Observation of combined/optimized therapy of Lamivudine and Adefovir Dipivoxyl for hepatitis B-induced decompensated cirrhosis with baseline HBV DNA>1,000 IU/mL

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Abstract

Objective : **This study aimed to observe and compare the efficacy and safety of the combined therapy and two different optimized therapies of lamivudine (LAM) and adefovir dipivoxil (ADV), as well as entecavir (ETV) monotherapy in patients with hepatitis B-induced decompensated cirrhosis.**

Method : **A total of 127 patients with decompensated cirrhosis were divided into four groups, and each group received different doses of regimens: initial combination of LAM and ADV, ADV add-on therapies with previous 12-week LAM, ADV add-on therapies with previous 24-week LAM, and ETV monotherapy.**

Results : **At the end of the treatment, the level of alanine aminotransferase (ALT), albumin (ALB) and total bilirubin (TBIL) in the combination therapy group and 12-week optimized therapy group were significantly improved. For the 24-week optimized therapy group, only ALT levels revealed a significant improvement. There were no obvious differences in the normalization rate of ALT, negative conversion rate of HBV DNA and HBeAg, as well as improvement in Child-Pugh scores among the combination therapy group, 12-week optimized therapy group, and ETV monotherapy group. However, the difference among these three groups and the 24-week optimized therapy group were significant. Differences were not observed in the HBeAg seroconversion between each group. Differences in blood urea nitrogen, serum creatinine, creatine kinase, or other serious adverse effects were not observed in each group at the end of the 96-week treatment.**

Conclusion : **Combination therapy and early ADV addition were the preferred approaches in the antiviral strategy for the treatment of hepatitis B-induced decompensated cirrhosis.** (Acta gastroenterol. belg., **2017**, 80, **9-13**).

Key words : Hepatitis B, decompensated liver cirrhosis, lamivudine, adefovir dipivoxil.

Abbreviations : HBV, Chronic hepatitis B virus ; HCC, hepatocellular carcinoma ; LAM, Lamivudine ; ADV, adefovirdipivoxil ; HBsAg, hepatitis B surface antigen ; HBeAg, hepatitis B antigen ; ALT, alanine aminotransferase ; TBIL, total bilirubin ; ALB: albumin.

Introduction

Chronic hepatitis B virus (HBV) infection has become a global health problem. This major health problem has affected approximately 350 million people worldwide (1). There are increased risks for carriers of HBV to develop into cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC) (2). Decompensated liver cirrhosis belongs to end-stage liver disease, and the prognosis for patients with compensated and decompensated cirrhosis had a 84% (3) and 14-35% (4) probability of survival at five years. For decompensated cirrhosis patients, traditional treatment involves general treatment, anti-fibrotic therapy, and ascites and complications treatment. Liver transplantation has been recognized as an effective therapy, but is limited by many factors and is not widely available.

Recently, antiviral therapy for decompensated hepatic cirrhosis has received broad acceptance, since it could remarkably improve prognosis and liver function. Some studies found that active HBV replication was a risk factor for cirrhosis development, and further disease progression after cirrhosis is developed (5). Accordingly, inhibiting viral replication has been regarded as a focus in therapy. Lamivudine (LAM) and adefovir dipivoxil (ADV) are commonly used antiviral agents in clinic. LAM is a first generation nucleoside analogue that leads to the rapid suppression of HBV replication. It has promising therapeutic effects in patients with decompensated cirrhosis. However, its long-term LAM therapy could induce drug-resistant mutations, which increase with extended treatment durations (16%-32% at one year of therapy to 70% at four years of therapy) (6). Making matters worse, these mutations are associated with the malignant progress of liver disease, and results in the reduction of disease susceptibility to LAM (7). ADV is another orally administered bioavailable nucleotide analogue, which has antiviral activity against wild-type HBV and LAM-resistant HBV mutants (6). For patients with LAM-resistance, continuing or discontinuing LAM treatment and switching to other antiviral agent such as ADV is another option (8). Entecavir (ETV) is a cyclopentyl guanosine analogue that has been shown to

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exhibit superior biochemical, virological and histological efficacy, compared with other antiviral drugs (9).

In clinical practice, due to low cost, treatment with LAM monotherapy has been prevalent. The continued treatment with ADV was only given to patients who had suboptimal virologic responses after 12 or 24 weeks of treatment. In order to achieve better therapeutic benefits and decrease the occurrence of drug-resistance, rational therapeutic regimens were investigated by many scholars. However, little is known on the long term effect of different regimens. In this study, the long term clinical outcome of combination therapy and optimized therapy for hepatitis B-induced decompensated cirrhosis were assessed and compared.

Methods and Patients

Patients and study design

A total of 127 patients diagnosed with hepatitis B-induced decompensated cirrhosis between January 2010 and March 2013 at the Department of Gastroenterology, The People's Hospital of Sichuan Province were enrolled into this study. The diagnosis of hepatitis B-induced decompensated cirrhosis was performed according to the Guideline of Prevention and Treatment for Chronic Hepatitis B (2010 Version) (10). Inclusion criteria were as follows: patients who were positive for hepatitis B surface antigen (HBsAg), patients who were hepatitis Be antigen (HBeAg) positive or negative with the manifestation of cirrhosis, patients with serum HBV DNA level $>1\times10^3$ copies/mL, and patients with Child-Pugh score B or C. Patients were excluded from the study if they were co-infected with hepatitis A, hepatitis C, hepatitis D, hepatitis E and HIV, or were previously treated with nucleotide/nucleoside analogues. Informed consents were obtained from all the participants. This procedure was approved by the Institutional Review Board of Sichuan Provincial People's Hospital.

After liver protection and diuretic therapy, all the patients were randomly divided into four groups: LAM and ADV combination therapy group, 12-week optimized therapy group, 24-week optimized therapy group, and entecavir (ETV) monotherapy group. Patients in the combination therapy group were simultaneously treated with 100 mg/d of LAM (GlaxoSmithKline) and 10 mg/d of ADV (GlaxoSmithKline). Patients in the 12-week optimized therapy and 24-week optimized therapy groups received LAM for 12 and 24 weeks, respectively. Patients with serum HBV DNA level $>1\times10^3$ copies/mL were given an add-on treatment of ADV. Patients in the ETV monotherapy group received 0.5 mg/d of ETV (Bristol-Myers Squibb). Therapeutic duration in each group lasted for 96 weeks, and therapeutic effects were evaluated with the following clinical parameters: alanine aminotransferase (ALT), total bilirubin (TBIL), albumin (ALB), normalization rate of ALT, seroconversion rate of HBV-DNA, negative conversion rate, and Child-Pugh score.

Detection of clinical parameters

Liver function, renal function and CK level were determined using an Abbott C16000 Automatic Biochemistry analyzer. Serum HBV DNA was measured by ABI 7500 Fast Real-Time polymerase chain reaction (Applied Biosystems).

Statistical analysis

Statistical analyses were performed by SPSS 13.0 software. Continuous variables were presented as mean ± standard deviation (SD), and compared with *t*-test between groups or ANOVA; and appropriate post-hoc tests were used for comparing three or more groups. Categorical variables were presented as frequency (percentage) and compared using Chi-square test. *P*-values less than 0.05 was considered statistically significant.

Table 1. — **Clinical characteristics of the study subjects**

	LAM+ADV group	12-week optimized therapy group	24-week optimized therapy group	ETV therapy group
n	35	35	35	22
Age (years)	53.4±11.2	55.1±11.3	54.7±12.3	49.6±12.7
Gender (male/female), *n*	21/14	23/12	19/16	16/6
ALT (U/L)	101.9±61.6	101.1±67.7	98.0±68.9	111.9±96.3
TBIL (μmol/L)	53.0±38.7	61.4±30.8	56.1±35.4	53.4±34.5
ALB (g/L)	29.8±4.3	30.1±3.1	30.3±3.6	31.7±3.8
UR (mmol/L)	5.9±2.5	6.2±2.4	6.1±2.2	5.32±1.7
CR (μmol/L)	72.6±19.6	71.1±21.2	72.9±21.0	65.98±16.6
PT (s)	17.4±2.9	16.9±4.1	16.0±3.8	17.5±2.3
CK (mmol/L)	118.3±65.5	119.7±60.5	110.1±55.1	122.6±65.5
Child-Pugh score (B/C), *n*	18/17	17/18	19/16	10/12

Data are presented as means ± SD. ALT: alanine aminotransferase; TBIL: total bilirubin; ALB: albumin; UR: urea; CR: creatinine; PT: prothrombin time; CK: creatine kinase.

Results

Baseline characteristics

Table 1 lists the clinical characteristics of patients in each group. There were no statistical differences in age and level of ALT, TBIL, ALB, UR, PT, CK and HBV-DNA between each group.

Clinical efficacy of different treatments

Liver function

Table 2 summarizes the indexes of liver function of different treatment groups. At the end of the 96-week treatment, the level of ALT, ALB and yTBIL in the combination therapy group and 12-week optimized therapy group were significantly improved ($P<0.05$ or $P<0.01$). In the 24-week optimized therapy group, the difference in ALT before and after the treatment was statistically significant ($P<0.05$); while the difference in ALB and TBIL was not statistically significant ($P>0.05$). In the ETV monotherapy group, the difference in ALT ($P<0.05$) and TBIL ($P<0.01$) was statistically significant, but there was no obvious change in ALB ($P>0.05$).

Virologic responses

After treatment, there were no significant differences between the LAM+ADV combination therapy group and ETV monotherapy group in recovery rate of ALT and negative conversion rate of HBV DNA. Both groups achieved a better effect than the optimized therapy group, and the 12-week optimized therapy group was superior to the 24-week optimized therapy group (Table 3).

Seroconversion rate and Child–Pugh scores

The percentage of HBeAg seroconversion was 30.0%, 22.2%, 15.8% and 27.3% in the combination therapy group, 12-week optimized therapy group, 24-week optimized therapy group and ETV monotherapy group, respectively. No distinct difference was observed between each group in HBeAg seroconversion. There were only 1 case in combination therapy group and 1 case in ETV monotherapy group occurred HBsAg seroconversion. There were no differences in HBsAg loss and seroconversion rates occurred between each group.

In the combination therapy group, 17 patients had CP score C at baseline, in which 10 (59%) patients improved to CP scores B (six, 35%) and A (four, 23%). Furthermore, 18 patients with CP score B at baseline, in which eight (44%) patients improved to CP score A and three (17%) patients deteriorated to CP score C. In addition, in the 12-week optimized therapy group, eight (44%) patients improved to CP score C to B; and among the 17 patients with CP score B at baseline, nine (53%) patients improved to CP scores A and one (6%) patient deteriorated to CP score C. In 24-week optimized therapy group, six (37%) patients improved to CP score B (five, 31%) and CP score A (one, 6%). Furthermore, four (21%) patients improved from CP scores B to A and three (16%) patients deteriorated to CP score C. In the ETV monotherapy group, among the 12 patients with CP score C at baseline, seven (58%) patients improved to CP scores A (two, 17%) and B (5, 41%), while among the 10 patients with CP score B at baseline, five (50%) patients improved to CP score A and one (10%) patient deteriorated to CP score C. There were no differences in CP score changes between the combination therapy group, 12-week optimized therapy group and ETV monotherapy group; but the changes in these groups were significantly greater than the 24-week optimized therapy group.

Safety

During the treatment phase, the doses of the regimens were safe and well-tolerated. Statistical analysis (Table 4) revealed that there were no significant diffe-

Table 2. — **The changes of the index of liver function for the four group**

Group	ALT (U/L)		TBIL (μmol/L)		ALB (g/L)	
	Pre treatment	Post treatment	Pre treatment	Post treatment	Pre treatment	Post treatment
LAM+ADV	101.9±61.6	52.3±44.5**	53.0±38.7	42.4±29.3*	29.8±4.3	34.5±5.6**
12-week optimized therapy	101.1±67.7	63.0±53.6**	61.4±30.8	50.4±20.9**	30.0±3.1	33.4±4.2**
24-week optimized therapy	98.0±68.9	70.0±55.8*	56.1±35.4	57.6±30.8	30.3±3.6	31.7±4.6
ETV therapy	111.9±96.3	61.0±63.1*	32.1±33.1	57.6±30.8**	31.7±3.8	36.6±16.6

Compared with that before treatment *$P<0.05$, **$P<0.01$.

Table 3. — **Virologic response and HBeAg seroconversion of different treatment groups**

	LAM+ADV	12-week optimized therapy	24-week optimized therapy	ETV therapy
Recover rate of ALT, n (%)	27 (77.1 %)	22 (62.9 %)*	19 (54.3 %)**	15 (68.2 %)
Negative conversion rate of HBV DNA, n (%)	28 (80.0 %)	23 (65.7 %)*	19 (54.3 %)**	17 (77.3 %)
HBeAg seroconversion rate	6/20 (30.0 %)	4/18 (22.2 %)	3/19 (15.8 %)	3/11 (27.3 %)

Compared with ETV therapy, *$P<0.05$. Compared with 12-week optimized therapy, *$P<0.05$.

rences in the changes of BUN, CR and CK in each group before and after medication. And there were no patients became drug resistance in each group. Furthermore, no other serious adverse effects were observed.

Discussion

In this study, improvements in liver function were observed in all therapy groups. Furthermore, long term safety was also demonstrated, and none of the patients had significant side-effects. In addition, renal function and CK level were not influenced by the treatments. Consistent with previous studies, initial combination therapy revealed superior efficacy. The superiority of the combination treatment of LAM and ADV was demonstrated by the comparison with ETV monotherapy, which advised the use of hepatitis B virus-infected decompensated cirrhosis as first-line treatment. Combination treatment increased virologic response, improved liver function, and reduced drug resistance. From the long term perspective, it has also lightened the economic burden of patients.

Active viral replication was always occurred in patients with hepatitis B-induced decompensated cirrhosis. Inhibiting or eliminating the replication of hepatitis virus is the key to improve their disease conditions. As mentioned in many guidelines for decompensated cirrhosis, antiviral treatment has been proposed, irrespective of HBV DNA level or ALT level (11). The development of anti-viral agents plays a significant role in antivirus therapy, and their effects have been well-recognized. A meta-analysis revealed that nucleoside/nucleotide analogues used in patients with decompensated HBV cirrhosis were associated with improved virological, biochemical and clinical parameters at one year (12). Currently, both LAM and ADV were frequently used; but their mechanisms of antiviral action were slightly different. LAM was phosphorylated to active metabolites, and competed for incorporation into viral DNA; thus, acting as a chain terminator of DNA synthesis. ADV inhibited the activity of both reverse transcriptase and DNA polymerase, and incorporated into HBV DNA, causing a chain termination (2).

LAM is an inexpensive agent, but its long term monotherapy might cause serious drug resistance. ADV is an oral bioavailable drug. Its usage is limited by its potency and slow onset of action (12), and its nephrotoxicity is also a major concern (13). Furthermore, the combination therapy of LAM and ADV revealed more advantages than monotherapy. Proper drug combinations had a synergetic effect, as well as less mutations and better suppression on HBV DNA; and this has been identified in clinical research (14). Despite the confirmation of the beneficial effect of combination therapy, initial LAM monotherapy continues to be used in Asia and in other parts of the world (15). ADV was added after LAM therapy when incomplete viral responses occur. The adverse effect of LAM mutations can be overcomed by the timely use of ADV (16), which was demonstrated by George in a trial of long-term therapy with initial treatment of LAM and rescued by ADV (17).

In order to achieve ideal curative effects, the strategy of antiviral treatment requires further optimization. In this study, we also compared the efficacy of optimized ADV add-on therapies with previous 12-week and 24-week courses of LAM. Compared with 24-week optimized therapy, 12-week optimized therapy produced a higher rate of ALT normalization, greater suppression on HBV DNA, better HBeAg seroconversion, as well as the improvement in Child-Pugh scores. This result demonstrated that for patients who had a poor response (HBV DNA level $>1\times10^3$ copies/mL) to LAM monotherapy, early ADV addition would be more effective. However, whether the addition of ADV was necessary in case poor response occurs at an earlier time, or even before 12 weeks, future studies needs to be carried out to address this issue.

Conclusion

Liver function was severely damaged in patients with decompensated cirrhosis. The replication and infection of HBV aggravated their disease situation, and even threatens the life of patients. Antiviral treatment has been proven safe and efficacious. However, due to the inevitability of drug- resistance, rational dosage regimens need to be constantly optimized. In this study, 127 patients received four different doses of regimens for 96 weeks. Both the initial combination therapy, 12-week optimized therapy, 24-week optimized therapy and ETV monotherapy were assessed to be safe and with efficacy. From the current observation on clinical efficiency, initial combination therapy and the early addition of ADV could achieve an almost equivalent effect to ETV monotherapy. Hence, these might be the preferred approach in antiviral strategies.

Table 4. — **The comparison of renal function and CK level**

Group	BUN (mmol/L)		CR (μmol/L)		CK (mmol/L)	
	Pre treatment	Post treatment	Pre treatment	Post treatment	Pre treatment	Post treatment
LAM+ADV	5.9±2.5	6.1±2.1	72.6±19.6	75.7±16.2	118.3±65.5	112.5±45.7
12-week optimized therapy	6.2±2.4	6.2±2.1	71.1±21.2	73.9±18.3	119.7±60.5	120.7±48.6
24-week optimized therapy	6.1±2.2	6.3±2.2	72.9±21.0	79.6±19.9	110.1±55.1	106.5±43.5
ETV therapy	5.3±1.7	5.3±1.6	66.0±16.6	64.5±18.7	122.6±65.5	97.5±35.5

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