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Switching to tenofovir disoproxil fumarate *versus* continuing treatment in chronic hepatitis B patients who maintain long-term virological response to entecavir therapy: a randomized trial

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Ethics statement

Research was ethically conducted in accordance with the World Medical Association Declaration of Helsinki. The study protocol was approved by the appropriate institutional Ethics Committees.

ABSTRACT

No controlled trial in patients with chronic hepatitis B virus (HBV) infection on long-term entecavir (ETV) treatment, comparing switching to tenofovir disoproxil fumarate (TDF) with continuing the therapy, has been reported. Twenty-seven nucleos(t)ide-naïve patients with chronic HBV who underwent ETV therapy for ≥ 5 years and maintained virological response were included, and randomized into two groups: one group continued ETV, and the other switched to TDF, in a 1:2 ratio. The primary endpoint was change from baseline in serum hepatitis B surface antigen (HBsAg) level at week 48. The baseline characteristics were not different between 19 patients in the TDF group and 8 patients in the ETV group. Mean decreases in HBsAg level at week 48 were 0.023 and 0.042 $\log_{10}$ IU/mL in the TDF and ETV groups, respectively ($P = 0.94$). The mean drops in hepatitis B core-related antigens (HBcrAg) were also not different between the TDF and ETV groups at week 48 ($P = 0.80$). HBV DNA was sustainedly $< 2.1 \log_{10}$ copies/mL in all patients throughout the study period. In contrast, the mean aminotransferase levels were significantly higher in the TDF group than in the ETV group at weeks 12, 24 and 36, although being within the reference range. Estimated glomerular filtration rate was lower in the TDF group than in the ETV group at weeks 24 ($P = 0.016$) and 48 ($P = 0.003$). In conclusion, we could not find the effect on reducing HBsAg level by switching to TDF in chronic hepatitis B patients with maintained virological response to ETV for ≥ 5 years.

KEYWORDS ETV, HBV, nucleos(t)ide analogs, RCT, TDF

1. INTRODUCTION

Hepatitis B virus (HBV) infection affects about 250 million people worldwide and is the major cause of cirrhosis and liver cancer, accounting for 780 000 deaths annually.¹ The annual incidence rates of hepatocellular carcinoma were reported to be 0.3–0.6% in non-cirrhotic patients and 2.2–3.7% in cirrhotic patients if left untreated.² The ultimate goal of antiviral therapy in patients with persistent HBV infection is to improve survival and quality of life, by inhibiting activity of hepatitis and progression of fibrosis in order to reduce the risk of liver cancer. Hepatitis B surface antigen (HBsAg) is considered the most effective surrogate marker for achieving this treatment goal, thereby HBsAg seroclearance (*i.e.* ‘functional cure’) should be the long-term end-point of antiviral therapy in patients with HBV infection.³⁻⁷

As potent antiviral treatments, nucleos(t)ide analogs are widely used, and entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are recommended as the first-line treatment choice, because of a high genetic barrier to drug resistance.⁸⁻¹⁰ However, since nucleos(t)ide analogs suppress viral replication by inhibiting reverse transcription and terminating DNA chain elongation, covalently closed circular DNA persists in the nucleus of hepatocytes, from which HBsAg and various other viral proteins are transcribed and translated. Among them, hepatitis B core-related antigens (HBcrAg) include hepatitis B core, hepatitis B e antigen (HBeAg) and an artificial core-related protein (p22cr), which are all products of the precore/core gene.^{11,12}

Though few randomized controlled trials comparing TDF to ETV have been published, in Japanese phase III trials including nucleos(t)ide-naïve chronic hepatitis B patients, there was no difference between the two drugs with respect to the reduction of serum HBV-DNA level at week 24, which was the primary endpoint of the study. As

the secondary endpoint, reduction in HBsAg level was significantly greater in the TDF arm than in the ETV arm, and such effect was evident in HBeAg-positive patients.¹³ However in HBeAg-negative patients or patients who maintained virological response to ETV, the effect of TDF on reducing HBsAg levels remains to be determined.

In this study, we randomly assigned patients with chronic hepatitis B whose HBV DNA had been suppressed by ETV therapy for a long term to two groups: one group continued ETV and the other group switched to TDF, and compared the effect on reducing HBsAg levels. We also evaluated the efficacy of both strategies in reducing HBcrAg and HBeAg levels and maintaining low aminotransferase and HBV-DNA levels, as well as their safety profile by monitoring estimated glomerular filtration rate (eGFR) and serum phosphorus levels.

2. METHODS

2.1 Study patients

The study included nucleos(t)ide-naïve patients with chronic hepatitis B, defined as HBsAg-positive and HBV DNA-positive for at least 6 months before treatment, who subsequently underwent ETV therapy for a long term. Patients were included, if they had been treated with ETV for 5 years or longer, had an HBV DNA $<2.1 \log_{10}$ copies/mL (equivalent to $1.3 \log_{10}$ IU/mL), but were still HBsAg-positive. The exclusion criteria were as follows: 1) previous use of other nucleos(t)ide analogs, 2) presence of resistance to nucleos(t)ide analogs, 3) use of corticosteroids or immunomodulatory drugs, 4) presence of antibodies to hepatitis C virus and other likely causes of chronic liver disease, such as autoimmune or alcoholic liver diseases, 5) presence of clinical signs of decompensated cirrhosis or hepatocellular carcinoma, 6) presence of severe comorbidities (ex. impaired renal, cardiac or respiratory function) and 7) women who are possibly pregnant, expectant mothers, and lactating mothers.

The procedures performed in this study were in accordance with the Helsinki Declaration of 1964 (2013 revision), and were approved by the ethical committee of the institute. Written informed consent was obtained from each patient. This study was registered in the UMIN Clinical Trials Registry (registration ID number, UMIN000021793).

2.2 Study Design

This is a single-center, randomized, controlled, and parallel-arm comparison study (**Figure 1**). Thirty-seven patients were recruited from June 2014 to January 2017, and 27 were stratified by their HBeAg status and randomized in a 1:2 ratio into two

groups: one group continued ETV ($n = 8$), whereas the other switched to TDF ($n = 19$). ETV (Baraclude; Bristol-Myers K.K., Tokyo, Japan) was given orally at a dose of 0.5 mg, once daily under fasted conditions. TDF (Tenozet; GlaxoSmithKline K.K., Tokyo) was given orally at a dose of 300 mg, once daily. All patients were followed up at the 12-week intervals for at least 48 weeks after randomization. The primary efficacy endpoint was change from baseline in serum HBsAg level at week 48. The secondary endpoints were changes from baseline in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), HBcrAg, eGFR, and phosphorus levels.

2.3 Clinical Evaluations

Complete blood counts, serum AST, ALT, creatinine and phosphorus levels were determined by standard procedures. eGFR ($\text{mL min}/1.73 \text{ m}^2$) was calculated using the following equation generated by the Japanese Society of Nephrology: $194 \times \text{serum creatinine}^{-1.094} \times (\text{Age})^{-0.287} \times (0.739 \text{ if female})$.

HBsAg was measured by chemiluminescent microparticle immunoassay (Architect HBsAg QT, Abbott Japan Corp., Tokyo, Japan) as described elsewhere.¹⁴ HBeAg and anti-HBe were detected by chemiluminescence enzyme immunoassay. HBcrAg was also detected by chemiluminescence enzyme immunoassay (Fuji-Rebio, Tokyo).¹² HBV DNA was measured by real-time polymerase chain reaction assay (COBAS TaqMan HBV Test, ver. 2.0; Roche Diagnostics K.K., Tokyo, Japan).¹⁵ Genotypes of HBV were identified by enzyme-linked immunosorbent assay with monoclonal antibodies to type-specific epitopes in the preS2-region (Institute of Immunology, Tokyo, Japan).¹⁶ Drug-resistant mutations (at codons 180, 181, 184, 202, 204, 236, and 250 of the HBV reverse transcriptase domain) were detected by PCR-

Invader technology (BML, Tokyo, Japan).¹⁷

When informed consent had been obtained, liver biopsy was performed before starting therapy. Histopathological findings were assessed by grading inflammatory activity and staging fibrosis according to the METAVIR scoring system.¹⁸ An experienced pathologist blinded to the clinical data performed these evaluations.

2.4 Statistical Analysis

Statistical analysis was performed with R software (The R Foundation for Statistical Computing, Vienna, Austria). Sample size was not calculated because of the pilot nature of the current study. Distributions of continuous variables were analyzed by the Mann-Whitney *U* test. Differences in proportions were tested by Fisher's exact test. A two-tailed *P*-value of less than 0.05 was considered to indicate statistical significance.

3. RESULTS

3.1 Characteristics of patients

Baseline characteristics of the patients are shown in **Table 1**. Nineteen patients were assigned to receive TDF 300 mg and eight patients to ETV 0.5 mg daily. Mean ALT level was normal on proceeding ETV treatment in both groups. The HBeAg, which was a stratification factor in this study, was positive in 3 (16%) in the TDF group and 1(13%) in the ETV group. HBV DNA was $<2.1 \log_{10}$ copies/mL in all patients, but positive in 2 patients in each treatment group. The most common genotype was C in both groups (89% in the TDF group and 100% in the ETV group). Thirteen patients in the TDF group and five in the ETV group underwent liver biopsies before the start of ETV therapy. Owing to random assignment, there were no differences in clinical characteristics between the two groups.

3.2 Efficacy

Table 2 shows the results of the primary and secondary endpoints (at week 48). Changes from baseline in serum HBsAg level at weeks 12, 24, 36, and 48 are shown in **Figure 2A**. At week 48 after randomization, the mean drops were 0.023 and 0.042 $\log_{10}$ IU/ml in the TDF and ETV groups, respectively, which showed no statistical difference ($P = 0.94$). No patients experienced HBsAg loss during the study period. Changes from baseline in serum HBcrAg level at weeks 12, 24, 36, and 48 are shown in **Figure 2B**. At week 48, the mean drops were 0.095 and 0.11 $\log_{10}$ U/ml in the TDF and ETV groups, respectively, which showed no statistical difference ($P = 0.80$). Three patients in the TDF group and one in the ETV group were HBeAg positive at assignment, but no one experienced HBeAg loss during the observation (data not shown).

Serum HBV DNA was sustainedly $<2.1 \log_{10}$ copies/mL in all patients throughout the study period, and the proportions of patients with positive HBV DNA were similar between the TDF and ETV groups (data not shown).

Changes from baseline in serum AST and ALT levels at weeks 12, 24, 36, and 48 after randomization to TDF or ETV are shown in **Figure 3**. The AST and ALT levels changed within the reference range in most patients, since they were normal on long-term ETV treatment at the assignment. The AST and ALT levels were significantly higher in the TDF group than in the ETV group at weeks 12 ($P = 0.011$ and 0.052 , respectively), 24 ($P = 0.014$ and 0.018 , respectively) and 36 ($P = 0.0077$ and 0.025 , respectively), although not significantly at week 48 ($P = 0.051$ and 0.21 , respectively).

3.3 Safety

Changes from baseline in eGFR at weeks 12, 24, 36, and 48 are shown in **Figure 4A**. eGFR was significantly lower in the TDF group than in the ETV group at weeks 24 ($P = 0.016$) and 48 ($P = 0.003$). The changes in serum phosphorus levels from baseline at weeks 12, 24, 36 and 48 are shown in **Figure 4B**. Mean changes in phosphorus were small in both groups and showed no statistical difference at week 48 after randomization ($P = 0.71$).

4. DISCUSSION

To our knowledge, this is the first report of a randomized controlled trial in chronic hepatitis B patients on long-term ETV treatment, comparing switching to TDF with continuing the therapy. In this study involving patients with maintained virological response to ETV treatment, no statistically significant differences were observed between the two groups regarding changes in serum HBsAg (as the primary endpoint) or HBcrAg levels. However, the AST and ALT levels were significantly higher in the TDF group than in the ETV group. The decrease in eGFR was significantly larger in the TDF group than in the ETV group, and careful monitoring of renal function is therefore necessary in patients receiving TDF.

The Japanese phase III study that we previously mentioned is the only randomized prospective controlled trial comparing TDF to ETV. In the clinical trial including nucleos(t)ide-naïve patients, the TDF group showed significantly greater reduction in mean HBsAg level (as the secondary endpoint), compared to the ETV group. Further analyses showed that the HBsAg reduction in the TDF group was predominant in HBeAg-positive patients and in those with high ALT level.¹³ In contrast, the present study included only patients who had been treated with ETV for 5 years or longer, and more than 80% of whom were HBeAg negative. The patients' backgrounds of the present study were different from those of the previous study including nucleos(t)ide-naïve patients, and similar to those of the previous studies following participants in global clinical trials in a long term.^{19,20} Because ETV, as well as TDF, has a high genetic barrier, more than 90% of patients have undetectable HBV DNA and less than 2% have drug resistance after 5 years of ETV therapy.

The HBcrAg assay is an enzyme immunoassay developed in Japan, which

measures serum levels of all antigens transcribed from the pre-core/core gene, including hepatitis B core, HBeAg, and p22cr, simultaneously, using monoclonal antibodies that recognize epitopes common to the denatured antigens. Though serum HBcrAg has been reported to reflect intracellular levels of covalently closed circular DNA, unlike HBsAg, it is not transcribed nor translated from the integrated HBV sequences.⁵ A model for predicting relapse after discontinuation of nucleos(t)ide analog by scoring the HBsAg and HBcrAg levels has been proposed.²¹ More recently, it has been reported that elevation of HBcrAg levels is associated with the risk of hepatocellular carcinoma in chronic hepatitis B patients.²²

It has recently been reported that serum interferon- λ 3 levels are higher in patients treated with nucleotide including TDF compared with those treated with nucleoside including ETV.²³ Endogenous interferon- λ 3 may induce interferon-stimulated genes expression and results in a reduction of HBsAg production. A further study is necessary to investigate whether interferon- λ 3 expression contributes to reduction of HBsAg in clinical samples obtained from patients switching to TDF.

This study had several limitations. First, the number of patients was small, and the follow-up period was short. Second, although there was no difference in the changes of serum phosphate, we have not measured the bone mineral density. Recently, tenofovir alafenamide, with reduced bone and renal toxicities has been approved.^{24,25} From now on, we need to assess the efficacy and safety of switching to tenofovir alafenamide in chronic hepatitis B patients on other nucleos(t)ide analogs for a long term.

In conclusion, among chronic hepatitis B patients with maintained virological response to ETV for 5 years or longer, we could not find any beneficial effect on

ETV-to-TDF Switching for CHB

reducing HBsAg level by switching to TDF. Furthermore, even in patients with reserved renal function, eGFR decreased in the TDF group. Switching to TDF is not recommended for patients with impaired renal function.

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CONFLICTS OF INTEREST

The authors declare that they have no financial conflict of interest.

AUTHOR CONTRIBUTIONS

A Iida-Ueno, M Enomoto, R Kozuka, A Tamori, and N Kawada contributed to this work. A Iida-Ueno and M Enomoto analyzed the data and wrote the article. M Enomoto, R Kozuka, A Tamori, and N Kawada provided the samples.

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FIGURE LEGENDS

FIGURE 1 Patient enrollment and follow-up. Patients were stratified by their hepatitis B e antigen (HBeAg) status and randomized in a 1:2 ratio into two groups: one group continued entecavir (ETV), whereas the other switched to tenofovir disoproxil fumarate (TDF). The primary efficacy endpoint was change from baseline in serum hepatitis B surface antigen (HBsAg) level at week 48.

FIGURE 2 Mean changes in (A) aspartate aminotransferase (AST) (U/L) and (B) alanine aminotransferase (ALT) (U/L) levels in patients with chronic hepatitis B at weeks 12, 24, 36, and 48 after randomization to the tenofovir disoproxil fumarate (TDF) or entecavir (ETV) group. AST and ALT levels were significantly higher in the TDF group than in the ETV group at weeks 12 ($P = 0.011$ and 0.052 , respectively), 24 ($P = 0.014$ and 0.018 , respectively), and 36 ($P = 0.0077$ and 0.025 , respectively).

FIGURE 3 Mean changes in (A) hepatitis B surface antigen (HBsAg) ($\log_{10}$ IU/mL) and (B) hepatitis B core-related antigen (HBcrAg) ($\log_{10}$ U/mL) levels in patients with chronic hepatitis B at weeks 12, 24, 36, and 48 after randomization to the tenofovir disoproxil fumarate (TDF) or entecavir (ETV) group. At week 48, the mean decreases in HBsAg level in the TDF and ETV groups were 0.023 and $0.042 \log_{10}$ IU/mL, respectively ($P = 0.94$), and the mean decreases in HBcrAg level in the TDF and ETV groups were 0.095 and $0.11 \log_{10}$ U/mL, respectively ($P = 0.80$).

FIGURE 4 Mean changes in (A) estimated glomerular filtration rate (mL/min/1.73 m²) and (B) serum phosphorus (mg/dL) levels in patients with chronic hepatitis B at weeks 12, 24, 36, and 48 after randomization to the tenofovir disoproxil fumarate (TDF) or entecavir (ETV) group. Estimated glomerular filtration rate was significantly lower in the TDF group than in the ETV group at weeks 24 ($P = 0.016$) and 48 ($P = 0.003$).

TABLE 1 Characteristics of patients

	TDF group (n = 19)	ETV group (n = 8)	<i>p</i> -value
Age (years)	56 ± 10	54 ± 10	0.58
Sex (%Male)	15 (79%)	6 (75%)	>0.99
Duration of proceeding ETV treatment (years)	7.2 ± 1.7	6.4 ± 1.7	0.14
AST (U/L)	22 ± 6	22 ± 6	0.92
ALT (U/L)	23 ± 10	19 ± 7	0.39
eGFR (ml/min/1.73 m ²)	73.4 ± 13.1	74.4 ± 12.1	0.81
Phosphorus (mg/dl)	3.2 ± 0.5	3.2 ± 0.4	0.83
Platelet (x10 ³ /μL)	197 ± 60	187 ± 62	0.91
HBsAg (Log ₁₀ IU/L)	2.88 ± 0.81	3.13 ± 0.31	0.56
HBeAg-positive (%)	3 (16%)	1 (13%)	>0.99
HBcrAg (Log ₁₀ U/L)	3.8 ± 1.1	4.4 ± 0.8	0.10
HBV-DNA (Signal pos./neg.)	2/17	2/6	0.56
HBV genotype (A/B/C)	0/2/17	0/0/8	>0.99
Grade (A1/A2/A3)	8/5/0	2/3/0	0.61
Stage (F1/F2/F3/F4)	6/1/2/4	2/3/0/0	0.079

Results are shown as number (%) or mean ± standard deviation.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; 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; TDF, tenofovir disoproxil fumarate.

TABLE 2 Results of the primary and secondary endpoints (at week 48)

	TDF group (n = 19)	ETV group (n = 8)	<i>P</i> value
HBsAg (Log ₁₀ IU/L)	−0.023 ± 0.092	−0.042 ± 0.139	0.94
HBcrAg (Log ₁₀ U/L)	−0.095 ± 0.19	−0.11 ± 0.17	0.80
AST (U/L)	+5.2 ± 5.9	+1.1 ± 2.9	0.051
ALT (U/L)	+5.7 ± 7.1	+2.0 ± 7.1	0.21
eGFR (mL/min/1.73 m ²)	−3.45 ± 5.42	+3.20 ± 3.15	0.003
Phosphorus (mg/dL)	+0.05 ± 0.41	+0.15 ± 0.62	0.71

Results are shown as changes from baseline.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; ETV, entecavir; HBcrAg, hepatitis B core-related antigen; HBsAg, hepatitis B surface antigen; TDF, tenofovir disoproxil fumarate.

Figure 1

190x254mm (96 x 96 DPI)

A. HBsAg **B. HBcrAg**

Figure 2

190x254mm (96 x 96 DPI)

A. AST

B. ALT

Figure 3

190x254mm (96 x 96 DPI)

A. eGFR **B. Phosphorus**

Figure 4

190x254mm (96 x 96 DPI)