Monotherapy versus combinations of nucleos(t)ide in treatment-naive hepatitis B decompensated cirrhotic patients: A nested case-control study

Lei Li¹#, Wei Liu²#, Yuhan Chen¹, Peng Li¹, Feili Wei³, Chunlei Fan¹, Peiling Dong¹, Bing Li¹, Dexi Chen³ and Huiguo Ding¹*  

¹Department of Gastroenterology and Hepatology, Beijing You'an Hospital Affiliated with Capital Medical University, Beijing 100069, China.  
²Department of Internal Medicine, Beijing Ji Shui Tan Hospital Affiliated with Peking University, Beijing, Beijing 100035, China.  
³Viral Laboratory of Liver Diseases Research Institute, Capital Medical University, Beijing 100069, China.  

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The data are limited on the long-term clinical outcome of monotherapy versus combinations of nucleos(t)ide analog (NUCs) for hepatitis B related decompensated cirrhotic patients. This study was to evaluate the efficacy in treatment-naive patients using NUCs monotherapy or combinations. Three hundred and six patients with decompensated hepatitis B cirrhosis were selected from cirrhosis cohort and divided into treatment-naive (n = 260) and control groups (n = 46). Antiviral therapies included monotherapy of lamivudine (LAM, n = 39), adefovir (ADV, n = 73), telbivudine (LDT, n = 36), entecavir (ETV, n = 48), and combinations of LAM+ADV (n = 39) or LDT+ADV (n = 25). Of these patients, 193 in antiviral therapy and 39 control group were included for analysis over two years. The cumulative drug-resistance rate at two year was higher in the LAM (37.9%), ADV (21.2%), LDT (23.3%) than in the ETV monotherapy (2.6%), and with combinations of LAM+ADV (8.7%) or LDT+ADV (6.3%), respectively, P < 0.001. Serum hepatitis B virus (HBV) DNA undetectability in the ETV and the LDT+ADV group was higher than in the LAM, ADV and LAM+ADV group at over two years (P < 0.05). The child-pugh score (CPs) in the antiviral therapy group was decreased at two years (P < 0.05). In the control group and drug-resistant patients, however, CPs was increased. The two years cumulative incidence of liver failure in the antiviral therapy group was significantly less than the control group (OR 24.9, 95%; CI 6.5 to 94.7, P = 0.001). The total cumulative survival rate in the antiviral therapy group was higher than in control group (OR 4.2, 95%; CI 1.4 to 12.9, P = 0.017). The combinations of NUCs therapy and ETV monotherapy are optimum management for hepatitis B related decompensated cirrhotic patients.

Key words: Hepatitis B, decompensated cirrhosis, nucleos(t)ide analogs, hepatocellular carcinoma, drug resistance.

INTRODUCTION

Chronic hepatitis B virus (HBV) infections, the main etiology of liver cirrhosis and hepatocellular carcinoma

*Corresponding author. E-mail: dinghuiguo@medmail.com.cn. Tel: 8610-83997155. Fax: 8610-63295525.  
#These authors contributed equally to this work.
(HCC) remain a major public health problem worldwide, especially in China (Lok and McMahon, 2009; Liaw et al., 2008; Tanaka et al., 2011). After infection with HBV, the cumulative 5-year incidence of liver cirrhosis is 8 to 20%; among these cases, the annual incidence of HCC is 2 to 5% (Tanaka et al., 2011; Tan, 2011; Asia-Pacific Working Party on Prevention of Hepatocellular Carcinoma, 2010). The most effective methods to prevent HCC is to control HBV infection through vaccination (Asia-Pacific Working Party on Prevention of Hepatocellular Carcinoma, 2010; Lim et al., 2009). In patients already infected with HBV, antiviral therapy remains the best strategy to prevent liver cirrhosis and HCC (Lim et al., 2009; Chan et al., 2012; Kwon and Lok, 2011; Kim et al., 2011). Major progress in the treatment of chronic hepatitis B has recently been made during the last decade with the development of antiviral drugs, especially nucleos(t)ide analogs (NUCs) (Fung et al., 2011; Liaw et al., 2011; Zhang et al., 2011). Some data supporting the benefit of antiviral therapy on the prevention of HCC in chronic hepatitis B patients has been shown in a few randomized controlled trials (Zhang et al., 2011; Jin et al., 2011; Lim et al., 2011; Tujios and Lee, 2012). Nonetheless, antiviral drug resistance is important in determining the success of long-term therapy for chronic hepatitis B patients (Yeh et al., 2011; Papatheodoridis et al., 2010).

In recent clinical study data, the development of resistance to NUCs is associated with exacerbation of liver disease, including development of cirrhosis and HCC (Yeh et al., 2011), in addition, the risk of HCC remains high in HBV-related cirrhosis in patients who are treatment-naïve using NUCs (Papatheodoridis et al., 2010). Decompensated cirrhosis is an end-stage characterized by high mortality and extremely high risk of HCC. In HBV-related decompensated cirrhosis patients, antiviral therapy using NUCs is recommended by global guidelines from 2005 (Liaw et al., 2008; Chinese Medical Association, 2005; Jhaveri and Murray, 2007; European Association For The Study of The Liver (EASL), 2009). However, antiviral therapy for decompensated cirrhosis patients is still a problem for clinicians because of the lack of clinical evidence-based data. In recent clinical studies (Liaw et al., 2011), ETV and LAM had similar effects on one-year mortality. However, more patients taking ETV tended to attain ALT normalization, HBV-DNA undetectability, and reduction of the model for end-stage liver disease scores, with no drug resistance. Therefore, ETV was recommended as the first-line monotherapy for patients with HBV-related decompensated cirrhosis because of low drug-resistance (Tujios and Lee, 2012; Jhaveri and Murray, 2007; Singal and Fontana, 2001). However, data are limited on the long-term safety, effectiveness and HCC incidence of ETV monotherapy versus combinations of NUCs in HBV-related decompensated cirrhotic patients. Therefore, the aim of this study was to evaluate the long-term outcome in patients with HBV-related decompensated cirrhosis treatment-naïve using NUCs in real-life clinical practice.

MATERIALS AND METHODS

Patients

The clinical records of 306 patients from hepatitis B-related decompensated cirrhosis cohort from January, 2008 to December, 2011 were enrolled. The clinical parameters of gender, age, presence of liver cirrhosis with portal hypertension, alcohol abuse, and HCC family history were recorded. All patients were positive for hepatitis B surface antigen (HBsAg). No patient had detectable liver tumors (except hemangiomias and cirrhotic regenerative nodules) prior to entry into this cohort study. A diagnostic workup of decompensated liver cirrhosis was performed, including a clinical manifestation, physical examination, and laboratory tests according to the criteria suggested by the Chinese Medical Association in 2005 for liver diseases (Chinese Medical Association, 2005). These included (1) chronic hepatitis B history and/or signs; (2) abnormal liver function accompanied by portal hypertension, such as hepatic encephalopathy, ascites or variceal bleeding with child-pugh scores (CPs) score ≥ 7; (3) B-ultrasound scanning (LOGIQ9, GE Company, USA) and CT (GE HISPEED DXI, GE company, USA) consistent with the signs of liver cirrhosis without images of liver cancer; and (4) no NUCs medicine taken prior to study entry. No patients met the exclusion criteria of (1) any co-infection, such as hepatitis A virus, hepatitis C virus, hepatitis E virus, hepatitis D virus, Epstein-Barr virus, cytomegalovirus and human immunodeficiency virus (HIV) or bacterial infections; (2) long-term use of liver toxicity drug; (3) HCC or metastatic liver cancer; (4) poor compliance and uncontrolled serious cardio-vascular, respiratory, digestive and nervous system diseases; (5) pregnant or lactating; (6) CPs ≥ 12. Alcohol abuse was defined as in this study (1) alcohol abuse more than 5 years; or (2) drinking equivalent to ethanol ≥ 40 g/d for men or ≥ 20 g/d for women, or heavy drinking in recent 2 weeks equivalent to ethanol≥80 g/d.

The study protocol was approved by the Ethical Committee of Beijing YouAn Hospital, Capital Medical University. Investigators explained the study in detail to all patients and/or their relatives. Consent forms were obtained from all participants when they were recruited.

Study endpoints

Endpoints of these patients were death, liver transplantation, loss follow-up, and or HCC diagnosed according to the criteria suggested by the Chinese Anticancer Association (2001). The diagnostic criteria of HCC were (1) serum AFP > 400 ng/ml and B-ultrasound and CT positive findings; or (2) serum AFP < 400 ng/ml and B-ultrasound and CT scanning positive findings or echoguided liver biopsy pathology positive findings. Serum AFP was tested by electrochemiluminescence (Abbott Ltd, USA).

Antiviral therapies

In HBV-related decompensated cirrhotic patients of this cohort, antiviral therapies were included monotherapy of lamivudine (LAM) 100 mg/d, adefovir (ADV)10 mg/d, telbivudine (LDT) 600 mg/d, or entecavir (ETV) 0.5 mg/d; or combinations of LAM 100 mg/d and ADV 10 mg/d (LAM ADV), or LDT 600 mg/d and ADV 10 mg/d (LDT ADV) according to the clinician real-life practices. We divided 306 patients into an antiviral therapy group (n = 260) and a control group (n = 46). The antiviral therapies were LAM (n = 39), ADV (n = 73), LDT (n = 36), ETV (n = 48), LAM+ADV (n = 39), and LDT+ADV (n = 25). Patients were followed up every 3 months and virology, biochemical and clinical parameters were obtained. Of these patients, 74 were excluded because of less than 24 months of follow-up; thus, 193 patients in the antiviral therapy group and 39 in
Enrolled patients (n=306)

Antiviral group (n=260)
- LAM (n=39)
- ADV (n=73)
- LDT (n=36)
- ETV (n=48)
- LAM+ADV (n=39)
- LDT+ADV (n=30)

Control group (n=46)
- Control (n=44)
- Control (n=39)

67 (follow-up <24m or lost) were excluded
193 were included in the analysis

Figure 1. A flow chart of enrolled patients.

the control group were included for analysis (Figure 1). Antiviral therapies patients were subdivided into a drug-resistant group (n = 34) and complete virological response (CVR) group (n = 159) according to whether drug-resistance before they reached endpoints. All patients also received individual supporting treatment to prevent complications, for example, correcting water and electrolyte balance; infusion of albumin, plasma, or antibiotics for bacterial infections.

Assessment of liver and renal function
Parameters of liver and renal biochemical profiles, such as alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBIL), albumin, blood urea nitrogen (BUN), creatinine level (Cr), and creatinine kinase (CK) were tested with an Olympus automatic biochemical analyzer (Olympus AU640, Japan). Prothrombin time (PT) and prothrombin activity (PTA) were measured by blood coagulation analyzer (AcL Top, Beckman Coulter, USA). Child-Pugh score (CPs) was calculated according to the parameters (Committee of Liver Cancer, Chinese Anti-cancer Association, 2001). Liver failure was diagnosed including a clinical manifestation, physical examination, and laboratory tests according to the criteria suggested by the Chinese Medical Association for Liver Diseases (Chinese Medical Association, 2005).

Virology assay
Serum hepatitis B markers were detected by electrochemiluminescence immunoassay using a Roche E170 modular immunoassay analyzer following the manufacturer’s protocols (Roche Diagnostics, Germany). The serum HBV-DNA was quantified by real-time polymerase chain reaction (PCR) (FQ-PCR Kit, DaAn Gene Co., China) using a GeneAmp 5700 Sequence Detection System (PE Applied Biosystems, USA). The lower limit of HBV DNA detection was 500 copies/ml. The CVR was defined as the HBV-DNA undetectability and ALT normalization in 24 weeks after antiviral therapies. The HBV DNA-negative (undetectability) was defined as serum HBV DNA < 500 copies/ml twice for two consecutive months.

Antiviral resistance
Antiviral resistance was defined as the conversion of HBV DNA to a positive, namely virologic rebound or the detection by sequence analysis of mutations know to be related to drug resistance during NUCs treatment. Rescue treatment was performed if antiviral resistance or serum HBV DNA was sustained as positive over the course of 24 weeks of therapy according to guidelines (Chinese Medical Association, 2005; European Association For The Study of The Liver (EASL), 2009).

Detection of HBV polymerase sequence
Serum HBV DNA was extracted according to the instructions of a commercial kit (Qiagen Blood Kit, USA), using Platinum Taq DNA polymerase high fidelity (Invitrogen, USA) for nested PCR amplification. The first round of the primer sequences were: P54: 5’-TYCCCTGTTGTTGGCT CCAAGTTCC-3’ (nt54-75), P1287: 5’- CATACTGGAACCTCTAGGC-3’ (nt1267-1287). The second round of primer sequences were: P253: 5’
Table 1. Clinical characterizations of enrolled patients at baseline.

<table>
<thead>
<tr>
<th>Group</th>
<th>Gender (M/F)</th>
<th>Age (year)</th>
<th>FHH (%)</th>
<th>AA (%)</th>
<th>CPs</th>
<th>qHBVDNA (log)</th>
<th>HBeAg(+) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAM (n=29)</td>
<td>20/9</td>
<td>50.5±10.1</td>
<td>20.6</td>
<td>13.7</td>
<td>8.3±1.7</td>
<td>4.9±1.8</td>
<td>65.5</td>
</tr>
<tr>
<td>ADV (n=57)</td>
<td>41/16</td>
<td>48.7±10.2</td>
<td>19.3</td>
<td>12.3</td>
<td>8.1±2.4</td>
<td>4.7±1.8</td>
<td>66.7</td>
</tr>
<tr>
<td>LDT (n=30)</td>
<td>19/11</td>
<td>52.5±13.7</td>
<td>16.7</td>
<td>10.0</td>
<td>8.0±2.5</td>
<td>4.6±2.0</td>
<td>56.7</td>
</tr>
<tr>
<td>ETV (n=38)</td>
<td>29/9</td>
<td>54.7±11.8</td>
<td>23.7</td>
<td>13.1</td>
<td>7.8±1.9</td>
<td>5.1±1.9</td>
<td>60.5</td>
</tr>
<tr>
<td>LAM+ADV (n=23)</td>
<td>15/8</td>
<td>54.9±13.6</td>
<td>21.7</td>
<td>13.0</td>
<td>8.6±2.3</td>
<td>5.0±1.8</td>
<td>65.2</td>
</tr>
<tr>
<td>LDT+ADV (n=16)</td>
<td>11/5</td>
<td>51.7±12.6</td>
<td>18.7</td>
<td>12.5</td>
<td>8.3±2.5</td>
<td>4.8±1.6</td>
<td>68.7</td>
</tr>
<tr>
<td>Control (n=39)</td>
<td>24/15</td>
<td>52.2±10.8</td>
<td>17.9</td>
<td>10.2</td>
<td>7.8±2.0</td>
<td>4.9±1.7</td>
<td>64.5</td>
</tr>
</tbody>
</table>

FHH: family history of hepatitis B, AA: alcohol abuse, qHBVDNA: quantified HBV-DNA, CPs: Child-Pugh score

Table 2. Summary of the frequency of ascites, hospitalization, CPs in the course of antiviral therapies over 2 years.

<table>
<thead>
<tr>
<th>Group</th>
<th>CPs at baseline</th>
<th>CPs at 2-year</th>
<th>Frequency of ascites per year (time)</th>
<th>Frequency of hospitalization per year (time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAM (n=29)</td>
<td>8.5±1.9</td>
<td>7.0±2.3*</td>
<td>1.8±0.9</td>
<td>1.8±1.1</td>
</tr>
<tr>
<td>ADV (n=57)</td>
<td>8.0±2.1</td>
<td>6.1±1.7*</td>
<td>1.7±1.2</td>
<td>1.8±1.2</td>
</tr>
<tr>
<td>LDT (n=30)</td>
<td>8.3±2.2</td>
<td>6.2±1.9*</td>
<td>1.8±0.8</td>
<td>1.8±1.2</td>
</tr>
<tr>
<td>ETV (n=38)</td>
<td>8.5±2.0</td>
<td>6.7±1.6*</td>
<td>1.5±1.3</td>
<td>1.6±0.6</td>
</tr>
<tr>
<td>LAM+ADV (n=23)</td>
<td>8.7±2.4</td>
<td>6.4±1.5*</td>
<td>1.6±0.8</td>
<td>1.8±1.1</td>
</tr>
<tr>
<td>LDT+ADV (n=16)</td>
<td>8.4±2.2</td>
<td>6.2±1.6*</td>
<td>1.4±0.6</td>
<td>1.3±1.0**</td>
</tr>
<tr>
<td>DR (n=34)</td>
<td>8.4±2.5</td>
<td>9.0±2.7</td>
<td>1.98±1.0</td>
<td>2.42±0.9</td>
</tr>
<tr>
<td>CVR (n=159)</td>
<td>8.6±1.9</td>
<td>6.0±1.6**</td>
<td>1.16±0.8**</td>
<td>0.63±0.4**</td>
</tr>
<tr>
<td>Control (n=39)</td>
<td>7.9±2.1</td>
<td>9.2±2.6</td>
<td>2.1±1.1</td>
<td>2.6±1.7</td>
</tr>
</tbody>
</table>

DR: Drug resistance, CVR: complete virological response, CPs: Child-Pugh score *compared with baseline, P < 0.05; **compared with control, P<0.05.

Safety assessment

Abnormal renal functions were defined as serum BUN level > 7 mmol/L and serum Cr > 106 umol/L (upper limit of normal range). Abnormal CK was defined as serum CK level > 170 U/L (upper limit of normal range).

Statistical analysis

Parametrical data were expressed in means with standard deviations (SD) when normal distribution was assumed. Statistical analysis was conducted using statistical package for social sciences (SPSS) (version 16.0). A student's t-test, analysis of variance and log-rank test were used to compare means between groups. A 2-test was used for analysis when appropriate. Logistic regression analysis was performed to evaluate the association of variables with death or liver failure. The Kaplan-Meier method was used to estimate the accumulative survival. Differences were considered to be significant if P < 0.05.

RESULTS

Clinical characteristics

No difference in gender, age, family history of hepatitis B, alcohol abuse, CPs or HBeAg positive and HBV DNA level was seen between groups at baseline (P > 0.05; Table1). HBeAg-positive patients were accounted for 63.7%. According to whether drug-resistance occurred by 2 years, 34 (17.6%) patients had antiviral resistance and were regarded as a drug-resistant group.

Rescue therapies

The rescue therapy at 2 years was higher in the LAM, ADV and LDT monotherapy than in ETV monotherapy or combinations of NUCs (Figure 2A). This suggested that ETV monotherapy and combinations of NUCs were superior to LAM, ADV, and LDT monotherapy.

Child-pugh score

The CPs of each antiviral therapy group was significantly decreased at one and two years, compared with baseline (P < 0.05) (Table 2). In the control group and drug-resistant
resistant patients, however, CPs was increased at 2 years (P > 0.05).

Virological response

The patients of monotherapy with ETV and the combinations of LDT+ADV showed a significant decline in HBV DNA level compared to baseline in 12 weeks (Figure 2B) (P < 0.05). HBV DNA undetectability in ETV group and LDT+ADV group was higher than in LAM, ADV and LAM+ADV group at one year (P < 0.05). HBeAg seroconversion and loss were shown in Table 3. The combinations of LDT+ADV therapy had a higher HBeAg loss at one-year (63.6%), and two-year (72.7%) than LAM, ADV, or ETV monotherapy. HBV DNA undetectability for the combinations of LDT+ADV therapy was similar to ETV monotherapy over the 2 years.

Drug resistance

The two-year cumulative drug-resistance rate in LAM, ADV, LDT, ETV, LAM+ADV, and LDT+ADV groups were 37.9, 21.1, 23.3, 2.6, 8.7, and 6.3%, respectively. The two-year cumulative drug-resistance rate of ETV monotherapy and combinations of NUCs were significantly lower than for the LAM (OR 22.6, 95%; CI =
Abnormal BUN and Cr in the antiviral therapy group were not significantly changed in the course of treatment over two years compared to baseline (P > 0.05). Eleven patients had elevated CK in the course of antiviral therapy (Table 3).

**Prognosis**

The cumulative survival rate in the drug-resistant, CVR and control group was 91.2, 96.9, and 84.6%. The total cumulative survival rate in the antiviral therapy group was significantly higher than in the control group (Figure 2C) (OR 4.2, 95%; CI 1.4 to 12.9, P = 0.017). No significant difference was seen in two years survival between the drug-resistant group and CVR group (P = 0.132). In the course of the two-year follow-up, eight patients died in the antiviral therapy group. Of those, four died of chronic liver failure, three of HCC, and one of hepatorenal syndrome. Six patients died in the control group, three of chronic liver failure, two of HCC, and one of hepatorenal syndrome. By logistic regression analysis, HCC and liver failure were independent risk factors for predicting poor prognosis in two years (HCC: 95%; CI 2.8 to 37.5, P < 0.001; and liver failure 95%; CI 2.9 to 49.4, P = 0.001). However, no statistically significant difference was seen between mutations related drug-resistance and occurrence of HCC (P > 0.05, Table 4). The cumulative incidence of liver failure in drug-resistant, CVR and control groups were 5.9, 0.6, and 28.2%. The two-year cumulative incidence of liver failure in the antiviral therapy group was significantly less than the control group (OR 24.9, 95%; CI 6.5 to 94.7, P = 0.001).

**Frequency of actites and hospitalization**

The frequency of actites per year in the LDT+ADV group was lower (1.4 ± 0.6), but not significantly different than the control group (P = 0.608). The frequency of hospitalization per year in the LDT+ADV group was lower (1.3 ± 1.0) than the control group (Table 2) (P = 0.021, 95%; CI 0.759 to 3.086). The main reasons for hospitalization were liver failure, esophageal variceal bleeding or HCC.

**Safety**

Abnormal BUN and Cr in the antiviral therapy group were not significantly changed in the course of treatment over two years compared to baseline (P > 0.05). Eleven patients had elevated CK in the course of antiviral therapy (Table 3).

**DISCUSSION**

HBV infection remains a global public health problem. The geographical distribution of the rates of chronic HBV infection and HCC are strikingly parallel. The incidence rate and mortality of HBV-related cirrhosis and HCC, however, have significantly increased (Lok and McMahon, 2009; Liaw et al., 2008; Tanaka et al., 2011). To date, the reasons and mechanisms of the different clinical outcomes after HBV infection are still unknown. Substantial clinical evidence shows that the differences in clinical outcomes after HBV infection might be related to HBV DNA level, antiviral treatment response, and immune activation (Ohishi and Chayama, 2012; Di Marco et al., 2005; Bae et al., 2005). All guidelines for the prevention and treatment of chronic hepatitis B both in China and in other countries clearly state that the main aim of treatment for chronic hepatitis B is to bring down the incidence rate and death rate of liver cirrhosis and liver cancer, to prolong life and to improve living conditions (Tujios and Lee, 2012; European Association for the Study of the Liver, 2012). However, for patients with liver cirrhosis, especially those in the decompensation period, clinical outcomes after antiviral therapy with nucleoside analogs are unclear (Kwon and Lok, 2011; Das et al., 2010; Manolakopoulos et al., 2009). NUCs are effective drugs for the suppression of HBV reproduction and a good compliance in most chronic hepatitis B patients, especially in HBV-related cirrhosis patients. Optimizing antiviral drugs for decompensated HBV-related cirrhosis still remains a difficult problem for clinicians.

Di Marco first reported the clinical effect of LAM treatment with 59 cases of HBV-related cirrhosis (45 child-Pugh with A and 4 with B), showing that a sustained suppression of HBV DNA significantly improved the prognosis of patients with liver cirrhosis (Di Marco et al., 2005). Bae reported that 58.2% of patients showed complete antiviral responses using LAM in decompensated HBV-related cirrhosis, which can improve the clinical prognosis (Bae et al., 2005). However, the failure of antiviral treatment or drug resistance are dangerous factors for liver disease progression and increase the incidence of liver cancer (Yeh et al., 2011; Zoulim, 2011). A single randomized double-blind controlled trial of LAM in patients with HBeAg and/or high serum HBV DNA levels showed that antiviral therapy prevented disease progression and reduced the incidence of HCC (Liaw et al., 2011; Nishida et al., 2008). By comparing the clinical efficacy and safety of LDT and LAM in chronic HBV hepatitis, found similar results (Hann, 2010). Therefore, LDT is still suggested to be safe for patients with HBV-related decompensated cirrhosis. For choosing NUCs, however, ETV has a potent antiviral effect and low rates of drug resistance and is the first-line monotherapy for patients with HBV-related decompensated cirrhosis by updated guidelines and publications (Tujios and Lee, 2012; Singal and Fontana, 2001; Keating, 2011). In this study, we found HBV DNA undetectability in ETV
monotherapy and combination LDT+ADV therapy group was higher than in LAM, ADV, and LDT monotherapy over two years. Rescue therapy rates at two years were higher in the LAM, ADV, and LDT monotherapy groups, at 37.9, 21.1, and 23.3%, respectively. However, a recent clinical study found that cirrhotic complications cannot be avoided and reversed with potent antiviral suppression of HBV-DNA by rescue therapy (Yeh et al., 2011). Therefore, optimizing antiviral drugs for treatment-naive HBV-related patients is very important. The combinations LDT+ADV had a higher HBeAg loss rate (63.6% at one year, 72.7% at two years) than the LAM, ADV, and ETV monotherapy in this study. The HBeAg loss with antiviral treatment of chronic hepatitis B are important indications of substantial virological response (Lok and McMahon, 2009; Liaw et al., 2008; Tanaka et al., 2011; Tan, 2011). However, the clinical implications of HBeAg loss in HBV-related cirrhosis, especially for decompensated patients, still remains unclear. No change in renal function related to antiviral drugs was found in the two-year follow-up. These data strongly suggested that ETV monotherapy and combinations of NUCs are superior to LAM, ADV, or LDT

<table>
<thead>
<tr>
<th>Mutations</th>
<th>HCC (n=10)</th>
<th>non-HCC (n=24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rtM204V</td>
<td>+</td>
<td>2(20.0%)</td>
<td>0(0.0%)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>8(80.0%)</td>
<td>24(100.0%)</td>
</tr>
<tr>
<td>rtM204I</td>
<td>+</td>
<td>0(0.0%)</td>
<td>7(29.2%)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>10(100.0%)</td>
<td>17(70.8%)</td>
</tr>
<tr>
<td>rtA181T</td>
<td>+</td>
<td>3(30.0%)</td>
<td>3(12.5%)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>7(70.0%)</td>
<td>21(87.5%)</td>
</tr>
<tr>
<td>rtL180M</td>
<td>+</td>
<td>1(10.0%)</td>
<td>3(12.5%)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>9(90.0%)</td>
<td>21(87.5%)</td>
</tr>
<tr>
<td>rtL80I</td>
<td>+</td>
<td>0(0.0%)</td>
<td>2(8.3%)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>10(100.0%)</td>
<td>22(91.7%)</td>
</tr>
<tr>
<td>rtN236T</td>
<td>+</td>
<td>1(10.0%)</td>
<td>1(4.2%)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>9(90.0%)</td>
<td>23(95.8%)</td>
</tr>
<tr>
<td>rtT184I</td>
<td>+</td>
<td>0(0.0%)</td>
<td>1(4.2%)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>10(100.0%)</td>
<td>23(95.8%)</td>
</tr>
<tr>
<td>rtS202G</td>
<td>+</td>
<td>1(10.0%)</td>
<td>0(0.0%)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>9(90.0%)</td>
<td>24(100.0%)</td>
</tr>
</tbody>
</table>

|                                   | 8/2         | 19/5         | 0.956  |
| gender (M/F)                      | Age (mean±SD) | 53.9±11.5  | 51.5±13.9 | 0.783  |
| HCC family history                | 3(30%)       | 2(8.3%)     | 0.104  |
| Alcohol abuse                     | 1(10%)       | 3(12.5%)    | 0.837  |
| HBVDNA (log) baseline             | 5.6±1.7      | 5.1±1.9     | 0.862  |

+: positive, -: negative.
monotherapy.

A greater effect was observed in patients who achieved sustained virological response, while the benefit in non-responders is unclear (Zhang et al., 2011; Papatheodoridis et al., 2010; Ohishi and Chayama, 2012). In our study, we found that antiviral treatment by both monotherapy and combinations of NUC significantly improved liver function. The CPs in the antiviral therapy group was significantly decreased in two years compared to baseline. If antiviral drug-resistance occurred, however, the CPs increased. Therefore, we can conclude that antiviral therapy might have benefits for compensated HBV-related cirrhosis. More effective and more affordable antiviral therapies are needed for patients with HBV-related compensated cirrhosis. A few studies showed that the failure of antiviral therapy of chronic hepatitis B or drug resistance increases the risk of liver cirrhosis and causes the progression of liver disease (Heo et al., 2010; Greece Cohort Study Group, 2011). Our study found that, although combinations of LDT+ADV and ETV monotherapy showed a similar clinical efficacy and drug two years. The combinations therapy more quickly controlled the reproduction of HBV-DNA in 12 weeks. Therefore, we hypothesize that the long-term efficacy of combinations of NUCs therapy are more effective than monotherapy in suppressing the reproduction of HBV DNA, reduce the incidence of antiviral drug resistance and prolong survival. The relationship between drug resistance and incidence of HCC or bad prognosis will be further investigated in our next project.

Conclusion

For HBV-related compensated cirrhotic patients, an effective antiviral therapy can improve long-term clinical outcomes. However, antiviral resistance can significantly increase incidence of liver failure. The efficacy and safety of combinations of NUCs and ETV monotherapy at two years are similar and superior to the LAM, ADV and LDT monotherapy. The long-term safety and cirrhotic complications warrant further monitoring.

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