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Switching to tenofovir alafenamide versus continued therapy in chronic hepatitis B patients who were treated with entecavir

A prospective, multicenter, randomized controlled study

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Abstract

Backgrounds: Entecavir (ETV) and tenofovir alafenamide fumarate (TAF) have been used widely to treat patients with chronic hepatitis B virus (HBV) infection, but it is still unclear how best to use these drugs. Although some studies compared the efficacies of treatment switch from ETV to TAF, there has been no randomized study.

Methods: We performed a prospective multicenter randomized controlled study in which subjects were enrolled from April 2018 to June 2019 and observed for 2 years until March 2021 to clarify the efficacy and safety of switching from ETV to TAF.

Results: Thirty-three patients were enrolled and randomized into 2 groups, and a total of 30 patients were evaluated; a TAF-switching group (n = 16) and an ETV-continuing group (n = 14). The mean age of the 30 patients was 61 years old and 18 patients (60%) were male. The serum HBV DNA in all patients were below detection limit. The mean change in hepatitis B surface antigen (HBsAg) levels after 2 years was not significantly different between the TAF and ETV groups (–0.08 vs –0.20 log IU/mL, $P = .07$). Comparing the group with a HBsAg decline (≤ –0.1 log IU/mL) and a group without a HBsAg decline in an overall analysis, the prior ETV duration was significantly shorter in the HBsAg-declined group (49 vs 92 months, $P = .03$). Although the eGFR levels tended to decrease in the TAF group compared to ETV (–6.15 vs –2.26 mL/min/1.73 m^2, $P = .09$), no significant differences were observed in patients with baseline eGFR < 60 (–2.49 vs 0.40 mL/min/1.73 m^2, $P = .25$).

Conclusion: The efficacy and safety were comparable in the TAF-switching group and the ETV-continuing group. Because the present study was conducted in limited patients, a larger study will be required.

Abbreviations: ALT = alanine aminotransferase, ANCOVA = analysis of covariance, cccDNA = covalently closed circular DNA, eGFR = estimated glomerular filtration rate, ETV = entecavir, HBcrAg = hepatitis B core-related antigen, HBeAg = hepatitis B e antigen, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, IFN = interferon, IP = inorganic phosphorus, NA = nucleos(t)ide analogue, PLT = platelet counts, TAF = tenofovir alafenamide fumarate, TDF = tenofovir disoproxil fumarate.

Keywords: ETV, HBsAg, switch, TAF

1. Introduction

The World Health Organization estimated that 296 million people were infected with chronic hepatitis B, which resulted in 820,000 deaths, mostly from cirrhosis and hepatocellular carcinoma (HCC) in 2019.[1] The genome of hepatitis B virus (HBV) translocates to the nucleus and a covalently closed circular DNA (cccDNA) is formed after HBV infects hepatocytes.[2] It is difficult to eliminate HBV completely because of the stability of cccDNA. The level of cccDNA in the liver correlates with the serum level of hepatitis B surface antigen (HBsAg),[3] and it has been reported that high levels of HBsAg increase the risk of liver carcinogenesis in patients with a low viral load.[4] The goal of anti-HBV therapies is the removal of serum HBsAg, termed "functional cure,"[5,6] but this is rarely achieved with clinically available therapies such as nucleos(t)ide analogues (NAs) and

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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interferons (IFNs). HBsAg quantification is considered to be a surrogate marker of efficient viral suppression during NA treatments that make serum HBV DNA undetectable in most patients.[7]

NAs including entecavir (ETV) and tenofovir disoproxil fumarate (TDF) have been widely used for the treatment of chronic HBV infection.[8] Both agents inhibit the reverse transcription of the HBV genome and HBV DNA in the serum can be reduced rapidly. Therefore, these have been considered a first-line therapy. However, ETV has minimal efficacy in reducing the serum HBsAg levels and in reducing the risk of developing of HCC in chronic hepatitis B patients with advanced liver fibrosis.[9–11] Also, long-term use of TDF causes renal toxic effects in some patients and is associated with a reduction in mineral bone density and an increase in markers of bone turnover.[12,13]

A novel NA, tenofovir alafenamide fumarate (TAF), has also been available from 2017 in Japan for the treatment of chronic hepatitis B. TAF is a new prodrug of tenofovir that is as effective as TDF in HBV suppression. Also, because TAF has greater stability in plasma than TDF, TAF is able to deliver the active metabolite more efficiently to target cells at a substantially lower dose.[12,13] For the above reasons, TAF was added to the first-line antiviral agents for the treatment of HBV infection.[5,6]

It was reported that TDF reduces the serum HBsAg level significantly more than ETV[10] and that TAF is not inferior to TDF in HBsAg suppression.[12,13] Therefore, it is assumed that the efficacy of TAF in HBsAg reduction may be superior to ETV. ETV has been widely used in Japan since 2006, and some studies have reported the efficacies of treatment switch from ETV to TAF. However, there has been no randomized study for the evaluation of ETV-TAF switch so far and it is still questioned whether such a treatment switch is better than continuation of ETV. In this study, we firstly performed a prospective randomized controlled study to verify the hypothesis that the HBsAg reduction in the TAF-switching group may be significantly greater than that in the ETV-continuing group.

2. Materials and Methods

2.1. Study design, setting, and sample sizes

This study was a prospective open-label multicenter randomized double-arm controlled trial. The participants were assigned to a TAF-switching group or an ETV-continuing group equally (Fig. 1) using a random number table created by a random number program at the research office, which were not disclosed to investigators. Based on the average decrease in HBsAg 48 weeks after administration in a phase 3 clinical study for TDF, it was calculated that 52 patients in each group were required to show a significant difference under a condition of an α value 0.05 in the two-sided test and an analysis power 0.8. With the expectation of dropout of about 10%, the inclusion of 60 patients in each group was planned.

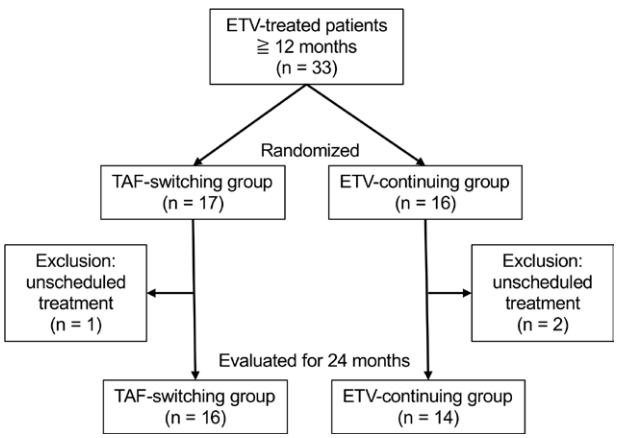

Figure 1. Flow-chart of randomization and evaluation in this study.

Inclusion criteria were as follows: ETV 0.5 mg/day had been administered for >1 year continuously; HBsAg in the serum had been continuously positive; The serum HBV DNA levels were less than 3.3 log IU/mL; patients ≥ 20 years old; they had no history of decompensated liver cirrhosis, liver cancer, or other malignancies. The exclusion criteria were as follows: patients receiving IFN or immunosuppressive therapies; presence of hypophosphatemia (<2.5 mg/dL); pregnant women and women suspected of being pregnant; breast-feeding women; and coinfection with hepatitis C virus or human immunodeficiency virus.

2.2. Participants

Participants were enrolled from April 2018 to June 2019 and were observed for 2 years until March 2021 in 5 hospitals. Among the 33 enrolled patients, 3 patients were excluded due to unscheduled treatments and a total of 30 patients were evaluated. The median age of the randomized patients was 61 years old (interquartile range, 50–68); 18 patients (60%) were male, and 12 patients (40%) were female. After randomization, 16 patients (median age, 63; interquartile range, 50–68; 7 males and 9 females) were evaluated as the TAF switching group and 14 patients (median age, 60; interquartile range, 51–68; 11 males and 3 females) were evaluated as the ETV continuing group.

2.3. Intervention

ETV at 0.5 mg/day was administered orally while fasting, and TAF at 25 mg/day was administered orally after a meal. The patients were observed every 3 months for 24 months and the clinical data were collected at 3, 6, 9, 12, 18, and 24 months after enrollment.

2.4. Comparison

The serum levels of HBsAg were quantified using a chemiluminescent enzyme immunoassay with LUMIPULSE HBsAg-HQ (Fujirebio, Tokyo, Japan). Hepatitis B e antigen (HBeAg) was assessed using a chemiluminescent immunoassay by ARCHITECT (Abbott Japan, Tokyo, Japan). The HBV DNA levels were quantified using quantitative PCR assays with Cobas TaqMan HBV Auto, according to the manufacturer's protocol (Roche Diagnostics, Tokyo, Japan). Hepatitis B core-related antigen (HBcrAg) was tested using a chemiluminescent enzyme immunoassay with LUMIPULSE (Fujirebio). HBV genotypes were determined using the IMMUNIS HBV genotype EIA kit (Institute of Immunology, Tokyo, Japan). As a liver fibrosis marker, FIB-4 index was calculated as follows: FIB-4 = age (years) × aspartate aminotransferase (U/L)/(platelet counts [PLT, 10^9/l] × √ alanine aminotransferase [ALT, U/L]).[14] Imaging tests including abdominal ultrasonography or computed tomography test were performed for the screening of liver cancer.

2.5. Ethics and end point

The primary efficacy endpoint was the change of serum HBsAg and HBsAg normalization at 24 months, and the secondary endpoints were the serum HBV DNA sustained normalization, the changes of ALT, the HBeAg sero-clearance, estimated glomerular filtration rate (eGFR), and inorganic phosphorus (IP).

The description of the Case Report Form for the data collection was made by the attending physicians. The principal investigators of each institution submitted the case report form to the research office. Before the submission, information that

could identify an individual was deleted. This study was registered on University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR, ID: UMIN000032201). The study protocol conformed to the guidelines described in the Declaration of Helsinki and was approved by the Medical Ethics Committee of Tohoku University (approval no. 2018-2-177). Written informed consent was obtained from each patient.

2.6. Statistical analysis

Statistical analysis was performed using JMP version 14.2 (SAS Institute Inc., Cary, NC). Statistical comparisons were performed using a χ^2 test for the comparison of frequencies between the 2 groups or a Wilcoxon rank sum test for the comparison of continuous variables between 2 groups. As an additional analysis to eliminate the effects of an uneven distribution of gender, only male patients were analyzed using analysis of covariance (ANCOVA) to adjust the parameters with baseline data in comparisons between the TAF and ETV groups. $P < .05$ was considered to indicate a statistically significant difference.

3. Results

3.1. Clinical characteristics of the enrolled patients

The mean age of the 30 patients who were evaluated in the present study was 61 years old and 18 patients (60%) were male. The median ALT, PLT, and HBsAg were 19 U/L, 18.2 × 10^4/μL, and 2.9 log IU/mL, respectively. The HBV DNA of all patients were below detection limit. A total of 11 (37%) and 18 (60%) patients were infected with HBV genotype B and C, respectively, and 1 patient was undetermined. The clinical characteristics of the chronic hepatitis B patients in the TAF switching group (n = 16) and the ETV continuing group (n = 14) are shown in Table 1. The proportion of males and the serum levels of γ-GTP in the TAF group were significantly higher than those in the ETV group. Other characteristics were not significantly different between the 2 groups. The serum HBV DNA levels were undetectable in all patients.

3.2. Comparison of the antiviral effects between the TAF and ETV groups

At first, the change of HBsAg from the randomization (ΔHBsAg) was evaluated. A minus value indicates a decline of HBsAg in comparison with the baseline. There was no significant difference in the mean change of HBsAg at 12 months (–0.06 vs –0.11 log IU/mL, $P = .17$) and at 24 months (–0.08 vs –0.20 log IU/mL, $P = .07$) between the TAF and ETV groups (Fig. 2A).

The mean changes in ALT (ΔALT) from the baseline were similar to those of HBsAg in both groups at 12 months (0.4 vs –2.4 U/l, $P = .08$) and at 24 months (0.5 vs –1.0 U/l, $P = .17$) (Fig. 2B). There were 3 patients who were positive for HBeAg at randomization, and HBeAg sero-clearance was achieved in 1/2 (50%) patients in the TAF group and 0/1 (0%) patients in the ETV group. No patients developed liver cancer during the observation period.

At the time of randomization, the proportion of males in the ETV group was significantly higher than that in the TAF group. Then, to eliminate the effect of uneven distribution of gender, we analyzed only male patients (Table 2) and compared the parameters using ANCOVA to adjust with the baseline data (Fig. 3). ΔHBsAg was not significantly different between the TAF group and the ETV group at 24 months (–0.14 vs –0.22 log IU/mL, $P = .57$) (Fig. 3A). Similarly, ΔALT was not significantly different between the two groups (–4.5 vs 0.3 U/L, $P = .83$) (Fig. 3B).

3.3. Factors associated with HBsAg decline

Table 3 shows the clinical baseline characteristics of patients with a HBsAg decline of 0.1 log IU/mL or more (HBsAg-declined group) and those with a HBsAg decline less than 0.1 log IU/mL (HBsAg-stable group) at 24 months in overall patients. Because 6 patients lacked data of HBsAg at 24 months, we evaluated 24 cases for this analysis. Interestingly, prior ETV duration was significantly shorter in the HBsAg-declined group than in the HBsAg-stable group (49 vs 92 months, $P = .03$). The levels of γ-GTP tended to be higher in the HBsAg-declined group than in the HBsAg-stable group (27 vs 18 U/l, $P = .06$). The reason is

Table 1

Clinical characteristics of the patients evaluated in this study.

Characteristics	Overall, n = 30	TAF group, n = 16	ETV group, n = 14	*P* value (TAF vs ETV)
Age, yr	61 (39–75)	63 (43–74)	60 (39–75)	.819
Sex, male/female	18/12	7/9	11/3	.048
T-Bil, mg/dL	0.9 (0.7–1.1)	0.8 (0.7–1.0)	0.9 (0.8–1.2)	.346
AST, U/L	23 (21–27)	22 (19–26)	23 (21–27)	.358
ALT, U/L	19 (17–24)	18 (17–21)	24 (17–39)	.054
γ-GTP, U/L	19 (17–40)	18 (17–19)	26 (19–47)	.009
Alb, g/dL	4.4 (4.2–4.6)	4.3 (4.2–4.5)	4.5 (4.4–4.7)	.200
Cr, mg/dL	0.77 (0.66–0.91)	0.75 (0.62–0.86)	0.83 (0.69–1.00)	.114
eGFR, mL/min/1.73 m^2	59.2 (49.5–72.4)	61.0 (53.4–77.0)	55.1 (47.6–69.0)	.146
IP, mg/dL	3.3 (3.1–3.7)	3.2 (3.1–3.6)	3.5 (3.3–3.6)	.499
PLT, ×10^4/μL	18.2 (15.5–22.9)	17.8 (15.5–22.9)	18.7 (16.1–21.1)	.983
FIB-4 index	1.59 (1.17–2.17)	1.62 (1.26–2.14)	1.55 (1.13–2.10)	.819
AFP, ng/mL	2.9 (2.2–3.4)	2.6 (2.1–3.4)	2.9 (2.2–3.3)	1.000
HBV DNA, log IU/mL	BDL (BDL-BDL)	BDL (BDL-BDL)	BDL (BDL-BDL)	1.000
HBsAg, log IU/mL	2.90 (2.38–3.16)	2.86 (2.38–3.32)	2.93 (2.67–3.06)	.575
HBeAg, +/–	3/27	4/12	2/12	.507
HBcrAg, log U/mL	3.6 (3.2–5.3)	3.2 (BDL-3.4)	BDL (BDL-1.9)	.608
HBV genotype, B/C/unknown	11/18/1	6/9/1	5/9/0	.511
Prior ETV duration, months	81 (43–105)	87 (49–119)	59 (42–89)	.329
Previous IFN-α treatment, yes/no	1/29	1/15	0/14	.340

Median (interquartile range) or number is indicated.

AFP = α fetoprotein, Alb = albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BDL = below detection limit, Cr = creatinine, eGFR = estimated glomerular filtration rate, ETV = entecavir, γ-GTP = γ-glutamyltransferase, HBcrAg = hepatitis B core-related antigen, HBeAg = hepatitis B e antigen, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, IP = inorganic phosphorus, PLT = platelet counts, TAF = tenofovir arafenamide, T-Bil = total bilirubin.

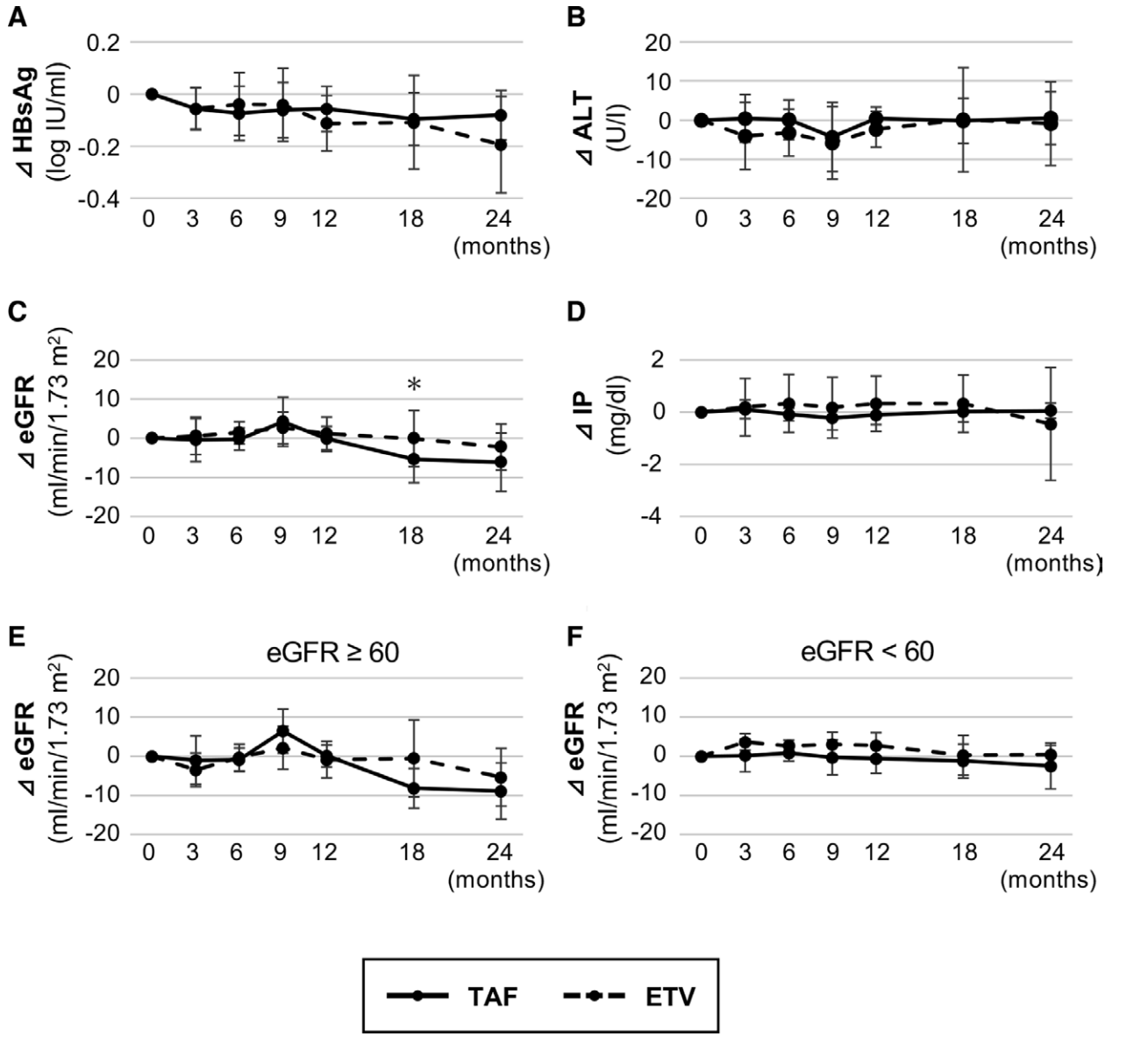

Figure 2. Comparison of the changes in the assessed parameters from baseline between TAF-switching group and ETV-continuing group. (A–D) The changes of HBsAg (A), ALT (B), eGFR (C), and IP (D). (E,F) eGFR change in patients with eGFR ≥ 60 mL/min/1.73 m^2 (E) and eGFR < 60 mL/min/1.73 m^2 (F). Solid lines indicate means of TAF-switching group and dotted lines indicate those of ETV-continuing group. Error bars indicate standard deviations (SDs). *, $P < .05$. ALT = alanine aminotransferase, eGFR = estimated glomerular filtration rate, ETV = entecavir, HBsAg = hepatitis B surface antigen, IP = inorganic phosphorus, TAF = tenofovir alafenamide fumarate.

unclear, but because the γ-GTP levels were significantly higher in the ETV group at baseline, there was a possibility that the ETV group might had an advantage at this point due to the uneven distribution of gender. There was no statistical difference in FIB-4 index and HBsAg levels.

Next, the clinical baseline characteristics were compared to patients with HBsAg decline of 0.1 log IU/mL or more and those without in the TAF group (Table 4). HBsAg-declined patients tended to have lower PLT (16.4 vs 22.7 × 10^4/μL, $P = .09$) and higher FIB-4 levels (2.08 vs 1.26, $P = .12$). Therefore, it was suggested that switching to TAF might decrease HBsAg more in patients with advanced liver fibrosis. Also, HBsAg-declined patients tended to have lower HBsAg (2.85 vs 3.34 log IU/mL, $P = .17$) at randomization. The patients with both low PLT (<19.3 × 10^4/μL) and low HBsAg (<3.46 log IU/mL) at randomization had a significantly larger decline in HBsAg than the patients without (–0.1 vs –0.05 log IU/mL, $P = .03$) (Fig. 4A). Figure 4B shows the HBsAg change in each patient in TAF-group with both low PLT and low HBsAg or those without. The HBsAg levels of all 8 patients with both low PLT and low HBsAg declined from baseline to 24 months. Importantly, such a difference was not observed in the ETV group (–0.16 vs –0.21 log IU/mL, $P = .87$). The patients with high FIB-4 index (≥1.67) and those with a short prior ETV duration (<87 months) tended to have a larger decline of HBsAg, but the differences were not significant (Fig. 4A).

3.4. Comparison of safety profiles between the TAF and ETV groups

The eGFR levels tended to decline more in the TAF group than in the ETV group at 12 months (ΔeGFR, –0.19 vs 1.22 mL/min/1.73 m^2, $P = .19$), 18 months (–5.41 vs –0.07 mL/min/1.73 m^2, $P = .01$), and 24 months (–6.15 vs –2.26 mL/min/1.73 m^2, $P = .09$), and the differences were statistically significant only at 18 months (Fig. 2C). However, this result might be influenced by the uneven distribution of gender between TAF group and ETV group. When we analyzed only male patients using ANCOVA, there was no significantly difference in the ΔeGFR

Table 2

Clinical characteristics of the male patients evaluated in this study.

Characteristics	Overall, n = 18	TAF group, n = 7	ETV group, n = 11	*P* value (TAF vs ETV)
Age, yr	61 (49–68)	64 (51–67)	59 (47–68)	.751
T-Bil, mg/dL	1.0 (0.9–1.2)	1.0 (0.9–1.2)	0.9 (0.9–1.2)	.584
AST, U/L	23 (21–27)	22 (20–27)	23 (21–31)	.585
ALT, U/L	22 (17–35)	20 (18–24)	24 (18–40)	.275
γ-GTP, U/L	24 (18–44)	17 (16–35)	27 (20–55)	.160
Alb, g/dL	4.5 (4.2–4.6)	4.2 (4.1–4.5)	4.5 (4.4–4.8)	.158
Cr, mg/dL	0.86 (0.79–0.94)	0.86 (0.82–0.89)	0.92 (0.79–0.96)	.555
eGFR, mL/min/1.73 m^2	50.9 (47.8–57.8)	51.4 (50.1–56.1)	48.8 (45.5–61.2)	.497
IP, mg/dL	3.1 (2.8–3.6)	2.8 (2.5–3.0)	3.5 (3.1–3.7)	.059
PLT, $\times 10^4$/mL	18.7 (16.2–21.5)	16.4 (15.2–19.8)	19.2 (18.2–22.4)	.258
FIB-4 index	1.51 (1.13–2.00)	1.60 (1.37–2.21)	1.50 (1.05–1.60)	.298
AFP, ng/mL	2.9 (2.2–3.5)	2.8 (2.4–3.3)	2.9 (2.1–3.5)	.957
HBV DNA, log IU/mL	BDL (BDL-BDL)	BDL (BDL-BDL)	BDL (BDL-BDL)	1.000
HBsAg, IU/mL	762 (231–1157)	241 (166–721)	835 (578–1247)	.160
HBeAg, +/–	1/17	0/7	1/10	1.000
HBcrAg, log U/mL	BDL (BDL-BDL)	BDL (BDL-1.6)	BDL (BDL-BDL)	.317
HBV genotype, B/C/unknown	7/11/0	3/4/0	4/7/0	.783
Prior ETV duration, months	54 (41–101)	82 (41–111)	49 (41–87)	.618
Previous IFN-α treatment, yes/no	0/18	0/7	0/11	-

Median (interquartile range) or number is indicated.

AFP = α fetoprotein, Alb = albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BDL = below detection limit, Cr = creatinine, eGFR = estimated glomerular filtration rate, ETV = entecavir, γ-GTP = γ-glutamyltransferase, HBcrAg = hepatitis B core-related antigen, HBeAg = hepatitis B e antigen, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, IP = inorganic phosphorus, PLT = platelet counts, TAF = tenofovir arafenamide, T-Bil = total bilirubin.

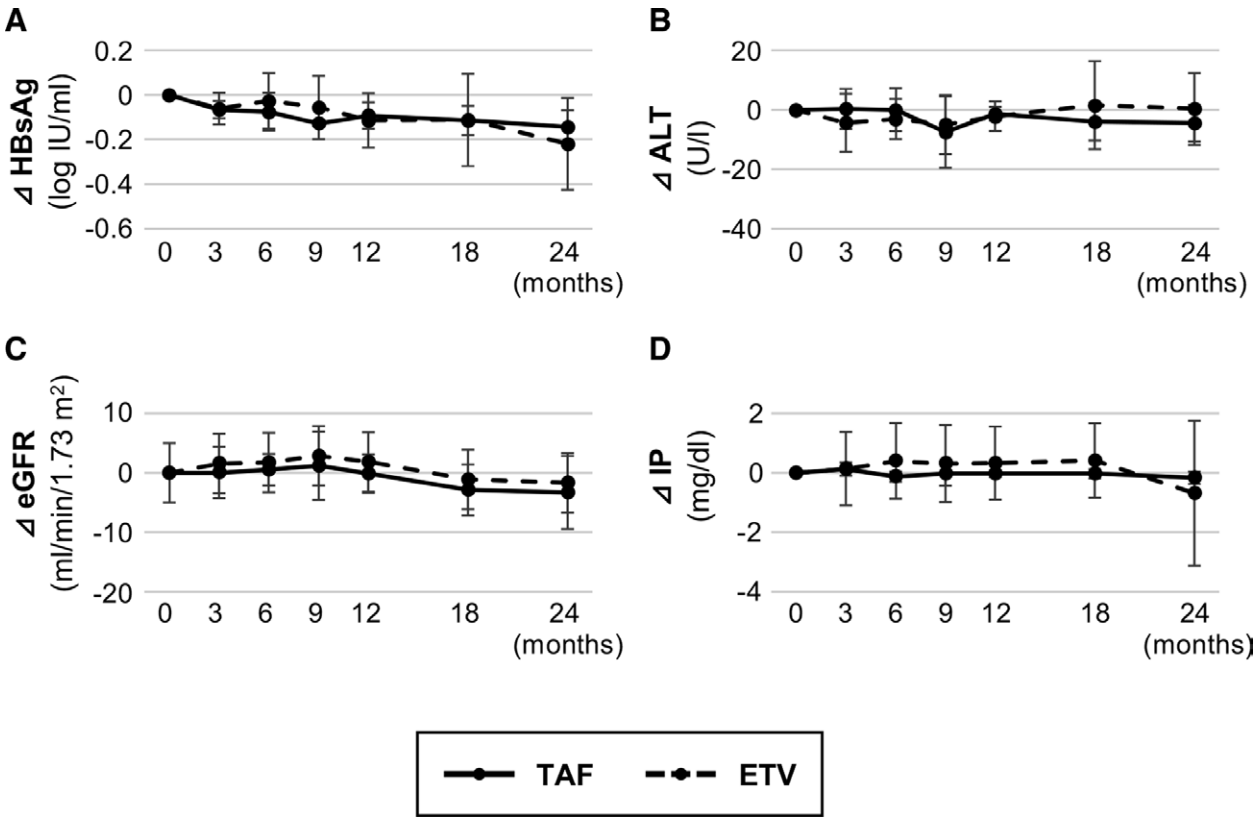

Figure 3. Comparison of the changes in the assessed parameters from baseline between TAF-switching group and ETV-continuing group only in male patients. (A–D) The changes of HBsAg (A), ALT (B), eGFR (C), and IP (D). Solid lines indicate means of TAF-switching group and dotted lines indicate those of ETV-continuing group. Error bars indicate standard deviations (SDs). ALT = alanine aminotransferase, eGFR = estimated glomerular filtration rate, ETV = entecavir, HBsAg = hepatitis B surface antigen, IP = inorganic phosphorus, TAF = tenofovir alafenamide fumarate.

at all time points including at 18 months (–2.90 vs –1.12 mL/min/1.73 m^2, *P* = .55) (Fig. 3C). Additionally, in patients with eGFR <60 mL/min/1.73 m^2 at randomization (n = 15), there were no differences in the two groups at 18 months (–1.22 vs 0.26 mL/min/1.73 m^2, *P* = .44), at 24 months (–2.49 vs 0.40 mL/min/1.73 m^2, *P* = .25) and at other time points (Fig. 2E and F). Therefore, we considered that TAF is tolerable for patients with mild renal dysfunction as ETV.

Table 3

Clinical characteristics of the patients with HBsAg-declined group or HBsAg-stable group.

Characteristics	HBsAg-declined*, n = 13	HBsAg-stable†, n = 11	*P* value
Age, yr	54 (42–74)	59 (43–74)	.310
Sex, male/female	9/4	4/7	.107
T-Bil, mg/dL	0.9 (0.7–1.0)	0.8 (0.8–1.2)	.537
AST, U/L	25 (20–31)	22 (21–23)	.210
ALT, U/L	24 (15–40)	18 (17–22)	.162
γ-GTP, U/L	27 (18–47)	18 (14–20)	.055
Alb, g/dL	4.4 (4.1–4.6)	4.4 (4.3–4.6)	.415
Cr, mg/dL	0.76 (0.67–0.89)	0.73 (0.62–0.96)	.862
eGFR, mL/min/1.73 m^2	61.9 (52.8–73.5)	60.3 (48.8–80.7)	.931
IP, mg/dL	3.5 (3.1–3.8)	3.3 (3.0–3.7)	.539
PLT, $\times 10^4/\mu L$	17.7 (14.4–20.2)	20.9 (15.6–23.6)	.385
FIB-4 index	1.50 (1.15–2.15)	1.53 (1.06–2.16)	.931
AFP, ng/mL	2.8 (2.2–4.1)	2.9 (2.1–3.8)	.843
HBV DNA, log IU/mL	BDL (BDL-BDL)	BDL (BDL-BDL)	-
HBsAg, log IU/mL	2.91 (2.56–3.17)	3.09 (2.38–3.45)	.543
HBeAg, +/–	1/12	2/9	.439
HBcrAg, log U/mL	4.3 (3.7–4.8)	3.4 (3.2–5.8)	.696
HBV genotype, B/C/unknown	5/8/0	3/7/1	.494
Prior ETV duration, months	49 (14–117)	92 (14–175)	.030
Previous IFN-α treatment, yes/no	0/13	1/10	.267
Treatment group, TAF/ETV	5/8	7/4	.219

Median (interquartile range) or number is indicated.

AFP = α fetoprotein, Alb = albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BDL = below detection limit, Cr = creatinine, eGFR = estimated glomerular filtration rate, ETV = entecavir, γ-GTP = γ-glutamyltransferase, HBcrAg = hepatitis B core-related antigen, HBeAg = hepatitis B e antigen, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, IP = inorganic phosphorus, PLT = platelet counts, TAF = tenofovir arafenamide, T-Bil = total bilirubin.

* ⊿ HBsAg (24 months) ≤ –0.1 logIU/mL.

† ⊿ HBsAg (24 months) > –0.1 logIU/mL.

Table 4

Clinical characteristics of the patients with HBsAg-declined or HBsAg-stable in TAF-switching group.

	TAF group		
Characteristics	HBsAg-declined*, n = 5	HBsAg-stable†, n = 7	*P* value
Age, yr	53 (47–68)	59 (46–66)	.935
Sex, male/female	3/2	1/6	.098
T-Bil, mg/dL	0.8 (0.7–1.2)	0.8 (0.6–0.8)	.671
AST, U/L	26 (18–27)	22 (21–23)	.566
ALT, U/L	18 (13–26)	18 (17–19)	.935
γ-GTP, U/L	18 (16–45)	17 (13–18)	.190
Alb, g/dL	4.4 (4.1–4.7)	4.3 (4.2–4.4)	.849
Cr, mg/dL	0.78 (0.66–0.90)	0.69 (0.59–0.76)	.168
eGFR, mL/min/1.73 m^2	61.6 (52.8–68.8)	69.6 (58.2–82.2)	.223
IP, mg/dL	3.3 (3.0–3.9)	3.2 (3.1–3.8)	.924
PLT, $\times 10^4/\mu L$	16.4 (14.2–17.8)	22.7 (15.6–24.9)	.088
FIB-4 index	2.08 (1.37–2.27)	1.26 (1.06–2.13)	.123
AFP, ng/mL	2.4 (2.2–4.6)	2.9 (1.7–5.1)	.705
HBV DNA, log IU/mL	BDL (BDL-BDL)	BDL (BDL-BDL)	1.000
HBsAg, log IU/mL	2.85 (2.37–3.15)	3.34 (2.75–3.62)	.168
HBeAg, +/–	0/5	2/5	.190
HBcrAg, log U/mL	BDL (BDL-BDL)	3.4 (3.2–5.8)	-
HBV genotype, B/C/unknown	3/2/0	2/4/1	.455
Prior ETV duration, months	48.8 (33.6–98.7)	92.4 (78.0–124.9)	.223
Previous IFN-α treatment, yes/no	0/5	1/6	.377

Median (interquartile range) or number is indicated.

AFP = α fetoprotein, Alb = albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BDL = below detection limit, Cr = creatinine, eGFR = estimated glomerular filtration rate, ETV = entecavir, γ-GTP = γ-glutamyltransferase, HBcrAg = hepatitis B core-related antigen, HBeAg = hepatitis B e antigen, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, IP = inorganic phosphorus, PLT = platelet counts, TAF = tenofovir arafenamide, T-Bil = total bilirubin.

* ⊿ HBsAg (24 months) ≤ –0.1 logIU/mL.

† ⊿ HBsAg (24 months) > –0.1 logIU/mL.

The changes in the serum IP levels (ΔIP) were not significantly different in the TAF and ETV groups at 12 months (–0.12 vs 0.32 mg/dL, *P* = .27), 18 months (0.02 vs 0.32 mg/dL, *P* = .97), and 24 months (0.06 vs –0.46 mg/dL, *P* = .52) (Fig. 2D). Similar results were obtained from the male data using ANCOVA for the ΔIP at 12 months (–0.03 vs 0.32 mg/dL, *P* = .58), 18 months (–0.03 vs 0.41 mg/dL, *P* = .64), and 24 months (–0.17 vs –0.69 mg/dL, *P* = .44) (Fig. 3D).

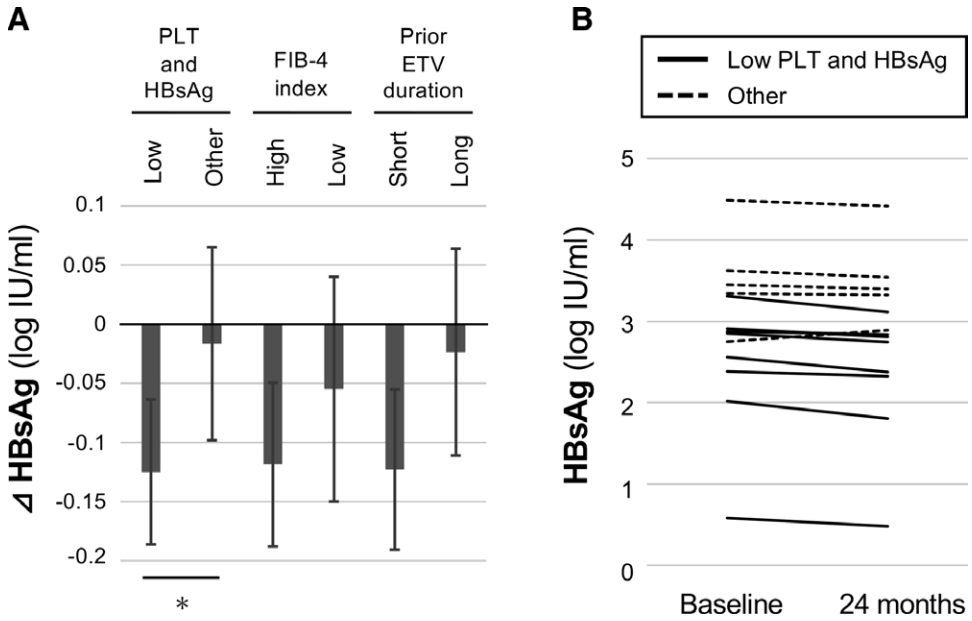

Figure 4. Changes of HBsAg between baseline and 24 months later in patients of the TAF-switching group. (A) Comparison of HBsAg changes between patients with both low PLT (< 19.3×10^4/μL) and low HBsAg (< 3.46 log IU/mL) and those without, between patients with high FIB-4 index (≥1.67) and those with low FIB-4 index (<1.67), and between patients with short prior ETV duration (<87 months) and those with long duration (≥87 months). Bars and error bars indicate means and SDs, respectively. *, $P < .05$. (B) HBsAg levels at baseline and 24 months later in each patient of TAF-switching group. Solid lines indicate patients with both low PLT and low HBsAg and dotted lines indicate those without. ETV = entecavir, HBsAg = hepatitis B surface antigen, PLT = platelet counts, SD = standard deviation, TAF = tenofovir alafenamide fumarate.

4. Discussion

In this study, we firstly performed a randomized controlled study to evaluate the efficacy and safety of patients with chronic hepatitis B after switching from ETV to TAF. We aimed to verify the hypothesis that an effect of TAF-switching on the HBsAg decline is greater, but the results after 24 months were comparable. When comparing the patients with HBsAg decline and those without, the prior ETV duration was shorter in the group with declined HBsAg. Also, in the TAF group, HBsAg was more declined in patients with advanced liver fibrosis.

As a non-randomized study for treatment switch from ETV to TAF, Kumada et al compared the percent decline rate of HBsAg before and after switching and showed that the percentage of the HBsAg decline was greater than 12 months after switching than before (–5.56% vs –3.03%, $P < .0001$).[15] Uchida et al reported that the degree of the HBsAg reduction during the TAF administration period tended to be more than that during the ETV administration period (–0.068 vs –0.041 log U/mL, $P = .07$).[16] However, in these studies, the evaluation timings of ETV and TAF after the start of NAs were different due to the study protocols. More recently, Itokawa et al[17] reported a retrospective study to compare ETV-TAF switch and continuous ETV using a propensity score matching that showed there was no significant decline of HBsAg after 48 weeks. Also, Hagiwara et al[18] performed a prospective controlled trial in which treatment switch was selected on patients' request and showed no differences in HBsAg decline and renal/bone safety. It might be difficult to obtain further effects after switching to TAF because all cases in the present study had HBV DNA ≤ 1.0 log IU/mL at the time of switching to TAF. However, it has been reported that switching treatment from ETV to TAF is effective on HBV DNA suppression in patients with an inadequate reduction of HBV DNA during ETV treatment,[19,20] and TAF can be expected to be useful in such a cohort. Also, in this study, the prior ETV duration was significantly shorter in the HBsAg-declined group. This suggests that the timing of the treatment switch or evaluation may affect the outcome of the HBsAg decline.

It was reported that the blood levels of the antiviral cytokine IFN-λ3 were significantly higher in patients treated with acyclic nucleotide phosphonates, adefovir dipivoxil, and TDF than in patients treated with lamivudine or ETV.[21] In that study, the addition of adefovir dipivoxil and TDF to colorectal cancer-derived cell lines induced IFN-λ3 production, and the culture supernatant suppressed HBsAg production in HBV-expressing HCC cell lines. Additionally, these drugs inhibited IL-10 production and reciprocally induced IL-12p70 and tumor necrosis factor-α production from peripheral blood mononuclear cells.[22] These data suggest that tenofovir may have an antiviral effect mediated by the immune system in addition to the reverse transcriptase inhibitory effect. In our previous randomized controlled study, treatment switch from ETV to TDF reduced HBsAg significantly more in HBeAg-positive patients than in HBeAg-negative patients.[23] Also, in treatment-naïve patients, TDF showed significantly greater effects on the HBsAg reduction in HBeAg-positive patients.[10] Because HBeAg has immunomodulatory effects[24] and alters the intracellular trafficking pathway,[25] the status of HBeAg may alter the results in the HBsAg decline by tenofovir. However, the present study could not show this point because only 10% (3/30) were HBeAg-positive patients.

This study showed that HBsAg was decreased more in those with both low PLT and low HBsAg in the TAF group. It has been previously reported that the HBsAg levels and liver fibrosis are inversely correlated in HBeAg-positive patients,[26,27] which may be due to a decrease in HBsAg production or secretion in hepatocytes, or a decrease in the host's ability to replicate viruses. In this study, as in a previous report,[28] patients in the TAF switching group with low baseline HBsAg levels, compared to patients with high baseline HBsAg levels, tended to show the decreased HBsAg levels. Therefore, it may be beneficial to switch from ETV to TAF in patients with low PLT and low HBsAg levels. However, in contrast to these data, another report showed that the HBsAg reduction after switching to TAF became higher than that during the ETV administration period in patients with high serum levels of HBsAg (≥100 IU/mL) without liver cirrhosis.[16] This point should be clarified in a large study.

It has been reported that ETV does not affect the renal function even in patients with severe renal dysfunction.[29] TDF, a prodrug of tenofovir, causes kidney tubular dysfunction in 10.6% of patients with human immunodeficiency virus[30] and it has been known that its long-term administration results in renal damage and decreased bone mineral density. TAF is also a prodrug of tenofovir, but it is more stable in plasma than TDF, and its metabolite can reach hepatocytes at high concentrations.[31] A phase 3 study comparing TDF and TAF reported that the reduction of eGFR and bone mineral density was significantly lower in TAF-treated patients.[32] Regarding the effect of TAF on renal function compared to ETV, renal dysfunction was similar even when switching from ETV to TAF.[16–18,20,28] In this study, eGFR was more likely to be reduced in the TAF group than in the ETV group, but there was no significant difference between the ETV group and the TAF group in cases with a baseline eGFR of less than 60 mL/min/1.73 m^2. Therefore, TAF may be safe in patients with mild renal impairment.

There are some limitations in the present study. First, the number of included patients were limited. It was difficult for us to include planned numbers of patients because there were more patients and investigators who did not want to participate a randomized control study than we expected. This is a major limitation and the results need to be validated in a larger study. Second, group assignments were intended to be equal in the study design, but sex differences were unintentionally made due to the small study size. Third, HBcrAg has been reported to be associated with hepatic cccDNA,[33] but due to lack of relevant data, HBcrAg changes could not be evaluated. Fourth, although tenofovir can affect bone mineral density,[32] this could not be evaluated.

In conclusion, our study showed that the effects of switching from ETV to TAF on serum HBsAg levels and renal functions were comparable to continuation of ETV. To clarify the strategy for maximizing the benefit from NAs including TAF, further larger studies are needed.

Author contributions

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