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Combination lamivudine and adefovir *versus* entecavir for the treatment of naïve chronic hepatitis B patients: A pilot study

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Statistical Analysis C
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Background: The aim of this study was to compare the effect of combination lamivudine (LAM) and adefovir dipivoxil (ADV) *versus* entecavir (ETV) monotherapy for naïve HBeAg-positive chronic hepatitis B (CHB) patients.

Material/Methods: Fifty enrolled patients with CHB were evenly divided into 2 groups: a group treated with of lamivudine (LAM) (100 mg/day) plus adefovir (ADV) (10 mg/day) combination, and a group treated with entecavir (ETV) (0.5 mg/day). Serum levels of ALT, AST, creatinine, bilirubin, HBsAg, HBeAg and HBV viral load, and genotypic resistance were analyzed at 0, 12, 24, 52, and 104 weeks. HBV DNA levels were determined by real-time PCR and HBsAg and HBeAg by chemiluminescence. Serum levels of ALT, AST, creatinine, and bilirubin were measured by an automatic biochemical analyzer. Data analysis was performed with SPSS 12.0 software.

Results: There were no significant differences in the virological response (VR) rates between LAM+ADV and ETV cohorts at 24, 52, and 104 weeks (P>0.05). The HBeAg seroconversion rates were 28% and 20%, and the biochemical response (BR) rates were 88% and 84% at week 104 in the LAM+ADV and ETV groups, respectively. The rates of undetectable HBV DNA, HBeAg seroconversion, and ALT normalization rates were similar in both cohorts. No virological breakthrough or serious adverse effects were noted for any patient during the study period.

Conclusions: Both LAM + ADV combination therapy and ETV monotherapy were effective and safe in the treatment of naïve HBeAg-positive CHB patients. However, further studies are needed to obtain long-term results.

Key words: chronic hepatitis B • HBeAg-positive • lamivudine • adefovir dipivoxil • entecavir

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Background

Hepatitis B virus (HBV) is a major health problem worldwide, and is the most serious type of viral hepatitis. It can cause chronic liver disease and lead to liver cirrhosis and cancer [1]. HBeAg-positive chronic hepatitis B (CHB) patients usually have high levels of HBV DNA, and high risk of liver cancer [2]. Therefore, effective antiviral therapy is necessary in the treatment of HBeAg-positive CHB patients.

Current nucleos(t)ide analogues for CHB patients in China include lamivudine, adefovir dipivoxil, entecavir, and telbivudine. Patients who need long-term treatment usually need initial therapy involving either a combination of nucleoside/nucleotide analogs or monotherapy with higher efficiency and lower resistance, such as entecavir or tenofovir disoproxil (tenofovir disoproxil is not approved for HBV use in China). However, the guidelines did not advocate the initial use of combination therapy in 2008 at the time of initiation of the current study.

It is well established that the use of LAM is safe and effective [3]. Nevertheless, long-term use of lamivudine unfortunately leads to emergence of resistance to hepatitis B virus (YMDD) mutants. Despite this, lamivudine is still used widely because it is well tolerated. ADV has been strongly considered as a rescue therapeutic agent for the treatment of resistant mutants [4,5]. The clinical efficacy of entecavir has been studied in several randomized, double-blind, and multicenter trials [6]. Oral entecavir was found to be an effective and generally well tolerated treatment [7].

Previous studies have shown that combination therapy can reduce the viral resistance anti-HBV agents, permitting their use in long-term therapy [8]. Adding ADV to LAM enhanced the virological and biochemical responses in LAM-resistant patients [9], and adding ADV to LAM increased efficacy compared to ADV monotherapy in LAM-resistant patients [10,11]. Thus, LAM and ADV were considered as a *de novo* combination treatment, and entecavir (ETV) was recommended as first line monotherapy for long-term treatment of naïve CHB patients. Additionally, the cost of LAM combined with ADV is less than ETV monotherapy in China.

Both LAM +ADV combination therapy and ETV monotherapy are effective in naïve HBeAg-negative CHB patients [12]. However, it is unclear whether the combination of LAM and ADV is effective in HBeAg positive patients. The aim of this study was to evaluate and compare the effect of LAM plus ADV or ETV monotherapy in the treatment of naïve HBeAg-positive CHB patients.

Material and Methods

Informed consent was obtained from each patient, and ethics approval for this study was given by the Ethics Committee at the Third Affiliated Hospital of Wenzhou Medical College. There were 50 patients enrolled in this study. All patients were outpatients between November 2008 and June 2010. HBsAg was present in all the patients for at least 6 months prior to enrollment. All of the patients were both HBV DNA and HBeAg positive. The minimum level of HBV DNA was 10^4 copies/ml. Patients in whom the liver enzymes were elevated more than twice the ULN, but not more than 10 times, were enrolled without liver biopsy. Patients whose liver enzymes were elevated less than twice the ULN had liver biopsies to analyze the relation of hepatic grades of inflammation and stages of fibrosis. Patients with inflammation grade ≥2 or fibrosis stage ≥2 were enrolled in this study. Patients co-infected with hepatitis A virus, hepatitis C virus, hepatitis D virus, hepatitis E virus, or human immunodeficiency virus (HIV) or with alcoholic cirrhosis, autoimmune hepatitis, organ transplantation, HCC, or other severe diseases such as renal insufficiency were excluded from this study. Moreover, children and pregnant women were excluded.

This study aimed to evaluate and compare the efficacy of combination lamivudine plus adefovir *versus* entecavir monotherapy. Patients in the combination therapy group received LAM 100 mg and ADV 10 mg per day and the monotherapy group received ETV 0.5 mg per day. Clinical data were collected at baseline and every 3 months after retreatment. The primary efficacy outcomes were ALT normalization, reduction in HBV DNA, and seroconversion of HBeAg. We contacted the patients by phone every 3 months to increase patient compliance.

Serum assay methodology

Serum levels of ALT, AST, and bilirubin were measured at baseline and again at weeks 12, 24, 52, and 104 of the treatment using an Automatic Biochemistry analyzer (Olympus AU5431, Olympus Corporation, Tokyo, Japan) according to the manufacturer's instructions. The status of HBsAg, HBeAg, and antibody to HBeAg (anti-HBe) were measured by a microparticle enzyme-linked immunosorbent assay as recommended by the manufacturer (ELISA, Abbott Laboratories, United States) at each time point (week 0, 12, 24, 52, and 104) during treatment.

HBV DNA quantitation

From cell lysates, DNA was extracted and amplified by real-time PCR. The amplification was performed according to the protocol provided by Daan Gene Co., Shenzhen, China, the manufacturer of the primers, using an ABI7500 cycler: 93°C for 2 min, 93°C for 45 sec, followed b 55°C 60 sec 10 cycles, and 93°C for 30 sec followed by 55°C 45 sec 30 cycles. Values under or over the detection range were recorded as 2.7 or 9 $\log_{10}$ copies/ml, respectively.

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Table 1. Characteristics of patients at baseline.

Characteristic	LAM + ADV	ETV	P value
Patients enrolled	25	25	
Age (yrs)	33.4±9.8	30.8±7.1	0.28
Gender (males %)	20 (80%)	19 (76%)	0.21
HBeAg (S/CO)	2.64±0.64	2.44±0.79	0.35
HBV DNA (copies/ml)	6.02±1.62	5.94±1.25	0.837
ALT (IU/L)	Median=173	Median=156	0.83
AST (IU/L)	Median=92	Median=77	0.71
TBil (μmol/L)	21.14±17.06	13.82±3.55	0.14
Cr (μmol/L)	59.12±11.30	59.55±13.02	0.90

Definitions

The biochemical response (BR) was defined as normalization of ALT levels. Virological response was defined as a decrease in serum HBV DNA to undetectable levels by PCR assays (<500 copies/mL). HBeAg response was defined as seroconversion of HBeAg. Virological breakthrough was defined as an increase in serum HBV DNA by 1log10 (10-fold) above nadir, or to detectable level (≥500 copies/mL) after achieving virological response during retreatment.

Statistical analysis

Comparisons between groups of variables were performed using the *t*-test, and a chi-square test or Fisher's exact test. Repeated measure ANOVA was used to analyze the differences at various time points. All tests were 2-sided and used a significance level of P<0.05. Data handling and analysis were performed with SPSS software for Windows, version 13.0 (SPSS Inc, Chicago, IL, USA).

Results

Characteristics of the study patients

As described in Table 1, 50 patients were included in either the LAM + ADV combination group (n=25) or the ETV monotherapy group (n=25). In the combination group, 20 patients were male (80%), with a mean age of 33.4±9.8 years (range, 18–52 years). In the monotherapy group, there were 19 males (76%) and mean age was 30.8±7.1 years (range 18–45 years).

The median level of HBV DNA in the LAM + ADV group was 6.02±1.6 (range 8.27×10^4–2.90×10^8 copies/mL). The median level of ALT was 173 IU/L (range 28–456 IU/L). In the ETV monotherapy group, the median level of HBV DNA was 5.94±1.2 (range 1.06×10^4–3.51×10^8 copies/ mL) and the mean ALT was 156 IU/L (range 64–531 IU/L). There were no significant differences in baseline characteristics between the 2 groups.

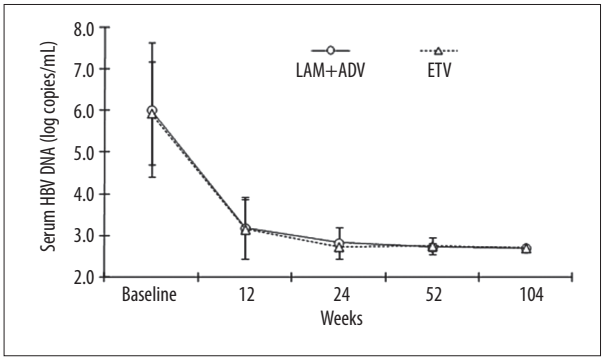

Figure 1. The decreasing trend of HBV DNA over time.

Virological response

As shown in Figure 1, HBV DNA levels decreased in the LAM + ADV group from 3.18±0.73 to 2.82±0.38, 2.72±0.09, and 2.70±0.00 at weeks 12, 24, 52, and 104, respectively, of treatment. In the ETV group, HBV DNA levels decreased from 3.15±0.72 to 2.73±0.10, 2.75±0.21, 2.70±0.00 at weeks 12, 24, 52, and 104, respectively. There was no statistically significant difference between the 2 groups (P=0.879, 0.272, 0.592, and 1.000 at weeks 12, 24, 52, and 104, respectively).

One patient quit ETV+ADV therapy because of poor efficacy (the HBV-DNA of this patient could still be detected) in the LAM + ADV group in week 52. No HBV resistant mutations were found in this patient. The compliance of the patients was good. Therefore, it is possible that the poor drug response in some patients was due to drug resistance [13] that could not be detected. Another patient stopped taking the medicine on his own. This patient's HBV had no detectable resistance genes. Both cases were considered to be non-responders.

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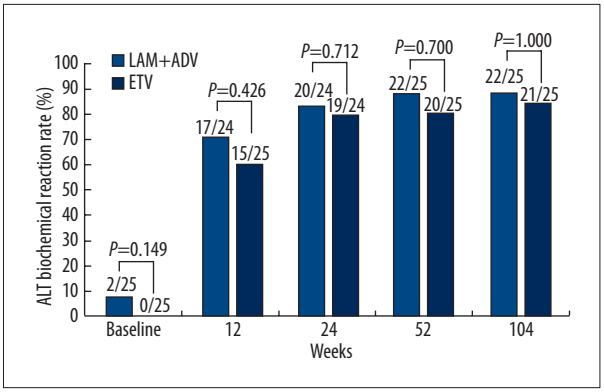

Figure 2. The decreasing trend of HBeAg with time.

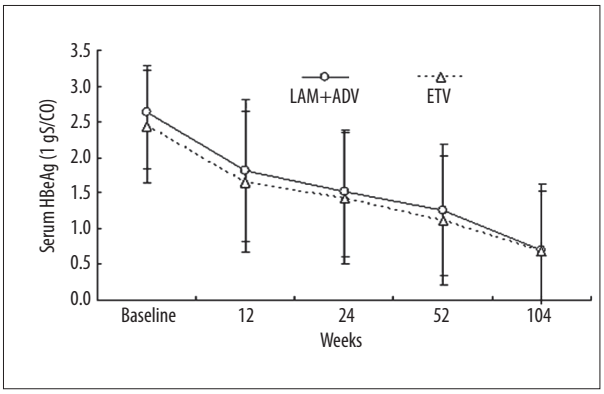

Figure 3. HBeAg-negativity rate of the 2 groups in different times.

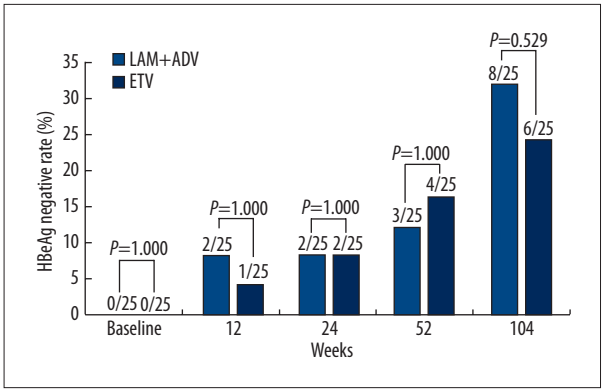

Figure 4. HBeAg seroconversion rates between the 2 groups at various times.

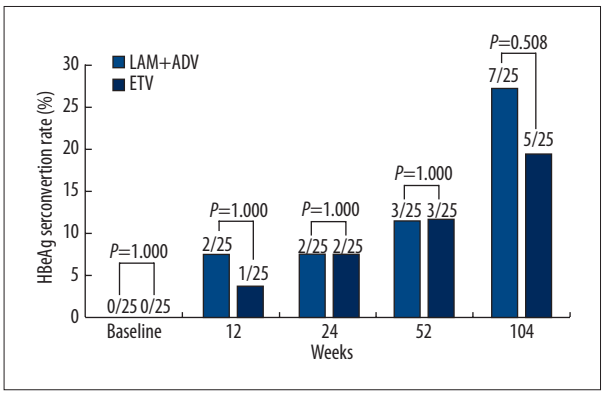

Figure 5. ALT biochemical response rates of the 2 groups at various times.

HBeAg response

As described in Figure 2, HBeAg levels in the LAM + ADV group were 1.81±1.01, 1.52±0.86, 1.26±0.93, and 0.71±0.93 at weeks 12, 24, 52, and 104 of treatment, respectively. In the ETV group, the levels of HBeAg were 1.66±0.99, 1.43±0.92, 1.12±0.91, and 0.69±0.83 at weeks 12, 24, 52, and 104, respectively. There were no statistically significant differences between these 2 groups (P=0.668, 0.729, 0.614, and 0.955 at weeks 12, 24, 52, and 104, respectively).

Of the 25 patients in the LAM + ADV group, 8% (2/25), 8% (2/25), 12% (3/25), and 32% (8/25) achieved HBeAg negative status by weeks 12, 24, 52, and 104, respectively. Of the other 25 patients in the ETV group, 4% (1/25), 8% (2/25), 16% (4/25), and 24% (6/25) of patients had undetectable HBV DNA by weeks 12, 24, 52, and 104, respectively. There were no statistically significant differences between the HBeAg seroconversion rates between the 2 groups at various times (Figure 3).

Of the 25 patients in the LAM + ADV group, 8% (2/25), 8% (2/25), 12% (3/25), and 28% (7/25) of patients achieved HBeAg seroconversion by weeks 12, 24, 52, and 104, respectively. Of the other 25 patients in the ETV group, 4% (1/25), 8% (2/25), 12% (3/25), and 20% (5/25) of patients had HBeAg seroconversion by weeks 12, 24, 52 and 104, respectively. There were no statistically significant differences in HBeAg seroconversion rates between these 2 groups at various times (Figure 4).

Biochemical response

Of the 25 patients receiving LAM + ADV, 71% (17/24), 83% (20/24), 88% (22/25), and 88% (22/25) of patient had ALT normalization by weeks 12, 24, 52, and 104, respectively. Of the 25 patients receiving ETV, 60% (15/25), 79% (19/24), 80% (20/25), and 84% (21/25) of patients had ALT normalization by weeks 12, 24, 52, and 104, respectively. There were no statistically significant differences in the ALT normalization rates between the 2 groups at various times (Figure 5).

Adverse effects

Both monotherapy and combination therapy were well tolerated. No patient in either group discontinued the drug during the period except the 2 cases considered to be non-responders. Adverse effects in the ETV group were noted in only 1 patient by week 12 who had a serum total bilirubin level that was

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slightly increased to 33.3 mmol/L. This was monitored closely, but did not require any additional treatment. The total bilirubin of this patient normalized by week 24 and remained within normal limits for the duration of the study period.

Virological breakthrough and drug resistance

During the 104-week treatment period, virological breakthrough did not occur in any of the 50 patients included in this study. However, the 2 groups each had 1 case of non-response to treatment. No LAM- or ADV-associated mutations were detected.

Discussion

Management of CHB has improved greatly with the development of orally available nucleosides. Unfortunately, there are no agents available with sufficient efficacy and safety to fully eradicate HBV. In addition, long-term therapy is often associated with the development of antiviral drug resistance. Drug resistance is one of the most important factors limiting long-term nucleoside treatment for CHB patients [14]. Based on the paradigm that a drug combination is more effective than monotherapy for the treatment of human immunodeficiency virus (HIV), the same approach may be appropriate for chronic hepatitis B. Few studies have assessed combination therapy in chronic hepatitis B [12,15,16]. From those studies, it was shown that *de novo* combination therapy with LAM and ADV was better than add-on combination therapy in terms of changes in Child-Pugh score, viral inhibition, and renal function [15]. Patients treated with LAM plus ADV exhibited significantly greater virological, biochemical, and serological responses compared with LAM alone [16], but not compared with entecavir.

Lamivudine is an inexpensive agent, with few adverse effects. However, there are very high rates of resistance with long-term LAM monotherapy [17–20]. Adefovir is a nucleotide analog that has been shown to be effective against LAM-resistant HBV. Entecavir is a potent HBV inhibitor with a high barrier to resistance [21–26]. According to the 2012 EASL guidelines, entecavir can be confidently used as first-line monotherapy. However, which agents should be combined, duration of therapy, and when to change or stop treatment remain unclear [27].

An important question is whether combination therapy is necessary according to the conclusion from the current study. Initial combination therapy or use of agents with a high genetic barrier is recommended in patients with a high risk of developing drug resistance and potentially life-threatening disease (e.g., cirrhosis). Based on this principle, the best option for naïve CHB patients who are HBeAg-positive or have serious liver disease, such as cirrhosis, is either combination treatment or monotherapy with high genetic barrier drugs to reduce the occurrence of HBV resistance. In our study, more patients in the combination treatment group achieved HBeAg seroconversion than in the monotherapy group, although the differences in HBeAg seroconversion rates between the 2 groups were not statistically significant. Many factors have been found to be associated with HBeAg seroconversion, including decreased titers of HBeAg in the serum and increased grades of lobular inflammation in the liver [28]. Whether *de novo* combination therapy with LAM and ADV could affect HBeAg seroconversion long-term remains to be determined.

In the patients with severe acute exacerbation of chronic hepatitis B, entecavir monotherapy treatment may achieve better virological response in the long run, but this has been associated with increased short-term mortality [29]. Entecavir monotherapy did not reduce the incidence of hepatic carcinoma in patients with cirrhosis in Japan [30]. Based on these observations, *de novo* combination of lamivudine and adefovir may be a better choice than entecavir monotherapy, especially in severe CHB or cirrhosis.

There are several shortcomings in the present study. The number of subjects was small because the number of patients treated with *de novo* combination therapy is limited in China. The limit of detection of HBV-DNA was 500 copies/ml, which was not as low as that used in several other studies, and which might account for differences observed in the current study compared to previous ones.

Conclusions

In conclusion, the current study shows that there was no statistical significance between the 2 groups in terms of rates of HBV DNA negativity, HBeAg negativity, HBeAg seroconversion, and ALT biochemical response. These findings indicate that the combination of LAM plus ADV is as good as entecavir monotherapy for the treatment of naïve CHB patients who are HBeAg-positive.

Acknowledgments

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