



Biochemical response to lamivudine treatment in HBeAg negative chronic hepatitis B patients in Iran

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Received: 2005-10-19 Accepted: 2006-11-18

Biochemical response to lamivudine treatment in HBeAg negative chronic hepatitis B patients in Iran. *World J Gastroenterol* 2006; 12(26): 4203-4205

<http://www.wjgnet.com/1007-9327/12/4203.asp>

Abstract

AIM: To study the effect of a one-year lamivudine regimen in patients with chronic hepatitis B.

METHODS: Medical records of HBeAg negative hepatitis B patients who attended a hepatitis clinic in Tehran between March 2002-March 2004 were evaluated. The patients received 100 mg lamivudine tablets once daily for at least 12 mo. Liver enzymes and complete blood count were checked at baseline and the end of treatment (12th mo) and 6 mo after discontinuation of treatment.

RESULTS: Of all patients, 24 were excluded. Of 71 patients left, 58 (81.7%) were men. Mean age of the patients was 38 ± 14 years. Mean level of ALT in serum was 1437 ± 205 nkat/L at baseline with a significant reduction at the end of treatment to a mean level of 723 ± 92 nkat/L ($P = 0.002$). In 38 patients (53.5%), the ALT level was normal after one-year treatment. Five patients (7.3%) relapsed (biochemically) within 6 mo after discontinuing lamivudine therapy (the patients with good end of treatment response). Mean level of AST in serum was 1060 ± 105 nkat/L at baseline which decreased significantly to 652 ± 75 nkat/L at the end of treatment ($P = 0.002$).

CONCLUSION: Over half (53.5%) of chronic hepatitis B patients with HBeAg negative have normal liver enzyme level at 12-mo lamivudine therapy.

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Key words: Chronic hepatitis B; Lamivudine; HBeAg

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INTRODUCTION

Chronic hepatitis B is a pandemic disease which has been under constant focus because it has long-term serious complications such as hepatic cirrhosis and hepatocellular carcinoma, while it is a preventable condition. About 350 million people have the condition all around the world with 200 000 patients living in Iran^[1]. Length of drug therapy, frequency of recurrences after primary remission, cost of drug regimen and resistance to treatment have led investigators to look for the best and most cost-effective therapeutic regimens for chronic hepatitis B in numerous studies throughout the world. A study in Canada estimated the annual cost of medical care for a patient with chronic hepatitis as high as \$2191 while a cirrhotic patient's medical care costs summed up to an estimated \$11 228 each year^[2].

The objectives of treatment in chronic hepatitis B patients are suppression of viral replication as well as reduction in hepatic inflammation. Lamivudine is a nucleoside analogue which prevents the viral DNA synthesis. Markers such as HBeAg, liver enzymes especially ALT and HBV DNA are used for monitoring patients' response to treatment. Many studies assessed the effectiveness of a number of different therapeutic regimens in different community contexts^[3,4]. In the present study, we investigated the effect of a one-year lamivudine regimen in HBeAg negative patients with chronic hepatitis B who attended a hepatitis clinic in Tehran.

MATERIALS AND METHODS

Patients

Ninety-five medical records of HBeAg negative hepatitis B patients who were registered in a hepatitis clinic in Tehran during March 2002 to March 2004 were evaluated; these patients had positive HBsAg, positive HBeAb, negative HBeAg and sustained or intermittent increased ALT for more than 6 mo. Serum HBV DNA loads were measured by quantitative real-time PCR with primers that amplify

Table 1 Frequency of response and serum liver enzymes during 12-mo treatment of HBeAg negative patients with lamivudine (*n* = 71)

	Baseline	3 mo		6 mo		12 mo	
		Mean	Frequency of response	Mean	Frequency of response	Mean	Frequency of response
ALT (nkat/L)	1437 ± 205	1060 ± 122	65 (91.5%)	813 ± 160	61 (85.9%)	723 ± 92	38 (53.5%)
AST (nkat/L)	1060 ± 105	960 ± 77	68 (95.7%)	770 ± 88	63 (88.7%)	652 ± 75	36 (50.1%)

P = 0.002 for ALT between baseline and 12 mo treatment levels; *P* = 0.002 for AST between baseline and 12 mo treatment levels.

a highly conserved region of the surface gene^[5] and with a detection system that employed molecular beacon technology^[6]. The assay was calibrated using international HBV standards and a plasmid control containing a full-length cloned copy of HBV ayw. The assay has a 7 log₁₀ linear response, with a lower limit of detection of 2×10^5 copies/L and an intraassay coefficient of variability of 15%. All patients with a serum ALT level of more than 2 times of upper normal limit, serum HBV DNA more than 10^5 copies/mL with histopathologic features in liver biopsy consistent with chronic hepatitis (\geq F2) in the Knodell score, [also known as the histologic activity index (HAI)], were included. Those who had evidence of other liver diseases such as hepatitis C, autoimmune liver diseases, non alcoholic fatty liver disease (NAFLD) and non alcoholic steatohepatitis (NASH) in sonography and liver biopsy, and biliary tract diseases, thyroid diseases were excluded. Also, all cases of non-compliance with therapy were excluded.

Methods

Lamivudine was prescribed at a dosage of 100 mg daily. All patients had used the drug for at least 12 mo. Liver enzymes (AST, ALT), complete blood cell counts were checked and recorded at baseline, mo 3 and 6 of treatment, the end of one year treatment and 6 mo after discontinuation of treatment. Forty-two patients had detected serum HBV DNA loads at the end of treatment for their own interest in evaluation of some virological responses.

Statistical analysis

The data were analyzed by SPSS and paired *t* test was used to compare the variables before and after treatment. *P* < 0.05 was taken as significant.

RESULTS

Of all medical records, 24 were withdrawn from the study: 16 patients did not take the prescribed drug correctly, and 8 patients had a follow-up period of less than 6 mo. Of 71 patients left, 58 were men. Mean age of the patients was 38 ± 14 years. The youngest patient was 12 years old while the oldest was 71. Mean weight of patients was 68 ± 14 kg. The lowest weight was 38 kg while the highest was 115 kg. Biochemical markers are as follows: Mean level of hemoglobin was 144 ± 17 g/L with lowest value of 109 g/L and highest value of 175 g/L. Mean white blood cells count was $(6.39 \pm 2.2) \times 10^9$ /L with lowest count of 3.1×10^9 /L and highest count of 11.6×10^9 /L. Mean prothrombin time was 14.3 ± 4.5 s at baseline with

Table 2 Liver serum markers after 3 and 6 mo of termination of one-year regimen in patients who responded to treatment (*n* = 38)

	12 mo Mean	After 3 mo		After 6 mo	
		Mean	Frequency of normal level	Mean	Frequency of normal level
ALT (nkat/L)	538 ± 90	688 ± 157	28 (73.7%)	902 ± 238	25 (65.8%)
AST (nkat/L)	447 ± 122	677 ± 143	32 (84.2%)	803 ± 210	28 (73.7%)

P < 0.04 between 12 mo of and after 6 mo cessation of treatment for ALT, *P* < 0.03 between 12 mo of and after 6 mo cessation of treatment for AST.

shortest time of 11 s and longest time of 46 s. Mean platelet count was $(199.9 \pm 9.03) \times 10^9$ /L. Of all patients, 20 (28.2%) were diagnosed by clinical manifestation while a major proportion of patients (32%-45.0%) were diagnosed incidentally by routine examination on the blood they donated. Only 7 patients were diagnosed through screening and checkups.

In terms of probable routes of transmission, 43.7% had a history of dental procedure, 15.5% had a tattoo and 12.7% underwent a surgical procedure. Of all patients, 44 (62%) had no family history of hepatic disease. Those who had a positive family history had a sibling with the condition, while 4 mothers and 8 fathers had the condition.

A biopsy was taken from 37 patients before the treatment. The biopsy samples were reported based on Knodell score. Of these samples, 73% had a score of less than 6. The liver enzyme levels before, during and after treatment with lamivudine were compared. As shown in Table 1, mean level of ALT in serum was 1437 ± 205 nkat/L at baseline with a significant reduction after treatment to a mean level of 723 ± 92 nkat/L (*P* = 0.002). In 53.5% of patients the ALT level was normal after one-year treatment. Mean level of AST in serum was 1060 ± 105 nkat/L at baseline which decreased significantly to 652 ± 75 nkat/L after treatment (*P* = 0.002). Of 38 (53.5%) patients who responded to treatment, 28 (73.7%) and 25 (65.8%) patients had normal ALT levels after 3 and 6 mo of termination of one-year regimen, respectively. There was no significant elevation of ALT and AST after 3 mo of cessation of treatment compared to 12 mo of treatment, while there was a significant difference between ALT and AST level at 6 mo after termination of and 12 mo of treatment (*P* < 0.04 and *P* < 0.03, respectively, Table 2). At the end of treatment, HBV DNAs were measured in 42 cases and was negative in 24 cases.

Mild adverse events were seen in 12 patients including fatigue in five patients, headache in three, myalgia in two, decreased appetite in two, but there were no reports of therapy discontinuation.

DISCUSSION

The major proportion of the patients were men and the age distribution of sample can be regarded as an adult population. The probable routes of transmission in order of frequency were a history of dental procedure, having a tattoo and a history of surgical procedure, which is consistent with other studies^[7,8]. However, to confirm these results, studies to evaluate the precise role of these risk factors in the transmission of hepatitis B are needed. It is clear that the risk of transmission of hepatitis *via* these procedures has not been evaluated completely in our study. The most frequent event leading to diagnosis was blood donation, which is consistent with other studies^[9]. The most significant factor under focus in our study was the changes in serum levels of liver enzyme especially ALT after treatment by lamivudine. As presented earlier the reduction in serum level of ALK, AST, and ALT were significant at 12 mo of therapy.

In a 3-year retrospective study in the United States, the therapeutic response markers of 119 patients were analyzed. The results showed that 61% of patients had a normal ALT level after treatment. The ALT serum level at baseline was not a significant predictor for response to therapy by lamivudine^[10]. Similar results were reported by a Chinese study on 129 patients with chronic hepatitis. In the current study 60.3% of patients completing a one-year lamivudine treatment had a normal ALT level while the ALT level was normal in only 24.5% of controls at 12 mo. The difference was significant^[11]. A recent study in Pakistan showed that a course of one-year lamivudine treatment was associated with significant reduction in ALT serum level, the treatment was more effective in patients with HBeAg at baseline^[12]. In another study in Austria, 72% of the intervention group had normal ALT level while 29% of controls had normal ALT level^[13]. Most studies of one-year lamivudine treatment for patients with chronic hepatitis B showed a reduction of liver enzyme to normal level at 12 mo^[14-18]. In our study, 53.5% of patients had normal liver enzyme level at 12 mo of lamivudine therapy, which is slightly lower than that of other studies.

In patients whose enzyme level was not normal after lamivudine treatment (50% of patients), it is likely that a resistant mutant is present which warrants further study for confirmation.

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S- Editor Pan BR L- Editor Zhu LH E- Editor Bai SH