ORIGINAL Article

Efficacy of Lamivudine Treatment in Thai Chronic Hepatitis B Patients

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ABSTRACT

Background: Lamivudine is an effective agent for chronic hepatitis B (CHB). One year lamivudine treatment significantly suppresses hepatitis B viral replication, improves hepatic necroinflammatory activity and prevents progression of fibrosis. However, there are limited data on the extended lamivudine treatment for CHB patients in Thailand.

Objective: To evaluated therapeutic efficacy of lamivudine and determined factors that related to complete response at 12 months.

Patients and Methods: Retrospectively, we collected data of CHB patients treated with lamivudine and followed in Hepatitis Clinic, Siriraj Hospital during 1998-2002. Overall, there were 93 patients included in the study. All received lamivudine 100 mg once daily for at least 6 months to 2 years. We defined the responses to treatment into biochemical, serological, virological and complete response.

Results: Of 93 patients, 75 were men and 18 were female. Fifty-two cases (55.9%) were HBeAg positive. Mean age was 45.7 (17-68) years. All patients continued lamivudine with safety. Biochemical response among HBeAg positive patients was not significantly different from those with HBeAg negative at 6, 12, 18 ,24 months. In HBeAg positive group, HBeAg seroconversion was 36.4% and 41.7% and complete response was 42.4% and 30% at 12 and 24 months, respectively. More than 90% of HBeAg negative patients had virological response with 63.6% and 50% had complete response at 12 and 24 months, respectively. No significant predictive factor for complete response at 12 months was found in both HBeAg positive and negative groups. Thirteen patients (14%) had flare ALT during lamivudine treatment but most of then had normalization of ALT after continue lamivudine treatment.

Conclusion: Lamivudine treatment in Thai CHB patients is effective in terms of biochemical, virological, serological and complete response in both HBeAg positive and HBeAg negative patients.

Key words : Lamivudine, chronic hepatitis B, Thai

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BACKGROUND

Hepatitis B virus is the most common cause of hepatitis in human throughout the world with more than 350 millions people being infected with this virus. The major consequences of hepatitis B infection are development of cirrhosis and hepatocellular carcinoma! However, the incidence of hepatitis B infection varies from country to country. The incidence is high in developing countries whereas it is much lower in development countries. Among developing countries, 5-20% of population have been infected with hepatitis B virus and approximately 25% of infected people die earlier from cirrhosis and hepatocellular carcinoma[2]. In Thailand, it is estimated that about 5% of population are chronically infected with HBV.

Lamivudine, a nucleoside analogue, is an effective therapy for the treatment of chronic hepatitis B by inhibiting HBV polymerase enzyme[3]. Lamivudine is well absorbed and bioavailibity is more than 80% when taken orally and well tolerated with a safety profile equivalent to that of placebo. Lamivudine is excreted via the kidney[4] and is the only nucleoside analogue currently approved for the treatment of chronic hepatitis B[5]. However, the treatment of chronic hepatitis B with lamivudine needs a long period of treatment therefore some drug resistance occurs. Recent study from Lai *et al*[6], showed that one year treatment of lamivudine increased the rate of HBeAg seroconversion and statistically decreased the number of hepatitis and cirrhosis. Liaw *et al*[7] also showed that the seroconversion rate was increased if patients were treated for more than 2 years. Multi-center Asian Study[8] also showed that the rate of HBeAg seroconversion increased correspondingly with the longer treatment duration, 17, 27, 33 and 47% at 1, 2, 3 and 4 years, respectively. However, the effectiveness of lamivudine treatment in Thailand has never been studied. The objective of this study is to determine the result of lamivudine treatment in Thai chronic hepatitis B patients with either HBeAg negative at Siriraj Hospital.

OBJECTIVE

To study the efficacy of lamivudine treatment in Thai chronic hepatitis B patients

PATIENTS AND METHODS

Patients

Medical records of patients with chronic hepatitis B who attended the Hepatitis Clinic, Siriraj Hospital during 1998-2002 were reviewed. The inclusion criteria were 1) Patients with chronic hepatitis and have HBsAg positive more than 6 months. 2) Serum ALT more than or epual to 1.5 times upper limit of normal. 3) HBV DNA more than 200,000 copies per milliliter and/or 4) necro-inflammatory score from liver biopsy more than or equal to 4 by using Knodell's scoring systems. The exclusion criteria were co-infected with hepatitis C, hepatitis D or human immunodeficiency

Table 1 Baseline characteristics of patients (N = 93)

	Mean ± SD	Rang (Min-Max)
Sex (male)	80.6%	
Age (years)	45.7 ± 10.2	(17-18)
ALT (IU/ml)	195.0 ± 190.8	(63-1420)
AST(IU/ml)	132.7 ± 128.8	(60-682)
Albumin (g/dl)	4.2 ± 0.6	(2.0-5.2)
Globulin (g/dl)	3.7 ± 0.7	(2.4-5.3)
HBV DNA (copies/ml)	2204.8 ± 12831.1 × 10^6	(0.39-90000 × 10^6)
HAI score	8.4 ± 4.2	(4-17)
Fibrosis score	1.3 ± 1.2	(0-4)
No. of positive HBeAg	55.9%	
No. of prior interferon therapy	22.6%	
No. of patients at 6, 12, 18, 24 mo	92,77,61,39	

**Quantitative data (SD (min-max)*

virus.

Lamivudine Treatment

All patients received 100 mg of lamivudine orally once a day for at least 6 months.

Evaluation Criteria of Response

1. Biochemical response: ALT level after treatment less than or equal to 40 IU/ml
2. Serological response: Loss of HBeAg loss and/or seroconversion of HBeAg.
3. Virological response: Disappearance of HBV DNA after treatment.
4. Complete response :
   a. Patients with HBeAg positive: ALT less than or equal to 40 IU/ml and HBeAg seroconversion (HBeAg negative and HBeAg negative and HBeAb positive)
   b. Patients with HBeAg negative: ALT less than or equal to 40 IU/ml with disappearance of HBV DNA (less than 200,000 copiea/mL.)
5. Flare ALT: Increase of ALT for more than 2 times after previously normalization of ALT during lamivudine treatment and detectable HBV DNA by quantitative methods.

Biochemical response was evaluated at 6, 12, 18, and 24 months. Serological response, virological response, and complete response were evaluated at 12 and 24 months.

RESULTS

A total of 93 chronic hepatitis B patients were enrolled in this study and assigend to receive lamivudine 100 mg once daily for 6 months to 2 years. The baseline characteristics was showed in Table 1. All patients received lamivudine without any serious side effects. Of the 92 patients who received 100 mg lamivudine for the first 6 months, 77, 61 and 39 patients continued receiving lamivudine 100 mg for 12, 18, and 24 months, respectively. Three patients were lost to follow-up because of the economic and travelling problems. Serum ALT level decreased rapidly during the first three months of treatment in all patients and decreased gradually until the end of the study (Figure 1).

In HBeAg positive patients, biochemical response at 6, 12, 18, 24 months were 60%, 50.5%, 71%, 75%, respectively which were not different from HBeAg negative group, 59.5%, 61.5%, 63%, 50%, respectively (Table 2).

For HBeAg positive patients who were evaluated at 12 and 24 months, HBeAg seroconversion was found 41.75% and 36.4%, respectively and complete response was found 42.4% and 30%, respectively (Table 3). In HBeAg negative group, virological response was foun 95.5 % and 92.9%, respectively and complete response was achieved 63.6% and 50% at 12 and 24 months, respectively (Table 3).

Thirteen patients (14%) had ALT flare (1 patients each at 6, 9, and 15 months, 4 patients at 18 months, and 3 patients at 24 months or more). All of these patients continued receiving lamivudine and most had ALT decreased. There were 9 patients who stopped lamivudine after achieving complete response. Four out of nine patients were still having normal ALT after 6-18 months of follow-up.

In this study, we found no factor that can predict

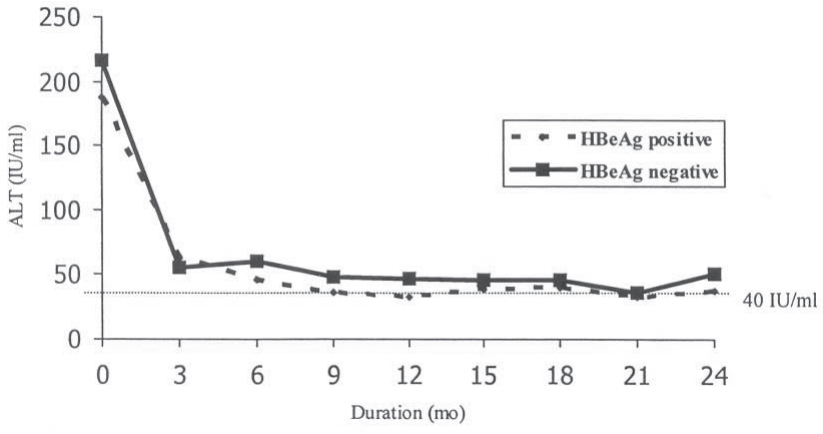

Figure 1 Level of ALT after treatment

Table 2 Proportions of patients with biochemical response after different duration of treatments

Duration (months)	% of patients with biochemical response		p value
	HBeAg positive	HbeAg negative	
6	60.0%	59.5%	0.959
12	80.5%	61.8%	0.072
18	71.0%	63.0%	0.517
24	75.0%	50.0%	0.151

Table 3 Precent of patients who response to treatment

	12 months	24 months
HBeAg positive patients		
HBeAg loss	31.8% (14/44)	33.3% (4/12)
HBeAg seroconversion	41.7% (15/36)	36.4% (4/11)
Complete response	42.4% (14/33)	30.0% (3/10)
HBeAg negative patients		
Virological response	95.5% (21/22)	92.6% (13/14)
Complete response	63.6% (14/22)	50.0% (7/14)

the likelihood of response at 12 months in both HBeAg positive and HBeAg negative groups, i.e., age, sex, pretreatment ALT level, pretreatment HBV-DNA, HAI score, previous Interferon treatment as showed in Table 4.

DISCUSSION

Our retrospective study in which the data were collected from the patients files from Hepatitis Clinic, Siriraj Hospital. Lamivudine was well tolerated. In many previous studies, lamivudine was demonstrated having rapid and consistent suppression of serum HBV-DNA level with normalization of ALT and significant improvement in liver histology. Lamivudine, through its viral inhibition results in enhanced seroconversion, reduces hepatic inflammatory activity and slows the progression of fibrosis in chronic hepatitis B patients with ongoing viral replication and compensated liver diseases. In this study, we found that biochemical response between HBeAg positive and negative were not different significantly. When we focused in the HBeAg positive group, there were lost of HBeAg in 31.8% and 33.3% and HBeAg seroconversion in 41.7% and 36.4% at 12 and 24 months, respectively. These results were not different from previous studies e.g., Leung *et al*[9] reported HBeAg seroconversion rate of 22% and 29% at 12 and 24 months. Complete response rate in our study in the HBeAg positive group was 42.4% and 30% at 12 and 24 months, respectively. These results were comparable to the results of interferon treatment from the meta-analysis of 15 randomized controlled trials which showed HBeAg loss in 33%, HBeAg seroconversion in 18%, but biochemical response was found in only 23% in interferon treated patients[10].

Previous studies demonstrated a high pretreatment ALT and low serum HBV-DNA were good predictors for response to interferon[11-13] and pretreatment ALT for lamivudine[14]. There was no significant predictor for complete response at 12 months including age, sex, pretreatment ALT, pretreatment HBV-DNA, HAI score and previous interferon treatment. All patients with low serum HBV-DNA had complete response at 12 months compared to 54% in patients with high serum HBV-DNA. However, this difference did not reach statistically significant, which may be attributed to the small numbers of patients in our study.

In HBeAg negative group, virological response was more than 90% and complete response was 63.6% and 50% at 12 and 24 months, respectively which were not different from previous studies[15-17]. Similarly, there was no predictor of the complete response at 12 months in this group (Table 4).

Our study found flare ALT in 13 patients (14%)

Table 4 Predictive factors of complete response at 12 months

		Complete response at 12 months		
		Yes (%)	No (%)	p value
HBeAg positive				
Age	≤50	17 (58.6)	12 (41.4)	
	>50	2 (50.0)	2 (50.0)	1.000
Sex	Male	18 (62.1)	11 (37.9)	
	Female	1 (25.0)	3 (75.0)	0.386
Pretreatment ALT				
	≤200 (IU/ml)	15 (62.5)	9 (37.5)	
	>200	4 (44.4)	5 (55.6)	0.350
Pretreatment HBV DNA				
	High*(copies/ml)	6 (54.5)	5 (45.5)	
	Low	4 (100.0)	0	0.302
HAI-Score (means ± SD)		8.4 ± 5.7	7.1 ± 4.4	0.731
Prior IFN treatment				
	Yes	5 (55.6)	4 (44.4)	
	No	14 (58.3)	10 (41.7)	0.886
HBeAg negative				
Age	≤50	6 (42.9)	8 (57.1)	
	>50	2 (25.0)	6 (75.0)	0.402
Sex	Male	6 (37.5)	10 (62.5)	
	Female	2 (33.3)	4 (66.7)	1.000
Pretreatment ALT				
	≤200 (IU/ml)	7 (43.8)	9 (56.3)	
	>200	1 (16.7)	5 (83.3)	0.497
Pretreatment HBV DNA				
	High*(copies/ml)	1 (12.5)	7 (87.5)	
	Low	4 (66.7)	2 (33.3)	0.126
HAI-Score (means ± SD)		7.2 ± 4.1	9.7 ± 3.0	0.391
Prior IFN treatment				
	Yes	1 (20.0)	4 (80.0)	
	No	7 (41.2)	10 (58.8)	0.736

**High HBV-DNA : more than 30×10^6 copies/ml*

and most happened after 18 months assuming from YMDD mutation (but not confirmed by genotypic analysis). This is similar to the results from previous studies that showed genotypic resistance in 14% and 38% at 12 and 24 months, respectively[7-9].

There were nine patients who were able to stop lamivudine treatment after complete response. Four out of nine patients still had normal ALT after 6-18 months of follow-up. Studies from Chang and Song[8,18] found that most of patients remained having normal ALT after continued lamivudine response 38.73%. Another study by Schiff *et al*[19] showed the durability of HBeAg seroconversion of 81% and ALT normalization of 65%. Our study found the durability of ALT normalization of 44% but more of patients and longer period of follow-up may be needed.

In conclusion, lamivudine therapy is effective in Thai chronic hepatitis B patients in the term of biochemical, virological, serological or complete response and in both HBeAg positive and negative patients. The results are not different from previous lamivudine studies. Lamivudine is well tolerated. Our study failed to find any predictor for the complete response at 12 months of lamivudine therapy. However, further study with more patients and longer periods is needed.

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