ФАРМАЦЕВТИЧЕСКИЕ НАУКИ

CLINICAL AND VIRUSOLOGICAL OUTCOMES OF TENOFOVIR ALAFENAMIDE TREATMENT IN PATIENTS WITH HEPATITIS B VIRUS INFECTION

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Introduction

WHO estimates that 296 million people were living with chronic hepatitis B infection in 2019, with 1.5 million new infections each year. The latest data shows that 10.6-11.6 % of Mongolian population are infected with hepatitis B virus infection.

Goal

Evaluate the clinical and virological outcome of tenofovir alafenamide treatment in patients with hepatitis B infection.

Materials and Methods

The clinical trials have evaluated TAF in HBeAg positive and HBeAg negative HBV patients. The trials have similar design and randomized,Single-blind, the subjects are unaware of which group they have been assigned to studies. The primary efficacy endpoint was the proportion of patients with HBV-DNA<29IU/ml at weeks 96. Other virological result endpoints were the proportion of patients with HBsAg seroconversion at weeks 96.

Results

The virologic endpoints, an HBV-DNA < 29 IU/ml at weeks 96, was achieved by 243(79.1%) receiving TAF, 111(75.4)% of patients which were non-inferior to the 106(78.5%) patients receiving TDF (95% confidence interval (CI 9.7–2.5); p = 0.26. After of treatment at week 96, significant higher rates of ALT normalization was seen in the TAF group compared to the TDF group (209(68%) "vs" 83(56.4%) "vs" 82(60.8%), p = 0.001) Result: At 96 weeks of treatment, patients receiving TAF hed significantly smaller reductions in bone mineral density(BMD) compared with patients receiving TDF. At weeks 96, median changes in eGFR were signifi-cantly smaller in the TAF recipients compared with the TDF recipients.

Conclusion:

TAF and switching from TDF to TAF are similar efficacy and safety in long-term treatment of TDF.

Key words: HBV-DNA, qHBsAg, HBeAg, tenofovir alafenamid fumarate, tenofovirdisoproxil fumarate

Introduction

WHO estimates that 296 million people were living with chronic hepatitis B infection in 2019, with 1.5 million new infections each year. The latest data shows that 10.6-11.6 % of Mongolian population are infected with hepatitis B virus infection.

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 fall currently fall into two classes of treatments for chronic HBV infection: interferons and nucleoside or nucleotide analogs.

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 Treatment of Chronic Hepatitis B and updates the previous hepatitis B virus (HBV) guidelines from 2009. The 2018 updated guidance for CHB includes updates on treatment since the 2016 HBV guidelines (notably the use of tenofovir alafenamide) and guidance on screening, counseling, and prevention; specialized virologic and serologic tests; monitoring of untreated patients; and treatment of hepatitis B in special populations, including persons with viral coinfections, acute hepatitis B, recipients of immunosuppressive therapy, and transplant recipients [1, 2, 3, 4, 5]. Since the publication of the 2016 AASLD Hepatitis B Guidelines, tenofovir alafenamide (TAF) has been approved for the treatment of CHB by the Ministry of Health of Mongolia.

Our study's primary objective was to compare the evaluate the clinical and virological results 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 Cohort

The study was approved by the Ethics Committee of the "Ach" Medical University of Mongolia. The primary objective of this study is to compare the There were no other significant between-group differences in *virological and clinical results* of tenofovir alafenamide versus tenofovir disoproxil in treatment-naive and treatment-experienced adults with hepatitis B e antigen (HBeAg)-negative chronic hepatitis B virus infection. All research participants must give their permission to be part of a study and they taken pertinent

information to make an "informed" consent to participate.

A total of 589 patients were enrolled across studies, with 218 HBeAg-negative patients and 371 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 metastasis, 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 breast-feeding were excluded from the study. Eligible patients had a separate consent to this study.

Clinical Staging

The clinical stages were based on the medical history of all patients. Participants were screened for inclusion for the study if they were 18-70 years age and, having taken part in 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, 307 patients were randomized to the TAF treatment group, 147 patients were randomized to the TDF treatment group, and 135 patients switched from TDF to TAF before treatment. In chronic hepatitis B patients receiving long-term sequential Neucleos(t)ides, most of these CHB patients experienced drug resistance and were switched to TDF. However, some of the patients on long-term TDF experienced impairment of renal function and bone mineral density. After TAF was available in clinical practice, these patients were given the option to switch from TDF to TAF. Randomization was stratified by plasma HBV DNA level ≥ 7 to < 8 $\log_{10}$ IU/mL, ≥ 8 $\log_{10}$ IU/mL and oral antiviral treatment status (treatment-naive ".vs" treatment-experienced) at screening. Randomization was performed using an interactive web response system.

The primary *virological result* endpoint was the proportion of patients with HBV-DNA < 29 IU/ml after weeks 96 of starting treatment. Other prespecified results endpoints were the proportion of patients with HBsAg seroconversion to anti-HBs at week 96. Other prespecified efficacy endpoints were the proportion of patients with ALT normalization at weeks 96. Efficacy and safety outcomes at 96 weeks after starting treatment were evaluated. No mention is made regarding tracking adverse events or the need to stop or switch therapies because of events.

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 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).

Results

The general characteristics of the patients are summarized in Table 1. The recruited subjects came from different regions and places.

The number of samples collected from each province approximately of people living in the provinces and people living in the capital city (35.7% ".vs" 64.3%). The rate of participation was with 352 (59.8%) higher amongst women than amongst men 237 (40.2%) $p < 0.05$).

Table 1.

General characteristics of study population

Variables		Total	TAF(25mg)	TDF(300mg)	TDF-TAF
		N=589(%)	n=307	n=147	N=135
Age groups	<30	37(6.2)	17(5.5)	11(7.5)	9(6.6)
	30-39	110(18.6)	51(16.6)	36(24.5)	23(17.0)
	40-49	215(36.5)	123(40.0)	50(34.0)	42(31.1)
	50-59	136(23.0)	66(21.5)	31(21.1)	39(28.8)
	>59	91(15.4%)	52(16.9)	18(12.2)	21(15.5)
	($M^{+\backslash -}$m)	44.7±12.2			
HBeAg negative		218(38.1)	121(55.5)	53(24.3)	44(20.1)
HBeAg positive		371(61.9)	186(50.2)	94(25.3)	91(24.5)
Gender	Male (%)	237(40.2)	114	67	56
	Female (%)	352(59.8)	192	81	79
Regions	Ulaanbaatar	379(64.3)	212	78	89
	Other	210(35.7)	111	63	36

The *virological* endpoints, an HBV-DNA < 29 IU/ml at weeks 96, was achieved by 243(79.1%) receiving TAF, 111(75.4)% of patients which were non-inferior to the 106(78.5%) patients receiving TDF (95% confidence interval (CI 9.7–2.5); p = 0.26. At week 96, significant higher rates of ALT normalization was seen in the TAF group compared to the TDF group (209(68%) "vs" 83(56.4%) "vs" 82(60.8%), p = 0.001)

(Figure 1). TAF and switching from TDF to TAF were similar efficacy and safety in long-term treatment of TDF. More patients in the TAF group experienced HBsAg loss than in the TDF and TDF-TAF group 2.1% ".vs" 1.0% and 2.1% but this was not statistically significant (Figure 1).

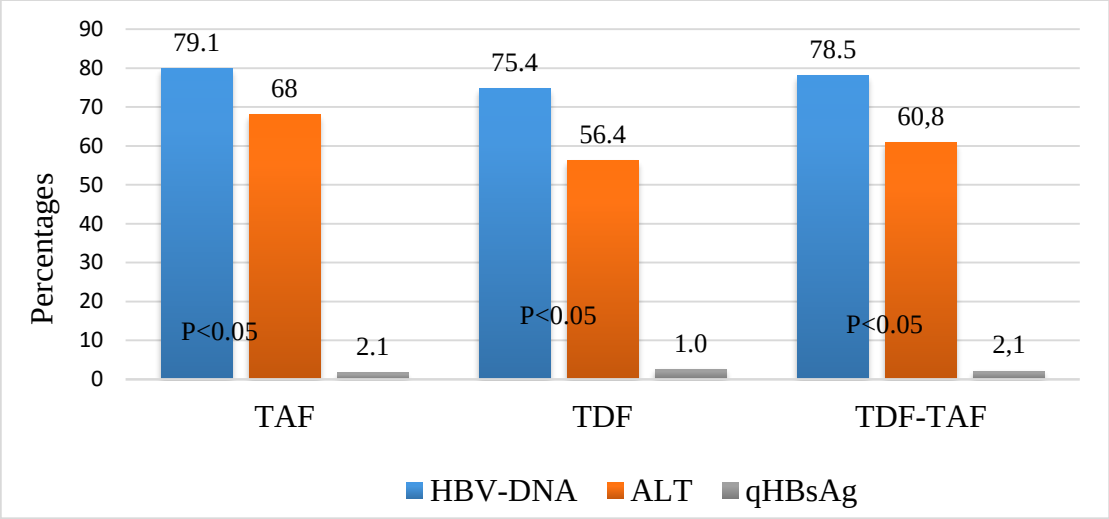

Figure 1. Virological outcome *endpoints in patients at weeks 96. TAF-tenofovir alafenamide fumarate, TDF- tenofovir disoproxil fumarate, TDF-TAF switching tenofovir disoproxil fumarate to tenofovir alafenamide at 96 weeks. P-values for the chi square analyses.*

There were no significant differences in baseline characteristics between the two treatment groups (Table 2).

Table 2.

***Virological outcome* of groups**

Variables	TAF (25mg) n=307	TDF(300mg) n=147	TDF-TAF n=135	Proportional difference (CI)	P-value
HBV-DNA < 29IU/mL	243(79.1%)	111(75.4%)	106(78.5%)	1.7% (-3.7 to7.3)	0.46
ALT-normalization*	209(68%)	83(56.4%)	82(60.8%)	17.9% (8.0 to 27.7)	0.0005

†Using 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 218 HBeAg-negative patients were randomized and received treatment with either TAF 25 mg or TDF 300 mg and TDF-TAF. The *virological results* endpoint of an HBV-DNA level < 29 IU/ml at week 96 was achieved by 93.6% patients receiving TAF, which was non-inferior to the 91.2% patients receiving TDF and 93.4% patients receiving TDF to TAF (p = 0.48). At week 96, significant higher proportions of ALT normalization were seen in the TAF group compared to the TDF treated group (68% ".vs" 56.3%, p = 0.001) but those proportions did not differ from the TDF-TAF group (63%). Rates of HBsAg loss by week 96 were approximately 1% in all three groups regardless of which treatment was received (Table 3).

Table 3.

***Virological results* endpoints of HBeAg-negative patients at 96 weeks.**

Variables	TAF 25mg	TDF 300mg	TDF-TAF 300mg-25mg	*p-value
	n = 121	n = 53	n = 44	
	N (%)	N (%)	N (%)	
HBV-DNA < 29 IU/mL	113(93.6)	48(91.2)	41(93.4)	0.480
ALT - normalization†	82(68)[a]	30 (56.4)[a]	29 (63)	0.000
HBsAg loss	1 (1.2)	2 (1.1)	-	0.520

One-way ANOVA result; Tukey multiple post-hoc comparison result: [a]p = 0.05, All others were not significant. †Using 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 371 HBeAg-positive patients were randomized and received treatment with either TAF 25 mg or TDF 300 mg or TDF-TAF. The *virological results* endpoint of an HBV DNA level < 29 IU/ml at week 96 was achieved in 70.9% patients receiving TAF, 63.5% receiving TDF and 72.2% of patients receiving TDF to TAF with no significant differences (p = 0.26). At week 96, significant higher rates of ALT normalization were seen in the TAF group that the TDF group (45.5% ".vs" 38.5%, p = 0.046). Rates of HBsAg loss by week 96 were very low and only 1 patient in the TAF group, 2 in the TDF and 3 patients in the TDF-TAF group achieved it p = 0.51 (Table 4).

Table 4.

***Virological* endpoints of HBeAg-positive patients at 96 weeks.**

Variables	TAF 25mg	TDF 300mg	TDF-TAF 300mg-25mg	*p-value
	n = 186	n = 94	n = 91	
	N (%)	N (%)	N (%)	
HBV-DNA < 29IU/mL	132 (70.9)	60 (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 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.

We created clinical result defining criteria. This definition did not assess any measurable change in liver function that could objectively indicate meaningful recovery from a clinical standpoint. (Table 5).

Table 5.

Clinical result defining criteria of TAF

Clinical signs	Before antiviral treatment (%)	Antiviral treatment at weeks				
		12	24	36	48	96
		(%)				
Cholestatic syndrome	110(35.8)	31%	29%	25%	25%	21%
Fatigue	236(76.9)	75%	75%	70%	61%	58%
Dyspepsia	245(79.8)	76%	70%	68%	63%	59%
Hemorrhagic syndrome	158(51.4)	49%	49%	48%	47%	46%
inflammatory arthritis	39(12.7)	12%	12%	10%	10%	9%
inflammatory dermatitis	41(13.3)	12%	11%	9%	8%	6%

Clinical manifestations were fatigue 76.9% and 35.9% had jaundice, 79.8% dyspepsia synrome, 51.4% hemorrhagic syndrome, and 12.7% arthritis, 13.3% showed signs of dermatitis in the TAF group before starting antiviral therapy. Clinical symptoms gradually decreased to 3.7-20.8% during antiviral therapy at 96 weeks. After 96 weeks of TAF treatment with fatigue at least 40% of patients improved. No significant changes over time were detected.No deaths were observed in this study (Table 5).

In those patients who switched from TDF to TAF at weeks 24 there was a significant improvement in creatinine clearance at week 48 and the patients on long-term TAF maintained stable serum creatine. (Figure 2).

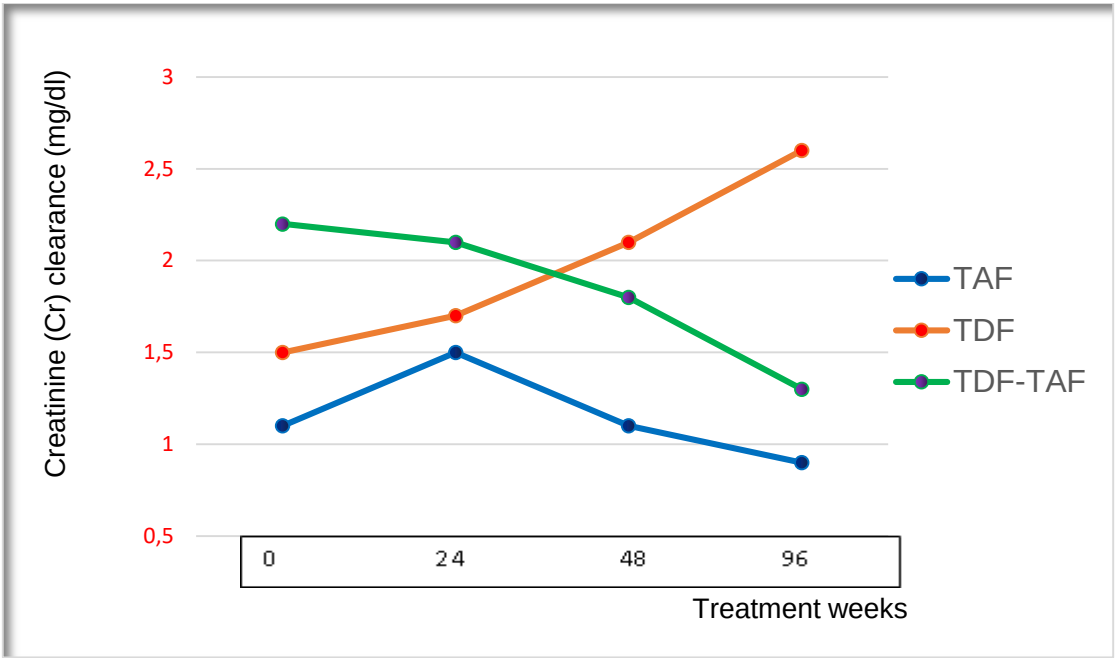

Figure 2. Creatinine clearance at week 24 and 48, 96 weeks of treatment groups

After 96 weeks of treapy have shown that, patients receiving TAF had significantly smaller reductions in bone mineral density (BMD) compared with patients receiving TDF. At weeks 96, median changes in eGFR were significantly smaller in the TAF recipients compared with the TDF recipients. None of the patients experienced serious renal-related adverse effects or proximal renal tubulopathy, including Fanconi syndrome, in the three groups.

Discussion

In 2012, 78 cases of liver cancer per 100 000 individuals were registered and very high prevalence of HBV/HDV co-infection amongst the Mongolian population. Data relating to the use of TAF in certain specific populations are currently limited. They underline the importance of prevention against HBV and the high risk of HDV superinfection amongst HBsAg positives. Both TAF and TDF are prodrugs of tenofovir. However, TAF requires a much lower dose in order to achieve therapeutic levels of tenofovir, which implies that TAF may have less impact on notable harms associated with 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 favourable pharmacological profile of TAF permits a marked (one-tenth) reduction in dosage and 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 versus 1% of TDF patients) and LDL-C levels > 300 mg/dL (in 4% of TAF patients ".vs" no TDF patients) effects that have not been 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 are on 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 below 29 IU/ml, in April 2017 EASL added TAF to its list of recommended first-line therapies for treatment of CHB. It is presumed that the other liver societies, including APASL and AASLD, will do the same in their next guidelines [1,3]. In two major clinical trials, compared to TDF recipients, 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 [19,8]. Patients treated with TAF in both studies also had smaller mean increases in serum creatinine, although the difference was only statistically significant in the study of HBeAg-positive patients [3,4,6]. An analysis of patients who had been treated with TDF for 96 weeks and then switched to TAF found that there were improvements in renal and BMD measures that occurred only 24 weeks after the switch [5,7,9,12].

The mechanism behind the bone toxicity associated with TDF is not entirely clear [8-15]. In study cohort, we found a high rate of HIV-infected patients on TDF-containing regimens with proteinuria and albuminuria. 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 randomized phase 3 trials for novel antiretrovirals, which may be partially explained by the older age of patients and higher proportion of comorbidities in a real-life cohort. Therefore, data from real-life cohorts are very important to assess changes in short-and/or 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. Compared with non-TDF regimens, TDF treatment has been associated with lower lipid levels. This lipid-lowering function is also considered to be an effect of circulating levels of TFV [22-23]. Consistent with previous findings, in the current study, despite an increase in total cholesterol, triglycerides and LDL cholesterol after the TDF-to-TAF switch, no treatment difference was found in the LDL:HDL cholesterol ratio, an essential predictor of cardiovascular risk [24].

Limitations and Future Study

HBV infection has become a chronic condition rather than an acute life-threatening disease in developed countries, thanks to consistent innovation and 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 co-morbidity. Treatments that balance optimal efficacy with the potential for improved long-term safety are needed for all patients. In this review, we consider the evolution and development of tenofovir alafenamide (TAF) - a novel pro-drug of tenofovir which offers high antiviral efficacy at doses over ten times lower than tenofovir disoproxil fumarate (TDF). Emerging clinical data 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, demonstrated in diverse groups including patients.

Although we do not currently have a time frame for this, 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 have laid the groundwork for researching a host of new therapies and strategic approaches, including those listed earlier, that may lead us closer to this. But we did decided Substantially longer term follow up will be required to determine if the differences in adverse bone effects and adverse kidney effects seen with TAF in comparison to TDF are clinically relevant and how they compare to what has been seen with long-term TDF therapy.

Conclusions

Data from Mongolian adult the study population show that TAF is non-inferior to TDF in efficacy in both HBeAg-negative and HBeAg-positive patients, with high rates of viral suppression overall.

TAF treatment has the same efficacy as TDF treatment in the study population. However, TAF treatment results more safety profile compared with TDF treatment.TAF was well tolerated with low rates of adverse events, comparable to TDF. A significantly lower decrease in the estimated glomerular filtration rate (eGFR) was observed in patients receiving TAF compared with patients receiving TDF and loss of bone mineral density at the ankle and proximal femur was significantly lower in the TAF groups.

Conflict of Interest

The authors state no conflict of interest.

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