

ORIGINAL ARTICLE

Hepatitis B surface antigen reduction as a result of switching from long-term entecavir administration to tenofovir

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Key words

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Abstract

Background and Aim: Loss of hepatitis B surface antigen (HBsAg) is an important goal in the treatment of chronic hepatitis B. We investigated whether switching from long-term entecavir (ETV) administration to tenofovir (TFV) (tenofovir alafenamide [TAF] or tenofovir disoproxil fumarate [TDF]) could contribute to the reduction of HBsAg levels.

Methods: The degree of HBsAg reduction by 48 weeks in 30 patients following switching from ETV to TFV was compared with results from 147 patients who continued ETV as a control.

Results: TFV group switched to TFV after mean 6.79 years of ETV administration. HBV-DNA levels remained below 1.0 log IU/mL in all cases in both groups during 48 weeks. Median HBsAg reduction at 48 weeks was 0.075 (−0.05 to 0.38) log IU/mL in the TFV switch group, and 0.070 (−0.28 to 0.50) in the ETV continuation group, which was not statistically significant ($p = 0.5$). In a subgroup of hepatitis B e antigen negative patients whose HBsAg had not been reduced (HBsAg reduction ≤ 0 log IU/mL) in the 48 weeks prior to entry into the study, HBsAg reduction was significantly higher in the TFV switch group than in the ETV continuation group (0.15 [0.07–0.135] in TFV, 0.09 [−0.14 to 0.25] log IU/mL in ETV, $p = 0.04$).

Conclusion: Although HBsAg reduction is equivalent with ETV continuation and switching to TFV in all patients at 48 weeks, switching from ETV to TFV could provide an alternative therapeutic strategy toward HBsAg elimination in a specific sub-population of patients.

Introduction

Hepatitis B virus (HBV) infection can cause liver cirrhosis and hepatocellular carcinoma (HCC).¹ The loss of hepatitis B surface antigen (HBsAg) is known to reduce the risk of cirrhosis and HCC,² therefore loss of HBsAg through natural course or antiviral treatment is the most important goal in the treatment of chronic hepatitis B.^{3,4}

Recently, nucleotide/nucleoside analog (NA) therapy has been widely used, which enables viral suppression and HCC suppression.^{5,6} However, considering the low rate of HBsAg elimination during NA therapy, administration must be continued for a long period of time.^{7–10} Therefore, new therapeutic strategies

are required which target HBsAg clearance in patients undergoing long-term NA administration.

We previously reported that switching to pegylated interferon (PEG-IFN) after long-term NA administration can reduce HBsAg levels.¹¹ Some studies have also shown the HBsAg-reducing effect of PEG-IFN.^{12–15} However, PEG-IFN treatment is difficult to administer to many patients due to its side effects.

Tenofovir (TFV) (tenofovir alafenamide [TAF] or tenofovir disoproxil fumarate [TDF]) has been clinically applied in recent years, with its effectiveness being reported in many cases.^{16–21} Currently, most HBV patients in Japan undergo entecavir (ETV) therapy, but their HBsAg elimination rate is low. Switching from entecavir to tenofovir is therefore

considered as a therapeutic strategy for HBsAg reduction in these patients. In this study, we examined the effects of switching to tenofovir on HBsAg levels in patients with long-term entecavir administration.

Methods

Patients. This was a retrospective analysis of a single hospital cohort. Subjects were all patients who had switched from ETV to TFV between January 2016 and June 2018. Thirty patients who met the following inclusion criteria were enrolled into the study: (i) ETV administration for more than 1 year; (ii) HBV-DNA level < 1.0 log IU/mL; (iii) HBsAg > 1 log IU/mL at switching; and (iv) no evidence of co-infection with hepatitis C virus or human immunodeficiency virus. In addition, 147 patients who met the above criteria and received ETV alone over the same period were included as controls. The primary endpoint of the study was HBsAg reduction by the 48th week after switching from ETV to TFV. The study protocol is shown in Figure 1. This study was approved by the ethics committee of Musashino Red Cross Hospital in accordance with the Declaration of Helsinki.

Measurements. Hepatitis B e-antigen (HBeAg) was measured using commercially available enzyme immunoassay kits. Quantitative measurements of HBV-DNA and HBsAg were performed using real-time polymerase chain reaction (PCR) (Roche), and chemiluminescent immunoassay (CLIA) (Abbott Japan), respectively. Cases in which HBsAg had been reduced (HBsAg reduction > 0 log IU/mL) in the 48 weeks prior to study entry were defined as the prior HBsAg-reduced group, and the remaining cases were defined as the prior HBsAg non-reduced group (HBsAg reduction from 48 weeks before the study entry to the start of the study ≤ 0 log IU/mL).

Histological evaluation. We performed a liver biopsy in 169 patients at the start time of ETV treatment. All liver biopsy specimens were laparoscopically obtained using 13G needles or through percutaneous ultrasound-guided liver biopsy using 15G needles. All specimens were fixed, paraffin-embedded, and stained using hematoxylin–eosin and Masson's trichrome. A biopsy sample with a minimum size of 15-mm was required for diagnosis. Two senior pathologists who were blinded to the clinical data independently evaluated all the liver biopsy samples. We defined hepatic fibrosis (stage) as stage 1, zone 3 perisinusoidal fibrosis;

stage 2, zone 3 perisinusoidal fibrosis with portal fibrosis; stage 3, zone 3 perisinusoidal fibrosis and portal fibrosis with bridging fibrosis; or stage 4, cirrhosis, according to METAVIR score.

Statistical analysis. Categorical data were compared using chi-squared and Fisher's exact tests. Continuous variable distributions were analyzed using Mann–Whitney *U* test. In all cases, *P* values of < 0.05 were considered statistically significant. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan)²² and a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics on entry. Patient characteristics (at the time of switching from ETV to TFV in the TFV group) are shown in Table 1. In the TFV group, 19 patients received TAF and 11 received TDF. HBV-DNA level was below 1.0 log IU/mL in all cases. No differences were observed in HBsAg levels, previous ETV treatment periods, or fibrosis stage between TFV and ETV groups in HBeAg positive or negative patients.

Reduction of HBsAg at 48 weeks. HBV-DNA levels remained below 1.0 log IU/mL in all cases in both groups. When HBsAg reduction at 48 weeks was examined in all patients, the values were 0.075 (-0.05 to 0.38) log IU/mL and 0.070 (-0.28 to 0.50) log IU/mL for the TFV and ETV groups, respectively, and no significant difference was observed between the groups ($P = 0.5$, Fig. 2). HBsAg reduction in HBeAg-positive patients was 0.080 (0.03–0.12) log IU/mL for the TFV group and 0.030 (-0.28 to 0.36) log IU/mL for the ETV group ($P = 0.1$). In HBeAg-negative patients, these values were 0.070 (-0.05 to 0.38) log IU/mL for the TFV group and 0.075 (-0.27 to 0.50) log IU/mL for the ETV group ($P = 0.8$). Patients were then stratified by prior treatment effect on HBsAg and HBeAg status, and subgroup analysis was performed. In an HBeAg-negative at entry, HBsAg non-reduced subgroup, HBsAg reduction values were 0.15 (0.07–0.135) log IU/mL in the TFV group ($n = 7$) and 0.09 (-0.14 to 0.25) log IU/mL in the ETV group ($n = 32$), respectively. This reduction was significantly higher in the TFV group than the ETV group ($P = 0.04$, Table 2). No significant differences were observed in the other subgroups between TFV and ETV.

Discussion

In this study, no differences were observed in the reduction of HBsAg between the group which switched from ETV to TFV and the group with continued ETV treatment. However, a significant reduction in HBsAg was observed in a subgroup of HBeAg-negative patients whose HBsAg was not reduced during ETV therapy. In such cases, HBsAg reduction could be expected following a switch to TFV.

Since HBsAg loss in ETV therapy is rare, alternative treatments aimed for HBsAg loss are necessary. As an alternative treatment, there have been few reports examining HBsAg reductions following a switch from ETV to TFV.^{23,24} Switching to TFV was not found to enhance HBsAg reduction in these

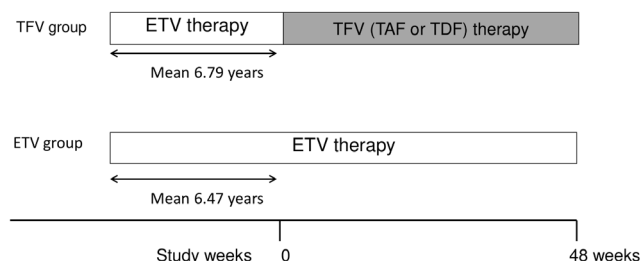


Figure 1 The study design of treatment. ETV, entecavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

Table 1 Patient characteristics

	HBeAg positive		P value	HBeAg negative		P value
	TFV group	ETV group		TFV group	ETV group	
Patients number	8 (TAF:4, TDF:4)	13		22 (TAF:15, TDF:7)	134	
Age (years)	54.4 ± 15	59.3 ± 15	0.5	55.3 ± 14	61.1 ± 12	0.04
Sex, male/female	5/3	5/8	0.4	16/6	71/63	0.1
HBsAg (log IU/mL)	3.40 ± 0.46	3.54 ± 0.60	0.9	2.75 ± 0.81	2.89 ± 0.76	0.5
HBV-DNA (log IU/mL)	<2.1	<2.1	1	<2.1	<2.1	1
AST (IU/l)	24.6 ± 5.3	24.3 ± 5.4	0.9	27.6 ± 19	23.8 ± 7.7	0.1
ALT (IU/l)	23.0 ± 6.3	18.7 ± 4.9	0.1	26.4 ± 28	20.7 ± 12	0.1
Fibrosis stage (at the start of ETV treatment), F0-1/2/3/4	4/1/1/0	5/6/0/1	0.3	12/5/2/1	77/26/23/5	0.7
Previous ETV treatment (years)	6.8 ± 2.8	5.9 ± 2.4	0.4	6.8 ± 3.8	6.5 ± 3.0	0.7

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBeAg, hepatitis B e-antigen; HBV-DNA, hepatitis B virus DNA; ETV, entecavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

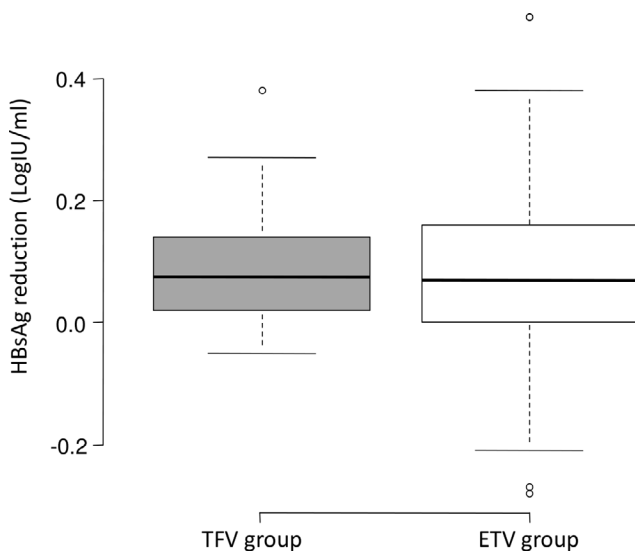


Figure 2 Hepatitis B surface antigen (HBsAg) reduction at 48 weeks.

studies; our study also observed similar results. Therefore, switching from ETV to TFV in all patients is of little clinical significance. However, as shown in this study, in HBeAg-negative cases in which HBsAg reduction was not obtained during ETV treatment, reduction of HBsAg can be obtained by switching to TFV and it is one of the new findings in this study. Because

switching to TFV can promote HBsAg reduction in comparison with continued ETV in a specific subpopulation of patients, switching to TFV may be one therapeutic strategy in such cases and it may be possible to shorten the period until HBsAg elimination the switching to TFV.

It has been reported that nucleotide analogues (adefovir or TFV) but not NAs (ETV or lamivudine) induces interferon-λ3 production, resulting in a reduction of HBsAg.²⁵ Based on these results, this study was conducted considering the possibility that the switching from ETV to TFV may contribute to the reduction of HBsAg. As a future study, it is necessary to identify cases that can reduce HBsAg by switching from ETV to TFV by examining baseline and changes of interferon-λ3.

There were several limitations to this study. In order to verify the therapeutic effect of switching to TFV, the number of cases is small and the observation period is still short. It is necessary to verify these findings in a bigger number of patients, and to examine long-term therapeutic effects past 1 year. We previously reported that the therapeutic effects of TAF and TDF in naïve patients were comparable,^{26,27} and the HBsAg reduction by TAF and TDF was analyzed in the same group in this study. However, considering it has not sufficiently been verified whether the treatment effect of switching is equivalent, it is necessary to compare effects between TAF and TDF in a large cohort.

In conclusion, although HBsAg reduction by switching from ETV to TFV is equivalent to ETV continuation across all patients, TFV switching can obtain significant HBsAg reduction

Table 2 Subgroup analysis in HBsAg reduction

	HBeAg status	HBsAg reduction at 48 weeks (log IU/mL)		P value
		TFV	ETV	
Prior HBsAg non-reduced group	Negative	0.15 (0.07–0.135)	0.09 (–0.14 to 0.25)	0.04
	Positive	0.055 (0.03–0.08)	0.10 (0.02–0.16)	0.8
Prior HBsAg reduced group	Negative	0.02 (–0.05 to 0.25)	0.065 (–0.27 to 0.50)	0.3
	Positive	0.09 (0.05–0.12)	0.025 (–0.28 to 0.36)	0.06

ETV, entecavir; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; TFV, tenofovir.

in HBeAg-negative, prior HBsAg non-reduced cases. Therefore, it should be considered as one therapeutic strategy toward HBsAg elimination in such cases.

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