Efficacy and safety of tenofovir alafenamide fumarate in nucleoside analogue treatment-naïve patients with chronic hepatitis B

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Abstract. Tenofovir alafenamide fumarate (TAF) is a first-line drug for the antiviral treatment of patients with chronic hepatitis B (CHB) in China. In the present study, the efficacy and renal safety of TAF were evaluated in treatment-naive patients with CHB. Patients with CHB who had not been previously treated with nucleoside analogues (NAs) were recruited before TAF treatment was initiated. Changes in the levels of hepatitis B virus (HBV) DNA, hepatitis B e antigen (HBeAg) and hepatitis B surface antigen (HBsAg) were analyzed at 24 and 48 weeks using immunoassays. In addition, liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) were analyzed using transient elastography, while alanine aminotransferase (ALT), triglyceride (TG), total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) levels, calcium (Ca) and inorganic phosphorus (IP) levels were measured using biochemistry assay. In addition, the estimated glomerular filtration rate (eGFR) was calculated. After 48 weeks, the ALT normalization rate was 95.24% (40/42), the complete virological response (HBV DNA <20 IU/ml) rate was 69.05% (29/42) and the HBeAg seroconversion rate was 8.57% (3/35). The levels of HBV DNA and HBsAg were significantly decreased from the baseline at 5.49±1.95 to 1.26±0.66 log$_{10}$ IU/ml and from 3.59±0.81 to 3.32±0.55 log$_{10}$ IU/ml after 48 weeks of treatment, respectively. Compared with that in the baseline measurements, LSM at 48 weeks was significantly decreased from 13.00±8.15 to 8.66±4.45 kPa. No significant differences were observed in the TG, TC, LDL-C, CAP, eGFR, Ca and IP measurements. According to the baseline ALT levels, patients were divided into group A [ALT ≤1 x upper limit of normal (ULN); ULN=50 U/l; n=21], group B (1 x ULN < ALT <2 x ULN; n=22) and group C (ALT ≥2 x ULN; n=18). A significant decrease in HBsAg levels was observed in group B (3.63±0.68 vs. 3.53±0.63 log$_{10}$ IU/ml) and group C (4.15±0.57 vs. 3.66±0.48 log$_{10}$ IU/ml) at 24 weeks compared with the baseline. In conclusion, TAF was found to be effective and safe in NA treatment-naive patients with CHB. Moreover, the higher the ALT levels, the more prominent the curative effect from TAF treatment. Therefore, NA treatment-naive CHB patients could benefit from TAF treatment in real world.

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Introduction

Tenofovir alafenamide fumarate (TAF) is a targeted prodrug of tenofovir [phosphonomethyl pentanedioic acid (PMPA)], a nucleotide reverse-transcriptase inhibitor. The active component, tenofovir diphosphate, is integrated into the viral DNA by hepatitis B virus (HBV) reverse transcriptase, resulting in the interruption of DNA strand synthesis, which inhibits hepatitis B virus replication (1). In November 2018, the China Food and Drug Administration approved TAF for the treatment of chronic hepatitis B (CHB) virus infection in adults and adolescents (2). The main goal of treatment is to maximize the long-term inhibition of HBV replication, prevent disease progression and the occurrence of hepatocellular carcinoma, so as to improve the quality of life and prolong the survival time of patients (2). As tenofovir (TFV) cannot be absorbed by the intestine through the intestinal wall due to its own chemical structure, it must have prodrugs. Tenofovir dipivoxil fumarate (TDF) and TAF are both prodrugs of TFV. Compared with TDF, another novel tenofovir prodrug, TAF exhibits superior plasma stability and can exert more prominent liver-targeting ability. In addition, TAF can achieve similar antiviral effects at

lower doses whilst also being associated with lower incidence of side-effects, including renal dysfunction and reduction of bone mineral density (3). Therefore, TAF has been listed as the first-line drug for the antiviral treatment of CHB in The Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2019 edition) in China (4). It has also been listed in the Guidelines for the Prevention and Treatment of Chronic Hepatitis B formulated by the American Association for the Study Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) (5). In China, compared with the old guidelines, the 2019 guidelines include more updates and highlights, expanding the indications of anti-viral therapy (4). Antiviral therapy should be recommended for patients with positive HBV DNA, elevated transaminase (excluding other reasons), normal transaminase but high-risk factors or liver tissue biopsy with inflammation and fibrosis. For the initial treatment of CHB, selection of potent and low resistance drugs is emphasized, where entecavir, TDF and TAF are recommended (6). However, the market time of TAF in China remains short and real-world data (RWD) are insufficient. Therefore, the present study was conducted to examine the efficacy and safety of TAF in the context of the new guidelines.

Patients and methods

Patients. All cases in the present study were derived from the follow-up study cohort of Tianjin Second People's Hospital (Tianjin, China) between December 2019 and September 2020. The present study retrospectively analyzed 212 patients with CHB who were initially treated with TAF. However, 151 patients were excluded, mainly due to incomplete follow up data.. Overall, a total of 61 patients entered the study. Among them, 45 patients were hepatitis B e antigen (HBeAg)-positive. A total of 61 patients (age, 42.13±12.30) were followed up for 24 weeks, of whom 42 were followed up for 48 weeks (age, 43.39±13.41), including 35 patients who were tested HBeAg-positive. According to the baseline ALT levels, 61 patients were divided into group A [ALT≤50 U/l; upper limit of normal (ULN)=50 U/l; n=21], group B (50 U/l < ALT <100 U/l; n=22) and group C (ALT ≥100 U/l; n=18). All patients met the diagnostic and therapeutic criteria of the Guidelines for the Prevention and Treatment of Chronic Hepatitis B in China (4), which were jointly formulated by the Chinese Society of Hepatology and Infectious Diseases in 2019. The present study was approved by the Medical Ethics Committee of Tianjin Second People's Hospital, was performed according to the principles of the Declaration of Helsinki and all patients provided written informed consent prior to participation in the study.

Criteria for patient selection. The inclusion criteria were as follows: i) Patients diagnosed with CHB who had never been treated with NAs previously; ii) patients with a liver stiffness measurement (LSM) indicating evidence of fibrosis but with normal alanine aminotransferase (ALT) levels. The ALT normal range was 9-50 U/l. The exclusion criteria were as follows: i) Patients with other hepatitis virus superinfec-tions (for example, hepatitis A, C, D, E and G), alcoholic liver disease, drug-induced liver injury or autoimmune liver disease; ii) pregnant or lactating women; iii) patients with decompensated cirrhosis, hepatocellular carcinoma and liver failure; and iv) patients with CHB who had previously been treated with NAs.

Treatment. All patients purchased and used TAF (developed and produced by Gilead Sciences, Inc.) in the outpatient department, who participated in the outpatient follow-up study after providing informed consent. The patients were treated with 25 mg TAF orally, once daily.

Detection methods and observation indices. All blood was collected on an empty stomach in the morning 1 week before TAF treatment (0 W), 24 weeks and 48 weeks. Blood biochem-istry was detected using a Hitachi 7180 automatic biochemical instrument (Hitachi, Ltd.). The volume of blood collected from each patient was 3 ml. ALT was tested through liver function. The ALT test kit (cat. no. AUZ8705) was provided by FujiFilm Wako Pure Chemical Corporation. The ALT normal value range was 9-50 U/l. Renal series tests included serum creati-nine (SCr), calcium and inorganic phosphorus. SCr test kit (cat. no. KH213) was provided by FujiFilm Wako Pure Chemical Corporation. The normal range of SCr was 57-97 μmol/l. The Modification of Diet in Renal Disease (MDRD) equa-tion was used to calculate the estimated glomerular filtration rate (eGFR) as follows: For females, eGFR = 170 x (SCr) - 1.234 x (age) - 0.179 x 0.79; and for males, eGFR = 170 x (SCr) - 1.234 x (age) - 0.179. The normal range of eGFR was 90-120 ml/min/1.73 m^2. The calcium (Ca; Arsenazo III method; cat. no. CA7290) and inorganic phosphorus (IP; phosphomo-lybdate method; cat. no. IP7340) assay kits were provided by Maccura Biotechnology Co., Ltd. The normal ranges of Ca and IP were 2.11-2.52 and 0.85-1.51 mmol/l, respectively. The triglyceride (TG; glycerol-3-phosphate-peroxidase method; cat. no. AUZ8611) and total cholesterol (TC; enzyme method; cat. no. AUZ8842) test kits were provided by Beckman Coulter Experimental System (Suzhou) Co., Ltd. The normal range values for TG and TC were 0.38-2.30 and 2.4-5.2 mmol/l, respectively. The low-density lipoprotein-cholesterol (LDL-C) test kit (direct method surfactant clearance method; cat. no. LD7152) was provided by Beijing Leadman Biochemistry Co., Ltd. The normal range values for LDL-C were 2.07-3.37 mmol/l. Blood lipid tests included TG, TC and LDL-C. The levels of hepatitis B surface antigen (HBsAg; cat. no. 6C36-78), HBeAg (cat. no. 6C32-77) and hepatitis B e antibody (HBeAb; cat. no. 6C34-77) were measured using the Architect I2000SR electrochemiluminescence immunoassay analyzer (Abbott Pharmaceutical Co., Ltd.). The volume of blood collected from each patient was 2 ml. HBsAg, HBeAg and HBeAb were obtained through Hepatitis B five items tests. The immunoassay kits were also provided by Abbott Pharmaceutical Co. Ltd. The HBsAg level was expressed in IU/ml and the detection range was 0-124,950 IU/ml. HBsAg <0.05 IU/ml was defined as negative. HBeAg and HBeAb levels were determined semi-quantitatively, and expressed as the ratio of absorbance to critical value (S/CO). HBeAg >1.0 S/CO and HBeAb <1.0 S/CO were defined as positive. HBeAg seroconversion rate was the ratio of HBeAg-negative and HBeAb-positive patients. HBV DNA level was tested
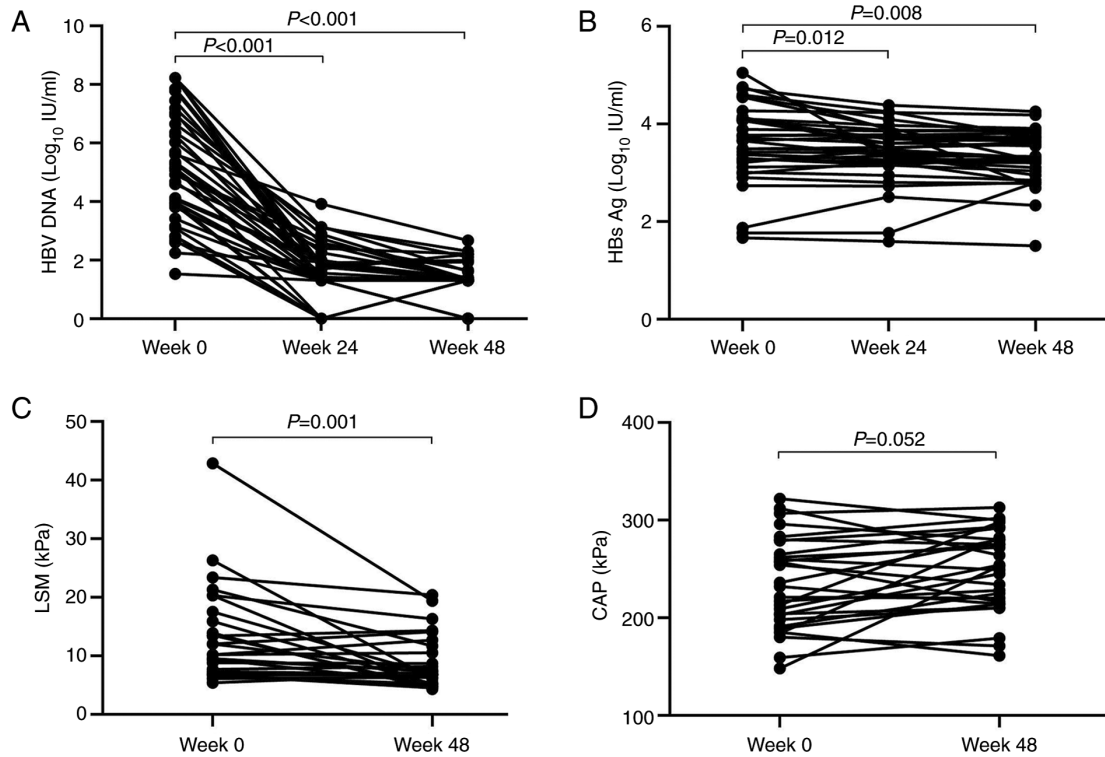
Figure 1. Effects of TAF on HBV DNA quantification, the HBsAg levels, LSM and CAP. The effects of TAF on (A) HBV DNA quantification and (B) HBsAg levels after 24 and 48 weeks of treatment. The effects of TAF on (C) liver stiffness and (D) CAP 48 weeks after treatment. TAF, tenofovir alafenamide fumarate; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; LSM, liver stiffness measurement; CAP, controlled attenuation parameter.

using highly sensitive HBV DNA detection. The volume of blood collected from each patient was 5 ml. The highly sensitive HBV DNA (cat. no. 04894570190) was extracted and amplified using the Roche COBAS AmpliPrep automatic nucleic acid separation and purification instrument (Roche Molecular Diagnostics). The detection reagent was provided by Roche Diagnostics. The detection limit was 20 IU/ml, as the early virological negative rate of HBV DNA was defined as the proportion of HBV DNA <20 IU/ml at 12 weeks, but this was not included in the present article.

The complete virological response rate was defined as the rate of patients with HBV DNA <20 IU/ml. All tests were performed at the Institute of Liver Disease, Tianjin Second People's Hospital (Tianjin, China). The LSM and controlled attenuation parameter (CAP) were measured through transient elastography and used FibroScan® 502 touch (Echosens). The normal range values for LSM and CAP were 7.3 kPa and 238 dB/m, respectively. LSM and CAP ranges were 2.4-75 kPa and 100-400 dB/m, respectively.

Statistical analysis. Statistical evaluation was conducted using the SPSS 21.0 statistical software (IBM Corp.). Continuous data were expressed as the mean ± standard deviation. Comparisons between two groups of data were assessed using Student's paired t-tests. Comparisons at three time points were assessed using one-way repeated measures ANOVA followed by paired t-tests with Bonferroni's correction. Kruskal-Wallis test followed by Dunn's post hoc test was used to compare the levels of HBV DNA and HBsAg among the three groups A-C. Categorical count data were analyzed using the χ^2 test. $P<0.05$ was considered to be the point of minimal statistical significance for all

Table I. Baseline characteristics of patients with chronic hepatitis B initially treated with TAF (n=61).

Parameter	Data
Age, years	43.64±14.98
Male proportion	45 (73.8)
Hepatitis B e antigen-positive proportion	45 (73.8)
Cirrhosis proportion	7 (11.5)
Proportion with abnormal ALT levels	40 (65.6)
ALT level, U/l	188.17±97.71
Hepatitis B virus DNA quantification, $\log_{10}$ IU/ml	5.49±1.95
Hepatitis B surface antigen quantification, $\log_{10}$ IU/ml	3.59±0.81
Liver stiffness measurement, kPa	13.00±8.15
Controlled attenuation parameter, dB/m	234.62±47.38
Estimated glomerular filtration rate, ml/min/1.73m²	105.28±12.45
Calcium, mmol/l	2.34±0.12
Inorganic phosphorus, mmol/l	1.11±0.19

Data are either presented as N (%) or mean ± standard deviation. ALT, alanine aminotransferase.

differences. Before data analysis, the test for homogeneity of variance was required, and a normality test was performed by the Shapiro-Wilk test.
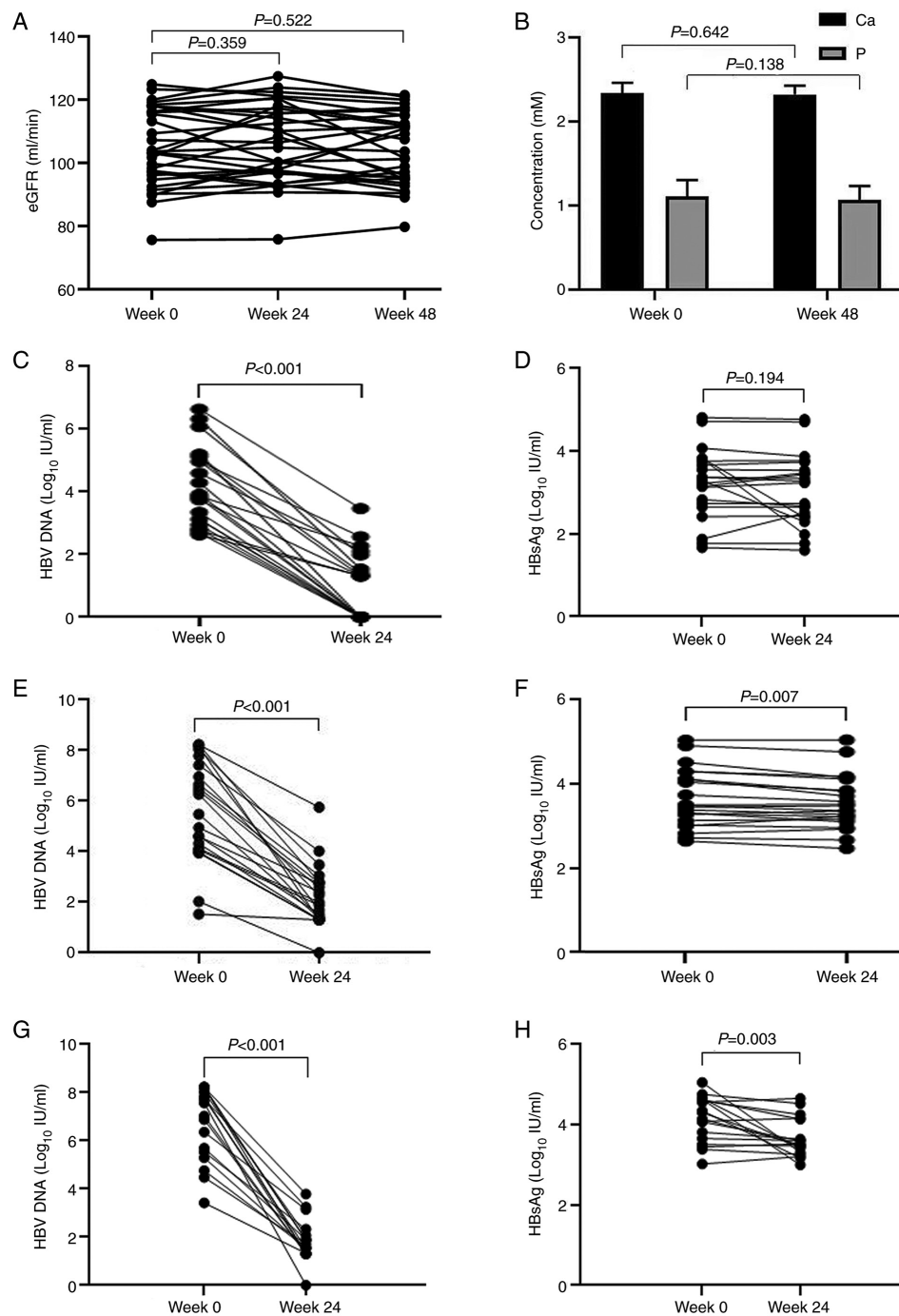
Figure 2. Renal safety of TAF and changes in HBV DNA and HBsAg levels in the three groups before and after 24 weeks of TAF treatment. (A) Changes in eGFR after 24 and 48 weeks of TAF treatment. (B) Changes in Ca and IP after 48 weeks of TAF treatment. Changes in (C) HBV DNA and (D) HBsAg levels in group A before and after 24 weeks of TAF treatment. Changes in (E) HBV DNA and (F) HBsAg levels in group B before and after 24 weeks of TAF treatment. Changes in (G) HBV DNA and (H) HBsAg levels in group C before and after 24 weeks of TAF treatment. TAF, tenofovir alafenamide fumarate; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; eGFR, estimated glomerular filtration rate; Ca, calcium; IP, inorganic phosphorus.

Results

Basic information of the patients. Among the 61 patients, 45 were male (73.8%) and 45 patients tested positive for HBeAg (73.8%). In addition, there were seven cases of liver cirrhosis (11.5%). The baseline level of ALT was 188.17±97.71 U/l, the proportion of patients with abnormal ALT levels was 65.6% (40/61), the quantitative HBV DNA value was 5.49±1.95 $\log_{10}$ IU/ml and the quantitative HBsAg value was 3.59±0.81 $\log_{10}$ IU/ml (Table I).

Efficacy evaluation after 24 and 48 weeks of TAF treatment. After 24 and 48 weeks of TAF treatment, the proportion patients with ALT returning to normal levels was 52.46 (32/61) and 95.24% (40/42), respectively (P<0.05). The complete virological response rate (patients with HBV DNA levels <20 IU/ml) was 39.34 (24/61) and 69.05% (29/42) on weeks 24 and 48, respectively (P<0.05). The HBeAg seroconversion rate was 8.57% (3/35) and the HBsAg-negative rate was 0 at 48 weeks. The mean HBV DNA levels among all patients at baseline was 5.49±1.95 $\log_{10}$ IU/ml (Table I), which reached 1.61±0.96 (P<0.001 vs. baseline) and
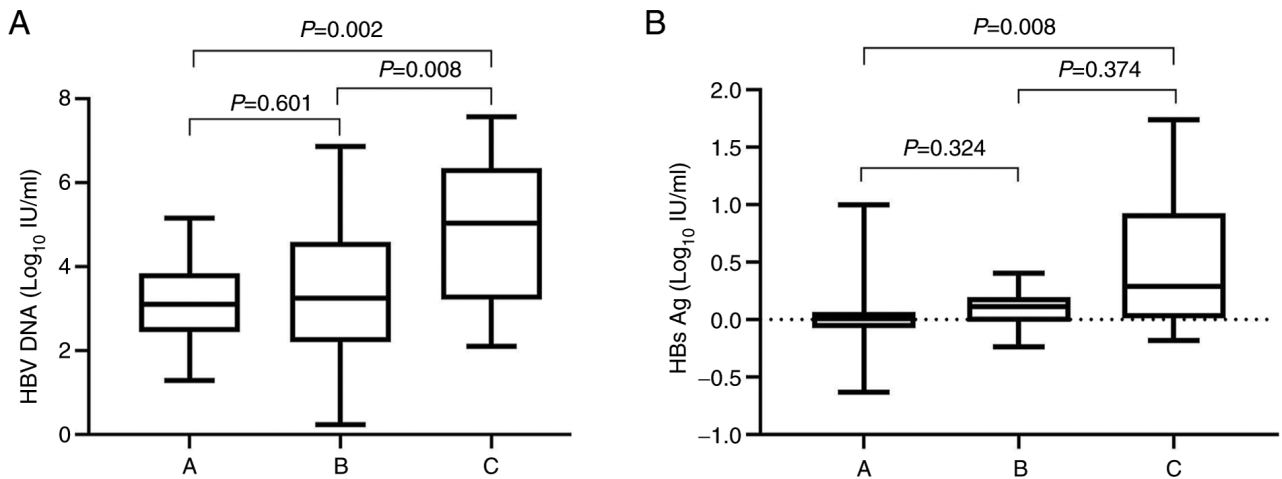
Figure 3. Effect of TAF on HBV DNA and HBsAg levels in the three groups. (A) Comparison of HBV DNA levels in the three groups. (B) Comparison of HBsAg in the three groups. TAF, tenofovir alafenamide fumarate; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen.

1.26 ± 0.66 $\log_{10}$ IU/m ($P<0.001$ vs. baseline) at 24 and 48 weeks, respectively (Fig. 1A). The HBsAg level was 3.59 ± 0.81 $\log_{10}$ IU/m at baseline (Table I), which reached 3.42 ± 0.61 ($P<0.05$ vs. baseline) and 3.32 ± 0.55 $\log_{10}$ IU/ml ($P<0.01$ vs. baseline) at 24 and 48 weeks, respectively (Fig. 1B). The LSM after 48 weeks of TAF treatment was 8.66 ± 4.45 kPa. Compared with the baseline value of 13.00 ± 8.15 kPa (Table I), the difference was statistically significant ($P<0.01$; Fig. 1C). The CAP values before and 48 weeks after treatment were 234.62 ± 47.38 (Table I) and 248.59 ± 41.51 dB/m, respectively (Fig. 1D).

Safety assessment after 48 weeks of TAF treatment. The eGFR was 105.28 ± 12.45 ml/min/1.73 m^2 at baseline (Table I), which then reached 106.31 ± 12.40 and 104.39 ± 11.33 ml/min/1.73 m^2 at 24 and 48 weeks, respectively (Fig. 2A). The Ca value was 2.34 ± 0.12 (Table I) and 2.32 ± 0.10 mmol/l at baseline and 48 weeks, respectively (Fig. 2B). The IP value was 1.11 ± 0.19 (Table I) and 1.07 ± 0.16 mmol/l at baseline and at 48 weeks, respectively (Fig. 2B).

Comparison of treatment efficacy in the different groups according to the ALT level. In group A, which was normal at baseline for all ALT levels, the early negative rate of HBV DNA was 52.38% (11/21) and the HBV DNA quantification was 4.10 ± 1.23 $\log_{10}$ IU/ml before treatment and 0.97 ± 1.07 $\log_{10}$ IU/ml after 24 weeks of treatment ($P<0.001$; Fig. 2C). After 24 weeks of treatment, the HBsAg level changed from 3.22 ± 0.85 to 3.06 ± 0.87 $\log_{10}$ IU/ml (Fig. 2D). In group B, the early normalization rate of ALT was 84% (18/22) and the negative rate of HBV DNA was 24% (5/22). HBV DNA quantification was 5.69 ± 2.01 $\log_{10}$ IU/ml before treatment and 2.24 ± 1.13 $\log_{10}$ IU/ml after 24 weeks of treatment ($P<0.001$; Fig. 2E). The level of HBsAg decreased from 3.63 ± 0.68 to 3.53 ± 0.63 $\log_{10}$ IU/ml ($P<0.01$; Fig. 2F). In group C, the normalization rate of ALT was 73.68% (13/18) and the negative rate of HBV DNA was 26.31% (5/18) after 24 weeks of treatment. HBV DNA quantification was 6.79 ± 1.56 $\log_{10}$ IU/ml before treatment and 1.89 ± 0.77 $\log_{10}$ IU/ml after 24 weeks of treatment ($P<0.001$; Fig. 2G). The levels of HBsAg decreased from 4.15 ± 0.57 to 3.66 ± 0.48 $\log_{10}$ IU/ml ($P<0.01$; Fig. 2H). The decreased levels of HBV DNA among three groups were as
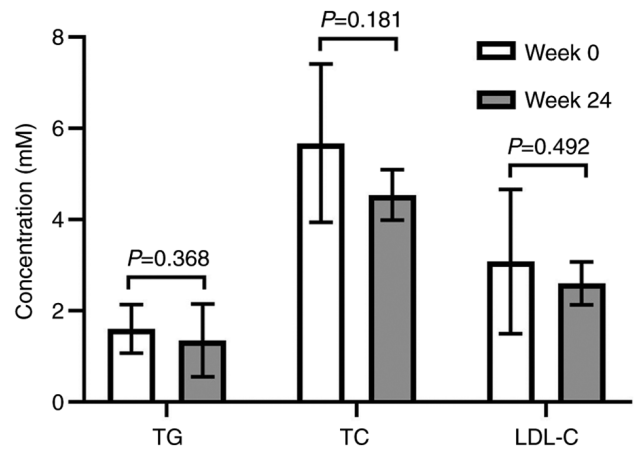

Figure 4. Effect of TAF on serum lipid parameters. The effects of TAF on serum lipid parameter at 48 weeks. TAF, tenofovir alafenamide fumarate; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein-cholesterol.

follows: Group A vs. group B ($P=0.601$), group A vs. group C ($P=0.002$) and group B vs. group C ($P=0.008$). The decreased levels of HBsAg among three groups were as follows: Group A vs. group B ($P=0.324$), group A vs. group C ($P=0.008$) and group B vs. group C ($P=0.374$). In addition, compared with group A and group B, levels of HBV DNA and HBsAg were increased by the most significant extent in group C before and 24 weeks after treatment ($P<0.05$; Fig. 3A and B).

After 48 weeks of TAF treatment, the TG levels (1.35 ± 0.80 mmol/l) were decreased compared with the baseline value (1.60 ± 0.53 mmol/l), whereas the TC level (4.54 ± 0.55 mmol/l) was decreased compared with the baseline value (5.68 ± 1.74 mmol/l) and the LDL-C level (2.60 ± 0.47 mmol/l) was decreased compared with the baseline value (3.08 ± 1.58 mmol/l). However, no statistical significance was observed (Fig. 4).

Discussion

HBV infection remains a global health concern due to its high incidence and mortality rates. According to the estimates made

by the World Health Organization (WHO) in 2016, there were ~292 million individuals infected with HBV worldwide (7). There is sufficient evidence to indicate that CHB is a major cause of liver failure and hepatocellular carcinoma (8,9). To reduce the risk of HBV infection, Anti-hepatitis B vaccinations and perinatal antiviral treatment, which are effective and safe (10), have been applied. TAF is a phosphonamide prodrug of tenofovir that is converted into its corresponding active metabolite tenofovir diphosphate, which is effective against both HBV and HIV infection (4,11). In view of the shortest marketing time of TAF in China, the lack of RWD derived from the medical environment and insufficient information reflecting the actual diagnosis, treatment process and health status of patients available, the present study aimed to investigate the efficacy of TAF in patients with CHB. The majority of data on the efficacy and safety of TAF in patients with chronic HBV infection were obtained from global multicenter, randomized, double-blind, controlled studies (12-14).

In the present study, results after 24 and 48 weeks of TAF treatment revealed that the ALT normalization and complete virological response rates were gradually increased as the duration of TAF treatment increased, where the HBeAg seroconversion rate was 8.57% at 48 weeks, similar to 10% reported in a previous study on TAF (4). In addition, the ALT normalization rate of ALT after 24 weeks of TAF treatment was only 52.46%, which was <81.8% (13) but increased to 95.24% at 48 weeks, which was higher compared with 72% and 83% reported by previous TAF global phase III clinical trials (6,8). In Study 108, 425 patients with CHB who were tested HBeAg-negative were enrolled, whilst 873 patients tested positive for HBeAg were enrolled in Study 110 (8). It was hypothesized that the reason for the above situation was that the cases in the present study were derived from the 'real world', where some patients with abnormal liver function had unstable transaminase activity during the early stages of antiviral treatment. As the antiviral treatment time increases, HBV DNA levels were reduced, where some patients may have taken hepatoprotective drugs, resulting in a significant increase in the normalization rate of ALT at 48 weeks.

In the present study, in which patients with HBeAg-positive CHB accounted for 73.8% of the cases, the HBV DNA response rate (HBV-DNA <20 IU/ml) at 24 weeks of TAF treatment was 39.34%, which was higher compared with the value of 36.4% obtained in the study by Ibrahim *et al* (15). Considering HBV DNA response rate was HBV-DNA <10 IU/ml in the study by Ibrahim *et al* (15), this was likely due to the different sensitivities of the tests used for HBV DNA detection between the two studies. In addition, the proportion of HBeAg-positive patients in the study by Ibrahim *et al* (15) was 75.4%, differed from the present study's follow-up cases, which could have resulted in differences in the HBV DNA level at baseline and differences in the complete virological response rate after 24 weeks of TAF treatment. In the present study, the seroconversion rate of HBeAg at 48 weeks was consistent with that in Study 110 (10%) (8). Results of the present study demonstrated that TAF effectively inhibited viral replication whilst also alleviating liver inflammation and fibrosis, which is consistent with findings previously reported regarding the effects of TAF (16-19). It was previously demonstrated that the annual incidence of spontaneous HBsAg clearance worldwide

is 1-2% (20). However, data on TDF treatment for patients with HBeAg-positive CHB after 5 years demonstrated that the HBsAg clearance rate is only 10% (21). In the present study, after 48 weeks of TAF treatment, although the overall HBsAg level was significantly lower compared with that at baseline, there was no HBsAg clearance. Therefore, TAF could not affect the low HBsAg clearance rate, meaning that NA would generally require long-term treatment plans (22,23).

For patients testing positive for serum HBV DNA with abnormally elevated levels of ALT (excluding elevated ALT levels due to other causes), with normal ALT levels but with high-risk factors or liver biopsy results indicating inflammation and fibrosis, the 2019 Guidelines recommended the initiation of antiviral therapy, which is higher than the grade of evidence and recommendation made in the 2015 version Guidelines (24,25). Previous studies performed a large number of histopathological examinations on the liver tissues from patients with CHB with normal ALT levels, which found varying degrees of liver inflammation, necrosis and fibrosis (26-28). Therefore, by comparing changes in the HBV DNA and HBsAg levels among the normal ALT (group A) and abnormal ALT (group B and group C) groups, the present study found that TAF exerted a potent inhibitory effect on viral replication in the different subgroups. Additionally, these aforementioned results also confirmed that ALT levels did not affect the inhibitory effects of TAF on HBV DNA, which was consistent with previous findings (29). Although TDF and TAF are most effective in both HBeAg-positive and -negative populations, TAF is more effective in general (29). Although abnormal ALT is no longer the most important indication for antiviral treatment in the new guidelines (4), it was found that the higher the ALT levels during the course of TAF treatment, the larger the decrease observed in the HBV DNA and HBsAg levels. It is considered that the increase in ALT levels may affect the process of HBV clearance (30). Therefore, it is suggested that high levels of inflammation during early stages of antiviral therapy may lead to improved virological inhibition and immune clearance. However, whether the more potent liver-targeting effects of TAF will lead to potential immune regulation warrants further investigation. Tong *et al* (31) reported that low levels of HBV DNA (<2,000 IU/ml) and HBsAg (<1,000 IU/ml) were the basic criteria for defining low risk of hepatocellular carcinoma. Results of the present study demonstrated that TAF potently reduced HBV DNA and HBsAg levels in 24 weeks, particularly in the population with elevated ALT levels. Therefore, long-term observation of the effects of TAF treatment on the risk of hepatocellular carcinoma may become the focus of further research.

Considering the good stability of TAF in plasma and the high efficiency of hepatocyte-targeted delivery, only a <1/10 of the TDF dose (300 mg) required can achieve similar antiviral effects (6,8). According to data from a previous clinical trial (32), this difference with TDF may improve the safety of TAF, particularly in patients with abnormal renal function and bone mineral density. A recent study (33) also confirmed that TAF treatment significantly reduced the incidence of renal adverse events during long-term antiviral treatment, which is almost consistent with the results of the present study. The eGFR, Ca and IP exhibited no significant changes before and after TAF treatment, suggesting that TAF exerted little to no

nephrotoxicity after short-term treatment. A previous study demonstrated that transforming TDF into TAF significantly improved the eGFR of patients (34), which further supports the renal safety of TAF. Although previous studies have indicated that the conversion from TDF to TAF can increase blood lipid and TC levels due to the increasing LDL-C, the ratio of TC/high-density lipoprotein remain unaltered (21,35). The present study demonstrated that TAF treatment did not affect blood lipid levels or the degree of hepatic steatosis within 48 weeks. Therefore, whether TAF may increase the degree of hepatic steatosis require further investigation.

In conclusion, as demonstrated by the findings of the present study, TAF is effective and safe for NA-naive patients with CHB, leading to a higher biochemical and virological response rate, decreased HBsAg levels and improved liver fibrosis with a stable renal safety profile. Further analysis revealed that the higher the baseline ALT levels, the more significant the reduction in HBV DNA and HBsAg levels after 24 weeks. However, due to the small sample size and short follow-up time, the data may be biased and the efficacy of TAF cannot be evaluated more objectively. In addition, renal tubular and bone indicators were not evaluated, which renders it impossible to fully evaluate the safety of TAF. At present, in terms of RWD, particularly in China, there remains to be a lack of clinical randomized, double-blind, controlled studies on TAF with large sample sizes. Therefore, difficulty remains to fully address the efficacy and potential safety problems of TAF. Therefore, further clinical research is required to provide sufficient evidence on the efficacy and safety of TAF.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

YZ, WW and PC were responsible for the conception and design of the study. WK and FL were responsible for acquisition of data. BJ, LJ and HL were responsible for data interpretation. All authors have read and approved the final manuscript. PC and WK confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved by the Medical Ethics Committee of Tianjin Second People's Hospital (Tianjin, China), was performed according to the principles of the Declaration of Helsinki and all patients provided written informed consent prior to participation in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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