Clinical Course of Partial Virological Responders Under Prolonged Entecavir Monotherapy in Patients with Chronic Hepatitis B

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- ABSTRACT -

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Studies about long-term entecavir (ETV) therapy for partial virological response (PVR) are lacking. This study aimed to assess the clinical course of PVR patients receiving ETV therapy and analyze the efficacy of tenofovir (TDF). We retrospectively evaluated 130 patients who showed a PVR to ETV. Among these patients, 102 were nucleot(s)ide analogue (NUC)-naïve and 28 were lamivudine (LAM)-experienced. The cumulative rates of VR were 54.1%, 70.8%, and 83.7% for the NUC-naïve group and 37.0%, 42.8%, and 42.8% for the LAM-experienced group after 24, 36, and 48 months of ETV therapy, respectively (P=0.008). Low HBV DNA level at 12 months (P<0.001) and absence of a LAM treatment history (P =0.031) were significant associated factors for VR. In VR prediction at 36 months of ETV therapy in NUC- naïve patients, HBV DNA level <95 IU/ml at 12 months showed a 92.9% sensitivity and a 78.3% specificity (AUROC, 0.909; P<0.001). ETV resistance did not develop in NUC- naïve patients with HBV DNA levels <95 IU/ml at 12 months. The cumulative probability of VR in patients who switched to or additionally received TDF was 91.3% at 15 months. Prolonged ETV therapy induced a VR without the risk of ETV resistance in NUC-naïve patients with HBV DNA levels <95 IU/ml at 12 months. All

patients with LAM-experienced or NUC- naïve with HBV DNA levels ≥ 95 IU/ml at 12 months should be switched to TDF rescue therapy.

Key words: entecavir; chronic hepatitis B; partial virological response; tenofovir

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I. INTRODUCTION

Entecavir (ETV) is the drug of first choice for hepatitis B virus (HBV) infection because of its potent antiviral activity, high genetic barrier to resistance, and rare side effects [Asselah and Marcellin, 2013; Osborn, 2011; Tenney et al., 2009]. Despite the high efficacy of ETV, cases have been described with insufficient viral suppression or antiviral resistance leading to an increased risk of liver cirrhosis or hepatocellular carcinoma [Zoulim and Locarnini, 2012]. Therefore, early viral suppression has become increasingly important for reducing the incidence of these liver complications [Hadziyannis et al., 2006; Yuen et al., 2001]. Current guidelines for chronic hepatitis B recommend a change to more potent drug in case of partial virological response (PVR) to lamivudine (LAM), telbivudine (LdT), or adefovir (ADV). However, the optimal management of patients with PVR under ETV is still debatable. Adding another drug such as tenofovir (TDF) has been suggested for patients with PVR to ETV. However, some studies reported that long-term ETV therapy could result in virological response (VR) without antiviral resistance in nucleot(s)ide analogue (NUC)-naïve chronic hepatitis B patients with PVR to ETV therapy [Kwon et al., 2013; Luo et al., 2013; Zoutendijk et al., 2011]. In the previous multicenter study, 21% (36/175) of treatment-naïve patients developed PVR at week 48, and 81% (29/36) of patients with PVR achieved VR during prolonged ETV therapy, with no cases of ETV resistance [Zoutendijk et al., 2011]. Therefore, physicians responsible for the treatment of patients who do not achieve VR after long-term ETV administration face a difficult choice between continuing the treatment and switching to alternative therapies.

TDF is a nucleotide reverse transcriptase inhibitor developed for the treatment of chronic hepatitis B and characterized by high efficacy of viral suppression and low rate of drug resistance [EASL, 2012; Gao et al., 2014]. In particular, the cumulative rate of VR was reported to be 96.6% during 24 weeks of TDF rescue therapy in patients who failed to achieve VR to multiple NUCs treatment [Kim et al., 2012]. In addition, it was demonstrated that 79% of patients with no response to LAM or ADV achieved VR (HBV DNA levels <400 copies/mL) after an average of 23 weeks of TDF treatment, and hepatitis B "e" antigen (HBeAg) loss was observed in 24% of them [van Bommel et al., 2010]. However, few studies have investigated the efficacy of TDF rescue therapy in patients with PVR to ETV. Recently, few studies reported the efficacy of TDF rescue therapy in the patients with PVR to ETV. In one study, patients with suboptimal response (failure to achieve >1 log10 HBV-DNA reduction during the last 24 weeks of treatment) to ETV (n=14) achieved 100% of HBV-DNA and ALT normalization within a median duration of 30 weeks [Pan et al., 2012]. Another study showed that the cumulative virological response rates of TDF rescue therapy were 83% and 100% at 6 months and 12 months, respectively [Yip et al., 2012].

Therefore, the present study aimed to determine the cumulative rate of VR in prolonged ETV therapy and to analyze the factors leading to VR and ETV resistance. The efficacy of TDF rescue therapy in patients with PVR to ETV was also evaluated.

II. PATIENTS AND METHODS

A. Patients

Records of patients who were treated for HBV infection with ETV (0.5 mg daily) for 12 months between January 2008 and December 2012 and developed PVR were retrospectively reviewed. PVR was defined as serum HBV DNA detectable by polymerase chain reaction (PCR) (>20 IU/mL) even in the presence of >1 log10 reduction of the initial level with ETV therapy at 12 months [EASL, 2012]. Chronic hepatitis B was defined as detectable hepatitis B surface antigen for more than 6 months, serum HBV DNA level ≥20,000 IU/mL for HBeAg-positive or ≥2,000 IU/mL for HBeAg-negative patients, and elevated serum alanine aminotransferase (ALT) levels. Patients who had human immunodeficiency virus/hepatitis C virus co-infection, hepatocellular carcinoma (HCC), or other malignancies were excluded, as well as those who showed poor drug compliance. Adherence rates < 90% were defined as poor compliance in the study. To obtain information regarding adherence to medication, we reviewed medical records and prescription. After excluding 23 cases of HCC, 11 cases of other malignancies, 38 cases of poor compliance, and 43 cases lost to follow-up, 130 out of 245 patients were included in the study. Among them, 102 subjects were treatment-naïve, and 28 had undergone treatment with LAM or a combination of LAM and ADV. The average follow-up period was 34.9 months. Twenty-three of the PVR patients who underwent TDF rescue therapy were included in the subgroup analysis (Fig. 1). The study was approved by the Institutional Review Board of Ajou University Hospital (MED-MDB-14-453).

B. Methods

Patients' data were collected every 3–6 months during the follow-up period. Baseline characteristics (age, sex, co-infections, underlying disease, and prior HBV therapy) and results of serologic tests (HBsAg, HBeAg, anti-HBe antibody, HBV DNA level, ALT, total bilirubin, platelet count, creatinine, and albumin) were recorded. Abdomen ultrasound examination and computed tomography were used to detect liver cirrhosis. HBV DNA levels were quantified by real-time PCR using the COBAS TaqMan HBV test (Roche Diagnostics, Branchburg, NJ, USA) with the low detection limit of 20 IU/mL. Restriction fragment mass polymorphism (RFMP) was used to detect LAM- and ETV-resistant mutations. This analysis was performed using primers with the sequences 5'-TCC TAC GAC CCC TGC TCG TGT TAC-'3 (nucleotide 177–200) and 5'-CTG TAA ATA GAC CTA TTG ATT GGA-'3 (nucleotide 959–982). Sequence analysis was performed with an ABI PRISM 310 Genetic Analyzer (Applied Biosystems, New York, NY, USA) [Cho et al., 2010; Hong et al., 2004; Kim et al., 2013]

C. Statistical Analysis

Categorical values are described as proportions (%), and continuous values are described as means ± standard deviation (SD) or medians (range). Categorical variables were assessed using the chi-square test. Continuous variables were assessed using the t-test. Cumulative rates of complete viral suppression were analyzed using the Kaplan–Meier method, and the log-rank test was used for comparisons between the groups. Cox proportional hazard regression models were used to estimate univariate and multivariate

hazard ratio and associated confidence intervals (CIs). Area under receiver operating characteristic (ROC) curves was calculated for the identification of cut-off values predicting VR. A p value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS 19.0.

III. RESULTS

A. Patients characteristics

Baseline and on-treatment (at 12 months) characteristics of the 130 patients who developed PVR under ETV therapy are summarized in Table 1. The average age was 44.2 years, and 67.7% of the patients were male. There were no significant differences in age; sex; presence of cirrhosis; HBV DNA level; levels of ALT, creatinine, and bilirubin; platelet counts; and follow-up durations between the NUC-naïve and LAM-experienced subjects. There were significantly more HBeAg-positive patients in the NUC-naïve group (81.3% vs. 60.7%, p = 0.022).

B. Virological and serological response to prolonged ETV therapy

1. Cumulative rate of VR

102 NUC-naïve and 28 LAM-experienced patients showed PVR to ETV therapy were analyzed (mean treatment period of 34.9 months). The cumulative rates of VR were 54.1%, 70.8%, and 83.7% for the NUC-naïve group and 37.0%, 42.8%, and 42.8% for the LAM-

2. Changes in the HBV DNA levels

Changes in the HBV DNA levels during the prolonged ETV therapy are depicted in Figure 2. There was a significant difference in the extent of reduction between the NUC-naïve groups and the LAM-experienced groups achieved between months 12 and 24 (−0.56

Log10 IU/L vs. −0.06 Log10 IU/L, p = 0.022) and months 12 and 36 (−0.73 Log10 IU/L vs. −0.09 Log10 IU/L, p = 0.048). However, there was no significant difference in HBV DNA reduction between months 12 and 48 (Table 2).

3. Cumulative rate of HBeAg loss

At 12 months of ETV therapy, 83 patients were HBeAg-positive in the NUC-naïve group and 17 patients in the LAM-experienced group. During the follow-up period, HBeAg loss occurred in 30 of the 83 patients (36.1%) in the treatment-naïve group and six of the 17 patients (35.3%) in the LAM-experienced group. The cumulative rates of HBeAg loss were 19.1%, 31.5%, and 54.9% for the NUC-naïve group and 25.0%, 31.8%, and 45.5% for the LAM-experienced group after 24, 36, and 48 months of ETV therapy, respectively. There was no significant difference in HBeAg loss between the two groups (p = 0.912) (Table 2).

4. Factors associated with VR and predictive cut-off level of HBV DNA

Factors associated with VR were analyzed in patients with PVR to ETV therapy. The univariate Cox proportional hazard analysis revealed that low HBV DNA level at 12 months (p < 0.001), more reduction of HBV DNA levels from baseline to 12 months (p < 0.001), HBeAg positivity (p = 0.002), and absence of LAM treatment history (p = 0.017) were associated with VR. In the multivariate analysis, low HBV DNA level at 12 months (p < 0.001) and absence of LAM treatment history (p = 0.047) were significant independent predictive factors for VR (Table 3).

We analyzed the cut-off value of HBV DNA level among NUC-naïve patients. The area under the ROC curve of HBV DNA level at 12 months of ETV therapy that predicted VR at 36 months was 0.909 (confidence interval, 0.852−0.965, P< 0.001). Based on Youden's J statistic, the cut-off value of HBV DNA level was 95 IU/ml with a sensitivity of 92.9% and a specificity of 78.3% (Fig. 3A). The positive predictive value was 94.0%, and the negative predictive value was 75.0% (Fig. 3B). The cumulative rates of VR for NUC-naïve patients after 24, 36, and 48 months of prolonged ETV therapy were 85.7%, 93.6%, and 95.7% in the group with HBV DNA levels <95 IU/ml at 12 months and 15.6%, 34.7%, and 54.6% in the group with HBV DNA levels _95 IU/ml at 12 months. There was a significant difference between the two groups (P<0.001) (Fig. 4).

5. Development of ETV resistance

Resistance to ETV developed in six of the 102 NUC-naïve patients (5.9%) and six of the 28 LAM-experienced patients (21.4%) during the mean follow-up period of 34.9 months. The number of patients with ETV resistance was significantly higher in the LAM-experienced group (p = 0.022) than in NUC-naïve group. It was found that all the 12 ETV resistant patients had LAM resistance mutations: rt180M/rt204V and rt202G (n = 7), rt184I (n = 2), rt184I/rt184L (n = 2), and rt202G/rt184I (n = 1). The average time of developing ETV resistance was 40.8 months, and the shortest time of developing resistance was 24 months after the ETV therapy. The univariate cox proportional hazard analysis revealed that high HBV DNA level at 12 months and a history of treatment with LAM were associated with ETV resistance (p-values of 0.003 and 0.018, respectively). HBV DNA level at 12

months and LAM treatment history also showed significant associations with ETV resistance in the multivariate analysis (p-values of 0.005 and 0.048, respectively) (Table 4).

The development of ETV resistance among NUC-naïve patients was compared between 50 patients with HBV DNA levels <95 IU/ml at 12 months and 52 patients with HBV DNA levels ≥95 IU/ml at 12 months. No patient developed ETV resistance with HBV DNA levels <95 IU/ml at 12 months, but six of 52 (11.5%) patients developed ETV resistance with HBV DNA levels ≥95 IU/ml at 12 months. The number of patients with ETV resistance was significantly higher in patients with HBV DNA levels ≥95 IU/ml at 12 months than in patients with HBV DNA levels <95 IU/ml at 12 months (P<0.001). No patients who achieved VR developed resistance to ETV during the study course.

C. TDF rescue therapy in patients with PVR to ETV

Subgroup analysis was conducted in the 23 patients with PVR to ETV therapy who underwent TDF rescue therapy. Three of these patients were switched to TDF because of resistance to ETV. Nineteen of the 23 patients (82.6%) developed VR by month 15 after the initiation of the TDF rescue therapy. The cumulative rates of VR were 56.5%, 73.9%, 82.6%, 91.3%, and 91.3% after 3, 6, 9, 12, and 15 months, respectively. There was no significant difference in the VR rates between the groups with and without ETV resistance (p = 0.592), suggesting that the effect of the TDF rescue therapy was independent from resistance to ETV.

C. TDF rescue therapy versus prolonged ETV therapy

VR between the patients who switched ETV to TDF and those who continued ETV after identifying PVR during ETV treatment was analyzed. Patients with LAM-experienced or HBV DNA level ≥95 IU/ml at 12 months were excluded, because they showed poor efficacy in prolonged ETV therapy in previous analysis. The cumulative rate of VR was 91.3% at 12 months of switching to TDF in the TDF rescue group, and 85.7% at additional 12 months of ETV in the prolonged ETV-treatment group. However, the cumulative rate of VR was found to be significantly higher in the TDF rescue therapy group than that in the prolonged ETV treatment group (log-rank test, P=0.015).

IV. DISCUSSION

The European Association for the Study of the Liver (EASL) guidelines for chronic hepatitis B recommend adding other drugs or switching to alternative antiviral agents in patients receiving ETV or TDF with a PVR at week 48 [EASL, 2012]. However, recent studies suggest that VR can be achieved in patients with PVR upon prolonged ETV treatment [Chen et al., 2014; Kwon et al., 2013; Zoutendijk et al., 2011]. A previous study showed that maintaining ETV treatment for 15 additional months led to VR in 81% of NUC-naïve patients with PVR. Moreover, 95% of patients with HBV DNA level <1000 IU/mL achieved VR, as opposed to only 57% of patients with HBV DNA level ≥1000 IU/mL. Accordingly, the authors proposed that treatment alteration is not needed in NUC-naïve PVR patients with HBV DNA level <1000 IU/mL [Zoutendijk et al., 2011].

In the study by Chen et al. [Chen et al., 2014], only eight of 41 (19.5%) LAM-experienced patients with PVR at 12 months achieved VR during the prolonged therapy. The present study analyzed the efficacy of prolonged ETV therapy and factors associated with VR in NUC-naïve and LAM-experienced patients with PVR to ETV. The cumulative rates of VR were 83.7% in the treatment-naïve group and 42.8% in the LAM-experienced group after 48 months ($p = 0.008$). Moreover, ETV resistance was more frequent in the LAM-experienced group than NUC-naïve group. Therefore, it would be better to change TDF in patients with a history of LAM treatment.

An absence of LAM treatment history and low HBV DNA level at 12 months showed significant associations with achieving VR (p-values of 0.047 and <0.001, respectively) in the present study. The majority of the previous studies reported that high viral load at baseline or at the time of PVR affects VR [Chen et al., 2014; Ko et al., 2012; Kwon et al., 2013; Zoutendijk et al., 2011]. A previous study showed that baseline serum HBV DNA level of ≥8 log10 IU/mL (9.8% vs. 46.9%; p < 0.001), serum HBV DNA level at 12 weeks ≥2000 IU/mL (3.7% vs. 20.3%, p < 0.001), and detectable serum HBV DNA (≥20 IU/mL) at week 24 (28.8% vs. 87.5%; p < 0.001) were significantly associated with PVR in patients receiving ETV [Kwon et al., 2013]. However, only HBV DNA level at the time of PVR but not at baseline affected VR in the present study. In agreement with these data, Chen et al. reported that NUC-naïve patients with HBV DNA level ≥2000 copies/mL at the time of PVR had a poor response to the therapy [Chen et al., 2014], and Zoutendijk et al. showed that patients with HBV DNA ≥ 1000 IU/mL at 12 months had worse results than those with HBV DNA <1,000 IU/mL [Zoutendijk et al., 2011].

ROC curve analysis performed to determine the cut-off value of HBV DNA level among NUC-naïve patients predicting VR at 36 months yielded the value of 95 IU/ml, with a fairly good discrimination capability reflected by the area under the ROC curve of 0.909. The sensitivity of this cut-off HBV DNA level at 12 months for predicting VR was 92.9%, and the positive predictive value was 94.0%. Therefore, switching to TDF in patients with HBV DNA level ≥95 IU/ml at 12 months of ETV therapy can be recommended.

In the present study, high HBV DNA level at 12 months ($p = 0.005$) and prior LAM treatment ($p = 0.046$) were found to be associated with the development of ETV resistance. The occurrence rate of ETV resistance was compared between the patients with HBV DNA levels <95 IU/ml and those with HBV DNA levels ≥95 IU/ml at 12 months to investigate the role of this cut-off value of HBV DNA in predicting ETV resistance. During the follow-up period, ETV resistance did not occur in the patients with HBV DNA levels <95 IU/ml at 12 months. In contrast, ETV resistance occurred frequently (11.5%, 6/52) in the patients with HBV DNA levels ≥95 IU/ml at 12 months. Moreover, no ETV resistance occurred in the patients who achieved VR within 36 months of ETV administration. These findings suggest that continuation of ETV treatment is more likely to result in VR without the risk of resistance in patients with HBV DNA levels <95 IU/ml at 12 months.

TDF rescue therapy was reported to be effective in patients with HBV refractory or resistant to ETV [Kim et al., 2012; Leemans et al.; Pan et al., 2012]. According to a previous report, all patients initially non-responsive to ETV achieved undetectable HBV DNA levels and ALT normalization within a median period of 30 weeks after switching to TDF [Pan et al., 2012]. In the present study, the cumulative rate of VR in patients with PVR to ETV therapy was 91.3% 15 months after switching to TDF, proving the effectiveness of TDF rescue therapy. Furthermore, it was shown that resistance to ETV did not affect the efficiency of TDF treatment (log rank $p = 0.592$). A previous study suggested that resistance to LAM (rtM204 and/or rtL180M mutations) or ETV (rtM204V, rtL180M, and rtS202G mutations) did not affect TDF therapy because of the structural differences between TDF and ETV/LAM [Ghany and Doo, 2009].

The cumulative rate of VR was found to be significantly higher in the TDF rescue therapy group compared with that of the prolonged ETV treatment group with NUC-naive and HBV DNA level <95 IU/ml at 12 months. However, the cumulative rates of VR were 93.6%, and 95.7% after 36 and 48 months of prolonged ETV therapy, respectively, in patients with NUC-naive and HBV DNA level <95 IU/ml at 12 months. Moreover, no patient developed ETV resistance during the follow-up period. Therefore, continuing the ETV therapy may be an option for the treatment of NUC-naïve patients with HBV DNA level 95IU/ml at 12months.

Our study is limited in that the number of patients in the analysis was relatively small, and all patients received a 0.5 mg/day ETV dose, regardless of prior treatment history or antiviral resistance.

V. CONCLUSION

In conclusion, prolonged ETV therapy induced a VR without the risk of ETV resistance in NUC-Naïve patients with HBV DNA levels <95 IU/mL at 12 months. All patients with LAM-experienced or NUC-naïve with HBV DNA levels ≥95IU/mL at 12 months should be switched to TDF-rescue therapy.

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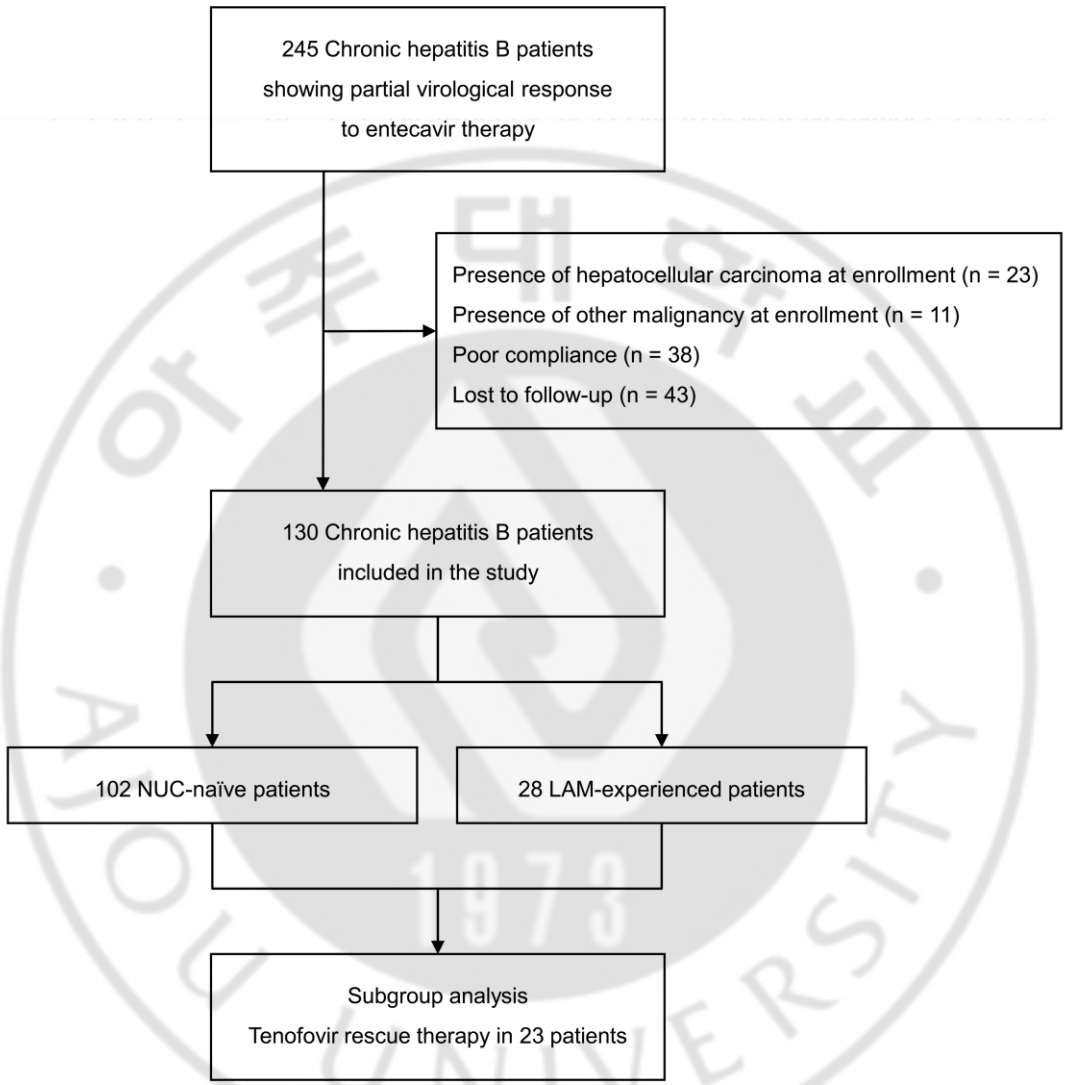


Fig. 1. Flow diagram of the study population. One-hundred and thirty out of 245 patients were included, and 23 patients underwent tenofovir rescue therapy.

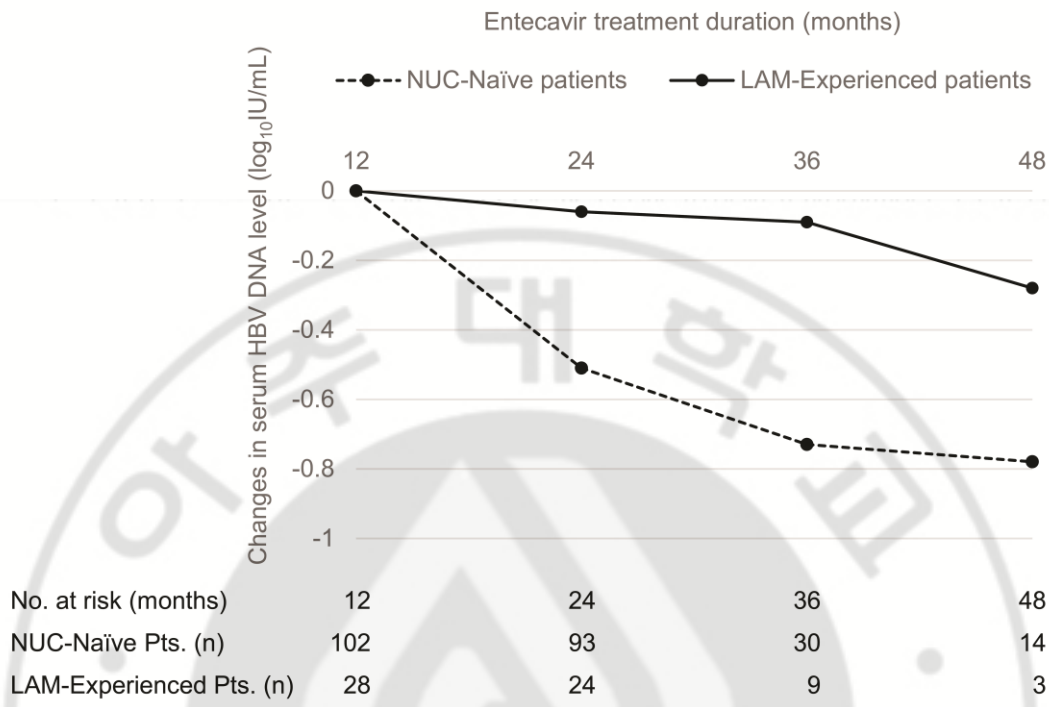


Fig. 2. Changes in serum HBV DNA levels starting from 12 months of entecavir therapy. There was a significant difference in the extent of reduction between the NUC-naive group and the LAM-experienced group achieved between months 12 and 24 ($P<0.022$) and months 12 and 36 ($P<0.048$).

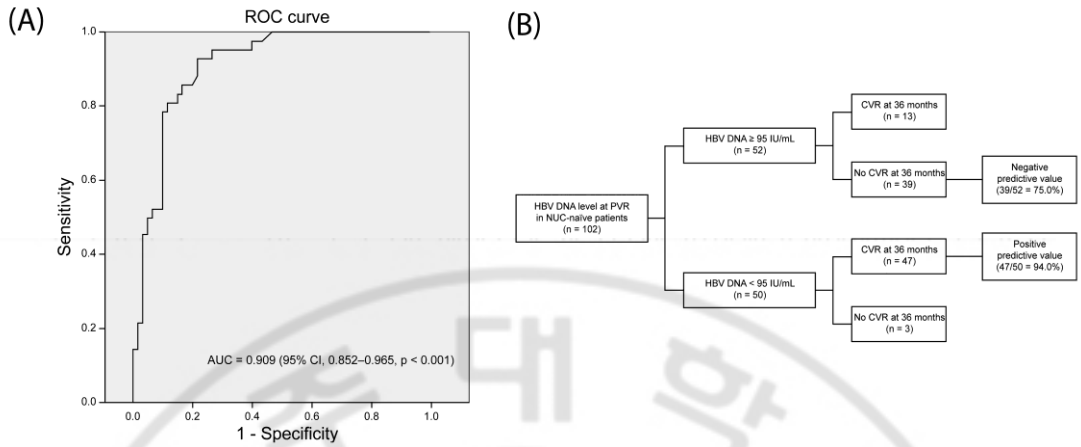
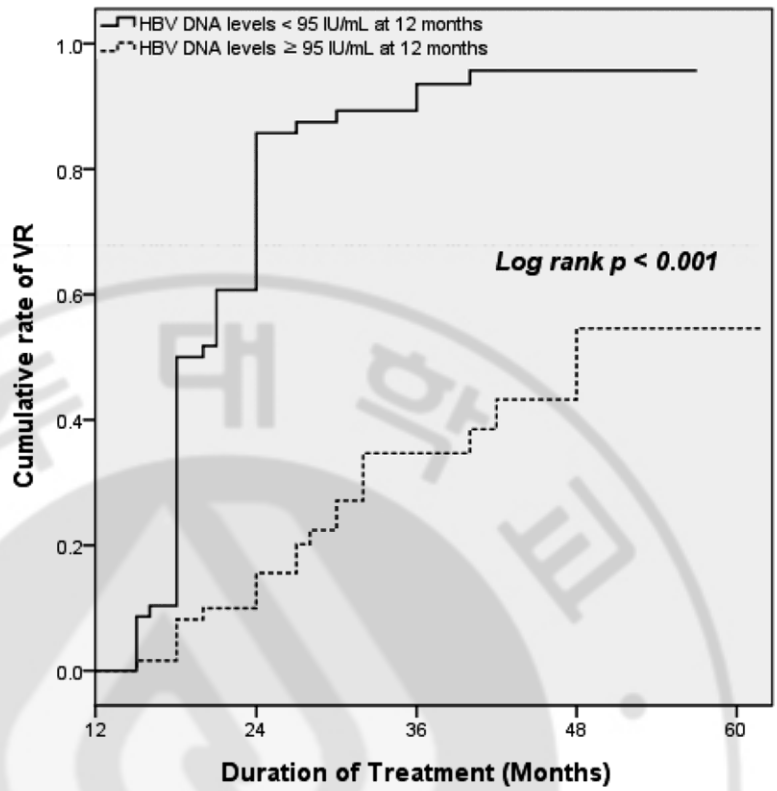


Fig. 3. Analysis of the serum HBV level at 12 months as a predictor of achieving virological response (VR) at 36 months. (A) The area under the receiver operating characteristic curve of HBV DNA level at 12 months predicting VR among NUC-naïve patients. (B) Prediction of achieving VR at 36 months based on the HBV level at 12 months among NUC-naive patients (HBV DNA cut-off level: 95 IU/ml).



No. at risk	12	24	36	48
HBV DNA level < 95 IU/mL	50	17	4	1
HBV DNA level ≥ 95 IU/mL	52	33	14	1

Fig. 4. Kaplan–Meier curves for the cumulative rates of virological response (VR) during prolonged entecavir therapy in patients with partial virological response. A comparison of NUC-naïve patients with HBV DNA levels <95 IU/ml and HBV DNA levels ≥ 95 IU/ml at 12 months.

Table 1. Baseline and on-treatment characteristics of the patients with partial virological response.

Variables	Total (n=130)	NUC-naïve Pts. (n=102)	LAM-Experienced Pts. (n=28)	*P* value
Age (years)	44.2 (19-72)	43.2 (19-72)	47.8 (28-68)	0.072
Male (%)	88 (67.7%)	71 (69.6%)	17 (60.7%)	0.373
Cirrhosis	25 (19.2%)	18 (17.6%)	7 (25%)	0.382
HBeAg Positive	100 (76.9%)	82 (80.4%)	17 (60.7%)	0.022
HBV DNA (Log_{10}IU/mL)				
At baseline	7.51 (±0.84)	7.62 (±0.73)	7.09 (±1.06)	0.062
At PVR (12 months)	2.33 (±0.82)	2.27 (±0.80)	2.57 (±0.87)	0.099
ALT (U/L)	38.5 (8-439)	29.3 (8-439)	29.1 (12-55)	0.087
Creatinine (mg/dL)	1.01 (0.6-1.7)	1.02 (0.7-1.7)	0.99 (0.6-1.4)	0.297
Bilirubin (mg/dL)	1.10 (0.3-3.9)	1.05 (0.3-3.9)	0.98 (0.5-2.1)	0.633
Platelet ($x10^3$/μL)	165 (46-322)	169 (46-322)	151 (73-229)	0.263
Follow-up time (months)	34.9 (13-62)	34.7 (13-60)	36.9 (13-62)	0.975
Prior treatment				
LAM alone	24 (18.5%)		24 (85.7%)	
LAM + ADF	4 (3.1%)		4 (14.3%)	

Data are presented as mean (range or SD) or n (%).

Baseline data are the values at 12 months of starting entecavir therapy.

NUC: nucleot(s)ide analogue; LAM: lamivudine; HBeAg: hepatitis B e antigen; ALT: alanine aminotransferase.

Table 2. The efficacy of prolonged entecavir therapy.

	NUC-Naïve pts. (n=102)	LAM-Experienced pts. (n=28)	*P* value
Reduction of HBV DNA level after 12 months (log10 IU/mL), mean SD			Independent T-test
Month 12-24	-0.51 ± 0.63	-0.06 ± 1.39	0.021
Month 12-36	-0.73 ± 0.71	-0.09 ± 1.19	0.048
Month 12-48	-0.78 ± 0.87	-0.28 ± 0.87	0.436
Virological response, cumulative incidence			Log-rank test
Month 24	54.1%	37.0%	
Month 36	70.8%	42.8%	0.008
Month 48	83.7%	42.8%	
HBeAg loss, cumulative incidence			Log-rank test
Month 24	19.1%	25.0%	
Month 36	31.5%	31.8%	0.912
Month 48	54.9%	45.5%	

Table 3. Factors associated with virological response during prolonged entecavir therapy.

	Univariate analysis			Multivariate analysis		
	95% confidence interval	HR	*P* value	95% confidence interval	HR	*P* value
Age	0.987-1.028	1.007	0.476			
Male	0.750-1.984	1.220	0.423			
Cirrhosis	0.899-2.742	1.570	0.113			
HBeAg (+)	0.257-0.703	0.425	0.002	0.354-1.288	0.675	0.233
HBV DNA Level at baseline	0.691-1140	0.888	0.350			
HBV DNA Level at 12 months	0.178-0.427	0.275	<0.001	0.156-0.456	0.266	<0.001
Reduction of HBV DNA level from baseline to12 months	1.276-2.128	1.648	<0.001	0.772-1.383	1.034	0.824
ALT	0.992-1.003	0.997	0.379			
Creatinine	0.308-4.671	1.200	0.793			
Bilirubin	0.973-2.355	1.514	0.066	0.879-1.203	1.028	0.726
Platelet	0.992-1.001	0.996	0.130			
Treatment-experience	0.228-0.865	0.444	0.017	0.230-0.976	0.492	0.047

Table 4. Factors associated with entecavir resistance.

	Univariate analysis			Multivariate analysis		
	95% confidence interval	HR	*P* value	95% confidence interval	HR	*P* value
Age	0.947-1.050	0.997	0.906			
Male	0.379-5.781	1.481	0.572			
Cirrhosis	0.044-2.895	0.356	0.334			
HBeAg (+)	0.322-7.524	1.556	0.583			
HBV DNA level at baseline	0.416-1.466	0.781	0.442			
HBV DNA level at 12 months	1.437-5.484	2.808	0.003	1.372-5.627	2.779	0.005
ALT	0.999-1.017	1.008	0.090	0.997-1.006	1.002	0.455
Creatinine	0.028-31.190	0.940	0.972			
Bilirubin	0.078-2.142	0.410	0.290			
Platelet	0.992-1.017	1.004	0.478			
LAM-experience	1.285-14.821	4.364	0.018	1.022-13.534	3.720	0.046

- 국문요약 -

엔테카비어 치료에 부분 바이러스 반응을 보인 환자에서 엔테카비어 유지치료를 한 만성 B 형 간염 환자의 경과

엔테카비어 치료에 부분 바이러스 반응을 보인 만성 B 형 간염환자의 장기 치료효과에 대한 연구가 부족한 상태이다. 이 연구의 목적은 엔테카비어 치료에 부분 바이러스 반응을 보인 환자의 임상적 경과 및 테노포비어의 효과를 알아보고자 하였다. 엔테카비어에 부분 바이러스 반응을 보인 130 명의 환자를 후향적으로 연구하였다. 102 명은 뉴클레오타(시)드 유사체 초치료 환자였으며, 28 명은 라미부딘 경험자였다. 바이러스 반응의 누적율은 엔테카비어 치료 후 24 개월, 36 개월, 48 개월째 뉴클레오타(시)드 유사체 초치료 환자군에서는 54.1%, 70.8%, 83.7%, 그리고 라미부딘 경험 37.0%, 42.8%, 42.8% 였다 (P=0.008). 12 개월째 낮은 HBV DNA 레벨 (P<0.001)과 라미부딘 치료 무경험 (P =0.031) 이 바이러스 반응에 유의하게 관계된 요소였다. 뉴클레오타(시)드 유사체 초치료 환자에서 12 개월째 HBV DNA 레벨 95 IU/ml 를 기준으로 한경우, 36 개월째 바이러스 반응의 민감도는 92.9% 이고 특이도는 78.3% 였다 (AUROC, 0.909; P<0.001). 엔테카비어 내성은 뉴클레오타(시)드 유사체 초치료이면서, 12 개월째 HBV DNA 레벨 95 IU/ml 미만인 환자에서는 나타나지 않았다. 테노포비어로 약제를 변경하거나 추가한 환자의 누적 바이러스 반응율은 15 개월째 91.3%로 나타났다. 뉴클레오타(시)드 유사체 초치료이면서, 12 개월째 HBV DNA 레벨 95 IU/ml 미만인 환자는 엔테카비어 유지치료로 바이러스 반응을 기대할 수 있겠다.

라미부딘 경험자 혹은 뉴클레오타(시)드 유사체 초치료이면서, 12 개월째 HBV DNA 레벨 95 IU/ml 이상인 환자는 테노포비어로의 치료 변경이 필요하겠다.

핵심어: 엔테카비어; 만성 B 형 간염, 부분 바이러스 반응, 테노포비어