

## LAMIVUDINE AS INITIAL TREATMENT FOR CHRONIC HEPATITIS B IN THE UNITED STATES

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### ABSTRACT

**Background** Although the nucleoside analogue lamivudine has shown promise in patients with chronic hepatitis B, long-term data on patients from the United States are lacking.

**Methods** We randomly assigned previously untreated patients with chronic hepatitis B to receive either 100 mg of oral lamivudine or placebo daily for 52 weeks. We then followed them for an additional 16 weeks to evaluate post-treatment safety and the durability of responses. The primary end point with respect to efficacy was a reduction of at least 2 points in the score on the Histologic Activity Index. On this scale, scores can range from 0 (normal) to 22 (most severe abnormalities).

**Results** Of the 143 randomized patients, 137 were included in the efficacy analysis: 66 in the lamivudine group and 71 in the placebo group. The other six patients were excluded at the base-line visit because of the absence of a documented history of hepatitis B surface antigen for at least six months. After 52 weeks of treatment, lamivudine recipients were more likely than placebo recipients to have a histologic response (52 percent vs. 23 percent,  $P < 0.001$ ), loss of hepatitis B e antigen (HBeAg) in serum (32 percent vs. 11 percent,  $P = 0.003$ ), sustained suppression of serum hepatitis B virus (HBV) DNA to undetectable levels (44 percent vs. 16 percent,  $P < 0.001$ ), and sustained normalization of serum alanine aminotransferase levels (41 percent vs. 7 percent,  $P < 0.001$ ), and they were less likely to have increased hepatic fibrosis (5 percent vs. 20 percent,  $P = 0.01$ ). Lamivudine recipients were also more likely to undergo HBeAg seroconversion, defined as the loss of HBeAg, undetectable levels of serum HBV DNA, and the appearance of antibodies against HBeAg (17 percent vs. 6 percent,  $P = 0.04$ ). HBeAg responses persisted in most patients for 16 weeks after the discontinuation of treatment. Lamivudine was well tolerated. Self-limited post-treatment elevations in serum alanine aminotransferase were more common in lamivudine recipients: 25 percent had serum alanine aminotransferase levels that were at least three times base-line levels, as compared with 8 percent of placebo recipients ( $P = 0.01$ ). The clinical condition of all patients remained stable during the study.

**Conclusions** In U.S. patients with previously untreated chronic hepatitis B, one year of lamivudine therapy had favorable effects on histologic, virologic, and biochemical features of the disease and was well tolerated. HBeAg responses were usually sustained after treatment. (N Engl J Med 1999;341:1256-63.)

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**H**EPATITIS B virus (HBV) infects more than 300 million people worldwide, contributing to debilitating illness and death.<sup>1</sup> Until recently, the only antiviral drug for the treatment of hepatitis B was interferon.<sup>2-4</sup>

In preliminary studies of patients with chronic hepatitis B, lamivudine, an oral nucleoside analogue,<sup>5</sup> was well tolerated and suppressed serum levels of HBV DNA profoundly.<sup>6-9</sup> We therefore conducted a one-year study of the efficacy of lamivudine in patients with chronic hepatitis B. After our data on patients had been collected, Lai et al.<sup>10</sup> reported the results of a placebo-controlled study in which they found histologic, biochemical, and serologic improvement in patients in Hong Kong after 12 months of lamivudine therapy.

The natural history of HBV infection differs between Asian and Western patients. Asian patients, who usually become infected perinatally, rarely have an acute hepatitis-like clinical syndrome but almost invariably remain chronically infected and are at substantial risk for cirrhosis and hepatocellular carcinoma. Western patients, who are usually infected as adults by percutaneous or sexual exposure, typically have an acute hepatitis-like clinical illness and rarely become chronically infected.<sup>1,11-15</sup> In addition, Asian patients, especially those with normal or near-normal aminotransferase activity, have less of a response to interferon therapy than Western patients.<sup>16</sup> We postulated that such differences in the natural history of chronic hepatitis B and the responsiveness to interferon between Asian and Western patients would be reflected by a difference in response to lamivudine in Western patients with chronic hepatitis B. Moreover, in the study by Lai et al.,<sup>10</sup> therapy was continued indefinitely and the effect of stopping therapy was not

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assessed. Our study included a four-month follow-up period, which allowed us to evaluate post-treatment effects and the durability of serologic responses.

## METHODS

### Study Design

Between May 1995 and August 1997, we conducted a prospective, randomized, double-blind, placebo-controlled study of previously untreated patients with chronic hepatitis B in 34 U.S. centers. Patients received either 100 mg of lamivudine (EpiVir-HBV, Glaxo Wellcome, Research Triangle Park, N.C.) per day orally or matching placebo for 52 weeks and were then monitored for an additional 16 weeks. The patients were assessed two and four weeks after the initiation of therapy and every four weeks thereafter. Liver biopsies were performed at base line, unless they had been done within the previous 12 months, and at week 52. The study was approved by the institutional review boards at participating medical centers, and all patients gave written, informed consent.

### Patients

When this study was conducted, the results of the placebo-controlled efficacy study by Lai et al.<sup>10</sup> were not available, and the only approved therapy was interferon alfa, an injectable drug with substantial side effects. Potential subjects had to acknowledge that by participating in the study, they were willing to forgo interferon therapy.

To be eligible, patients had to be at least 18 years of age; to have had detectable serum hepatitis B surface antigen (HBsAg) for at least six months, serum hepatitis B e antigen (HBeAg) for at least one month, and serum alanine aminotransferase levels that were 1.3 to 10 times the upper limit of the normal range for at least three months. Patients also had to have evidence of chronic hepatitis on liver biopsy and detectable levels of serum HBV DNA according to a hybridization assay (Abbott Diagnostics, North Chicago, Ill.). The limit of detection of this assay was approximately 1.6 pg ( $10^6$  genomes) per milliliter.

Patients were excluded if they had any of the following: previous antiviral treatment for hepatitis B; treatment with antiviral agents, immunomodulatory drugs, or corticosteroids within six months before the study began; a bilirubin level of more than 2.5 mg per deciliter ( $43 \mu\text{mol}$  per liter); a prothrombin time that was more than three seconds longer than normal; an albumin level of less than 3.5 g per deciliter; a history of ascites, variceal hemorrhage, or hepatic encephalopathy; coinfection with hepatitis C virus, hepatitis D virus, or the human immunodeficiency virus; a nuclear antibody titer of more than 1:160; a creatinine level of more than 1.5 mg per deciliter ( $130 \mu\text{mol}$  per liter); a hemoglobin level of less than 11 g per deciliter; a white-cell count of less than 3000 per cubic millimeter, a neutrophil count of less than 1500 per cubic millimeter, and a platelet count of less than 100,000 per cubic millimeter; or the presence of confounding medical illness or other types of liver disease. Women who were pregnant or breastfeeding were also excluded.

### End Points

The primary end point was an improvement of at least 2 points in the score on the Histologic Activity Index.<sup>17</sup> On this index, scores can range from 0 (normal) to 22 (the most severe abnormalities) and are the sum of four histologic components: the severity of periportal necrosis (range of scores, 0 to 10), intralobular necrosis (0 to 4), portal inflammation (0 to 4), and fibrosis (0 to 4). A reduction of at least 2 points has been validated as a clinically meaningful indicator of histologic changes in patients with chronic viral hepatitis.<sup>10,18-20</sup> The scores for the Histologic Activity Index were calculated by an independent histopathologist who examined all slides of liver-biopsy specimens and who was unaware of the patients' treatment assignments or the times

at which the specimens had been obtained. In addition, he performed a blinded ranking comparison, using a method validated previously,<sup>2,10</sup> of paired biopsy slides for each patient — one obtained before treatment and the other obtained at week 52 — in which he separately graded necroinflammatory features and determined the stage of fibrosis. After the code was broken, the results of these comparisons were used to determine whether the findings on the liver-biopsy specimen obtained at week 52 were better than, worse than, or the same as those for biopsy specimens obtained at base line.

Secondary end points included the loss of detectable levels of HBeAg and HBV DNA in serum and the appearance of antibody to HBeAg (referred to as HBeAg seroconversion); worsening fibrosis, on the basis of the ranked assessment of paired biopsy specimens; sustained return of serum alanine aminotransferase levels to normal; sustained suppression of serum levels of HBV DNA (i.e., the absence of detectable levels on two consecutive measurements and thereafter until the end of therapy); the loss of detectable levels of serum HBeAg or of HBsAg; and adverse effects. During the 16-week follow-up period (weeks 53 to 68), the durability of the response was assessed and the patients were monitored for adverse effects. Efficacy outcomes were subjected to a modified intention-to-treat analysis that included all randomized patients who met the entry criteria; analyses with fewer than 66 patients in the lamivudine group or 71 patients in the placebo group reflect the exclusion of patients whose serologic or biochemical status at base line differed from that at screening. For the histologic analyses, patients who had missing biopsy data were counted as having no response. All patients who received at least one dose of lamivudine or placebo were included in the analyses of adverse effects.

### Genetic Analysis

Mutations in the YMDD (tyrosine, methionine, aspartate, and aspartate) motif of HBV polymerase, which have been associated with potential resistance of HBV to lamivudine,<sup>21-23</sup> were assessed in HBV DNA amplified by the polymerase chain reaction.<sup>10,24</sup> HBV DNA was obtained from stored serum samples obtained at week 52.

### Statistical Analysis

We anticipated that 50 percent of the patients in the lamivudine group and 10 percent of those in the placebo group would have a reduction of at least 2 points in the score on the Histologic Activity Index. We determined that at least 120 patients would be needed to allow the study to have a two-tailed significance level of 0.05 and a power of 99 percent. We further assumed that base-line liver-biopsy samples might be inadequate for histologic evaluation in 5 percent of patients, that base-line Histologic Activity Index scores would be less than 2 in up to 10 percent of patients, that 10 percent of patients might withdraw from the trial, that 10 percent might decline to undergo a second liver biopsy, and that 5 percent of the liver-biopsy samples obtained at the end of treatment would be inadequate for histologic evaluation. These assumptions and the classification of all patients with missing histologic data as having no response to treatment would result in an apparent histologic response in 33 percent of lamivudine recipients and 7 percent of placebo recipients, giving the study a power of 90 percent.

Statistical tests (the Mantel-Haenszel test, the van Elteren test, Fisher's exact test, and the signed-rank test) for comparisons between treatment groups and resulting P values were two-tailed.<sup>25</sup> Logistic-regression models, adjusted for base-line covariates (serum alanine aminotransferase and HBV DNA levels, scores on the Histologic Activity Index, race, age, sex, weight, and presence or absence of cirrhosis), were used to assess the effect of covariates on efficacy outcomes.<sup>25</sup> No interim analyses were performed.

## RESULTS

We screened 217 patients and enrolled 143: 72 were randomly assigned to the placebo group and 71 to the lamivudine group. Six of the 143 patients

were excluded at the base-line visit because of the absence of a documented history of serum HBsAg for at least six months. Of these six, two withdrew before receiving any treatment. Therefore, the modified intention-to-treat population consisted of 137 patients: 66 received lamivudine and 71 placebo. For the assessments of histologic response, paired biopsy data were available for 104 of the 137 patients. There were no statistically significant differences between the two groups with respect to demographic or clinical features at base line, with the exception of the route of acquisition of the infection and serum levels of HBV DNA. Serum levels of HBV DNA were higher in the lamivudine group at base line (Table 1). The condition of all the patients was stable at enrollment and remained so during the study.

### Histologic Response

In the lamivudine group, 34 of 66 patients (52 percent) had a reduction of at least 2 points in the Histologic Activity Index score, as compared with 16 of 71 patients (23 percent) in the placebo group ( $P < 0.001$ ). The inclusion of the six randomized patients who met the eligibility criteria at screening but not at entry had no effect on the results (37 of 71 lamivudine recipients [52 percent] vs. 16 of 72 placebo recipients [22 percent],  $P < 0.001$ ). Histologic worsening, defined as an increase of at least 2 points in the Histologic Activity Index score, occurred in 7 of 66 lamivudine recipients (11 percent) and 17 of 71 placebo recipients (24 percent,  $P < 0.001$ ).

In a blinded ranking of pretreatment and post-treatment liver-biopsy specimens, we identified a decrease in necroinflammatory activity in specimens from 42 of 66 lamivudine recipients (64 percent) and 24 of 71 placebo recipients (34 percent,  $P = 0.001$ ) and increased fibrosis in specimens from 3 of 66 lamivudine recipients (5 percent) and 14 of 71 placebo recipients (20 percent,  $P = 0.01$ ). The median reduction in the score of the Histologic Activity Index was 3 in the lamivudine group and 0 in the placebo group. Lamivudine recipients with HBeAg seroconversion (i.e., loss of serum HBeAg, undetectable levels on serum HBV DNA, and the presence of antibodies against HBeAg) or loss of serum HBeAg had median reductions in the scores on the Histologic Activity Index of 6 and 5, respectively. Lamivudine recipients with no change in HBeAg status had median reductions in scores of 3 and 2, respectively.

### Virologic Response

Lamivudine suppressed serum HBV DNA to undetectable levels in nearly all treated patients, within a median of four weeks. The cumulative percentage of patients in whom serum HBV DNA levels were undetectable at least once during treatment was 98 percent in the lamivudine group (62 of 63 patients) and 33 percent in the placebo group (23 of 69 pa-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	LAMIVUDINE GROUP (N=66)	PLACEBO GROUP (N=71)
Age (yr)		
Median	40	38
Range	18-73	20-67
Male sex (%)	86	80
Weight (kg)		
Median	78.1	74.5
Range	51-145	45-168
Race (%)		
White	59	56
Asian	24	17
Black	15	18
Other or unknown	2	9
Route of HBV acquisition (%)*		
Injection-drug use	3	0
Perinatal	23	8
Sexual	29	35
Transfusion	8	3
Other or unknown	38	54
Cirrhosis (%)	6	14
Histologic Activity Index score		
Median	10	11
Range	0-15†	3-17
Serum HBV DNA (pg/ml)‡		
Median	102.2	56.5
Range	0.8-1753†	0.8-653
Serum alanine aminotransferase (U/liter)		
Median	125	135
Range	46-401†	33-592
Serum bilirubin (mg/dl)§		
Median	0.7	0.7
Range	0.3-2.2	0.3-2.0
Serum albumin (g/dl)		
Median	3.9	3.8
Range	2.9-4.5	2.9-4.6

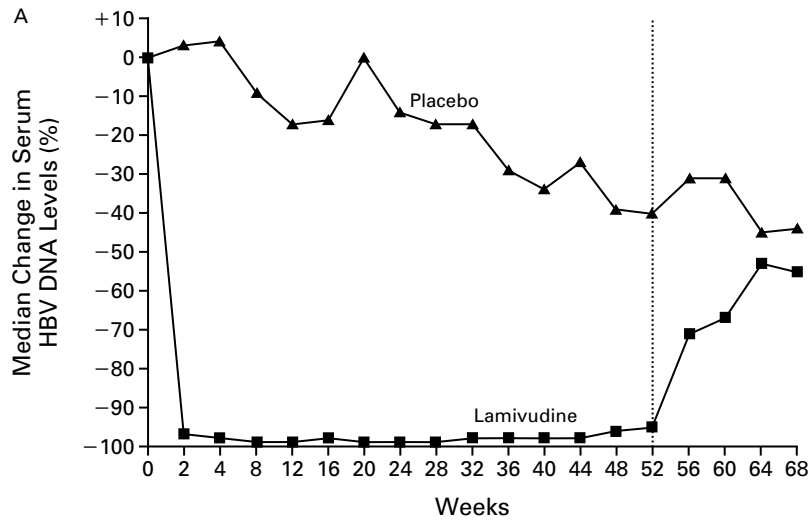
\*The results of the assessment of the effect of lamivudine treatment on the primary histologic end point were the same ( $P < 0.001$ ) whether or not the results were adjusted for the route of HBV acquisition.  $P = 0.36$  for the interaction between the type of treatment and the route of HBV acquisition. Because of rounding, not all percentages sum to 100.

†Values such as a Histologic Activity Index score of 0, a serum HBV DNA level of less than 1.6 pg per milliliter (all such measurements were assigned a value of 0.8 in the calculation of the medians), or a normal serum alanine aminotransferase level were exclusion criteria. Subjects who had such values at base line had had acceptable values at screening. These patients were allowed to continue therapy and were included in the safety analysis but not in the efficacy analysis.

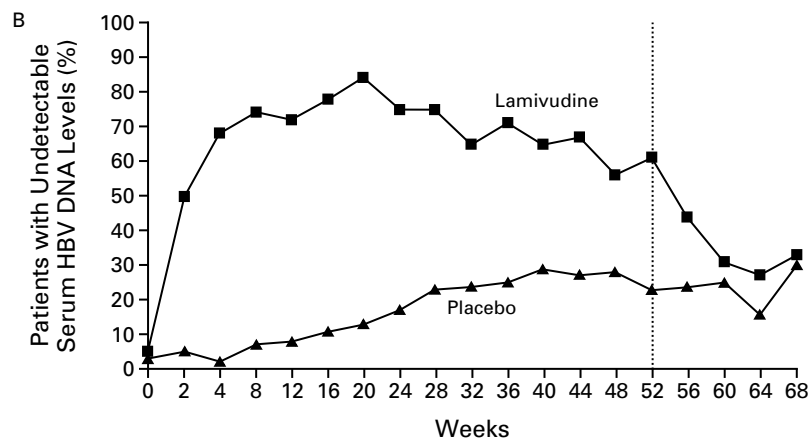
‡The results of the assessment of the effect of lamivudine treatment on the primary histologic end point were the same ( $P < 0.001$ ) whether or not the results were adjusted for serum HBV DNA levels at base line.  $P = 0.34$  for the interaction between the type of treatment and serum HBV DNA levels at base line.

§To convert values for bilirubin to micromoles per deciliter, multiply by 17.1.

tients). The cumulative percentage with sustained suppression of serum HBV DNA levels through week 52 was 44 percent in the lamivudine group (28 of 63 patients) and 16 percent in the placebo group (11 of 69 patients,  $P < 0.001$ ). Among the lamivudine recipients, the median level of suppression of serum HBV DNA levels ranged from 95 to 99 percent



No. EVALUATED	
Placebo	65 62 61 59 64 61 62 59 56 58 59 55 56 54 56 50 48 50 53
Lamivudine	63 60 62 61 58 60 62 59 56 57 58 55 51 54 54 48 51 51 52



No. EVALUATED	
Placebo	65 62 61 59 64 61 62 59 56 58 59 55 56 54 56 50 48 50 53
Lamivudine	63 60 62 61 58 60 62 59 56 57 58 55 51 54 54 48 51 51 52

**Figure 1.** Median Changes in Serum HBV DNA Levels from Base Line (Panel A) and Percentages of Patients with Undetectable Serum HBV DNA Levels (Panel B).

Serum HBV DNA levels were measured with a liquid hybridization assay with a limit of detection of 1.6 pg per milliliter. In Panel A, the reduction in serum HBV DNA levels in the placebo group may represent regression toward the mean, perhaps because patients with more active hepatitis, who may be having spontaneous flares that accompany reductions in the rate of viral replication, are more likely to be included in clinical studies. The dotted line in each panel marks the end of treatment.

throughout the 52 weeks of therapy. Among placebo recipients, serum levels of HBV DNA fell gradually during treatment, with a median level of suppression of approximately 40 percent (Fig. 1A). The percentage of patients at each study visit with undetectable serum HBV DNA levels is shown in Figure 1B.

By week 52 of therapy, lamivudine recipients were

more likely than placebo recipients to have had HBeAg seroconversion (11 of 63 [17 percent] vs. 4 of 69 [6 percent],  $P=0.04$ ) and to have lost serum HBeAg (21 of 66 [32 percent] vs. 8 of 71 [11 percent],  $P=0.003$ ). Sixteen weeks after the end of treatment, 11 of 63 lamivudine recipients (17 percent) had undergone HBeAg seroconversion (3 who had previ-

ously seroconverted reverted, and 3 underwent seroconversion for the first time, for a net change of 0 and a maintenance of the serologic response in 8 [73 percent] of the 11 who had undergone HBeAg seroconversion at week 52). A total of 6 of 69 placebo recipients (9 percent) had undergone HBeAg seroconversion at week 68. Similarly, 16 weeks after the end of treatment, 19 of 66 lamivudine recipients (29 percent) did not have serum HBeAg (it was present in 4 in whom it had been absent at week 52 and absent in 2 in whom it had been present at week 52, for a net loss of 2 patients and a maintenance of the serologic response in 81 percent). A total of 11 of 71 placebo recipients (15 percent) did not have serum HBeAg at week 68 (it was present in 1 in whom it had been absent at week 52 and absent in 4 in whom it had been present at week 52, for a net gain of 3 and a maintenance of the serologic response in 88 percent). Loss of serum HBsAg occurred in 1 of 66 lamivudine recipients (2 percent) but in none of 71 placebo recipients.

As compared with patients who received lamivudine for 3 months<sup>6</sup> or 6 months,<sup>9</sup> whose serum HBV DNA levels returned to base line within 2 months after the end of treatment, our patients, who received lamivudine for 12 months, had a slower return of detectable serum HBV DNA levels (Fig. 2), and the median levels were approximately 55 percent below the base-line levels at week 68 (Fig. 1).

To identify the potential effect of base-line variables on the histologic and serologic responses, we performed logistic-regression analyses that included base-

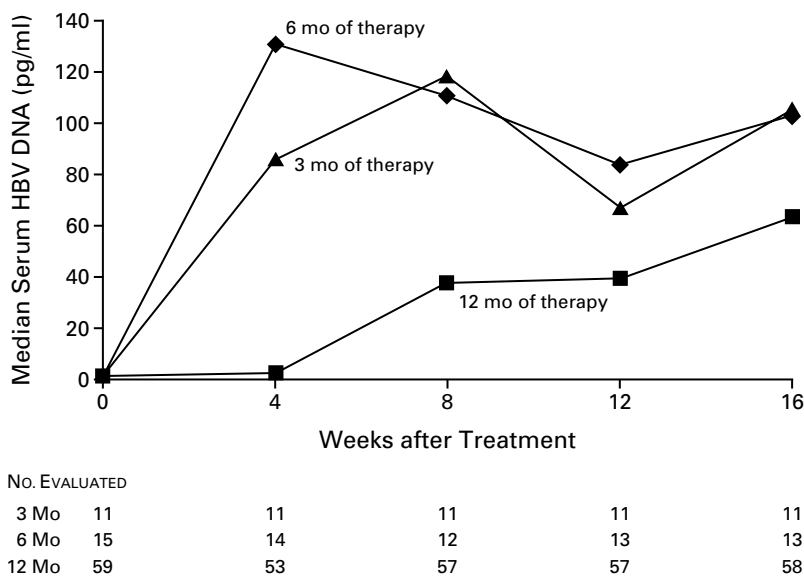
line characteristics as covariates. The likelihood of a histologic response (odds ratio, 7.5; 95 percent confidence interval, 2.7 to 20.9;  $P < 0.001$ ) and of HBeAg seroconversion (odds ratio, 9.7; 95 percent confidence interval, 1.7 to 56.1;  $P = 0.01$ ) remained significantly higher among lamivudine recipients than among placebo recipients after adjustment for the base-line covariates of serum alanine aminotransferase levels, serum HBV DNA levels, Histologic Activity Index score, race (Asian, white, black, or other or unknown), age, sex, weight, and the presence or absence of cirrhosis.

#### Biochemical Response

During the 52 weeks of treatment, serum alanine aminotransferase levels returned to normal and remained so in 27 of 66 lamivudine recipients (41 percent) and 5 of 68 placebo recipients (7 percent,  $P < 0.001$ ).

#### Adverse Events

Lamivudine was well tolerated, with an incidence of adverse events that was similar to that for placebo. The most common adverse events were malaise or fatigue and nausea or vomiting (Table 2). There were no deaths or instances of hepatic decompensation during the study. The frequency of grade III or IV abnormalities in clinical laboratory values was similar in the two study groups (Table 2). During therapy, similar proportions of both groups had elevations in serum alanine aminotransferase (Table 3). After therapy, serum alanine aminotransferase levels that were



**Figure 2.** Median Serum HBV DNA Levels after 3, 6, and 12 Months of Lamivudine Therapy.

The 12-month data are from the current study; the 3-month and 6-month data are from Dienstag et al.<sup>6</sup> and Nevens et al.,<sup>9</sup> respectively. The limit of detection of the assay that we used is 1.6 pg per milliliter.

**TABLE 2. ADVERSE CLINICAL AND LABORATORY EVENTS DURING 52 WEEKS OF THERAPY AND 16 WEEKS OF FOLLOW-UP.\***

ADVERSE EVENT	LAMIVUDINE GROUP (N=70)	PLACEBO GROUP (N=71)
	percentage of patients	
Events during treatment and follow-up		
Malaise or fatigue	19	20
Nausea or vomiting	9	15
Headache	9	8
Muscle pain	0	8
Abdominal discomfort	4	7
Sleep disorder	7	4
Paresthesias	3	7
Rash	6	8
Diarrhea	6	6
Grade III or IV laboratory abnormalities during treatment†		
Alanine aminotransferase	10	13
Albumin	0	3
Amylase	0	1
Lipase	9	7
Creatine kinase	9	4
Platelets	0	3

\*Only adverse events that were reported by at least 5 percent of patients are listed. Two of the 143 randomized patients withdrew before receiving treatment (one in each group) and were therefore excluded from the analysis of adverse effects.

†Grade III and IV abnormalities are defined as follows: for alanine aminotransferase, a value 3.1 to 10 times the base-line value and more than 10 times the base-line value, respectively; for albumin, a value of 2.0 to 2.4 g per deciliter and less than 2.0 g per deciliter; for amylase, a value 3.1 to 10 times the base-line value and more than 10 times the base-line value; for lipase, a value 2.6 to 5 times the upper limit of normal and more than 5 times the upper limit of normal; for bilirubin, a value 5.1 to 10 times the upper limit of normal and more than 10 times the upper limit of normal; for creatine kinase, a value 7 to 9.9 times the base-line value and at least 10 times the base-line value; for hemoglobin, a value of 6.4 to 7.9 g per deciliter and less than 6.4 g per deciliter; for the neutrophil count, a value of 500 to 740 per cubic millimeter and less than 500 per cubic millimeter; for the platelet count, a value of 20,000 to 49,000 per cubic millimeter and less than 20,000 per cubic millimeter; for the white-cell count, a value of 1000 to 1400 per cubic millimeter and less than 1000 per cubic millimeter. None of the patients in either group had grade III or IV abnormalities in serum bilirubin levels, hemoglobin levels, neutrophil counts, or white-cell counts.

at least three times the base-line values were more common among lamivudine recipients than among placebo recipients (25 percent vs. 8 percent,  $P=0.01$ ); however, none of the patients who had elevations in serum alanine aminotransferase levels had hepatic decompensation (Table 3). Elevations in serum alanine aminotransferase during therapy were more frequently associated with HBeAg seroconversion and loss of HBeAg in the lamivudine group (4 of 18 patients [22 percent] and 6 of 18 patients [33 percent], respectively) than in the placebo group (0 of 18 and 2 of 19 patients [11 percent], respectively).

**Viral Variants**

We analyzed HBV DNA amplified from serum samples obtained at the end of treatment (week 52) from

**TABLE 3. INCIDENCE OF ELEVATIONS IN SERUM ALANINE AMINOTRANSFERASE LEVELS DURING 52 WEEKS OF TREATMENT AND 16 WEEKS OF FOLLOW-UP.\***

VARIABLE	LAMIVUDINE GROUP	PLACEBO GROUP
	no. of patients (%)	
<b>During therapy</b>		
Grade III abnormality in ALT	7 (10)	9 (13)
Grade IV abnormality in ALT	0	0
ALT $\geq 2$ times above base-line levels	18 (26)	19 (27)
ALT $\geq 3$ times above base-line levels	7 (10)	9 (13)
ALT $\geq 2$ times above base-line levels and $>500$ U/liter	1 (1)	7 (10)
ALT $\geq 2$ times above base-line levels and bilirubin $\geq 2$ times above base-line levels	0	0
<b>During follow-up</b>		
Grade III abnormality in ALT	14 (22)	4 (6)†
Grade IV abnormality in ALT	2 (3)	1 (2)
ALT $\geq 2$ times above base-line levels	19 (29)	13 (20)
ALT $\geq 3$ times above base-line levels	16 (25)	5 (8)†
ALT $\geq 2$ times above base-line levels and $>500$ U/liter	12 (18)	6 (9)
ALT $\geq 2$ times above base-line levels and bilirubin $\geq 2$ times above base-line levels	1 (2)	1 (2)

\*A grade III abnormality was defined as a serum alanine aminotransferase (ALT) value that was 3.1 to 10 times the base-line value, and a grade IV abnormality as a value that was more than 10 times the base-line value. The respective numbers of patients in the lamivudine group and the placebo group were 70 and 71 during therapy and 65 and 66 during follow-up.

† $P=0.01$  by the two-tailed Fisher's exact test, without adjustment for multiple comparisons.

44 lamivudine recipients for whom adequate serum samples were available. Fourteen (32 percent) had detectable mutations in the YMDD motif of HBV polymerase; only patients with the wild-type sequence had HBeAg seroconversion. Median serum HBV DNA levels and serum alanine aminotransferase levels were similar at base line in the group with YMDD mutations and the group with the wild-type sequence (132 and 87 pg per milliliter and 120 and 111 U per liter, respectively). Despite such apparent genotypic resistance, the patients with YMDD mutations had lower median serum HBV DNA levels (47 pg per milliliter) and serum alanine aminotransferase levels (77 U per liter) at week 52 than at base line, significantly so in the case of serum HBV DNA levels ( $P<0.001$  by the signed-rank test). At week 52, 19 of 30 patients with the wild-type sequence (63 percent) and 6 of 14 patients with YMDD mutations (43 percent) had a histologic response. Sixteen weeks after the discontinuation of therapy, the median serum HBV DNA and alanine aminotransferase levels in the group with YMDD mutations were 112 pg per milliliter

and 110 U per liter, respectively — values that were close to the base-line levels.

### DISCUSSION

In U.S. patients with previously untreated chronic hepatitis B, treatment with lamivudine for one year was well tolerated, decreased histologic liver abnormalities, and increased the rate of HBeAg seroconversion (defined as the loss of HBeAg in serum, undetectable serum HBV DNA levels, and the presence of antibodies against HBeAg). Lamivudine also increased the rates of loss of serum HBeAg, suppression of serum HBV DNA levels, and normalization of serum alanine aminotransferase levels. Hepatic necro-inflammatory activity was decreased, and the progression of hepatic fibrosis was retarded. Loss of serum HBeAg occurred by week 52 in 32 percent of lamivudine-treated patients, similar to the 33 percent rate reported in a meta-analysis of interferon-treated patients.<sup>4</sup> In contrast to reports suggesting that the efficacy of interferon was reduced in Asian patients,<sup>16</sup> our findings and those of Lai et al.<sup>10</sup> suggest that the effects of lamivudine are similar in Asian and Western populations.

Furthermore, by incorporating the cessation of therapy into our study design, we determined that the virologic response was maintained 16 weeks after the end of treatment in 73 percent of lamivudine-treated patients who had HBeAg seroconversion and 81 percent of those with loss of serum HBeAg by week 52. A recent study that used an extended-treatment protocol found that such HBeAg responses were maintained for a median of 19 months after treatment in more than 80 percent of patients.<sup>26</sup> Therefore, continuation of treatment with lamivudine until there is an HBeAg response would be a reasonable strategy. Continued follow-up would allow reinstitution of therapy for the minority of patients in whom the response is not sustained.

Post-treatment monitoring for safety revealed that elevations in serum alanine aminotransferase were more common after lamivudine therapy than after placebo. There have been reports of occasional, severe elevations in serum alanine aminotransferase after treatment<sup>27</sup>; in our study, however, these elevations were not clinically severe and were not associated with hepatic decompensation.

Loss of HBsAg, reported in 8 to 10 percent of interferon-treated patients,<sup>2,4</sup> occurred in only one lamivudine recipient in our study. In recent studies that compared lamivudine and interferon, however, loss of HBsAg was rare in both groups.<sup>28,29</sup> Whether lamivudine therapy will be followed by late losses of HBsAg and improvements in the natural history of chronic hepatitis B after an HBeAg response, as occurs after interferon therapy,<sup>30-32</sup> remains to be seen.

Although serum HBV DNA levels are suppressed during lamivudine treatment in almost all patients,

HBV subpopulations with YMDD mutations eventually emerge in some patients and are associated with diminished therapeutic responses.<sup>10,33</sup> We identified such mutations at one year in 32 percent of the 44 lamivudine recipients for whom we had adequate serum samples — a proportion that is more than twice that reported in Asian patients (14 percent).<sup>10</sup> Despite the occurrence of YMDD mutations, however, serum HBV DNA and alanine aminotransferase levels at the end of treatment with lamivudine remained lower than the base-line levels. These findings may be explained by the observation that HBV with YMDD mutations is less replication-competent in vitro than wild-type HBV.<sup>24,34</sup> Longer-term monitoring of patients with such mutations and those without them is ongoing.

The goal of antiviral therapy is to arrest or delay the progressive HBV-associated hepatic injury, and histologic improvements are thought to be effected by the suppression of viral replication. In patients who are treated with interferon, sustained reductions in serum HBV DNA levels occur primarily in those with HBeAg responses. In contrast, in our study, substantial reductions in serum HBV DNA levels occurred in virtually all lamivudine recipients, independent of the HBeAg responses. Therefore, patients who have not had HBeAg seroconversion or loss of HBeAg after one year of lamivudine treatment are candidates for extended treatment in order to maintain the suppression of viral replication and, as a result, stop or attenuate the liver damage. Preliminary data suggest that long-term therapy is well tolerated<sup>35</sup>; studies to assess the effects of long-term suppressive therapy in patients who do not seroconvert are in progress.

Which should be first-line therapy — interferon or lamivudine? Favoring interferon are the limited duration of treatment and the absence of a recognized effect of HBV mutations on efficacy. Favoring lamivudine are the lower likelihood of side effects, the convenience of administration, and the fact that the histologic benefit is seen in the majority of patients, not just those with HBeAg responses. It is uncertain whether the results of treatment with a combination of lamivudine and interferon would be better than the results of treatment with either drug alone. On the basis of initial reports from two controlled studies, however, combination therapy does not appear to have greater benefit than lamivudine monotherapy.<sup>28,29</sup>

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### APPENDIX

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