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BRIEF ARTICLE

Efficacy of combined therapy in patients with hepatitis B virus-related decompensated cirrhosis

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Abstract

AIM: To investigate the efficacy and safety of combined *de novo* lamivudine (LAM) and adefovir dipivoxil (ADV) therapy in hepatitis B virus (HBV)-related decompensated liver cirrhosis patients.

METHODS: One hundred and forty patients with HBV-related decompensated cirrhosis were recruited, 70 patients were treated with combined LAM and ADV *de novo* therapy, and the other 70 patients were treated with LAM alone as controls. The follow-up period was 144 wk. All patients with LAM resistance were shifted to ADV.

RESULTS: The percentage of HBV-related decompensated cirrhosis patients with undetectable HBV DNA in *de novo* combination group was 51.6% (33/64), 84.2% (48/57), and 92.3% (49/53) by weeks 48, 96, and 144, respectively. In monotherapy group, HBV DNA negativity rate was 46.1% (30/65), 56.1% (32/57), and 39.2% (20/51) by weeks 48, 96 and 144, respectively. There was a significant difference between the two groups by weeks 96 and 144 (P = 0.012 and 0.001). The hepatitis B e antigen seroconversion rate was 28.1% (9/32), 40.0% (12/30), and 53.6% (15/28) in the combination group by weeks 48, 96 and 144, respectively, and 24.2% (8/33), 31.0% (9/29), and 37.0% (10/27) by weeks 48, 96 and 144, respectively, in monotherapy group. A total of 68.6% (44/64), 84.2% (48/57), and 92.5% (49/53) patients achieved alanine aminotransferase (ALT) normalization by weeks 48, 96 and 144, respectively in the combination group. In monotherpy group, the ALT normalization rate was 64.6% (42/65) by week 48, 73.7% (42/57) by week 96, and 80.4% (41/51) by week 144. No patients in the combination group exhibited detectable resistance for at least 144 wk. The cumulative resistance rate in monotherapy group at weeks 48, 96, and 144 was 20.0%, 36.8%, and 56.9%. Both combination group and monotherapy group demonstrated an improvement in Child-Turcotte Pugh and Model for End-Stage Liver Disease scores at weeks 48, 96, and 144. All patients tolerated both combination and monotherapy. The ceratinine levels and glomerular filtration rate remained normal in all patients during the follow-up period.

CONCLUSION: In HBV-related decompensated liver cirrhosis patients, the combined *de novo* LAM and ADV therapy is more efficacious and safer compared to LAM alone.

Key words: Liver cirrhosis; Lamivudine; Adefovir dipivoxil; Efficacy; Alanine transaminase

Core tip: Present treatment guidelines advocate oral nucleos(t)ide analogues in decompensated chronic hepatitis B (CHB) patients. Studies with lamivudine

(LAM) have demonstrated decreased mortality and improved liver function in CHB decompensated patients. However, LAM resistance mutations emerging during monotherapy can negate therapeutic benefit. Adefovir dipivoxil had no cross resistance with LAM. Consistent with outcomes in patients with LAM-resistance, no patient in *de novo* combination therapy group showed detectable resistance up to 144 wk in this study. The *de novo* combination therapy markedly improved liver function, reduced Child-Turcotte Pugh and Model for End-Stage Liver Disease scores in hepatitis B virus-related decompensated cirrhosis patients.

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INTRODUCTION

It is estimated that over 350 million people worldwide are chronically infected with hepatitis B virus (HBV). The majority of these individuals reside in the Asia-Pacific region[1]. Chronic hepatitis B (CHB) infection is the principal cause of liver cirrhosis and hepatocellular carcinoma (HCC). In cirrhotic patients, the 5-year probability of decompensation is 15%-20%, and the risk increases as the HBV DNA level increases[2]. The 5-year survival rate in decompensated cirrhosis patients is 14%-35%, compared to 84% for those with compensated cirrhosis[3].

Previous studies have shown that high serum HBV DNA is a major risk factor for disease progression to cirrhosis or HCC. Lamivudine (LAM) is the first nucleoside analog widely prescribed for CHB patients due to its antiviral efficacy and safety profile. LAM is found effective for patients with HBV-related decompensated liver cirrhosis[4,5]. However, LAM is associated with a high risk of drug resistance and virological breakthrough[6]. Adefovir dipivoxil (ADV) exhibits specificity, low drug resistance, and no cross resistance with other nucleoside analogs, which has been strongly considered as a rescue therapeutic agent to combat resistance[7,8]. In China, as the first approved drug for CHB patients, LAM has been widely prescribed for its clinical efficacy and low cost. Clinical trials have demonstrated the superiority of combined LAM and ADV therapy compared to ADV monotherapy in LAM resistant patients[9,10]. In this study, LAM and ADV are utilized as *de novo* combination treatment. To date, no study has been performed to systematically evaluate the efficacy and safety of *de novo* combined therapy in patients with HBV-related decompensated liver cirrhosis.

In this study, we aimed to compare the efficacy and safety of *de novo* combination therapy with monotherapy in patients with HBV-related decompensated liver cirrhosis.

MATERIALS AND METHODS

Study population

From January 2007 to December 2008, 140 consecutive nucleoside analogs treatment-naïve patients with HBV-related decompensated cirrhosis were enrolled in this study in the First Affiliated Hospital of Zhejiang University.

Diagnostic criteria: The diagnosis of decompensated liver cirrhosis was based on clinical, laboratory, previous histological, ultrasonographic and radiological signs of cirrhosis with Child-Turcotte-Pugh (CTP) score. The inclusion criteria for this study were as follows: aged 18-65 years, with HBV DNA $\geqslant 10^3$ copies/mL, a CTP score of 7-12 (inclusive), calculated serum creatinine clearance $\geqslant$ 50 mL/min, hemoglobin $\geqslant$ 75 g/L, total white blood cell $\geqslant 2.5\times10^9$/L, platelet count $\geqslant 30 \times 10^9$/L, α-fetoprotein $\leqslant$ 20 ng/mL, and no evidence of HCC.

Exclusion criteria: Patients were excluded for resistance to LAM, co-infection with hepatitis C virus, hepatitis D virus, hepatitis E virus or human immunodeficiency virus, and autoimmune hepatitis, alcoholic cirrhosis, hepatorenal syndrome, grade 3 or 4 hepatic encephalopathy, or spontaneous bacterial peritonitis, and severe heart, renal, brain diseases.

Study design

Among 140 patients with HBV-related decompensated cirrhosis, 70 patients were treated with *de novo* combination therapy of 100 mg/d LAM and 10 mg/d ADV; the other 70 patients were treated with 100 mg/d LAM alone as controls. The duration of the treatment was 144 wk. All patients who exhibited LAM resistance were administered ADV.

All patients were followed up every 3-6 mo with examinations of liver and renal function, prothrombin time (PT), international normalized ratio (INR), serum HBV DNA, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B e antigen (HBeAg), hepatitis B e antibody (anti-HBe), and hepatitis B core antibody (anti-HBc), as well as ultrasonographic or computerized tomography examination. Routine biochemical and hematological tests, and clinical examination were performed at all clinical visits.

Biochemical and virological analysis

Biochemistry, hematology, PT, INR, and urinalysis were analyzed immediately. Serum hepatitis B viral markers, including HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc were detected using commercially available enzyme immunoassays (Abbott Laboratories, Chicago, IL, United States). Serum HBV DNA was measured by polymerase chain reaction with a linear range between 1×10^3 and 5×10^8 copies/mL (Shanghai ZJ Bio-Tech Co., Ltd., China). LAM and ADV associated mutations were assessed by direct sequencing.

Ethics

Informed consent for inclusion in the study was obtained

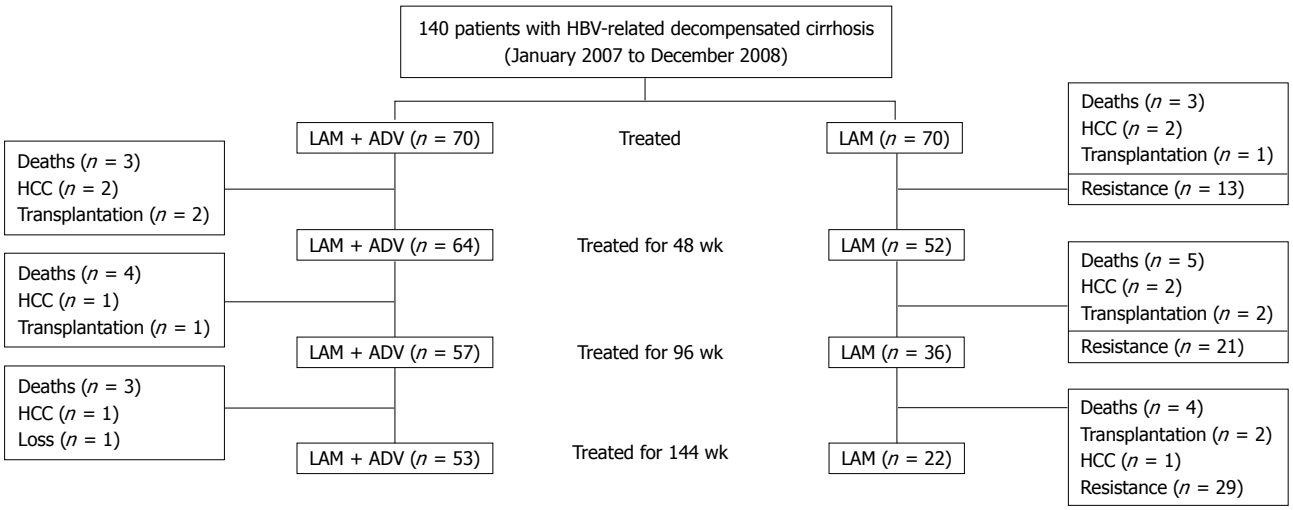

Figure 1 Flow chart of patients disposition in *de novo* lamivudine and adefovir dipivoxil combination group and lamivudine monotherapy group. HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; ADV: Adefovir dipivoxil; LAM: Lamivudine.

Table 1 Baseline characteristics of patients with hepatitis B virus-related decompensated cirrhosis (mean ± SD)

Characteristics	*De novo* combination group (*n* = 70)	Lamivudine group (*n* = 70)	*P* value
Age (yr)	46.8 ± 10.3	47.1 ± 10.9	0.91
Male/female	41/29	40/30	0.89
ALT (IU/L)	134.6 ± 101.3	132.4 ± 120.8	0.78
TBIL (μmol/L)	38.5 ± 12.1	37.8 ± 11.9	0.84
Albumin (g/dL)	3.2 ± 0.7	3.3 ± 0.6 0.34	
Prothrombin time (s)	17.1 ± 4.5	17.6 ± 3.1	0.61
HBV DNA (log10 copies/mL)	6.87 ± 1.21	6.94 ± 1.15	0.73
HBeAg positive	34 (48.6)	33 (47.1)	0.94
Platelet count (× 10^9/L)	78.9 ± 24.2	76.7 ± 32.3	0.67
Creatinine (μmol/L)	89.7 ± 12.3	88.6 ± 13.1	0.45
GFR (mL/min)	115.2 ± 34.5	113.5 ± 22.9	0.68
CTP score	8.9 ± 2.1	8.8 ± 1.7	0.83
CTP class			
A	6 (8.6)	7 (10)	0.65
B	48 (68.6)	49 (70)	0.77
C	16 (22.9)	14 (20)	0.59
MELD score	12.4 ± 3.7	11.9 ± 2.5	0.75

ALT: Alanine aminotransferase; TBIL: Total bilirubin; GFR: Glomerular filtration rate; HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen; CTP: Child-Turcotte-Pugh score; MELD: Model for End-Stage Liver Disease.

from all patients before recruitment. This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Zhejiang University.

Statistical analysis

Statistical analysis was conducted using SPSS (version 16.0, IL, United States). Continuous variables were expressed as mean ± SD. Continuous variables were examined using the Students's *t* test or Mann-Whitney *U* test. Categorical variables were compared by χ^2 test. A *P* value < 0.05 was considered statistically significant.

RESULTS

Patients

A total of 140 patients were recruited: 70 received LAM and ADV d*e novo* combination therapy and 70 received LAM monotherapy. Baseline characteristics were comparable between the two groups and are shown in Table 1. In *de novo* combination therapy group, 37 (52.9%) patients exhibited ascites, 9 (12.8%) exhibited episodes of hepatic encephalopathy, and 15 (21.4%) exhibited variceal bleeding. In LAM monotherapy group, 36 (51.4%) patients presented ascites, 8 (11.4%) presented episodes of hepatic encephalopathy, and 16 (22.9%) exhibited variceal bleeding. No patent in either group discontinued antiviral therapy during the study period. The characteristics of the patients during the 144 wk are shown in Figure 1.

Virological, serological, and biochemical responses

The percentage of HBV related decompensated cirrhosis patients with undetectable HBV DNA in the *de novo* combination group was 51.6% (33/64), 84.2% (48/57) and 92.3% (49/53) by weeks 48, 96, and 144, respectively. In the monotherapy group, the rate of HBV DNA negativity was 46.1% (30/65), 56.1% (32/57) and 39.2% (20/51) by weeks 48, 96, and 144, respectively. A significant difference was observed between the two groups by weeks 96 and 144 ($P = 0.012$ and 0.001).

Patients who were HBeAg-positive at baseline, 34/70 (48.6%) in *de novo* combination group and 33/70 (47.1%) in monotherapy group, exhibited HBeAg seroconversion: 28.1% (9/32) *vs* 24.2% (8/33) by week 48 ($P = 0.372$), 40.0% (12/30) *vs* 31.0% (9/29) by week 96 ($P = 0.021$), and 53.6% (15/28) *vs* 37.0% (10/27) by week 144 ($P = 0.014$), respectively.

Of the 70 decompensated cirrhosis patients receiving *de novo* combination therapy, 68.6% (44/64), 84.2% (48/57) and 92.5% (49/53) of the patients achieved alanine aminotransferase (ALT) normalization by weeks 48, 96 and 144, respectively. In monotherpy group, the ALT

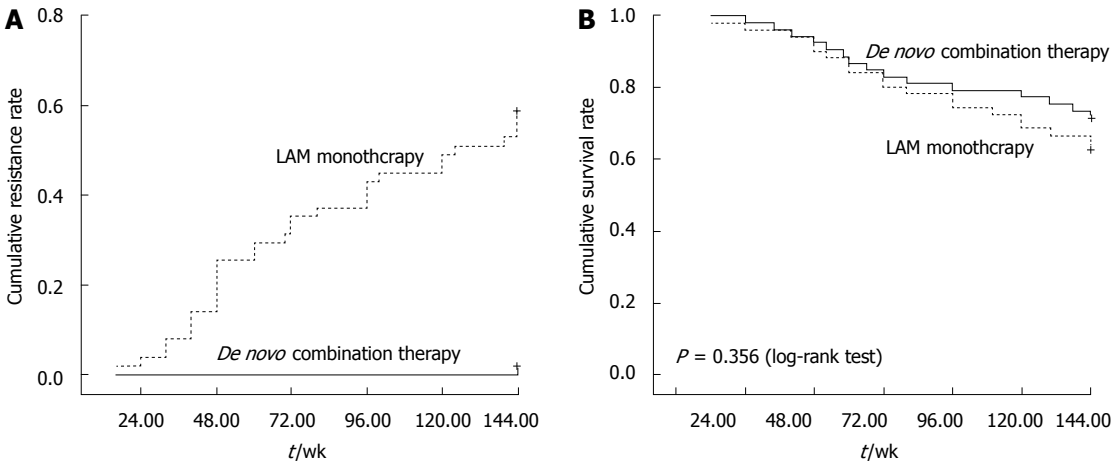

Figure 2 Kaplan-Meier analysis of cumulative resistance (A) and survival (B) rate in patients with hepatitis B virus-related decompensated cirrhosis on *de novo* lamivudine and adefovir dipivoxil combination therapy and lamivudine monotherapy. A: No resistance occurred in *de novo* combination group up to 144 wk. The cumulative resistance rate in lamivudine monotherapy group at weeks 48, 96 and 144 was 20%, 36.8% and 56.9%, respectively; B: The cumulative survival rate in *de novo* combination group was 91.4%, 81.6% and 75.7% at weeks 48, 96 and 144, respectively. The cumulative survival rate in lamivudine monotherapy group was 90.6%, 81.6% and 72.8%, respectively.

Table 2 Comparison of change in hepatic and renal function between two treatment groups (mean ± SD)

Characteristics	*De novo* combination group				Lamivudine monotherapy group			
	Baseline	48 wk	96 wk	144 wk	Baseline	48 wk	96 wk	144 wk
Hepatic function								
Albumin (g/dL)	3.2 ± 0.7	3.5 ± 0.4	3.8 ± 0.1	4.1 ± 0.3[a]	3.3 ± 0.6	3.4 ± 0.3	3.6 ± 0.8	3.8 ± 0.3[c]
TBIL (μmol/L)	38.5 ± 12.1	24.3 ± 11.4	20.4 ± 10.8	16.1 ± 6.7[a]	37.8 ± 11.9	26.5 ± 12.3	23.2 ± 10.5	18.1 ± 12.3
PT (s)	17.1 ± 4.5	14.5 ± 5.3	13.3 ± 9.1[a]	11.4 ± 5.8[a]	17.6 ± 3.1	15.4 ± 3.5	14.5 ± 6.9	13.4 ± 5.8[c]
CTP score	8.9 ± 2.1	7.0 ± 1.2	6.3 ± 2.7[a]	5.7 ± 1.9[a]	8.8 ± 1.7	7.6 ± 2.4	6.6 ± 1.9	6.1 ± 3.8
MELD score	12.4 ± 3.7	10.0 ± 6.5	9.6 ± 5.3	8.8 ± 2.7[a]	11.9 ± 2.5	10.8 ± 3.7	8.9.7 ± 4.8	8.9 ± 4.3
Renal function								
BUN (mmol/L)	6.7 ± 0.7	6.8 ± 1.4	7.1 ± 1.1	6.9 ± 0.3	6.8 ± 0.6	7.4 ± 1.3	7.2 ± 0.8	7.0 ± 1.1
Cr (μmol/L)	96.1 ± 12.3	98.3 ± 8.9	97.8 ± 10.7	99.7 ± 9.6	95.6 ± 12.1	97.8 ± 7.9	98.6 ± 12.7	99.5 ± 9.7
GFR (mL/min)	115.2 ± 34.5	112.8 ± 56.3	103.4 ± 76.1	109.1 ± 21.5	113.5 ± 22.9	107.6 ± 13.4	112.4 ± 45.5	109.4 ± 13.4

[a]$P < 0.05$ *vs* baseline combination group; [c]$P < 0.05$ *vs* lamivudine monotherapy group. TBIL: Total bilirubin; PT: Prothrombin time; CTP: Child-Turcotte-Pugh score, MELD: Model for End-Stage Liver Disease; BUN: Blood urine nitrogen; Cr: Creatinine; GFR: Glomerular filtration rate.

normalization rate was 64.6% (42/65) by week 48, 73.7% (42/57) by week 96, and 80.4% (41/51) by week 144, respectively. Compared to *de novo* combination therapy group, ALT normalization rates were lower in monotherapy group by weeks 96 and 144 ($P = 0.026$ and 0.037).

Drug resistance

No patient in the *de novo* combination group exhibited detectable resistance within 144 wk. The cumulative resistance rate in monotherapy group at weeks 48, 96 and 144 was 20%, 36.8%, and 56.9%, respectively as shown in Figure 2A, significantly higher compared to *de novo* combination group.

Change in hepatic function

Through week 144, both *de novo* combination group and monotherapy group achieved improvement in hepatic function, as evaluated by change from baseline in serum albumin, total bilirubin, prothrombin time; the degree of improvement in *de novo* combination group for albumin and prothrombin at week 144 was superior to monotherapy group, as shown in Table 2.

Both *de novo* combination and monotherapy groups demonstrated an improvement in CTP and Model for End-Stage Liver Disease (MELD) scores at weeks 48, 96 and 144. The mean change from baseline in CTP scores was -1.9, -2.6, and -3.2 at weeks 48, 96 and 144, respectively, for *de novo* combination group, and -1.7, -2.2 and -2.7 at weeks 48, 96, and 144, respectively, for monotherapy group. As a result, 45 (84.9%) of cirrhosis patients in *de novo* combination therapy group achieved CTP class A (score 5 or 6) after 144 wk of treatment, whereas in monotherapy group 68.6% (35/51) of patients achieved CTP class A after 144 wk.

The mean change from baseline in MELD scores was -2.4, -3.2, and -4.0 at weeks 48, 96, and 144, respectively, for *de novo* combination group, and -1.8, -2.3, and -3.0 at weeks 48, 96 and 144, respectively, for monotherapy group as shown in Table 2.

The 70 patients with decompensated cirrhosis in *de novo* combination therapy group exhibited a cumulative HCC incidence of 3.1% at week 48, 5.3% at week 96,

and 7.5% at week 144, respectively; four patients developed HCC during the follow-up period. In monotherapy group, the cumulative incidence of HCC was 3.1%, 7.0% and 9.8% at weeks 48, 96 and 144, respectively; five patients developed HCC during the follow-up period. In addition, the cumulative mortality or orthotopic liver transplantation rate was 8.6%, 18.4% and 24.3% at weeks 48, 96 and 144, respectively in *de novo* combination group, and 9.4%, 18.4% and 27.2% at weeks 48, 96 and 144, respectively, in the monotherapy group, as shown in Figure 2B.

Side effects

All patients in this study tolerated both the *de novo* combination therapy and monotherapy. No patient in either group discontinued the treatment during the follow-up period. In the *de novo* combination group, the blood urine nitrogen (BUN) of three patients increased to 8.6, 9.1 and 9.7 mmol/L respectively, without a concomitant increase in creatinine levels. BUN level of these patients were normalized during the follow-up period. The creatinine levels and glomerular filtration rate remained normal in all patients during the follow-up period, as shown in Table 2.

DISCUSSION

A consensus on the benefit of antiviral therapy for HBV-related cirrhosis has been achieved. Liaw *et al*[11] reported that continuous treatment with LAM delays clinical progression in patients with CHB and advanced fibrosis or cirrhosis by significantly reducing the incidence of hepatic decompensation and risk of HCC. However, LAM exhibits a high incidence of resistance mutations compared to other nucleos(t)ide analogs. The current CHB treatment guidelines advocate initial combination therapy or agents with a high genetic barrier for patients with a high risk of developing drug resistance and potentially life-threatening associated diseases, such as HBV-related liver cirrhosis[12-14]. A combination with other drugs that do not share cross resistance may promote or exhibit synergistic antiviral effects; most importantly, it may exhibit the potential to prevent resistance. Ghany *et al*[15] recently reported that extended combined therapy with LAM and ADV was associated with a high rate of long-term virological and biochemical response; none of the 22 combination therapy treated CHB patients developed resistance for up to 192 wk. Fan *et al*[16] demonstrated that *de novo* combination therapy with LAM and ADV was superior to add-on combination therapy in terms of CTP score, virus inhibition, and renal function. In this study, for patients with HBV-related decompensated liver cirrhosis, *de novo* combination therapy resulted in a superior virological response than monotherapy at weeks 96 and 144. The cumulative tyrosinemethionine-aspartic acid-aspartic acid resistance rate was higher in monotherapy group by weeks 48, 96 and 144, whereas none of the *de novo* combination therapy treated patients developed resistance during the follow-up period.

Higher HBeAg seroconversion rates and ALT normalization rates were also observed in *de novo* combination group compared to LAM monotherapy group at weeks 96 and 144. It is well known that HBeAg seroconversion is accompanied by biochemical and histological regression of liver diseases. Previous studies have indicated that combination therapy is efficacious in preventing drug resistance, but does not improve virological and serological response[17]. Our results and other studies suggest that *de novo* combination therapy can not only prevent drug resistance, but also improve virological and serological response[15,16]. Further elucidation concerning the mechanisms underlying the higher negative rates of HBV DNA and higher rates of HBeAg seroconversion by *de novo* combination therapy is warranted. In general, patients with CHB-related liver cirrhosis exhibit lower levels of HBV DNA and HBeAg compared with patients with CHB. Alternatively, during the course of HBV-related liver cirrhosis, the antiviral immune response is vigorously activated. In concordance with the findings of previous studies, the results that we present in this study suggest that *de novo* combination therapy is potentially suitable as an initial treatment for HBV-related decompensated liver cirrhosis in order to reduce resistance.

Previous clinical studies have demonstrated the positive effects of LAM therapy on the functional improvement in patients with HBV-related decompensated liver cirrhosis[4,5,18]. However, these benefits were offset due to drug-resistance. The CTP and MELD scores, both of which reflect components of liver function, including serum albumin, total bilirubin, and prothrombin time, were markedly improved during *de novo* combination therapy. These results clearly indicate that due to inhibition of HBV replication, *de novo* combination treatment potentially prevents clinical progression to liver failure, reduces complication risk, and delays or avoids the need for liver transplantation.

Renal impairment is a known risk of severe liver disease and is considered a potential side effect of *de novo* combination therapy. In this study, both *de novo* combination and monotherapy were well-tolerated, with no case of renal failure attributable to combination therapy.

This study has several limitations. It was not randomized or blinded, as this would be difficult for patients with CHB-related decompensated liver cirrhosis. This may contribute to the discord in results among previous studies.

In conclusion, this study demonstrated that *de novo* combination therapy is superior to monotherpy in suppressing HBV DNA and achieving ALT normalization and HBeAg seroconversion by weeks 96 and 144. Both treatments improved liver function as measured by reduction of CTP and MELD scores. In HBV-related decompensated liver cirrhosis patients, *de novo* combination therapy has also been proven safe. Our findings strongly support *de novo* combination therapy as a viable and effective therapeutic strategy in patients with HBV-related decompensated liver cirrhosis.

COMMENTS

Background

The mortality rate of hepatitis B virus (HBV)-related decompensated cirrhosis is very high. Recommended treatment options are nucleos(t)ide analogues. There are few reports regarding the issue of treatment for these patients with *de novo* combination therapy or monotherapy.

Research frontiers

In China, tenofovir is not available yet and entecavir is expensive for most patients. Combination therapy with lamivudine (LAM) and adefovir dipivoxil (ADV) is better than ADV in LAM-resistance chronic hepatitis B (CHB) patients. But in patients with HBV-related decompensated live cirrhosis, it remains unclear whether *de novo* combination therapy is better than monotherapy. In this study, the authors demonstrate that LAM and ADV *de novo* combination therapy is more effective than LAM monotherapy for patients with HBV-related decompensated liver cirrhosis.

Innovations and breakthroughs

Many clinical studies showed that the combined LAM and ADV therapy is more effective than ADV monotherapy after LAM-resistance. However, the efficacy of *de novo* LAM and ADV combination therapy in patients with HBV-related decompensated liver cirrhosis is unclear. This is the first study to report that *de novo* LAM and ADV is more effective than LAM monotherapy, especially the combination therapy can reduce the drug resistance.

Applications

By understanding that LAM and ADV *de novo* combination therapy is more effective than LAM monotherapy in patients with HBV-related decompensated liver cirrhosis, this study may represent a future strategy for therapeutic intervention in CHB patients with HBV-related decompensated liver cirrhosis.

Terminology

De novo combination therapy means combination with two or more drugs form the beginning of the treatment. The diagnosis of decompensated liver cirrhosis was based on clinical, laboratory, previous histological, ultrasonographic and radiological signs of cirrhosis with Child-Turcotte-Pugh (CTP) score. The CTP score is a system to assess the disease stage for decompensated cirrhotic patients.

Peer review

This is a good clinical study in which the authors compared the effect of *de novo* LAM and ADV combination therapy with LAM monotherapy. The authors concluded that LAM and ADV should be combined at the beginning for treatment of the patients with HBV-related decompensated liver cirrhosis.

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