Comparison of the antiviral effects of entecavir and adefovir dipivoxil in chronic HBV infection : a randomized control trial

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Abstract

Aims : **The purpose of this study is to compare the antiviral efficacy of entecavir (ETV) and adefovir dipivoxil (ADV) at various time points during the treatment.**

Methods : **A randomized, controlled, open-label study was designed to analyze the kinetics of HBeAg seroconversion, HBV DNA level, and liver and renal functions in 72 ETV-treated chronic hepatitis B (CHB) patients and 66 ADV-treated CHB patients. The data was collected every 12 weeks up to 96 weeks after drug administration.**

Results : **The negative rate of HBeAg seroconversion was significantly increased at 24 weeks in ETV-treated patients, whereas in ADV-treated patients, these changes were not significant. The serum HBV DNA levels were significantly decreased from 24 weeks in both ETV- and ADV-treated patients. Other than ETV showing significantly decreased levels of HBV DNA at 24 weeks when compared with ADV, there was no difference in virological response between two treatments at any other time points. The serum alanine aminotransferase (ALT) and total bilirubin (TBIL) levels were significantly decreased 12 weeks after either ETV- or ADV-treated patients without differences between two treatments. The urea nitrogen levels were in normal range and there was no difference between two groups.**

Conclusions : **Our study suggested that both ETV and ADV could be used as monotherapy for nucleotide-naive patients, but ETV has displayed potential efficacy in HBeAg seroconversion.** (Acta gastroenterol. belg., **2012**, 75, **316-321**).

Key words : adefovir dipivoxil, antiviral therapy, chronic hepatitis B, entecavir.

Introduction

Human hepatitis B virus (HBV) is the major cause of chronic hepatitis and its carriers are at high risks to develop hepatic cirrhosis and hepatocellular carcinoma (HCC) (1). Approximately 15% to 40% of chronic HBV carriers would develop these complications during their life-time (2).

Therapeutic interventions with antiviral agents have improved the clinical outcomes of chronic HBV (CHB) patients by improving the functional capacity of remnant liver (3,4). Currently, the oral antivirals, such as nucleotide/nucleoside (NUC) analogues, are the main treatment of choice for chronic HBV hepatitis. Different types of NUC analogues, such as lamivudine (LVD), adefovir dipivoxil (ADV), entecavir (ETV) and telbivudine, have been widely accepted in clinical setting as the main therapeutic strategy for fighting chronic HB hepatitis (5). These agents could markedly suppress the wild-type hepatitis B virus (HBV) replication, improve liver functional capacity and potentially reduce the incidence of hepatic fibrosis/cirrhosis (6,7). Due to high rates of drug resistance, lamivudine (LVD) and telbivudine have been removed from first-line of recommendations for NUC-naive patients in the CHB guidelines, whereas, entecavir has been recommended as first-line of antiviral drugs because of inherently lower rates of drug resistance (8).

Lamivudine is the first approved NUC analogue for the treatment of HBV infection (9,10). The *in vitro* and *in vivo* studies have demonstrated the effectiveness of LVD by suppressing HBV DNA replication, improving hepatic transaminase levels, preserving normal liver histology, inducing hepatitis B e antigen (HBeAg) seroconversion, and suppressing hepatocarcinogenesis in CHB (4,11). However, the effectiveness of LVD was limited because of frequent development of drug resistance (12). Adefovir dipivoxil (ADV) was approved in 2002 as the second oral antiviral drug for HBV infection (10). ADV has been utilized as a standard rescue treatment for patients with LVD-resistant HBV infection (13,14). However, ADV administration is able to cause nephrotoxicity in patients with impaired renal functions (15,16).

Entecavir (ETV) is the newest oral antiviral drug approved in the United States for the treatment of chronic hepatitis B. ETV is a cyclopentyl guanosine analogue and a selective inhibitor of HBV replication *in vitro* and *in vivo* (17,18). In clinical trials, ETV administration exhibited strong anti-HBV activity with a marked decline in serum HBV DNA levels and a significant improvement in liver histology (9,19). Recently, clinical treatment guidelines have recommended ETV and tenofovir as the confident first-line NUC analogues for NUC-naive CHB patients, including those with cirrhosis (20). However, ADV is still drug of choice for treatment of NUC-naive hepatitis B patient in many countries. There are only few clinical trials available which have made direct comparison between ADV and ETV. Therefore, the purpose of this study is to compare the kinetics of antiviral efficacy of ETV and ADV in a randomized,

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controlled, open-label trial, and also to provide further recommendations for the selection of these two oral antivirals in the treatment of NUC-naive patients.

Methods

Patients

This was a randomized, controlled, open-label trial in which patients were recruited with newly diagnosis of CHB infection at our hospital from January 2006 to June 2006 (117 males, 21 females). All of these patients were NUC-naive patients and never received interferon or other immune or cytokine based therapies. These patients were not suffering from concurrent infections with hepatitis A, C, D, E or human immunodeficiency virus before the initiation of the study. CHB infection was diagnosed according to the clinical manifestations, biochemistry tests, and molecular tests, etc.

Patients were excluded from this trial if they : 1) had autoimmune hepatitis or other diseases treated with corticosteroids, immunosuppressants or chemotherapeutic agents ; 2) had history of alcohol abuse (≥ 80 g/day for over 1 month) ; 3) were female with HCG (+) ; 4) had positive HBeAg with HBV DNA level lower than 1×10^5 copies/mL or negative HBeAg with HBV DNA level lower than 1×10^4 copies/mL ; and 5) had evidence for HCC before the initiation of therapy or HCC was diagnosed before the study. HCC was diagnosed by B-ultrasound and the level of serum alpha-fetoprotein.

The patients were grouped into two arms based on oral antiviral regimens (ETV 0.5 mg *vs*. ADV 10 mg once daily for 96 weeks) by a computerized randomization procedure. Briefly, randomization was conducted by recruiting center and each participant was randomly assigned number. Patients with odd number were given ETV treatment while patients with even number were given ADV. Totally, 72 participants were assigned to ETV treatment while 69 participants were assigned to ADV treatment. However, 3 patients in the ADV groups suffered from HCC before 96 weeks and they were excluded from the data analysis. This study was approved by the Ethic Committee for Human Study of Second Xiangya Hospital of Central South University and all patients provided written informed consent.

Follow-up visit

The patients were scheduled to visit the clinic every 12 weeks. At every visit, patients underwent routine general examination, along with biochemical (ALT, TBIL, ALB) and virologic (HBV DNA level, HBeAg) assays.

Endpoints

The primary outcome of this study was clinical virologic response (VR), defined as 1 $\log_{10}$ IU/ml decrease in serum HBV DNA level from baseline at 12 weeks of therapy. Secondary endpoints were HBeAg seroconversion and ALT normalization.

Laboratory tests

Serum alanine aminotransferase (ALT), total bilirubin (TBIL), albumin (ALB), and urea nitrogen (UN) and creatinine clearance levels were measured using automated techniques. Hepatitis B e antigen was determined using commercially available enzyme immunoassay in our hospital. Serum HBV DNA levels were measured using a quantitative real-time polymerase chain reaction (PCR). Real-time PCR of HBV DNA level was performed using an ABI-7500 Real-time PCR system (AB Applied Biosystems, CA, USA).

Statistical analysis

Data was analyzed using the statistical package for the Social Sciences Version 16.0 (SPSS 16.0). Means of two groups or two time points were compared using two-tailed Student's *t-test or* χ^2 test. A $p < 0.05$ was considered to be significant.

Results

1. *There is no significant difference between two groups in baseline characteristics*

Baseline characteristics of the study population are presented in Table I. No significant difference in baseline characteristics was observed between ETV and ADV groups, including the gender distribution, cirrhosis, average age variation, HBeAg positive rates, the mean HBV DNA levels, ALT, ALB, TBIL, UN as well as median duration of follow-up in weeks (*ps* > 0.05). These results suggested that there were no bias for the selection of subjects in this trial.

2. *Both ETV and ADV suppressed HBV replication, but ETV significantly increased the negative rate of HBeAg*

All of the 141 patients had not taken any antiviral treatment before this trial. Seventy-two patients received ETV 0.5 mg and 69 patients received ADV 10 mg once daily for 96 weeks no matter whether HBeAg was negative or positive. Three patients in the ADV groups suffered from HCC before 96 weeks and their data were excluded from the analysis. The HBeAg-negative rates were significantly increased at 24, 48, and 96 weeks in ETV-treated patients, whereas ADV-treatment group showed no significant increase in HBeAg-negative rates. The negative rates of HBeAg were 36.1%, 47.2%, 68.1% and 79.2% after ETV treatment at 12, 24, 48 and 96 weeks, respectively. The negative rates of HBeAg were 37.9%. 42.4%, 53% and 53% after ADV treatment at 12, 24, 48 and 96 weeks, respectively (Table II). The average HBV DNA levels were significantly decreased when compared with the baseline levels for two groups at 12, 24, 48, and 96 weeks of treatments. There were no

Table I. — **Baseline characteristics of HB patients**

Total (n = 138)	ETV	ADV	*p* value
Sample size	72	66	
Mean age (range in yrs)	36 (19-70)	36 (17-58)	0.1
Male : Female	58 : 14	59 : 7	0.1
Median follow-up weeks	96	96	
HBeAg (%) Positive rate Negative rate	 52 (72.2%) 20 (27.8%)	 42 (63.6%) 24 (36.4%)	 0.5 0.5
HBV lgDNA (mean ± SD) HBeAg+ (mean ± SD) HBeAg- (mean ± SD)	7.47 (± 0.182) 7.63 (± 0.223) 7.04 (± 0.307)	7.65 (± 0.205) 8.08 (± 0.221) 6.85 (± .361)	0.5 1.0 0.2
ALT (IU/L, mean ± SD)	173.85 (± 17.68)	185.17 (± 20.83)	0.7
TBIL (mmol/L, mean ± SD)	24.67 (± 1.815)	31.72 (± 4.553)	0.5
ALB (g/L, mean ± SD)	44.60 (± 0.766)	47.09 (± 2.127)	0.5
UN (mmol/L, mean ± SD)	5.07 (± 0.769)	5.05 (± 0.595)	0.8
Cirrhosis	2 (2.8%)	3 (4.5%)	0.1

Table II. — **The negative rate of HBe Antigen**

Time (week)	ETV (%)	χ^2 value	*p* value	ADV (%D)	χ^2 value	*p* value	χ^2 value	*p* value
		(*vs*. baseline)			(*vs*. baseline)		(between groups)	
0 (baseline)	20 (27.8)			24 (36.4)			1.169	.5
12	26 (36.1)	1.150	.5	25 (37.9)	.032	.5	.046	.5
24	34 (47.2)	5.807	.02	28 (42.4)	.508	.5	.320	.5
48	49 (68.1)	23.401	.000	35 (53)	3.708	.1	3.264	.1
96	57 (79.2)	38.212	.000	35 (53)	3.708	.1	10.585	.01

Table III. — **HBV DNA logarithmic levels**

Time (week)	ETV (mean ± SD)	*p* value (*vs*. baseline)	ADV (mean ± SD)	*p* value (*vs*. baseline)	*p* value (between groups)
0 (baseline)	7.47 ± 0.182		7.65 ± 0.205		0.783
12	5.89 ± 0.532	0.05	5.34 ± 0.285	0.05	0.461
24	3.79 ± 0.162	0.000	4.63 ± 0.205	0.000	0.002
48	4.93 ± 0.252	0.000	4.41 ± 0.242	0.000	0.32
96	4.60 ± 0.308	0.000	4.77 ± 0.272	0.000	0.312

differences in antiviral response between two treatment groups at 12, 48, and 96 weeks, but exhibited significant difference at 24 weeks (Table III). We also found that the HBV DNA levels in 2 ADV patients were already lowered below the examination limitation at 24 weeks, but it increased at 48 weeks. The HBV DNA levels in 5 ETV patients were already lowered below the examination limitation at 48 weeks, but it increased at 96 weeks.

3. *Anti-viral treatments with ETV and ADV improved liver function*

As described above, there were no significant differences in the baseline levels of ALT and TBIL in two treatment groups. After being treated with ETV or ADV, both the ALT and TBIL levels were significantly decreased at 12, 24, 48, and 96 weeks (*ps* < 0.05). There were no significant differences in ALT concentrations between two groups at each time point (ETV *vs*. ADV : 48.34 ± 3.337 (IU/L) *vs*. 54.41 ± 5.349 (IU/L) at 12 weeks ; 34.91 ± 2.430 (IU/L) *vs*. 42.07 ± 3.630 (IU/L) at 24 weeks). After 36 weeks, the mean ALT values were dropped back to normal range (Fig. 1). Similarly, there were no significant differences in TBIL levels between two groups from 12 weeks (Fig. 2). The decrease in ALT levels was more obvious than that in TBIL. This suggests that the anti-virus treatment improved the liver function. No significant changes in serum albumin levels were observed. The urea function was evaluated by nitrogen level and creatinine clearance.

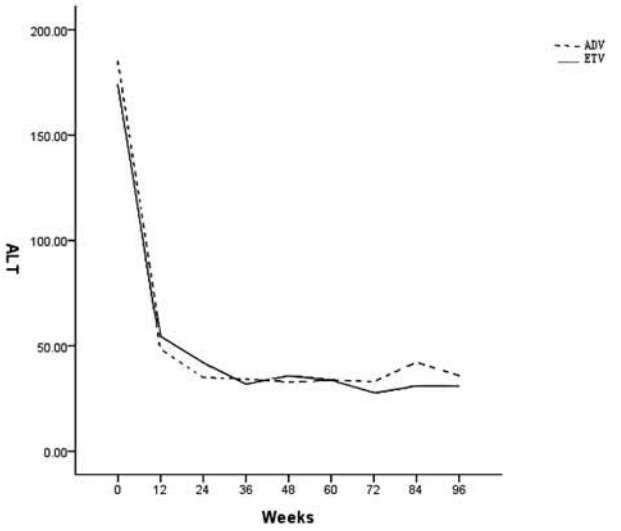

Fig. 1. — Changes in serum ALT levels after ETV and ADV treatments. No differences in the baseline between ETV and ADV treatments were observed. Twelve weeks after treatment, serum ALT levels were significant decreased and ALT value drop in the normal range at 36 weeks post treatments. There are no significant differences between two treatments at all of the time points.

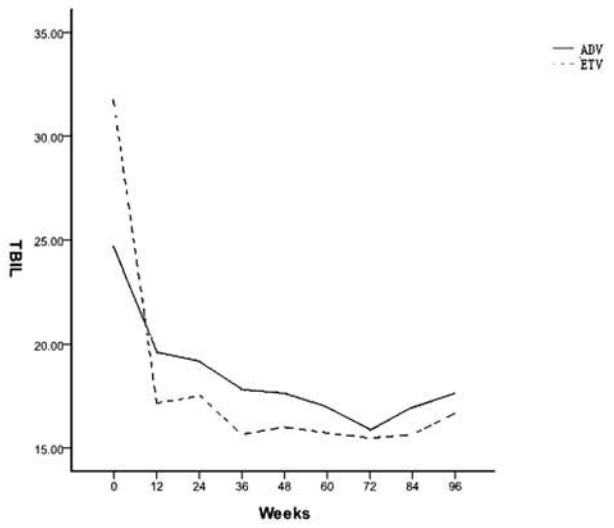

Fig. 2. — Changes in serum TBIL levels after ETV and ADV treatments. No differences in the baseline between ETV and ADV treatments were seen. Twelve weeks after treatment, serum TBIL levels were significant decreased and they fluctuated at different time points. There were no significant differences between two treatments.

Table IV. — **Urea nitrogen levels**

Time (week)	ETV (mean ± SD)	*p* value (*vs*. baseline)	ADV (mean ± SD)	*p* value (*vs*. baseline)	*p* value (between groups)
0 (baseline)	5.07 ± 0.769		5.05 ± 0.595		0.815
24	5.05 ± 0.752	0.896	5.11 ± 0.763	0.606	0.697
48	5.14 ± 0.756	0.572	5.07 ± 0.776	0.862	0.547
96	4.99 ± 0.678	0.477	4.94 ± 0.839	0.424	0.740

The average urea nitrogen levels were at normal range at 12, 24, 48, and 96 weeks post ETV or ADV treatment (Table IV). The creatinine clearance at baseline and 96 weeks post ETV (101.21 ± 10.86 mL/min and 100.60 ± 11.30 mL/min, respectively) or ADV (97.85 ± 17.62 mL/min and 99.03 ± 12.96 mL/min, respectively) treatment was measured. No differences were observed between treatments or between baseline and 96 weeks (Table V).

Discussion

NUC analogues mainly target the reverse transcriptase of hepatitis B virus (HBV) to inhibit viral replication. With rare complication of drug resistance, the continuous therapy of entecavir has displayed the ability to suppress viral replication over prolonged periods of time, and to prevent clinical progression of disease to serious complications like liver cirrhosis (21). Previous studies have demonstrated that both entecavir and adefovir could significantly inhibit HBV replication and result in low or undetectable HBV DNA levels (22,23). Reducing HBV DNA levels also promote histological preservation and normalization of ALT levels (4,11), subsequently prevent progression of hepatitis to cirrhosis (22,23). Also, durable HBeAg seroconversion has been shown to be associated with improved prognosis (20). In this study, we compared the efficacy of ETV and ADV on HBeAg seroconversion, HBV DNA replication and liver function improvement, at different time points within 96 weeks of treatments. Both ETV and ADV significantly decreased serum levels of HBV DNA, ALT, and TBIL at different time points. ETV significantly increased the seroconversion for HBeAg-positive infections, thus providing a proof of more potent antiviral drug in seroconversion in NUC-naive hepatitis patients.

Patients with chronic HBV hepatitis are clinically classified into HBeAg-positive or HBeAg-negative categories. The HBeAg-positive infections have been demonstrated to be accompanied by a high level of HBV replication whereas HBeAg-negative infections usually tend to have lower levels of HBV DNA. However, in this study, we demonstrated that there were no differences in HBV DNA baseline levels of HBeAg-positive and

Table V. — **Renal creatinine clearance**

Time (week)	ETV (mean ± SD)	ADV (mean ± SD)	*p* value
0	101.21 ± 10.86	97.85 ± 17.62	0.176
96	100.60 ± 11.30	99.03 ± 12.96	0.449

HBeAg-negative patients. This may relate to the local characteristics of a specific subpopulation. Strikingly, entecavir was more effective in increasing seroconversion in treating HBeAg-positive patients. The negative rates of HBeAg were increased 8.3%, 19.4%, 40.3%, and 51.4% after entecavir treatment at 12, 24, 48, and 96 weeks, respectively. Whereas the negative rates of HBeAg were only increased 1.5%, 6%, 16.6% and 16.6% after adefovir treatment at 12, 24, 48, and 96 weeks, respectively (Table II). Although the HBV DNA levels were significantly decreased in both entecavir- and adefovir-treated patients at 12, 24, 48, and 96 weeks, it further decreased in entecavir-treated patients at 24 weeks post treatment. However, there were no differences between these two groups at 12, 48, and 96 weeks (Table III). These results suggested that : 1) entecavir and adefovir although exhibited similar potential in inhibiting HBV DNA replication, but entecavir displayed strong potency and rapidefficacy ; and 2) the role of adefovir in inhibiting HBV DNA replication didn't cause a parallel change in conversion of HBeAg. Although increase of HBeAg seroconversion might decrease the morbidity and mortality associated with CHB, loss of HBeAg and seroconversion to anti-HBeAg will ensure that these benefits persist even after therapy being discontinued. Thus, a long-term observation for anti-HBeAg will be a more valuable parameter to evaluate the antiviral efficacy.

As discussed above, reduction of HBV DNA levels can promote histological improvement and normalization of ALT concentrations (4,11). In this study, we found that after 12 weeks, treatments with entecavir or adefovir significantly decreased serum alanine aminotransferase (ALT) concentrations (Fig. 1). Notably, ALT levels returned to normal values after 24 weeks. The serum total bilirubin (TBIL) was also decreased after 12 weeks, but its levels fluctuated at different time points (Fig. 2). The urea nitrogen levels displayed no changes (Table IV). Our data demonstrated that both entecavir and adefovir significantly improved liver functions. Although reports revealed that ADV administration could cause nephrotoxicity in patients with impaired renal functions (15,16), but no nephrotoxicity was observed in ADV- or ETV-treated patients in this study.

One major problem with the use of oral antiviral NUC analogues is induction of drug resistance. Particularly, when being administered alone, they are not able to permanently eradicate HBV, and long-term maintenance therapy is required. However, prolonged treatments are frequently associated with the emergence of drug-resistant HBV mutants (24). Indeed, high rates of resistance have resulted in removal of lamivudine and telbivudine from first-line of recommendations for treatment-naive patients. ETV has been thought to have very low rates of resistance (0.5% after 2-year treatment), whereas ADV caused 29% resistance in negative HBeAg patients after 5-year treatment (25). In this study, we observed that in 2 ADV patients and 5 ETV patients, the HBV DNA levels were lowered below the examination limitation at 24 or 48 weeks, but with time it increased again. If this finding was proposed to be mediated by drug resistance, the rate of ADV-resistance is lower while ETV-resistance is higher than that in the published reports. Unfortunately, the genotype analysis for drug resistance was not available in current study. Therefore, the observation in ETV-treated patients may suggest the existence of non-compliance and more tightly monitoring of the trial might be helpful. A common solution to deal with resistance might be opting for combination therapy. Treatment with multiple NUC analogs might increase the time to develop resistance, as well as enhance reductions in HBV DNA. Our study suggested that ETV and ADV treatments resulted in significant inhibition of HBV DNA replication in NUC-naive patients. Thus, combination of therapy cannot currently be recommended for treatment-naive patients unless a genotype analysis has been performed and mutations are present.

There were only few reports that had compared the early antiviral efficacy of ETV and ADV in a smaller number of patients and data was only collected for 48 weeks or 12 months (8,26). However, the small sample size and short observation period limited the clinical utility of these studies. Advantages of our current study include the comparison of single treatment at different time point up to 96 weeks and comparison of two treatments at each time point as well as randomized and homogeneous group of patients because of the strict exclusion. Indeed, the antiviral effect of ETV and ADV in nucleotide/nucleoside-naive patients in our study is consistent with results from previous *in vitro* and *in vivo* studies, including phase III randomized clinical trials (2, 10,13,14,17). However, we acknowledge that there were several limitations to this study, such as no exclusion of alcohol abuse (high cutoff for the daily alcohol use) and no assessment of non-compliance. This may make the general conclusions eligible for bias. In conclusion, both ETV and ADV could be used as monotherapy in nucleotide/nucleoside-naive patients, however, ETV proved to be more efficacious in HBeAg conversion.

Conflict of Interest

The authors declared no conflicts of interest.

Ethical approval

This study was approved by the Ethic Committee for Human Study of Second Xiangya Hospital of Central South University and all patients provided written informed consent.

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