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One-year efficacy of tenofovir alafenamide in patients with chronic hepatitis B

An observational study

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Abstract

Non-inferior antiviral efficacy and better renal safety have been reported in chronic hepatitis B patients with tenofovir alafenamide (TAF) treatment. The experience in real-world clinical practice is limited.

We aimed to explore the efficacy after 1-year TAF treatment.

A total of 148 patients (42 HBeAg-positive and 106 HBeAg-negative) with TAF treatment ≥1 year were included. Virological suppression (<20 IU/mL or undetectable), HBsAg level, alanine aminotransferase (ALT) normalization (≤36 U/L), and estimated glomerular filtration rate (eGFR) were analyzed at 1 year. Multivariate logistic regression analysis was performed to determine the associated factors for virological suppression and ALT normalization.

Virological suppression was achieved in 83% and the 1-year median decline of hepatitis B virus DNA was 5.18 log IU/mL. ALT normalization occurred in 75.7%. HBsAg level decreased at a median of 0.27 log IU/mL with significant difference from baseline ($P < .001$). Baseline ALT (odds ratio [OR] 1.005, 95% confidence interval [CI] 1.000–1.010, $P = .036$) and hepatitis B virus DNA (OR 0.222, 95% CI 0.079–0.621, $P = .004$) were significant factors for 1-year virological suppression. Age (OR 1.064, 95% CI 1.003–1.130, $P = .041$) was associated with ALT normalization. Significant changes were observed in creatinine (mean increase 0.03 mg/dL, $P = .011$) and eGFR (mean decrease 2.6 mL/min/1.73 m^2, $P = .004$) after 1-year TAF treatment.

One-year TAF treatment came to good virological response, modest ALT normalization rate and significant HBsAg decline. The observation of significant changes in eGFR warranted further studies.

Abbreviations: ALT = alanine aminotransferase, eGFR = estimated glomerular filtration rate, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HDV = hepatitis D virus, NA = nucleos(t)ide analogue, TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumurate.

Keywords: alanine aminotransferase normalization, chronic hepatitis B, estimated glomerular filtration rate, tenofovir alafenamide, virological suppression

1. Introduction

Tenofovir alafenamide (TAF) is a novel prodrug of tenofovir. It was developed to have greater stability in plasma, thereby allowing more efficient transportation of the active metabolite, tenofovir diphosphate, to hepatocytes than tenofovir disoproxil fumarate (TDF).[1] Given at a lower dose, TAF can reduce the circulating concentrations of tenofovir by around 90% lower

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than TDF.[2] The reduced systemic exposure of tenofovir therefore offers improved safety profiles of bone density and renal function reservation, demonstrated in international clinical trials.[3–5] Since the non-inferior antiviral efficacy to TDF and better bone and renal safety,[3,4] TAF has been recommended as one of the first-line nucleos(t)ide analogue (NA) monotherapy options for the management of adult patients with chronic hepatitis B virus (HBV) infection in current guidelines and treatment consensus.[6–9]

Several studies have been reported addressing switching or sequential therapy from entecavir[10–14] or TDF[5,15,16] to TAF in chronic hepatitis B (CHB) treatment. However, the efficacy of TAF monotherapy in real-world practice was rarely discussed. In 2 large phase 3 clinical trials on reports of 48-week TAF treatment,[3,4] DNA suppression (<29 IU/mL) was achieved at 94% and 64% in HBeAg-negative and HBeAg-positive patients, respectively. Normalization of alanine aminotransferase (ALT) by central laboratory criteria occurred in 83% of HBeAg-native and 72% of HBeAg-positive patients. The rates of HBeAg loss and seroconversion were 14% and 10%, respectively. The mean increases in serum creatinine (0.01 mg/dL in both HBeAg-positive and negative) and median decreases in estimated glomerular filtration rate (eGFR) (0.6 mL/min in HBeAg-positive; 1.8 mL/min in HBeAg-negative) were small. A study in Japan recruited 67 patients with TAF treatment and 48-week efficacy was analyzed in 14 TAF- and 45 TDF-treated patients (naïve in treatment).[17] The results found that ALT normalization (≤40 U/L) occurred in 100%, mean declines in HBV DNA and HBsAg levels were 5.0 and 0.15 log IU/mL, respectively, and mean decrease in eGFR (2.30 mL/min) was not significant in TAF subgroup. A most recent real-world study from the Canadian Hepatitis B Network (CanHepB) on 176 TAF-treated patients (143 switched from other NA and 33 NA-naïve) showed 1-year achievement of undetectable HBV DNA in 75% of NA-naïve patients.[18]

With small patient number in current real-world experience (n=14 and n=33),[17,18] we conducted a larger scaled, retrospective cohort study with to explore 1-year efficacy of TAF monotherapy in real-world clinical practice.

2. Materials and methods

2.1. Patients

In Taiwan, TAF has been reimbursed for the treatment of CHB since 2019 May. Patients with positive HBsAg for >6 months and under TAF monotherapy were retrospectively reviewed in electronic medical records from May 2019 to January 2020. The inclusion criteria were ALT ≥2*x* upper limit of normal (ULN, 36 U/L) at entry; baseline HBV DNA ≥2000 IU/mL in HBeAg-negative and ≥20,000 IU/mL in HBeAg-positive status; end of previous NA treatment for at least 6 months before entry; TAF therapy for at least 12 months; if cirrhosis, HBV DNA ≥2000 IU/mL regardless of ALT level and HBeAg status. Patients with coinfection with hepatitis C virus (HCV), hepatitis D virus (HDV) or human immunodeficiency virus (HIV), concomitant alcoholic liver disease or autoimmune liver disease, history of hepatocellular carcinoma, prophylactic antiviral therapy before chemotherapy, and hepatic decompensation were excluded. This study was conducted under the approval of Chang Gung Memorial Hospital institutional review board (IRB No. 202100202B0).

2.2. Clinical and laboratory assessments

Demographic information of age, gender, body mass index (BMI), and history of diabetes mellitus (DM) and previous HBV treatment were recorded from electronic medical records. Laboratory data including aspartate aminotransferase (AST), ALT, total bilirubin, creatinine, HBeAg, anti-HBe, anti-HCV, anti-HDV, HBV genotype, HBsAg, and HBV DNA were collected. eGFR was calculated using the chronic kidney disease epidemiology collaboration equation. The serum HBsAg and HBV DNA levels were logarithmically transformed for analysis. Virological suppression was defined as HBV DNA <20 IU/mL or undetected. ALT normalization was defined as ALT ≤36 U/L by laboratory criteria. HBeAg seroconversion/seroclearance was defined as loss of HBeAg with/without anti-HBe during treatment. Stored serums were retrieved as possible for assays of HBV genotype, HBsAg, and HBV DNA if any incomplete data. HBV genotype was determined by polymerase chain reaction-restriction fragment length polymorphism of the surface gene of HBV. Serum HBsAg levels were quantified using the Roche Elecsys HBsAg II quant assay (detection limit, 0.05–52,000 IU/mL; Roche Diagnostics, Mannheim, Germany) according to the manufacturer's instructions. Serum HBV DNA was assayed by COBAS AmpliPrep/COBAS TaqMan HBV Test, version 2.0 (lower limit of detection: 20 IU/mL, Roche Diagnostics, Mannheim, Germany). HBeAg, anti-HBe, and anti-HCV were tested with electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics GmbH, Mannheim, Germany). Anti-HDV was assayed with enzyme immunoassay kit (General Biologicals Corp., Hsinchu, Taiwan). Cirrhosis was diagnosed by pathology or presence of both ultrasonographic features of coarse liver parenchyma plus splenomegaly/endoscopic varices. Fatty liver was defined by ultrasonographic findings of bright parenchyma, increased hepatorenal contrast, deep parenchymal attenuation, and blurred vasculature.[19]

2.3. Statistical analysis

Continuous variables were expressed as means and standard deviations (S.D.) or medians and interquartile ranges (IQR) as appropriate after testing for normal distribution using the Kolmogorov–Smirnov test and were compared by independent Student *t* test or Mann–Whitney *U*-test between 2 different groups. Paired comparison of variables between baseline and 1 year was performed using paired *t* test or Wilcoxon signed-rank test. Categorical variables were presented as the number of cases (proportions) and compared by Chi-squared or Fisher exact tests when appropriate. Comparison of the proportion in eGFR of ≥90 and 60 to 90 mL/min/1.73 m^2 at baseline and 1 year was performed by McNemar test. Multivariate logistic regression analysis was performed using variables with *P* value <.1 in univariate analysis for the associated factors with virological suppression and ALT normalization. Statistical analysis was performed by Statistics Package for Social Science (IBM SPSS Statistical Professional version 25.0; IBM, Armonk, NY). A 2-tailed $P < .05$ was considered statistically significant.

3. Results

A total of 148 patients were included for analysis. The mean age was 52.8 years. There were 106 (71.6%) men, 42 (28.4%) HBeAg-positive, 109 (73.6%) genotype B, 75 (50.7%) treat-

Table 1

Baseline clinical characteristics in overall, HBeAg-positive, and HBeAg-negative patients.

	Overall	HBeAg-positive	HBeAg-negative
No	148	42	106
Age, yrs	52.8 ± 11.5	44.6 ± 10.1	56.1 ± 10.4
Males	106 (71.6)	27 (64.3)	79 (74.5)
Genotype			
B	109 (73.6)	27 (64.3)	82 (77.4)
C	39 (26.4)	15 (35.7)	24 (22.6)
Treatment-naïve	75 (50.7)	22 (52.4)	53 (50)
Cirrhosis	15 (10.1)	3 (7.1)	12 (11.3)
DM	17 (11.5)	4 (9.5)	13 (12.3)
Fatty liver	80 (54.1)	26 (61.9)	54 (50.9)
BMI, kg/m^2	25.7 ± 3.6	25.6 ± 4.3	25.8 ± 3.4
AST, U/L	82 (58–134)	79 (54–134)	84 (61–133)
ALT, U/L	148 (99–235)	153 (98–241)	143 (99–230)
Total bilirubin, mg/dL	0.7 (0.6–0.9)	0.7 (0.6–0.9)	0.7 (0.6–1.0)
AFP, ng/mL	3.5 (2.3–5.7)	3.4 (2.3–8.0)	3.5 (2.4–5.4)
HBV DNA, log IU/mL	6.59 (5.39–8.04)	8.24 (7.64–8.69)	6.05 (5.18–7.05)
HBsAg, log IU/mL	3.17 (2.62–3.80)	4.17 (3.67–4.62)	2.95 (2.46–3.35)
Creatinine, mg/dL	0.83 ± 0.22	0.81 ± 0.19	0.85 ± 0.22
eGFR, mL/min/1.73 m^2	96.4 ± 16.8	103.2 ± 13.9	92.8 ± 15.9
Treatment duration, mo	17.5 (15.1–20.2)	18.1 (16.1–20.8)	17.1 (15.1–20.0)

Presented by mean ± SD or number (%).

BMI = body mass index, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate (by CKD-EPI equation).

ment-naïve, 15 (10.1%) cirrhosis, 17 (11.5%) DM, and 80 (54.1%) fatty liver. The mean BMI was 25.7 ± 3.6 kg/m^2, median levels of ALT, HBsAg, and HBV DNA were 148 U/L, 3.17 and 6.59 log IU/mL, respectively. The mean creatinine and eGFR were 0.83 mg/dL and 96.4 mL/min/1.73 m^2, respectively. Overall median treatment duration was 17.5 months. HBeAg seroclearance and seroconversion occurred in 11 (26.2%) and 10 (23.8%) among 42 HBeAg-positive patients. None developed acute kidney injury, hepatic decompensation, complications related to cirrhosis, or hepatocellular carcinoma during treatment period. The baseline clinical characteristics in entire cohort and subgroups of HBeAg status were shown in Table 1.

3.1. Virological suppression and HBsAg decline

Follow-up HBV DNA levels at 1 year were available in 142 patients (40 HBeAg-positive, 102 HBeAg-negative). Virological suppression was achieved in 118 (83.1%) patients, 27 (67.5%) in positive HBeAg, and 91 (89.2%) in negative HBeAg. The overall median 1-year decline of HBV DNA was 5.18, 6.53, and 4.69 log IU/mL in HBeAg-positive and HBeAg-negative patients, respectively. Patients who achieved virological suppression at 1 year were significantly older (54.0 years vs 47.8 years, $P = .016$), had lower proportion of HBeAg positivity (22.9% vs 54.2%, $P = .004$) and fatty liver (50% vs 75%, $P = .044$), lower median levels of baseline HBV DNA (6.29 log IU/mL vs 8.18 log IU/mL, $P < .001$), and HBsAg (3.04 log IU/mL vs 3.73 log IU/mL, $P < .001$) and higher median ALT level (159 U/L vs 107 U/L, $P = .026$) (Table 2) than those without. In multivariate logistic regression analysis with variables of $P < .1$ (age, fatty liver, BMI, HBeAg positivity, ALT, HBV DNA, and HBsAg) in univariate analysis, baseline ALT (odds ratio [OR] 1.005, 95% confidence interval [CI] 1.000–1.010, $P = .036$) and HBV DNA (OR 0.222, 95% CI 0.079–0.621, $P = .004$) were significant factors for HBV DNA suppression at 1 year (Table 3, Table S1, Supplemental Digital Content, http://links.lww.com/MD2/B31).

Table 2

Comparison of baseline characteristics between patients with and without virological suppression at 1 year.

	Non-virological suppression	Virological suppression	*P*
No	24	118	
Age, yrs	47.8 ± 12.5	54.0 ± 11.1	.016
Males	18 (75)	83 (70.3)	.832
Genotype			.764
B	19 (79.2)	87 (73.7)	
C	5 (20.8)	31 (26.3)	
HBeAg (+)	13 (54.2)	27 (22.9)	.004
Treatment-naïve	12 (50)	57 (48.3)	1.000
Cirrhosis	2 (8.3)	12 (10.2)	1.000
DM	4 (16.7)	13 (11)	.490
Fatty liver	18 (75)	59 (50)	.044
BMI, kg/m^2	27.0 ± 3.9	25.4 ± 3.5	.062
AST, U/L	70 (53–100)	90 (60–136)	.072
ALT, U/L	107 (91–184)	159 (104–254)	.026
Total bilirubin, mg/dL	0.8 (0.7–1.0)	0.7 (0.6–0.9)	.118
AFP, ng/mL	4.8 (2.5–8.0)	3.3 (2.2–5.6)	.247
HBV DNA, log IU/mL*	8.18 (7.31–8.82)	6.29 (5.29–7.48)	<.001
HBsAg, log IU/mL	3.73 (3.27–4.67)	3.04 (2.60–3.71)	<.001
Creatinine, mg/dL	0.84 ± 0.32	0.84 ± 0.18	.953
eGFR, mL/min/1.73 m^2	101.4 ± 21.8	94.4 ± 14.4	.073

Presented by mean ± SD or number (%).

BMI = body mass index, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate (by CKD-EPI equation).

* Follow-up HBV DNA available in 142 patients.

The median level of HBsAg at 1 year was 2.75 log IU/mL and 1-year decline was 0.27 log IU/mL (0.65 and 0.19 log IU/mL in HBeAg-positive and HBeAg-negative patients, respectively). The difference was significant from baseline (3.17 log IU/mL, $P < .001$, Fig. 1A). No patients achieved HBsAg seroclearance.

3.2. ALT normalization

There were 112 (75.7%) patients with normal ALT at 1 year, 26 (61.9%) and 86 (81.1%) in HBeAg-positive and HBeAg-negative patients, respectively. The median level of ALT at 1 year was 25 (18–39) U/L, which was significantly lower than

Table 3

Summary of the associated factors for viral suppression and ALT normalization in multivariate logistic regression analysis.

	OR	95% CI	*P*
Viral suppression			
ALT, U/L	1.005	1.000–1.010	.036
HBV DNA, log IU/mL	0.222	0.079–0.621	.004
Fatty liver	0.246	0.053–1.152	.075
ALT normalization			
Age, yrs	1.064	1.003–1.130	.041
Fatty liver	0.262	0.056–1.215	.087

ALT = alanine aminotransferase, CI = confidence interval, OR = odds ratio.

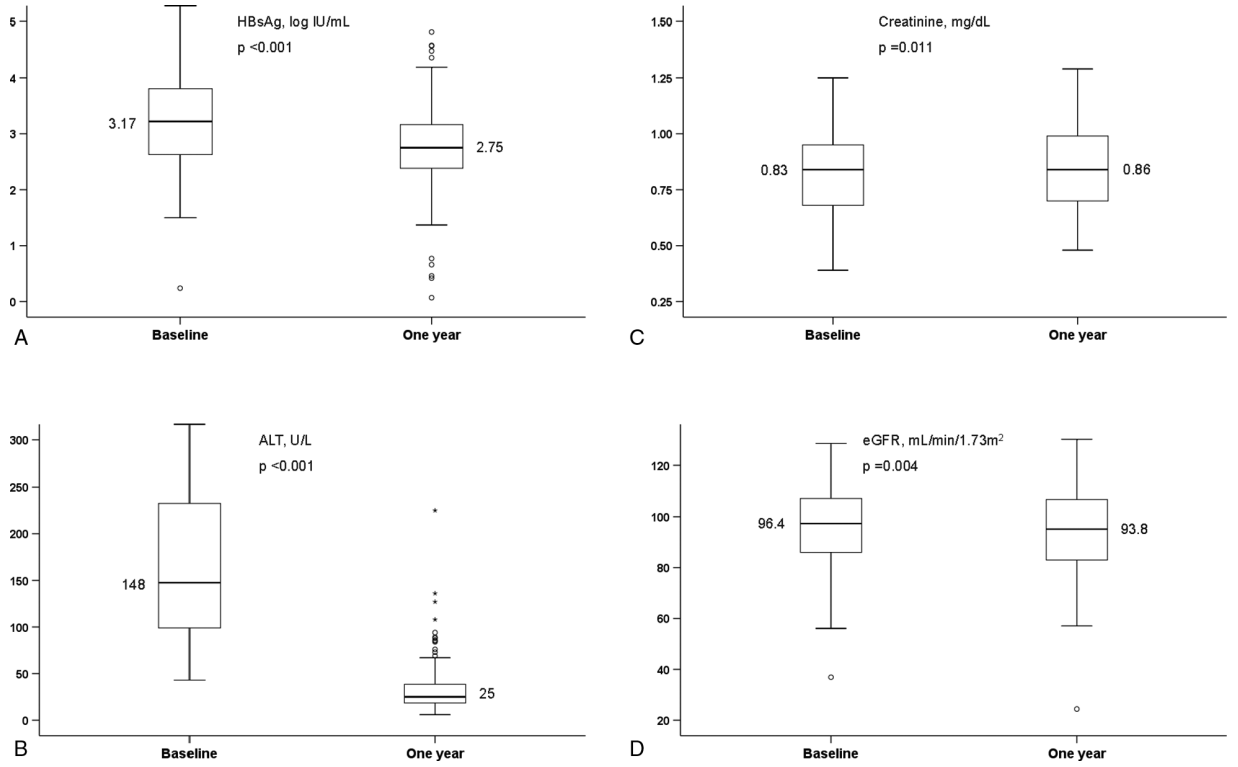

Figure 1. The changes of HBsAg, alanine aminotransferase (ALT), creatinine and estimated glomerular filtration rate (eGFR) from baseline to 1 year under tenofovir alafenamide (TAF) treatment. (A) One-year decline in HBsAg level (3.17–2.75 log IU/mL, $P < .001$); (B) decrease in ALT level (148–25 U/L, $P < .001$); (C) increase in creatinine (0.83–0.86 mg/dL, $P = .011$); (D) decrease in eGFR (96.4–93.8 mL/min/1.73 m^2, $P = .004$).

baseline ($P < .001$, Fig. 1B). The patients with normal ALT was significantly older (54.3 years vs 48.2 years, $P = .005$), had lower proportion of positive HBeAg (23.2% vs 44.4%, $P = .025$), fatty liver (47.3% vs 75%, $P = .007$), lower levels of BMI (25.1 kg/m^2 vs 27.7 kg/m^2, $P < .001$) and eGFR (93.9 mL/min/1.73 m^2 vs 100.7 mL/min/1.73 m^2, $P = .045$), higher median levels of AST (89 U/L vs 63 U/L, $P = .006$) and ALT (160 U/L vs 129 U/L, $P = .056$) than those with persistently elevated ALT (Table S2, Supplemental Digital Content, http://links.lww.com/MD2/B32). In multivariate logistic regression analysis with variables of $P < .1$ (age, fatty liver, BMI, HBeAg positivity, AST, ALT, and HBsAg) in univariate analysis, only age (OR 1.064, 95% CI 1.003–1.130, $P = .041$) was the significant factors associated with ALT normalization at 1 year (Table 3, Table S3, Supplemental Digital Content, http://links.lww.com/MD2/B33).

3.3. The changes of creatinine and eGFR

There were 102 patients with paired creatinine and eGFR (baseline and 1 year) for comparison. The level of creatinine at 1 year (0.86 mg/dL) was significantly higher than baseline (0.83 mg/dL, $P = .011$) and eGFR at 1 year (93.8 mL/min/1.73 m^2) was significantly lower than baseline (96.4 mL/min/1.73 m^2, $P = .004$) even though the numerical changes were small (−0.03 mg/dL in creatinine and −2.6 mL/min/1.73 m^2 in eGFR) (Fig. 1C and D). Of the 71 patients with baseline eGFR ≥90 mL/min/1.73 m^2, 11 (15.5%) moved to eGFR 60 to 90 mL/min/1.73 m^2. On the other hand, 5 (17.8%) of 28 patients with eGFR 60 to 90 mL/min/1.73 m^2 shifted to ≥90 mL/min/1.73 m^2. Among these 99 patients, the proportion of eGFR at ≥90 and 60 to 90 mL/min/1.73 m^2 was not different between the timepoint of baseline and 1 year ($P = .210$). Two of 3 patients with baseline eGFR <60 mL/min/1.73 m^2 remained at the same stage and one shifted to 60 to 90 mL/min/1.73 m^2 at 1 year (Table S4, Supplemental Digital Content, http://links.lww.com/MD2/B34).

4. Discussion

This study explored the 1-year efficacy of TAF monotherapy to CHB and changes in creatinine and eGFR in a real-world cohort. TAF could decrease HBV DNA by 5.18 log IU/mL, HBsAg by 0.27 log IU/mL, and achieve HBeAg loss/seroconversion at 26.2%/23.8% and ALT normalization at 75.7%. Unlike the results of international clinical trials, present study showed that creatinine increased and eGFR decreased significantly at 1 year although the changes from baseline were small.

In 2 phase 3 clinical trials, TAF has demonstrated its non-inferior efficacy of virological suppression at week 48 to TDF.[3,4] Like the clinical trial results, the overall virological suppression rate was 83.1% (67.5% in HBeAg-positive and 89.2% in HBeAg-negative) in present study. In addition, HBV DNA decline at 1 year (5.18 log IU/mL) was similar to 5.0 log IU/mL in a real-world study from Japan.[17] The declines of HBV DNA in HBeAg-positive patients were ≥6 log IU/mL in both present study and the clinical trial.[4] The reported efficacy of virological suppression in TAF treatment was summarized in Table 4. As the evidence shown in literature[20,21] by other NAs, present study confirmed that higher ALT and lower HBV DNA at baseline were the significant factors for virological suppression after 1-year TAF treatment (Table 3, Table S1, Supplemen-

Table 4

Summary of reported 1-year efficacy and renal safety in past studies.

	Viral suppression (%, log IU/mL)		ALT normalization, %	HBsAg, log IU/mL	Cr, mg/dL	eGFR	Reference
Clinical trial, HBeAg (+), n = 581	64	6.06	72	NA	↑0.01	0.6*	[4]
Clinical trial, HBeAg (−), n = 285	94	NA	83	0.09	↑0.01	1.8*	[3]
Japan, n = 14	NA	5.0	100	0.15	NA	2.3*	[17]
4 HBeAg (+)							
10 HBeAg (−)							
Canada, n = 33	75	NA	NA	NA	NA	NA	[18]
Present study							
n = 148	83.1	5.18	75.7	0.27	↑0.03	2.6†	
42 HBeAg (+)	67.5	6.53	61.9	0.65	↑0.03	2.7†	
106 HBeAg (−)	89.2	4.69	81.1	0.19	↑0.03	2.5†	

ALT = alanine aminotransferase, eGFR = estimated glomerular filtration rate, NA = not available.
* mL/min.
† mL/min/1.73 m^2.

tal Digital Content, http://links.lww.com/MD2/B31). Of interesting was that existence of fatty liver had a trend of negative influence on virological suppression at marginal significance (OR 0.262, $P = .087$, Table 3). Hepatic steatosis has been reported not associated with treatment response or negatively correlated with complete viral response,[22,23] but the relationship with TAF treatment has not been investigated yet. Recruitment of more patients with TAF treatment may further validate the impact of fatty liver.

HBsAg levels can decrease significantly after long-term NA therapy,[24,25] but the decline was slow. The 1-year median decreases were 0.11 and 0.22 log IU/mL in TDF-treated and entecavir-treated HBeAg-negative patients, respectively. These findings were compatible with our result by a median of 0.19 log IU/mL on real-world background. The pooled 1-year decrease at 0.27 log IU/mL in present study was greater than 0.15 log IU/mL in Japan[17] (Table 4), which could be explained by different patient numbers and genotype distribution.

Normal on-treatment ALT is associated with a lower risk of hepatic events in patients receiving NA treatment.[26] Our observation in overall ALT normalization rate of 75.7% was consistent with 68% to 78% of patients receiving TDF or entecavir.[21] In subgroups by HBeAg status, the rate of 81.1% in HBeAg-negative patients was the same as the result (83%) in clinical trial, but the rate of 61.9% in HBeAg-positive patients was lower than that (72%) in clinical trial after 1-year TAF treatment (Table 4). As coexistence of fatty liver in patients with CHB is regarded as one of most plausible reasons for persistent elevated ALT,[26] fatty liver seemed to play a role in obstructing the way to normal ALT, as shown in our study (OR 0.262, $P = .087$) (Table 3). The reason why age was a significant factor associated with ALT normalization is unknown. It may be explained by the observation that patients with undetected HBV DNA at 1 year were significantly older in present study.

The international clinical trials observed that eGFR decreased without statistical significance after 1-year TAF treatment and increased by a median of 0.94 mL/min after 1-year switch from TDF to TAF.[3–5] The declines in eGFR in present study (2.6, 2.7, and 2.5 mL/min/1.73 m^2 in overall, HBeAg-positive and HBeAg negative, respectively) were higher as compared with the mentioned trials,[3,4] but were comparable with the real-world result in Japan (2.3 mL/min).[17] Recent switching studies found inconsistent results in changes of eGFR after starting TAF. Most of them showed no significant change from baseline.[10,12,14,15] By contrast, one study on 61 Asian patients revealed significant decrease of eGFR (96.3 mL/min vs 90.9 mL/min, $P < .01$) at week 72 after switching to TAF.[16] Another study[11] on 313 CHB patients showed eGFR increased (0.40 and 2.68 mL/min/1.73 m^2) in baseline <60 mL/min/1.73 m^2 but decreased (0.61 and 1.75 mL/min/1.73 m^2) in baseline ≥60 mL/min/1.73 m^2. Together with the present results that eGFR could significantly decline after 1-year TAF treatment ($P = .004$), there seemed to be possibility of renal function deterioration in TAF-treated CHB patients and TAF may not guarantee the reversibility of eGFR decrease in clinical practice. Of course, there were discrepancy in study population and clinical characteristics between real-world studies and clinical trials. It was uncertain whether the small changes in renal parameters will raise clinical significance. The global trial has revealed very small changes in creatinine (+0.003 mg/dL) and eGFR (−1.2 mL/min) in pooled population at week 96[27] and provided longer-term safety. More studies with patient diversity in real world, however, are needed to clarify the renal outcomes in TAF treatment. In addition, regular follow-up in renal function is still suggested during TAF treatment.

There are some limitations in present study. First, patient number was not large enough. We enrolled the patients who fulfilled the inclusion criteria from May 2019 when TAF was reimbursed, to January 2020. During this limited time, we have tried our best to collect clinical information as complete as possible and 148 patients were included for analysis. As far as we know, it was much more than the numbers in current real-world studies[17,18] assessing the efficacy of TAF-initiated treatment. Second, depending on the distinction by some physicians in clinical practice, paired creatinine and eGFR at baseline and 1 year were only available in ~70% patients. Even by this modest proportion, the findings of significant eGFR decline were consistent with the observations in some real-world and switching study cohorts and present study has pointed out the probability of renal deterioration by TAF. Furthermore, our observation may throw light on future investigations on the renal safety under TAF treatment. Third, the study period was only 1 year. Future studies with longer follow-up time and comparison of efficacy among different NAs are ongoing.

In summary, this real-world cohort study demonstrated good virological response, modest ALT normalization rate, and significant HBsAg decline after 1-year TAF treatment. Of

importance, significant changes in creatinine and eGFR could still be observed even TAF has reduced systemic exposure of tenofovir. Large-scaled and longer-term studies are warranted.

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