

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

MARCH 9, 2006

VOL. 354 NO. 10

A Comparison of Entecavir and Lamivudine for HBeAg-Positive Chronic Hepatitis B

Ting-Tsung Chang, M.D., Robert G. Gish, M.D., Robert de Man, M.D., Adrian Gadano, M.D., José Sollano, M.D., You-Chen Chao, M.D., Anna S. Lok, M.D., Kwang-Hyub Han, M.D., Zachary Goodman, M.D., Ph.D., Jin Zhu, Ph.D., Anne Cross, Ph.D., Deborah DeHertogh, M.D., Richard Wilber, M.D., Richard Colonno, Ph.D., and David Apelian, M.D., Ph.D., for the BEHoLD A1463022 Study Group*

ABSTRACT

BACKGROUND

Entecavir is a potent and selective guanosine analogue with significant activity against hepatitis B virus (HBV).

METHODS

In this phase 3, double-blind trial, we randomly assigned 715 patients with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B who had not previously received a nucleoside analogue to receive either 0.5 mg of entecavir or 100 mg of lamivudine once daily for a minimum of 52 weeks. The primary efficacy end point was histologic improvement (a decrease by at least two points in the Knodell necroinflammatory score, without worsening of fibrosis) at week 48. Secondary end points included a reduction in the serum HBV DNA level, HBeAg loss and seroconversion, and normalization of the alanine aminotransferase level.

RESULTS

Histologic improvement after 48 weeks occurred in 226 of 314 patients in the entecavir group (72 percent) and 195 of 314 patients in the lamivudine group (62 percent, $P=0.009$). More patients in the entecavir group than in the lamivudine group had undetectable serum HBV DNA levels according to a polymerase-chain-reaction assay (67 percent vs. 36 percent, $P<0.001$) and normalization of alanine aminotransferase levels (68 percent vs. 60 percent, $P=0.02$). The mean reduction in serum HBV DNA from baseline to week 48 was greater with entecavir than with lamivudine (6.9 vs. 5.4 log [on a base-10 scale] copies per milliliter, $P<0.001$). HBeAg seroconversion occurred in 21 percent of entecavir-treated patients and 18 percent of those treated with lamivudine ($P=0.33$). No viral resistance to entecavir was detected. Safety was similar in the two groups.

CONCLUSIONS

Among patients with HBeAg-positive chronic hepatitis B, the rates of histologic, virologic, and biochemical improvement are significantly higher with entecavir than with lamivudine. The safety profile of the two agents is similar, and there is no evidence of viral resistance to entecavir. (ClinicalTrials.gov number, NCT00035633.)

From the National Cheng Kung University Medical College, Tainan, Taiwan (T.-T.C.); California Pacific Medical Center, San Francisco (R.G.G.); University Hospital Rotterdam, Rotterdam, the Netherlands (R.M.); Hospital Italiano, Buenos Aires (A.G.); the University of Santo Tomas, Manila, the Philippines (J.S.); Tri-Service General Hospital, Taipei, Taiwan (Y.-C.C.); the University of Michigan, Ann Arbor (A.S.L.); Severance Hospital, Yonsei University College of Medicine, Seoul, Korea (K.-H.H.); Armed Forces Institute of Pathology, Washington, D.C. (Z.G.); Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, Conn. (J.Z., A.C., R.W., R.C.); the University of Connecticut, Farmington (D.D.); and Globelmmune, Louisville, Colo. (D.A.). Address reprint requests to Dr. Chang at the Department of Internal Medicine, National Cheng Kung University Hospital, 138 Sheng-Li Rd., Tainan, Taiwan 704, or at tchang@mail.ncku.edu.tw.

*Other members of the Benefits of Entecavir for Hepatitis B Liver Disease (BEHoLD) A1463022 Study Group are listed in the Appendix.

N Engl J Med 2006;354:1001-10.

Copyright © 2006 Massachusetts Medical Society.

CHRONIC HEPATITIS B AFFECTS MORE than 350 million people worldwide and each year is responsible for more than 1 million deaths from cirrhosis and hepatocellular carcinoma.^{1,2} Suppression of hepatitis B virus (HBV) replication is a principal goal of long-term hepatitis B therapy.³ Studies of long-term lamivudine treatment in patients with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B have found that maintenance of virologic suppression is associated with improved histologic findings in the liver.^{4,5} Liaw and coworkers have shown that lamivudine treatment delays the progression of disease among patients with chronic hepatitis B and advanced liver disease, probably by suppressing viral replication and hepatic necroinflammation.⁶ In addition, two recent prospective studies from Taiwan found that among persons infected with HBV, higher plasma HBV DNA levels are associated with an increased risk of hepatocellular carcinoma, reinforcing the importance of controlling viral replication among patients with chronic hepatitis B.^{7,8}

Five medications are currently available for the treatment of HBeAg-positive chronic HBV infection: interferon alfa, lamivudine, pegylated interferon alfa-2a, adefovir dipivoxil, and entecavir. Interferon alfa is effective in only 30 to 40 percent of patients and is associated with a high incidence of adverse events.^{9,10} Lamivudine suppresses viral replication and results in HBeAg seroconversion in 16 to 17 percent of patients and histologic improvement in 52 to 56 percent after one year of therapy.^{11,12} However, within four years, the rate of emergence of lamivudine-resistant HBV mutants approaches 70 percent,¹³⁻¹⁵ and resistance is usually associated with a rebound in viral load and often with exacerbation of hepatitis.¹⁶⁻¹⁹ Pegylated interferon alfa-2a appears to have better efficacy than lamivudine in HBeAg-positive patients 6 months after the completion of a 48-week treatment course; however, the rate of adverse events associated with pegylated interferon alfa-2a is higher than it is with lamivudine.²⁰ One year of treatment with adefovir dipivoxil results in a median reduction in the HBV DNA level of 3.52 log (on a base-10 scale) copies per milliliter, histologic improvement in 53 percent of patients, and HBeAg seroconversion in 12 percent of patients.²¹ After three years of treatment, resistance to adefovir develops in up to 3 percent of

HBeAg-positive patients and 5.9 percent of HBeAg-negative patients.^{22,23}

Entecavir (Baraclude, Bristol-Myers Squibb) is a potent and selective inhibitor of HBV DNA polymerase.²⁴ Preclinical studies in woodchucks demonstrated the antiviral activity of entecavir and its potential to reduce the incidence of hepatocellular carcinoma and improve survival.²⁵ In a randomized phase 2 trial in HBeAg-positive and HBeAg-negative patients who had not previously received a nucleoside analogue, entecavir at a dose of 0.5 mg once daily resulted in a significantly greater mean reduction in HBV DNA at 22 weeks than did lamivudine at a dose of 100 mg once daily (4.72 vs. 3.36 log copies per milliliter, $P < 0.001$).²⁶ Entecavir had a safety and adverse-reaction profile similar to that of lamivudine. The efficacy and tolerability of entecavir were also demonstrated in phase 2 and phase 3 trials of patients whose disease was refractory to lamivudine.^{27,28} The current study was designed to compare the efficacy and safety of 48 weeks of therapy with entecavir with 48 weeks of therapy with lamivudine (EpiVir-HBV, GlaxoSmithKline) in patients with HBeAg-positive chronic hepatitis B who had not previously received a nucleoside analogue.

METHODS

STUDY DESIGN

This study was a double-blind, double-dummy, randomized, controlled trial. Patients were recruited from 137 centers worldwide, including Europe (41 centers), North America (40), Asia (26), Australia (12), and South America (18), and received entecavir at a dose of 0.5 mg once daily or lamivudine at a dose of 100 mg once daily for a minimum of 52 weeks. Treatment assignments were allocated centrally on the basis of permuted block sizes of four that were assigned within each center.

The study was conducted in accordance with the ethics principles of the Declaration of Helsinki and was consistent with Good Clinical Practice guidelines and applicable local regulatory requirements. Written informed consent was obtained from all randomly assigned patients.

The study was designed by the sponsor (Bristol-Myers Squibb) in collaboration with expert hepatologists who comprised the Benefits of Entecavir for Hepatitis B Liver Disease (BEHoLD) Study

Group. The sponsor collected the data, monitored the conduct of the study, performed the statistical analyses, and coordinated the writing of the manuscript with all authors. Data were unblinded for statistical analysis after the database was locked. The authors had access to the complete study reports, were actively involved in data analysis and interpretation, and approved the final manuscript. The academic authors vouch for the veracity and completeness of the data and the data analyses.

Clinical-management decisions were defined by protocol and made at week 52 on the basis of the results of the Quantiplex (Chiron) branched-chain DNA and HBeAg assays on serum samples obtained at the visit at week 48. Patients who had a response (defined by an HBV DNA level below 0.7 megaequivalents [MEq] per milliliter and HBeAg loss) or a nonresponse (defined by an HBV DNA level of 0.7 MEq per milliliter or greater) discontinued study treatment at week 52. Patients who had only a virologic response (defined by an HBV DNA level below 0.7 MEq per milliliter and no HBeAg loss) were offered continued study therapy for up to 96 weeks.

STUDY POPULATION

Eligible patients were 16 years of age or older and had HBeAg-positive chronic hepatitis B and compensated liver function (a total serum bilirubin level of 2.5 mg per deciliter [42.8 μ mol per liter] or less; a prothrombin time not more than three seconds longer than normal or an international normalized ratio not greater than 1.5; a serum albumin level of at least 3.0 g per deciliter; and no history of variceal bleeding or hepatic encephalopathy). Eligible patients also had detectable hepatitis B surface antigen (HBsAg) for at least 24 weeks before screening, evidence of chronic hepatitis on a baseline liver-biopsy specimen obtained within 52 weeks before randomization, evidence of HBV DNA by any commercial assay at least 4 weeks before screening, an HBV DNA level of at least 3 MEq per milliliter by the branched-chain DNA assay at screening, and a serum alanine aminotransferase level 1.3 to 10.0 times the upper limit of normal at screening.

Exclusion criteria included coinfection with hepatitis C, hepatitis D, or the human immunodeficiency virus; the presence of other forms of liver disease; use of interferon alfa, thymosin α , or antiviral agents with activity against hepatitis B

within 24 weeks before randomization; prior lamivudine therapy lasting more than 12 weeks; an alpha fetoprotein level greater than 100 ng per milliliter; a history of ascites requiring diuretics or paracentesis; and previous treatment with entecavir.

EFFICACY END POINTS

The primary efficacy end point was the proportion of patients with histologic improvement, defined as improvement by at least two points in the Knodell necroinflammatory score with no worsening in the Knodell fibrosis score at week 48, relative to baseline.²⁹ Biopsies were scheduled to be performed at baseline (unless one had been performed within one year before randomization) and at week 48. Liver-biopsy specimens were evaluated by a central, independent histopathologist who was unaware of patients' treatment assignment, biopsy sequence, and clinical outcome. For analyses of the primary efficacy end point, patients who could be evaluated had adequate baseline biopsy specimens with a Knodell necroinflammatory score of at least 2.

Secondary efficacy end points at week 48 included the reduction in HBV DNA level from baseline and the proportion of patients with undetectable HBV DNA, as measured by the Roche COBAS Amplicor PCR assay (version 2.0; lower limit of quantification, 300 copies per milliliter); the decrease in the Ishak fibrosis score; HBeAg loss; HBeAg seroconversion (HBeAg loss and the appearance of HBe antibody); and normalization of serum alanine aminotransferase. Normalization of alanine aminotransferase was defined by the protocol as an alanine aminotransferase value less than 1.25 times the upper limit of normal; the data were subsequently reanalyzed according to a more stringent definition of normalization (an alanine aminotransferase value no greater than the upper limit of normal).

Patients who had a response at week 48 and discontinued treatment were followed for 24 weeks after treatment. In this way we investigated whether the virologic and serologic benefits of antiviral therapy were sustained.

SAFETY ANALYSIS

The safety analysis included data from all 709 treated patients during treatment, including the second year of treatment for patients who continued for more than 52 weeks. The primary safety

end point was the proportion of patients who discontinued the study medication because of clinical or laboratory-determined adverse events. Other safety evaluations included analyses of adverse events, serious adverse events, and deaths. Hepatitis flares during treatment were defined as elevations in the alanine aminotransferase level to more than twice the baseline level and to more than 10 times the upper limit of normal. Post-treatment flares were defined as elevations in alanine aminotransferase to more than twice the reference level and to more than 10 times the upper limit of normal, where the reference level was the lesser of the baseline value and end-of-treatment value.

RESISTANCE ANALYSIS

An extensive resistance analysis was undertaken to identify emerging HBV polymerase substitutions that may be associated with reduced susceptibility to entecavir. All 339 available paired samples from patients in the entecavir group were submitted for genotypic analysis. HBV DNA was extracted and amplified by polymerase chain reaction (PCR), and amino acids 1 through 344 of the reverse transcriptase were sequenced as described elsewhere.³⁰ Substitutions that emerged during therapy were inserted into recombinant clones and analyzed in cell-culture phenotypic assays for any effect on susceptibility to entecavir.³⁰ Within the lamivudine group, genotypic and phenotypic analyses were performed only on samples from patients meeting the criterion for virologic rebound (defined as a confirmed increase in HBV DNA by at least 1 log copy per milliliter from the nadir value, according to a PCR assay, during the administration of study medication).

STATISTICAL ANALYSIS

A two-stage evaluation of efficacy was planned.³¹ First, noninferiority to lamivudine was tested, and if noninferiority was established, a second test for superiority was conducted. The planned sample size, 315 per group, had 90 percent power to demonstrate noninferiority with respect to the primary efficacy end point, assuming response rates of 60 percent for lamivudine and 64 percent for entecavir, a 25 percent rate of missing biopsy specimens obtained at week 48, and a -10 percent boundary for the 95 percent lower confidence limit for the difference in proportions. The study had a single primary end point (histologic improvement).

Patients with missing or inadequate biopsy specimens obtained at week 48 were considered not to have had a histologic response. In proportion analyses of HBV DNA values, HBV serologic data, and alanine aminotransferase levels, treated patients with a missing value for an end point were considered not to have had a response for that end point. To compare the means of continuous variables, we used t-tests based on linear regression models, adjusted for baseline measurements. There were no interim analyses of efficacy. All reported P values are two-sided and were not adjusted for multiple testing.

RESULTS

STUDY POPULATION

Of 1056 patients who were enrolled and screened, 715 were randomly assigned (357 to the entecavir group and 358 to the lamivudine group), and 709 (354 in the entecavir group and 355 in the lamivudine group) received, in a blinded fashion, at least one dose of study drug. Three hundred fourteen patients in each treatment group had adequate baseline liver-biopsy specimens with a Knodell necroinflammatory score of 2 or greater. The two treatment groups were well balanced at baseline (Table 1).

Among those who started receiving the study drug, 340 patients assigned to the entecavir group (95 percent) and 321 patients assigned to the lamivudine group (90 percent) completed 52 weeks of treatment. The difference in these proportions was attributable mainly to the greater number of discontinuations due to adverse events in the lamivudine group (nine, vs. one in the entecavir group) and the greater number of losses to follow-up in the lamivudine group (eight vs. three, respectively).

HISTOLOGIC AND BIOCHEMICAL END POINTS

More patients in the entecavir group than in the lamivudine group underwent a biopsy at week 48. Twenty-two and 45 patients, respectively ($P=0.004$), with adequate baseline biopsy specimens had specimens obtained at week 48 that could not be evaluated (Table 2). The primary analysis met the initial test for noninferiority, and we proceeded to test for superiority. Entecavir treatment resulted in a significantly higher rate of histologic improvement than lamivudine treatment at week 48, with 72 percent and 62 percent of the patients,

Table 1. Demographic and Baseline Characteristics of the Patients.*

Characteristic	Entecavir (N=354)	Lamivudine (N=355)	P Value
Age — yr	35±13	35±13	1.00
Male sex — no. (%)	274 (77)	261 (74)	0.26
Race or ethnic group — no. (%)†			
Asian	204 (58)	202 (57)	0.91
White	140 (40)	141 (40)	
Black	8 (2)	8 (2)	
Other	2 (<1)	4 (1)	
Region — no. (%)			
Asia or Australia	172 (49)	167 (47)	0.76
Europe	84 (24)	88 (25)	
North America	47 (13)	55 (15)	
South America	51 (14)	45 (13)	
Knodell necroinflammatory score‡	7.8±2.98	7.7±2.99	0.67
Ishak fibrosis score‡	2.3±1.27	2.3±1.29	1.00
Score ≥3 (bridging fibrosis) — %	34	32	0.68
Score ≥5 (cirrhosis) — %	8	8	1.00
Mean HBV DNA level			
By branched-chain DNA assay — MEq/ml	2.56±1.05	2.61±1.03	0.52
By PCR assay — log copies/ml	9.62±2.01	9.69±1.99	0.64
HBeAg-positive — no. (%)	348 (98)	351 (99)	0.55
HBeAg antibody-negative — no. (%)	342 (97)	346 (97)	0.52
Viral genotype — no. (%)			
A	94 (27)	100 (28)	0.24
B	68 (19)	77 (22)	
C	111 (31)	90 (25)	
D	37 (10)	49 (14)	
F	20 (6)	12 (3)	
Other, indeterminate, or missing	24 (7)	27 (8)	
Alanine aminotransferase — IU/liter	140.5±114.3	146.3±132.3	0.53
Prior anti-HBV therapy — no. (%)			
Interferon	46 (13)	46 (13)	1.00
Lamivudine	10 (3)	10 (3)	1.00

* Plus-minus values are means ±SD. The Knodell necroinflammatory score can range from 0 to 18, with higher scores indicating more severe hepatitis. The Ishak fibrosis score can range from 0 to 6, with higher scores indicating more extensive fibrosis and scores of 5 or higher indicating cirrhosis. HBV denotes hepatitis B virus, PCR polymerase chain reaction, and HBeAg hepatitis B e antigen.

† Race or ethnic group was determined by the investigator.

‡ Adequate baseline biopsy specimens were available for 329 patients in the entecavir group and 330 patients in the lamivudine group.

respectively, reaching this primary end point (difference estimate, 9.9; 95 percent confidence interval, 2.6 to 17.2; P=0.009) (Table 2). Treatment with entecavir and lamivudine resulted in improved Ishak fibrosis scores in 39 percent and 35

percent of the patients, respectively (P=0.41). In 8 percent of the entecavir-treated patients and 10 percent of the lamivudine-treated patients, the Ishak fibrosis score worsened. The alanine aminotransferase level was normalized in a higher

Table 2. Histologic Improvement at Week 48 (Primary Study End Point).*

End Point	Entecavir (N=354)	Lamivudine (N=355)	Difference Estimate (95% CI)†	P Value
Adequate baseline biopsy specimen with Knodell necroinflammatory score ≥ 2 — no.	314	314		
Histologic improvement — no. (%)‡	226 (72)	195 (62)	9.9 (2.6–17.2)	0.009
No improvement — no. (%)	66 (21)	74 (24)		
Mean Knodell necroinflammatory score§				
Baseline	8.2	8.1		
Week 48	4.4	4.6		

* Higher scores on the Knodell necroinflammatory scale indicate more severe hepatitis. CI denotes confidence interval.

† The difference estimate was calculated for the entecavir group as compared with the lamivudine group.

‡ Histologic improvement was defined as an improvement by at least two points in the necroinflammatory component of the Knodell score, with no worsening in the fibrosis component of the score.

§ There were 292 treated patients in the entecavir group and 269 treated patients in the lamivudine group with adequate pairs of biopsy specimens.

proportion of entecavir-treated patients than lamivudine-treated patients at week 48 (68 percent vs. 60 percent, $P=0.02$) (Table 3).

VIROLOGIC AND SEROLOGIC END POINTS

HBV DNA levels in the entecavir group fell throughout treatment; HBV DNA was undetectable by PCR assay in 67 percent of the patients in this group at week 48 (Table 3 and Fig. 1A). In contrast, viral loads in the lamivudine group remained distributed over a wide range of values, and by week 48, HBV DNA was undetectable by PCR assay in 36 percent of the patients in that group ($P<0.001$ for the comparison with the entecavir group). The mean reduction from baseline in the serum HBV DNA level by PCR assay at week 48 was also greater in the entecavir group (6.9 log copies per milliliter) than in the lamivudine group (5.4 log copies per milliliter, $P<0.001$) (Table 3 and Fig. 1B).

HBeAg loss and seroconversion occurred in 22 percent and 21 percent, respectively, of the patients in the entecavir group (Table 3). These rates were similar to those in the lamivudine group (20 percent and 18 percent, respectively; $P=0.45$ for the comparison of HBeAg loss between the groups and $P=0.33$ for the comparison of HBeAg seroconversion between the groups). HBsAg loss occurred in six patients in the entecavir group (2 percent) and four in the lamivudine group (1 percent).

RESPONSES AT WEEK 48 AND AFTER TREATMENT

At week 48, 74 patients in the entecavir group (21 percent) and 67 in the lamivudine group (19 per-

cent) had a protocol-defined response (HBV DNA level of less than 0.7 MEq per milliliter and HBeAg loss). Two hundred forty-seven patients in the entecavir group (70 percent) and 165 in the lamivudine group (46 percent) had a virologic response (HBV DNA level of less than 0.7 MEq per milliliter, without HBeAg loss). There was a nonresponse (HBV DNA level, ≥ 0.7 MEq per milliliter) in 19 patients in the entecavir group (5 percent) and 94 in the lamivudine group (26 percent).

Among the patients with a protocol-defined response, 82 percent of those in the entecavir group (61 of 74) and 73 percent of those in the lamivudine group (49 of 67) had a sustained response 24 weeks after the discontinuation of treatment. Of the patients with a response at week 48 who discontinued therapy, 41 percent (25 of 61) of those in the entecavir group and 41 percent (20 of 49) of those in the lamivudine group had undetectable HBV DNA by PCR, and 84 percent (51 of 61) and 82 percent (40 of 49), respectively, had normalization of alanine aminotransferase.

RESISTANCE

There was no evidence of emerging resistant variants to entecavir by week 48 among the 339 evaluated patients assigned to receive entecavir. During entecavir therapy, substitutions were noted at several residues within the viral reverse transcriptase, but none appeared in more than three patients, and none were associated with reduced susceptibility to entecavir when examined in phenotypic assays. Six patients in the entecavir group (2 percent) and 63 patients in the lamivudine group

Table 3. Virologic, Biochemical, and Serologic End Points at Week 48.*

End Point	Entecavir (N=354)	Lamivudine (N=355)	Difference Estimate (95% CI)†	P Value
Virologic				
HBV DNA <300 copies/ml by PCR assay — no. (%)	236 (67)	129 (36)	30.3 (23.3 to 37.3)	<0.001
HBV DNA <0.7 MEq/ml by branched-chain DNA assay — no. (%)	322 (91)	232 (65)	25.6 (19.8 to 31.4)	<0.001
Mean change in HBV DNA from baseline by PCR assay — log copies/ml‡	-6.9±2.0	-5.4±2.6	-1.52 (-1.78 to -1.27)	<0.001
Biochemical				
ALT normalization (≤1× ULN) — no. (%)	242 (68)	213 (60)	8.4 (1.3 to 15.4)	0.02
Serologic				
Loss of HBeAg — no. (%)	78 (22)	70 (20)	2.3 (-3.7 to 8.3)	0.45
HBeAg seroconversion — no. (%)	74 (21)	64 (18)	2.9 (-2.9 to 8.7)	0.33
HBsAg loss — no. (%)	6 (2)	4 (1)	0.6 (-1.2 to 2.3)	0.52

* Plus-minus values are means ±SD. CI denotes confidence interval, HBV hepatitis B virus, PCR polymerase chain reaction, ALT alanine aminotransferase, ULN upper limit of normal, HBeAg hepatitis B e antigen, and HBsAg hepatitis B surface antigen.

† The difference estimate was calculated for the entecavir group as compared with the lamivudine group.

‡ There were 340 patients in the entecavir group and 324 patients in the lamivudine group with paired baseline and week-48 HBV DNA measurements. Samples in which HBV DNA was undetectable were assigned a value of 299 copies per milliliter.

(18 percent) had virologic rebound during the first year of drug administration. Genotypic analysis of isolates obtained at week 48 from the six entecavir-treated patients revealed no emerging substitutions when baseline samples were compared with those obtained at week 48. Samples obtained at week 48 retained full phenotypic susceptibility to entecavir. Genotypic analysis of isolates obtained at week 48 from the patients in the lamivudine group with virologic rebound revealed that 45 of 63 (71 percent) had mutations in the YMDD motif of the HBV polymerase gene.

SAFETY AND ADVERSE EVENTS

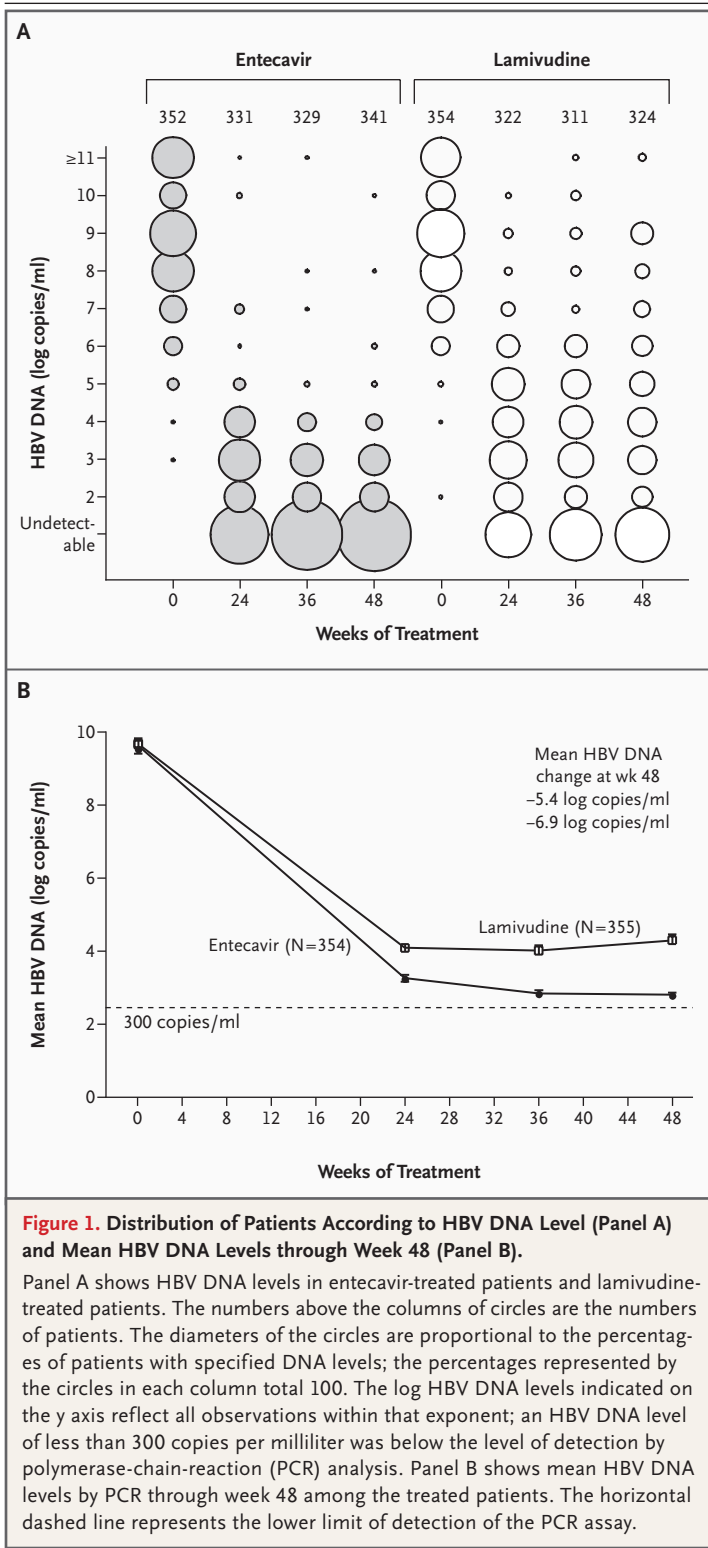
Mean exposure to study therapy at the time the database was locked was 75 weeks for entecavir and 65 weeks for lamivudine. The frequency of adverse events during treatment was similar in the two groups (Table 4). The most frequent adverse events were headache, upper respiratory tract infection, nasopharyngitis, cough, pyrexia, upper abdominal pain, fatigue, and diarrhea, most of which were of mild-to-moderate severity. The frequencies of serious adverse events were also similar in the two treatment groups. There were fewer discontinuations due to adverse events in the entecavir group (one) than in the lamivudine group (nine); four of the nine patients in the lamivudine group and the patient in the entecavir group dis-

continued treatment because of an increase in alanine aminotransferase.

Elevations in alanine aminotransferase were observed less frequently in the entecavir group than in the lamivudine group (Table 4). Alanine aminotransferase flares during treatment were observed in 12 entecavir-treated patients (3 percent) and 23 lamivudine-treated patients (6 percent). In the entecavir group, all the alanine aminotransferase flares during treatment were associated with a reduction in HBV DNA by at least 2 log copies per milliliter, and all but one were self-limiting with continued treatment. None of the entecavir-treated patients had hepatic decompensation.

In the lamivudine group, approximately half the alanine aminotransferase flares during treatment (12 of 23) were associated with increasing HBV DNA levels. The majority of the flares persisted until the time of treatment discontinuation. One of the lamivudine-treated patients had hepatic decompensation associated with a flare and died during follow-up. At the time the database was locked, alanine aminotransferase flares had occurred in 2 of 134 patients (1 percent) in the entecavir group and 9 of 129 patients (7 percent) in the lamivudine group who underwent post-treatment follow-up.

Two deaths occurred during the on-treatment



period, both in the lamivudine group. Neither was judged to be related to study therapy. One patient died from sudden dyspnea, and one death was of undetermined cause.

DISCUSSION

This study was a large, active-control trial of two nucleoside therapies in patients with HBeAg-positive chronic hepatitis. When the trial began, lamivudine was the only nucleoside approved to treat chronic hepatitis B. Not only did it serve as an active comparator; it also enabled all the patients to receive potential benefit from antiviral therapy.

Lamivudine treatment has been associated with histologic improvement and with reductions in both Child-Pugh score and the development of hepatocellular carcinoma.^{4,5,32} This reduction in disease progression probably arises from the effective suppression of HBV replication, the underlying cause of liver necroinflammation and fibrosis. However, the frequent development of lamivudine resistance can result in a rebound in viral load and a loss of histologic benefit.⁴

In the current study, entecavir was associated with significantly higher rates of histologic, virologic, and biochemical improvement than was lamivudine. The efficacy of entecavir appears to result from its potent suppression of HBV replication. Entecavir suppressed HBV DNA by a mean of nearly 7 log copies per milliliter, and 67 percent of the patients in the entecavir group had undetectable levels of HBV DNA by PCR assay within 48 weeks after the start of treatment.

Histologic examination of the liver remains the definitive method of assessing disease progression, and arresting or reversing liver damage is a principal goal of long-term hepatitis B therapy. The improved histologic benefit of entecavir as compared with lamivudine and its greater effect on viral suppression suggest that with long-term treatment, entecavir might also reduce the risk of end-stage liver disease and hepatocellular carcinoma.

A direct consequence of the potent viral suppression associated with entecavir is the absence of emergence of drug resistance by week 48. In vitro experiments and clinical studies have dem-

Table 4. Summary of Cumulative Safety Data.*

Timing and Event	Entecavir (N = 354)	Lamivudine (N = 355)	P Value
	<i>no. of patients (%)</i>		
During treatment			
Any adverse event	306 (86)	297 (84)	0.34
Serious adverse event	27 (8)	30 (8)	0.78
Discontinuation due to adverse event	1 (<1)	9 (3)	0.02
ALT >2× baseline and >10× ULN†	12 (3)	23 (6)	0.08
ALT >2× baseline and >5× ULN‡	37 (10)	59 (17)	0.02
Death	0	2 (<1)	0.50
Post-treatment follow-up§			
ALT >2× reference value and >10× ULN¶	2 (1)	9 (7)	0.03
ALT > 2× reference value and >5× ULN‡	3 (2)	16 (12)	0.002

* ALT denotes alanine aminotransferase, and ULN upper limit of normal.

† According to the protocol, these findings constituted the definition of an alanine aminotransferase flare during treatment.

‡ The analysis was conducted post hoc.

§ There were 134 patients in the entecavir group and 129 in the lamivudine group who had entered post-treatment follow-up at the time the database was locked.

¶ According to the protocol, these findings constituted the definition of a post-treatment alanine aminotransferase flare. The reference level was the lesser of the baseline and end-of-treatment alanine aminotransferase values.

onstrated that resistance to entecavir develops only, and infrequently, when HBV contains pre-existing lamivudine-associated resistance substitutions (rtL180M and rtM204V) and when an additional substitution (rtT184G, rtS202I, or rtM250V) is selected.³⁰ The potential for resistance after longer exposure to entecavir treatment is currently being monitored.

On the basis of its extensive use in both chronic hepatitis B and HIV infection, lamivudine is established as a well-tolerated antiviral therapy. The similar tolerability profiles of entecavir and lamivudine in this study are evidence that entecavir is well tolerated by patients with chronic hepatitis B; however, continued surveillance is necessary to confirm its long-term safety. Fewer patients in the entecavir group than in the lamivudine group had alanine aminotransferase flares during treatment, and the flares that did occur during entecavir therapy were temporally associated with reductions in HBV DNA. Flares after treatment, during six months of follow-up, were also uncommon among the patients assigned to receive entecavir.

The advent of more potent antiviral agents for the treatment of chronic hepatitis B offers the potential to control HBV replication and to arrest or halt the progression of liver disease. Entecavir,

which provided response rates that were significantly higher than those of an existing oral antiviral agent in a large population of patients who had not previously received a nucleoside analogue, has demonstrated benefit as a primary therapy for HBeAg-positive chronic hepatitis B.

Presented in part at the 55th annual meeting of the American Association for the Study of Liver Diseases, October 31, 2004, and the 14th biennial meeting of the Asian Pacific Association for the Study of the Liver, December 14, 2004.

Drs. Gadano, Gish, Han, and Lok report having received consulting fees from Bristol-Myers Squibb; Drs. Gish and Lok, consulting fees and lecture fees from Roche and grant support from Schering-Plough and Gilead; Drs. Gish and Goodman, consulting fees from Schering-Plough; Dr. Gish, consulting fees and lecture fees from InterMune, lecture fees from Schering-Plough, and grant support from the National Cancer Institute; Drs. de Man, Goodman, and Lok, consulting fees from Gilead; Dr. Lok, consulting fees from GlaxoSmithKline, Innogenetics, XTL, Idun, Idenix, Nabi, PowderMed, and Anadys and grant support from Valeant and the National Institutes of Health; Drs. Chang, Han, and Gish, lecture fees from Bristol-Myers Squibb; Dr. de Man, lecture fees from GlaxoSmithKline and Gilead and grant support from Biotest; Dr. Sollano, lecture fees from Novartis and Hi-Esai; Drs. Gish, Goodman, Han, and Lok, grant support from Bristol-Myers Squibb; Drs. de Man and Lok, grant support from GlaxoSmithKline; Drs. de Man, Gish, and Lok, grant support from Roche; and Drs. Goodman and Lok, grant support from Idenix. Dr. Apelian and Dr. DeHertogh were members of the Bristol-Myers Squibb Pharmaceutical Research Institute (Wallingford, Conn.) at the time this research was conducted. No other potential conflict of interest relevant to this article was reported.

We are indebted to Bruce Kreter, Pharm.D. (Bristol-Myers Squibb), for his contribution to the manuscript.

APPENDIX

Bristol-Myers Squibb scientists were D. Tenney, R. Rose, and S. Levine.

In addition to the authors, the BEHoLD A1463022 Study Group included the following investigators: *North America* — F. Anderson, T. Boyer, R. Brown, D. Chua, D. Dieterich, L. Cisneros Garza, S. Gordon, S. Han, R. Herring, S. Joshi, R. Koff, D. LaBrecque, S. Lee, W. Lee, P. Martin, S. Mehta, A. Min, G. Minuk, K. O'Riordan, P. Pockros, K.R. Reddy, R. Reindollar, R. Rubin, V. Rustgi, J. Sattler, E. Schiff, A.O. Shakil, M. Sherman, M. Shiffman, C. Smith, N. Tsai, B. Tung, L. Tyrrell, and G. Wu. *South America* — A. Barone, F. Bessone, F. Carrilho, H. Cheinquer, H. Coelho, H. Fainboim, J. Ferrandiz, M. Ferraz, R. Filho, R. Focaccia, F. Goncales, L. Lyra, H. Sette, M. Silva, R. Terg, and E. Zumaeta. *Asia, Pacific Islands, and Australia* — S. Abdurachman, N. Akbar, M. Arguillas, S.W. Cho, G. Cooksley, P. Desmond, J. George, S. Huang, E.K. Ooi, I. Kronborg, C.L. Lai, S.T. Lai, J. Lao-Tan, A. Lee, S.D. Lee, H.H. Lin, C.C. Lim, G.H. Lo, Y.W. Luk, G. Marinos, J. Menon, I. Merican, J. Olynyk, S. Roberts, M. Rosmawati, J. Sasadeusz, W. Sievert, S. Strasser, C.K. Tan, S.S. Wu, S.K. Yoon, and F. Zano. *Europe and Middle East* — Y. Baruch, M. Bassendine, A. Boron-Kaczmarek, M.R. Brunetto, G. Carosi, P. Chalupa, A. Gladysz, B. Gocman, Z. Gonciarz, V. Gorbakov, W. Halota, M. Heim, Y. Horsmans, V. Isakov, J. Juszczyk, W. Kryczka, G.A. Kullak-Ublick, J. Kuydowicz, Y. Lurie, T. Mach, F. Mazzotta, P. Mills, R. Modrzewska, D. Mutimer, F. Nevens, A. Nimer, M. Oltman, C. Pedersen, V. Pokrovsky, V. Rafalsky, M. Rizzetto, D. Shouval, M. Sikora, G. Storzshakov, H. Thomas, R. Tur-Kaspa, H. Van Vlietberghe, A. Yakovlev, and K. Zhdanov.

REFERENCES

- World Health Organization. Hepatitis B fact sheet WHO/204. Geneva: World Health Organization, October 2000. (Accessed February 10, 2006, at <http://www.who.int/mediacentre/factsheets/fs204/en>.)
- Lee WM. Hepatitis B virus infection. *N Engl J Med* 1997;337:1733-45.
- Liaw Y-F, Leung N, Guan R, Lau GK, Merican I. Asian-Pacific consensus statement on the management of chronic hepatitis B: an update. *J Gastroenterol Hepatol* 2003;18:239-45.
- Dienstag JL, Goldin RD, Heathcote EJ, et al. Histological outcome during long-term lamivudine therapy. *Gastroenterology* 2003;124:105-17.
- Leung NW, 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.
- Liaw YF, Sung JY, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004;351:1521-31.
- Yu MW, Yeh SH, Chen PJ, et al. Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men. *J Natl Cancer Inst* 2005;97:265-72.
- Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006;295:65-73.
- Krogsgaard K, Bindslev N, Christensen E, et al. The treatment effect of alpha interferon in chronic hepatitis B is independent of pre-treatment variables: results based on individual patient data from 10 clinical controlled trials. *J Hepatol* 1994;21:646-55.
- Intron A (interferon alfa-2b recombinant). Kenilworth, N.J.: Schering Corporation, 2002 (package insert).
- 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.
- Lai CL, Chien RN, Leung NW, et al. A one-year trial of lamivudine for chronic hepatitis B. *N Engl J Med* 1998;339:61-8.
- Lau DT, Khokhar MF, Doo E, et al. Long-term therapy of chronic hepatitis B with lamivudine. *Hepatology* 2000;32:828-34.
- Chang TT, Lai CL, Chien RN, et al. Four years of lamivudine treatment in Chinese patients with chronic hepatitis B. *J Gastroenterol Hepatol* 2004;19:1276-82.
- Liaw YF, Leung NW, Chang TT, et al. Effects of extended lamivudine therapy in Asian patients with chronic hepatitis B. *Gastroenterology* 2000;119:172-80.
- Liaw YF. Impact of YMDD mutations during lamivudine therapy in patients with chronic hepatitis B. *Antivir Chem Chemother* 2001;12:Suppl 1:67-71.
- Mutimer D. Hepatitis B virus infection: resistance to antiviral agents. *J Clin Virol* 2001;21:239-42.
- Liaw YF, Chien RN, Yeh CT, Tsai SL, Chu CM. Acute exacerbation and hepatitis B virus clearance after emergence of YMDD motif mutation during lamivudine therapy. *Hepatology* 1999;30:567-72.
- Ayres A, Bartholomeusz A, Lau G, Lam KC, Lee JY, Locarnini S. Lamivudine and famciclovir resistant hepatitis B virus associated with fatal hepatic failure. *J Clin Virol* 2003;27:111-6.
- Lau GK, Piratvisuth T, Luo KX, et al. Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2005;352:2682-95.
- Marcellin P, Chang TT, Lim SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003;348:808-16.
- Marcellin P, Chang TT, Lim SG, et al. Long-term efficacy and safety of adefovir dipivoxil (ADV) in HBeAg+ chronic hepatitis B patients: increasing serologic, virologic, and biochemical response over time. *Hepatology* 2004;40:Suppl 1:665A. abstract.
- Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. *N Engl J Med* 2005;352:2673-81.
- Innaimo SF, Seifer M, Bisacchi GS, Standing DN, Zahler R, Colonna RJ. Identification of BMS-200475 as a potent and selective inhibitor of hepatitis B virus. *Antimicrob Agents Chemother* 1997;41:1444-8.
- Colonna RJ, Genovesi EV, Medina I, et al. Long-term entecavir treatment results in sustained antiviral efficacy and prolonged life span in the woodchuck model of chronic hepatitis infection. *J Infect Dis* 2001;184:1236-45.
- Lai CL, Rosmawati M, Lao J, et al. Entecavir is superior to lamivudine in reducing hepatitis B virus DNA in patients with chronic hepatitis B infection. *Gastroenterology* 2002;123:1831-8.
- Chang TT, Gish RG, Hadziyannis SJ, et al. A dose-ranging study of the efficacy and tolerability of entecavir in lamivudine-refractory chronic hepatitis B patients. *Gastroenterology* 2005;129:1198-209.
- Sherman M, Yurdaydin C, Sollano J, et al. Entecavir is superior to continued lamivudine for the treatment of lamivudine-refractory HBeAg(+) chronic hepatitis B: results in Phase III study ETV-026. *Hepatology* 2004;40:Suppl 1:664A. abstract.
- Knodel 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.
- Tenney DJ, Levine SM, Rose RE, et al. Clinical emergence of entecavir-resistant hepatitis B virus requires additional substitutions in virus already resistant to lamivudine. *Antimicrob Agents Chemother* 2004;48:3498-507.
- Dunnett CW, Gent M. An alternative to the use of two-sided tests in clinical trials. *Stat Med* 1996;15:1729-38.
- Goodman Z, Dhillon AP, Wu PC, et al. Lamivudine treatment reduces progression to cirrhosis in patients with chronic hepatitis B. *J Hepatol* 1999;30:Suppl 1:59. abstract.

Copyright © 2006 Massachusetts Medical Society.