ORIGINAL ARTICLE

Efficacy of Lamivudine Therapy on Decompensated Liver Cirrhosis Due to Chronic Hepatitis B

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Background and Aims: The aim of this study was to determine the effect of lamivudine on liver function and clinical status of the patients with decompensated cirrhosis arising from hepatitis B virus (HBV).
Methods: In a clinical trial on the basis of liver consideration in 55 patients with cirrhosis that had positive HBsAg and HBV DNA, Child-Pugh score more than 8 and some other criteria were treated with lamivudine. In these patients, serum level of bilirubin, albumin, ALT, AST and also the PT-INR were controlled at the beginning of study and then at intervals of 2 to 6 months and finally 12 months after the start of treatment.
Results: Five patients died in the first 6 months of treatments. The following results are related to 50 patients being under treatment with lamivudine at least for a period of 6 months. In these patients mean Child-Pugh score was decreased from 11 ± 2 to 7 ± 1 (P < 0.0001). All of the patients tolerated this drug very well.
Conclusions: Lamivudine can be effective in improvement of liver function in patients with decompensated liver cirrhosis resulting from HBV, but for determination of proper period of treatment, further studies are necessary.
Keywords: Lamivudine, Hepatitis B, Hepatitis C, Cirrhosis

Introduction

Hepatitis B virus (HBV) is the leading cause of chronic liver diseases, including chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC) [1, 2]. Among people living in endemic areas, such as South East Asia, China and Africa, approximately 10% are at risk of developing cirrhosis and HCC as a direct consequence of chronic HBV infection [3]. Cirrhosis is the result of chronic inflammation and of the progressive increase of fibrosis. The complications of cirrhosis such as ascites, esophageal varices, bleeding, hepatic encephalopathy and HCC mainly explain the high rate of morbidity and mortality. To date, antiviral chemotherapy remains the only option for controlling infection in these individuals. Interferon (IFN-α) has proven benefit in a well defined group of

patients with hepatitis B but has made little impact on the global burden of chronic liver diseases [2].

Lamivudine (LAM), an oral cytosine nucleoside analog, is the (-)-beta-enantiomer of 2, 3-dideoxy-3-thiacytidine. LAM interferes with HBV reverse

transcriptase (DNA polymerase) activity, leading to the inhibition of HBV replication [4, 5]. Long-term treatment with LAM is not an option because it leads to drug resistance in most cases [6]. LAM treatment, especially for chronic HBV-infected patients with cirrhosis, may also acts as a bridge to more definitive treatments, such as liver transplantation. Several non-Asian studies from North America and Europe have shown the efficacy of long-term use of LAM [7-9]. Some studies have assessed the efficacy of long-term use of LAM treatment of a large number of Japanese patients with chronic hepatitis B. To acquire more data on these issues, some Iranian patients with decompensated cirrhosis cooperated in this study.

Materials and Methods

A total of 55 patients with decompensated cirrhosis based on Child-Pugh-Turcotte (CPT) score of ≥8 at the time of enrollment who visited Imam Khomeini Hospital, Medical Sciences/University of Tehran, from 2003 to 2004 were included in the present study. In gastroenterology the Child-Pugh score (sometimes the Child-Turcotte-Pugh score) is used to assess the prognosis of chronic liver disease, mainly cirrhosis. The score employs five clinical measures of liver disease including serum albumin, bilirubin, PT-INR, ascites, and hepatic encephalopathy. Each measure is scored 1-3, with 3 indicating most severe derangement [1]. The patients were treated with LAM over 12 months. All patients had hepatitis B surface antigen (HBsAg) for at least 12 months and detectable serum HBV-DNA. Patients were excluded if HCV-Ab or HIV-Ab was positive. Serum creatinin wasn't more than 2 mg/dl in any of them. At baseline, none had evidence of hepatocellular carcinoma detected by ultrasonography or computed tomography (CT) of the abdomen. There were 34 men (68%) and 16 women (32%) aged between 35 and 61 years, with a median age of 51 years. Thirty-one of 55 Patients had negative HBeAg with positive HBV-DNA, which was consistent with the precore mutant variant. The degree of coagulopathy was measured by the international ratio of prothrombin time (PT-INR) and the median of PT-INR was 1.7 ± 0.2. Among the 55 patients, ascites was found in 42 patients by sonography and encephalopathy in 28 ones.

Patients were treated with LAM, 100 mg/day for 12 months and were prospectively followed up for 12 months after initiation of treatment. Baseline levels of PT-INR, bilirubin, albumin, AST, ALT and Child-Pugh score were measured every 2 months from the initiation of LAM therapy. Ascites and encephalopathy evaluation were carried out in each follow up. At last data was analyzed using repeated measured ANOVA, Friedman and t-tests. P ≤ 0.05 was considered as significant. Ethical committee of our University accepted the study.

Results

Five patients died at first six months, whose data is available in Table 1. The biochemical and clinical outcomes of other 50 patients are summarized in Figures 1-3. There was a significant improvement in the CPT score with LAM therapy; so that, the mean values of serum albumin reached from 2.6 to 3.8, PT from 1.7 to 1.2 and bilirubin from 4.5 to 1.3. There was also a significant decrease in liver enzymes and number of patients with ascites or hepatic encephalopathy. No difference was seen in Child-Pugh score improvement between precore mutant and non-precore mutant patients (P = 0.09). Four (22%) of nineteen non-precore mutant patients after 6-months and five (26%) after 12-months treatment showed HBeAg seroconversion. No serious adverse effects could be attributed directly to

Table 1. Demographic, serologic and clinical profiles of five dead patients

| No.	Sex	Age (yr)	Child-Pugh score	Duration of LAM treatment (wk)	Reason of death
1	Male	45	12	14	Hepatic failure
2	Female	60	14	2	Hepatic failure and hepatorenal syndrome
3	Male	48	13	4	Hepatic failure and esophageal varices hemorrhage
4	Male	51	13	10	Hepatic failure
5	Male	38	12	12	Hepatic failure and sepsis

PT-INR: International ratio of prothrombin time; AST: Aspartate transaminase; ALT: Alanine transaminase.
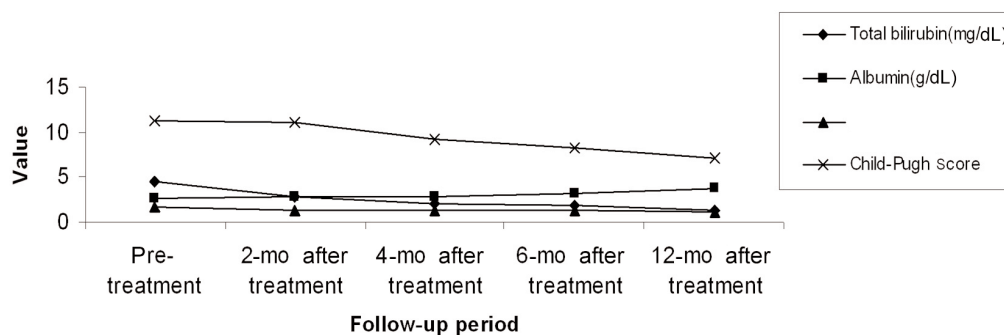
Figure 1. Biochemical and Child-Pugh score changes at 12-months follow-up period. Data were analyzed by repeated measures ANOVA test (P<0.0001).
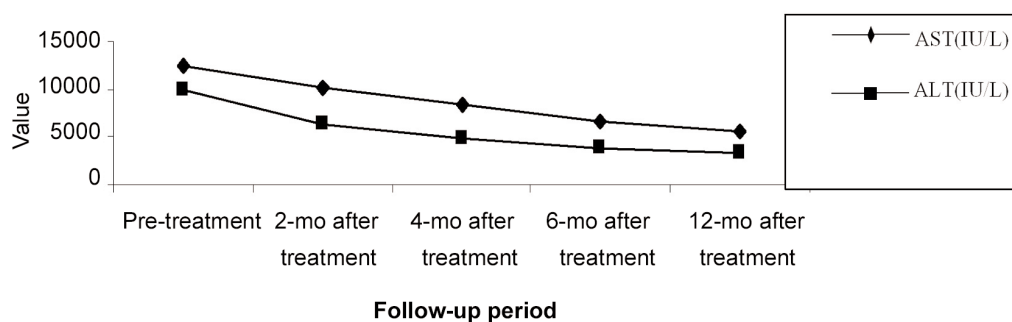
Figure 2. AST and ALT changes during 12-mo follow up period. Data was analyzed by Repeated Measures ANOVA test (P<0.0001).
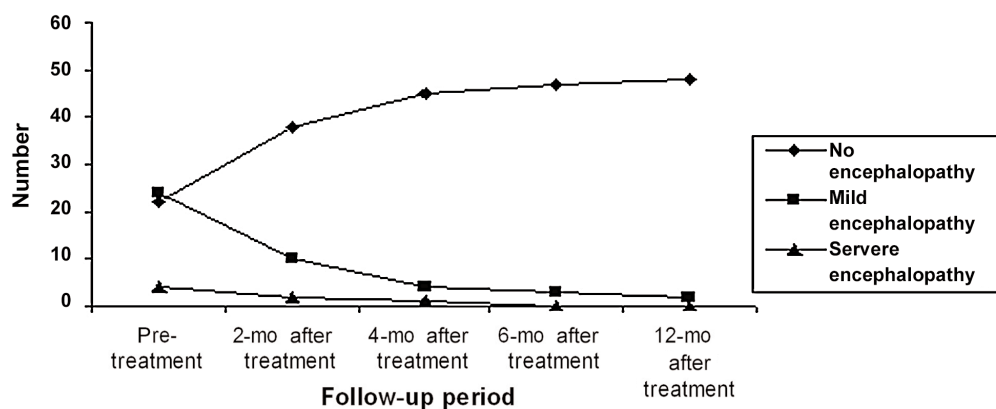
Figure 3. Ascites changes during 12-month treatment with lamivudine. N=50, Friedman test, P<0.001.

LAM treatment. LAM was generally well-tolerated in all patients during the entire follow-up period.

Discussion

Liver transplantation is generally regarded as the treatment of choice for decompensated cirrhosis. However, decompensated cirrhosis with HBV infection is regarded as a relative contraindication for liver transplantation because recurrent HBV infection is the most common causes of death [10, 11]. The prognosis of decompensated cirrhosis resulting from chronic hepatitis B is poor, and the benefits of treatment with interferon are outweighed by serious side effects and by the risk of fatal exacerbation of disease activity. LAM rapidly reduces HBV-DNA in serum to undetectable levels [11-14]. In Villeneuve *et al.* study, 22 of 23 patients (96%) with decompensated HBV-cirrhosis and

CPT score of ≥8 at baseline had a decrease in CPT score of ≥2 points following LAM therapy [11]. Decrease of CPT score of ≥4 points was found in our study too. Yao and Bass reported that nine of 13 patients (69%) with severely decompensated HBV-cirrhosis and CPT score of ≥10 had clinical improvement after mean LAM treatment duration of 17.5 months [15].

It is as like as our study which the severity of ascites and encephalopathy decreased significantly after 12-months LAM therapy. Yao *et al.* reported that liver transplant candidates receiving LAM were less likely to undergo transplantation than untreated historical controls who were matched for age, gender, and illness severity at the time of listing (35% vs. 74%, P = 0.04). In addition, a significantly greater proportion of the LAM-treated patients experienced an improvement ≥3 points in their CPT score compared with the untreated historical controls (61% vs. 50%, P = 0.0001) [14]. In another study, decrease in serum ALT, AST, bilirubin and increase in serum albumin and reduction in Child Pugh score was found in 5 (11.1%) patients. Also in our study there was a significant decrease in serum ALT, AST, bilirubin and increase in serum albumin and reduction in Child Pugh score [16]. In a prospective study of LAM treatment in 154 North American HBsAg-positive with decompensated HBV-cirrhosis, more than 80% of treated patients had suppression of HBV-DNA to undetectable levels by the branched-chain DNA (b DNA) assay within 8 weeks of initiating antiviral treatment. The actuarial 3-year survival of all patients and those who survived beyond the first 6 months of treatment was 72% and 88% respectively [17]. In present study, LAM was well-tolerated in all patients without any serious adverse effect during the follow-up period. The excellent safety profile of LAM has been reported previously by other investigators [17-21].

In conclusion, LAM treatment is effective in suppressing HBV-DNA and can achieve significant improvement in the clinical and biochemical status of liver function therefore, it is recommended that LAM therapy should be administered early in patients with decompensated cirrhosis and with CPT scores ≥8, so that the clinical improvement is greater. We are also concerned about the appearance of resistant variants following early treatment. Interestingly, clinical and biochemical deterioration did not occur after the emergence of LAM-resistant HBV. Therefore, further studies using a larger number of patients with mild and severe decompensated cirrhosis are required to determine the optimal timing of LAM therapy and confirm the results of the present study.

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