

ORIGINAL ARTICLE

## Lamivudine for Patients with Chronic Hepatitis B and Advanced Liver Disease

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### ABSTRACT

#### BACKGROUND

The effectiveness of antiviral therapy in preventing disease progression in patients with chronic hepatitis B and advanced fibrosis or cirrhosis is unknown.

#### METHODS

Patients with chronic hepatitis B who had histologically confirmed cirrhosis or advanced fibrosis were randomly assigned in a 2:1 ratio to receive lamivudine (100 mg per day) or placebo for a maximum of five years. Of 651 patients, 436 were assigned to receive lamivudine and 215 to receive placebo. The primary end point was time to disease progression, defined by hepatic decompensation, hepatocellular carcinoma, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or death related to liver disease. An independent data and safety monitoring board monitored the progress of the study and performed interim analyses of the data.

#### RESULTS

We randomly assigned 651 patients (98 percent Asian and 85 percent male) to receive lamivudine or placebo. The study was terminated after a median duration of treatment of 32.4 months (range, 0 to 42) owing to a significant difference between treatment groups in the number of end points reached. End points were reached by 7.8 percent of the patients receiving lamivudine and 17.7 percent of those receiving placebo (hazard ratio for disease progression, 0.45;  $P=0.001$ ). The Child–Pugh score increased in 3.4 percent of the patients receiving lamivudine and 8.8 percent of those receiving placebo (hazard ratio, 0.45;  $P=0.02$ ), whereas hepatocellular carcinoma occurred in 3.9 percent of those in the lamivudine group and 7.4 percent of those in the placebo group (hazard ratio, 0.49;  $P=0.047$ ). Genotypic resistance YMDD mutations developed in 49 percent of the patients treated with lamivudine, and the Child–Pugh score was more likely to increase in patients with these mutations than in the other patients treated with lamivudine (7 percent vs. <1 percent). Overall, 12 percent of the patients in the lamivudine group and 18 percent of the patients in the placebo group reported serious adverse events.

#### CONCLUSIONS

Continuous treatment with lamivudine delays clinical progression in patients with chronic hepatitis B and advanced fibrosis or cirrhosis by significantly reducing the incidence of hepatic decompensation and the risk of hepatocellular carcinoma.

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**C**HRONIC HEPATITIS B IS A SERIOUS problem worldwide.<sup>1</sup> Among patients with active viral replication, cirrhosis will develop in 15 to 20 percent within five years.<sup>2,3</sup> For patients with cirrhosis, acute exacerbation can occur, the disease may progress, and the incidence of hepatocellular carcinoma is greatly increased (70 to 90 percent of cases of hepatocellular carcinoma occur against a background of cirrhosis).<sup>4,5</sup> Because of these complications, five-year survival rates may be as low as 55 percent.<sup>6</sup> Ultimately, 40 percent of Asian men with chronic hepatitis B die of either complications of cirrhosis or hepatocellular carcinoma.<sup>7</sup>

Patients with persistent seropositivity for hepatitis B e antigen (HBeAg) or an increased serum alanine aminotransferase level after HBeAg seroconversion have a significantly increased risk of cirrhosis and hepatocellular carcinoma.<sup>8-11</sup> This is consistent with experimental models showing important roles for continuing hepatitis B virus (HBV) replication and the resultant hepatic inflammatory response in hepatocarcinogenesis.<sup>12</sup> Thus, the suppression of HBV and the reduction of necroinflammatory activity in chronic hepatitis B may prevent cirrhosis and, consequently, liver failure and hepatocellular carcinoma.<sup>13</sup>

Patients who have a response to interferon therapy have substantially fewer life-threatening liver complications than those who do not have a response,<sup>14</sup> although the evidence of the effect of this therapy on the incidence of hepatocellular carcinoma is less conclusive.<sup>15-17</sup> Use of interferon is restricted by cost, side effects, and, among patients with cirrhosis, the risk of liver failure during a flare of hepatitis. These limitations do not apply to oral antiviral agents, such as lamivudine, which can produce marked viral suppression, reduction of hepatic necroinflammatory activity,<sup>18,19</sup> histologic improvement of liver fibrosis,<sup>20,21</sup> and improved liver function,<sup>22</sup> even in patients with decompensation.<sup>23,24</sup> However, long-term therapy with lamivudine leads to viral breakthrough in some patients, owing to the emergence of genotypic resistance tyrosine, methionine, aspartate, aspartate (YMDD) mutations.<sup>25</sup> The possible implications of a resumption of necroinflammatory activity<sup>21,26</sup> include flares of hepatitis, which may lead to liver failure and death, and a gradual erosion of hepatic function, which may lead to decompensation or cirrhosis.

It has not been possible to devise treatment guidelines for the subgroup of patients with HBV-related cirrhosis or advanced hepatic fibrosis.<sup>27,28</sup> Therefore, we conducted a prospective, randomized, double-blind, placebo-controlled trial to assess the efficacy of lamivudine in terms of the clinical progression of disease in patients with chronic hepatitis B and advanced fibrosis or cirrhosis. This study was conducted at multiple centers in countries in the Asian-Pacific region, where chronic hepatitis B is a major cause of morbidity and mortality from cirrhosis and where hepatocellular carcinoma is a major cause of death.

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## METHODS

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### STUDY DESIGN

We planned to conduct this multicenter, centrally randomized, double-blind, placebo-controlled, parallel group study for five years or less. Patients were randomly assigned in a 2:1 ratio to receive lamivudine (100 mg per day) or placebo within 30 days after screening. Of 651 patients, 436 were assigned to receive lamivudine and 215 to receive placebo. During the double-blind phase, treatment was stopped for patients who reached a clinically confirmed end point (disease progression) or had HBeAg seroconversion. Patients who reached an end point were offered open-label lamivudine for one year, and patients who had HBeAg seroconversion were followed up after therapy and had the option to receive lamivudine as an open-label treatment in the event of serologic relapse. If the trial was terminated according to predefined criteria, patients were to be offered open-label treatment for one year.

The data reported in this article are from the double-blind phase of the study, including follow-up after treatment, up to the time of termination.

### PATIENTS

Patients over 16 years of age with chronic hepatitis B were eligible for recruitment if they had been positive for hepatitis B surface antigen (HBsAg) for at least six months, were positive for HBeAg or negative for HBeAg with detectable HBV DNA at screening, and had had a liver biopsy showing an Ishak fibrosis score of at least 4 (where 0 indicates no fibrosis and 6 indicates cirrhosis) at screening or during the previous two years. Biopsy slides were reviewed by one centrally appointed independent

histopathologist who was blinded to the treatment assignments.

Patients were excluded if they had any of the following: evidence of hepatocellular carcinoma (suspicious foci on hepatic ultrasonography at screening or a rising serum level of alpha-fetoprotein), a serum alanine aminotransferase level more than 10 times the upper limit of normal, any evidence of hepatic decompensation (as defined by the study protocol), autoimmune hepatitis, coinfection with hepatitis C or D virus or human immunodeficiency virus, other serious concurrent illness (e.g., alcoholism, uncontrolled diabetes, or cancer), pancreatic amylase or lipase levels more than two times the upper limit of normal, an elevated serum creatinine level, a hemoglobin level of less than 8 g per deciliter, a white-cell count below 1500 per cubic millimeter, a platelet count of 50,000 per cubic millimeter or less, treatment with immunomodulatory or chronic antiviral therapy within the 6 months before screening, treatment with any investigational drug within the 30 days before the study began, or any previous treatment with lamivudine. Women who were pregnant were also excluded.

#### ASSESSMENTS

Patients were assessed at baseline, at the end of months 1 and 3, and at every three months thereafter for clinical evidence of hepatic decompensation or other complications. They were also questioned about adverse events, concurrent medications, and study drug accountability; blood was taken for hematology and biochemistry profiles; serum samples were tested for HBeAg, hepatitis B e antibody, and alpha-fetoprotein; and the prothrombin time was measured. At baseline and every six months thereafter, serum was assayed for HBsAg and hepatitis B surface antibody, and liver ultrasonography was performed. HBeAg seroconversion was considered confirmed if two consecutive samples taken at least a month apart were positive for hepatitis B e antibody and negative for HBeAg. Hepatic ultrasonography and liver biopsy or fine-needle aspiration were performed as clinically indicated to investigate or confirm a diagnosis of hepatocellular carcinoma.

Serum samples were collected at baseline and at months 1, 12, 24, 36, 48, and 60 and analyzed for HBV DNA levels at a central laboratory. HBV DNA was determined by a branched-chain hybridization assay (Versant HBV DNA Quantitative Assay,

Bayer Diagnostics, with a lower limit of detection of 0.7 mEq per milliliter). Results were unavailable to the investigators until after the completion of the study, and serum HBV DNA assays were not permitted at the investigators' sites during double-blind therapy but were allowed after confirmed HBeAg seroconversion or during open-label lamivudine therapy. Samples collected at baseline, at annual visits, and at the completion of treatment were also analyzed for the presence of YMDD mutations by polymerase-chain-reaction assay and restriction-fragment-length polymorphism assay. Samples collected at all scheduled visits from patients with clinical end points were also tested for YMDD mutations.

#### END POINTS

The primary end point was time to disease progression, as defined by the first occurrence of any of the following: an increase of at least 2 points in the Child–Pugh score (an assessment of the severity of liver disease [range, 5 to 15, where 5 indicates good liver function and 15 indicates poor liver function] calculated on the basis of the serum bilirubin and albumin levels, the prothrombin time, and the presence and degree of ascites or encephalopathy), spontaneous bacterial peritonitis with proven sepsis, renal insufficiency, bleeding gastric or esophageal varices, the development of hepatocellular carcinoma, or death related to liver disease. Patients with a first clinical end point were followed for subsequent end points. Any increase in the Child–Pugh score due solely to laboratory parameters was confirmed on two consecutive visits at least one month apart. For patients with albumin levels below 35 g per liter or bilirubin levels greater than 34.2  $\mu$ mol per liter (2 mg per deciliter) at baseline, confirmatory tests were conducted one week after the first test. Renal insufficiency was defined as a decrease in creatinine clearance to 50 ml per minute (0.8 ml per second) or less that was confirmed two times, at least one week apart. Hepatocellular carcinoma was diagnosed on the basis of results of ultrasonography, selective arteriography, imaging of hepatic tumors during the vascular phase, serum levels of alpha-fetoprotein, or by cytologic or histologic evaluation. The evidence for each end point was reviewed and confirmed by a blinded clinical end-points committee composed of three internationally recognized hepatologists.

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	Lamivudine Group (N=436)	Placebo Group (N=215)
Male sex — no. (%)	370 (85)	182 (85)
Asian — no. (%)	426 (98)	210 (98)
Age — yr		
Median	43	44
Range	17–74	22–71
Child–Pugh score — no. (%)†		
5	341 (78)	156 (73)
6	75 (17)	41 (19)
≥7	20 (5)	18 (8)
Ishak fibrosis score — no. (%)‡		
4	176 (40)	76 (35)‡
5	127 (29)	55 (26)
6	133 (31)	84 (39)
HBV DNA — mEq/ml		
Median	11.7	21.5
Range	<0.7–109,800	<0.7–4234
HBV DNA ≥0.7 mEq/ml — no. (%)§	345 (79)	174 (81)
Positive for HBeAg — no. (%)	252 (58)	124 (58)
Alpha-fetoprotein — μg/liter		
Median	8.6	9.8
Range	0.7–600	1.2–298
Albumin — g/liter		
Median	42	41
Range	28–54	27–52
Alanine aminotransferase — U/liter		
Median	70	68
Range	14–959	7–821
Alanine aminotransferase >1 time the upper limit of normal — no. (%)	338 (78)	171 (80)

**SAFETY**

All adverse events, regardless of their possible association with the disease or study treatment, were recorded. Adverse events were considered to be serious if the investigator determined that they jeopardized the patient, were life-threatening, or would result in hospitalization, disability, or death.

**DATA AND SAFETY MONITORING BOARD**

The data and safety monitoring board consisted of three independent hepatologists, who were not members of the end-points committee, and an independent statistician. The board protected the ethical interests and safety of the patients by re-

viewing interim analyses. The board was empowered to recommend termination of the study on the basis of safety concerns or as soon as sufficient evidence indicated that lamivudine was statistically superior to placebo or that lamivudine did not provide a significant advantage over placebo.

**STATISTICAL ANALYSES**

Sample size was determined on the basis of the primary analysis of time to disease progression. To estimate power, the annual rate of disease progression was assumed to be 20 percent for the placebo group,<sup>8,9,29</sup> whereas a reduction in this rate of one third (to 13.3 percent) for the lamivudine group

**Table 1. (Continued.)**

Characteristic	Lamivudine Group (N=436)	Placebo Group (N=215)
Aspartate aminotransferase — U/liter		
Median	52	54
Range	14–686	17–367
Bilirubin — $\mu\text{mol/liter}$ ¶		
Median	13.7	13.7
Range	3.0–50.0	1.7–58.1
Creatinine — $\mu\text{mol/liter}$		
Median	88	88
Range	35–173	35–135
Hemoglobin — g/dl		
Median	14.7	14.6
Range	8.4–19.0	9.2–17.8
Platelet count per $\text{mm}^3$		
Median	145,000	131,000
Range	14,000–401,000	41,000–360,000
Prothrombin time — sec		
Median	12.5	12.8
Range	8.0–23.8	9.8–27.6
White-cell count per $\text{mm}^3$		
Median	5330	5300
Range	1980–11,600	2200–11,500

\* There were no significant differences between the two treatment groups. The patients' race was recorded by the investigators, on the basis of the interviews and evaluations of the patients.

† The Child–Pugh score (range, 5 to 15, where 5 indicates good liver function and 15 poor liver function) is a measure of the severity of liver disease.

‡ The Ishak fibrosis score (range, 0 to 6) is a measure of the degree of fibrosis in liver-biopsy specimens. Scores of 0 to 4 indicate no or moderate fibrosis, and 5 or 6 severe fibrosis or cirrhosis.

§ All patients had detectable HBV DNA at screening; 0.7 meq per milliliter equals approximately  $7 \times 10^5$  copies per milliliter.

¶ To convert values for bilirubin to milligrams per deciliter, divide by 17.1.

|| To convert values for creatinine to milligrams per deciliter, divide by 88.4.

was considered to be a clinically relevant treatment effect. This difference corresponds to a hazard ratio of 0.64. For the study to have a power of 90 percent at the 5 percent level of significance, with a ratio of 2:1 for the random assignment of patients to lamivudine or placebo, 240 end points would need to be observed.<sup>30</sup> Assuming a dropout rate of 25 percent during a five-year period, the number of patients required overall was estimated to be 600.

We used a sequential, asymmetric trial with the triangular test<sup>31</sup> to monitor the primary efficacy end point of time to clinical disease progression. At each interim analysis, the test statistics were calculated and compared with straight-line stop-

ping boundaries. At each inspection, the “Christmas tree” correction<sup>31</sup> was applied to the continuous boundaries to account for the unpredictable number and timing of interim analyses.

The first interim analysis was scheduled for 18 months after the completion of patient recruitment, and subsequent interim analyses were to be performed between 6 and 12 months after the first interim analysis; the aim was to have approximately 35 events between interim analyses. The intention-to-treat analysis included all patients who were randomly assigned to receive either lamivudine or placebo. Treatments were compared with the use of a Cox proportional-hazards model,<sup>32</sup> with each analysis allowing for the covariates of country, sex,

baseline alanine aminotransferase levels, and baseline Child–Pugh and fibrosis scores. The data from patients without end points were censored as of the date that treatment was stopped (if the data and safety monitoring board terminated the trial) or at the last date of available follow-up after treatment (if the trial was terminated for other reasons). Because the study was stopped at the second interim analysis with strict stopping criteria applied at the first interim analysis, adjustments that had to be made to the final P values and estimates were negligible (an increase in the P value of <0.001 and an increase of <0.002 for the hazard ratio).

The study was conducted in accordance with good clinical practice and all applicable regulations, including the Declaration of Helsinki (modified in 1996). Each investigator ensured that the protocol was reviewed and approved by the local ethics committee. Written informed consent was obtained from each patient before enrollment in the study.

The study was designed by the academic investigators in conjunction with medical staff from GlaxoSmithKline. The data were collected by the investigators and analyzed by GlaxoSmithKline. Each author had access to the data. This article was written by a committee consisting of seven authors (Drs. Liaw, Sung, Chow, and Farrell; and Mrs. Shue, Mr. Keene, and Dr. Dixon, who are GlaxoSmithKline employees). The committee mem-

bers vouch for the validity and completeness of the data and the veracity of the data analysis.

## RESULTS

### CHARACTERISTICS OF THE PATIENTS

The intention-to-treat population consisted of 651 patients who were randomly assigned to treatment at 41 sites across Australia, China, Hong Kong, Malaysia, New Zealand, the Philippines, Singapore, Taiwan, and Thailand; 436 patients were assigned to receive lamivudine and 215 to receive placebo. In each treatment group, 85 percent of the patients were male and 98 percent were Asian. The treatment groups were also well matched in terms of age, laboratory results at baseline, and Ishak fibrosis scores (Table 1). The median Child–Pugh score at baseline was 5 (range, 5 to 9), and no patient had evidence of hepatocellular carcinoma, renal insufficiency, bleeding varices, or spontaneous bacterial peritonitis at study entry.

### STUDY TERMINATION AND END POINTS

At the recommendation of the data and safety monitoring board, the double-blind phase of the study was terminated at the second interim analysis, because results had crossed the predefined boundary for showing efficacy. At this time, 67 patients had achieved HBeAg seroconversion, 52 had stopped therapy for other reasons, and 68 end

**Table 2. Disease Progression during Double-Blind Treatment and Follow-up after Treatment.\***

Variable	Lamivudine Group (N=436)	Placebo Group (N=215)	Hazard Ratio (95% CI)†‡	P Value
	<i>no. of patients (%)</i>			
Overall disease progression	34 (7.8)‡	38 (17.7)	0.45 (0.28–0.73)	0.001
Increase in Child–Pugh score	15 (3.4)	19 (8.8)	0.45 (0.22–0.90)	0.02
Hepatocellular carcinoma§	17 (3.9)	16 (7.4)	0.49 (0.25–0.99)	0.047
Renal insufficiency	2 (0.5)	0	—	—
Bleeding varices	2 (0.5)	3 (1.4)	—	—
Spontaneous bacterial peritonitis	0	0	—	—
Liver-related death	0	0	—	—

\* Only one patient reached an end point during follow-up before the termination of the study. Dashes denote not applicable.

† Hazard ratios were derived from a Cox model adjusted for country, sex, baseline alanine aminotransferase level, Child–Pugh score, and Ishak fibrosis score. CI denotes confidence interval, unadjusted for interim analyses.

‡ Two patients fulfilled two criteria simultaneously at end-point confirmation.

§ When five cases of hepatocellular carcinoma diagnosed during the first year were excluded, the hazard ratio was 0.47 (95 percent confidence interval, 0.22 to 1.00; P=0.052).

points had occurred. Four additional end points occurred between the data cutoff for the second interim analysis and termination of the study, a period of 20 weeks. The median duration of treatment was 32.4 months (range, 0 to 42 months); 71 percent of the patients had received study medication for at least 30 months when the study was terminated.

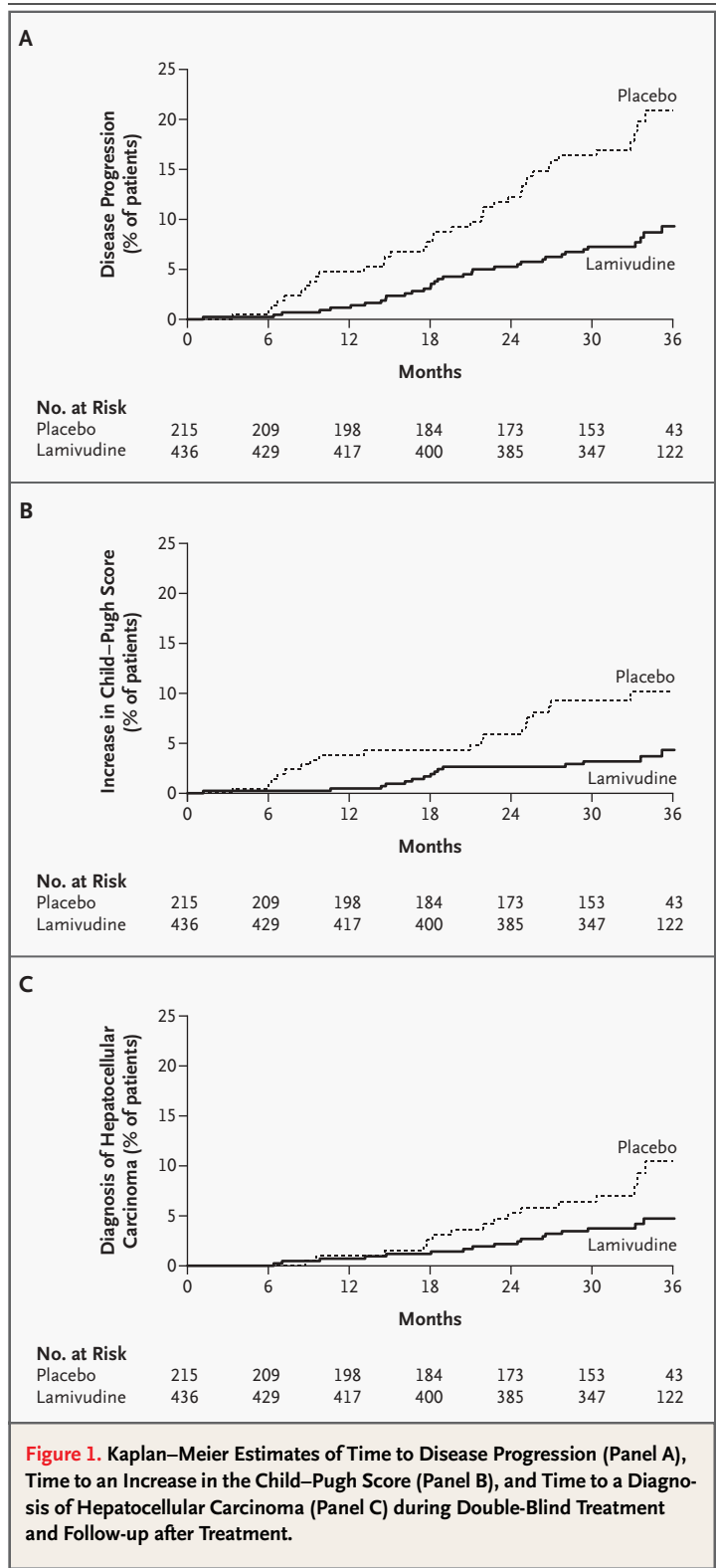
Overall, 72 patients reached clinical end points; 34 of 436 (7.8 percent) in the lamivudine group and 38 of 215 (17.7 percent) in the placebo group ( $P=0.001$ ) (Table 2). An increase in the Child–Pugh score occurred in 15 patients (3.4 percent) in the lamivudine group and 19 patients (8.8 percent) in the placebo group ( $P=0.02$ ). Hepatocellular carcinoma occurred in 17 patients (3.9 percent) who received lamivudine and 16 patients (7.4 percent) who received placebo ( $P=0.047$ ). There were no cases of death related to liver disease or spontaneous bacterial peritonitis that were not already accounted for by the other defined clinical end points, and only two cases of renal insufficiency and five cases of bleeding varices.

Kaplan–Meier estimates of the proportion of patients with disease progression after three years are shown in Figure 1. Hepatocellular carcinoma developed in five patients during the first year of the study, two in the placebo group and three in the lamivudine group. Even if these tumors had existed but had not been detected before study entry, the exclusion of the patients would not have affected the result of the primary analysis of time to disease progression. However, for the time to a diagnosis of hepatocellular carcinoma, the hazard ratio changed from 0.49 ( $P=0.047$ ) to 0.47 ( $P=0.052$ ).

The incidence of disease progression in various subgroups is shown in Table 3. Covariate modeling of time to disease progression showed that the factors other than treatment that significantly affected outcome were the Child–Pugh score at baseline and the Ishak fibrosis score at baseline. In both instances, higher scores were associated with a greater frequency of end points.

**YMDD MUTATIONS**

Two patients had evidence of YMDD mutations at baseline, and 5 patients had no samples after baseline, so data on the emergence of YMDD mutations during therapy were available for 644 patients. After baseline, at least one sample with evidence of YMDD mutations was found in 209 of 430 pa-



**Figure 1.** Kaplan–Meier Estimates of Time to Disease Progression (Panel A), Time to an Increase in the Child–Pugh Score (Panel B), and Time to a Diagnosis of Hepatocellular Carcinoma (Panel C) during Double-Blind Treatment and Follow-up after Treatment.

**Table 3. Association between Pretreatment Variables and the Incidence of Disease Progression.**

Variable at Baseline	Incidence of Disease Progression	
	Lamivudine Group (N=436) no./total no. (%)	Placebo Group (N=215) no./total no. (%)
Sex		
Male	32/370 (9)	30/182 (16)
Female	2/66 (3)	8/33 (24)
Child–Pugh score		
5	16/341 (5)	18/156 (12)
6	9/75 (12)	12/41 (29)
≥7	9/20 (45)	8/18 (44)
Ishak fibrosis score		
≤4	8/176 (5)	9/76 (12)
5	11/127 (9)	9/55 (16)
6	15/133 (11)	20/84 (24)
HBeAg status		
Positive	15/252 (6)	25/124 (20)
Negative	19/182 (10)	13/91 (14)
HBV DNA		
Below the lower limit of quantitation	4/89 (4)	9/41 (22)
0.7–10 meq/ml	14/123 (11)	9/51 (18)
>10–100 meq/ml	6/103 (6)	8/50 (16)
>100 meq/ml	10/119 (8)	12/73 (16)
Serum alanine aminotransferase		
≤2 times the upper limit of normal	27/274 (10)	25/132 (19)
>2 times the upper limit of normal	7/162 (4)	13/83 (16)

tients (49 percent) in the lamivudine group and 11 of 214 patients (5 percent) in the placebo group. Only 5 percent of patients without YMDD mutations had detectable HBV DNA breakthrough, as compared with 62 percent of patients with YMDD mutations in the lamivudine group.

Patients in the lamivudine group who had YMDD mutations were more likely to have an increased Child–Pugh score than those without YMDD mutations ( $P<0.001$ ), but they were less likely to reach an end point than were patients in the placebo group ( $P>0.05$ ) (Table 4).

#### ADVERSE EVENTS

Overall, 12 percent of the patients in the lamivudine group and 18 percent of the patients in the placebo group reported serious adverse events. The incidence and nature of adverse events were similar among patients who received lamivudine and those who received placebo (Table 5). In addition, elevations in serum alanine aminotransferase to levels at least three times as great as the levels at

baseline occurred in 12 percent of patients receiving lamivudine and 25 percent of patients receiving placebo.

There were 12 deaths among patients originally assigned to receive lamivudine and 4 among those originally assigned to the placebo group. Nine patients died while they were receiving lamivudine (seven during open-label treatment with lamivudine), and seven died during follow-up after treatment. Two patients in the lamivudine group died during double-blind therapy (1 died from preexisting lymphoma; the other drowned after a myocardial infarction), and 14 died after a clinical end point had been reached. These 14 deaths were attributed to hepatocellular carcinoma (8 patients) and an increased Child–Pugh score (6 patients). Eight of the 10 patients originally assigned to receive lamivudine who died after reaching a clinical end point had evidence of YMDD mutations.

#### DISCUSSION

The most important finding of this study is that lamivudine reduces the risk of liver complications for patients with chronic hepatitis B and cirrhosis or advanced fibrosis. The magnitude of protection conferred by lamivudine is substantial, with a reduction of approximately 50 percent in disease progression during a median period of 32 months of treatment.

The study was stopped early because the large and significant difference between the treatment groups with respect to the primary end point (time to disease progression) met the predefined efficacy criteria for termination. Treatment differences for individual end points were a secondary consideration, but the results showed significant differences between the two treatments with respect to both an increase in the Child–Pugh score and the incidence of hepatocellular carcinoma. Studies with longer follow-up and more potent or sustained therapy would be required to establish the full potential of antiviral therapy as a strategy to prevent liver cancer, to measure the potential improvements in survival, and to identify the subgroups of patients who would obtain the greatest benefit from treatment.

Chronic hepatitis B is a highly variable disease in which factors such as the age of the patient, the duration of infection, the immune response of the host, and the viral genotype influence the activity, rate of progression, and severity of liver disease.

Although our study was not powered for reliable subgroup analysis, pretreatment variables related to disease progression were high fibrosis scores and Child–Pugh scores at baseline. This is consistent with the high rates of hepatocellular carcinoma observed among patients with advanced stages of liver disease.<sup>33</sup>

The main reservation about the long-term use of lamivudine has been the emergence of YMDD mutations, which has occasionally been associated with severe, and even fatal, flares of hepatitis.<sup>25,34</sup> In light of this uncertainty, the finding that treatment with lamivudine for a median period of 32 months reduces the rates of hepatic decompensation and hepatocellular carcinoma without increasing the number of serious adverse events is important. Even among patients who developed YMDD mutations, clinical end points occurred less frequently than among patients receiving placebo. However, patients with YMDD mutations were more likely to have an increase in the Child–Pugh score and to die for reasons related to clinical end points than were those patients who did not have YMDD mutations. This may be because the resumption of viral replication restores the potential for facilitating disease progression. The long-term effects of lamivudine on disease progression are not known. Since the present trial was started, treatment with a combination of adefovir dipivoxil and lamivudine has been shown to suppress replication of YMDD mutations and improve liver function in patients with hepatic decompensation.<sup>35</sup> The adverse effects of YMDD mutations may be overcome by the addition of adefovir dipivoxil, but we did not assess this possibility in our population. The potential adverse effects of lamivudine treatment must be considered in any therapeutic plan.

In summary, this multicenter, prospective, randomized, double-blind, placebo-controlled trial of lamivudine in patients with chronic hepatitis B and cirrhosis or advanced fibrosis showed that lamivudine decreased progression of the disease, thereby reducing clinically important complications. In particular, treatment with lamivudine approximately halved the rate of hepatic decompensation during 32 months of continuous treatment and appeared to have similar efficacy in reducing the rate of hepatocellular carcinoma. The emergence of YMDD mutations reduced the benefit of lamivudine but did not negate it, despite the occurrence of more end points due to decompensation among patients with YMDD mutations than among those without

**Table 4. Incidence of Clinical End Points According to Evidence of YMDD Mutations.**

Clinical End Point	Lamivudine Group		Placebo Group (N=214)
	Negative for YMDD Mutations (N=221)	Positive for YMDD Mutations (N=209)	
	<i>number (percent)</i>		
Total	11 (5)	23 (11)	38 (18)
Increase in Child–Pugh score $\geq 2$	1 (<1)	14 (7)	19 (9)
Hepatocellular carcinoma	8 (4)	9 (4)	16 (7)

**Table 5. Incidence of Adverse Events during Double-Blind Phase.**

Variable	Lamivudine Group (N=436)	Placebo Group (N=215)	P Value*
	<i>no. (%)</i>		
Death	2 (<1)	0	0.89
Any serious adverse event	54 (12)	38 (18)	0.09
Any adverse event†	335 (77)	178 (83)	0.11
Ear, nose, or throat infections	97 (22)	44 (20)	0.67
Abdominal discomfort or pain	77 (18)	43 (20)	0.54
Malaise or fatigue	65 (15)	42 (20)	0.17
Headache	64 (15)	21 (10)	0.10
Cough	62 (14)	15 (7)	0.008
Diarrhea	33 (8)	29 (13)	0.03
Viral respiratory infections	39 (9)	21 (10)	0.84

\* P values were calculated on the basis of the two-sided Fisher's exact test.

† The adverse events shown are those that occurred in at least 10 percent of the patients in a treatment group.

the mutations. Our results provide the opportunity to develop strategies to achieve even better outcomes for patients with chronic hepatitis B and cirrhosis or advanced fibrosis by means of sustained viral suppression by minimizing or preventing the effects of drug resistance.

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## APPENDIX

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