A Randomized Controlled Trial of Lamivudine to Treat Acute Hepatitis B

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The role of antivirals in patients with acute viral hepatitis B (AVH-B) has not been evaluated in controlled trials. The aim of this study was to evaluate the efficacy of lamivudine in patients with AVH-B. AVH-B patients with serum bilirubin of more than 5 mg/dL were randomized to receive either 100 mg of lamivudine daily for 3 months (group 1, $n = 31$) or placebo (group 2, $n = 40$). Patients were considered to have severe AVH-B if they fulfilled 2 of 3 criteria: (1) hepatic encephalopathy; (2) serum bilirubin ≥ 10.0 mg/dL; and (3) international normalized ratio (INR) ≥ 1.6. At week 4, HBV DNA levels were significantly lower ($P = 0.037$) in group 1 (median: 3.6721 log copies/mL) than group 2 (median: 4.2721 log copies/mL). Thereafter, HBV DNA levels were comparable in the 2 groups. The improvement in serum bilirubin, ALT, and INR values was similar in the 2 groups. Twenty-two patients (71%) in group 1 and 25 patients (62.5%) in group 2 had severe AVH-B. Results were similar when patients with severe AVH-B were analyzed separately. After 12 and 18 months, 93.5% and 92.5%, respectively, of patients in the lamivudine group and 96.7% and 97.5%, respectively, of patients in the placebo group lost HBsAg. There were no deaths in either group. After 1 year, 21 patients (67.7%) in group 1 and 34 patients (85%) in group 2 developed protective anti-HBs titers ($P = 0.096$). All HBeAg-positive patients in both groups lost e antigen and anti-HBe developed in 71% and 87.5% of patients in groups 1 and 2, respectively ($P = 0.132$). *Conclusion:* Though lamivudine causes a greater decrease in levels of HBV DNA, it does not cause significantly greater biochemical and clinical improvement as compared to placebo in patients with acute hepatitis B. (HEPATOLOGY 2007;45:97-101.)

Acute viral hepatitis B (AVH-B) is successfully cleared in more than 95% of immunocompetent patients. The remainder of patients may develop either chronic HBV infection or, in a small proportion, fulminant hepatitis.

The accepted criteria for defining clinical and serologic recovery from acute hepatitis B are clearance of circulating hepatitis B surface antigen (HBsAg) and appearance of the antibodies to HBsAg (anti-HBs), with normalization of serum aminotransferases. Nevertheless, a recent long-term study noted that occult HBV infection might persist in the liver up to 10 years after clinical resolution.[1]

Lamivudine is a potent inhibitor of HBV replication that works by causing chain termination of an RNA-dependent HBV polymerase.[2] It has been administered successfully to immunocompromised patients with AVH-B.[3,4]

Since a proportion of patients with AVH-B develop severe hepatitis and fulminant hepatic failure, a logical hypothesis is that rapid reduction in the HBV DNA levels through the use of antiviral agents could result in a less intense host response against the hepatitis B virus. However, the experience with lamivudine treatment of immunocompetent patients with AVH-B has been limited to only a few case reports,[5,6] a published abstract of a larger series[7] and a pilot study.[8]

The aim of this study was to evaluate the efficacy, utility, and safety of lamivudine in treating immunocompetent patients with AVH-B.

Patients and Methods

From January 2002 to March 2005, 138 patients with acute hepatitis B were seen in the Liver Disease Follow-Up Clinic of G.B. Pant Hospital, New Delhi, India. Only the 71 patients who fulfilled the inclusion criteria were enrolled in this study.

Abbreviations: AVH-B, acute viral hepatitis B; HBsAg, hepatitis B surface antigen;

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The diagnosis of acute hepatitis B was based on recent-onset acute illness including prodromal symptoms, jaundice, and other typical symptoms. Laboratory test results that supported the diagnosis of acute hepatitis were serum ALT and serum bilirubin levels at more than 2.5 times the upper limit and a positive IgM anti-HBc test. Ultrasound and esophagogastroduodenoscopy were performed to look for evidence of chronic liver disease. All patients had normal alpha-fetoprotein levels.

Appropriate serologic tests performed within 7 days of presentation were used to look for coinfection with hepatitis A, hepatitis C, hepatitis D, and hepatitis E, and HIV.

Patients with coinfection, a history of hepatotoxic drug intake or alcohol use of more than 20 g/day, or any evidence of past chronic liver disease at presentation or during follow-up were excluded. Patients were also excluded if they had serum bilirubin of less than 5 mg/dL at presentation.

Patients were classified as having severe AVH-B if they fulfilled any 2 of 3 criteria:[8] (1) hepatic encephalopathy; (2) serum bilirubin $\geq$ 10.0 mg/dL; and (3) international normalized ratio (INR) $\geq$ 1.6.

The patients were randomized into 2 groups: group 1, treatment with 100 mg of lamivudine daily for 3 months; and group 2, the placebo. Randomization was done with a random number table. The initial study and randomization were planned to enroll 120 patients or continue the study until 3 years had elapsed, whichever was earlier. Individual rather than block randomization was done. The investigators as well as the patients were blinded to the randomization. The patients in the placebo group received a placebo pill.

Every week for the first month and then monthly during treatment, all patients were monitored for clinical evidence and grade of hepatic encephalopathy and impaired coagulation (abnormal INR) and had their AST/ALT, serum albumin and bilirubin levels measured. HBV serology, including serum HBsAg, HBeAg, and anti-HBe, was checked at baseline and every 3 months. Anti-HBs titers were checked at 6 and 12 months. A quantitative HBV DNA assay was performed on days 0 and 4, every week in weeks 1-4, every month for the next 2 months, and then every 3 months for the next 12 months.

All patients were followed for at least 12 months after the onset of AVH-B. Development of protective anti-HBs (>10 IU/L) was specifically looked for.

Exacerbation of chronic hepatitis B was excluded by investigating thoroughly for any evidence of chronic liver disease by ultrasound, upper GI endoscopy, or measuring for low albumin at presentation. Ultrasound was repeated at 6 and 12 months, and if there was any suspicion, upper GI endosopy was also repeated. Liver function tests were done at every hospital visit.

HBsAg, HBeAg, IgM anti-HBc, anti-HBs, and anti-HBe were tested by commercially available enzyme-linked immunoassays. Serum quantitative HBV DNA assay was performed by use of an ultrasensitive hybrid capture assay (Digene Labs, Gaithersburg, MD) whose lower limit of detection is 4,700 copies/mL. An arbitrary value of 4,700 copies/mL was assigned to values less than 4,700 copies/mL for analysis purposes. In such patients detection of HBV DNA was done by an in-house qualitative PCR test to indicate whether the patient was negative or positive for viral DNA. The lower limit of detection was 600 copies/mL.[9,10]

Statistics. Statistical analysis was performed by standard methods. Continuous variables were analyzed using the independent Student *t* test. Fischer's exact test and the chi-square test were used to analyze categorical data. A *P* value of less than 0.05 was considered statistically significant. All the statistical calculations were done using SPSS 10.05 software.

Results

Thirty-one patients were in the lamivudine group and 40 patients in the placebo group. Both groups were comparable in age, sex distribution, interval from onset of jaundice to start of therapy, and serum bilirubin, ALT, INR, and HBV DNA levels at the start of therapy. Twenty-two patients (71%) in the lamivudine group and 25 patients (62.5%) in the placebo group had severe AVH-B. Two patients (6.5%) in the lamivudine group and 1 patient (2.5%) in the placebo group presented with hepatic encephalopathy. The baseline characteristics of the patients are shown in Table 1.

All patients were HBsAg positive at presentation: 60 (84.5%) were HBeAg positive (26 [83.9%] in the lamivudine group and 34 [85%] in the placebo group) and 11(15.5%) were serum HBeAg negative (5 [16.1%] in the lamivudine group and 6 [15%] in the placebo group); all patients were serum IgM anti-HBc positive. None of the patients was anti-HBe positive at presentation.

Mean $\pm$ SD and median (range) log copies of serum HBV DNA were comparable ($P = 0.657$) in severe cases (5.4081 $\pm$ 1.0277; 5.1280 [4.01-8.60]) and nonsevere cases (5.2925 $\pm$ 1.0424;5.1114 [4.0-8.46]).

Virological Follow-Up of Patients. Figure 1 shows the median and interquartile HBV DNA levels in both groups of patients. At week 4, HBV DNA levels were significantly lower ($P = 0.037$) in the lamivudine-treated group (median: 3.6721 log copies/mL) than in the placebo-treated group (median: 4.2721 log copies/mL).

Table 1. Baseline Characteristics of Patients

Characteristic	Lamivudine (n = 31)	Placebo (n = 40)	P
Age (years)			0.820
Mean ± SD	37.2 ± 15.9	36.4 ± 13.3	
Median (range)	35(12-78)	36(10-70)	
Male sex, N (%)	20 (64.5)	32 (80)	0.181
Severe hepatitis N(%)	22 (71)	25 (62.5)	0.614
Hepatic encephalopathy at start of therapy [n (%)]			
Grade 0	0	0	0.577
Grade1	0	0	
Grade2	0	0	
Grade3	2 (6.5)	1 (2.5)	
Grade4	0	0	
Interval from onset to start of therapy (days)			
Mean ± SD	18.2 ± 9.2	14.6 ± 7.6	0.067
Median (range)	20.0 (6.0-45)	14.0 (2-40)	
Bilirubin at start of therapy (mg/dL)			
Mean ± SD	10.9 ± 5.7	12.3 ± 6.7	0.365
Median (range)	10.3(5.0-27)	10.5(5.0-27)	
ALT at start of therapy (IU/L)			
Mean ± SD	1658.6 ± 1309.6	1253.4 ± 1004.2	0.144
Median (range)	1250.0 (211-6400)	886.0 (124-3697)	
INR at start of therapy			
Mean ± SD	2.0 ± 0.86	1.89 ± 0.41	0.434
Median (range)	1.68 (1.6-4.5)	1.74 (1.55-3.24)	
HBeAg positive [n (%)]	26 (83.9)	34 (85)	1.00
IgM-anti-HBc positive [n (%)]	31 (100)	40 (100)	1.00
Detectable HBV DNA (>4,700 copies/mL) [n (%)]	31 (100)	40 (100)	1.00
HBV DNA at start of therapy (log copies/mL)			
Mean ± SD	5.531 ± 1.133	5.243 ± 0.932	0.245
Median (range)	5.135 (4.16-8.6)	5.085 (4.0-8.48)	

Thereafter, there was no difference in HBV DNA levels between the 2 groups of patients. Figure 2 shows the proportion of patients who were HBVDNA positive (>600 copies/mL) in both groups. All patients were HBV DNA positive (100%) at the start, and this decreased to about 20% in both the lamivudine and placebo groups after 1year.

After 1 year, 29 patients (93.5%) in the lamivudine group and 37 patients (92.5%) in the placebo group lost HBsAg. After 18 months, 30 patients (96.7%) in the lamivudine group and 39 patients (97.5%) in the placebo group lost HBsAg.

Follow-up of patients who were still HBsAg positive after 1 year is depicted in Table 2. The 2 patients (one from each group) who were still HBsAg positive after 18 months developed chronic hepatitis B. Both underwent liver biopsy, which showed no fibrosis and only minimal inflammation. The lamivudine-treated patient had F0 fibrosis and a hepatic activity index (HAI) of 1. The placebo-treated patient had F0 fibrosis and an HAI of 2.

All the patients who were HBeAg positive (26 in the lamivudine group and 34 in the placebo group) became HBeAg negative. Overall, anti-HBe developed in 22 of 31

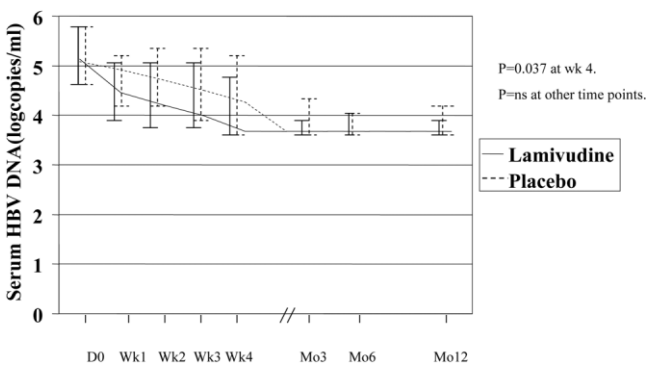

Fig. 1. Median and interquartile HBV DNA levels in both groups of patients during the course of treatment and during follow-up.

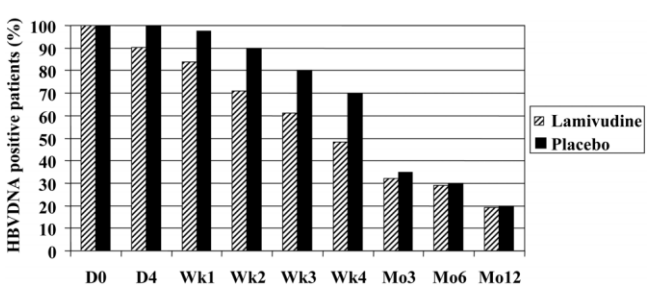

Fig. 2. Proportion of patients who were HBVDNA positive (>600 copies/mL) at various time points in both groups.

Table 2. Follow-Up of Patients Who Were HBsAg-Positive After 12 Months

Patient Number	Group	12 Months			18 Months		
		HBsAg	HBV DNA (log cp/mL)	ALT (IU/L)	HBsAg	HBV DNA (log cp/mL)	ALT (IU/L)
1	Lam	+	4.09	51	−	<600 copies/mL	35
2*	Lam	+	4.38	50	+	4.1	49
3*	Placebo	+	4.82	48	+	4.08	59
4	Placebo	+	4.36	52	−	<600 copies/mL	32
5	Placebo	+	<600 copies/mL	40	−	<600 copies/mL	30

*These 2 patients developed chronic hepatitis B.

patients (71%) in the lamivudine group and 35 of 40 patients (87.5%) in the placebo group ($P = 0.132$).

There was a slightly lower rate of development of protective anti-HBs in patients treated with lamivudine. After 1 year, 21 patients (67.7%) in the lamivudine group and 34 patients (85%) in the placebo group developed protective anti-HBs titers. However, the difference between the 2 groups was not significant ($P = 0.096$). Among the patients with severe disease, 16 (72.2%) in the lamivudine group and 21 (84.0%) in the placebo group ($P = 0.346$) developed protective anti-HBs titers.

Biochemical Follow-Up of Patients. Figure 3 shows median and interquartile bilirubin levels in both groups of patients. There was no significant difference between the lamivudine-treated and placebo-treated patients. Among the severe cases also, the results were similar.

Figure 4 shows the median and interquartile ALT levels in both group of patients. There was no significant difference between the lamivudine-treated and the placebo-treated patients. The results were also similar among those with severe disease.

Similarly, there was no significant difference between groups in trends of INR improvement.

Clinical Outcomes of Patients. There was no mortality in either group. All the patients presenting with encephalopathy recovered within 1 week. There was also no significant difference in the clinical outcome between the lamivudine-treated and the placebo-treated groups.

Safety. No patient had a serious adverse event that could be attributed to lamivudine, and all patients tolerated therapy without dose modification or the need for early discontinuation. No patient developed pancreatitis, neuropathy, or renal impairment.

Discussion

This is the first randomized trial that has compared the use of lamivudine with placebo for the treatment of acute hepatitis B. In this study, we administered 100 mg of lamivudine daily over a short period (3 months) to patients with acute hepatitis B infection. The results showed that though lamivudine therapy in AVH-B causes a greater decrease in HBV DNA levels, the clinical benefit in biochemical and clinical improvement is modest even in severe cases.

Patients with acute HBV infection can develop chronic HBV infection or fulminant hepatitis (0.5%-2%).[1] Lamivudine has been administered successfully to immunocompromised patients and to liver transplant recipients with AVH-B.[3,4] The experience with lamivudine treatment of immunocompetent patients with AVH-B is limited. In a small study, 3 patients with acute hepatitis B were treated with lamivudine 150 mg daily. In all the patients, serum HBV DNA became undetectable, and HBsAg and HBeAg disappeared.[6]

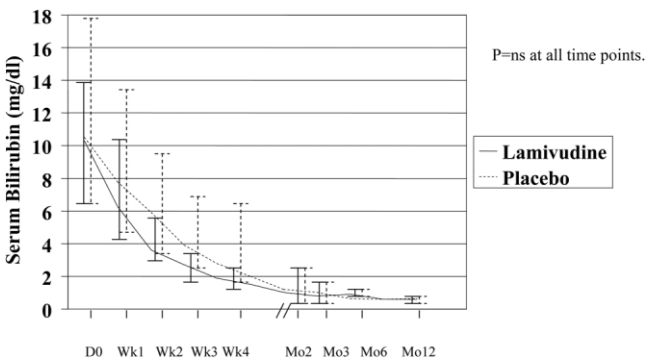

Fig. 3. Median and interquartile bilirubin levels in both groups of patients.

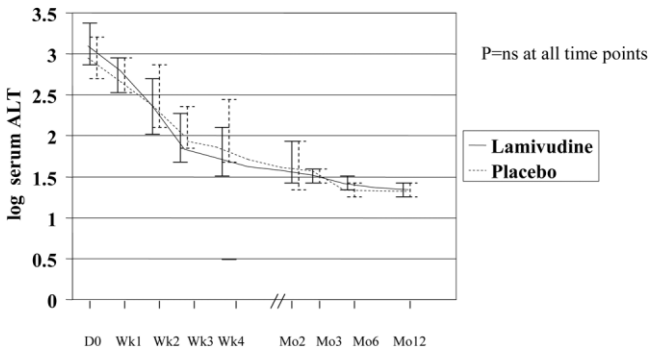

Fig. 4. Median and interquartile ALT levels in both groups of patients.

In a case report, a 74-year-old patient with acute hepatitis B and hepatic encephalopathy responded to lamivudine with the disappearance of serum HBsAg.[5]

In a study of 46 patients with severe acute hepatitis B (the criteria for severity were unclear), 3 months after lamivudine treatment, serum HBV DNA became undetectable in all the patients, and anti-HBe became positive in 87.5% of the patients.[7]

In another study, 15 patients with severe acute HBV infection were treated with lamivudine 100 mg daily for 3-6 months, with 5 patients having grade 1-4 encephalopathy prior to onset of treatment. Thirteen (86.6%) patients responded. Encephalopathy disappeared within 3 days of treatment. Serum HBV DNA became undetectable (by PCR) within 4 weeks, and liver enzymes normalized within 8 weeks. Anti-HBe developed in 9 of 11 HBeAg-positive patients within 12 weeks.[8]

Long-term lamivudine treatment is associated with the emergence of lamivudine-resistant mutants. However, lamivudine resistance rarely occurs during the first 36 weeks of therapy.[11] We administered lamivudine for only 12 weeks, thereby attempting to prevent the emergence of lamivudine resistance.

Although HBV DNA levels fell more rapidly in the patients who received lamivudine, there were no differences in the clinical course and outcome between the 2 treatment groups. Clinical recovery was no faster in the lamivudine-treated than in the placebo-treated patients.

More potent antiviral drugs such as entecavir and tenofovir are now available. It is possible that these antivirals may be useful in a select group of patients with severe acute hepatitis B. It could be advocated that patients with signs of fulminant hepatitis in centers with liver transplant facilities should be treated with potent antiviral drugs, as these patients might go to transplantation and it would be best to have HBV DNA levels as low as possible at the time of transplant. However, it would be worthwhile to measure HBV DNA levels in patients with such severe or fulminant hepatitis B, as their HBV DNA levels are likely to be low or undetectable.[12]

There is no clear explanation of why, despite a greater decrease in HBV DNA levels in the lamivudine group, the clinical benefits of biochemical and clinical improvement were unimpressive. The resolution of acute hepatitis B involves a complex interplay of innate and adaptive immune responses and cellular and humoral immunity. It is believed that HBV is a noncytopathic virus and that cytotoxic T lymphocytes mediate clearance of HBV-infected cells through a cytolytic process.[13,14] Therefore, as the injury during acute hepatitis B is mainly noncytolytic with some contribution from cytolytic mechanisms and HBV is primarily a noncytopathic virus, the decline in HBV DNA by lamivudine is not accompanied by a commensurate decline in serum bilirubin and ALT values.

In conclusion, although lamivudine caused a greater decrease in HBV DNA levels in patients with acute hepatitis B, it did not produce significant biochemical and clinical improvement compared to that in patients who received the placebo.

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