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BRIEF ARTICLE

Efficacy of telbivudine in HBeAg-positive chronic hepatitis B patients with high baseline ALT levels

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Abstract

AIM: To evaluate the efficacy and safety of telbivudine (LDT) in hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB) patients who have high baseline alanine aminotransferase (ALT) levels between 10 and 20 times the upper limit of normal.

METHODS: Forty HBeAg-positive CHB patients with high baseline ALT levels between 10 and 20 times the upper limit of normal were enrolled and received LDT monotherapy for 52 wk. Another forty patients with baseline ALT levels between 2 and 10 times the upper limit of normal were included as controls. We compared the virological, biochemical, serological and side effect profiles between the two groups at 52 wk.

RESULTS: By week 52, the mean decrease in hepatitis B virus (HBV) DNA level compared with baseline was 7.03 $\log_{10}$ copies/mL in the high baseline ALT group and 6.17 $\log_{10}$ copies/mL in the control group, respectively ($P < 0.05$). The proportion of patients in whom serum HBV DNA levels were undetectable by polymerase chain reaction assay was 72.5% in the high baseline ALT group and 60% in the control group, respectively ($P < 0.05$). In addition, 45.0% of patients in the high baseline ALT group and 27.5% of controls became HBeAg-negative, and 37.5% of those in the high baseline group and 22.5% of controls, respectively, had HBeAg seroconversion ($P < 0.05$) at week 52. Moreover, in the high baseline group, 4 out of 40 patients (10%) became hepatitis B surface antigen (HBsAg)-negative and 3 (7.5%) of them seroconverted (became HBsAg-positive). Only 1 patient in the control group became HBsAg-negative, but had no seroconversion. The ALT normalization rate, viral breakthrough, genotypic resistance to LDT, and elevations in creatine kinase levels were similar in the two groups over the 52 wk.

CONCLUSION: High baseline ALT level is a strong predictor for optimal results during LDT treatment.

Key words: Chronic hepatitis B; Hepatitis B e antigen; Serum alanine aminotransferase level; Telbivudine

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INTRODUCTION

Chronic infection with hepatitis B virus (HBV) affects

approximately 350 million people worldwide and is usually associated with continuing inflammatory activity and progression of liver diseases, which in turn lead to an increased risk of cirrhosis, decompensated liver disease, and hepatocellular carcinoma (HCC)[1,2]. Recently, several prospective follow-up studies of large cohorts of chronic hepatitis B (CHB) patients from Asia found that the presence of hepatitis B e antigen (HBeAg) and high levels of HBV DNA were independent risk factors for the subsequent development of advanced liver diseases[3]. Therefore, suppression of HBV replication is the main therapeutic goal in the treatment of CHB patients.

Up till now, seven drugs have been available for the treatment of CHB: they include conventional interferon α, pegylated interferon α, and nucleoside/nucleotide analogues (NUCs). NUCs for HBV therapy belong to three classes: L-nucleosides [lamivudine, telbivudine (LDT), emtricitabine], deoxyguanosine analogues (entecavir) and acyclic nucleoside phosphonates (adefovir and tenofovir). Lamivudine, adefovir, LDT, entecavir and interferon α have been approved in China for HBV treatment. LDT is an orally bioavailable L-nucleoside with potent and specific anti-HBV activity. It has been proved that LDT has a potent effect and a relatively high seroconversion rate for patients with CHB[4,5].

According to national and international guidelines, the antiviral treatment of patients with CHB is initiated when HBV DNA levels are above 2000 IU/mL and/or the serum alanine aminotransferase (ALT) levels are over 2 times the upper limit of normal (ULN), and liver biopsy shows moderate to severe active necroinflammation and/or fibrosis (e.g. at least A2F2 by METAVIR scoring)[6-8]. Many clinical trials have shown positive results of the antiviral treatments in hepatitis B patients with ALT levels between 2 and 10 times the ULN range. Nevertheless, a proportion of patients have serum ALT level over 10 times the ULN. There are few reports on the issue of whether to treat these patients right away or wait until a decline of ALT level. This paper summarizes the efficacy of LDT treatment in 40 hepatitis B patients with serum ALT level over 10 times the ULN range. We found that these patients obtained a better therapeutic effect when they received LDT treatment immediately.

MATERIALS AND METHODS

Patients and study design

This study was approved by the Ethics Review Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University. All patients provided written informed consent before antiviral therapy was given. The diagnosis of CHB was made according to the diagnostic standard from the National Program for Prevention and Treatment of Viral Hepatitis[9]. All patients were diagnosed as CHB based on hepatitis B surface antigen (HBsAg) positivity for more than 6 mo. Forty HBeAg-positive CHB patients were enrolled in this study. All of them had ALT levels between 10 and 20 times the upper normal level. Another 40 HBeAg-positive CHB patients whose ALT level was between 2 and 10 times the ULN were recruited as controls. All 80 CHB patients had serum HBV DNA level > 10^5 copies/mL and had never received anti-HBV therapy before. Patients were given LDT 600 mg daily as initial antiviral treatment for at least 52 wk. Patients were excluded from this study if they were coinfected with human immunodeficiency virus, hepatitis C virus, hepatitis D virus, had liver cirrhosis or hepatic decompensation, pancreatitis, hepatocellular carcinoma, fatty liver or alcoholic hepatitis.

The present study focused on main therapeutic endpoints at 52 wk for CHB patients with high baseline ALT levels, including proportions of patients with non-detectable serum HBV DNA, serum ALT normalization, HBeAg and HBsAg seroconversion and LDT resistance. Resistance was defined as emergence of treatment-associated resistance mutations, identified by direct sequencing of the amplified HBV DNA at baseline and from sera of all patients with serum HBV DNA > 3 $\log_{10}$ copies/mL at week 52. Viral breakthrough was defined as persistent (two consecutive determinations) on-treatment increase of serum HBV DNA > 1 $\log_{10}$ copies/mL above nadir level[10].

Serum assay

Analyses of liver function, renal function and creatine kinase level were performed at baseline and at week 2, 4, 8, 12, 16, 24, 32, 36, 48 and 52 of LDT therapy using the Automatic Biochemistry analyzer (Hitachi 7600). HBsAg, HBeAg, anti-HBc, anti-HBe and anti-HBs were quantified using radioimmunoassay (Abbott Laboratories Ltd.). HBV DNA was measured using the Amplicor HBV Test (Roche Diagnostics, Basel, Switzerland) with a detection limit of 300 copies/mL. LTD-associated mutations were assessed by direct sequencing.

Statistical analysis

Quantitative data were presented as mean ± SD, categorical data were presented as counts and percentages, and HBV DNA levels were presented as log transformation. Data were analyzed using the SPSS software package version 13.0 (SPSS Inc., Chicago, IL, USA). Pearson chi-square or Fisher exact tests were used for categorical variables. In all cases, *P* values less than 0.05 were considered statistically significant.

RESULTS

Patients

Baseline characteristics for all 80 HBeAg-positive CHB patients are presented in Table 1. In the high baseline ALT CHB patient group, patients consisted of 29 males and 11 females, with ages ranging from 21 to 38 years (28.12 ± 3.71 years). Baseline data are as follows: the median level of serum HBV DNA was 7.78×10^7 copies/mL (range: 4.67×10^5-8.58×10^9 copies/mL), the median ALT level was 658.0 IU/L (range: 513.0-978.0 IU/L).

Virological response

By week 52, the mean decrease in HBV DNA level compared with baseline was 7.03 $\log_{10}$ copies/mL in the high

Table 1 Patient baseline characteristics

Variables	High baseline ALT group	Controls
Patients (*n*)	40	40
Male, *n* (%)	29 (72.5)	28 (70)
Age (yr, mean ± SD)	28.12 ± 3.71	31.12 ± 5.43
ALT (IU/L)	885.6 ± 7.89	128.4 ± 5.33
TBiL (μmol/L)	45.43 ± 6.67	29.12 ± 2.56
HBV DNA (copies/mL)		
Median	7.78×10^8	7.56×10^8
Range	4.67×10^5-8.58×10^9	5.89×10^5-7.34×10^9

ALT: Alanine aminotransferase; TBiL: Total bilirubin; HBV: Hepatitis B virus.

Table 2 Efficacy and safety at week 52 *n* (%)

Variables	High baseline ALT group	Controls	*P* value
Decrease in HBV DNA level (log_{10} copies/mL)	7.03	6.17	< 0.05
HBV DNA negative rate	29/40 (72.5)	24/40 (60)	< 0.05
ALT normalization rate	30/40 (75.0)	31/40 (77.5)	> 0.05
HBeAg negative rate	18/40 (45.0)	11/40 (27.5)	< 0.05
HBeAg seroconversion rate	15/40 (37.5)	9/40 (22.5)	< 0.05
HBsAg negative rate	4/40 (10.0)	1/40 (2.5)	< 0.05
HBsAg seroconversion rate	3/40 (7.5)	0	< 0.05
Viral breakthrough	2/40 (5.7)	3/40 (7.5)	> 0.05
Viral resistance	1/40 (2.9)	2/40 (5)	> 0.05
Increased blood creatine kinase	5/40 (12.5)	4/40 (10)	> 0.05

ALT: Alanine aminotransferase; HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen.

baseline ALT group and 6.17 log_{10} copies/mL in the control group, respectively ($P < 0.05$). The proportion of patients in whom serum HBV DNA levels were undetectable by polymerase chain reaction assay was greater in the high baseline ALT group than in the control group (72.5% *vs* 60%, $P < 0.05$) as indicated in Table 2.

Serological response

At week 52, 45.0% of HBeAg-positive CHB patients in the high baseline ALT group and 27.5% ($P < 0.05$) of controls became HBeAg-negative, and 37.5% of those in the high baseline group and 22.5% of those in the control group had HBeAg seroconversion ($P < 0.05$). Moreover, in the high baseline group, 4 out of 40 patients (10%) became HBsAg-negative and 3 (7.5%) of them seroconverted (became HBsAb-positive). Only 1 patient in the control group became HBsAg-negative, but had no seroconversion (Table 2).

Biochemical response

At week 52, ALT normalization was achieved for 30 of the 40 patients (75.0%) in the high baseline ALT group and 31 of 40 patients (77.5%) in the control group ($P > 0.05$).

Resistance and side effects

As indicated in Table 2, viral breakthrough and genotypic resistance to LDT were similar between patients with high baseline ALT levels and controls. Resistance developed in 2.9% of patients with high baseline ALT levels and in 5% (2/40) of control patients. Consistent with previous reports, M204I was the only mutation associated with LDT resistance in this study. After the emergence of resistance, adefovir dipivoxil was added to treatment. Resistance patients are considered treatment failures in this study.

The frequencies of adverse events through week 52 were similar in both groups treated with LDT. Elevations in creatine kinase level through 52 wk were observed in 12.5% (5/40) of patients in the high baseline ALT group and in 10% (4/10) of controls, respectively. Grade 3 or 4 elevations in creatine kinase level (at least seven times the ULN) were found only in 1 patient in the high baseline ALT group and in 1 patient in the control group, respectively; levels decreased spontaneously during LDT treatment to normal within the next two visits (6 mo). No patients in either group stopped LDT treatment because of creatine kinase elevations in this study (Table 2).

DISCUSSION

The goal of therapy for hepatitis B is to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC and death. This goal can be achieved if HBV replication can be suppressed in a sustained manner, the accompanying reduction in histologic activity of chronic hepatitis lessening the risk of cirrhosis and decreasing the risk of HCC[11]. To date, two types of antiviral drugs can be used in the treatment of CHB: interferon and nucleoside/nucleotide analogs. In China, four types of nucleoside/nucleotide analogs (lamivudine, adefovir dipivoxil, entecavir and LDT) are available. Among them, LDT is potent and induces a relatively high seroconversion rate[12]. LDT has become widely used in anti-HBV therapy in China.

Besides serum HBV DNA levels and histological grade and stage of the liver disease, baseline ALT level of CHB patients is one of the determinants for the initiation of antiviral therapy. The antiviral effect of LDT is associated with the baseline ALT level, as in interferon and lamivudine therapy[13,14]. Taking HBeAg seroconversion as an example, 32% of patients with pretreatment ALT levels between 2 and 5 × ULN and 46% of those with ALT > 5 × ULN achieved HBeAg seroconversion after 2 years of treatment with LDT[5]. Our study focused, we believe for the first time, on the antiviral effect of LDT on HBeAg-positive patients whose baseline ALT level was 10-20 × ULN, showing the HBeAg seroconversion rate was 37.5% at 52 wk, which is the same as reported for peg-interferon therapy at 48 wk[15]. More encouragingly, our results also showed 7.5% (3/40) patients had HBsAg seroconversion at 52 wk after LDT treatment.

The main mechanism of ALT elevation in CHB patients is the activated immune response to eliminate HBV, which theoretically shows the positive association between ALT level and the degree of inmune activation. High baseline ALT level has been shown to be independently associ-

ated with an increased rate of HBeAg response after either interferon or NUC treatment[16,17]. In the present study, our results clearly showed that increased serum baseline ALT levels predict a higher HBeAg seroconversion when patients are treated with LDT.

HBeAg has been recognized as a successful serologic marker in the treatment of HBeAg-positive CHB[18]. Compared with other NUCs, LDT has a relatively high seroconversion rate. Whether this is related to its immune regulation ability needs further exploration. Evans *et al*[19] reported the relatively low expression of programmed death-1 receptor on CD8+ T cells in HBeAg-positive CHB patients who received LDT therapy and had HBeAg seroconversion, compared with those counterparts who did not achieve HBeAg seroconversion.

Entecavir and tenofovir are potent HBV inhibitors and they have a high barrier to resistance. They are widely used as first-line monotherapies in developed countries. However, in China tenofovir is not available yet, and entecavir is expensive for most patients. LDT and lamivudine are still widely used. In order to reduce the incidence of resistance to these drugs, optimal treatment has been used in clinical practice. For example, pretreatment serum HBV DNA $< 10^9$ $\log_{10}$ copies/mL and ALT levels $\geqslant 2 \times$ ULN for HBeAg-positive patients were shown to be associated with a high rate of non-detectable HBV DNA, a high rate of HBeAg seroconversion and lower resistance to LDT treatment after 2 years[5]. Our study also proved that if we select the right patients to treat with LDT, there will be optimal conditions to achieve the desired results. Taken together, if baseline serum HBV DNA $< 10^9$ $\log_{10}$ copies/mL and ALT levels $\geqslant$ 2-20 $\times$ ULN for HBeAg-positive patients, we can consider the administration of LDT treatment in daily clinical practice.

In conclusion, our results indicate relatively higher HBeAg and HBsAg seroconversion in HBeAg-positive CHB patients whose baseline ALT levels were 10-20 $\times$ ULN and who received LDT monotherapy immediately. In addition, there were no significant differences in safety between these patients and their counterparts with lower ALT levels. We suggest that this treatment strategy deserves clinical application.

COMMENTS

Background

There is a proportion of chronic hepatitis B (CHB) patients with serum alanine aminotransferase (ALT) levels over 10 times the upper limit of normal. There are few reports regarding the issue of treatment for these patients, whether to treat them right away or whether to wait until the decline of ALT level.

Research frontiers

In China tenofovir is not available yet, and entecavir is expensive for most patients. Telbivudine (LDT) and lamivudine are still widely used. In order to reduce the incidence of resistance to these drugs, optimal treatment has been used in clinical practice. However, how to select optimally for LDT has not been unequivocally addressed. In this study, the authors demonstrate relatively high hepatitis B e antigen (HBeAg) and hepatitis B surface antigen (HBsAg) seroconversion in HBeAg-positive CHB patients whose baseline ALT levels were 10-20 times the upper limit of normal (× ULN) and who received LDT monotherapy immediately.

Innovations and breakthroughs

Recent reports have highlighted the importance of baseline characteristics, such as serum hepatitis B virus (HBV) DNA level, ALT level and histological grade and stage, in antiviral therapy. This is the first study to report the antiviral effect of LDT on HBeAg-positive patients whose baseline ALT level was 10-20 × ULN, showing the HBeAg seroconversion rate was 37.5% at 52 wk. More encouragingly, our results also showed 7.5% (3/40) patients had HBsAg seroconversion at 52 wk after LDT treatment.

Applications

By understanding that the antiviral results are related to the baseline ALT levels in addition to HBV DNA titer, this study may represent a future strategy for therapeutic intervention in CHB patients with high baseline ALT level.

Terminology

ALT is a common indicator of liver damage and is one of the key predictors of initiation of antiviral therapy. This study suggests that high baseline ALT level is a strong predictor for optimal results during LDT treatment.

Peer review

This study shows favorable results in patients with high baseline ALT values. The authors conclude that in patients with high baseline ALT levels antiviral treatment with LDT should be started immediately.

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