의학박사 학위논문

만성 B 형 간염 초치료 환자와 항바이러스제 내성 환자에서의 테노포비어의 효과 비교

THE COMPARISON OF TENOFOVIR THERAPY BETWEEN NUCLEOS(T)IDE-NAÏVE AND NUCLEOS(T)IDE-RESISTANT CHRONIC HEPATITIS B

울산대학교대학원

의 학 과

박재호

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지도교수 박능화

이 논문을 의학박사 학위 논문으로 제출함

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박 재 호

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울 산 대 학 교 대 학 원

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ABSTRACT

Jae-ho, Park

Department of Internal Medicine,

Granduate School, University of Ulsan

Directed by Professor Neung Hwa Park, M.D., Ph.D.

Backgrounds: Uncontrolled hepatitis B virus infection can be cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma. Oral nucleos(t)ide analogues (NA) are very effective for viral suppression, however suboptimal response and genotypic resistance are major problem in treating chronic hepatitis B (CHB). Tenofovir disoproxil fumarate (TDF) is potent NA, and TDF is very effective for NA-failed CHB. However, there is controversy in TDF efficacy between NA-failed and NA-naïve patients. The present study aimed to compare the antiviral effects of TDF between NA-naïve and NA-failed CHB patients. In addition, we also compared antiviral effects of TDF according to mutation pattern in NA-failed CHB, especially multi-drug resistant (MDR).

Methods: Medical records of 735 patients with CHB who had treated with TDF were reviewed. Of the 735 eligible patients, 466 were NA-naïve and 269 were NA-failed prior to TDF therapy. The cumulative probability rates of clinical outcomes were calculated using the Kaplan–Meier method. We also performed multivariate Cox regression analysis to evaluate the association between mutation pattern and virologic response (VR) during TDF treatment for control of the potential confounders. A matched study population was constructed to compare the antiviral efficacy of TDF therapy by a propensity score analysis, because baseline characteristics of two groups were different significantly.

Results: One hundred eighty-eight CHB patients were selected after matching propensity score with 1:1 ratio. There was statistically significant difference in VR between the NA-naive and the NA-failed group (84 [89.3%] vs. 72 [76.5%], respectively; $P = 0.016$). NA-naïve patients showed higher cumulative rate of VR than NA-failed patients (78.6% vs. 58.3% at 12 months and 94.7% vs. 79.8% at 24 months; log-rank $P = 0.001$). Alanine transaminase (ALT) normalization rates, partial virolgoic response (PVR) and virologic breakthrough were not significantly different. Multivariate analysis using selected baseline factors identified HBV-DNA levels at starting TDF treatment ($P < 0.001$; OR, 0.790; 95% CI, 0.689-0.855), HBeAg positivity ($P = 0.003$; OR, 0.605; 95% CI, 0.415–0.834), as factors showing significant association with VR. We divided NA-failed group into three groups (NA-experienced, lamivudine-resistant, and MDR group). NA-experienced and lamivudine-resistant groups did not show significant difference in VR compared with NA-naïve group. However, MDR group showed lower VR than NA-naïve group (35 [66%] vs. 84 [89%], respectively; $P = 0.002$). In the multivariate analysis, MDR patients (OR, 0.502; 95% CI, 0.332–0.760; $P = 0.001$) remained predictive factor for VR.

Conclusions: In patients with NA-failed, the efficacy of TDF was lower than NA-naïve patients, especially MDR group. Therefore, TDF is best choice for naïve patients and early switching in NA-failed patients with low viral load state. Long term observational and well-controlled studies are warranted for proving these results.

Keywords: Tenofovir; nucleos(t)ide-naïve; nucleos(t)ide-failed; chronic hepatitis B

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Abbreviations

ADV, adefovir dipivoxil

AEs, adverse events

ALT, alanine transaminase

CHB, chronic hepatitis B

CI, confidence interval

DNA, deoxyribonucleic acid

ETV, entecavir

HBeAg, hepatitis B e antigen

HBsAg, hepatitis B surface antigen

HBV, hepatitis B virus

HCC, hepatocellular carcinoma

LAM, lamivudine

MDR, multi drug resistance

NA , nucleos(t)ide analogues

PCR-RFLP, polymerase chain reaction--restriction fragment length polymorphism

PVR, partial virologic response

OR, Odds ratios

TDF, tenofovir disoproxil fumarate

VBT, virologic breakthrough

VR, virologic response

INTRODUCTION

Uncontrolled Hepatitis B virus (HBV) infection is a serious public health problem worldwide and a major cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC), as a causative factor of liver disease in 240 million patients globally and death of 0.6 million patients annually [1]. The prevalence of HBV infection in the Korean population estimated by positive rates for hepatitis B surface antigen (HBsAg) was 8–9% for males and 5–6% for females before commercialization of an HBV vaccine in the early 1980s [2]. Thereafter, the prevalence of HBV infection tended to decline gradually due to the initiation of a vaccination program for newborn infants. The Ministry of Health and Welfare of South Korea reported that HBsAg positivity rate was 3.4% for males and 2.6% for females in 2012, with 3.0% of the total population being infected with HBV [3]. However, HBsAg is detected in approximately 70% of patients with chronic hepatitis or cirrhosis [4], and in 65–75% of HCC patients [5]. Therefore, chronic hepatitis B (CHB) infection is still a matter of importance for public health in Korea.

HBV DNA level is key factor in determining long-term outcomes in CHB patients [6]. Thus, lowering of HBV DNA levels can reduce risks of both cirrhosis and HCC development [7,8]. During the past decade, the introduction of antiviral agents has improved the management of patients with chronic HBV infection [9]. Oral nucleos(t)ide analogues (NA) are widely used to treat CHB and very effective for viral suppression. However, persistence of suboptimal response during long-term antiviral treatment is associated with the emergence of drug resistant viral strains, which could result in poor clinical outcomes [10].

Lamivudine (LAM), the first oral antiviral approved for treatment of CHB, is safe and well tolerated even in patients with decompensated liver cirrhosis [11]. However, the long-term use of LAM inevitably leads to the development of resistant HBV mutants. Cumulative incidence rate of LAM resistance after 1 year is 24%, 5 year is 60-70% [12]. Some patients may proceed to hepatic failure or HCC after LAM resistance. As salvage therapy to treat LAM-resistance, earlier studies suggested that adefovir dipivoxil (ADV) monotherapy had shown similar antiviral effects to combination therapy with LAM/ADV in the short-term, and a strategy of switching to ADV monotherapy had been widely adopted [13,14].

Unfortunately, after sequential monotherapy with LAM and ADV, multi-drug resistance (MDR) developed in a substantial number of patients [15,16]. In addition, since tenofovir disoproxil fumarate (TDF) is not available in many Asian countries, earlier treatment guidelines based on insufficient clinical experiences have recommended the use of entecavir (ETV) as one of the treatment options for CHB patients with LAM resistance [17]. However, in patients with pre-existing LAM-resistance, the rate of ETV resistance increases up to 51% after 5 years of sequential ETV treatment [18].

TDF is a potent, nucleotide analogue in first-line therapy of CHB [10,19]. Suppression of HBV can lead to regression of fibrosis and cirrhosis without emergence of resistance to TDF in NA-naïve patients [20,21]. TDF is also highly effective against LAM-resistant virus [22]. Recently, long-term TDF monotherapy has shown appropriate anti-viral efficacy without evidence of TDF resistance [23,24].

Recent studies about TDF are focused on efficacy of TDF monotherapy and TDF combination rescue therapy [25,26]. There are few studies about comparison of TDF efficacy between NA-naïve and NA-failed groups [27]. Efficacy of TDF has been found to be not significantly different between LAM-resistant and NA-naïve patients [28]. However, TDF efficacy between MDR and NA-naïve patients remains controversial [27,29,30]. Moreover, these studies are small number of enrolled patients, not well controlled design and do not have long periods of observation. Therefore, we aimed to evaluate long term efficacy of TDF in both NA-naïve and NA-failed CHB patients in Korea, especially MDR.

PATIENTS AND METHODS

1. Patient Population

Electronic medical records of 735 patients with CHB who had been treated with TDF (300 mg/day) for at least 6 months between January 2013 and April 2016 were reviewed. Four hundreds sixty-six patients were NA-naïve while 269 were failed to NA therapy prior to TDF rescue therapy. We defined NA-naïve group as naïve patients who had no other antiviral therapy, such as interferon or other nucleosides for at least 6 months prior to TDF therapy. NA-failed group was defined as incomplete virologic response (persistent or measurable HBVDNA levels during NA treatment for > 12 months), or as resistance to NA therapy prior to TDF based rescue therapy. NA-experienced groups was defined as patients who received prior NA treatment before TDF therapy without any documented HBV mutant gene. Inclusion criteria for this study were age > 18 years, serum HBsAg positivity and positive HBV DNA in serum for at least 6 months before TDF therapy. Patients with impaired renal function (serum creatinine > 1.5 mg/dL), antibodies to hepatitis C virus, antibodies to HIV, or autoimmune hepatitis were excluded. Additional exclusion criteria were pregnancy, lactation, and alcohol abuse (> 40 g/day of ethanol). Diagnoses of chronic hepatitis and liver cirrhosis were based on liver biopsy features or results of clinical, laboratory, and ultrasound data. Written informed consent was obtained from all patients participating in the study. This research was approved by the Institutional Review Board of Ulsan University Hospital.

2. Laboratory measurements

Liver and kidney function tests were performed every 3 months during TDF therapy. HBV DNA levels were quantified using the COBAS TaqMan HBV test (Roche, Branchburg, NJ, USA), which has a lower detection limit of 12 IU/mL (60 copies/mL). Specific HBV genotypes were identified using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis for surface gene of HBV. The two fragments of HBV genome between nucleotide positions 2823 and 2845 and 61 and 80 were amplified using PCR and the products were treated with restriction enzymes. Genotypic resistance was tested by restriction fragment mass polymorphism (RFMP; Genematrix, Youngin, Korea). The RFMP assay can detect 100 copies of HBV genome per milliliter. Patients underwent surveillance for HCC every 6 months and serial abdominal ultrasound and serum a-fetoprotein measurements were performed every 6-12 months.

3. Definitions

Virologic response (VR) was defined as the absence of serum HBV DNA by PCR assay (< 12 IU/mL) on two consecutive measurements during TDF therapy. Hepatitis B e antigen (HBeAg) seroconversion was defined as the loss of HBeAg accompanied by detection of anti-HBe and the absence of serum HBV DNA during treatment. Partial virologic response (PVR) was defined as a decrease in HBV DNA more than 1 log10 IU/mL but detectable HBV DNA after 6 months of therapy. Virologic breakthrough (VBT) was defined as more than 1 log10 IU/mL increase in serum HBV DNA from nadir on two consecutive measurements or on the last available measurement. Safety and tolerability were evaluated by the occurrence of adverse events (AEs), serious AEs, laboratory abnormalities, discontinuation of the study drug due to AEs, or death. Specific markers of renal abnormalities were confirmed (defined as two consecutive visits) based on increase in serum creatinine of at least 0.5 mg/dL above the baseline value, serum phosphate values of < 2 mg/dL, and creatinine clearance > 50 mL/min.

4. Statistical analysis

Serum HBV DNA (IU/mL) levels were logarithmically transformed for analysis. Continuous variables were compared using Student's t-test or paired t-test, while categorical variables were compared using the $\chi 2$ test. Cumulative probability rates of clinical outcomes were calculated using the Kaplan–Meier method. To identify factors predictive of clinical outcomes among baseline variables, clinical outcome variables were compared using $\chi 2$ test or univariate logistic regression. We also performed multivariate Cox regression analysis to evaluate the association between previous exposure to antivirals and VR during TDF treatment to control potential confounders. Propensity score estimated with presence of NA resistance as the dependent variable by multivariable logistic regression analysis. A full non-parsimonious model was developed that included all variables in age, sex, ratio of cirrhosis, initial HBV DNA level, ALT level, ratio of HBeAg positivity, duration of TDF therapy and the interaction between the variables. Model calibration was assessed with Hosmer & Lemeshow statistics ($\chi 2$=8.690, df=8, *P*-value=0.369). Propensity score matching was performed by Greedy matching using 0.01 standard deviations of the logit the propensity score. We were able to match 94 NA-naïve patients to 94 NA-resistant patients. Logistic regression was applied to generate a continuous propensity score ranging from 0 to 1. All data were analyzed using the SPSS version 23.0 for Windows statistical package (SPSS Inc., Chicago, IL, USA). A two-tailed *P*-value < 0.05 was considered statistically significant.

RESULTS

1. Baseline characteristics of study population

A total 735 patients started TDF therapy during the study periods. The genotype of all the patients are type C2. The mean age of the patients was 49 (range, 14-90 years), 493 (67%) patients were male and 478 (66%) patients were HBeAg positive. Three hundred eighty-seven (53%) patients had CHB and the other patients had liver cirrhosis. Mean alanine aminotransferase (ALT) level before treatment of TDF was 136 IU/L and mean treatment duration of TDF was 26 months (range, 6~45 months). Of the 735 patients, 466 patients were NA-naïve patients while 269 patients were NA-failed. Baseline characteristics according to treatment group are summarized in Table 1.

Patients in both groups had different baseline characteristics. Sex (62% vs. 76%, $P < 0.001$), presence of liver cirrhosis (52.3% vs. 38.7%, $P < 0.001$), HBeAg positivity (57% vs. 78%, $P < 0.001$) and duration of TDF therapy (22 months vs. 32 months, $P < 0.001$) are significantly different between two treatment groups. NA-naïve group had higher pre-treatment HBV DNA level than NA-failed group (6.25 vs. 4.07 log10 IU/mL, $P < 0.001$).

Table 1. The baseline characteristics of patients in the NA-naive and NA-failed groups

	NA-naïve (n=466)	NA-failed (n=269)	*P*-value
Age (years)	49.2 ± 11.6	50.6 ± 10.6	0.089
Sex (male/female)	289/177	204/65	< 0.001
Cirrhosis (n, %)	244 (52.3%)	104 (38.7%)	< 0.001
ALT (IU/L)	176 ± 298	68 ± 152	< 0.001
HBV DNA (log_{10} IU/mL)	6.25 ± 1.52	4.07 ± 1.73	< 0.001
HBeAg positivity (n, %)	267 (57.7%)	211 (78.7%)	< 0.001
Duration of TDF therapy (months)	22.5 ± 9.6	32.5 ± 9.2	< 0.001

Continuous variables are expressed as median (range or percentile) or mean ± standard deviation; ALT, alanine transaminase; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; NA, nucleos(t)ide analogues

2. Treatment response to TDF therapy

Overall clinical outcomes between NA-naïve and NA-failed group are shown in Table 2. The VR rates were compared using Kaplan-Meier test to determine whether there was any difference in VR rates between the NA-naïve and NA-failed groups. The rates of VR at 12 and 24 months were not significantly different between NA-naïve and NA-failed groups (72.3% vs. 75.3% at 12 months and 90.5% vs. 87.7% at 24 months; log-rank $P = 0.103$) (Fig. 1).

Rate of ALT normalization, HBeAg seroconversion and VBT are not different between two groups (87.1% vs. 92.9%, 16.1% vs. 10.8%, and 4.2% vs. 4.1%, respectively; $P = 0.191$, 0.11, 1.0, respectively). Twenty-seven patients (3.6%) had an increase in serum creatinine level during TDF treatment and seven patients had an increase in serum creatinine level > 0.5 mg/dL above the baseline value.

Table 2. Overall clinical outcomes between NA-naïve and NA-failed groups

	NA-naïve (n=466)	NA-failed (n=269)	*P*-value
ALT normalization, n (%)	91/100 (87.1%)	79/85 (92.9%)	0.191
Virologic response, n (%)	380/466 (81.5%)	239/269 (88.8%)	0.103
12 months	72.3 %	75.3 %	
24 months	90.5 %	87.7 %	
Partial Virologic Response, n (%)	245/466 (52.6%)	96/269 (35.7%)	< 0.001
HBeAg seroconversion, n (%)	43/267 (16.1%)	23/212 (10.8%)	0.110
Virologic breakthrough, n (%)	19/466 (4.2%)	11/269 (4.1%)	1.000

Continuous variables are expressed as median (range or percentile) or mean ± standard deviation; ALT, alanine transaminase; HBeAg, hepatitis B e antigen; NA, nucleos(t)ide analogues

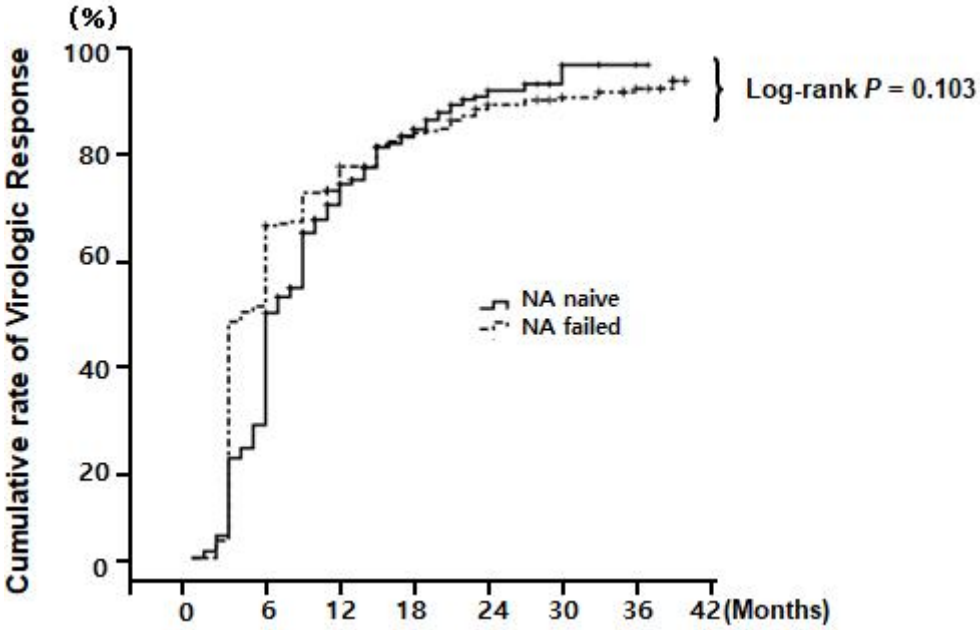

Figure 1. Cumulative rate of virologic response between NA-naïve group and NA-failed group

3. Predictors of VR in patients treated with TDF therapy

To determine whether there was any difference in rates of VR according to clinical and virologic factors such as genotypic resistance, viral load and HBeAg positivity, VR rates were compared according to these variables using multivariate Cox regression model. Univariate analysis revealed that absolute HBV DNA levels at the start of TDF treatment ($P < 0.001$), HBeAg positivity ($P < 0.001$), and absence of liver cirrhosis ($P = 0.023$) were significantly related to VR. In the multivariate analysis, HBV DNA level at the start of TDF treatment (OR, 0.556; 95% CI, 0.689–0.766; $P < 0.001$), and HBeAg positivity (OR, 0.531; 95% CI, 0.577–0.833; $P < 0.001$) showed the significant association with VR (Table 3).

Table 3. Univariate and multivariate Cox proportional hazard analysis to identify factors associated with VR

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	1.009	1.002-1.066	0.012			
Sex	0.957	0.810-1.131	0.604			
ALT	1.000	1.000-1.000	0.872			
Cirrhosis	0.832	0.710-0.976	0.023	1.001	0.835-1.200	0.990
HBV DNA □	0.755	0.723-0.789	< 0.001	0.556	0.689-0.766	< 0.001
NA-naïve vs. NA-failed	0.884	0.750-1.042	0.143			
HBeAg positivity	0.379	0.425-0.595	< 0.001	0.531	0.577-0.833	< 0.001

ALT, alanine transaminase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; NA, necleotide analogues; VR, virologic response; OR, odd ratio; CI, confidence interval, □ HBV DNA levels at start of TDF therapy

4. Propensity score matching

NA-failed patients appeared to have higher VR than NA-naïve patients. Even though, there was no significant difference in cumulative rate of VR on the multivariate analysis. In addition, NA-failed patients had significantly lower HBV DNA level than NA-naïve patients. Many variables including HBeAg positivity, ALT level, presence of liver cirrhosis, sex distribution and duration of TDF therapy were also significantly different between the two treatment groups. To compensate these limitations, we performed propensity score matching by 1:1 ratio.

After propensity score matching, 188 patients were selected (NA-naïve: 94 patients, NA-failed: 94 patients). Mean age of the patients was 50 (range, 23-90 years), 132 patients were male, and 112 patients had HBeAg positive. Eighty-four patients had CHB while, the others had liver cirrhosis. Mean ALT level before treatment of TDF was 123 IU/L and mean treatment duration of TDF was 27 months (range, 6~43 months). Baseline characteristics of patients after propensity score matching are shown in Table 4. Age, sex, presence of cirrhosis, ALT level, HBV DNA levels at start of TDF-based treatment, HBeAg positivity and duration of TDF therapy were not significantly different between NA-naïve and NA-failed groups. Among the NA-failed groups, 30 patients have LAM resistance, and 53 patients have MDR. The others have no documented mutant HBV strain.

Table 4. The baseline characteristics of patients in the NA-naive and NA-failed groups after propensity score matching

	NA-naïve (n=94)	NA-failed (n=94)	*P*-value
Age (years)	50.38 ± 10.93	51.03 ± 11.59	0.693
Sex (male/female)	63/31	69/25	0.339
Cirrhosis (n, %)	53 (56.4%)	51 (54.3%)	0.769
ALT (IU/L)	118.74 ± 160.62	128.68 ± 9.71	0.741
HBV DNA (log_{10} IU/mL)	5.17 ± 1.51	5.46 ± 1.77	0.227
HBeAg positivity (n, %)	54 (57.4%)	58 (61.7%)	0.552
Duration of TDF therapy (months)	27.34 ± 9.71	28.51 ± 11.06	0.442
Drug Resistance			
NA-experienced		11	
LAM-resistant		30	
Multi drug resistance		53	
LAM + ADV		23	
LAM + ETV		25	
LAM + ADV + ETV		5	

Continuous variables are expressed as median (range or percentile) or mean ± standard deviation ; ADV, adefovir dipivoxil; ALT, alanine transaminase; ETV, entecavir; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; LAM, lamivudine TDF, tenofovir; NA, necleos(t)ide analogues

5. Treatment response of TDF therapy after propensity score matching

Overall clinical outcomes between NA-naïve and NA-failed group are shown in Table 5. Of 94 NA-naïve patients, 84 (89.3%) achieved VR, while 72 (76.5%) of 94 NA-failed patients achieved VR ($P = 0.016$). NA-naïve patients showed higher cumulative rate of VR than NA-failed patients (78.6% vs. 58.3% at 12 months and 94.7% vs. 79.8% at 24 months, respectively; $P = 0.001$) (Fig. 2).

PVR between the two groups were not significantly different (41 patients [43.6%] vs. 53 patients [65.3%]; $P = 0.054$). Rates of ALT normalization, HBeAg seroconversion were not significantly different between the two groups (92% vs. 87.5% $P = 0.535$ and 24% vs. 17.2%, $P = 0.446$, respectively). NA-failed patients showed higher VBT, however the difference between the two groups was not significantly different (1 patient vs. 6 patients, $P = 0.059$).

Six patients (3.2%) had an increase in serum creatinine level during TDF treatment. And, two of these patients had an increase in serum creatinine level > 0.5 mg/dL above the baseline value.

Table 5. Overall clinical outcomes between NA-naïve and NA-failed groups after propensity score matching

	NA-naïve (n=94)	NA-failed (n=94)	*P*-value
ALT normalization	69/75 (92%)	42/48 (87.5%)	0.535
Virologic response	84/94 (89.3%)	72/94 (76.5%)	0.016
Partial virologic response	41/94 (43.6%)	53/94 (65.3%)	0.054
HBeAg seroconversion	13/54 (24%)	10/58 (17.2%)	0.446
Virologic breakthrough	1/94 (1.0%)	6/94 (6.4%)	0.059

Continuous variables are expressed as median (range or percentile) or mean ± standard deviation ; ALT, alanine transaminase; HBeAg, hepatitis B e antigen; NA, nucleos(t)ide analogues

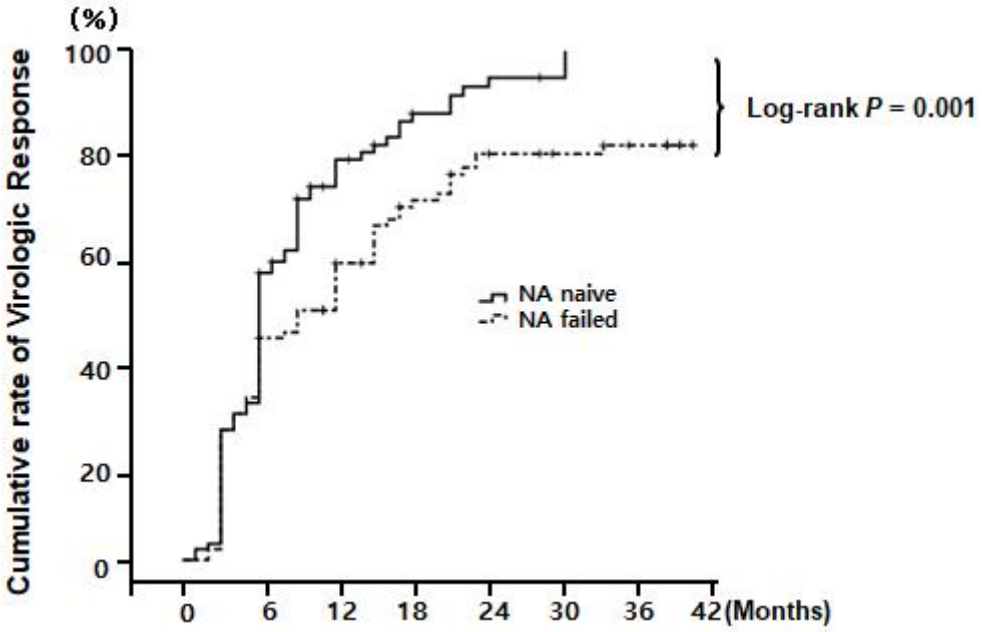

Figure 2. Cumulative rate of virologic response between NA-naïve group and NA-failed group after propensity score matching

6. Predictors of VR after propensity score matching

To determine whether there was any difference in the rates of VR according to clinical and virologic factors such as genotypic resistance, viral load and HBeAg positivity, VR rates were compared according to these variables using multivariate Cox regression model (Table 6). Univariate analysis revealed that HBV DNA level at the start of TDF treatment ($P < 0.001$), HBeAg positivity ($P < 0.001$), and NA-naive group ($P = 0.003$) was significantly related to VR. In the multivariate analysis, HBV DNA level at the start of TDF treatment (OR, 0.790; 95% CI, 0.689–0.855; $P < 0.001$) and HBeAg positivity (OR, 0.605; 95% CI, 0.415–0.834; $P = 0.003$) showed the significant associations with VR. Although NA-naïve patients showed higher VR in the univariate analysis, and they tended to have higher VR than NA-failed patients, but did not show significant difference between two groups in the multivariate analysis ($P = 0.07$).

Table 6. Univariate and multivariate Cox proportional hazard analysis to identify factors associated with VR after propensity score matching

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	1.009	0.997-1.021	0.154			
Sex	1.015	0.790-2.407	0.718			
ALT	1.000	1.000-1.001	0.197			
Cirrhosis	1.314	0.952-1.991	0.079			
HBV DNA	0.754	0.685-0.830	< 0.001	0.790	0.689-0.855	< 0.001
NA-naïve vs. NA-failed	1.621	1.172- 2.240	0.003	1.304	0.934-1.821	0.070
HBeAg positivity	0.463	0.334-0.641	< 0.001	0.605	0.415-0.834	0.003

ALT, alanine transaminase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; NA, necleotide analogues; VR, virologic response; OR, odd ratio; CI, confidence interval, □ HBV DNA levels at start of TDF therapy

7. Treatment response to TDF therapy according to drug mutation pattern

Next, we separately analyzed impacts of each drug resistance. We divided NA-failed patients into three groups according to each drug mutation (NA-experienced, LAM-resistant and MDR). A total of 10 (91%) of the 11 NA-experienced patients achieved VR, 27 (90%) of the 30 LAM-resistant patients achieved VR, whereas 35 (66%) of 53 MDR patients achieved VR ($P = 0.002$). The cumulative VR rates were compared using Kaplan-Meier test between each three groups and NA-naïve group. NA-experienced patients did not show significant difference in VR compared with NA-naïve patients (72.7% vs. 78.6% at 12 months and 90.9% vs. 94.7% at 24 months, respectively; $P = 0.885$). LAM-resistant patients also did not show significant difference in VR compared with NA-naïve patients (72.2% vs. 78.6% at 12 months and 100% vs. 94.7% at 24 months, respectively; $P = 0.330$) (Fig. 3). However, NA-naïve patients showed higher cumulative rate of VR than MDR patients (78.6% vs. 42.2% at 12 months and 94.7% vs. 68.6% at 24 months, respectively; $P < 0.001$). In the multivariate analysis, MDR patients (OR, 0.502; 95% CI, 0.332–0.760; $P = 0.001$) remained predictive factor for VR (Table 7).

Table 7 Univariate and multivariate Cox proportional hazard analysis to identify factors associated with VR after propensity score matching according to drug mutation

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
NA-naïve	1			1		
~~LAM experienced~~	~~0.536~~	~~0.232–1.241~~	~~0.146~~			
NA-experienced	~~0.602~~0.967	0.~~428~~500-~~0.845~~1.870	0.~~003~~920			~~0.894~~
~~ADV experienced~~	~~0.698~~	~~0.487–1.000~~	~~0.050~~			~~0.799~~
LAM-resistant	1.170	0.~~249~~758-~~707~~1.806	0.~~001~~480			
~~ETV experienced~~	~~0.699~~	~~0.483–1.011~~	~~0.057~~			

MDR~~ETV resistant~~	0.~~449~~401	0.~~276~~266-0.~~731~~604	< 0.001	0.~~456~~502	0.~~284 33~~2-0.~~732~~760	0.~~001~~001

LAM, lamivudine ; MDR, multi drug resistance ; NA, necleos(t)ide analogues; OR, odd ratio; CI, confidence interval

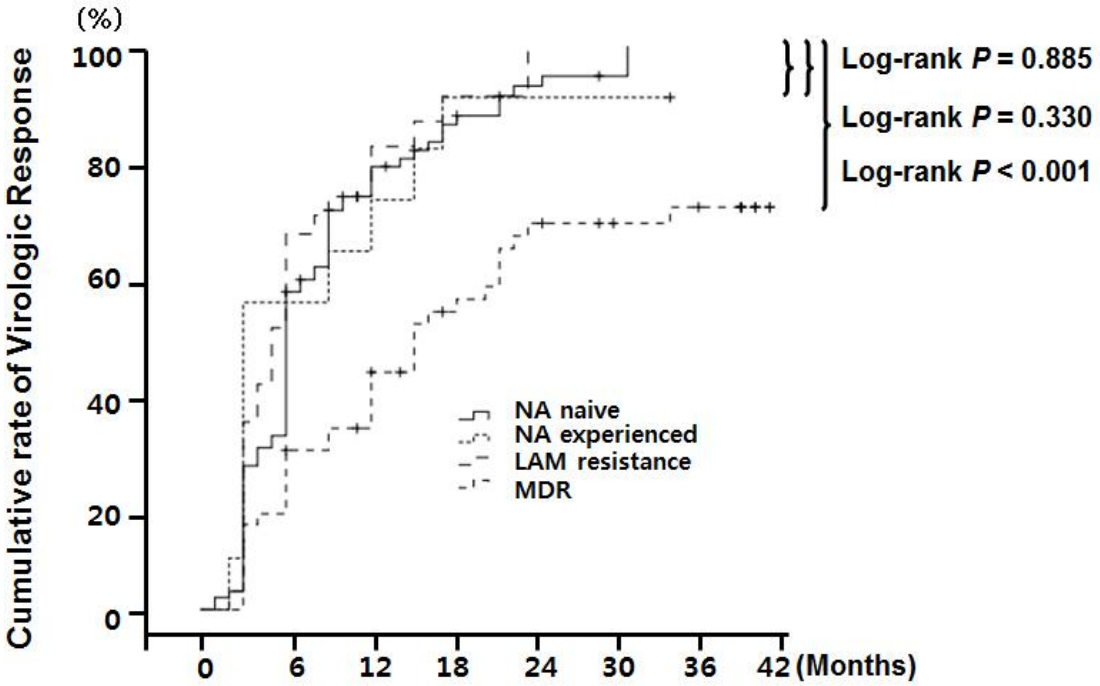

Figure 3. Cumulative rate of virologic response according to drug resistance after propensity score matching

DISCUSSION

The present study evaluated the therapeutic efficacy of TDF therapy in NA-naïve and NA-failed patients. After propensity score matching, NA-naïve patients showed high VR than the NA-failed group. In multivariate analysis, HBV DNA level at the start of TDF treatment, HBeAg positivity, and MDR patients were independent predictive factors for VR.

In the present study, 87.1%, 81.5%, and 16.1% of NA-naïve patients treated with TDF for about 3 years achieved VR, ALT normalization, and HBeAg seroconversion, respectively. These results are consistent with previous studies in Taiwan, except lower rate of HBeAg seroconversion [20,24]. Such differences could be explained by genotypes in HBV. In Asia, genotypes B and C are common [31]. Genotype B has favorable prognosis whereas, genotype C is associated poor prognosis. Unfortunately, most HBV patients in South Korea have genotype C [31]. In present study, all the patients are genotype C2. Differences in genotype might have resulted in lower HBeAg seroconversion rate in the present study.

TDF therapy is highly effective and safe for long-term suppression of HBV in NA-naïve patients [20,21]. Several studies reported that TDF therapy in NA-experienced patients showed comparable efficacy compared with NA-naïve patients [22,28]. There is no significant difference in treatment response between patients with LAM resistance and those without LAM resistance in previous study [28]. Cumulative VR in HBeAg negative patients is 82% vs. 81% at 12 months, 88% vs. 93% at 24 months, and cumulative VR in HBeAg positive patients is 43% vs. 39% at 12 months, 74% vs. 61% at 24 months [28]. Present study showed similar results. These results suggest that TDF therapy is effective for CHB treatment irrespective of LAM resistance.

Treatment responses were different between patients with ADV genotypic resistance and those without ADV resistance. It has been shown that rtA181T and rtN236T double mutation can reduce sensitivity to TDF by 10 fold in an in vitro study [32]. Major ADV-resistance mutation (rtN236T) has shown 3 to 4 fold reduced susceptibility to TDF in cell culture [33]. However, there is controversy in human studies. Patterson et al. [29] have reported that efficacy of TDF rescue therapy following failure of both LAM and ADV treatment was inferior to its efficacy in treatment naïve patients. Recent retrospective study in Korea has shown that

ADV experienced group is an independent predictive factor for VR compared to NA-naïve patients [27]. However, Keskin et al. [34] have shown no significant difference in VR between NA-naïve patients and ADV-resistant patients. In the present study, we have no single ADV resistance. Therefore we could not compare NA-naive and ADV-resistance.

There are limited data about comparison of TDF efficacy between NA-naïve and NA-resistant patients, especially patients with MDR. Among the MDR patients in present study, most of patients have LAM/ADV resistance or LAM/ETV resistance. We don't know whether the LAM/ETV resistance is predictive factor for VR or not. TDF therapy in MDR can show lower VR compared with TDF therapy in NA-naïve patients. Lower VR in MDR patients can be caused from the extensive multidrug-resistance profile[35]. Existing mutations due to prior use of antiviral agents can also lower the VR[35]. These relatively low VR can increase possibility of CHB progression and HCC. Therefore, TDF can be better choice for initial therapy for CHB.

In present study, treatment response of TDF was different after propensity score matching. Before propensity score matching, there were no significant difference in the cumulative VR at 12 or 24 months between NA-naïve and NA-failed groups (72.3% vs. 75.3% at 12 months and 90.5% vs. 87.7% at 24 months; $P = 0.103$). Baseline characteristics of two groups are significantly different, so we applied propensity score matching to make two groups similar. After propensity score matching, NA-naïve patients achieved higher VR than NA-failed patients (89.3% vs. 76.5%, $P = 0.016$). PVR between two groups were not significantly different, but NA-failed patients showed higher PVR tendency (43.6% vs. 65.3%; $P = 0.054$). These results were caused by different patients' characteristics between two groups. NA-naïve group had higher HBV DNA level, high percentage of liver cirrhosis and higher ALT level than NA-failed group. Propensity score matching can reduce the bias of difference in the two groups and make the two groups more similar [35].

The present study has several limitations. First, this study was conducted with retrospective design. Moreover, baseline characteristics of the two groups (NA-naïve and NA-failed) are significantly different. To overcome such limitation, we performed propensity score matching. Second, this study was performed in a single center (Ulsan University Hospital) and a restricted area. Third, genotypic resistance test was not performed in some

patients with NA-failed. Fourth, we used propensity score matching to make two groups similar. However, this method can only reduce bias in measured characteristics.

CONCLUSION

In patients with NA-failed, the efficacy of TDF was lower than NA-naive patients, especially MDR group. TDF is best choice for naive patients an early switching in NA-failed patients with low viral load state. Long term observational and well-controlled studies are warranted for proving these results.

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국문요약

배경 : 만성 B 형 간염은 만성 간염, 간경변 그리고 간세포암종의 원인이 될 수 있다. 경구용 항바이러스제는 바이러스 억제에 매우 효과적이지만, 유전자형 변이와 불충분한 반응은 만성 B 형 간염을 치료함에 있어 큰 문제가 되고 있다.엔테카비어 (entecavir)나 테노포비어 (tenofovir dixoproxil fumarate)는 강력한 항바이러스제로서, 만성 B 형 간염 초치료에 일차약제로 사용되고 있다. 그러나, 테노포비어 치료에 대한 아데포비어 (adefovir dipivoxil) 내성환자와 초 치료 환자에서의 효능차이에 대해서는 논란의 여지가 있다. 그리고, 초 치료 환자와 엔테카비어 내성환자에서 테노포비어 효능의 비교에 대한 연구결과 또한 제한적이다. 이에 본 연구는 항바이러스제 초 치료 환자들과 항바이러스제 치료실패 환자들에서 테노포비어의 효능을 비교하였다.

방법 : 테노포비어로 치료를 받은 환자 735 명의 만성 B 형 간염 환자의 의무기록을 조사하였다. 735 명 중 466 명은 초치료 환자였으며, 269 명은 항바이러스제 치료실패 환자들이었다. 양군에서 바이러스 반응, 부분 바이러스 반응, 바이러스 돌파 여부를 비교하였다. 초 치료 환자군과 항바이러스제 내성 환자들의 변수를 통제하기 위해, 프로펜시티 스코어 분석 (propensity score analysis)을 이용하여, 각각의 변수들을 보정한 양군에서 테노포비어 효과를 비교하였다.

결과 : 프로펜시티 스코어 분석을 통해 1:1 의 비율로 각군에서 94 명의 환자들이 선택되었다. 항바이러스제 초 치료 환자군이 항바이러스제 치료실패 군보다 바이러스 반응이 높았다 (84 [89.3%] vs. 72 [76.5%], $P = 0.016$). 항바이러스제 초 치료 환자군이 항바이러스제 치료실패 환자군보다 12 개월 및 24 개월에서 높은 누적 바이러스 반응율을 보였다 (78.6% vs. 58.3% at 12 months and 94.7% vs. 79.8% at 24 months; log-rank $P = 0.001$). 생화학적 반응, 부분 바이러스 반응 및 바이러스 돌파는 양군간에 유의미한 차이가 없었다. 다변량 회귀 분석에서 테노포비어 시작시점의 혈청 B 형간염 바이러스 DNA 양 (HBV DNA) (OR, 0.790; 95% CI, 0.689-0.855; $P < 0.001$), B 형 간염 e 항원 양성 (OR, 0.605; 95% CI, 0.415–0.834; $P = 0.003$)이 바이러스 반응의 독립적인 예측인자로 밝혀졌다. 항바이러스제 치료실패군을 항바이러스제 경험군, 라미부딘 내성군 및 다약제 내성군으로 나누어 분석하였다. 항바이러스제 경험군과 라미부딘 내성군은 항바

이러스제 초치료군과 비교하였을 때, 바이러스 반응의 유의미한 차이가 없었다. 그러나, 다약제 내성군은 초치료군보다 낮은 바이러스 반응율을 보였다 (35 [66%] vs. 84 [89%], respectively; $P = 0.002$). 다변량 회귀 분석에서도 다약제 내성군이 바이러스 반응의 독립적인 예측인자로 밝혀졌다 (OR, 0.502; 95% CI, 0.332–0.760; $P = 0.001$)

결론 : 테노포비어는 항바이러스 치료실패군에서 초치료군에 비해 낮은 항바이러스 효과를 보였다. 따라서, 테노포비어는 항바이러스제 초치료 환자와 항바이러스제 내성환자인 경우 혈청 바이러스양이 적은상태에서 조기약물 교체가 높은 효과를 보일것으로 사료되며 이를 입증하기 위해서 장기간의 연구가 필요하다.

중심단어 : 테노포비어, 항바이러스제 초치료환자, 항바이러스제 내성환자, 항바이러스제 치료실패 환자, 만성 B 형 간염