A ONE-YEAR TRIAL OF LAMIVUDINE FOR CHRONIC HEPATITIS B

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ABSTRACT

Background and Methods   In preliminary trials, lamivudine, an oral nucleoside analogue, has shown promise for the treatment of chronic hepatitis B. We conducted a one-year, double-blind trial of lamivudine in 358 Chinese patients with chronic hepatitis B. The patients were randomly assigned to receive 25 mg of lamivudine (142 patients), 100 mg of lamivudine (143), or placebo (73) orally once daily. The patients underwent liver biopsies before entering the study and after completing the assigned treatment regimen. The primary end point was a reduction of at least two points in the Knodell necroinflammatory score.

Results   Hepatic necroinflammatory activity improved by two points or more in 56 percent of the patients receiving 100 mg of lamivudine, 49 percent of those receiving 25 mg of lamivudine, and 25 percent of those receiving placebo ($P<0.001$ and $P=0.001$, respectively, for the comparisons of lamivudine treatment with placebo). Necroinflammatory activity worsened in 7 percent of the patients receiving 100 mg of lamivudine, 8 percent of those receiving 25 mg, and 26 percent of those receiving placebo. The 100-mg dose of lamivudine was associated with a reduced progression of fibrosis ($P=0.01$ for the comparison with placebo) and with the highest rate of hepatitis B e antigen (HBeAg) seroconversion (loss of HBeAg, development of antibody to HBeAg, and undetectable HBV DNA) (16 percent), the greatest suppression of HBV DNA (98 percent reduction at week 52 as compared with the base-line value), and the highest rate of sustained normalization of alanine aminotransferase levels (72 percent). Ninety-six percent of the patients completed the study. The incidence of adverse events was similar in all groups, and there were few serious events.

Conclusions   In a one-year study, lamivudine was associated with substantial histologic improvement in many patients with chronic hepatitis B. A daily dose of 100 mg was more effective than a daily dose of 25 mg. (N Engl J Med 1998;339:61-8.)

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THROUGHOUT the world, over 300 million people have chronic infection with hepatitis B virus (HBV), and more than 75 percent of those affected are of Asian origin.[1] Chronic HBV infection causes cirrhosis, liver cancer, and death.[2,3] The disease is endemic in Africa and Asia, where the virus is transmitted from mother to newborn or between close contacts in early childhood.[4-6] Chronically infected persons with viral replication are at highest risk for progressive liver disease.[7] Cirrhosis and hepatocellular carcinoma account for more than 50 percent of deaths in Asian men with chronic infection.[3]

Interferon alfa is currently the only treatment specifically approved by regulatory authorities throughout the world for chronic hepatitis B.[8,9] It is given by injection and has potentially dose-limiting side effects. The efficacy of interferon alfa is variable, but a meta-analysis showed that 33 percent of patients receiving the drug had a loss of hepatitis B e antigen (HBeAg), as compared with 12 percent of untreated controls.[8] Interferon alfa is least effective in Asian patients,[10,11] except those with elevated liver-enzyme levels.[12] The poor response is thought to be due to

immune tolerance to HBV after infection at birth or in early childhood.[12-15]

Lamivudine, an oral nucleoside analogue, inhibits viral DNA replication. The drug was well tolerated in controlled studies in patients with human immunodeficiency virus (HIV) infection at a dose of 600 mg per day for more than one year,[16] and in more than 3000 patients with chronic HBV infection. In phase 2 studies, all doses studied (5 to 600 mg per day for up to six months[17-20]) markedly reduced serum HBV DNA levels in Asians and whites. With doses of more than 100 mg per day, the median suppression of serum HBV DNA was greater than 98 percent in most patients during treatment. However, when treatment was stopped, serum HBV DNA levels generally returned to pretreatment values.

We conducted a study to determine whether a longer duration of viral suppression (one year) would result in improved histologic findings, higher HBeAg seroconversion rates, or both in patients with chronic hepatitis B.

METHODS

Patients

Eligible patients included males and females, 16 to 70 years old, with detectable hepatitis B surface antigen (HBsAg) and HBeAg in serum at the time of screening and for at least the previous six months, serum HBV DNA levels of at least 5 pg per milliliter (as determined with the use of a solution-hybridization assay; Abbott Diagnostics, Chicago), and alanine aminotransferase levels that were less than 10 times the upper limit of normal at screening and for at least the previous three months. The last criterion was chosen to exclude patients who might have spontaneous HBeAg seroconversion at the time of screening. Patients were excluded if they had hepatitis C or D or HIV infection; decompensated liver disease (defined by a serum bilirubin level more than 2.5 times the upper limit of normal, a prothrombin time prolonged by more than 3 seconds, and a serum albumin level lower than 3 g per deciliter or a history of ascites, variceal hemorrhage, or hepatic encephalopathy); or evidence of autoimmune hepatitis (defined as an antinuclear-antibody titer higher than 1:160). Patients were also excluded if they had received an investigational drug within 30 days before enrollment; any systemic antiviral therapy, immunomodulators, cytotoxic agents, or corticosteroids within 6 months; or lamivudine within 3 months.

The study was approved by the ethics committees at the participating centers, and all patients gave witnessed oral or written informed consent before enrollment. No interim analyses were performed.

Study Design

The patients were randomly assigned to receive 25 mg of lamivudine, 100 mg of lamivudine, or placebo, given orally once a day for 12 months (ratio of random assignments to the three groups, 2:2:1). All the patients had undergone liver biopsy within six months before screening. Biopsy specimens were evaluated with the use of a simplified histologic assessment for periportal and lobular hepatitis with or without bridging or confluent necrosis. Patients were assigned to one of two strata on the basis of the liver-biopsy findings: moderate or severe hepatitis or mild hepatitis.

After the first clinic visit (at base line), patients returned during weeks 2 and 4 and every four weeks thereafter through week 52. Serum was assayed for HBV DNA (at base line and weeks 2, 4, 8, 12, 24, 36, and 52), HBeAg and antibody to HBeAg (at base line and weeks 8, 24, 36, and 52), and HBsAg and antibody to HBsAg (at base line and week 52). At each clinic visit, laboratory tests were performed to determine the safety of the treatment, and adverse events since the previous visit were documented.

Evaluation

A liver biopsy was performed after one year of treatment to compare results with those of the pretreatment biopsy. Individual biopsy specimens were scored with the use of the Knodell index,[21] which grades the histologic activity of hepatitis on a scale from 0 to 22, with higher scores indicating more severe abnormalities. The overall Knodell score is the sum of the scores for periportal bridging necrosis (0 to 10), intralobular degeneration and focal necrosis (0 to 4), portal inflammation (0 to 4), and fibrosis (0 to 4). Response rates were based on the first three components of the score (i.e., necroinflammatory activity, on a scale of 0 to 18).

Before any analyses of the study data were performed, we decided to incorporate a histologic-response variable that would represent a clinically meaningful change and that could be assessed for each patient. Analysis of changes in the Knodell index in previous studies of patients with hepatitis B had shown that there was often an increase of two or more points over a period of one year, and there was rarely a decrease (i.e., improvement) of two or more points. Also, a one-point change could be due to interobserver and intraobserver variability or to biopsy variations (samples obtained from different parts of the liver). Hence, the histologic response was defined as a decrease of at least two points in the Knodell necroinflammatory score at 12 months, as compared with the base-line score. To reduce the potential for observer variability, biopsy specimens were evaluated by a single, independent histopathologist who was unaware of the treatment assignments and the sequence of the specimens.

The degree of fibrosis and necroinflammatory activity was also compared in each pair of biopsy specimens (with the investigator blinded with regard to treatment and biopsy sequence) to determine whether one specimen showed more severe necroinflammatory activity or more fibrosis (ranked response). Biopsy specimens were also scored on a scale of 0 to 3 according to the percentage of cells that were positive for hepatitis B core antigen (HBcAg) and hepatocyte HBV DNA on immunohistochemical staining (none, 0; <5 percent, 1; 5 to 25 percent, 2; and >25 percent, 3).

Secondary efficacy variables included HBeAg and HBsAg seroconversion, sustained suppression of HBV DNA, and sustained alanine aminotransferase response, defined as normal values on at least two consecutive visits, with no two consecutive abnormal values, or a single normal value at week 52.

Assays

Staining for HBcAg was performed with rabbit polyclonal antibody to HBcAg (Dakopatts, Copenhagen, Denmark) and indirect avidin–biotin–peroxidase immunohistochemical techniques (Americium, Chicago) with diaminobenzidine (Sigma, St. Louis).[22] Hepatic HBV DNA was localized in hepatocytes with the use of a nonisotopic in situ hybridization technique and a digoxigenin-labeled full-length human HBV DNA probe, prepared from a recombinant plasmid, pHBV130.4.[23]

Virus was assayed at the National University Hospital, Singapore. Serum HBV DNA was quantified with the use of a solution-hybridization assay (Abbott) that has a lower limit of detection of 1.6 pg per milliliter. HBeAg and antibody to HBeAg were detected by a qualitative HBeAg enzyme immunoassay (Abbott). HBsAg was detected with a monoclonal qualitative third-generation enzyme immunoassay (Auszyme, Abbott), and antibody to HBsAg was detected with the IMX Ausab microparticle enzyme immunoassay (Abbott).

In previous studies, sequencing of serum samples obtained from patients before and after treatment with lamivudine has identified two patterns of mutations that result in changes in the YMDD (tyrosine, methionine, aspartate, aspartate) region of the

HBV DNA polymerase and are associated with reduced sensitivity to lamivudine.[24,25] An assay has been developed to detect these two mutations (a leucine-to-methionine substitution at codon 528 in conjunction with a methionine-to-valine substitution at codon 552, or a solitary methionine-to-isoleucine substitution at codon 552). The assay has been used to determine the frequency and characteristics of the mutations and their clinical effects, if any. In our study, genotypic analysis was performed with a restriction-fragment–length polymorphism assay, which permits semiquantitative evaluation of mutations at both sites (codons 528 and 552 in the viral polymerase) that are linked to lamivudine resistance. With the use of established standards for mixed viral-genotype populations (wild-type and mutant HBV), the lower limit of detection for differentiating between the two viral genotypes has been determined to be 5 percent of the viral population. The assay has a lower limit of detection of approximately 100,000 copies of viral DNA per milliliter of serum.

Statistical Analysis

The patients were stratified according to the liver-biopsy findings (moderate or severe hepatitis and mild hepatitis), with the randomization weighted 2:1. Randomization was performed with a block size of 15 (10 in the stratum with moderate or severe hepatitis, and 5 in the stratum with mild hepatitis). Each center performed randomization for a full block of 15 patients before proceeding to the next block. The study had 80 percent power to detect a difference in histologic response between the treatment groups and the placebo group but not between the two treatment groups.

The intention-to-treat analysis included all patients with confirmed chronic hepatitis B who were randomly assigned to a treatment group. Analyses of histologic data were also performed in patients with pre- and post-treatment biopsy specimens that could be evaluated and base-line necroinflammatory scores of at least 2 (so that at least a two-point reduction in the score was possible). Analyses of safety included data for all patients who were randomly assigned to a treatment group and received at least one dose of study medication.

Base-line HBV DNA levels ($\log_{10}$) in the three groups were compared with the use of analysis of variance[26] adjusted for the center. Differences were tested with Fisher's exact test or the Cochran–Mantel–Haenszel test adjusted for the center.[27] The van Elteren test was used to compare changes from base line in the Knodell score among the three groups.[28] The time to events was analyzed with the log-rank test adjusted for all seven centers.[26] The Wilcoxon rank-sum test was used to compare differences among the three groups in the percentage change in HBV DNA levels at week 52.[26] All P values are two-sided.

RESULTS

Study Population

The study was conducted between July 1994 and July 1996. A total of 358 Chinese patients were randomly assigned to receive 25 mg of lamivudine (142 patients), 100 mg of lamivudine (143), or placebo (73). The intention-to-treat population comprised 357 patients because 1 patient in the placebo group did not have evidence of HBeAg for six months before enrollment.

The three groups were similar with respect to demographic and clinical characteristics and overall Knodell scores (Table 1). Five percent of the patients had evidence of cirrhosis at base line on liver biopsy. The median Knodell necroinflammatory score was 6. The base-line HBV DNA level was higher in the placebo group than in either lamivudine group (P=0.04

for the comparison with the 25-mg group, and P=0.08 for the comparison with the 100-mg group). Inclusion of base-line HBV DNA levels in a logistic-regression analysis of histologic responses did not affect the differences we observed among the three treatment groups.

As expected, the patients with moderate or severe hepatitis had higher median alanine aminotransferase values than the patients with mild hepatitis (2.0 vs. 0.9 times the upper limit of normal), a higher prevalence of cirrhosis (7 percent vs. 0 percent), and a higher median necroinflammatory score (9 vs. 4).

Histologic Findings

Changes in the necroinflammatory score could not be assessed in 12 patients in the placebo group and 24 patients in each of the lamivudine groups because they either had base-line scores of less than 2 or did not have pre- and post-treatment biopsy specimens that could be evaluated. In the intention-to-treat analysis (in which patients with biopsy data that were missing or could not be evaluated were considered to have had no response), both doses of lamivudine were more effective than placebo (P<0.001 and P=0.001 for the 100-mg and 25-mg doses, respectively) in reducing necroinflammatory activity by at least two points (Table 2). There was no significant difference in efficacy between the two lamivudine doses (P=0.27). The response rates were 49 and 56 percent for the 25-mg and 100-mg doses, respectively, as compared with 25 percent for placebo. The odds ratio for a response to 100 mg of lamivudine as compared with placebo was 4.0 (95 percent confidence interval, 2.1 to 7.4).

The results were similar with the analysis of histologic findings in the patients who had base-line Knodell necroinflammatory scores of at least 2 and pre- and post-treatment biopsy specimens that could be evaluated. Improvement in necroinflammatory activity occurred in 59 percent of the 25-mg group (70 of 118 patients), 67 percent of the 100-mg group (80 of 119), and 30 percent of the placebo group (18 of 60) (P<0.001 for the comparison between either lamivudine group and the placebo group). Nineteen of 60 patients in the placebo group (32 percent) had worsening of histologic findings, as compared with 12 of 118 patients receiving 25 mg of lamivudine (10 percent) and 8 of 119 receiving 100 mg (7 percent). The improvements in necroinflammatory activity were similar in the ranked assessments of pre- and post-treatment biopsy specimens (Fig. 1). The proportion of patients with worsening of fibrosis was lower in the group receiving 100 mg of lamivudine than in the placebo group (P=0.01).

The mean base-line Knodell scores were similar in the three groups (8 in the placebo group, 9 in the 25-mg group, and 8 in the 100-mg group). At week

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS.

CHARACTERISTIC	PLACEBO (N=72)	LAMIVUDINE		TOTAL (N=357)
		25 mg (N=142)	100 mg (N=143)	
Age — yr				
Median	29	33	31	32
Range	15–67	16–63	16–55	15–67
Male sex — %	72	73	74	73
Weight — kg				
Median	63.1	60.3	63.0	61.7
Range	38–78	38–90	36–100	36–100
Abnormal alanine aminotransferase levels — no. (%)	50 (69)	98 (69)	95 (66)	243 (68)
Positive for HBeAg — no. (%)*	71 (99)	142 (100)	143 (100)	356 (>99)
Positive for antibody to HBeAg — no. (%)	2 (3)	0 (0)	6 (4)	8 (2)
Positive for HBsAg — no. (%)	72 (100)	142 (100)	143 (100)	357 (100)
Positive for HBV DNA — no. (%)	70 (97)	135 (95)	140 (98)	345 (97)
Alanine aminotransferase — multiples of the upper limit of normal				
Median	1.5	1.4	1.5	1.5
Range	0–10	0–11	0–15	0–15
Serum HBV DNA — pg/ml				
Median	99.4	70.7	74.2	75.2
Range	1–990	1–763	1–516	1–990
Mean ±SD, $\log_{10}$	1.85±0.63	1.67±0.62†	1.80±0.54	1.76±0.59
Knodell histologic-activity score — no. (%)‡				
0–4	17 (25)	31 (23)	24 (18)	72 (22)
5–9	28 (41)	52 (39)	57 (44)	137 (41)
10–14	14 (21)	29 (22)	38 (29)	81 (24)
15–22	9 (13)	22 (16)	12 (9)	43 (13)

*One patient was HBeAg-positive at enrollment but HBeAg-negative at the first visit.

†P=0.04 for the comparison with placebo.

‡Data were available for 333 patients: 68 in the placebo group, 134 in the 25-mg group, and 131 in the 100-mg group.

52, the mean Knodell scores were lower in the 100-mg and 25-mg groups (5 and 6, respectively) than in the placebo group (8). There was a median reduction of two and three points in the scores in the 25-mg and 100-mg groups, respectively (indicating improvement), as compared with an increase of one point in the placebo group (indicating worsening).

Immunohistochemical staining of liver-biopsy specimens showed that HBcAg was reduced to the same extent in the lamivudine and placebo groups and that there was very little reduction in hepatocyte HBV DNA in all groups. However, the proportion of patients with a reduction in cytoplasmic HBcAg was higher in the two lamivudine groups combined (46 percent) than in the placebo group (33 percent).

HBeAg and HBsAg Seroconversion and Viral Levels

At one year, the proportions of patients with HBeAg seroconversion (loss of HBeAg and the development of antibody to HBeAg) and undetectable levels of HBV DNA were 13 percent in the 25-mg group (17 of 135 patients) and 16 percent in the 100-mg group (22 of 140), as compared with 4 percent in the placebo group (3 of 70; P=0.08 and

P=0.02, respectively). As compared with the patients without seroconversion, those with seroconversion had lower median HBV DNA levels, higher median alanine aminotransferase levels, and higher median Knodell necroinflammatory scores at base line. No patients had undetectable levels of HBsAg during the study.

In the group of patients receiving 100 mg of lamivudine, HBV DNA levels fell rapidly, with a median reduction of 97 percent after two weeks of therapy and a median reduction of 98 percent throughout the study. The percent reduction at week 52 was significantly greater in the 100-mg group (98 percent) than in either the 25-mg group (93 percent) or the placebo group (54 percent; P<0.001 for both comparisons). During treatment, 96 percent of the patients in the 100-mg group had undetectable HBV DNA on at least one occasion, as compared with 73 percent of the 25-mg group and 23 percent of the placebo group (P<0.001 for both comparisons).

Alanine Aminotransferase Response

Approximately 70 percent of the patients had elevated alanine aminotransferase levels at base line (Ta-

TABLE 2. HISTOLOGIC RESPONSES
AND CHANGES IN THE KNODELL SCORE.

VARIABLE	PLACEBO	LAMIVUDINE	
		25 mg	100 mg
Response*			
Total			
No.	72	142	143
Improvement — no. (%)	18 (25)	70 (49)†	80 (56)‡
Worsening — no. (%)	19 (26)	12 (8)	10 (7)
Patients with moderate or severe hepatitis			
No.	49	100	100
Improvement — no. (%)	14 (29)	59 (59)	63 (63)
Worsening — no. (%)	9 (18)	5 (5)	2 (2)
Patients with mild hepatitis			
No.	23	42	43
Improvement — no. (%)	4 (17)	11 (26)	17 (40)
Worsening — no. (%)	10 (43)	7 (17)	8 (19)
Knodell score§			
Base line			
Median	7	8	7
Mean ±SD	8±5	9±5	8±4
Range	2 to 21	1 to 18	0 to 18
Week 52			
Median	8	6	5
Mean ±SD	8±4	6±3	5±3
Range	1 to 17	0 to 15	1 to 14
Change			
Median	+1	−2	−3‡
Mean ±SD	0±4	−2±4	−3±4
Range	−9 to 10	−11 to 9	−14 to 7

*Histologic response was defined as a reduction of two or more points in the Knodell necroinflammatory score (components 1 through 3) between base line and week 52. The data are from an intention-to-treat analysis in which patients with biopsy data that were missing or could not be evaluated were considered to have had no response.

†P=0.001 for the comparison with placebo.

‡P<0.001 for the comparison with placebo.

§The data are for patients with pre- and post-treatment biopsy specimens that could be evaluated. Twelve patients in the placebo group and 22 in each lamivudine group had biopsy data that were missing or could not be evaluated. Two additional patients in each lamivudine group had base-line scores of less than 2.

ble 1). Figure 2 shows the time to a sustained alanine aminotransferase response (P<0.001 for either dose of lamivudine as compared with placebo); 65 percent of the patients in the 25-mg group (64 of 98) and 72 percent of those in the 100-mg group (68 of 95) had a sustained alanine aminotransferase response, as compared with 24 percent of the patients in the placebo group (12 of 50).

Genotypic Mutations

Analysis of HBV mutations during lamivudine therapy was undertaken with serum samples obtained from 335 patients at week 52. The incidence of genotypic mutations in the YMDD locus that confer a reduced sensitivity to lamivudine was 14 percent in both lamivudine groups (mixed wild-type and mutant HBV, 9 percent; mutant HBV alone, 5 percent). These mutations were not detected in any patients in the placebo group. In the patients with YMDD

mutations, HBV DNA and alanine aminotransferase levels did begin to rise but did not reach base-line levels by week 52. YMDD mutations were not associated with a decreased histologic response.

Safety

The study was completed by 94 percent of the patients in the 25-mg group, 97 percent of those in the 100-mg group, and 96 percent of those in the placebo group. Most patients received the assigned study drug for at least 50 weeks (median, 365 days; range, 2 to 409). The incidence of adverse events was similar in all treatment groups (Table 3), with no significant differences between either lamivudine group and the placebo group. No patients died, and none required liver transplantation.

Five patients (four in the 25-mg group and one in the 100-mg group) had serious adverse events, although none were considered to be drug-related. In the 25-mg group, one patient had transitional-cell carcinoma of the bladder and adenomatous hyperplasia of the liver; one had a torn ankle tendon, one had fever of unknown origin, and one had appendicitis requiring surgery. The infant of a patient in the 100-mg group who became pregnant during the study had cardiac dysrhythmia and mild mitral-valve prolapse; the baby was asymptomatic, with no signs of hemodynamic compromise.

Ten patients had laboratory abnormalities considered to be of major clinical concern. The incidence was higher in the group receiving placebo (5 of 73 patients, 7 percent) than in either the group receiving 25 mg of lamivudine (1 of 142, 0.7 percent) or the group receiving 100 mg of lamivudine (4 of 143, 3 percent). Three patients in the placebo group, one in the 25-mg group, and two in the 100-mg group had abnormal aspartate aminotransferase or alanine aminotransferase values; one patient in the placebo group and three in the 100-mg group had elevated creatine kinase levels (one of the three in the 100-mg group also had a high alanine aminotransferase value); and one patient in the placebo group had an increased amylase level, with ultrasonographic evidence of focal pancreatitis. There was no association between lamivudine therapy and clinically significant elevations in serum levels of alanine or aspartate aminotransferase, creatine kinase, amylase, or other hematologic or biochemical variables.

DISCUSSION

We found that lamivudine treatment led to significant histologic improvement in the majority of patients. In contrast, studies of interferon treatment have shown histologic improvement primarily in the few patients with serologic responses. Since the severe sequelae of chronic hepatitis B are due to progressive liver damage, it is important for treatment to produce substantial histologic improvement. In
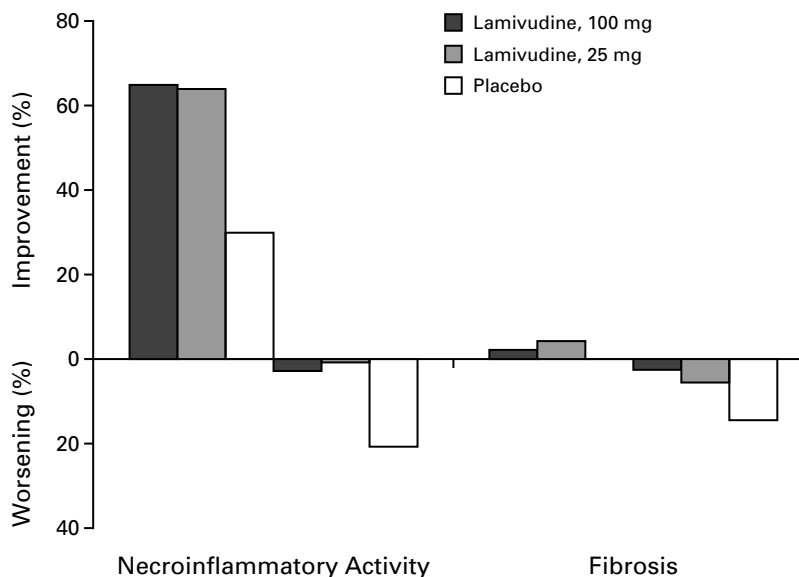
Figure 1. Improvement or Worsening of Necroinflammatory Activity and Fibrosis in Biopsy Specimens Obtained before and after Treatment with Lamivudine (25 or 100 mg) or Placebo.

Each pair of specimens was assessed to determine whether one specimen showed more severe necroinflammatory activity or more fibrosis than the other (ranked response). As compared with placebo, lamivudine significantly improved necroinflammatory activity (P<0.001), and the 100-mg dose significantly reduced the progression of fibrosis (P=0.01). Forty-four patients with available biopsy specimens were not evaluated for a ranked response.
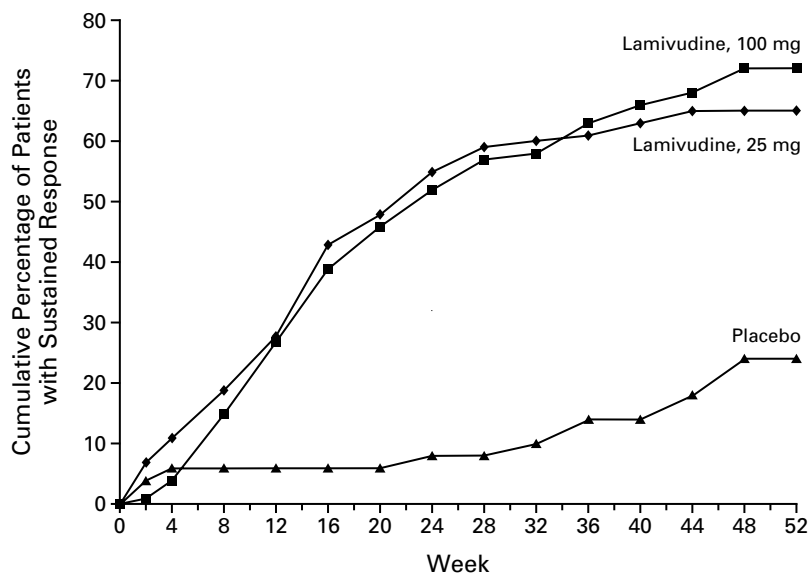
No. of Patients without Response

Placebo	50	48	47	47	47	47	47	46	46	45	43	43	41	38
25 mg	98	91	87	79	71	56	51	44	40	39	38	36	34	34
100 mg	95	94	91	81	69	58	51	46	41	40	35	32	30	27

Figure 2. Cumulative Percentage of Patients with Sustained Alanine Aminotransferase Responses.

The analysis was based on the intention-to-treat principle. P<0.001 for the comparison between each lamivudine group and placebo.

TABLE 3. MOST COMMON ADVERSE EVENTS.*

ADVERSE EVENT	PLACEBO (N=73)	LAMIVUDINE		TOTAL (N=358)
		25 mg (N=142)	100 mg (N=143)	
Respiratory infections — %†	29	35	35	34
Headache — %	19	16	15	16
Cough — %	16	16	15	16
Abdominal discomfort or pain — %	12	18	13	15
Diarrhea — %	10	14	17	14
Malaise and fatigue — %	19	12	13	14
Throat discomfort or pain — %	8	13	16	13
Nasal signs and symptoms — %	8	7	7	7
Dizziness — %	4	6	6	6
Nausea and vomiting — %	1	3	8	5
Fever — %	3	6	6	5
Chest symptoms — %	7	2	3	4
Abnormal liver-function results — %	8	4	2	4
Hair loss — %	5	0	2	2
Patients with ≥1 adverse event — no. (%)	56 (77)	110 (77)	114 (80)	280 (78)

*The most common adverse events were defined as those occurring in 5 percent or more of the patients in any treatment group.

†This category included viral infections of the respiratory tract, ear, nose, and throat, as well as nonviral ear, nose, and throat infections.

our study, the placebo group had measurable deterioration in the Knodell scores within a year. Lamivudine therapy significantly reversed necroinflammatory activity and induced a sustained normalization of alanine aminotransferase levels in 68 percent of the patients. The 100-mg dose of lamivudine also prevented the progression of fibrosis.

The development of mutant HBV in the lamivudine groups was associated with increases in both alanine aminotransferase and HBV DNA levels over the lowest values before the mutations developed, although at 52 weeks the levels were still lower than pretreatment values. The histologic improvements were maintained in spite of the development of mutations. Longer follow-up is needed to determine the clinical importance of these mutations.

The rate of HBeAg seroconversion was significantly higher in the patients receiving 100 mg of lamivudine per day (16 percent) than in those receiving placebo (4 percent). In Chinese patients treated with interferon, the rate of HBeAg seroconversion (defined as undetectable serum HBV DNA and loss of HBeAg) is about 20 percent, as compared with 8 percent in controls.[12] In our study, the patients treated with lamivudine in whom HBeAg seroconversion occurred had lower base-line levels of HBV DNA and higher base-line alanine aminotransferase levels than the patients without seroconversion. These

predictors of lamivudine-induced HBeAg seroconversion are similar to the predictors of interferon-induced HBeAg seroconversion, even though the two drugs have different mechanisms of action.[12,29] HBeAg seroconversion involves a reversion to a state of lower HBV replication that is often maintained for years (relapse rate, 10 to 30 percent). The results of a recent study in Germany suggest that patients with hepatitis B and HBeAg seroconversion induced by interferon alfa are generally at lower risk for clinical disease progression than those without seroconversion unless advanced cirrhosis is already present at the time of seroconversion.[30] Further studies are required to determine whether this finding applies to Chinese patients with hepatitis B who have been treated with lamivudine and whether lamivudine-induced HBeAg seroconversion is maintained after treatment.

In our study, both doses of lamivudine reduced serum HBV DNA levels, but the degree of suppression was significantly greater with the 100-mg dose. This result is in agreement with previous studies showing that lamivudine at daily doses of 100 mg or higher produced maximal HBV DNA suppression.[17-20]

Lamivudine was well tolerated in our study. In contrast, an earlier study reported elevated alanine aminotransferase levels in a few patients,[19] a finding that highlights the importance of concurrent placebo controls. The safety profile of lamivudine contrasts with that of interferon, which is associated with influenza-like symptoms, neutropenia, headache, alopecia, prolonged fatigue, and depression in some patients. In view of the substantial reductions in necroinflammatory activity and progression of fibrosis with lamivudine and its excellent safety profile, longer-term treatment should be evaluated.

APPENDIX

In addition to the authors, the following investigators were members of the Asia Hepatitis Lamivudine Study Group: University of Hong Kong, Hong Kong, China — M.F. Yuen and W.M. Wong; Chang Gung Memorial Hospital, Taipei, Taiwan — Y.F. Liaw; National University Hospital, Singapore — I. Yap; Singapore General Hospital, Singapore — H.S. Ng and W.C. Chow; and Glaxo Wellcome — L. Condreay.

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