Original Article
Cent Asian J Med Sci. 2020 December;6(4):222-231 https://doi.org/10.24079/CAJMS.2020.12.003

Central Asian Journal of Medical Sciences
CAJMS

Antiviral Efficacy and Safety of Tenofovir Alafenamide Compared to Tenofovir Disoproxil Fumarate in the Treatment of Chronic Hepatitis B

Tuvshinbayar Narangerel[1,2], Amaraa Ravdan[1], Gegeebadrakh Baljinnyam[1], Burmaajav Badrakh[2], Baatarkhuu Oidov[3]

[1]Department of Gastroenterology, State Second Central Hospital, Ulaanbaatar, Mongolia; [2]Department of Infectious Diseases, Ach University of Medical Sciences, Ulaanbaatar, Mongolia; [3]Department of Infectious Diseases, School of Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia

Submitted: May 2, 2020
Revised: May 10, 2020
Accepted: November 27, 2020

Corresponding Author
Tuvshinbayar Narangerel, MSc.
Department of Gastroenterology,
State Second Central Hospital,
Ulaanbaatar 13343, Mongolia
Tel: + 976-99059493
Fax: 976-70150225
E-mail: n.tuvshinbayar0403@gmail.com

Objectives: To provide compare of the efficacy and safety tenofovir alafenamide (TAF) to tenofovir disoproxil fumarate (TDF) in patients with HBeAg-negative and HBeAg-positive chronic hepatitis B. **Methods:** We performed a randomized, unblinded, non-inferiority study in which patients with compensated cirrhosis (Child-Pugh A and B stage) between 18-70 years old with a positive chronic hepatitis B test were randomized to receive either TAF, TDF, or were switched from TDF to TAF. The primary efficacy endpoint was the proportion of patients with HBV-DNA < 29 IU/ml at week 48. **Results:** The efficacy endpoint, an HBV-DNA < 29 IU/ml at weeks 48, was achieved by 251 (79.9 %) of 314 patients receiving TAF, which was not significantly different from the 113 (74.8 %) of 151 patients receiving TDF. After 48 weeks of treatment, patients receiving TAF had significantly smaller bone mineral density reductions than patients receiving TDF. At week 48, the median decrease in eGFR was significantly less in the TAF recipients than the TDF recipients. **Conclusion:** TAF treatment has the same efficacy as TDF treatment. However, TAF treatment had a better safety profile than TDF. Patients receiving TAF had a significantly smaller median decrease in the eGFR by the Cockcroft-Gault equation than patients receiving TDF.

Keywords: Hepatitis B, Tenofovir Alafenamide Fumarate, Tenofovir Disoproxil Fumarate, Adverse Effects, Safety

Introduction

Worldwide, an estimated two billion people have evidence of Hepatitis B viral infection, and approximately 240 million have chronic hepatitis B (CHB). In a previous 2017 study, a healthy representative group of Mongolian adults was screened for hepatitis B virus (HBV). These data showed that 11.1 % of the Mongolian adult population was infected with HBV [1].

Patients with chronic HBV may present in 1 of 4 states of infection: 1) state of immune tolerance, 2) with hepatitis B e antigen (HBeAg) positive CHB indicating active viral replication, 3) with hepatitis B surface antigen (HBsAg) indicating they are inactive carriers of HBV or have CHB, and 4) with HBeAg negative CHB. Several factors, such as serum HBV viral DNA concentrations, HBeAg status, and serum aminotransferases such as alanine aminotransferase (ALT), are useful in monitoring treatment and predicting long-term outcome [2].

Seven medications have been formally licensed by the United States Food and Drug Administration (FDA) for the treatment of chronic hepatitis B virus (HBV) infection: interferon-α, pegylated interferon-α, lamivudine, adefovir dipivoxil, entecavir, telbivudine, tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF). These drugs currently fall into two classes of treatments for chronic HBV infection: interferons and nucleoside or nucleotide analogs [3]. HBV-DNA polymerase is the main target for the nucleos(t)ide analogs such as TAF and TDV.

Treatment guidelines from the American Association for The Study of Liver Diseases (AASLD) 2018 Hepatitis B Guidance complements the AASLD 2016 Practice Guidelines for the Treatment of Chronic Hepatitis B and updates the previous HBV guidelines from 2009. The updated 2018 guidance for CHB includes the treatment updates since the 2016 HBV guidelines (notably the use of tenofovir alafenamide). It also provides guidance on screening, counseling, and prevention, specialized virologic and serologic tests, monitoring of untreated patients. It likewise provides guidance for treating HBV in special populations, including persons with viral coinfections, acute hepatitis B, recipients of immunosuppressive therapy, and transplant recipients. Since the publication of the 2016 AASLD Hepatitis B Guidelines, tenofovir alafenamide (TAF) has been approved for treating CHB by the Ministry of Health of Mongolia [4, 5].

The long-term safety of these nucleos(t)ide analogs is a concern. A low incidence of adverse effects with the use of TDF, including renal dysfunction with Fanconi-like syndrome and decreased bone mineral density leading to fractures, have been reported previously [5]. Long-term nucleos(t)ide analog treatment has been shown to be effective in suppressing HBV replication to levels below the detection limits in PCR assays, in histologic improvement, and in reducing the incidence of hepatocellular carcinoma. However, the loss or seroconversion of HBsAg is very rare. Because of this, long-term treatment is required in almost all cases [6, 7], sometimes leading to drug resistance, renal impairment, and bone mineral density (BMD) loss.

The requirement for long-term therapy in chronic HBV highlights the importance of their efficacy and safety profile in the Mongolian adult population. However, their true clinical relevance is yet to be established, and further studies with long-term clinical follow-up data are needed. Our study's primary objective was to compare the short-term efficacy, safety, and tolerability of tenofovir alafenamide and disoproxil fumarate in treatment-naive and treatment-experienced adults with HBeAg-negative and HBeAg-positive chronic hepatitis B virus infection.

Materials and Methods

Study population

A total of 603 patients were enrolled in our study, with 228 HBeAg-negative patients and 375 HBeAg-positive patients. Patients with a history of prior malignancy except skin cancer, significant concurrent medical illness, such as cardiac and renal diseases, hepatocellular carcinoma, intractable ascites that could not be controlled by medical therapy, isolated bone or brain metastases, chronic use of antiviral therapy known to have activity against HBV infection apart from study medications (e.g., lamivudine, adefovir dipivoxil) within the previous 6 months and female patients who were pregnant or breastfeeding were excluded from the study. Participants were screened for inclusion in the study if they had compensated cirrhosis (Child-Pugh A and B stage), were 18-70 years old, and had a positive HBV test. For both the HBeAg positive and negative groups, the principal inclusion criteria were a plasma HBV-DNA level ≥ 20,000 IU/mL, ALT ≥ 60 U/L for males or ALT ≥ 38 U/L for females that did not exceed ten times the upper limit of ALT normal and an estimated creatinine (Cr) clearance ≥ 50 mL/min (by Cockcroft-Gault method). Of these, 314 patients were randomized to the

TAF treatment group, 151 patients were randomized to the TDF treatment group, and 138 patients switched from TDF to TAF upon enrollment in our study.

Treatment groups

The patients were randomized into one of three unblinded treatment groups: 1) TDF 300 mg orally once daily, 2) TAF 25 mg orally with food once daily, and 3) TDF-treated patients who were TDF-resistant or developed renal impairment or BMD loss who desired to be switched from TDF to TAF when TAF became available in Mongolia. Randomization of the first two treatments was stratified by plasma HBV-DNA level ≥ 7 to < 8 log10 IU/mL, ≥ 8 log10 IU/mL and oral antiviral treatment status (treatment-naive vs. treatment-experienced) at screening. Randomization was performed using an interactive web response system.

Endpoints

The primary efficacy endpoint was the proportion of patients with HBV-DNA < 29 IU/ml after weeks 48 of starting treatment. Other prespecified efficacy endpoints were the proportion of patients with HBsAg seroconversion to anti-HBs at week 48. Other prespecified efficacy endpoints were the proportion of patients with ALT normalization at week 48. Efficacy and safety outcomes at 48 weeks after starting treatment were evaluated, and adverse events tracked.

Statistical analysis

Descriptive statistics and frequency distributions were computed for all the variables. The data were tested for normality using the Shapiro-Wilk test. For continuous variables, one-way ANOVA was carried out for more than two groups, followed by Tukey multiple comparison tests if the ANOVA result was significant. Independent t-tests were used for comparing two groups. The Chi-square test was used for categorical data. Statistical significance was determined at a p-value lower than 0.05. All statistical analyses were performed using SPSS (version 25).

Ethical statement

The research study was approved by the Research Ethics Committee of Ach University of Medical Sciences (№19/01/01). All participants gave written informed consent.

Results

The general characteristics of the patients are summarized in Table 1. The recruited subjects came from different regions and places. Approximately one-third of participants were recruited from the provinces, with the remainder from the capital city (37.2% vs. 62.8%).

Table 1. General characteristics of the study population.

Variables	TAF 25 mg n = 314	TDF 300 mg n = 151	TDF-TAF n = 138	Total n = 603	p-value
Age groups	N (%)	N (%)	N (%)	N (%)	
<30	17 (5.4)	11 (7.3)	9 (6.5)	37 (6.1)	0.097
30-39	52 (16.6)	37 (24.5)	23 (16.6)	112 (18.6)	
40-49	124 (39.5)	51 (33.8)	44 (31.9)	219 (36.3)	
50-59	68 (21.6)	33 (21.8)	40 (29)	141 (23.4)	
> 59	53 (16.9)	19 (12.6)	22 (16)	94 (15.6)	
Gender					
Male	116 (36.9)	68 (45)	57 (41.3)	241 (39.9)	0.356
Female	198 (63.1)	83 (55)	81 (58.7)	362 (60.1)	
HBeAg					
Negative	125 (39.8)	57 (37.7)	48 (34.7)	230 (38.1)	0.089
Positive	189 (60.2)	94 (62.3)	90 (65.3)	373 (61.9)	
Regions					
Ulaanbaatar	183 (58.2)	59 (39)	91 (65.9)	379 (62.8)	0.685
Other	131 (41.8)	92 (61)	47 (34.1)	224 (37.2)	

The rate of participation was higher among women (362, 60.1%) than men (241, 39.9%, p = 0.051). There were no significant differences in the percentage of patients receiving TAF or TDF with an HBV - DNA level < 29 IU/ml in all the major subgroup analyses, including age (< 60 years or ≥ 60 years), gender, baseline HBV-DNA level (< 29 IU/ml), treatment adherence (< 95% or ≥ 95%), region (Ulaanbaatar city, other regions), baseline ALT by AASLD criteria range (ALT males - 30 U/l, females - 19 U/l).

There were no other significant between-group differences in secondary or other efficacy outcomes. A key prespecified secondary efficacy outcome was the proportion of patients with HBsAg loss or HBsAg seroconversion by week 48. More patients in the TAF group experienced HBeAg loss than in the TDF and TDF-TAF group 5 (1.6%) vs. 4 (2.6%) and 2 (2.1%), but this was not statistically significant (Figure 1).

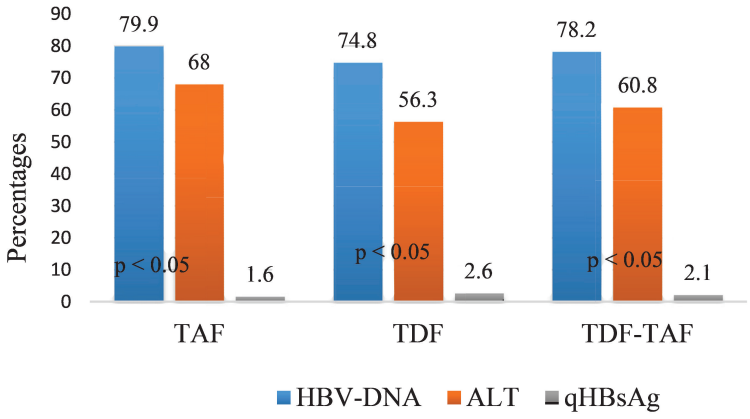

Figure 1. Primary and secondary antiviral efficacy endpoints in patients at weeks 48. TAF-tenofovir alafenamide fumarate, TDF - tenofovir disoproxil fumarate, TDF-TAF – switched from tenofovir disoproxil fumarate to tenofovir alafenamide. P-values are from chi-square analyses.

The primary efficacy endpoint, an HBV-DNA < 29 IU/ml at weeks 48, was achieved by 79.9% receiving TAF, which was non-inferior to the 74.8% of patients receiving TDF (95% confidence interval (CI 9.8 – 2.6); p = 0.250). At week 48, a significantly higher rate of ALT normalization was seen in the TAF group compared to the TDF group (68.0 vs. 56.3%, p = 0.001) (Table 2).

Table 2. Antiviral efficacy of groups

Variables	TAF 25mg n = 314	TDF 300mg N = 151	Proportional difference (CI)	p-value
HBV-DNA < 29IU/mL	251 (79.9%)	113 (74.8%)	1.8% (-3.6 to 7.2)	0.478
ALT-normalization†	214 (68%)	85 (56.3%)	17.9% (8.0 to 27.7)	0.001

†Using the American Association for the Study of Liver Diseases criteria of ≤ ALT 30 U/l for males and ≤ 19 U/l for females; ALT - alanine aminotransferase.

A total of 228 HBeAg-negative patients were randomized and received treatment with either TAF 25 mg, TDF 300 mg or were switched from TDF to TAF. The primary efficacy endpoint of an HBV-DNA level < 29 IU/ml at week 48 was achieved by 93.6% of patients receiving TAF, which was non-inferior to the 91.2% of patients receiving TDF and 93.4% of patients switching from TDF to TAF (p = 0.480). At week 48, a significantly higher proportion of patients with ALT normalization was seen in the TAF group compared to the TDF treated group (68% vs. 56.3%, p = 0.001). Still those proportions did not differ significantly from the TDF-TAF group (63%). Rates of HBsAg loss by week 48 were approximately 1% in all three groups regardless of which treatment was received (Table 3).

Table 3. Primary and secondary efficacy endpoints for HBeAg-negative patients at 48 weeks.

Variables	TAF 25mg	TDF 300mg	TDF-TAF	*p-value
	n = 125	n = 57	n = 46	
	N (%)	N (%)	N (%)	
HBV-DNA < 29 IU/mL	117 (93.6)	52 (91.2)	43(93.4)	0.480
ALT - normalization†	85 (68)	32 (56.3)	29 (63)	0.000
HBsAg loss	1 (1.2)	2 (1.1)	-	-

*Chi-square test; †Using the American Association for the Study of Liver Diseases criteria of ≤ ALT 30 U/l for males and ≤ 19 U/l for females; ALT - alanine aminotransferase.

A total of 375 HBeAg-positive patients were randomized and received treatment with either TAF 25 mg or TDF 300 mg or TDF-TAF. The primary efficacy endpoint of an HBV-DNA level < 29 IU/ml at week 48 was achieved in 70.9% of patients receiving TAF, 63.5% receiving TDF and 72.2% of patients receiving TDF to TAF with no significant differences (p = 0.260). At week 48, a significantly higher rate of ALT normalization was seen in the TAF group compared to the TDF group (45.5% vs. 38.5%, p = 0.046). Rates of HBsAg loss by week 48 were very low, and only one patient in the TAF group, two in the TDF and three patients in the TDF-TAF group achieved it p = 0.510 (Table 4).

Table 4. Primary and secondary efficacy endpoints for HBeAg-positive patients at 48 weeks.

Variables	TAF 25mg	TDF 300mg	TDF-TAF	p-value
	n = 189	n = 96	n = 90	
	N (%)	N (%)	N (%)	
HBV-DNA < 29 IU/mL	134 (70.9)	61 (63.5)	65 (72.2)	0.260
ALT-normalization†	86 (45.5)[a]	37 (38.5)[a]	46 (51.1)	0.017
HBsAg loss	1 (0.5)	2 (1)	3 (3.3)	0.510
HBeAg loss	15 (7.9)	9 (9.3)	11 (12.2)	0.450
HBeAg seroconversion	10 (5.2)	7 (7.2)	8 (8.8)	0.320

†Using the American Association for the Study of Liver Diseases criteria of ≤ ALT 30 U/l for males and ≤ 19 U/l for females; ALT - alanine aminotransferase.

After 48 weeks of treatment, patients receiving TAF had significantly smaller reductions in BMD than patients receiving TDF. At weeks 48, the median changes in eGFR were significantly less in the TAF recipients than the TDF recipients. None of the patients experienced serious renal-related adverse effects or proximal renal tubulopathy, including Fanconi syndrome, in either the TAF or TDF treatment groups. At week 48, patients treated with TAF had a significantly lower decrease in median eGFR levels than did those treated with TDF in both HBeAg-positive patients (TAF - 0.6 vs. TDF -5.3 mL/min, and TDF-TAF -2.0 mL/min p = 0.000) and HBeAg-negative patients (TAF -1.6 vs. TDF - 4.6 mL/min and TDF-TAF -2.4 mL/min p = 0.004) (Table 5, 6).

No patients with a normal T-score at baseline in either group developed osteoporosis, and there were no treatment-related fractures in either group. There was a significant improvement in creatinine clearance at week 48, and the patients on long-term TAF maintained a stable serum creatine. In HBeAg-positive patients the mean reduction from baseline BMD was significantly less at both the T score (mean change - 0.11% vs. - 1.61%, p < 0.000) and the Z score (mean change - 0.43% vs. -2.20%, p < 0.000) in the TAF, TDF-TAF groups than the TDF group (Table 5).

Table 5. Bone mineral density and kidney function at 48 weeks of treatment with TAF or TDF for HBeAg-positive chronic hepatitis B patients.

HBeAg-negative				
Variable	**TAF 25mg Mean ± SD**	**TDF 300mg Mean ± SD**	**TDF-TAF Mean ± SD**	***p-value**
T-score (%)	-0.11 ± 0.68[d]	-1.61 ± 1.37[d]	-1.1 ± 1.05	0.000
Z-score (%)	-0.43 ± 0.94[e]	-2.20 ± 1.66	-1.6 ± 1.18[e]	0.000
eGFR (ml/min)	-0.6 ± 0.97f	-5.3 ± 2.80[f]	-2.4 ± 1.23	0.000
Serum creatinine (mmol/l)	0.8 ± 1.01	2.6 ± 1.97[g]	1.5 ± 1.11[g]	0.021

*One-way ANOVA result; Tukey multiple post-hoc comparison result: [a]TAF ~ TDF, p = 0.026, [b]TAF ~ TDF-TAF, p = 0.046, [c]TAF ~ TDF, p = 0.012, [d]TAF ~ TDF, p = 0.038, [e]TAF~TDF-TAF, p = 0.001, [f]TAF~TDF, p = 0.05, [g]TDF~TDF-TAF, p = 0.001. All others were not significant; Z- score and T-score - bone mineral density of the ankle and proximal femur; eGFR - estimated glomerular filtration rate.

Similarly, in HBeAg-negative patients the mean reduction from baseline BMD in the TAF and TDF-TAF groups than the TDF group was significantly less for both the T-score (mean change - 0.28% vs. -2.11%, p < 0.000) and Z-score (mean change -0.89% vs. -2.25%, p < 0.000) (Table 6).

Table 6. Renal and bone safety at 48 weeks of treatment with TAF or TDF for HBeAg-negative chronic hepatitis B patients.

HBeAg-positive				
Variable	**TAF 25mg Mean ± SD**	**TDF 300mg Mean ± SD**	**TDF-TAF Mean ± SD**	***p-value**
T-score (%)	-0.28 ± 0.10[a]	-2.11 ± 1.53[a]	-1.51 ± 1.09	0.000
Z-score (%)	-0.89 ± 0.11[b]	-2.25 ± 1.60	-1.90 ± 1.23[b]	0.000
eGFR (ml/min)	1.6 ± 0.35[c]	4.6 ± 2.97[c]	2.0 ± 1.16	0.004
Serum creatinine (mmol/l)	0.8 ± 0.76	1.7 ± 1.59	1.2 ± 1.06	0.321

*One-way ANOVA result; Tukey multiple post-hoc comparison result: [a]TAF ~ TDF, p = 0.026, [b]TAF ~ TDF-TAF, p = 0.046, [c]TAF ~ TDF, p = 0.012, [d]TAF ~ TDF, p = 0.038, [e]TAF~TDF-TAF, p = 0.001, [f]TAF~TDF, p = 0.05, [g]TDF~TDF-TAF, p = 0.001. All others were not significant. Z- score and T-score - Bone mineral density of the ankle and proximal femur; eGFR - estimated glomerular filtration rate.

The most common adverse events were epigastric pain (TAF 3% vs. TDF 11% and TDF-TAF 8.6%), headache (TAF 0.6% vs. TDF 8.7% and TDF-TAF 2.8%), and nasopharyngitis (TAF 3.8% vs. TDF 1.9% and TDF-TAF 4.3%) through week 48. The most common grade 2 abnormality was an elevation of the ALT level (4, 1.1%), especially for HBeAg-positive patients. Of these, three (0.9%) patients treated with TAF and four (2.5%) with TDF and two (1.4%) with TDF-TAF experienced an ALT flare during the early treatment period, within 1-3 months, but all resolved without sequelae.

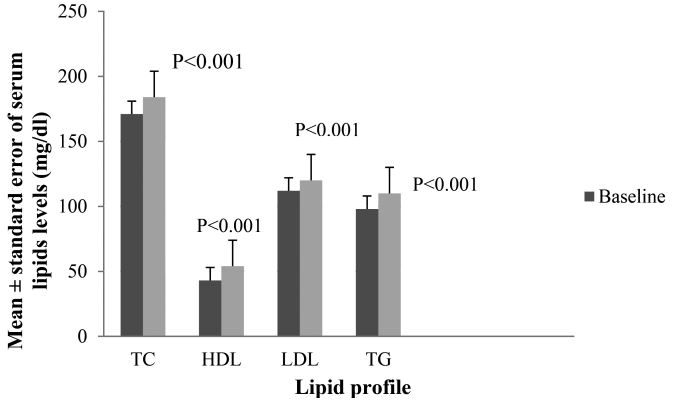

Figure 2. Change in hematic lipids at a median of 48 weeks after treatment tenofovir alafenamide and tenofovir disoproxil. TC-total cholesterol, HDL - high density lipoprotein, LDL - low density lipoprotein, TG – triglycerides. P-values are for paired t-tests.

All lipids increased significantly following treatment, with the mean TC for both treatments increasing from 171 ± 1.5 mg/dl before treatment to 184 ± 1.7 mg/dl after, mean HDL increasing from 43 ± 0.8 to 54 ± 0.6 mg/dl, mean LDL from 112 ± 1.3 to 120 ± 1.7 mg/dl and median TG from 98 ± 1.1 to 110 ± 1.4 mg/dl ($p < 0.000$ for all) (Figure 2).

Discussion

In 2012, 78 cases of liver cancer per 100,000 individuals were registered among the Mongolian population, with a very high prevalence of HBV/HDV coinfection. Data relating to the use of TAF in certain specific populations are currently limited. This underlines the importance of preventing HBV and the high risk of HDV superinfection among HBsAg positives.

Both TAF and TDF are prodrugs of tenofovir. However, TAF requires a much lower dose to achieve therapeutic levels of tenofovir, which implies that TAF may have less impact or notable harms associated with it than TDF, namely, bone-related disorders (fractures) and adverse renal outcomes. Given the bone and renal safety concerns associated with long-term TDF therapy, the more favorable pharmacological profile of TAF permits a marked (one-tenth) reduction in dosage. It thus reduces systemic exposure, potentially improving bone and renal safety. However, TAF has been shown to increase urine glucose levels (in 5% of TAF patients vs. 1% of TDF patients, $p = 0.0027$) and LDL-C levels > 300 mg/dL (in 4% of TAF patients vs. no TDF patients, $p = 0.0004$). These effects were not seen with TDF, although the majority of these patients with elevated urine glucose had pre-existing glycosuria at baseline or had risk factors that might contribute to elevated urine glucose levels. Given that HBV patients take these medications lifelong, the LDL increase can be a concern with long-term users of TAF. As well, the long-term clinical significance of differences in both renal and BMD changes between TAF and TDF is not known.

With clear evidence from major studies showing that TAF is safe, tolerable, and non-inferior to TDF in terms of achieving the primary endpoint (HBV-DNA levels < 29 IU/ml), in April 2017, the European Association for the Study of the Liver (EASL) added TAF to its list of recommended first-line therapies for CHB. It is presumed that the other liver societies, including the Asian Pacific Association for the Study of Liver (APASL) and the American Association for the Study of Liver Disease (AASLD), will do the same in their next guidelines [1, 3]. In two major clinical trials, comparing TDF to TAF, TAF-treated patients had significantly smaller decreases in bone mineral density at both the hip and spine in both HBeAg-positive and HBeAg-negative patients [8]. Patients treated with TAF in both studies also had smaller mean increases in serum creatinine, although the difference was only statistically significant for HBeAg-positive patients [3 ,4, 6]. An analysis of patients treated with TDF for 96 weeks and then switched to TAF experienced the same improvements in renal and BMD measures that occurred 24 weeks after the switch [5, 7].

The mechanism behind the bone toxicity associated with TDF is not entirely clear [8-15]. They found a high rate of HIV-infected patients on TDF-containing regimens with proteinuria and albuminuria in other studies and ours. Moderately and severely increased proteinuria was detected in 32% and 8% of patients, respectively. Furthermore, moderately increased albuminuria was found in 17% and severely increased albuminuria in 3% of patients. Interestingly, these rates are higher than those reported in the randomized phase 3 trials for novel antiretrovirals, which may be partially explained by our patients' older age and the higher proportion of comorbidities in our real-life cohort. Therefore, data from real-life cohorts is very important in assessing short- and long-term toxicity [16, 17, 21]. As found in previous TDF-to-TAF switch studies, we observed an increase in total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol. This lipid-lowering effect is considered to result from the reduction of circulating levels of TFV [22-23]. Consistent with previous findings, in the current study, we found that despite an increase in total cholesterol, triglycerides, and LDL cholesterol after the TDF-to-TAF switch, no difference was found in the LDL:HDL cholesterol ratio, an essential predictor of cardiovascular risk [24].

HBV infection has become a chronic condition rather than an acute life-threatening disease in developed countries, thanks to consistent innovation and the evolution of effective interventions. Although longevity, viral suppression and the prevention of viral transmission remain key goals, more needs to be achieved to encompass the vision of attaining an optimum level of overall health. Treatment choices and management practices should ensure patients' long-term health with minimal comorbidity. Treatments that balance optimal efficacy with the potential for improved long-term safety are needed for all patients. In this

study, we consider the evolution and development of tenofovir alafenamide (TAF) - a novel prodrug of tenofovir that offers high antiviral efficacy at doses over ten times lower than tenofovir disoproxil fumarate (TDF). Emerging clinical data in diverse groups, including our patients, suggest that TAF as a single tablet regimen offers highly effective viral suppression in treatment-naïve and treatment-experienced patients with an improved renal and bone safety profile compared to TDF.

Limitations and future study

Ours was an open-label study. Blinded trials are subject to less bias than an open trial because they minimize the effect of treatment knowledge on reporting of outcomes. However, the impact of this was likely minimal since our study focused on laboratory results. Although the time frame is unknown, experts in the field are optimistic that the substantial progress made in recent years in our knowledge of HBV virology and the immunological response to it has laid the groundwork for studying a host of new therapies and strategic approaches, including those listed earlier, that may lead us closer to a cure. Substantially long-term follow-up will be required to determine if the differences in adverse bone and kidney effects seen with TAF compared to TDF are clinically relevant and how they compare to what has been seen with long-term TDF therapy.

Conclusions

Our study shows that TAF is noninferior to TDF in efficacy in both HBeAg-negative and HBeAg-positive patients, with high rates of viral suppression overall. TAF treatment has the same treatment efficacy as TDF in the Mongolian adult study population. However, TAF treatment had a better safety profile than TDF. TAF was well tolerated with low rates of adverse events, comparable to TDF. A significantly lower decline in the estimated glomerular filtration rate (eGFR) was observed in patients receiving TAF than in patients receiving TDF, and loss of bone mineral density at the ankle and proximal femur was significantly lower with TAF. The most common adverse events were epigastric pain, headache and nasopharyngitis and dyslipidemia.

Conflict of Interest

The authors state no conflict of interest.

References

1. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection [accessed on 14 January 2018]. Available at: https://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059.
2. Dashtseren B, Bungert A, Bat-Ulzii P, Enkhbat M, Lhagva-Ochir O, Jargalsaikhan G, et al. Endemic prevalence of hepatitis, B and C in Mongolia: A nationwide survive among Mongolian adults. J Viral Hep 2017; 24: 759-67.
3. Hill A, Hughes S, Gotham D, Pozniak A. Tenofovir alafenamide versus tenofovir disoproxil fumarate is there a true difference in efficacy and safety? J Virus Erad 2018; 4: 73-80.
4. Ogawa E, Furusyo N, Mindie HN. Tenofovir alafenamide in the treatment of chronic hepatitis B design, development, and place in therapy. Drug Des Devel Ther 2017; 11: 3197-204.
5. Basit SA, Dawood A, Ryan J, Gish R. Tenofovir alafenamide for the treatment of chronic hepatitis B virus infection. Expert Rev Clin Pharmacol 2017; 10: 707-16.
6. Ruth B, Ivana C, Kosh A. Tenofovir alafenamide in the treatment of chronic hepatitis B virus infection: rationale and clinical trial evidence. Ther Adv Gastroenterol 2018; 11:1-12.
7. Buti M, Riveiro M, Esteban R. Tenofovir alafenamide fumarate: a new tenofovir prodrug for the treatment of chronic hepatitis B infection. J Infect Dis 2017; 216: S792-6.
8. Agarwal K, Brunetto M, Seto WK, Lim YS, Fung S, Marcellin P, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol 2018; 68: 672-81.
9. Agarwal K, Fung SK, Nguyen TT, Cheng W, Sicard E, Ryder SD, et al. Twenty-eight day safety, antiviral activity and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis B infection. J Hepatol 2015; 62: 533-40.
10. Schweitzer A, Horn J, Mikolajczyk RT. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet Gastroenterol Hepatol 2015; 386: 1546-55.
11. Nikolaos P, Prodromos H, Lavrentios P, Emmanouil S, Ioannis K, Evangelos A. Antiviral therapy leads to histological improvement of HBeAg-negative chronic hepatitis B patients. Ann Gastroenterol 2015; 28: 374-8.
12. Abdul BS, Dawood A, Ryan J, Gish R. Tenofovir alafenamide for the treatment of chronic hepatitis B virus infection. Expert Rev Clin Pharmacol 2017; 10: 707-16.

13. Buti M, Gane E, Seto WK, Chan HL, Chuang WL, Stepanova T, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol 2016; 1: 196–206.
14. Henry L, Maria B, Robert F, Stephen R, Adrian S, John F, et al. Efficacy and safety of tenofovir alafenamide at 96 weeks in chronic HBV patients with risk factors for use of tenofovir disoproxil fumarate. Therap Adv Gastroenterol 2010; 3: 73–6.
15. Samir K, Frank A, Jose R, Joseph J, David A, Amanda E, et al. Renal safety of tenofovir alafenamide vs. tenofovir disoproxil fumarate: a pooled analysis of 26 clinical trials. AIDS 2019; 33: 1455-65.
16. Kaneko S, Kurosaki M, Tamaki N, Itakura J, Hayashi T, Kirino S, et al. Tenofovir alafenamide for hepatitis B virus infection including switching therapy from tenofovir disoproxil fumarate. J Gastroenterol Hepatol 2019; 34: 2004-10.
17. Kim SU, Seo YS, Lee HA, Kim MN, Lee YR, Lee HW, et al. A multicenter study of entecavir vs tenofovir on prognosis of treatment chronic hepatitis B in South Korea. J Hepatol 2019; 71: 456-64.
18. Soheil T, Mohammad D, Shahnaz S. Tenofovir alafenamide: a new drug with various ambiguous aspects in treatment of chronic hepatitis B infection. Arch clin infect dis 2018; 14: e65343-4.
19. Chan HL, Fung S, Seto WK, Chuang WL, Chen CY, Kim HJ, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol 2016; 1: 185-95.
20. Cathcart AL, Chan HL, Bhardwaj N, Liu Y, Marcellin P, Pan CQ, et al. No Resistance to Tenofovir Alafenamide Detected through 96 Weeks of Treatment in Patients with Chronic Hepatitis B Infection. Antimicrob Agents Chemother 2018; 62: e01064-18.
21. Shafran SD, Di Perri G, Esser S, Lelièvre JD, Parczewski M. Planning HIV therapy to prevent future comorbidities: patient years for tenofovir alafenamide. HIV Med 2019; 20: 1-16.
22. Millan J, Pinto X, Munoz A, Zuniga M, Rubies-Prat J, Pallardo LF, et al. Lipoprotein ratios: Physiological significance and clinical usefulness in cardiovascular prevention. Vasc Health Risk Manag 2009; 5: 757-65.
23. Tungsiripat M, Kitch D, Glesby MJ, Gupta SK, Mellors JW, Moran L, et al. A pilot study to determine the impact on dyslipidemia of adding tenofovir to stable background antiretroviral therapy: ACTG 5206. AIDS 2010; 24: 1781-4.
24. Gupta SK, Post FA, Arribas JR, Eron JJ, Wohl DA, Clarke AE, et al. Renal safety of tenofovir alafenamide vs. tenofovir disoproxil fumarate: a pooled analysis of 26 clinical trials. AIDS 2019; 33: 1455-65.