n* = 106)	TAF group (*n* = 109)	*P* value
Creatinine (μmol/L)			
Before treatment	79.50 (66.05, 91.00)	83.30 (73.00, 93.90)	0.856
After 48 wk	72.00 (63.00, 83.00)	78.10 (61.00, 90.70)	0.194
Reduction	4.00 (-19.65, 19.50)	3.37 (-7.96, 26.13)	0.728
P (baseline *vs*. 48 wk)	0.053	0.105	
eGFR (mL/min/1.73 m^2)			
Before treatment	90.58 (79.84, 103.80)	97.19 (87.35, 106.38)	0.180
After 48 wk	106.37 (94.58, 113.15)	105.17 (88.15,129.56)	0.617
Reduction	-2.22 (-9.72, 16.75)	-4.17 (-227.89, 7.67)	0.093
P (baseline *vs*. 48 wk)	0.301	0.108	

Data are median M (P25, P75). TMF: Tenofovir amibufenamide; TAF: Tenofovir alafenamide; eGFR: Estimated glomerular filtration rate.

Table 3 Changes in blood lipid profiles between the tenofovir amibufenamide and tenofovir alafenamide groups

	TMF group (*n* = 106)	TAF group (*n* = 109)	*P* value
Triglycerides (mmol/L)			
Before treatment	1.57 ± 0.82	1.65 ± 1.19	0.719
After 48 wk	2.16 ± 1.34	1.81 ± 0.87	0.931
Reduction	-0.64 ± 1.02	0.19 ± 0.31	0.103
P (baseline *vs*. 48 wk)	0.099	0.359	
Total cholesterol (mg/dl)			
Before treatment	4.83 ± 1.09	4.30 ± 1.54	0.173
After 48 wk	4.82 ± 1.52	5.20 ± 0.99	0.581
Reduction	-0.23 ± 0.95	-1.02 ± 1.18	0.182
P (baseline *vs*. 48 wk)	0.822	0.045	
HDL (mmol/L)			
Before treatment	1.18 ± 0.21	1.10 ± 0.14	0.341
After 48 wk	1.43 ± 0.74	1.23 ± 0.31	0.977
Reduction	-0.23 ± 0.71	-0.09 ± 0.16	0.672
P (baseline *vs*. 48 wk)	0.430	0.225	
LDL (mmol/L)			
Before treatment	3.19 ± 0.91	3.20 ± 0.94	0.877
After 48 wk	3.15 ± 1.18	3.40 ± 0.71	0.428
Reduction	0.10 ± 0.94	-0.04 ± 0.9	0.791
P (baseline *vs*. 48 wk)	0.807	0.332	

Data are median M (P25, P75). TMF: Tenofovir amibufenamide; TAF: Tenofovir alafenamide; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

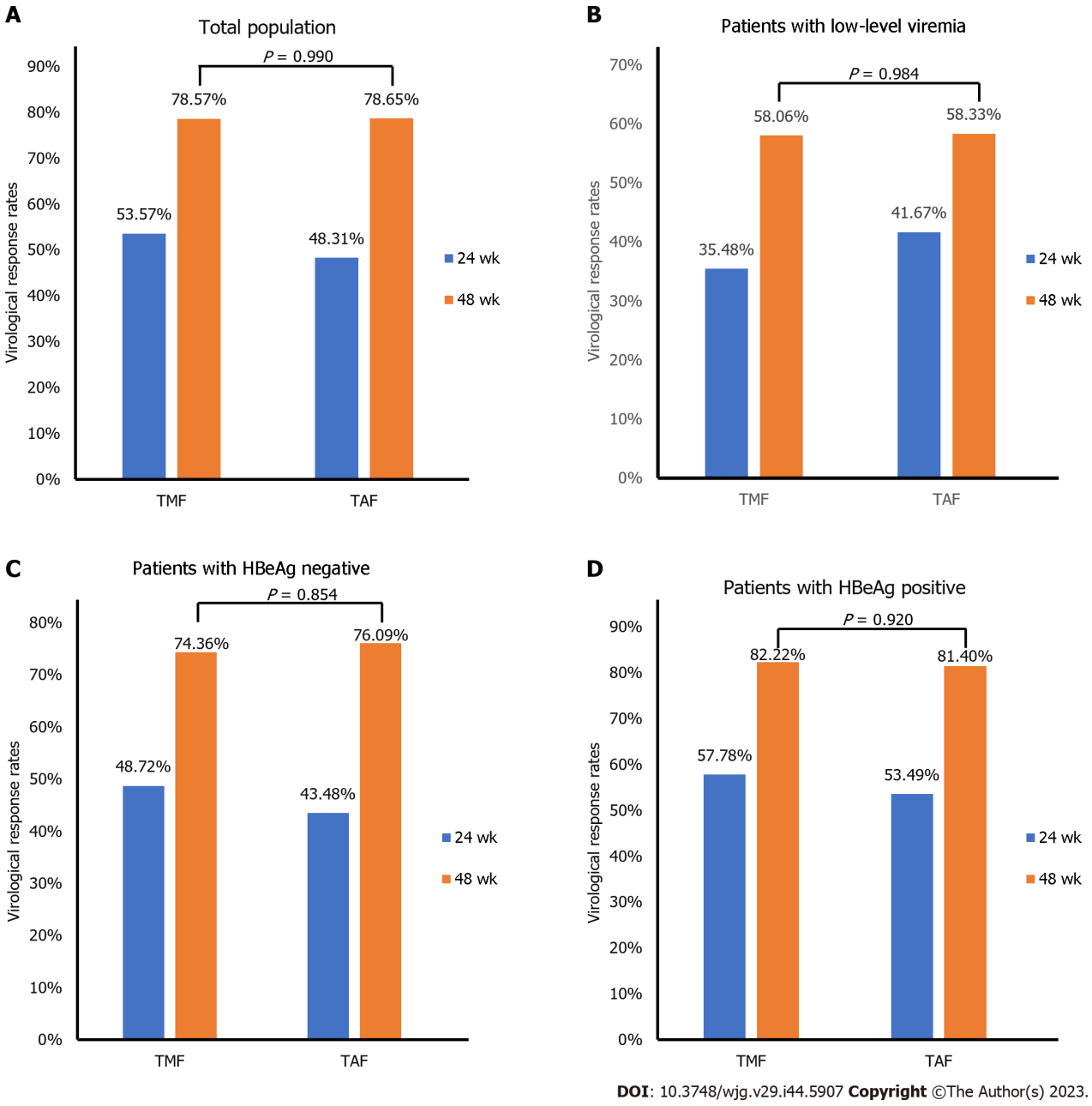

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Figure 2 Comparison of virological response rates between tenofovir amibufenamide and tenofovir alafenamide. A: Virological response (VR) rates of tenofovir amibufenamide (TMF) and tenofovir alafenamide (TAF) groups at 24 and 48 wk; B: VR rates of TMF and TAF groups at 24 and 48 wk with low-level viremia; C: VR rates of TMF and TAF groups at 24 and 48 wk with hepatitis B e antigen (HBeAg) negative; D: VR rates of TMF and TAF groups at 24 and 48 wk with HBeAg positive. TMF: Tenofovir amibufenamide; TAF: Tenofovir alafenamide; VR: Virological response; HBeAg: Hepatitis B e antigen.

and exhibits a similar potency in inhibiting HBV, even when administered at a mere 1/30 of TDF's dosage[17]. Another study, however, revealed that both TMF and TAF displayed enhanced anti-HBV activity and corrective effects on liver biochemical metabolism disturbances relative to TDF *in vitro* and *in vivo*, with TMF exhibiting marginally superior performance to TAF[11]. Given the relatively recent introduction of TMF to the Chinese market and the scarcity of real-world research data for the Chinese population, limited information exists regarding its safety and efficacy.

Consequently, we conducted a real-world investigation to assess the safety and effectiveness of TMF in treating patients with CHB in Southern China. Our findings indicated that, apart from a few mild side effects, TMF did not induce any serious reactions, thus establishing its safety for the treatment of CHB.

In our present study, we observed that the antiviral effectiveness of the TMF and TAF treatment groups was comparable across various patient subpopulations, including the general population, those with LLV, and HBeAg-positive and HBeAg-negative individuals. Throughout the 48-wk TMF treatment duration, no instances of virological breakthrough were encountered. In the 48th week, prior research demonstrated the sustained non-inferiority of VR rates between TMF and TDF treatments, regardless of HBeAg status[13]. Another study corroborated that TAF maintained its efficacy in inhibiting HBV replication relative to TDF, with no emergence of virologic resistance[18]. These findings align with our results, substantiating the equivalent antiviral potency of TMF and TAF in patients with CHB following 48 wk of

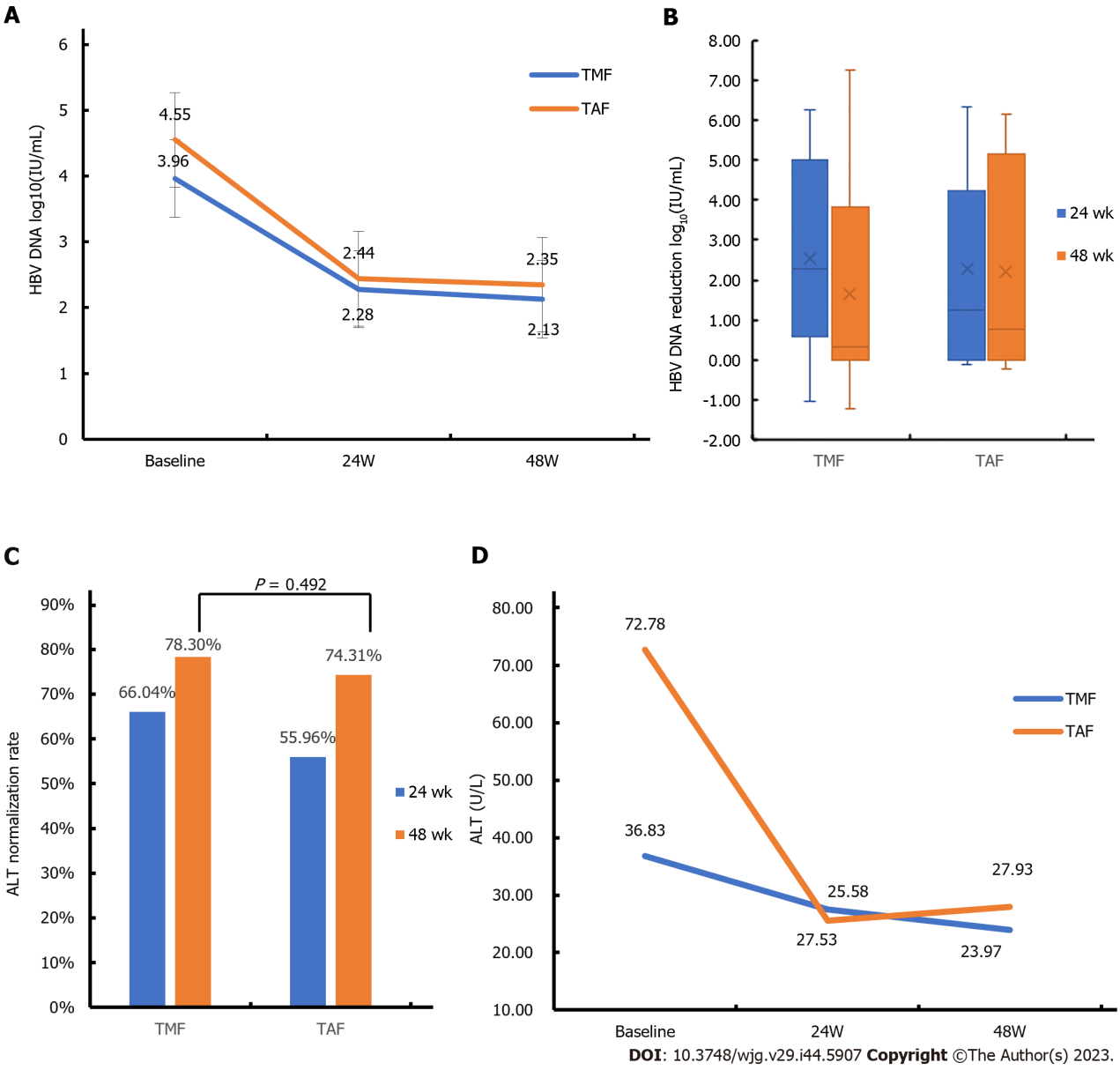

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Figure 3 Comparison of changes in hepatitis B virus DNA level, the ratios of alanine aminotransferase normalization and alanine aminotransferase level between the tenofovir amibufenamide and tenofovir alafenamide groups. A: Hepatitis B virus (HBV) DNA levels at baseline week, 24 wk and 48 wk in the tenofovir amibufenamide (TMF) and tenofovir alafenamide (TAF) groups; B: HBV-DNA reduction from 24 wk to 48 wk in the TMF and TAF groups; C: Alanine aminotransferase (ALT) normalization rate of TMF and TAF groups at 24 and 48 wk; D: ALT levels at baseline week, 24 wk and 48 wk in the TMF and TAF groups. TMF: Tenofovir amibufenamide; TAF: Tenofovir alafenamide; ALT: Alanine aminotransferase; HBV: Hepatitis B virus.

therapy.

The significance of achieving on-treatment ALT normalization in CHB patients has been emphasized in recent literature. A large-scale observational study revealed that patients who attained normal on-treatment ALT in the first 48 wk of antiviral treatment exhibited a reduced risk of hepatic events[19]. Liu *et al*[13] reported a notably higher ALT normalization rate for TMF-treated patients compared to those receiving TDF. Concurrently, Agarwal *et al*[18] observed a significantly greater ALT normalization rate among CHB patients treated with TAF relative to TDF recipients. In contrast, our study established that, at week 48, the rate of ALT normalization in the TMF group was comparable to that in the TAF group. These findings, taken together with the virological inhibition rate and biochemical response, confirm the equivalent efficacy of TMF and TAF in the treatment of CHB patients over a 48-wk period.

Prior research has demonstrated the nephrotoxic and osteotoxic effects of TFV[20], emphasizing the need to consider nephrotoxicity when developing TFV prodrugs. Renal impairment associated with TDF primarily arises from proximal tubulopathy[21], with the ensuing tubular dysfunction evidenced by increased serum Cr and reduced serum phosphate levels. The superior renal safety profile of TAF, compared to TDF, is attributable to the primary elimination of TAF through fecal excretion, with less than 1% excreted renally[22].

Since all NAs are eliminated *via* the kidneys, it is crucial for clinicians to monitor for progression of renal dysfunction [23]. The ability of TAF to reduce the risk of renal damage renders it a favorable option for CHB patients who have potential or associated risk factors for renal damage. Studies have confirmed that TAF can continuously enhance renal

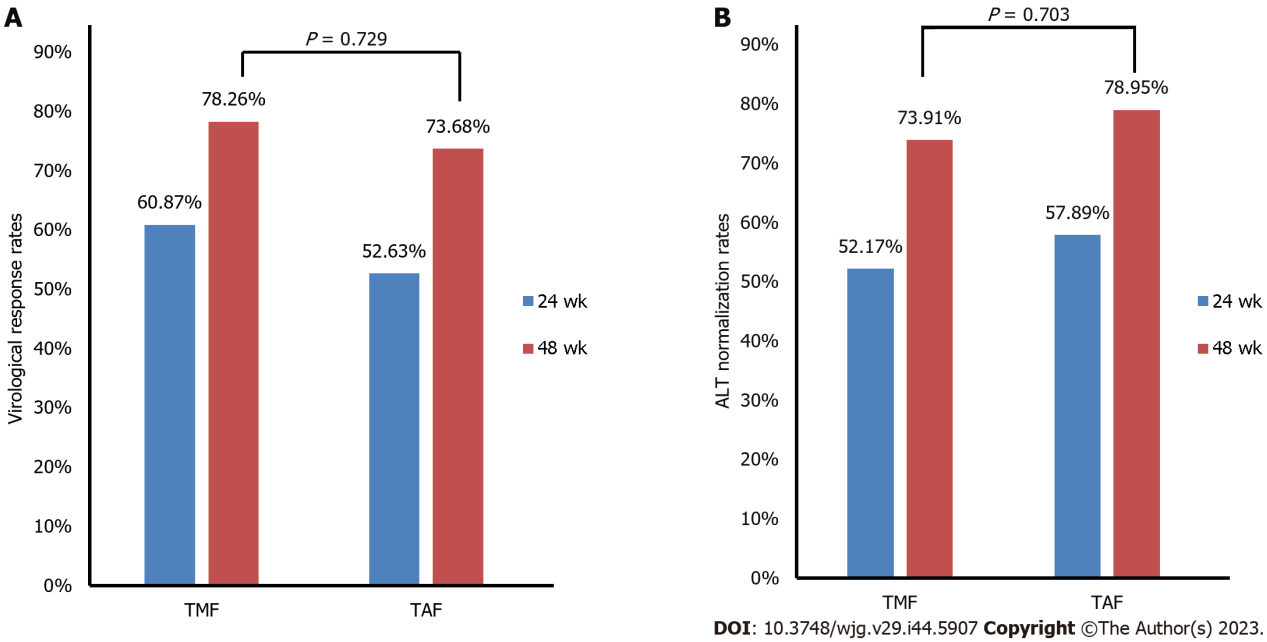

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Figure 4 Comparison of the virological response rate and the alanine aminotransferase normalization rate between tenofovir amibufenamide and tenofovir alafenamide groups in patients with cirrhosis. A: Virological response rates of tenofovir amibufenamide (TMF) and tenofovir alafenamide (TAF) groups at 24 and 48 wk; B: Alanine aminotransferase normalization rate of TMF and TAF groups at 24 and 48 wk. TMF: Tenofovir amibufenamide; TAF: Tenofovir alafenamide; ALT: Alanine aminotransferase.

function and maintain bone safety in patients with CHB[7,24]. Our findings indicate that the renal safety profile of the TMF group is comparable to that of the TAF group, suggesting that TMF could emerge as a novel therapeutic option for CHB patients, particularly those with an elevated risk of renal damage.

TDF and TAF are both efficacious nucleoside analogs, with TAF being preferred over TDF due to its lower incidence of renal and bone toxicities. However, there is evidence indicating a worsening of the lipid profile following the transition from TDF- to TAF-containing antiretroviral regimens in patients with HIV, as documented in clinical trials and observational studies[25,26]. Given the association between dyslipidemia, cardiovascular disease, and metabolic/non-alcoholic fatty liver disease-which may elevate the risk of HCC-it becomes imperative to determine whether TAF monotherapy alone adversely affects lipid profiles in CHB patients. This study compared lipid profile alterations in a cohort of CHB patients managed with either TMF or TAF over a 48-wk observation period. The findings indicated a significant increase in serum TC levels in the TAF group (4.3 ± 1.54 *vs*. 5.2 ± 0.99, mg/dL, $P < 0.05$) compared to the TMF cohort (4.83 ± 1.09 *vs* . 4.82 ± 1.52 mg/dL, $P > 0.05$). Therefore, this study suggests that TAF might contribute to the worsening of lipid profiles, whereas TMF appears to have a negligible impact on serum lipids. These conclusions are in contrast with the findings presented by Li *et al*[27] Despite these insights, the underlying mechanism by which TFV affects serum lipids remains to be elucidated. Further research is essential to fully understand this aspect. Nevertheless, physicians should monitor lipid levels vigilantly in patients at the higher end of the normal range when prescribing TAF.

Chronic HBV infection constitutes the primary cause of liver cirrhosis in China and may progress to decompensated liver cirrhosis and primary liver cancer, severely impacting the quality of life of patients. An increasing body of evidence indicates that sustained and effective antiviral therapy can reverse liver fibrosis and cirrhosis[4,28]. Therefore, our study evaluated the efficacy and safety of treatment in patients with cirrhosis.

In cirrhotic patients, the FIB-4 score reduction observed in the TAF cohort was significantly more pronounced than that in the TMF cohort. This could be partly attributed to the marginally higher ALT normalization rate associated with TAF treatment and the limited sample size of both groups. In contrast, no significant difference was discerned in the LSM values between the TMF and TAF groups. However, implications of these findings are not entirely clear, as it remains uncertain if the changes reflect true fibrosis regression or merely a biochemical variation. The observed decline in FIB-4 scores is noteworthy, warranting further research to ascertain if such biochemical alterations correspond to actual histological improvements. Where appropriate, liver tissue biopsies should be considered for conclusive evidence.

Our study is not without limitations. Firstly, the follow-up period of 48 wk may be insufficient to fully capture the antiviral effect, and a more extended timeframe would provide a clearer representation. Secondly, serum Cr and eGFR were employed as markers of renal function in this study, but incorporating indicators reflecting renal tubular function could bolster the study's reliability based on established clinical pharmacological research. Thirdly, the applicability of our findings is restricted, as TMF is not available worldwide. Fourthly, our study did not include data on bone health, such as that obtained *via* DEXA scans, and relied on serum Cr as a surrogate marker for renal function. Lastly, as a single-center retrospective study, future multi-center investigations with larger cohort and longer follow-up durations for CHB patients are essential to corroborate our findings.

CONCLUSION

In summary, our results indicate that TMF demonstrates comparable efficacy to TAF in terms of VR, ALT normalization rate, and renal safety among CHB patients in China. Nevertheless, TMF has an advantage over TAF in patients with hyperlipidemia. Additionally, TMF exhibits effectiveness and safety in cirrhotic patients. Collectively, these results suggest that TMF presents a viable therapeutic alternative for patients with CHB.

ARTICLE HIGHLIGHTS

Research background

Hepatitis B virus (HBV) infection may lead to cirrhosis and hepatocellular carcinoma, and the exploration of optimal antiviral drugs can improve patient prognosis.

Research motivation

Tenofovir amibufenamide (TMF) is a new antiviral drug with limited research on its safety and efficacy. Our research may provide new evidence for the treatment of patients with HBV infection.

Research objectives

To compare the efficacy and safety of TMF and tenofovir alafenamide (TAF) for 48 wk in patients with chronic hepatitis B (CHB). The primary outcome was the proportion of virological responses (VR) at 48 wk. Additional outcomes included the changes of renal function and lipid characteristic markers at weeks 24 and 48 compared to baseline.

Research methods

In this retrospective study, we enrolled a total of 587 patients who had been HBsAg positive for more than 6 mo. Of the enrolled patients, 215 were included in the final analysis and were divided into two groups based on their drug selection: The TMF group and the TAF group.

Research results

The VR rates of the TMF group and TAF group were comparable at 24 and 48 wk of treatment ($P > 0.05$). In patients with low-level viremia, hepatitis B e antigen (HBeAg) positive, and HBeAg negative, their VR rates are also similar. The alanine transaminase (ALT) normalization rate and renal safety of TMF are also comparable to those of TAF. However, total cholesterol levels increased in the TAF group ($P = 0.045$). In patients with liver cirrhosis, the renal safety, VR, and ALT normalization rate were comparable between the TMF group and the TAF group.

Research conclusions

TMF is as effective as TAF in treating CHB and has considerable safety. Moreover, TMF may have more advantages in lipid profile compared to TAF.

Research perspectives

The design and research of new nucleotide analogs should continue in the hope of achieving clinical cure of hepatitis B infection as soon as possible.

FOOTNOTES

Author contributions: Fu L designed the research and supervised the study; Peng WT, Chen KY, Zhou NQ, and Yang FL collected the clinical data; Peng WT, Liu JQ, and Jiang C performed the experiments and wrote the manuscript; Peng SF assisted in experiments; all authors critically reviewed the final manuscript.

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Informed consent statement: The study is a retrospective study that will maximize the protection of the rights and privacy of the study participants, and the content of the study and the results of the study do not involve personal privacy and commercial interests, exempt from informed consent.

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