Sequential HBV Treatment With Tenofovir Alafenamide for Patients With Chronic Hepatitis B: Week 96 Results From a Real-world, Multicenter Cohort Study

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Abstract

Background and Aims

Outcome data of sequential hepatitis B virus treatment with tenofovir alafenamide (TAF) are limited. We aimed to assess the effectiveness and renal safety of TAF in chronic hepatitis B (CHB) patients who were previously treated with entecavir (ETV), tenofovir disoproxil fumarate (TDF), or nucleos(t)ide analog (NA) combination.

Methods

This multicenter, retrospective, cohort study included 458 consecutive CHB patients who switched to TAF monotherapy after at least two years of treatment with another NA. The longitudinal virological/laboratory responses were evaluated up to 96 weeks after switchover. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR)<60 mL/min/1.73m^2.

Results

The proportions of HBV DNA suppression (HBV DNA<20 IU/mL) at week 96 were 99.0%, 97.8%, and 98.4% in the prior ETV (n=198), TDF (n=137), and NA combination (n=123) groups, respectively. Almost all patients with HBV DNA of 20-2000 IU/mL at baseline achieved HBV DNA suppression at week 96. On multivariable generalized estimated equation (GEE) analysis, a low quantitative hepatitis surface antigen (qHBsAg) level at baseline was associated with a lower follow-up qHBsAg level (coefficient 0.81, *P*<0.001). The eGFR showed greater improvement in patients with CKD compared to those with non-CKD according to the multivariable GEE analysis (coefficient 21.7, *P*<0.001). However, the increase of eGFR reached a peak between weeks 24 and 48.

Conclusions

Based on this longitudinal data analysis up to 96 weeks, sequential NA therapy with a switch to TAF is a good option to better achieve high viral suppression and renal safety.

Introduction

Chronic hepatitis B (CHB) remains one of the leading causes of cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality worldwide [1, 2]. Antiviral treatment with potent nucleos(t)ide analogues (NA) such as entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide fumarate (TAF) is widespread, and they have been recommended as first-line oral agents that can reduce the risk of HCC development and liver-related complications [3–5]. Hepatitis B surface antigen (HBsAg) seroclearance is currently regarded as the functional cure because this is uncommon among treated patients [6, 7], thus for almost all patients lifelong NA treatment is necessary.

TAF is the newest NA drug approved for use in hepatitis B virus (HBV) treatment in Japan, at the end of 2016.
It is a prodrug of tenofovir, a nucleotide analogue that inhibits reverse transcription of both HBV and human immunodeficiency virus (HIV) [8]. Other first-line drugs with ETV and TDF were approved in 2005 and 2008, respectively, and good virological efficacy has been provided [9–11], although impaired kidney function and decreased bone mineral density (BMD) have been reported in long-term TDF treatment [12, 13]. Therefore, the majority of CHB patients continue to be treated with ETV or TDF. According to ongoing phase III trials of the efficacy and safety of TAF versus TDF for CHB patients [14–16], TAF has been shown to be virologically effective and well tolerated, with improved renal and bone safety for patients switching from TDF. Unfortunately, data, including real-world data, on the effectiveness and safety of TAF following switching from ETV or NA combinations is lacking.

We recently published real-world data on the effectiveness and renal safety of TAF for patients who had previously been treated with ETV or NA combinations [17]. Our results showed that the rate of HBV DNA suppression significantly increased and that a continued reduction of the quantitative HBsAg (qHBsAg) level was noted at week 48. Moreover, the estimated glomerular filtration rate (eGFR) was significantly improved in patients with chronic kidney disease (CKD) who were treated with a nucleotide analogue. Although advantages from the switchover were elucidated, the length of time for follow-up post switch was somewhat short, less than one year, thus, the purpose of this study was to examine virological, biochemical, and renal outcomes up to 96 weeks in a multicenter, real-world cohort of CHB patients who have switched to TAF from ETV, TDF, or an NA combination.

Patients And Methods

Patients

The Kyushu University Liver Disease Study (KULDS) Group consists of hepatologists from Kyushu University Hospital and its affiliated hospitals located in the northern Kyushu area of Japan. This multicenter, retrospective, observational cohort study consisted of consecutive patients from March 2017 until December 2018 who switched to a fixed-dose of TAF, 25mg orally once daily (Vemlidy; Gilead Sciences K.K., Tokyo, Japan).

Eligible patients were (1) aged 18 years and older with confirmed chronic HBV infection, and (2) NA treatment switching to TAF monotherapy from an at least two-year course of ETV, TDF, or an NA combination of lamivudine (LAM)/adeforvir (ADF), LAM/TDF, ETV/ADF, or ETV/TDF. Exclusion criteria included (1) duration of follow-up under two years: (2) viable HCC within three months before TAF initiation by imaging examination such as abdominal ultrasound, computed tomography, or magnetic resonance imaging; (3) positivity for antibody to HIV or positivity for hepatitis C antibody; (4) terminal illness; and (5) insufficient medical records for primary endpoints and objectives.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the STROBE statement.

It was approved by the Ethics Committees of Kyushu University Hospital and each study site and is registered as a clinical study on the University Hospital Medical Information Network (ID 000034696).

Laboratory, and virological assessments

All patients were followed every 8–12 weeks during TAF treatment.
Laboratory assessments included hematological analysis, serum biochemistry tests, and urinalysis, including measures of renal function. The eGFR was calculated with the following formulas [18]; for men eGFR (mL/min/1.73m^2) = 194 × serum creatinine level$^{-1.094}$ × age$^{-0.287}$ and for women eGFR = 194 × SCr$^{-1.094}$ × age$^{-0.287}$ × 0.739. As a renal safety endpoint, we defined CKD and the lower limit of the serum phosphorus level as an eGFR < 60 mL/min/1.73m^2 and serum phosphorus level < 2.5 mg/dL, respectively. Liver cirrhosis was defined by liver biopsy demonstrating a METAVIR F4 score, transient elastography (FibroScan®; Echosens, Paris, France) greater than 12.0 kPa [19], or ultrasound examination with signs of cirrhosis based on nodularity, portal velocity, liver size, caudate hypertrophy, echogenicity, portal vein diameter, and spleen size. These assessments were performed within three months before the initiation of TAF treatment.

Primary and secondary endpoints

The primary endpoint was the proportion of patients with HBV DNA suppression (less than 20 IU/mL, the lower limit of quantitation) as determined by real-time reverse transcriptase PCR assay (COBAS TaqMan HBV assay, Version 2.0) (Roche Molecular Diagnostics, Tokyo, Japan) at week 96 after switching to TAF. Key prespecified secondary endpoints were the longitudinal change of alanine aminotransferase (ALT), qHBsAg level, and eGFR. A patient was determined to have ALT normalization if ALT was less than 35 U/L for men or 25 U/L for women, according to the American Association for the Study of Liver Diseases (AASLD) normal range [3]. Moreover, we calculated complete response rates with both HBV DNA suppression and ALT normalization.

Statistical analysis

Statistical analyses were conducted using SPSS Statistics version 25.0 (IBM SPSS Inc, Chicago, IL, USA). Baseline continuous data are expressed as median (first-third quartile) or mean (± standard deviation) and categorical variables are reported as frequencies and percentages. Trends for continuous variables were assessed using the repeated measures ANOVA test. Univariate analyses were done using the Chi-square, Student's *t*, or Mann-Whitney U test, as appropriate. We used the multivariable generalized estimating equation (GEE) model adjusted for age, sex, body mass index (BMI), cirrhosis, hypertension, diabetes mellitus, and previous NA regimen to estimate coefficients associated with baseline parameters or factors to changes in ALT, qHBsAg level, and eGFR. The results are expressed as coefficients and their 95% confidence interval (CI). A *P* value less than 0.05 was regarded as statistically significant in all analyses.

Results

Patient characteristics

A total of 478 patients who switched to TAF were identified during the study period.

Twenty were excluded in accordance with the criteria, leaving the data of 458 available for analysis. Of the eligible patients, 198 (43.2%) received ETV, 137 (29.9%) TDF, and 123 (26.9%) an NA combination before switching to TAF. Demographic and baseline characteristics according to the previous NA treatment are shown in Table 1. Median treatment durations of the previous drug for the ETV, TDF, and NA combination groups were 7.0, 4.5, and 4.3 years, respectively.

Table 1
Baseline characteristics according to the previous nucleos(t)ide analog (NA) treatment

Previous NA regimen	Entecavir	Tenofovir disoproxil fumarate	NA combination
Number	**198**	**137**	**123**
Age	61 (50–69)	51 (43–66)	61 (53–68)
range	26–90	29–79	33–84
Male	124 (62.6)	78 (56.9)	81 (65.9)
Body mass index (kg/m^2)	22.4 (20.3–24.3)	22.3 (20.5–24.9)	22.9 (20.9–25.2)
Cirrhosis	27 (13.6)	20 (14.6)	23 (18.7)
History of HCC	19 (9.6)	16 (11.7)	22 (17.9)
Hypertension	58 (29.3)	14 (10.2)	25 (20.3)
Diabetes	26 (13.1)	14 (10.2)	16 (13.0)
Albumin (g/L)	43 (41–45)	43 (41–45)	44 (41–46)
Total bilirubin (mg/dL)	0.8 (0.5–1.1)	0.7 (0.5-1.0)	0.7 (0.4-1.0)
AST (U/L)	24 (19–29)	25 (22–32)	24 (20–30)
ALT (U/L)	20 (14–27)	24 (18–34)	20 (16–31)
gGTP (U/L)	24 (17–44)	21 (15–40)	21 (15–42)
eGFR (mL/min/1.73m^2)	71 (61–82)	74 (62–85)	69 (55–81)
30–60	44 (22.2)	29 (21.2)	34 (27.6)
15- < 30	2 (1.0)	2 (1.5)	3 (2.4)
Phosphorus (mg/dL)	3.3 (3.0-3.6)	3.3 (2.8–3.7)	3.0 (2.6–3.5)
AFP (ng/mL)	2.9 (2.0-3.4)	3.0 (2.2–4.4)	3.0 (2.1–3.7)
Platelet count (10^3/μL)	178 (146–218)	184 (144–235)	183 (139–221)
HBeAg positive	28 (14.1)	31 (22.6)	27 (22.0)

Data are n (%) or median (first-third quartile).

HCC, hepatocellular carcinoma; AST, aspartate aminotransferase; ALT, alanine aminotransferase; gGTP, gamma-glutamyl transpeptidase; eGFR, estimated glomerular filtration rate; AFP, alpha-fetoprotein; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LAM, lamivudine; ADV, adefovir; ETV, entecavir; TDF, tenofovir disoproxil fumarate.

Previous NA regimen	Entecavir	Tenofovir disoproxil fumarate	NA combination
HBV DNA (IU/mL)	152 (76.8)	130 (94.9)	113 (91.9)
< 20 + or negative	34 (17.2)	7 (5.1)	10 (8.1)
20 – 2,000	12 (6.1)	0	0
> 2,000			
Previous NA treatment duration (year)	5.0 (4.3–7.4)	3.2 (2.6–3.5)	4.3 (3.2–9.2)
Previous NAs combination			44 (35.8)
LAM + ADV			39 (31.7)
LAM + TDF			3 (2.4)
ETV + ADV			37 (30.1)
ETV + TDF			
Data are n (%) or median (first-third quartile).			
HCC, hepatocellular carcinoma; AST, aspartate aminotransferase; ALT, alanine aminotransferase; gGTP, gamma-glutamyl transpeptidase; eGFR, estimated glomerular filtration rate; AFP, alpha-fetoprotein; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LAM, lamivudine; ADV, adefovir; ETV, entecavir; TDF, tenofovir disoproxil fumarate.			

In the prior ETV group, the median age was 61, 124 (62.6%) were male, 27 (13.6%) had compensated cirrhosis, and 28 (14.1%) were hepatitis B e antigen (HBeAg)-positive at baseline. Approximately 23% had HBV DNA more than 20 IU/mL. In the prior TDF group, the median age was 51, 78 (56.9%) were male, 20 (14.6%) had compensated cirrhosis, and 31 (22.6%) were HBeAg-positive at baseline. Unlike the prior ETV group, almost all (94.9%) had HBV DNA less than 20 IU/mL. In the prior NA combination group, the median age was 61, 81 (65.9%) were male, 23 (18.7%) had compensated cirrhosis, and 27 (22.0%) were HBeAg-positive at baseline. Similar to the prior TDF group, almost all (91.9%) had HBV DNA less than 20 IU/mL. Furthermore, in the prior TDF and NA combination groups, none of the patients had uncontrolled HBV DNA (> 2,000 IU/mL).

Virological and biochemical responses 96 weeks after switching to TAF

The proportions of HBV DNA suppression at week 96 after switchover were 99.0% (196/198), 97.8% (134/137), and 98.4% (121/123) in the prior ETV, TDF, and NA combination groups, respectively. Of the 46 patients who had prior ETV with HBV DNA of 20-2000 IU/mL at baseline, most achieved HBV DNA suppression from the early stage of TAF treatment, and at week 96 the proportion was 95.7% (42/44) (Table 2). Regardless of the prior treatment regimen, none experienced HBV breakthrough during the follow-up period. In contrast, the achievement rates of HBeAg loss for patients HBeAg-positive at baseline

remained low; under 30% in all prior treatment groups (Table 2). Even though patients had a low-titer of HBeAg (< 10 S/CO) at baseline, only 35–40% had achieved HBeAg loss at week 96.

Table 2
HBeAg loss and HBV DNA suppression after switching to tenofovir alafenamide

	HBeAg titer at baseline (S/CO)	HBeAg loss at week 48	HBeAg loss at week 96	HBV DNA level at baseline (IU/mL)	HBV DNA suppression at week 48	HBV DNA suppression at week 96
Previous ETV						
HBeAg-positive at baseline (n = 28)	1 - <10	3 / 8 (37.5)	3 / 8 (37.5)			
	10 - <100	1 / 5 (20.0)	2 / 5 (40.0)			
	>100	1 / 10 (10.0)	1 / 10 (10.0)			
	Unknown	1 / 5 (20.0)	2 / 5 (40.0)			
HBV DNA-positive at baseline (n = 46)				20-2000	33 / 34 (97.1)	33 / 34 (97.1)
				> 2000	9 / 12 (75.0)	11 / 12 (91.7)
HBV DNA suppression at baseline (n = 152)				< 20	152 / 152 (100)	152 / 152 (100)
Previous TDF						
HBeAg-positive at baseline (n = 31)	1 - <10	5 / 18 (27.8)	7 / 18 (38.9)			
	10 - <100	1 / 6 (16.7)	1 / 6 (16.7)			
	>100	1 / 7 (14.3)	1 / 7 (14.3)			
	Unknown	-	-			
HBV DNA-positive at baseline (n = 7)				20-2000	3 / 7 (42.9)	5 / 7 (71.4)
				> 2000	-	-
HBV DNA suppression at baseline (n = 129)				< 20	129 / 129 (100)	129 / 129 (100)

Data are n (%).

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ETV, entecavir; TDF, tenofovir disoproxil fumarate; NA, nucleos(t)ide analog.

	HBeAg titer at baseline (S/CO)	HBeAg loss at week 48	HBeAg loss at week 96	HBV DNA level at baseline (IU/mL)	HBV DNA suppression at week 48	HBV DNA suppression at week 96
Previous NA combination						
HBeAg-positive at baseline (n = 27)	1 - <10	3 / 11 (30.0)	4 / 11 (36.4)			
	10 - <100	1 / 8 (12.5)	1 / 8 (12.5)			
	>100	0 / 7	0 / 7			
	Unknown	0 / 1	0 / 1			
HBV DNA-positive at baseline (n = 10)				20-2000	7 / 10 (70.0)	8 / 10 (80.0)
				> 2000	-	-
HBV DNA suppression at baseline (n = 113)				< 20	113 / 113 (100)	113 / 113 (100)
Data are n (%).						
HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ETV, entecavir; TDF, tenofovir disoproxil fumarate; NA, nucleos(t)ide analog.						

The longitudinal ALT levels after switching to TAF are shown in Figs. 1–3 according to the prior NA regimen. Approximately 80% with prior ETV or an NA combination had normal ALT at baseline when using the 35/25 U/L cutoff of the AASLD guidelines. This showed no significant trend in the longitudinal levels, although the rates of ALT normalization slightly improved, from 82.3–90.4% and 78.0–83.7% in the prior ETV and NA combination groups, respectively. In contrast, the prior TDF group, in which the proportion of ALT normalization at baseline was relatively low (71.5%), achieved a significant increase in the rate of ALT normalization (86.1%) ($P < 0.05$). The proportions of complete response (both ALT normalization and HBV DNA suppression) at week 96 were 89.4%, 85.4%, and 82.9% in the prior ETV, TDF, and NA combination groups, respectively (**Supplementary Table 1**). There were significant decreases in the qHBsAg level across all time points, irrespective of prior NA regimen (all $P < 0.001$). Only seven patients (1.5%) achieved HBsAg loss during the follow-up period.

Analysis of the longitudinal eGFR and serum phosphorus level, Figs. 1–3, found no significant trend in patients who switched from ETV to TAF. In contrast, the eGFR of patients with CKD who switched from TDF or an NA combination improved from the early stage. The increase of eGFR reached a peak between weeks 24 and 48, then decreased slightly over time.

Factors associated with the changes of ALT, qHBsAg level, and eGFR

Results of our analysis of the factors associated with the changes in ALT, qHBsAg level, and eGFR at 96 weeks after switching to TAF are shown in Table 3. After adjusting for age, sex, BMI, cirrhosis, diabetes mellitus, and prior NA regimen, BMI (coefficient 1.69, 95%CI 0.89–2.49, P < 0.001) and cirrhosis (coefficient 4.03, 95%CI 0.32–7.74, P = 0.033) were associated with a longitudinal change in the ALT level. After adjusting for age, sex, cirrhosis, baseline HBeAg, baseline qHBsAg level, and prior NA regimen, age (coefficient − 7.75, 95%CI -14.3- -1.24, P = 0.020) and baseline qHBsAg level (coefficient 0.81, 95%CI 0.74–0.88, P < 0.001) were associated with a longitudinal change in the qHBsAg level. Lastly, after adjusting for age, sex, BMI, cirrhosis, diabetes mellitus, hypertension, baseline eGFR, and prior NA regimen, age (coefficient − 0.48, 95%CI -0.60- -0.36, P = 0.020) and baseline eGFR < 60 (coefficient 21.7, 95%CI 19.2–24.1, P < 0.001) were associated with a longitudinal change in eGFR.

Table 3
Generalized estimated equation analysis for estimated predictors of changes in ALT, qHBsAg, and eGFR levels after switching to tenofovir alafenamide

	ALT	
Characteristics	**Coefficient (95%CI)**	P**-value**
Age (year)	-0.11 (-0.47–0.25)	0.21
Male	1.69 (-3.13–6.51)	0.49
Body mass index (kg/m^2)	1.69 (0.89–2.49)	< 0.001
Cirrhosis	4.03 (0.32–7.74)	0.033
Diabetes	-2.57 (-7.01–1.87)	0.26
Previous NA regimen		
ETV monotherapy	Reference	
TDF monotherapy	-3.09 (-8.01–1.84)	0.22
NA combination	-1.24 (-6.07–3.60)	0.62
	qHBsAg	
Characteristics	**Coefficient (95%CI)**	P**-value**
Age (year)	-7.75 (-14.3 – -1.24)	0.020
Male	-55.1 (-297–187)	0.66
Cirrhosis	-9.70 (-130–111)	0.88
Baseline HBeAg-positive	-109 (-532–315)	0.61
Baseline qHBsAg	0.81 (0.74–0.88)	< 0.001
Previous NA regimen		
ETV monotherapy	Reference	
TDF monotherapy	27.4 (-259–314)	0.85
NA combination	150 (-98.5–399)	0.24
	eGFR	
Characteristics	**Coefficient (95%CI)**	P**-value**
Age (year)	-0.48 (-0.60 – -0.36)	< 0.001

ALT, alanine aminotransferase; qHBsAg, quantitative hepatitis B surface antigen; eGFR, estimated glomerular filtration rate; CI, confidence interval; NA, nucleos(t)ide analog; ETV, entecavir; TDF, tenofovir disoproxil fumarate; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

	ALT	
Male	-0.41 (-3.04–2.21)	0.76
Body mass index (kg/m^2)	-0.10 (-0.56–0.36)	0.67
Cirrhosis	-0.71 (-3.65–2.22)	0.63
Diabetes	2.14 (-2.23–6.51)	0.34
Hypertension	2.11 (-1.24–5.45)	0.22
Baseline eGFR (mL/min/1.73m^2)		
≥60	Reference	
<60	21.7 (19.2–24.1)	< 0.001
Previous NA regimen		
ETV monotherapy	Reference	
TDF/ADF included	-0.06 (-2.57–2.45)	0.96

ALT, alanine aminotransferase; qHBsAg, quantitative hepatitis B surface antigen; eGFR, estimated glomerular filtration rate; CI, confidence interval; NA, nucleos(t)ide analog; ETV, entecavir; TDF, tenofovir disoproxil fumarate; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

Discussion

In our previous cohort study, we showed the virological effectiveness and the renal safety 48 weeks after switching to TAF [17]. We noted that the durability of the results would need confirmation in longer term analysis. The present study done post-96 weeks confirmed the previous findings and clarified the long-term effects of switching to TAF.

We divided patients into three groups according to the prior NA regimen (ETV, TDF, or NA combination). Almost all had achieved HBV DNA suppression by week 96 post switchover, even those treated with an NA combination. Moreover, the prior NA regimen had little influence on the longitudinal changes of ALT, qHBsAg level, or eGFR. We believe that our study provides important insights into the effectiveness of a switch to TAF for patients with CHB who had been treated with older NAs.

Virological efficacy, including HBV DNA suppression and a decrease of the qHBsAg level, has contributed to a decline of the HCC incidence rate [20–22]. In our prior ETV group, 91.3% of the patients who had detectable HBV DNA at baseline achieved HBV DNA suppression at week 48, as did 95.7% at week 96. Similar findings were seen in the prior TDF and NA combination groups. These incremental improvements following switching to TAF were significant, even though our patients had already received NA treatment for an average duration of more than seven years. It is noteworthy that none of the patients under controlled virological condition by a prior NA regimen experienced viral breakthrough during the 96

weeks after switchover. In contrast, virological response with HBeAg loss was not adequately achieved at week 96. For those with a low-titer of HBeAg (< 10 S/CO) at baseline, fewer than half experienced HBeAg loss. The rate of HBsAg loss remained very low (approximately 1% annually), and the decline in the qHBsAg levels were small (approximately 0.1 logIU/mL annually). Nevertheless, a lower qHBsAg level at baseline was significantly associated with a decreased qHBsAg level.

Consistent with our previous study of 48 weeks [17], we did not observe significant positive changes in the rates of ALT normalization at 96 weeks after switching to TAF. More patients in the prior TDF group who had an elevated ALT level at baseline achieved ALT normalization when using the normal range proposed by AASLD, similar to a recent report [23]; however, as we noted, those who had higher BMI and cirrhosis were less likely to have an improvement in the ALT level at 96 weeks after adjustment for confounding factors. The evaluation of non-alcoholic fatty liver disease and steatohepatitis will be important in the monitoring of patients with elevated ALT levels.

The high prevalence of renal dysfunction highlights the long-term need for careful monitoring or switching to TAF from ADF or TDF treatment, as is recommended in the guidelines [3, 4]. Phase 3 clinical trials, in which virologically suppressed CHB patients were switched from TDF to TAF, showed improvements in kidney parameters at week 96 after switching [23]. One of the strengths of this study was the inclusion of patients with prior ETV or NA combination therapy, all of whom were treated with TAF for at least 96 weeks. In our multivariable GEE analysis that controlled cofounding factors with kidney function, patients of older age and without CKD were less likely to experience positive changes in eGFR. There was no statistically significant trend in eGFR over time for patients with without CKD: the decrement was approximately 1 mL/min/1.73m^2 per year, which is considered to be physiological reduction. Instead, the improvement in eGFR for those with CKD should be emphasized because the decline in eGFR was consistently more in those with lower baseline eGFR. It is also important to note that the incremental improvements following switching to TAF peeked between 24 and 48 weeks then decreased physiologically, but without a statistically significant trend.

Data on the 96 weeks after TAF switchover is currently lacking, so longer-term follow-up will be needed to fully characterize the virological and safety profiles. In addition to the fact that our patients had been previously treated with ETV or an NA combination, the strengths of this study are that it included many elderly (65 and over: $n = 167$) and CKD patients ($n = 114$), which empowers our interpretation. Moreover, we used GEE modeling, which controls for collinearity across variables, allows a bigger sample size to be examined, and makes it possible to better evaluate the related factors for improvements of ALT, qHBsAg level, and eGFR.

This study has several limitations. First, control with a continuing NA groups and data on bone mineral density are lacking, as we mentioned previously. These data will be necessary to better determine differences in clinical outcomes in future study. However, we have provided the data of 458 patients who have been treated with TAF for 96 weeks; to our knowledge, this is the largest real-world study of sequential treatment with TAF. Second, learning the background of or reasons for the switch to TAF for

each patient would be useful to more deeply understand the outcomes: another report suggested that patients who were switched to TAF had better adherence [25]. Last, we have not shown data on the NA drug resistance profile, including LMV, ADF, and ETV. Detailed information regarding the resistance profile would be helpful for the monitoring of intractable cases.

In summary, switching the drug used in HBV treatment to TAF was effective for HBV suppression and continued qHBsAg reduction at 96 weeks. The proportion of complete response reached a plateau at 48 weeks, irrespective of previous NA regimen. Patients with CKD who were previously treated with TDF or an NA combination had a favorable outcome with an improvement of eGFR within one year of switchover that was maintained over the 96 weeks of study.

Abbreviations

CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; NA, nucleos(t)ide analog; ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; BMD, bone mineral density; qHBsAg, quantitative hepatitis B surface antigen; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; LAM, lamivudine; ADF, adefovir; ALT, alanine aminotransferase; AASLD, American Association for the Study of Liver Diseases; GEE, generalized estimating equation; BMI, body mass index; CI, confidence interval; HBeAg, hepatitis B e antigen.

Declarations

Author contributions:

All authors were involved in the design of the study, acquisition of samples and/or analysis. EO drafted the manuscript. All authors contributed to the critical discussion of the results and approved the final version of the article.

Conflicts of interest:

EO has received speaker fees from Gilead Sciences and AbbVie. The other authors declare that they have no conflicts of interest.

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Figures

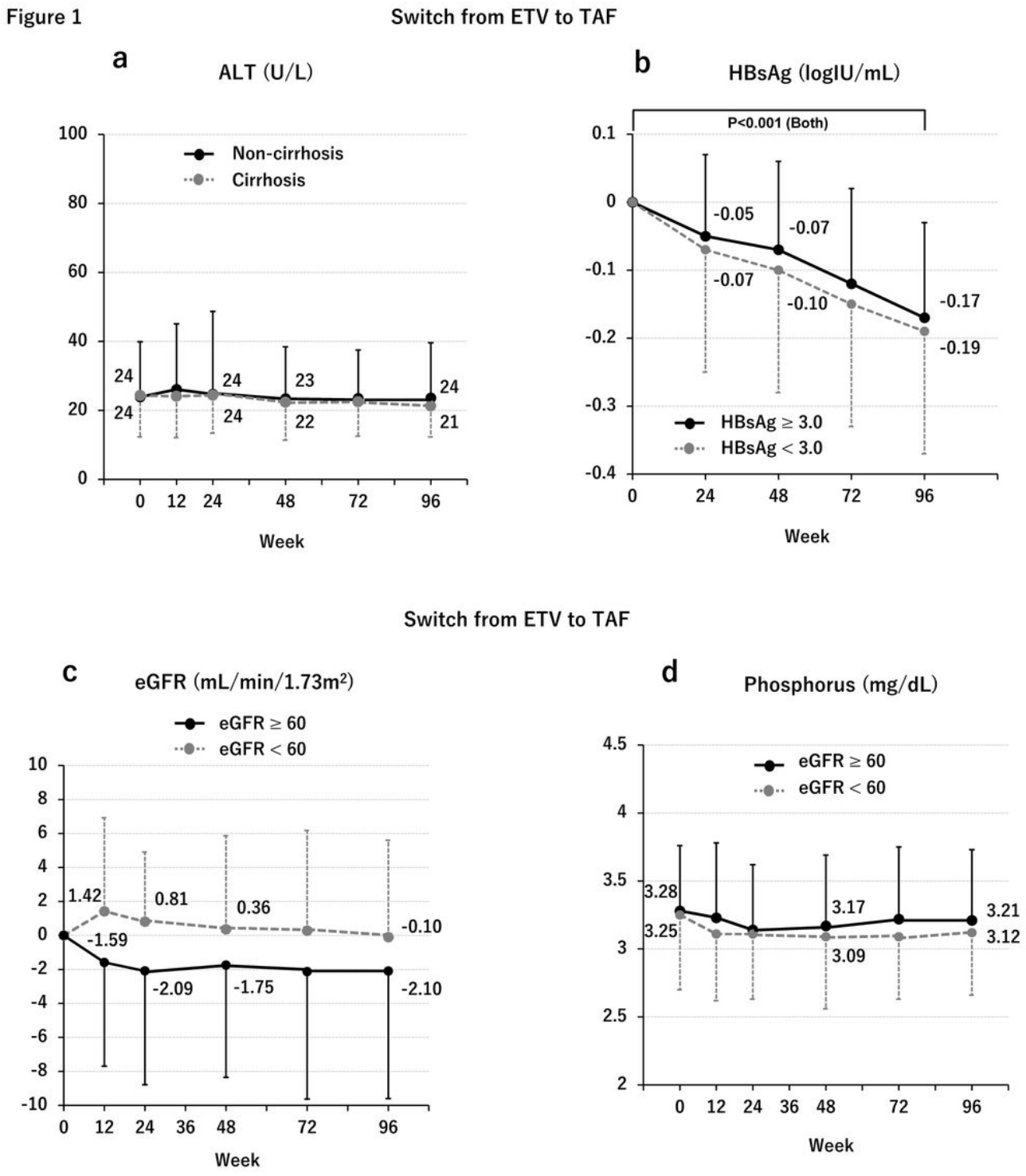

Figure 1

Longitudinal change in (a) ALT, (b) qHBsAg level, (c) eGFR, and (d) serum phosphorus level from baseline to 96 weeks after switching from ETV to TAF. Bars are expressed as mean ± standard deviation. ALT, alanine aminotransferase; qHBsAg, quantitative hepatitis B surface antigen; eGFR, estimated glomerular filtration rate; ETV, entecavir; TAF, tenofovir alafenamide.

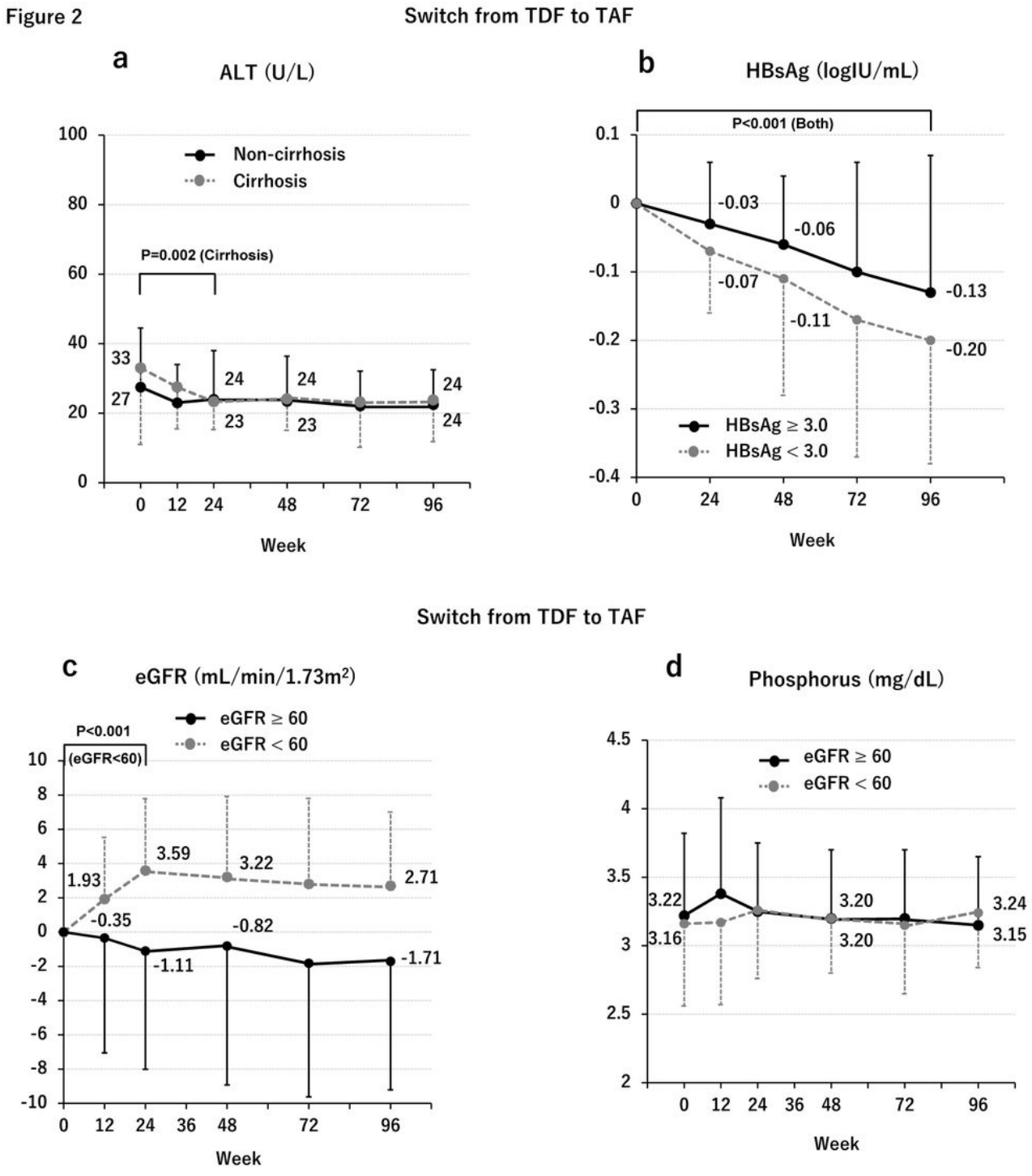

Figure 2

Longitudinal change in (a) ALT, (b) qHBsAg level, (c) eGFR, and (d) serum phosphorus level from baseline to 96 weeks after switching from TDF to TAF. Bars are expressed as mean ± standard deviation. ALT, alanine aminotransferase; qHBsAg, quantitative hepatitis B surface antigen; eGFR, estimated glomerular filtration rate; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide.

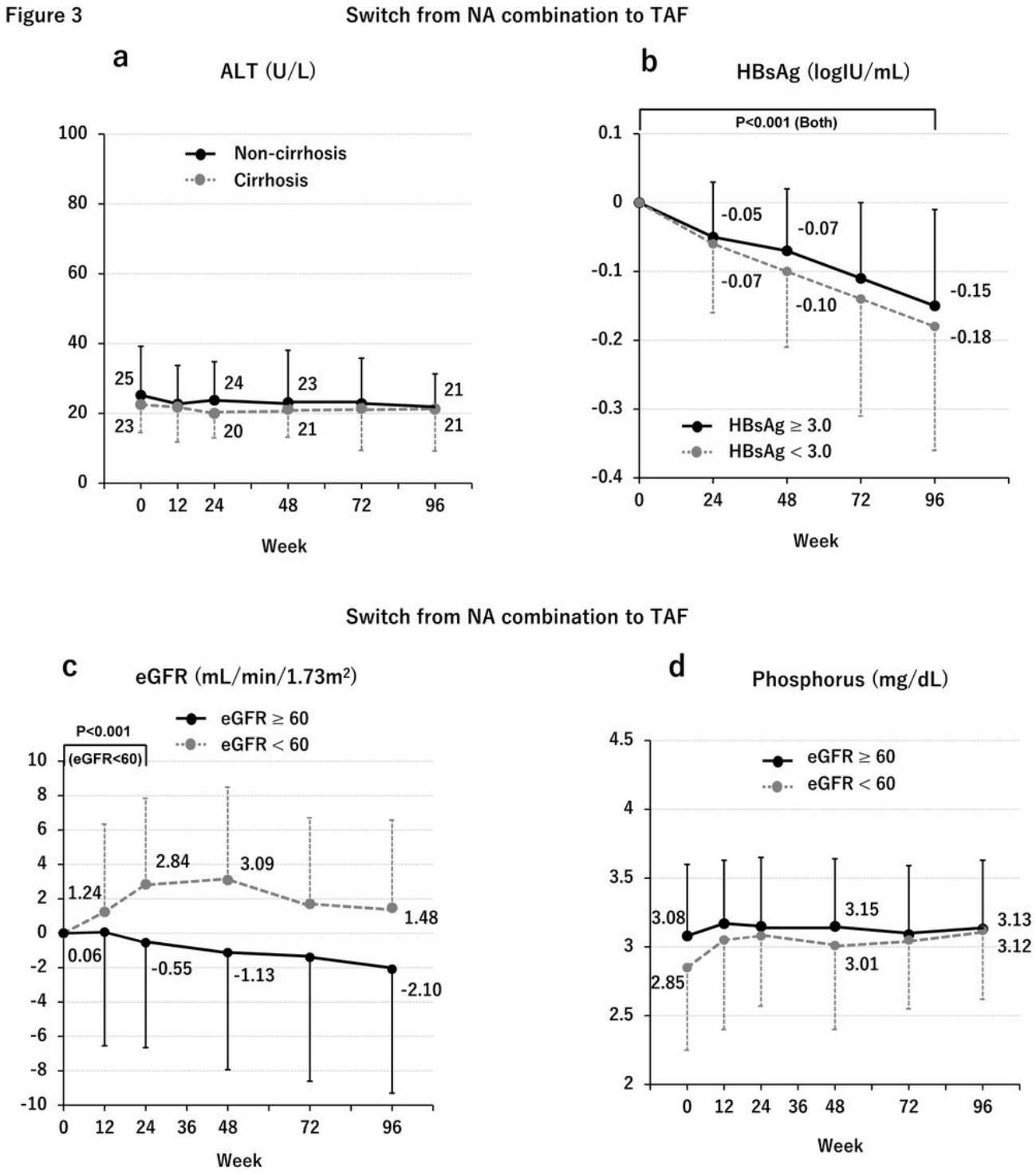

Figure 3

Longitudinal change in (a) ALT, (b) qHBsAg level, (c) eGFR, and (d) serum phosphorus level from baseline to 96 weeks after switching from NA combination to TAF. Bars are expressed as mean ± standard deviation. ALT, alanine aminotransferase; qHBsAg, quantitative hepatitis B surface antigen; eGFR, estimated glomerular filtration rate; NA, nucleos(t)ide analog; TAF, tenofovir alafenamide.

Supplementary Files

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