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ORIGINAL ARTICLE

Retrospective Cohort Study

Management of entecavir-resistant chronic hepatitis B with adefovir-based combination therapies

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Abstract

AIM: To evaluate the long-term efficacy adefovir (ADV)-based combination therapies in entecavir (ETV)-resistant chronic hepatitis B (CHB) patients.

METHODS: Fifty CHB patients with genotypic resistance to ETV at 13 medical centers in South Korea were included for the analysis. All the patients received rescue therapy with the combination of ADV plus ETV (ADV/ETV, *n* = 23) or ADV plus lamivudine (LMV) (ADV/LMV, *n* = 27) for more than 12 mo. Patients were monitored at least every 3-4 mo during ADV-based combination therapy by clinical examination as well as biochemical and virological assessments. Hepatitis B virus (HBV) DNA levels were measured by real-time PCR and logarithmically transformed for analysis. Cumulative rates of virologic response (VR; HBV DNA < 20 IU/mL) were calculated using the Kaplan-Meier method, and the difference was determined by a log-rank test. Multivariate logistic regression and Cox proportional hazards models were used to identify independent risk factors significantly associated with short-term and long-term VR, respectively.

RESULTS: Baseline median HBV DNA levels were 5.53 (2.81-7.63) $\log_{10}$ IU/mL. The most commonly observed ETV genotypic mutation sites were rt184 and rt202. Patients were treated for a median of 27 (12-45) mo. Overall, cumulative VR rates at 6, 12, 24, and 36 mo were 26%, 36%, 45%, and 68%, respectively. Patients treated with the ADV/ETV combination showed higher cumulative VR rates (35%, 43%, 65%, and 76%, respectively) than those with the ADV/LAM combination (18%, 30%, 30%, and 62%, respectively; $P = 0.048$). In the multivariate analysis, low baseline HBV DNA levels (< 5.2 $\log_{10}$ IU/mL) and initial virologic response at 3 mo (IVR-3; HBV DNA < 3.3 $\log_{10}$ IU/mL after 3 mo) were independent predictive factors for VR. Patients with favorable predictors achieved cumulative VR rates up to 90% at 36 mo. During the same period, the cumulative incidence of virologic breakthrough was as low as 6% in patients with the both favorable predictors.

CONCLUSION: If tenofovir is not available, ADV/ETV combination could be considered in ETV-resistant patients with low HBV DNA titers, and may be continued if IVR-3 is achieved.

Key words: Adefovir; Chronic hepatitis B; Entecavir; Lamivudine; Resistance

Core tip: Studies regarding optimal treatment strategies for entecavir-resistant chronic hepatitis B are sparse. Tenofovir may be the best option, but it is still not available in many countries. Where tenofovir is not available, adefovir plus entecavir can be considered an alternative treatment option in patients with favorable predictive factors. These factors included lower baseline hepatitis B virus (HBV) DNA levels (< 5.2 $\log_{10}$ IU/mL) and reduction of HBV DNA < 3.3 $\log_{10}$ IU/mL after 3 mo of treatment in our study. The present study will guide the treatment of entecavir-resistant chronic hepatitis B.

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection remains an important global health problem, and 15%-40% of infected patients may develop cirrhosis-related complications and/or hepatocellular carcinoma (HCC)[1]. Over the past decades, there have been great advances in the management of chronic hepatitis B (CHB) owing to the development of oral nucleos(t)ide analogues (NAs)[2]. The sustained suppression of serum HBV DNA by these agents has been associated with the prevention of liver disease progression and inhibition of HCC development[3,4]. However, a major shortcoming of these NAs is the high rate of virological relapse when treatment is discontinued[5,6]. Therefore, long-term or indefinite treatment with NAs is needed. Unfortunately, the risk of drug resistance increases in proportion to the duration of NAs therapy[7]. For example, cumulative lamivudine (LMV) resistance rates were reported to be 23% and 71% after 1 and 4 years of LMV therapy, respectively[8,9]. Moreover, NAs discontinuation sometimes results in hepatitis flares that may lead to fulminant hepatic failure and death[10]. Thus, the benefits of therapy are attenuated and subsequent therapeutic options may be limited.

Of the NAs, entecavir (ETV) is one of the most potent and safest antiviral agents for HBV infection, with a superior potency to LMV and adefovir (ADV)[11-13].

A previous study showed that the cumulative probability of ETV resistance in treatment naïve patients remained at only 1.2% after up to 5 years of treatment[14]. However, the rate is higher in LMV-resistant patients[15,16], and it may increase to 51% after 5 years of ETV therapy[14]. Resistance to ETV appears to occur through a two-hit mechanism with an initial selection of the M204V/I mutation followed by amino acid substitutions at rtT184, rtS202, or rtM250[17]. Consequently, for CHB patients with LMV resistance, current international guidelines recommend switching to tenofovir disoproxil fumarate (TDF), adding on TDF, or adding on ADV, but not switching to ETV monotherapy[18,19]. However, earlier international guidelines had recommended switching to 1 mg of ETV per day as a treatment option for CHB patients infected with HBV resistant to LMV due to insufficient clinical data[2,20]. As a result of sequential ETV monotherapy in LMV-resistant patients, resistance to ETV developed in a substantial number of patients currently.

For patients with an ETV-resistant CHB, switching to or adding on TDF or TDF-emtricitabine combination therapy are considered as therapeutic options, and combination therapy with ADV plus NAs may still be used in countries where TDF is not available[19,21,22]. It has been shown that both ADV and TDF are active *in vitro* against ETV-resistant HBV infection, but clinical data on the efficacy of ADV or TDF in patients infected with ETV-resistant HBV strains are limited[21,23-26].

Although there have been few reports on the short-term effects of ADV combination therapy for ETV-resistant HBV infection, especially for that developed after LMV-ETV sequential monotherapy[23,24,27], there is little available clinical information regarding the long-term effects of ADV combination therapy in such patients. Therefore, this study aimed to evaluate the long-term efficacy of combined ADV regimens over 48 wk in CHB patients with ETV resistance.

MATERIALS AND METHODS

Patients and study design

A total of 50 CHB patients with genotypic ETV resistance, who subsequently received rescue ADV-based combination therapy for more than 12 mo at 13 medical centers in South Korea between January 2008 and October 2012, were enrolled in this retrospective cohort study. ETV resistance was documented in all patients by genotypic analyses at the time of switching to ADV-based combination therapy. We excluded patients infected with other viruses such as hepatitis C virus, human immunodeficiency virus, or hepatitis D virus and those with other concomitant liver diseases such as alcoholic liver disease, autoimmune liver disease, or HCC. All patients were monitored at least every 3-4 mo during ADV-based combination therapy by clinical examination as well as biochemical and virological assessments.

The study was approved by the Institutional Review Boards of each institution, and informed written consent was obtained from all study participants, or their legal guardian. The protocol conforms to the ethical guidelines of the Declaration of Helsinki.

Laboratory assay

Routine biochemical tests were performed using standard laboratory procedures. Hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs), hepatitis B e antigen (HBeAg), and antibody to HBeAg (anti-HBe) levels were measured using a microparticle enzyme immunoassay (Abbott Laboratories, North Chicago, IL, United States). Serum HBV DNA levels were measured by the COBAS TaqMan PCR assay (Roche, Branchburg, NJ, United States; lower limit of detection: 20 IU/mL). Genotypic resistance to LMV, ADV, and ETV was determined by direct sequencing (TRUGENE HBV, Siemens Health Care Diagnostic Solutions, Tarrytown, NY, United States) or restriction fragment mass polymorphism analysis, as previously described[28].

Definitions

Primary non-response was defined as a failure to reduce serum HBV DNA levels by > 1 $\log_{10}$ IU/mL after 3 mo of treatment[29]. Initial virologic response at 3 mo (IVR-3) and virologic response (VR) were defined as an HBV DNA level < 3.3 $\log_{10}$ IU/mL after 3 mo of treatment[28,30] and an undetectable HBV DNA level (< 20 IU/mL) during treatment, respectively. A biochemical response was defined as normalization of serum alanine aminotransferase (ALT) levels. Virological breakthrough (VBT) was defined as an increase in serum HBV DNA level > 1 $\log_{10}$ IU/mL from the nadir during therapy.

Statistical analysis

HBV DNA levels were logarithmically transformed for analysis. Continuous variables were analyzed using the Mann-Whitney *U*-test, whereas categorical variables were analyzed using the χ^2 test. A repeated measure analysis was used to compare HBV DNA level reductions according to ADV combination regimens. Cumulative rates of VR and VBT were calculated using the Kaplan-Meier method, and the difference was determined by a log-rank test. Multivariate logistic regression and Cox proportional hazards models were used to identify independent risk factors significantly associated with short-term and long-term VR, respectively. Candidate variables with a *P*-value < 0.1 on univariate analysis were entered into the regression analysis. A *P*-value < 0.05 was considered significant. Statistical analyses were performed using SPSS, version 16 (SPSS Inc., Chicago, IL, United States) and the statistical review of the study was performed by a biomedical statistician.

Table 1 Baseline characteristics of the patients *n* (%)

Variables	Total (*n* = 50)
Age (yr)[1]	46.5 (22-74)
Male	37 (74)
HBeAg-positive	47 (94)
Cirrhosis	12 (24)
Antiviral history before ETV (naïve/clevudine/LMV)	2/2/46 (4/4/92)
Duration of ETV (mo)[1]	24 (13-58)
Serum ALT (IU/L)[1]	31 (5-1704)
Serum total bilirubin level (mg/dL)[1]	0.84 (0.28-4.30)
Serum albumin level (g/dL)[1]	4.2 (3.6-5.1)
INR[1]	1.01 (0.87-1.30)
Serum HBV DNA level (log_{10} IU/mL)[1]	5.53 (2.81-7.63)
Duration of ADV combination therapy (mo)[1]	27 (12-45)
Site of ETV-resistant mutations added on rtM204V/I	
rt184	19 (38)
rt202	22 (44)
rt173	1 (2)
rt169 + rt184	1 (2)
rt184 + rt202	6 (12)
rt184 + rt250	1 (2)
Patients with elevated ALT level above ULN	18 (36)
Rescue therapy regimens [(ADV + LMV)/(ADV + ETV)]	27/23 (54/46)

[1]Data are expressed as median (range). ADV: Adefovir; ALT: Alanine aminotransferase; ETV: Entecavir; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; INR: International normalized ratio; LMV: Lamivudine; ULN: Upper limit of normal.

RESULTS

Baseline characteristics of the patients

A total of 50 patients who met the inclusion criteria were analyzed. The patients' baseline characteristics are summarized in Table 1. Thirty-seven (74%) patients were men and the median age was 46.5 (22-74) years. Twelve patients (24%) had liver cirrhosis and 47 patients (94%) were positive for HBeAg. The median HBV DNA level was 5.53 (2.81-7.63) log_{10} IU/mL and 18 patients had elevated serum ALT levels above the upper limit of normal (40 IU/L). The most commonly observed ETV genotypic mutation sites were rt184 and rt202. The median duration of ETV therapy was 24 (13-58) mo. Out of the total 50 patients, 27 received ADV/LMV combination therapy and 23 received ADV/ETV combination therapy. The median duration of ADV combination therapy was 27 (12-45) mo.

Treatment response

Figure 1 shows the changes in mean HBV DNA levels during the first 12 mo of treatment. After the start of ADV combination therapy, serum HBV DNA levels declined continuously with overall mean changes of -2.14 log_{10} IU/mL, -2.37 log_{10} IU/mL, and -2.67 log_{10} IU/mL at months 3, 6, and 12, respectively. The mean reduction in serum HBV DNA levels from baseline to month 12 was significantly greater in the ADV/ETV combination group than in the ADV/LMV combination group (-2.77 *vs* -2.57 log_{10} IU/mL, P = 0.028) by repeated measure analysis (Figure 1). During the first year of treatment, VR (HBV DNA levels < 20 IU/mL)

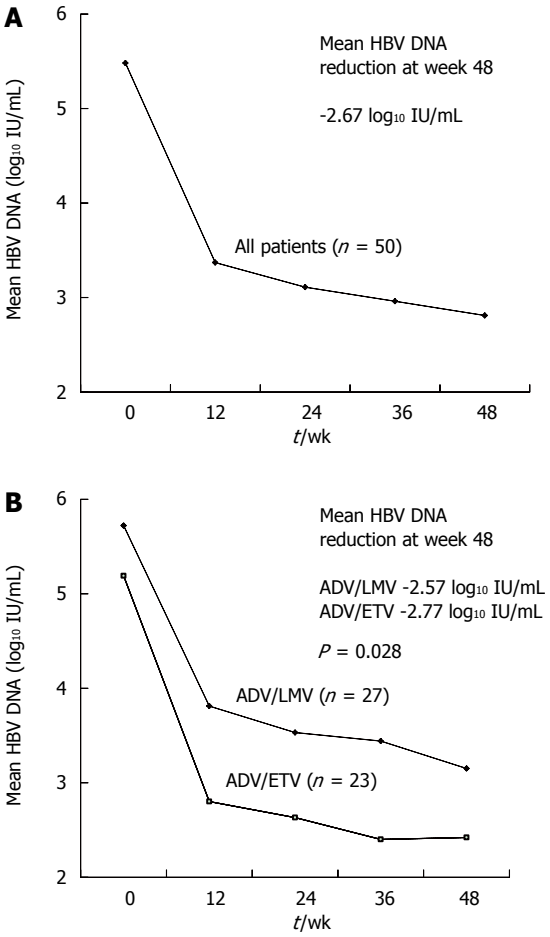

Figure 1 Changes of hepatitis B virus DNA levels during 48 wk. A: The overall mean changes of hepatitis B virus (HBV) DNA levels from baseline; B: The mean reduction of serum HBV DNA levels in adefovir plus entecavir (ADV/ETV) combination group and in the adefovir plus lamivudine (ADV/LMV) combination group.

and primary non-response were observed in 18 (36%) and 9 (18%) patients, respectively. Eight of the 18 patients who showed elevated serum ALT levels at baseline experienced normalization of serum ALT levels (44.4%). During the first year of ADV combination therapy, HBeAg loss occurred in 6 (12.8%) of the 47 HBeAg positive patients. Of these, one patient experienced HBeAg seroconversion.

During the long-term treatment period that lasted a median of 27 mo, VR, HBeAg loss, and biochemical response were achieved in an additional 9, 3, and 6 patients, respectively.

Cumulative VR rates at 6, 12, 24, and 36 mo were 26%, 36%, 45%, and 68%, respectively (Figure 2A). Cumulative VR rates at 6, 12, 24, and 36 mo were, respectively, 35%, 43%, 65%, and 76% in the ADV/ETV combination group and 18%, 30%, 30%, and 62% in the ADV/LMV combination group. There was a significant difference between the two groups (P = 0.048; Figure 2B).

Predictive factors of virologic response

Of the clinical features, a longer duration of ETV

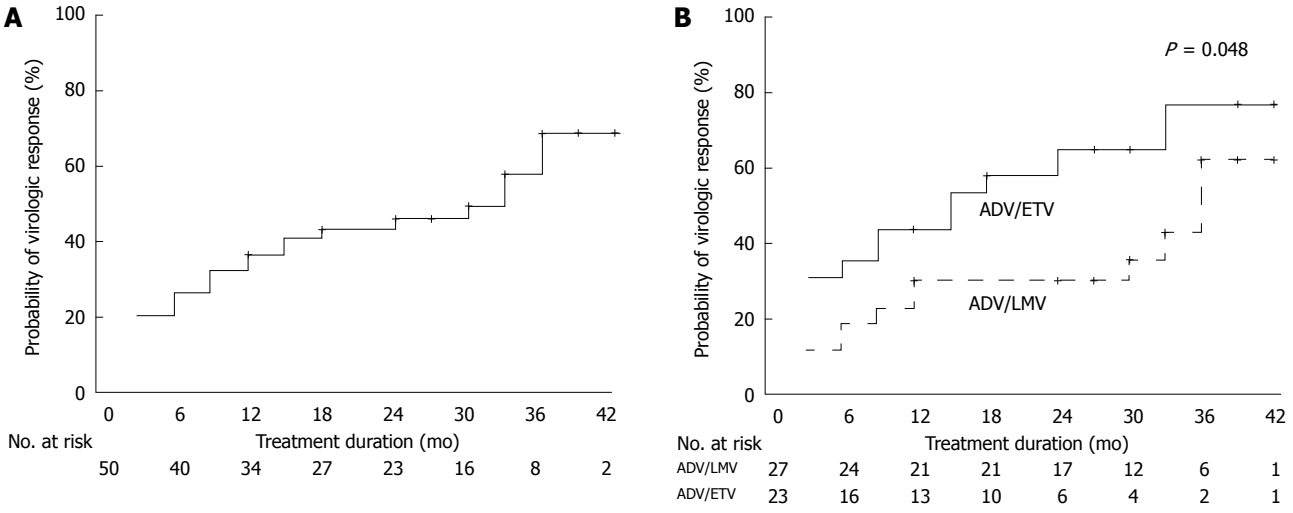

Figure 2 Virologic responses according to type of treatments up to 36 mo. A: Overall cumulative virologic response rates at 6, 12, 24, and 36 mo; B: Cumulative virologic response rates in the adefovir plus entecavir (ADV/ETV) combination group and in the adefovir plus lamivudine (ADV/LMV) combination group (P = 0.048).

Table 2 Comparison of clinical features between groups according to 1-year virologic response *n* (%)

	Patients without VR (n = 32)	Patients with VR (n = 18)	P value
Age (yr)[1]	47 (22-70)	42.5 (33-74)	0.413
Male	22 (68.8)	15 (83.3)	0.328
HBeAg-positive	31 (96.9)	16 (88.9)	0.291
Cirrhosis	8 (25)	4 (22.2)	1.000
Duration of ETV therapy (mo)[1]	24 (13-48)	36 (17-58)	0.003
Serum ALT level (IU/L)[1]	34.5 (12-918)	29 (5-1704)	0.210
Serum total bilirubin level (mg/dL)[1]	0.84 (0.31-1.99)	0.79 (0.28-4.30)	0.869
Serum albumin level (g/dL)[1]	4.2 (3.6-5.1)	4.3 (3.6-4.9)	0.691
INR[1]	1.01 (0.93-1.23)	1.02 (0.87-1.30)	0.848
Serum HBV DNA level (log_{10} IU/mL)[1]	6.16 (3.85-7.63)	4.24 (2.81-7.08)	< 0.001
Site of ETV-resistant mutations			0.441
rt184	12 (37.5)	7 (38.9)	
rt202	14 (43.8)	8 (44.4)	
rt173	0 (0)	1 (5.6)	
rt169 + rt184	0 (0)	1 (5.6)	
rt184 + rt202	5 (15.6)	1 (5.6)	
rt184 + rt250,	1 (3.1)	0 (0)	
Presence of IVR-3	7 (21.9)	17 (94.4)	< 0.001
Rescue therapy regimens (ADV/LMV *vs* ADV/ETV)	19 *vs* 13 (59.4 *vs* 40.6)	8 *vs* 10 (44.4 *vs* 55.6)	0.382

[1]Data are expressed as median (range). ADV: Adefovir; ALT: Alanine aminotransferase; ETV: Entecavir; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; INR: International normalized ratio; IVR-3: Initial virologic response at 3 mo; LMV: Lamivudine; VR: Virologic response.

Table 3 Multivariate analyses of clinical factors affecting one-year virologic response

	RR	95%CI	P value
Duration of ETV therapy (mo)	1.039	0.936-1.153	0.473
Serum HBV DNA level (< 5.2 log_{10} IU/mL)	7.614	1.160-49.986	0.034
Presence of IVR-3	24.862	2.398-257.781	0.007

ETV: Entecavir; HBV: Hepatitis B virus; IVR-3: Initial virologic response at 3 mo.

treatment prior to ADV combination therapy, low serum HBV DNA levels, and the achievement of IVR-3 were considered favorable factors for VR after 1-year of treatment. Other factors such as age, sex, cirrhosis, HBeAg status, serum ALT levels, international normalized ratio (INR), serum bilirubin levels, serum albumin levels, type of ETV resistance mutation, and type of ADV combination regimen were not significantly associated with VR (Table 2).

A multivariate logistic regression model was used to identify independent risk factors significantly associated with VR during the first year. In the univariate analysis, duration of ETV treatment prior to ADV combination therapy, serum HBV DNA levels, and IVR-3 were candidate variables for multivariate analysis (P < 0.1). In the multivariate analysis, IVR-3 and serum HBV DNA levels remained independent predictors of VR (Table 3).

A Cox proportional hazards model was used to identify independent risk factors significantly

Table 4 Univariate and multivariate analyses of factors affecting long-term virologic response

	Univariate analysis			Multivariate analysis		
	RR	95%CI	*P* value	RR	95%CI	*P* value
Age (yr)	1.011	0.973-1.050	0.586			
Sex (male)	1.156	0.488-2.740	0.741			
HBeAg positivity (-)	1.905	0.568-6.383	0.296			
Disease status (LC)	0.775	0.293-2.054	0.609			
Duration of ETV (mo)	1.077	1.036-1.119	< 0.001	1.022	0.970-1.076	0.419
Serum ALT (IU/L)	1.000	0.998-1.002	0.976			
Serum total bilirubin level (mg/dL)	1.405	0.774-2.550	0.264			
Serum albumin level (g/dL)	1.214	0.384-3.836	0.741			
INR	0.137	0.001-22.543	0.445			
Serum HBV DNA level (< 5.2 $\log_{10}$ IU/mL)	5.084	2.231-11.581	< 0.001	2.870	1.049-7.854	0.040
Type of ETV-resistant mutation (rtT184)	0.780	0.359-1.693	0.529			
Presence of IVR-3	8.822	3.228-24.114	< 0.001	4.417	1.402-13.918	0.011
Rescue therapy regimens (ADV/ETV)	2.007	0.928-4.338	0.077	1.678	0.683-4.119	0.259

ADV: Adefovir; ALT: Alanine aminotransferase; CHB: Chronic hepatitis B; ETV: Entecavir; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; INR: International normalized ratio; IVR-3: Initial virologic response at 3 mo; LC: Liver cirrhosis; LMV: Lamivudine.

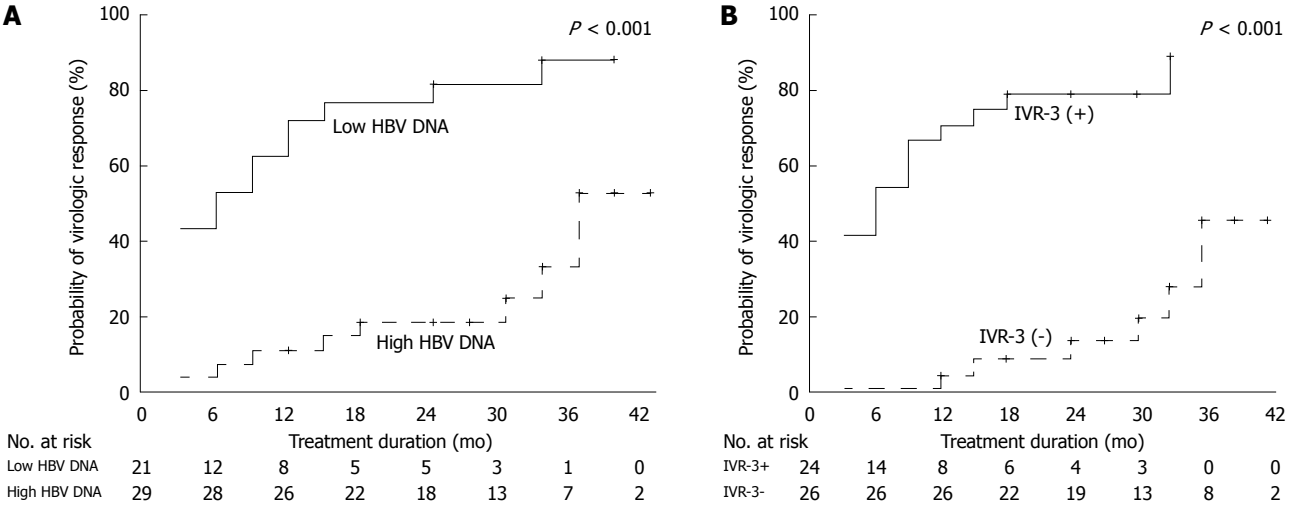

Figure 3 Virologic responses according to the presence of favorable factors. A: Cumulative virologic response rates in patients with low baseline serum hepatitis B virus (HBV) DNA levels and in patients with high baseline serum HBV DNA levels ($P < 0.001$); B: Cumulative virologic response rates in patients with and without initial virologic response-3 (IVR-3) ($P < 0.001$).

associated with long-term VR. The results were similar to the 1-year results detailed above (Table 4).

Impact of predictive factors on the long-term efficacy of ETV

Twenty-one patients (42%) had low baseline serum HBV DNA levels (< 5.2 $\log_{10}$ IU/mL) and IVR-3 was achieved in 24 of 50 (48%) patients. Patients with a low serum HBV DNA level or IVR-3 had a significantly higher probability of achieving VR. Cumulative VR rates at 6, 12, 24, and 36 mo were 52%, 71%, 81%, and 87% in patients with low baseline serum HBV DNA levels and 7%, 10%, 18%, and 52% in patients with high baseline serum HBV DNA levels, respectively($P < 0.001$; Figure 3A). Cumulative VR rates at 6, 12, 24, and 36 mo were 0%, 4%, 13%, and 46% in patients without IVR-3 and 54%, 71%, 80%, and 90% in patients with IVR-3, respectively ($P < 0.001$; Figure 3B). VR was achieved in only 18% (4/22) of patients without favorable predictors (no IVR-3 and a high HBV DNA level) and in 73% (8/11) of patients with one predictor. However, patients with two favorable predictors achieved VR in 88% of cases (15/17). During the treatment period, the respective cumulative incidence of VR at 36 mo according to the increasing number of favorable predictors was 38%, 85%, and 88%. There was a significant difference among the groups ($P < 0.001$; Figure 4).

Virological breakthrough

VBT was observed in 10 patients during the follow-up period. Cumulative VBT rates at 6, 12, 24, and 36 mo were 2%, 6%, 18%, and 26%, respectively (Figure 5A). Only one patient with VR (3.7%, 1/27) and one patient with two favorable predictors (4.5%, 1/22) experienced VBT. During the treatment period, the respective cumulative incidence of VBT at 36 mo according to the increasing number of favorable

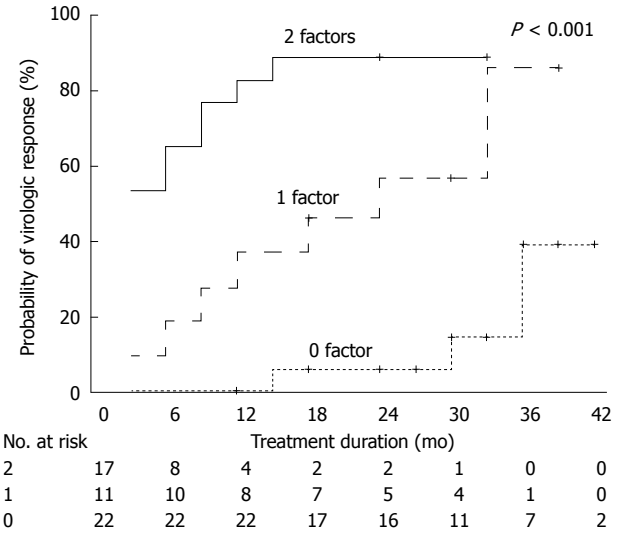

Figure 4 Virologic responses according to the number of predictive factors. Cumulative virologic response rates in patients with 2, 1, and 0 favorable factors are presented ($P < 0.001$).

predictors was 40%, 21%, and 6% (Figure 5B).

DISCUSSION

Although highly potent NAs with optimal genetic resistance profiles (ETV and TDF) have been introduced, prior NAs with lower genetic barriers continue to cause drug resistance, which is an important clinical problem. In particular, sequential monotherapy leads to the emergence of multi-drug resistant mutants, a matter of great concern in the management of CHB patients. So far, few studies have evaluated the efficacy of ADV combination therapy for ETV-resistant HBV infection. However, previous studies included small numbers of patients and/or patients with concurrent ADV resistance[21,23,27]. To our knowledge, this is one of the largest studies and the first long-term follow-up study (up to 4 years) of the efficacy of ADV-based combination therapy in ETV-resistant CHB patients.

Previous studies showed VR rates of about 50% to ADV/ETV combination therapy in patients with LMV- and ETV-resistant HBV infection[21,23,24]. In the present study, however, 27 of 50 (54%) patients showed a VR with respective cumulative VR rates of 36% and 68% at 12 and 36 mo. The reason for the relatively high VR in our study may be due to the difference in the study population and follow-up duration compared to previous studies. Our study excluded patients with prior ADV exposure in order to accurately evaluate the antiviral efficacy of ADV-based regimens in those with resistance to ETV, and the patients were followed up for a median of 27 mo (up to 4 years).

This study demonstrated that the antiviral efficacy of ADV/ETV combination therapy is superior to that of ADV/LMV combination therapy in patients with ETV resistance. During the first year of therapy, the mean

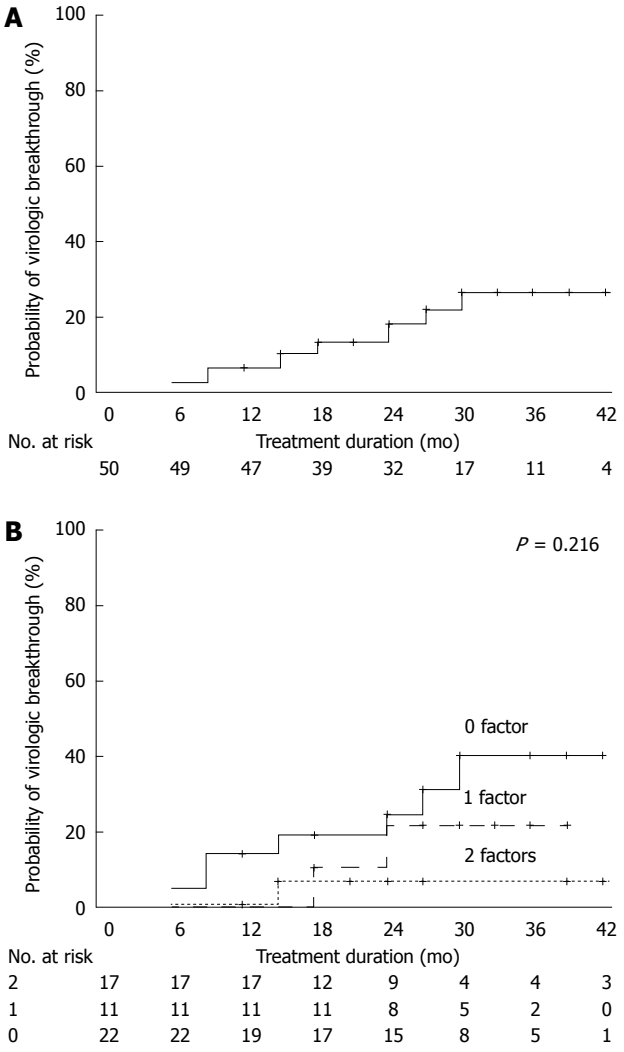

Figure 5 Development of virological breakthrough. A: Overall cumulative virological breakthrough (VBT) rates; B: Cumulative incidence of VBT at 36 mo according to the number of favorable predictors.

reduction in serum HBV DNA levels was significantly greater in the ADV/ETV combination group than in the ADV/LMV combination group (-2.77 *vs* -2.57 $\log_{10}$ IU/mL, $P = 0.028$) by repeated measure analysis. In addition, during the long-term follow-up period, the respective cumulative VR rates at 12 and 36 mo were 43% and 76% in the ADV/ETV combination group and 30% and 62% in the ADV/LMV combination group. There was a significant difference between the two groups ($P = 0.048$). This is the first such finding in ETV-resistant CHB patients; previous studies did not demonstrate the superiority of ADV/ETV combination therapy over ADV/LMV combination therapy in LMV- and ETV-resistant patients[24,27]. However, in a previous study, ADV/ETV combination therapy was used as rescue therapy in only 18 patients[24], which is a relatively small number for a comparison of the efficacy of the ADV/ETV and ADV/LMV regimens.

Another interesting finding of this study is the prognostic role of lower baseline HBV DNA levels and IVR-3, which are predictive factors for short-term and

long-term VR. ADV-based combination therapy has proven to be highly effective in patients with lower baseline HBV DNA levels or IVR-3. In fact, cumulative VR rates in patients with lower baseline HBV DNA levels or IVR-3 were very high, reaching 90% at 36 mo. In clinical practice, the ADV/ETV combination can be considered for ETV-resistant CHB patients with lower HBV DNA levels, and IVR-3 may help determine whether ADV/ETV combination therapy could be maintained or should be switched to TDF-based regimens.

A VBT was observed in 10 out of 50 patients during the follow-up period, with a cumulative VBT rate of 26% at 36 mo. Interestingly, only one patient with favorable predictors experienced VBT during the follow-up period, with a 6% cumulative VBT rate at 36 mo. No ADV mutations were found in this patient, and serum HBV DNA levels declined again despite maintaining therapy. This indicates a clinically useful long-term efficacy of ADV-based combination therapy in ETV-resistant patients in the presence of favorable predictors of VR such as a lower HBV DNA level and IVR-3.

TDF is a potent HBV inhibitor with a high genetic barrier to resistance and doesn't exhibit cross resistance with LMV or ETV[22,31]. In recent studies, TDF/ETV combination therapy showed excellent efficacy in patients with multi-drug resistance (MDR) and resulted in a relatively high rate of complete VR at an early time point, even in patients with triple resistance to LAM, ETV, and ADV[25,26]. When considering the potencies of TDF and ADV, a TDF/ETV combination should be superior to an ADV/ETV combination in CHB patients with MDR although comparative data of this is lacking. As there are countries where TDF is still not available, ADV/ETV combination could be considered an alternative option.

Our study has some limitations. First, the sample size was relatively small. However, considering the difficulty of including ETV-resistant CHB patients, the present study would be accepted as a valuable multicenter study and the largest one evaluating ADV-based combination therapy in ETV-resistant CHB patients. Second, the study was performed retrospectively. In future, a prospective study based on TDF mono- or combination therapy should be considered in ETV resistant CHB patients depending on TDF availability.

In conclusion, an ADV/ETV combination was superior to an ADV/LMV combination, and ADV-based combination therapy was effective in patients with favorable predictors.

In countries where tenofovir is not available, the ADV/ETV combination could be considered an alternative treatment option in ETV-resistant patients with a low HBV DNA titer, and may be continued if IVR-3 is achieved.

COMMENTS

Background

Antiviral resistance to hepatitis B virus (HBV) leads to attenuation of the therapeutic benefits and limits subsequent treatment options. Entecavir (ETV) is one of the most potent and the safest antiviral agents with high genetic barrier. Studies regarding optimal treatment strategies ETV-resistant chronic hepatitis B (CHB) are sparse.

Research frontiers

Both adefovir (ADV) and tenofovir (TDF) are active against ETV-resistant HBV infection *in vitro*, but clinical data on the efficacy of ADV or TDF in those patients are lacking. Therefore, additional study is needed to determine optimal treatment strategies in ETV-resistant CHB patients.

Innovations and breakthroughs

Previous few studies regarding the efficacy of ADV combination therapy for ETV-resistant CHB were conducted in small numbers of patients and evaluated short- term efficacy. This study is one of the largest studies and the first long-term follow-up study (up to 4 years). Furthermore, it shows predictive factors for virologic response (VR), which will be useful for guidance of the treatment strategy.

Applications

This study results suggest the ADV/ETV combination therapy could be considered an alternative treatment option in ETV-resistant CHB patients, especially in those with favorable predictive factors.

Terminology

Initial virologic response at 3 mo (IVR-3) is defined as an HBV DNA level < 3.3 $\log_{10}$ IU/mL after 3 mo of treatment and demonstrated as a predictive factor for VR.

Peer-review

Here the authors report original data on long term efficacy of ADV-based combination therapies, *i.e.,* ADV/ETV and ADV/LMV, on 50 CHB patients with genotypic resistance to ETV. They find higher rates of virological response in patients treated with ADV/ETV *vs* ADV/LMV and they identify low baseline HBV DNA levels and IVR-3 as independent predictive factor for VR. Although its interest is limited to countries where TDF is not available or not reimbursed, this study will be the largest one on this topic, hence worthy of attention and consideration.

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