

## **De novo combination therapy with lamivudine and adefovir dipivoxil in chronic hepatitis B patients**

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### **Abstract**

**AIM:** To investigate the appropriate time for combination therapy in HBeAg positive chronic hepatitis B (CHB) patients with decompensated cirrhosis.

**METHODS:** Thirty HBeAg positive CHB patients with decompensated cirrhosis were enrolled in the study. All of the patients were given 48 wk combination therapy with lamivudine (LAM) and adefovir dipivoxil (ADV). Briefly, 10 patients were given the *de novo* combination therapy with LAM and ADV, whereas the other 20 patients received ADV in addition to LAM after hepatitis B virus (HBV) genetic mutation.

**RESULTS:** Serum alanine aminotransferase and total bilirubin were both improved in the two groups at 4, 12, 24 and 48 wk after treatment. Serum albumin was also improved at 24 and 48 wk after combination therapy in both groups. The serum HBV DNA level was

still detectable in every patient in the two groups at 4 and 12 wk after combination treatment. However, in the *de novo* combination group, serum HBV DNA levels in 4 (40%) and 9 (90%) patients was decreased to below  $1 \times 10^3$  copies/mL at 24 and 48 wk after the combination treatment, respectively. In parallel, serum HBV DNA levels in 2 (20%) and 8 (40%) patients in the add-on combination group became undetectable at 24 and 48 wk after combination treatment, respectively. Furthermore, 6 (60%) patients in the *de novo* combination group achieved HBeAg seroconversion after 48 wk treatment, whereas only 4 (20%) patients in the add-on combination group achieved seroconversion. Child-Pugh score of patients in the *de novo* combination group was better than that of patients in the add-on combination group after 48 wk treatment. Moreover, patients in the *de novo* combination group had a significantly decreased serum creatinine level and elevated red blood cell counts.

**CONCLUSION:** *De novo* combination therapy with LAM and ADV was better than add-on combination therapy in terms of Child-Pugh score, virus inhibition and renal function.

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**Key words:** Hepatitis B; Chronic; Cirrhosis; Decompensated; *De novo* combination; Lamivudine; Adefovir dipivoxil

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## INTRODUCTION

Hepatitis B virus (HBV) is prevalent world-widely. World Health Origination estimates that approximately 400 million people are chronic HBV carriers around the world<sup>[1]</sup>. Chronic hepatitis B (CHB) is a leading cause of hepatic cirrhosis and hepatocellular carcinoma (HCC)<sup>[1]</sup>. Once cirrhosis develops, mortality is high in untreated patients. The 5 years mortality rate of CHB patients with decompensated cirrhosis is 86%<sup>[2]</sup>. Therefore, it is necessary to develop an effective therapy for those decompensated cirrhosis patients infected with chronic HBV.

The treatment for decompensated cirrhotic patients aims to delay the occurrence of HCC. Recommended therapy options are nucleos(t)ide analogues, such as lamivudine (LAM), adefovir dipivoxil (ADV) and entecavir (ETV). Previous studies showed that LAM is effective in cirrhotic patients infected with chronic HBV<sup>[3,4]</sup>. However, the clinical benefit of LAM is limited by the emergence of resistant mutant strains<sup>[5,6]</sup>. Recently, ADV has been strongly considered as a rescue therapeutic agent to resistant mutants<sup>[7,8]</sup>. Several studies showed that combination therapy with LAM and ADV is better than ADV monotherapy in LAM-resistant patients infected with HBV<sup>[7,9,10]</sup>. However, it remains unclear how to start the combination therapy in HBeAg positive patients with decompensated cirrhosis secondary to hepatitis B. In the present study, we aimed to evaluate the better combination therapy in HBeAg positive patients with decompensated cirrhosis secondary to hepatitis B.

## MATERIALS AND METHODS

### Patients

Adult patients who had CHB with decompensated cirrhosis and HBeAg positive were enrolled in the study from January 2008 to June 2010 in Peking University First Hospital and Shijiazhuang Fifth Hospital. The criteria for diagnosis of hepatitis were those which appear in the guidelines for prevention and treatment of CHB in China<sup>[11]</sup>. The diagnosis of decompensated cirrhosis was based on clinical, laboratory, previous histological, ultrasonographic and radiological signs of cirrhosis with at least one sign of liver decompensation (ascites, variceal bleeding, hepatic encephalopathy, non-obstructive jaundice). Patients co-infected with hepatitis A virus, hepatitis C virus, hepatitis D virus, hepatitis E virus, or human immunodeficiency virus and with alcoholic cirrhosis, autoimmune hepatitis, hepatorenal syndrome, HCC or severe heart, brain, renal diseases were excluded from the study. All of the patients were both HBV DNA and HBeAg positive. A total of 30 patients were enrolled in the study. Child-Pugh score was used to assess the clinical status of every patient<sup>[12]</sup>. Sixteen patients were at B stage (mean score: 8.4), and the other 14 patients were at C stage (mean score: 11.1).

### Treatment of patients

All of the patients were given LAM (100 mg/d QO,

GSK, Suzhou, China) at the beginning of treatment. Ten of them were then given ADV 10 mg/d (QO, GSK, Suzhou, China) over the following 2 wk (*de novo* combination arm), while the other 20 patients received ADV 10 mg/d in addition to LAM after HBV genetic YMDD mutation (add-on combination arm). The duration of combination treatment was 48 wk for both arms.

### Biochemical and virological analysis

Peripheral blood was taken from all of the patients in the morning with fasting for at least 8 h. HBsAg, HBsAg antibody (anti-HBs), HBeAg, HBeAg antibody (anti-HBe) and HBcAg antibody (anti-HBc) were detected by AxSYM MEI kits (Abbott Laboratories, United States). Serum HBV DNA level was measured by quantitative polymerase chain reaction (PCR) (Daan Gene Co., LTD of Sun Yansen University, Guangzhou, China) at certain time points (week 0, 4, 12, 24 and 48) during treatment. The detection limit of HBV DNA was  $1 \times 10^3$  copies/mL.

Routine biochemical and hematological tests were performed at the participating centers using automated techniques at certain time points (week 0, 4, 12, 24 and 48) during treatment. Child-Pugh score was also assessed simultaneously.

### Statistical analysis

Data were expressed as arithmetic mean  $\pm$  SD, median (range), or frequency and percentage when appropriate. Student *t* test was used to analyze the normally distributed quantitative variables between the two study groups. Mann-Whitney rank sum test was used to analyze the skewed data. All tests were two tailed, and *P* value less than 0.05 was considered statistically significant. All statistical calculations were done using the SPSS 16.0 (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, United States) statistical software.

## RESULTS

### Baseline characteristics

A total of 30 patients were enrolled in the study, including 17 males (56.7%) with a median age of 42 years (40-49 years). Data showed that serum alanine aminotransferase (ALT), total bilirubin (TBIL) and albumin (ALB) levels at baseline in the *de novo* combination patients were significantly lower than those in the add-on combination patients. However, mean serum HBV DNA level and Child-Pugh score were not different between the two groups. Table 1 shows the baseline characteristics of the study population.

### Virological response

The percentage of patients with undetectable HBV DNA in the *de novo* combination group was 0, 0, 40% and 90% at 4, 12, 24 and 48 wk after the treatment, respectively. However, it was 0, 0, 20% and 40% at each time point in the add-on combination group, respectively. Figure 1 shows that the percentage of patients

Table 1 Characteristics of patients at baseline, median (min-max)

Characteristic	<i>De novo</i> combination group ( <i>n</i> = 10)	Add-on combination group ( <i>n</i> = 20)	<i>P</i> value
Age (yr)	45.6 ± 8.2	45.2 ± 8.2	0.89
Gender (males, %)	6 (60%)	11 (55%)	1
Height (m)	1.7 ± 0.7	1.7 ± 0.9	0.58
Weight (kg)	68.9 ± 9.7	67.3 ± 10.5	0.69
BMI (kg/m <sup>2</sup> )	23.8 ± 1.8	23.7 ± 1.6	0.88
HBV DNA levels (log <sub>10</sub> , copies/mL)	6.23 ± 0.91	6.43 ± 0.95	0.58
Serum ALT (IU/L)	124 (82-156)	283 (187-321)	0
Serum TBIL (μmol/L)	49.5 (23-72)	73.5 (49.0-99.6)	0.001
Serum ALB (g/L)	29.75 (25.40-34.00)	26.65 (23.00-32.00)	0.021
Child-Pugh score	11 (9-13)	11 (9-13)	0.809
Red blood cell counts (× 10 <sup>12</sup> /L)	3.6 (3.0-4.5)	3.3 (1.9-5.0)	0.234
HB (g/L)	106 (90-120)	97 (75-115)	0.059
White blood cell counts (× 10 <sup>9</sup> /L)	3.85 (2.70-6.80)	3.75 (1.90-6.00)	0.657
Blood PLT count (× 10 <sup>9</sup> /L)	96 (76-150)	96 (50-112)	0.657
Serum BUN (mmol/L)	6.05 (3.70-8.10)	4.35 (1.90-8.50)	0.139
Serum Cr (μmol/L)	99.5 (77.0-145.0)	77.0 (40.0-156.0)	0.024

BMI: Body mass index; HBV: Hepatitis B virus; ALT: Alanine aminotransferase; TBIL: Total bilirubin; ALB: Albumin; HB: Hemoglobin; PLT: Platelet; BUN: Blood urine nitrogen; Cr: Creatinine.

with undetectable HBV DNA was significantly different between the two groups after the 48 wk treatment ( $P = 0.017$ ). Moreover, no patient in the two groups showed detectable virological resistance during the 48 wk combination treatment.

### Biochemical response

We showed that ALT, TBIL and ALB of patients were decreased in the two groups after treatment. Furthermore, 6 (60%) patients in the *de novo* combination group achieved HBeAg seroconversion, whereas only 4 (20%) patients in the add-on combination group achieved seroconversion ( $P = 0.045$ ).

Child-Pugh score at baseline was not statistically different in the two groups. Table 2 shows that Child-Pugh score in the *de novo* combination group was significantly lower than that in the add-on combination group after the 48 wk treatment.

### Hematological changes and renal function

Red blood cell counts and hemoglobin levels in the 2 groups showed no difference at baseline. However, red blood cell counts and hemoglobin in the *de novo* combination group were higher than those in the add-on combination group at 24 and 48 wk after treatment. White blood cell counts and platelet (PLT) level showed no difference between the two groups at baseline and during the treatment period.

Moreover, serum blood urine nitrogen (BUN) level was not different between the two groups at baseline and during treatment. Serum creatinine (Cr) at baseline in the *de novo* combination group was significantly higher than

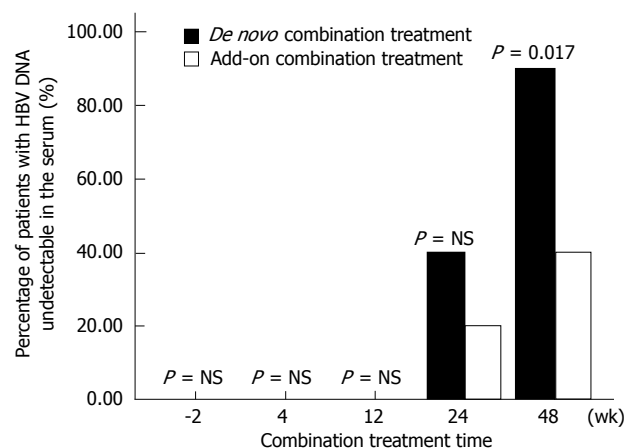


Figure 1 The percentage of decompensated cirrhotic chronic hepatitis B patients with undetectable hepatitis B virus (HBV) DNA in the serum of the two groups during the treatment period. NS: Not significant.

that in the add-on combination group. However, serum Cr level in the 2 groups was not significantly different after treatment (Table 3).

### Side effects

Both *de novo* combination treatment and add-on combination treatment were well tolerated. No patient in either group discontinued the drug during the period.

In the *de novo* combination group, serum BUN level of two patients was slightly increased, two patients had slight diarrhea, and one patient had nausea. In parallel, in the add-on combination group, serum BUN level of two patients was slightly increased, two patients had nausea, one patient had slight diarrhea, and one patient had upper gastrointestinal hemorrhage. All these symptoms disappeared after relevant management.

## DISCUSSION

In this retrospective study, we compared *de novo* combination therapy with add-on combination therapy in HBeAg positive and decompensated cirrhosis patients infected with HBV. The percentage of patients with undetectable HBV DNA was 40% (4/10) and 20% (4/20) in the *de novo* combination and add-on combination groups at 24 wk after treatment, respectively. However, this difference between two groups was not statistically different. The percentage of patients with undetectable HBV DNA in the *de novo* combination group (9/10, 90%) was significantly higher than that in the add-on combination group (8/20, 40%) at 48 wk after treatment. We, for the first time, compared *de novo* combination treatment with add-on combination treatment in cirrhotic decompensated patients secondary to hepatitis B. Some researchers compared LAM and ADV combination therapy with ADV monotherapy after LAM-induced viral genetic resistance. They showed that LAM and ADV combination therapy is a more effective treatment to get a virological response and has lower genetic resistance than ADV monothera-

Table 2 Biochemical responses of the patients, median (min-max)

	<i>De novo</i> combination group ( <i>n</i> = 10)					Add-on combination group ( <i>n</i> = 20)				
	2 wk before combination treatment	4 wk after combination treatment	12 wk after combination treatment	24 wk after combination treatment	48 wk after combination treatment	2 wk before combination treatment	4 wk after combination treatment	12 wk after combination treatment	24 wk after combination treatment	48 wk after combination treatment
Child-Pugh score	11 (9-13)	10 (8-12)	10 (8-12)	9 (7-11) <sup>c</sup>	7 (6-9) <sup>ca</sup>	11 (9-13)	10 (9-12)	10 (9-12)	10 (7-11) <sup>c</sup>	9 (7-10) <sup>c</sup>
Serum ALT (IU/L)	124 (82-156) <sup>a</sup>	111 (80-141) <sup>a</sup>	109 (69-125) <sup>a</sup>	89 (59-112) <sup>ca</sup>	49 (28-67) <sup>ca</sup>	283 (187-321)	251 (171-302) <sup>c</sup>	218 (146-277) <sup>c</sup>	173 (105-239) <sup>c</sup>	105 (65-186) <sup>c</sup>
Serum TBIL (μmol/L)	49.5 (23-72) <sup>a</sup>	47.3 (25.0-70.1) <sup>a</sup>	41.3 (25.5-63.0) <sup>a</sup>	37.8 (22.5-57.4) <sup>ca</sup>	31.0 (22.0-41.0) <sup>ca</sup>	73.5 (49.0-99.6)	68.3 (44.5-88.7)	63.5 (35.8-79.0) <sup>c</sup>	56.7 (32.0-72.3) <sup>c</sup>	41.2 (29.0-58.1) <sup>c</sup>
Serum ALB (g/L)	29.75 (25.40-34.00) <sup>a</sup>	30.15 (27.20-34.10) <sup>a</sup>	30.55 (27.60-33.00) <sup>a</sup>	32.80 (29.00-35.00) <sup>ca</sup>	34.00 (30.00-37.00) <sup>ca</sup>	26.65 (23.00-32.00)	28.20 (25.60-32.90)	27.85 (25.00-31.90)	28.75 (25.50-33.00) <sup>c</sup>	30.5 (28.0-34.8) <sup>c</sup>

<sup>a</sup>*P* < 0.05 vs add-on combination group; <sup>c</sup>*P* < 0.05 vs 2 wk before combination treatment in the same group. ALT: Alanine aminotransferase; TBIL: Total bilirubin; ALB: Albumin.

Table 3 Blood cell counts and renal function of the patients, median (min-max)

	<i>De novo</i> combination group ( <i>n</i> = 10)					Add-on combination group ( <i>n</i> = 20)				
	2 wk before combination treatment	4 wk after combination treatment	12 wk after combination treatment	24 wk after combination treatment	48 wk after combination treatment	2 wk before combination treatment	4 wk after combination treatment	12 wk after combination treatment	24 wk after combination treatment	48 wk after combination treatment
Red blood cell counts (× 10 <sup>12</sup> /L)	3.6 (3.0-4.5)	3.4 (3.0-4.3)	3.5 (2.9-4.1)	3.6 (3.1-4.0) <sup>a</sup>	3.8 (3.0-5.1) <sup>a</sup>	3.3 (1.9-5.0)	3.2 (2.3-4.1)	3.1 (2.5-4.0)	3.1 (2.5-3.9)	3.1 (2.7-3.4) <sup>c</sup>
HB (g/L)	106 (90-120)	104 (92-113) <sup>a</sup>	102 (99-115)	107 (94-114) <sup>a</sup>	105 (85-121) <sup>a</sup>	97 (75-115)	95 (80-114)	95 (85-111)	99 (88-112)	97 (84-105)
White blood cell counts (× 10 <sup>9</sup> /L)	3.85 (2.70-6.80)	3.90 (2.90-5.70)	3.80 (3.00-5.20)	3.95 (3.20-4.70)	4.00 (3.00-4.50)	3.75 (1.90-6.00)	3.75 (2.50-5.60)	3.70 (2.90-5.00)	3.75 (2.90-4.70)	3.85 (3.00-5.10)
Blood PLT counts (× 10 <sup>9</sup> /L)	96 (76-150)	90 (72-100)	94 (70-116)	95 (68-108)	98 (72-103)	96 (50-112)	94 (63-111)	92 (76-110)	90 (69-107)	93 (73-112)
Serum BUN (mmol/L)	6.05 (3.70-8.10)	5.90 (3.00-7.40)	5.65 (3.60-7.10)	5.50 (2.50-6.80)	5.45 (3.30-7.00)	4.35 (1.90-8.50)	5.25 (2.20-8.70)	5.00 (2.20-8.00)	5.00 (2.90-7.50)	4.95 (2.30-7.10)
Serum Cr (μmol/L)	99.5 (77.0-145.0) <sup>a</sup>	96.5 (76.0-141.0)	96.0 (69.0-112.0)	78.0 (56.0-99.0) <sup>c</sup>	78.5 (61.0-107.0) <sup>c</sup>	77.0 (40.0-156.0)	95.5 (61.0-124.0)	86.0 (68.0-131.0)	73.5 (42.0-132.0)	79.0 (41.0-132.0)

<sup>a</sup>*P* < 0.05 vs add-on combination group; <sup>c</sup>*P* < 0.05 vs 2 wk before combination treatment in the same group. HB: Hemoglobin; PLT: Platelet; BUN: Blood urine nitrogen; Cr: Creatinine.

py<sup>[7-9]</sup>. However, the efficiency of LAM and ADV combination therapy in treatment naïve patients with decompensated cirrhosis remains unclear. In the present study, we showed that *de novo* combination therapy was more effective than add-on combination therapy in terms of virological response and HBeAg seroconversion. No patient achieved virological resistance during combination treatment in both two groups.

It is known that HBeAg seroconversion is accompanied by biochemical and histological regression of liver disease<sup>[13,14]</sup>. Our data showed that the percentage of HBeAg seroconversion in the *de novo* combination group (6/10, 60%) was significantly higher than that in the add-on combination group (4/20, 20%).

Due to its simplicity in clinical practice, Child-Pugh score has been widely applied as the prognostic marker in patients with decompensated cirrhosis<sup>[15,16]</sup>. Child-Pugh score is one of the risk factors for assessing patients with decompensated cirrhosis<sup>[17]</sup>. In this study, Child-Pugh score of all patients was significantly decreased in the two groups after 24 and 48 wk combination treatment. Child-Pugh score at baseline was not

different between the two groups. However, the score in the *de novo* combination group was superior to that in the add-on combination group after 48 wk treatment. LAM and ADV combination therapy could improve clinical symptoms in patients with decompensated cirrhosis. But, *de novo* combination therapy was more effective in improving hepatic function than LAM and ADV combination therapy after genetic resistance.

ALT, TBIL and ALB of the patients were different at baseline between the two groups. However, these three parameters were all significantly decreased in the two groups during the treatment period. LAM and ADV combination therapy was an effective way to produce a biochemical response in CHB patients with decompensated cirrhosis.

It has been reported that ADV decreases renal function<sup>[18]</sup>. In our study, serum Cr and BUN levels of all patients were not increased during the treatment period. However, serum Cr level in the *de novo* combination group was significantly higher than that in the add-on combination group (104.0 ± 23.5 vs 83.0 ± 29.4, *P* < 0.05) at baseline. But serum Cr in the two groups was not dif-



ferent after the 48 wk treatment. Our data showed LAM and ADV combination therapy did not affect renal function during the treatment period. The *de novo* combination therapy could improve serum Cr level in the decompensated cirrhosis patients infected with chronic HBV.

Taken together, a higher percentage of patients with undetectable HBV DNA and HBeAg seroconversion was obtained from the *de novo* combination group than from the add-on combination group. Moreover, Child-Pugh score in patients with the *de novo* combination therapy was better than that in patients with the add-on combination therapy after 48 wk treatment. Therefore, HBeAg positive decompensated cirrhotic patients infected with chronic HBV should receive LAM and ADV combination therapy at the beginning of antiviral treatment.

In the present study, we have several shortcomings as follows. First, the number of subjects was small because the number of patients treated with *de novo* combination therapy was limited in China. Second, the period of the combination treatment was not long enough. Therefore, a larger number of subjects and longer treatment duration are required in our future study.

## COMMENTS

### Background

The mortality rate of chronic hepatitis B patients with decompensated cirrhosis is very high. Recommended therapy options are nucleos(t)ide analogues. But, the combination treatment option with nucleos(t)ide analogues for HBeAg positive patients with decompensated cirrhosis secondary to hepatitis B is not very clear.

### Research frontiers

Combination therapy with lamivudine (LAM) and adefovir dipivoxil (ADV) is better than ADV monotherapy in LAM-resistant patients infected with hepatitis B virus. But in HBeAg positive patients with decompensated cirrhosis secondary to hepatitis B, it remains unclear whether combination treatment at the beginning of therapy is better than add-on combination therapy. In this study, the authors demonstrate that *de novo* combination therapy is more effective than add-on combination therapy with LAM and ADV in HBeAg positive patients with decompensated cirrhosis secondary to hepatitis B.

### Innovations and breakthroughs

Some research showed that LAM and ADV combination therapy is more effective as a means to get a virological response and has lower genetic resistance than ADV monotherapy after LAM-induced viral genetic resistance. However, the efficiency of LAM and ADV combination therapy in naïve patients with decompensated cirrhosis is unclear. For the first time, this study compared *de novo* combination treatment with add-on combination treatment in the cirrhotic decompensated patients secondary to hepatitis B.

### Applications

By understanding that *de novo* combination therapy is more effective than add-on combination therapy, this study may represent a future strategy in the treatment of HBeAg positive patients with decompensated cirrhosis secondary to chronic hepatitis B.

### Terminology

*De novo* combination treatment means combination treatment with two or more drugs from the beginning of the treatment. Child-Pugh score is a system to assess the disease stage for decompensated cirrhotic patients.

### Peer review

In this study, the authors have made an attempt to determine the effective time frame for combined therapy used in HBeAg positive chronic hepatitis B patients with decompensated cirrhosis. Though the study is limited to only 30 patients, it is novel and contributes a substantial amount of knowledge to the field.

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