

CLINICAL TRIAL OF LAMIVUDINE IN CHILDREN WITH CHRONIC HEPATITIS B

MAUREEN M. JONAS, M.D., DEIRDRE A. KELLEY, M.D., JACEK MIZERSKI, M.D., ISABEL B. BADIA, M.D.,
JORGE A. AREIAS, M.D., KATHLEEN B. SCHWARZ, M.D., NANCY R. LITTLE, B.S., MARTIN J. GREENSMITH, PH.D.,
STEPHEN D. GARDNER, M.S.P.H., M. STEVE BELL, B.Sc., AND ETIENNE M. SOKAL, M.D.,
FOR THE INTERNATIONAL PEDIATRIC LAMIVUDINE INVESTIGATOR GROUP*

ABSTRACT

Background Lamivudine therapy is effective for chronic hepatitis B infection in adults. We evaluated the efficacy and tolerability of lamivudine as a treatment for chronic infection with hepatitis B virus (HBV) in children.

Methods Children with chronic hepatitis B were randomly assigned in a 2:1 ratio to receive either oral lamivudine (3 mg per kilogram of body weight; maximum, 100 mg) or placebo once daily for 52 weeks. The primary end point was virologic response (defined by the absence of serum hepatitis B e antigen and serum HBV DNA) at week 52 of treatment.

Results Of the 403 children screened, 191 were randomly assigned to receive lamivudine and 97 to receive placebo. The rate of virologic response at week 52 was higher among children who received lamivudine than among those who received placebo (23 percent vs. 13 percent, $P=0.04$). Lamivudine therapy was well tolerated and was also associated with higher rates of seroconversion from hepatitis B e antigen to hepatitis B e antibody, normalization of alanine aminotransferase levels, and suppression of HBV DNA.

Conclusions In children with chronic hepatitis B, 52 weeks of treatment with lamivudine was associated with a significantly higher rate of virologic response than was placebo. (N Engl J Med 2002;346:1706-13.)

Copyright © 2002 Massachusetts Medical Society.

CHRONIC hepatitis B is a widespread disease that affects more than 350 million people worldwide, or approximately 5 percent of the world's population.¹ Typically, the virus is actively replicating in infected children, as demonstrated by the presence of hepatitis B e antigen (HBeAg) in serum and high serum levels of hepatitis B virus (HBV) DNA. The course of the disease varies, and it may result in spontaneous viral clearance, prolonged latency, or progressive damage to the liver. Those who become infected early in life are at highest risk for chronic infection, cirrhosis, and hepatocellular carcinoma.^{2,3}

Therapeutic options for adults with chronic hepatitis B include the nucleoside analogue lamivudine (Epivir-HBV, GlaxoSmithKline) and the cytokine interferon alfa. Interferon alfa therapy is cumbersome

to deliver, is uncomfortable to receive, and has undesirable side effects. Since the rates of success of lamivudine therapy among adults are similar to those of interferon therapy, we undertook the present study to assess the safety and efficacy of lamivudine treatment in children with chronic hepatitis B.

METHODS

Study Design

This randomized, double-blind, placebo-controlled study was conducted between September 1998 and July 2000 at 40 centers in North America, South America, and Europe. The academic investigators actively participated in the design of the study and the interpretation of results. The sponsor held the data, but all investigators had full access to them. The writing, review, and final approval of the manuscript were performed by a committee of 11 persons, including 4 representatives from the research and development departments of GlaxoSmithKline.

Children who completed the trial were stratified on the basis of HBeAg status at 48 weeks and offered either open-label lamivudine treatment or observation for an additional 2 years. Data from the first six months of the open-label study are available.

Patients

Eligibility requirements included an age between 2 and 17 years at enrollment, seropositivity for hepatitis B surface antigen (HBsAg) for at least 6 months before enrollment, seropositivity for HBeAg, undetectable levels of antibody against HBeAg (anti-HBe), serum alanine aminotransferase values that were more than 1.3 times the upper limit of the normal range (but less than 500 IU per liter) for at least 3 months before enrollment, evidence of inflammation on liver biopsy,⁴ and measurable HBV DNA in serum on branched-chain DNA assay (Chiron/Bayer Quantiplex assay, version 1, with a lower limit of detection of 0.7 meq per milliliter).

Patients were excluded if they had received interferon within the previous 12 months or systemic antiviral agents, immunomodulatory drugs, cytotoxic agents, or corticosteroids within the previous 6 months. Patients were also excluded if they were coinfecting with the human immunodeficiency virus, hepatitis C virus, or hepatitis D virus or they had decompensated liver disease, renal insufficiency, pancreatitis, a clinically significant coexisting medical illness, or other types of liver disease. Women who were pregnant or breastfeeding were excluded. Liver biopsy to determine eligibility had

From Children's Hospital, Boston (M.M.J.); Diana Princess of Wales Hospital, Birmingham, United Kingdom (D.A.K.); John Paul II Hospital, Krakow, Poland (J.M.); Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina (I.B.B.); Hospital Geral de Santo Antonio, Porto, Portugal (J.A.A.); Johns Hopkins University, Baltimore (K.B.S.); GlaxoSmithKline, Research Triangle Park, N.C. (N.R.L., S.D.G., M.S.B.); GlaxoSmithKline, Greenford, United Kingdom (M.J.G.); and Cliniques Universitaires St. Luc, Brussels, Belgium (E.M.S.). Address reprint requests to Dr. Jonas at the Division of Gastroenterology, Children's Hospital, 300 Longwood Ave., Boston, MA 02115.

*Other members of the International Pediatric Lamivudine Investigator Group are listed in the Appendix.

to have been performed within 24 months before enrollment and at least 12 months after the completion of interferon therapy (for patients who had received interferon).

Patients or their parents or legal guardians provided written informed consent using a form approved by the appropriate institutional review board or ethics committee. We compared lamivudine with placebo, since there were no approved treatments for chronic hepatitis B in children when the trial was initiated.

Treatment

Randomization was performed at a central location. Patients were randomly assigned (in a 2:1 ratio) to receive either lamivudine solution at a dose of 3 mg per kilogram of body weight (maximal dose, 100 mg) or a matching placebo solution orally once daily for 52 weeks.⁵

Clinical and Virologic Procedures

Patients were assessed two, four, and eight weeks after the initiation of therapy, every eight weeks until week 48, and at week 52. Blood samples were drawn at each visit to monitor blood chemical and hematologic values. Female patients with childbearing potential were required to have a pregnancy test at every study visit. During the 52-week study, investigators and patients were unaware of the results of HBV DNA and HBsAg assays. The result of the HBeAg assay was disclosed at week 48 and used for stratification at week 52 for the follow-up study. Commercially available enzyme-linked immunoassays were used to measure HBeAg, anti-HBe, HBsAg, and antibody against HBsAg (anti-HBs) (HBe [rDNA] Enzyme Immunoassay, AxSym HBe Microparticle Enzyme Immunoassay, HBs Auszyme Enzyme Immunoassay, and Ausab Enzyme Immunoassay, respectively; all from Abbott Laboratories). All samples were analyzed at a central reference laboratory (Covance Clinical Laboratory Services); however, prothrombin times were determined at each center, and genotypic analysis for resistance mutations was performed at GlaxoSmithKline Virology Laboratories. Serum samples collected at base line and week 52 were frozen at -80°C for subsequent genotypic analysis for resistance mutations. Mutations in the YMDD (tyrosine, methionine, aspartate, and aspartate) motif of the reverse-transcriptase domain in the HBV polymerase gene were assessed by the polymerase chain reaction and restriction-fragment-length polymorphism assay.⁶

An independent histopathologist who was unaware of the patients' treatment assignments assessed liver-biopsy specimens obtained before treatment using the Knodell Histologic Activity Index.⁴ Scores for this index can range from 0 (normal) to 22 (severely abnormal) and represent the sum of four histologic components: the severity of periportal necrosis (range of scores, 0 to 10), intralobular necrosis (range of scores, 0 to 4), portal inflammation (range of scores, 0 to 4), and fibrosis (range of scores, 0 to 4).

Efficacy Assessments

All assessments of efficacy were based on data obtained after 52 weeks of treatment. The primary efficacy end point was virologic response, a composite measure defined by the loss of serum HBeAg and by the reduction of serum HBV DNA to undetectable levels — changes indicative of a durable remission.⁷ Secondary end points included sustained normalization of the alanine aminotransferase values (at least two consecutive values below the upper limit of the normal range without any subsequent abnormality through the end of therapy); seroconversion from HBeAg to anti-HBe, with or without the disappearance of HBV DNA; the loss of HBeAg; the loss of HBsAg; and the absence of detectable levels of HBV DNA in serum. Follow-up liver biopsy was not part of the protocol.

Safety Assessments

All patients were assessed for adverse events at each visit. Levels of alanine aminotransferase, albumin, bilirubin, amylase, lipase, cre-

atine kinase, hemoglobin, white cells, neutrophils, and platelets were assessed. Weight and height were measured.

Statistical Analysis

All analyses were prespecified. On the basis of similar studies of adults with chronic hepatitis B, we estimated that the rates of virologic response would be 25 percent among children in the lamivudine group and 9 percent among children in the placebo group. Given these estimated response rates, we calculated that 255 patients (170 in the lamivudine group and 85 in the placebo group) would be required for the study to have 80 percent power to detect an absolute difference between groups of 17 percent at an alpha level of 0.05. This sample size would also give the study 90 percent power to identify an absolute difference between groups of 34 percent with respect to the proportion of patients with the secondary end point of sustained normalization of alanine aminotransferase values.

We used a modified intention-to-treat analysis, which included all patients with confirmed chronic hepatitis B who were assigned to either treatment group, to assess efficacy. For the primary end point of virologic response, as well as for the secondary end points, patients who withdrew before week 52 or for whom data were missing at week 52 were considered to have had no response. All statistical tests (chi-square, Fisher's exact, and Wilcoxon rank-sum) for comparisons between treatment groups and resulting P values were two-sided.

For the analysis of safety, we analyzed the data according to the treatment received. We included all patients who were randomly assigned to either treatment group and who received at least one dose of study medication.

We used logistic-regression models to assess whether there were treatment-related differences in the rate of virologic response after adjustment for the following base-line factors: score on the Histologic Activity Index, alanine aminotransferase level, HBV DNA level, age, sex, racial or ethnic origin, body-mass index, weight, and presence or absence of cirrhosis. Logistic regression was also used to examine the differences between groups according to whether the patients had previously received interferon therapy and whether they had YMDD-variant HBV DNA.

RESULTS

Study Population

The numbers of patients who were screened, underwent randomization, withdrew from the study, and were analyzed are presented in Figure 1. There were no significant differences in demographic characteristics between the treatment groups (further information is available as Supplementary Appendix 1 with the full text of this article at <http://www.nejm.org>). Although at base line, the median alanine aminotransferase value (2.3 vs. 2.1 times the upper limit of the normal range) and HBV DNA level (1032 vs. 895 meq per milliliter) tended to be higher in the placebo group than in the lamivudine group, these differences were not statistically significant. Forty-five percent of the children had had no response to interferon therapy, and the proportions were similar in the lamivudine group and the placebo group (47 percent and 42 percent, respectively).

Pretreatment Liver Biopsy

Evaluations of liver-biopsy specimens obtained before treatment indicated that, although the median

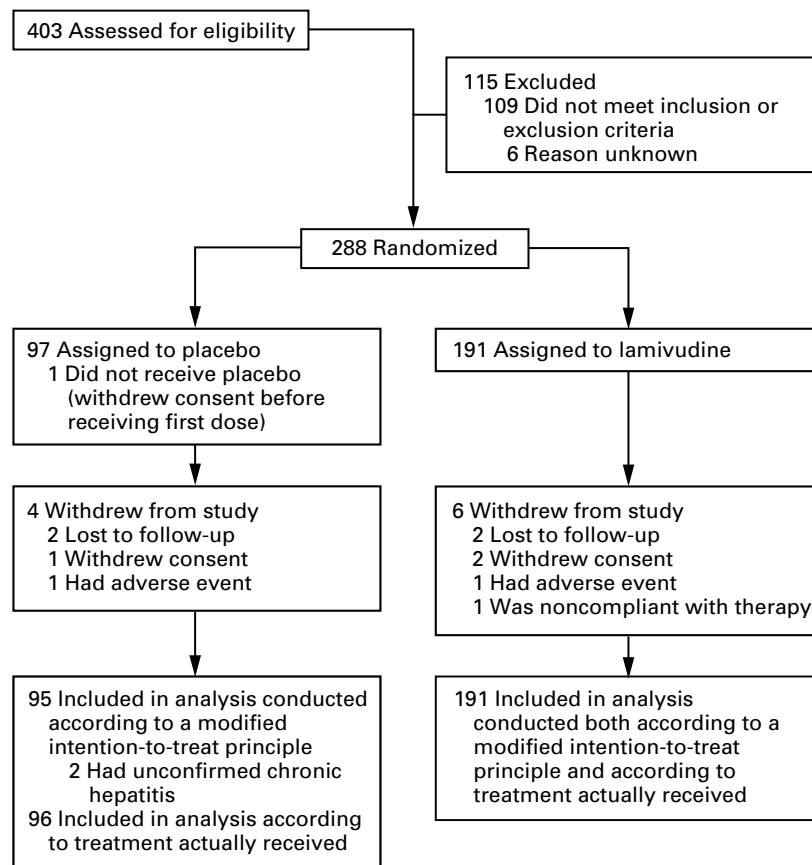


Figure 1. Numbers of Patients Included in or Excluded from Randomization and Subsequent Analyses.

total scores on the Histologic Activity Index and the median scores for necrosis and inflammation were similar in the two groups, the mean scores were higher in the placebo group than in the lamivudine group (Table 1). The range of scores was wide in both groups, however, and some children had severe disease with clinically significant fibrosis. Three patients had cirrhosis (two assigned to receive lamivudine and one assigned to receive placebo).

Efficacy

A virologic response had occurred by week 52 in 23 percent of children in the lamivudine group, as compared with 13 percent of children in the placebo group (44 of 191 vs. 12 of 95; odds ratio, 2.1; 95 percent confidence interval, 1.0 to 4.1; $P=0.04$) (Table 2). The median time to the normalization of alanine aminotransferase levels in the lamivudine group was 24 weeks (Fig. 2A). The rate of virologic response increased with increasing base-line alanine amino-

transferase values (Fig. 2B). Only 2 of the 44 patients in the lamivudine group who had a virologic response did not have detectable anti-HBe at week 52. However, in both patients, this antibody had been present at week 48 and was present again one month after treatment.

Logistic-regression analyses demonstrated that higher base-line alanine aminotransferase values and scores on the Histologic Activity Index were associated with a greater likelihood of virologic response. After adjustment for these factors, a logistic-regression model confirmed that the difference between lamivudine and placebo was significant (adjusted odds ratio, 3.89; 95 percent confidence interval, 1.66 to 9.08; $P=0.002$). The adjusted odds ratios and confidence intervals associated with various potential prognostic factors are presented in Table 3. Logistic-regression analysis showed that there were no significant differences in the rates of virologic response and normalization of alanine aminotransferase

TABLE 1. RESULTS OF LIVER BIOPSY PERFORMED BEFORE TREATMENT.*

HISTOLOGIC ACTIVITY INDEX SCORE	PLACEBO GROUP (N=95)	LAMIVUDINE GROUP (N=191)	P VALUE†
Total score			
Median	4	4	
Range	0–13	0–12	
Mean ±SD	5.7±2.7	4.7±2.2	0.002
Necrosis–inflammation score			
Median	3	3	
Range	0–10	0–9	
Mean ±SD	4.3±2.1	3.5±1.7	0.002
Fibrosis score			
Median	1	1	
Range	0–4	0–4	
Mean ±SD	1.4±0.9	1.2±0.8	0.035

*Liver biopsies were performed up to 24 months before enrollment in the study and at least 12 months after the completion of interferon therapy (in patients who had received interferon therapy). Scores for the Histologic Activity Index can range from 0 (normal) to 22 (severely abnormal) and are the sum of four histologic components: the severity of periportal necrosis (range of scores, 0 to 10), intralobular necrosis (range of scores, 0 to 4), portal inflammation (range of scores, 0 to 4), and fibrosis (range of scores, 0 to 4).

†P values were calculated with use of a Wilcoxon rank-sum test.

values between children who had previously received interferon and those who never received interferon.

Safety

The nature, incidence, and severity of adverse clinical events and abnormal laboratory values in patients receiving lamivudine were similar to those in

patients receiving placebo (see Supplementary Appendix 2 with the full text of this article at <http://www.nejm.org>). There were no deaths during the study. The incidence and extent of elevations in alanine aminotransferase values were similar in the two groups. In no patient was the alanine aminotransferase value elevated in association with hyperbilirubinemia or other signs of hepatic decompensation.

There was no significant difference between the lamivudine group and the placebo group in the change in the weight-for-age z scores from base line to week 52 (P=0.75). The median changes were 0.01 (range, –1.11 to 3.35) in the lamivudine group and 0.12 (range, –1.69 to 0.98) in the placebo group. Height-for-age z scores were calculated at the time of screening and at week 48; there was no significant difference between groups in the change in the height-for-age z score (P=0.61): the median change was 0.01 (range, –1.68 to 2.81) in the lamivudine group and 0.05 (range, –0.84 to 1.9) in the placebo group.

Analysis of HBV Genotypic Resistance

Serum samples were available for genotypic analysis from 90 percent of patients in the placebo group (86 of 96) and 87 percent of patients in the lamivudine group (166 of 191) at week 52. HBV DNA from 19 percent of patients in the lamivudine group (31 of 166) had detectable codon changes at site 552 (methionine to valine or isoleucine) in the C domain of the YMDD motif of the HBV polymerase gene. Demographic characteristics were similar between patients with YMDD-variant HBV DNA and patients with

TABLE 2. EFFICACY OF TREATMENT.*

RESPONSE AT WEEK 52	PLACEBO GROUP (N=95)	LAMIVUDINE GROUP (N=191)	ODDS RATIO (95% CI)	P VALUE†
	no. (%)			
Virologic response‡	12 (13)	44 (23)	2.1 (1.0–4.1)	0.04
Sustained normalization of alanine aminotransferase levels§	11 (12)	100 (55)	8.4 (4.2–16.9)	<0.001
Virologic response and acquisition of anti-HBe	12 (13)	42 (22)	1.9 (1.0–3.9)	0.06
Loss of HBeAg	14 (15)	50 (26)	2.1 (1.1–3.9)	0.03
HBV DNA undetectable¶	15 (16)	117 (61)	8.4 (4.5–15.7)	<0.001
Loss of HBsAg	0	3 (2)	—	—

*CI denotes confidence interval, anti-HBe hepatitis B e antibody, HBeAg hepatitis B e antigen, HBV hepatitis B virus, and HBsAg hepatitis B surface antigen.

†P values were calculated with the use of the chi-square test.

‡A virologic response was defined by the absence of HBeAg and HBV DNA in serum.

§Only patients with base-line alanine aminotransferase levels that exceeded the upper limit of the normal range were included in the analysis (88 in the placebo group and 183 in the lamivudine group).

¶Levels were undetectable on branched-chain DNA assay with a lower limit of detection of 0.7 meq per milliliter.

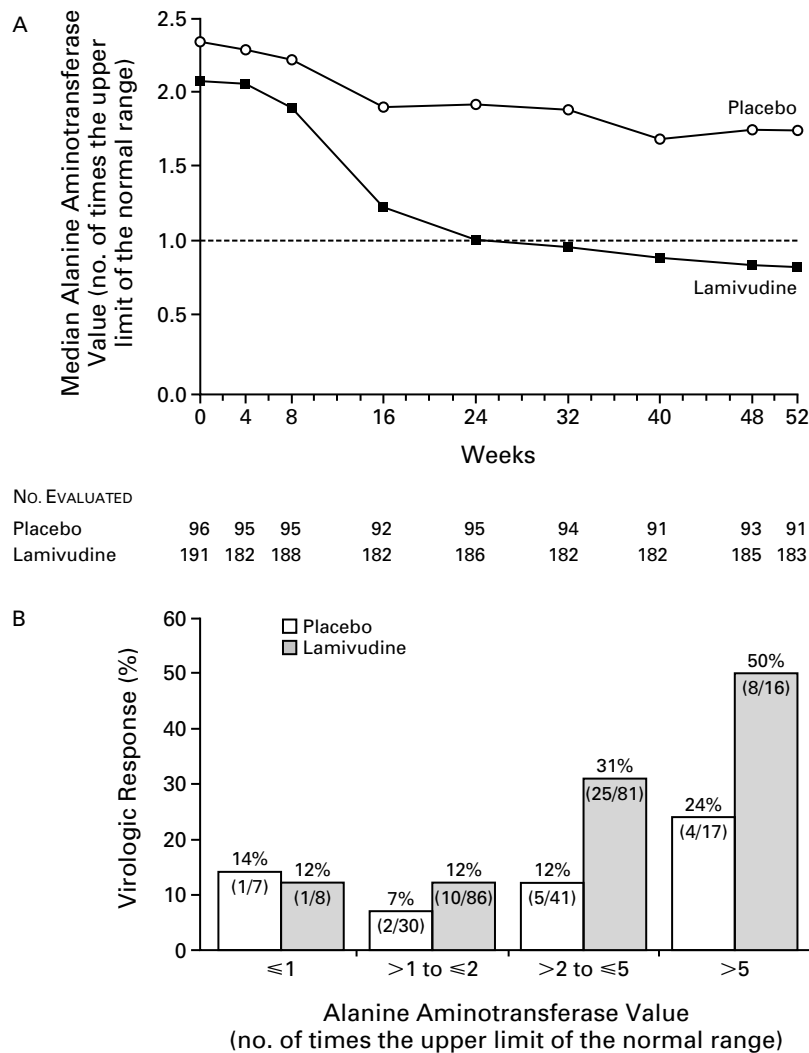


Figure 2. Median Alanine Aminotransferase Values during the 52-Week Treatment Period (Panel A) and Rates of Virologic Response According to the Base-Line Alanine Aminotransferase Value (Panel B). A virologic response was defined by the absence of hepatitis B e antigen and hepatitis B virus DNA in serum at 52 weeks. In Panel A, not all patients were evaluated at each follow-up visit. The dotted line indicates the upper limit of alanine aminotransferase values. In Panel B, values in parentheses are the number of patients with a response and the total number of patients with a base-line alanine aminotransferase value in that range.

the wild-type sequence. The median serum HBV DNA level tended to be higher at base line in the patients in whom the YMDD variant was present at 52 weeks (Table 4). Median alanine aminotransferase values, bilirubin levels, and scores for the Histologic Activity Index were similar in these two subgroups.

HBeAg disappeared during the study in only one child in whom the YMDD-variant HBV DNA was present at week 52. This child had anti-HBe and

normal alanine aminotransferase values at week 52. However, the median HBV DNA level in the 31 children with variant HBV was substantially lower at week 52 than at base line (Table 4). Among these patients, 29 percent had HBV DNA levels at week 52 that were below the limit of detection of a conventional assay and were measurable only by the polymerase chain reaction. Ninety-one percent of patients with detectable levels of HBV DNA at week 52 (20 of 22) had levels that were lower than the

TABLE 3. ADJUSTED ODDS RATIOS FOR VIROLOGIC RESPONSE TO LAMIVUDINE ASSOCIATED WITH POTENTIAL PROGNOSTIC VARIABLES.*

VARIABLE	LAMIVUDINE GROUP (N=191)	ADJUSTED ODDS RATIO (95% CI)	P VALUE
	no./total no. (%)		
Base-line alanine aminotransferase			<0.001
Twice the upper limit of the normal range or less	11/94 (12)	1.0	
More than twice the upper limit of the normal range	33/97 (34)	3.41 (1.75–6.66)	
Histologic Activity Index score†			0.002
0–4	12/113 (19)	1.0	
5–9	20/53 (38)	1.77 (0.95–3.29)	
10–14	2/7 (29)	2.57 (0.81–8.17)	
Base-line HBV DNA			0.04‡
<800 meq/ml	30/93 (32)	1.0	
≥800 meq/ml	14/98 (14)	0.25 (0.13–0.49)	
Racial or ethnic origin			0.54
White	29/139 (21)	1.0	
Asian	10/33 (30)	1.27 (0.61–2.66)	
Other	5/19 (26)	1.05 (0.40–2.76)	

*Odds ratios were adjusted for base-line alanine aminotransferase values and base-line Histologic Activity Index score and are based on a logistic-regression model that included the treatment assignment and the factor of interest. CI denotes confidence interval, and HBV hepatitis B virus.

†Scores for the Histologic Activity Index can range from 0 (normal) to 22 (severely abnormal) and are the sum of four histologic components: the severity of periportal necrosis (range of scores, 0 to 10), intralobular necrosis (range of scores, 0 to 4), portal inflammation (range of scores, 0 to 4), and fibrosis (range of scores, 0 to 4).

‡Subgroup analyses indicated an interaction between HBV DNA level and treatment, so the P value for this factor should be interpreted with caution.

base-line level. The median alanine aminotransferase value was also lower at week 52 than at base line in children with YMDD-variant HBV DNA (Table 4); the levels were normal in 45 percent (14 of 31).

Follow-up Study

During the first six months of open-label treatment with lamivudine, a virologic response occurred in an additional 10 percent of patients (12 of 123) who had previously been assigned to receive lamivudine. Among patients who were merely observed during follow-up because they had had a virologic response in the first year of treatment, 82 percent (33 of 40) had a sustained response. Patients who had had a response to lamivudine during the first year were as likely to have a sustained response as those who had had spontaneous clearance of HBeAg and HBV DNA.

DISCUSSION

This international study of children with chronic hepatitis B demonstrated that 52 weeks of treatment with lamivudine resulted in a higher rate of virologic response than did 52 weeks of placebo. The secondary end points of virologic response with the devel-

opment of anti-HBe and undetectable levels of HBV DNA and normalization of serum alanine aminotransferase values were also more frequent in lamivudine-treated children. These results are consistent with those in adults with chronic hepatitis B.⁸⁻¹¹

The average base-line alanine aminotransferase level and Histologic Activity Index score were higher in the placebo group, the latter significantly so. Since these factors have been associated with a virologic response in this and other studies, there may have been an intrinsic bias favoring placebo that would have minimized the differential effects of lamivudine.

Preparations of interferon alfa have been approved for the treatment of chronic hepatitis B in children. Although generally safe and effective, interferon has substantial limitations, including the need for repeated injections for six months, undesirable side effects such as growth impairment,¹² and a low rate of efficacy in patients with serum HBV DNA levels above 200 pg per milliliter or only minimally elevated levels of alanine aminotransferase.¹³⁻¹⁶ Our study included patients who had had no response to interferon therapy, and the rate of virologic response of 23 percent in the lamivudine group was similar to the rate of 26 percent reported with interferon ther-

TABLE 4. MEDIAN LEVELS OF HEPATITIS B VIRUS (HBV) DNA AND ALANINE AMINOTRANSFERASE, ACCORDING TO THE PRESENCE OR ABSENCE OF A MUTATION IN THE YMDD MOTIF.*

VARIABLE	No. OF PATIENTS	HBV DNA		ALANINE AMINOTRANSFERASE	
		BASE LINE	WEEK 52	BASE LINE	WEEK 52
		meq/ml		no. of times the upper limit of the normal range	
YMDD variant absent	135				
Median		753.2	0.35	2.0	0.8
Range		2.2–28,300	0.35–2604	0.7–16.9	0.2–3.7
YMDD variant present	31				
Median		1648	6.75	2.2	1.2
Range		158.5–13,018	0.35–1217	1.3–5.5	0.4–5.4

*Analyses for the YMDD (tyrosine, methionine, aspartate, and aspartate) motif were performed at base line and week 52 in 166 patients in the lamivudine group; the variant was found only at week 52.

apy in children.¹⁷ These results were achieved despite the fact that the median base-line levels of alanine aminotransferase were higher in the interferon study than in our study. As is the case with interferon, the rates of virologic response to lamivudine were higher with higher base-line levels of alanine aminotransferase.

The emergence of YMDD-variant HBV may reverse the response in some patients and has been considered a limitation of lamivudine therapy. This variant was detected in 19 percent of patients who received lamivudine for 52 weeks, as compared with 16 to 32 percent of adults in other studies.^{8–11} In these other studies, few adults with YMDD-variant HBV had lost HBeAg after one year of treatment. In some instances, liver disease may progress with continued treatment in patients with persistent viremia who have YMDD-variant HBV. However, long-term trials have indicated that seroconversion can still occur with extended treatment and that the presence of YMDD-variant HBV DNA does not necessarily signify a complete loss of efficacy or preclude HBeAg seroconversion.¹⁸ We found that the frequency of HBeAg responses was substantially lower with continued treatment but that the HBV DNA and alanine aminotransferase levels remained below base-line values in the majority of patients with YMDD-variant HBV, suggesting that the replicative ability of these viral variants was decreased.^{19,20} The optimal duration of treatment in children in whom YMDD-variant HBV develops has not been established, and longer-term follow-up is warranted.

We found that treatment of chronic hepatitis B with lamivudine for one year is safe in children and is superior to placebo, although neither approach is highly

efficacious. Efficacy may be improved by selecting patients whose alanine aminotransferase value is at least twice the upper limit of the normal range. Preliminary data suggest that virologic and biochemical responses achieved with lamivudine therapy are as durable as spontaneous responses, at least for the first six months. Although there are interim data to suggest that further therapeutic responses are achieved with longer therapy, the development of genotypic resistance may limit the benefits of extended therapy, since the long-term outcome of chronic hepatitis B in children with lamivudine-resistant mutants is unknown.

The study drug and funding for this research were provided by GlaxoSmithKline. Dr. Jonas serves as a consultant to GlaxoSmithKline as a member of the company's Hepatitis National Advisory Board.

We are indebted to Dr. Robert D. Goldin, of St. Mary's Hospital, London, for his work in assessing the liver-biopsy specimens, and to Vincent A. Lopez, of the Department of Clinical Virology, GlaxoSmithKline, for his work on viral genotype analyses.

APPENDIX

In addition to the authors, the International Pediatric Lamivudine Investigator Group includes the following: E.M. Alonso, Children's Memorial Hospital, Chicago; F. Alvarez, Hopital Ste.-Justine, Montreal; W. Balistreri, Children's Hospital Medical Center, Cincinnati; F. Bortolotti, Policlinico Universitario, Padua, Italy; J. Cabral, Hospital de D. Estefania, Lisbon, Portugal; H.S. Conjeevaram, University of Chicago Hospitals and Clinics, Chicago; K.E. Crissinger, Vanderbilt University School of Medicine, Nashville; G. Ferreira, Hospital Fernando da Fonseca, Amadora, Portugal; J.E. Fitzgerald, James Whitcomb Riley Hospital for Children, Indianapolis; D.A. Gremse, University of South Alabama, Mobile; H.I. Hann, Jefferson Medical College, Philadelphia; P. Harmatz, Children's Hospital Oakland, Oakland, Calif.; P. Jara, Ciudad Sanitaria La Paz, Madrid; S. Karyda, Ip-pokraton General Hospital, Thessaloniki, Greece; J.D. Lewis, Children's Center for Digestive Healthcare, Atlanta; E. Maller, Children's Hospital of Philadelphia, Philadelphia; N. Manolaki, Agia Sophia Children's Hospital, Athens, Greece; P. Mohan, Children's National Medical Center, Washington, D.C.; K.E. Murray, Children's Hospital and Medical Center, Seattle;

H. Pollack, New York University Medical Center, New York; G. Porta, Instituto da Ninos Prof. Pedro de Alcantara, São Paulo, Brazil; M.J. Rhoads, University of North Carolina School of Medicine, Chapel Hill; R.A. Schreiber, British Columbia Children's Hospital, Vancouver, B.C., Canada; W. Sluzewski, Klinika Obserwacyjno, Poznan, Poland; R. Sokol, Children's Hospital, Denver; R. Squires, Children's Medical Center of Dallas, Dallas; N. Tassopoulos, Western Attica General Hospital, Athens, Greece; T. Torro, Hospital Infantil Valle de Hebron, Barcelona, Spain; W.R. Treem, Duke University Medical Center, Durham, N.C.; P. Vajro, University of Naples, Naples, Italy; S. Weisdorf, Fairview University Medical Center, Minneapolis; and M. Woynarowski, Klinika Gastroenterologii Zywienia, Warsaw, Poland.

REFERENCES

1. Fact sheets: hepatitis B. Geneva: World Health Organization, October 2000.
2. Mahoney FJ. Update on diagnosis, management, and prevention of hepatitis B virus infection. *Clin Microbiol Rev* 1999;12:351-66.
3. Hsieh CC, Tzonou A, Zavitsanos X, Kaklamani E, Lan SJ, Trichopoulos D. Age at first establishment of chronic hepatitis B virus infection and hepatocellular carcinoma risk: a birth order study. *Am J Epidemiol* 1992;136:1115-21.
4. Knodell RG, Ishak KG, Black WC, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology* 1981;1:431-5.
5. Sokal EM, Roberts EA, Mieli-Vergani G, et al. A dose ranging study of the pharmacokinetics, safety, and preliminary efficacy of lamivudine in children and adolescents with chronic hepatitis B. *Antimicrob Agents Chemother* 2000;44:590-7.
6. Allen M, Gauthier J, DesLauriers M, et al. Two sensitive PCR-based methods for detection of hepatitis B virus variants associated with reduced susceptibility to lamivudine. *J Clin Microbiol* 1999;37:3338-47.
7. Lok AS, Heathcote EJ, Hoofnagle JH. Management of hepatitis B: 2000 — summary of a workshop. *Gastroenterology* 2001;120:1828-53.
8. Lai C-L, Chien R-N, Leung NWY, et al. A one-year trial of lamivudine for chronic hepatitis B. *N Engl J Med* 1998;339:61-8.
9. Dienstag JL, Schiff ER, Wright TL, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med* 1999;341:1256-63.
10. Schalm SW, Heathcote J, Cianciara J, et al. Lamivudine and alpha interferon combination treatment of patients with chronic hepatitis B infection: a randomised trial. *Gut* 2000;46:562-8.
11. Schiff E, Karayalcin S, Grimm I, et al. A placebo controlled study of lamivudine and interferon alpha-2b in patients with chronic hepatitis B who previously failed interferon therapy. *Hepatology* 1998;28:Suppl:388A. abstract.
12. Comanor L, Minor J, Conjeevaram HS, et al. Impact of chronic hepatitis B and interferon-alpha therapy on growth of children. *J Viral Hepat* 2001;8:139-47.
13. Jara P, Bortolotti F. Interferon- α treatment of chronic hepatitis B in childhood: a consensus advice based on experience in European children. *J Pediatr Gastroenterol Nutr* 1999;29:163-70.
14. Perrillo RP, Schiff ER, Davis GL, et al. A randomized, controlled trial of interferon alfa-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. *N Engl J Med* 1990;323:295-301.
15. Hoofnagle JH, Di Bisceglie AM. The treatment of chronic viral hepatitis. *N Engl J Med* 1997;336:347-56.
16. Malik A, Lee WM. Chronic hepatitis B virus infection: treatment strategies for the next millennium. *Ann Intern Med* 2000;132:723-31.
17. Sokal EM, Conjeevaram HS, Roberts EA, et al. Interferon alfa therapy for chronic hepatitis B in children: a multinational randomized controlled trial. *Gastroenterology* 1998;114:988-95.
18. Leung NWJ, Lai CL, Chang TT, et al. Extended lamivudine treatment in patients with chronic hepatitis B enhances hepatitis B e antigen seroconversion rates: results after 3 years of therapy. *Hepatology* 2001;33:1527-32.
19. Melegari M, Scaglioni PP, Wands JR. Hepatitis B virus mutants associated with 3TC and famciclovir administration are replication defective. *Hepatology* 1998;27:628-33.
20. Allen MI, Deslauriers M, Andrews CW, et al. Identification and characterization of mutations in hepatitis B virus resistant to lamivudine. *Hepatology* 1998;27:1670-7.

Copyright © 2002 Massachusetts Medical Society.

ELECTRONIC ACCESS TO THE JOURNAL'S CUMULATIVE INDEX

At the *Journal's* site on the World Wide Web (<http://www.nejm.org>) you can search an index of all articles published since January 1975 (abstracts 1975-1992, full-text 1993-present). You can search by author, key word, title, type of article, and date. The results will include the citations for the articles plus links to the abstracts of articles published since 1993. For nonsubscribers, time-limited access to single articles and 24-hour site access can also be ordered for a fee through the Internet (<http://www.nejm.org>).

CORRECTION

Clinical Trial of Lamivudine in Children with Chronic Hepatitis B

Clinical Trial of Lamivudine in Children with Chronic Hepatitis B . On page 1706, the last name of the second author should have been spelled "Kelly" rather than "Kelley."