

ORIGINAL ARTICLE

Telbivudine versus Lamivudine in Patients with Chronic Hepatitis B

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ABSTRACT

BACKGROUND

Reducing hepatitis B virus (HBV) replication to minimal levels is emerging as a key therapeutic goal for chronic hepatitis B.

METHODS

In this double-blind, phase 3 trial, 1370 patients with chronic hepatitis B were randomly assigned to receive 600 mg of telbivudine or 100 mg of lamivudine once daily. The primary efficacy end point was noninferiority of telbivudine to lamivudine for therapeutic response (i.e., a reduction in serum HBV DNA levels to fewer than 5 log₁₀ copies per milliliter, along with loss of hepatitis B e antigen [HBeAg] or normalization of alanine aminotransferase levels). Secondary efficacy measures included histologic response, changes in serum HBV DNA levels, and HBeAg responses.

RESULTS

At week 52, a significantly higher proportion of HBeAg-positive patients receiving telbivudine than of those receiving lamivudine had a therapeutic response (75.3% vs. 67.0%, $P=0.005$) or a histologic response (64.7% vs. 56.3%, $P=0.01$); telbivudine also was not inferior to lamivudine for these end points in HBeAg-negative patients. In HBeAg-positive and HBeAg-negative patients, telbivudine was superior to lamivudine with respect to the mean reduction in the number of copies of HBV DNA from baseline, the proportion of patients with a reduction in HBV DNA to levels undetectable by polymerase-chain-reaction assay, and development of resistance to the drug. Elevated creatine kinase levels were more common in patients who received telbivudine, whereas elevated alanine aminotransferase and aspartate aminotransferase levels were more common in those who received lamivudine.

CONCLUSIONS

Among patients with HBeAg-positive chronic hepatitis B, the rates of therapeutic and histologic response at 1 year were significantly higher in patients treated with telbivudine than in patients treated with lamivudine. In both the HBeAg-negative and the HBeAg-positive groups, telbivudine demonstrated greater HBV DNA suppression with less resistance than did lamivudine. (ClinicalTrials.gov number, NCT00057265.)

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FOR THE APPROXIMATELY 400 MILLION people with chronic hepatitis B virus (HBV) infection, the risk of progression to end-stage complications such as cirrhosis and hepatocellular carcinoma has been correlated with persistent HBV replication, as reflected by serum HBV DNA levels.¹ Correspondingly, prolonged suppression of HBV replication with antiviral therapy has been linked to reduced risks of end-stage disease manifestations, a finding that underscores the importance of long-lasting HBV suppression as a primary treatment goal.²⁻⁹

Multiple types of interferon, lamivudine, adefovir dipivoxil, entecavir, and telbivudine have been approved for the treatment of chronic hepatitis B. These agents vary with respect to antiviral and clinical efficacy, resistance profiles, and tolerability and safety.¹⁰ For long-term disease management, the clinical challenge is to determine how to use available agents most effectively to obtain consistent, profound, and long-lasting HBV suppression with good safety and convenience in a wide variety of health care settings.

Telbivudine (β -L-2'-deoxythymidine) is an orally bioavailable L-nucleoside with potent and specific anti-HBV activity.¹¹ In preclinical toxicologic testing, telbivudine had no mutagenic or carcinogenic effects and no appreciable embryonic or fetal toxic effects — findings that are particularly relevant for men and women in their reproductive years.¹² In initial clinical trials, treatment with telbivudine led to reductions in serum HBV DNA levels that were greater than those observed with lamivudine, and resistance to telbivudine developed less frequently than did resistance to lamivudine.^{13,14}

The present international phase 3 trial, designated Globe, compared the safety and efficacy of treatment with telbivudine with that of lamivudine, the most widely prescribed anti-hepatitis B agent worldwide, in patients with chronic hepatitis B. Patients with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B and those with HBeAg-negative chronic hepatitis B were evaluated to assess differences in therapeutic outcomes that may arise as a result of well-recognized differences in disease characteristics.^{10,15-17} Associations between early suppression of HBV replication and subsequent efficacy and resistance outcomes were assessed.^{14,18,19}

METHODS

PATIENTS

Men and women between 16 and 70 years of age who had HBeAg-positive or HBeAg-negative chronic hepatitis B were eligible to participate in the study. The study investigators recruited the patients from March 2003 until April 2004 after a review of medical records and the completion of screening procedures to establish their eligibility for the trial. Chronic hepatitis B was defined by detectable serum hepatitis B surface antigen (HBsAg), a serum alanine aminotransferase level 1.3 to 10.0 times the upper limit of normal, a serum HBV DNA level greater than $6 \log_{10}$ copies per milliliter, and compatible pretreatment liver histologic findings.

Exclusion criteria included coinfection with hepatitis C, hepatitis D, or the human immunodeficiency virus; evidence of hepatic decompensation, pancreatitis, or hepatocellular carcinoma; previous treatment for hepatitis B with nucleoside or nucleotide analogues or both; treatment with interferon or other immunomodulators within the previous 12 months; other forms of liver disease; a serum creatinine level greater than 1.5 mg per deciliter ($133 \mu\text{mol}$ per liter); a serum amylase or lipase level greater than 1.5 times the upper limit of normal; a prothrombin time prolonged by more than 3 seconds; a serum albumin level less than 3.3 g per deciliter; and a bilirubin level greater than 2.0 mg per deciliter ($34 \mu\text{mol}$ per liter). Eligible patients with a serum alpha fetoprotein level greater than 50 ng per milliliter required exclusion of underlying hepatocellular carcinoma.

STUDY DESIGN

This randomized, double-blind, active agent-controlled trial was conducted at 112 academic centers in 20 countries. Eligible subjects were randomly assigned centrally in a 1:1 ratio to receive 600 mg of telbivudine or 100 mg of lamivudine once daily as oral tablets. Treatment assignments were stratified according to HBeAg status (positive or negative) and serum alanine aminotransferase level (>2.5 or ≤ 2.5 times the upper limit of normal). Within each stratum, patients were randomly assigned in block sizes of four. Study drugs were sup-

plied in bottles containing telbivudine (Idenix Pharmaceuticals) or overencapsulated lamivudine tablets (GlaxoSmithKline). Primary data analyses were specified for a 52-week treatment period, with the cohort continuing into a second year for longer-term assessments.

Patient histories were obtained, physical examinations were conducted, and venipuncture samples for laboratory assessments were obtained at screening, at baseline, and at weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, and 52. Standardized tests were performed centrally by Quintiles Transnational. Serum HBV DNA levels were quantified by COBAS Amplicor HBV Monitor (Roche Molecular Systems), with a detection limit of 300 copies per milliliter. Serum samples obtained at screening, baseline, and week 2 were prediluted at a 1:1000 ratio to ensure that HBV DNA assessments were within the assay's linear range. Liver-biopsy specimens, collected before treatment and at week 52, were evaluated under blinded conditions by an independent expert with the use of the Knodell and Ishak histologic scoring systems.^{20,21}

The study was conducted in compliance with the ethics principles of the Declaration of Helsinki and was consistent with Good Clinical Practice guidelines and applicable local regulatory requirements, including institutional-review-board approval. All patients provided written informed consent. The informed-consent forms discussed alternative treatment with interferon, lamivudine, and adefovir dipivoxil in countries where these therapies were available. Clinical data were collected and monitored by Quintiles. The sponsors, Idenix Pharmaceuticals and Novartis Pharmaceuticals, conducted predefined statistical analyses; the investigators had full access to the data and contributed substantially to study design, data collection, and data analysis. The manuscript was written in collaboration by the first and last authors; all the other authors were actively involved in review of the manuscript and approval of the final version. The academic authors vouch for the veracity and completeness of the data and data analyses.

STUDY END POINTS

The primary efficacy end point was therapeutic response, defined as a reduction in the serum HBV DNA level to fewer than 5 log₁₀ copies per milliliter, as recommended in available treatment guidelines,^{22,23} coupled with either normalization of the alanine aminotransferase level or loss of detect-

able HBeAg. This composite end point captures indicators of liver disease and viral suppression used in clinical practice, similar to composite end points used in previous interferon and lamivudine trials.²⁴⁻²⁸

Histologic response, the key secondary efficacy end point, was defined as a reduction of at least two points in the Knodell necroinflammatory score, with no worsening in the Knodell fibrosis score. Other secondary efficacy measures included changes in the serum HBV DNA level, HBeAg and HBsAg loss and seroconversion, virologic response (a serum HBV DNA level below 5 log₁₀ copies per milliliter and HBeAg loss),²⁹ and normalization of the serum alanine aminotransferase level. Primary treatment failure was defined as completion of at least 24 weeks of treatment without two consecutive measurements of serum HBV DNA levels below 5 log₁₀ copies per milliliter. Safety evaluations included discontinuation of the study drug and analyses of adverse events and graded laboratory abnormalities.

HBV GENOTYPING, VIRAL BREAKTHROUGH, AND RESISTANCE

Viral breakthrough was defined as at least two consecutive determinations of an increase in HBV DNA by at least 1 log₁₀ copy per milliliter from nadir during 48 weeks of therapy, a definition consistent with recent recommendations.^{30,31} Resistance was defined as viral breakthrough with treatment-emergent resistance mutations.³¹ HBV DNA was amplified by polymerase chain reaction (PCR) from serum samples at screening or at baseline from all patients, serum samples at week 48 from patients with viral breakthrough, and from patients who received telbivudine and who had more than 3 log₁₀ copies of residual HBV DNA per milliliter at week 52. The 344-codon reverse transcriptase domain of the HBV polymerase gene was sequenced at an independent laboratory (Delft Diagnostic Laboratory). This automated method detects potential resistance mutations that comprise at least 25% of the amplified viral DNA and is consistent with previous methods.³²⁻³⁵

EARLY ANTIVIRAL RESPONSE VERSUS SUBSEQUENT OUTCOMES

Prespecified analyses assessed relationships between early antiviral responses and efficacy and resistance outcomes at 1 year. Patients were categorized at week 24 according to PCR analysis as being negative for serum HBV DNA, as having de-

tectable but fewer than $3 \log_{10}$ copies of HBV DNA per milliliter, as having from 3 to $4 \log_{10}$ copies per milliliter, or as having more than $4 \log_{10}$ copies per milliliter.

STATISTICAL ANALYSIS

The study design provided 99% power to demonstrate noninferiority of telbivudine to lamivudine for therapeutic response, assuming a noninferiority criterion of 15 percentage points, with enrollment of at least 600 HBeAg-positive and 400 HBeAg-negative patients. Analyses were based on all patients randomly assigned to treatment who received at least one dose of study medication. Analyses of histologic response included all patients with pretreatment liver-biopsy specimens that could be evaluated, as in previous studies.³²⁻³⁵ The primary analysis occurred at week 52, with longer-term assessments at week 104. An independent data and safety monitoring board and an external data-analysis center monitored safety. The patients, investigators, and sponsor remained unaware of treatment assignments throughout the study.

The study was intended to demonstrate effects in both HBeAg subpopulations or in the pooled population, if trends in the subpopulations warranted pooling. The primary end point was assessed by a three-step method.³⁶ First, both HBeAg subpopulations were analyzed separately with an alpha level of 0.04 (95.68% confidence interval). If both subpopulations met the noninferiority criteria (i.e., if confidence intervals for the treatment difference exceeded -15%), treatments would be compared for superiority within each subpopulation. If statistical significance was not established within both HBeAg subpopulations, a statistical test for interaction between the treatment group and HBeAg subpopulations was planned, with significance defined at the alpha level of 0.15.³⁷ With no interaction, a statistical analysis for the overall patient population would be performed with an alpha level of 0.000933 to protect the overall alpha at 0.00125.

Demonstration of noninferiority was a precursor to superiority testing. For the primary efficacy end point, noninferiority criteria were met in both HBeAg subpopulations, but superiority was not established for the primary end point in the HBeAg-negative population. HBeAg subpopulations were not pooled because of this statistical interaction between treatment effect and HBeAg

subpopulation. For secondary end points, treatment effects were compared, first for noninferiority and then for superiority, according to a prespecified hierarchy.

Treatment comparisons of categorical end points were assessed by a weighted Cochran-Mantel-Haenszel method adjusted for randomization strata. For continuous variables, analysis of variance was performed with each stratified group as a factor. Reported P values are two-sided and were not adjusted for multiple testing.

RESULTS

PATIENTS

Six hundred eighty-three patients were assigned to receive telbivudine and 687 to receive lamivudine; 3 patients declined to participate further after undergoing randomization. The intention-to-treat population consisted of 921 patients with HBeAg-positive chronic hepatitis B and 446 patients with HBeAg-negative chronic hepatitis B. The treatment groups were well matched at baseline for demographic and disease characteristics (Table 1). Eighteen patients receiving telbivudine (2.6%) and 32 receiving lamivudine (4.7%) withdrew before week 52. Among these, two in the telbivudine group (0.3%) and eight in the lamivudine group (1.2%) discontinued treatment because of adverse events, clinical disease progression, or lack of efficacy. Two of these patients — one with myopathy in the telbivudine group and one with urticaria in the lamivudine group — discontinued treatment because of serious adverse events that possibly were related to the study drugs.

THERAPEUTIC AND HISTOLOGIC RESPONSES

For all study end points, noninferiority criteria were met for telbivudine as compared with lamivudine, allowing for superiority testing. Among HBeAg-positive patients at week 52, significantly more patients in the telbivudine group than in the lamivudine group had either a therapeutic or a histologic response (Table 2). Among HBeAg-negative patients, the rates of therapeutic and histologic response were similar in both treatment groups at week 52, and thus the noninferiority criteria were met.

HBV DNA RESPONSES

Among both HBeAg-positive patients and HBeAg-negative patients, reduction in serum HBV DNA

Table 1. Baseline Characteristics.*

Characteristic	HBeAg-Positive Patients		HBeAg-Negative Patients	
	Telbivudine (N=458)	Lamivudine (N=463)	Telbivudine (N=222)	Lamivudine (N=224)
Years of age — mean (range)	32 (16–63)	33 (16–67)	43 (17–68)	43 (18–68)
Male sex — no. (%)	333 (73)	351 (76)	174 (78)	177 (79)
Weight in kg — mean (range)	66 (38–126)	68 (38–150)	72 (42–123)	71 (45–148)
Race or ethnic group — no. (%)†				
Chinese	265 (57.9)	265 (57.2)	116 (52.3)	102 (45.5)
Non-Chinese Asian	115 (25.1)	106 (22.9)	29 (13.1)	42 (18.8)
White	52 (11.4)	55 (11.9)	46 (20.7)	56 (25.0)
Black	4 (0.9)	7 (1.5)	3 (1.4)	3 (1.3)
Latino	2 (0.4)	4 (0.9)	2 (0.9)	4 (1.8)
Middle Eastern or Indian	8 (1.7)	7 (1.5)	6 (2.7)	4 (1.8)
Other	12 (2.6)	19 (4.1)	20 (9.0)	13 (5.8)
HBV genotype — no. (%)				
A	24 (5.2)	31 (6.7)	12 (5.4)	14 (6.2)
B	129 (28.2)	113 (24.4)	59 (26.6)	59 (26.3)
C	259 (56.6)	258 (55.7)	89 (40.1)	86 (38.4)
D	42 (9.2)	54 (11.7)	57 (25.7)	64 (28.6)
Other or unknown	4 (0.9)	7 (1.5)	5 (2.3)	1 (0.4)
Serum alanine aminotransferase — IU/liter‡				
Mean	146.4±5.37	158.9±6.30	137.0±6.94	143.7±8.74
Median (range)	111.0 (19–1137)	111.0 (25–1133)	99.0 (31–569)	98.5 (12–982)
Serum HBV DNA — log ₁₀ copies/ml				
Mean	9.5±0.09	9.5±0.09	7.7±0.12	7.4±0.10
Median (range)	9.6 (3.8–16.0)	9.6 (3.6–16.1)	7.2 (3.0–13.0)	7.1 (3.7–12.1)
Liver histologic findings§				
Mean total Knodell Histologic Activity Index score	8.9	9.0	9.0	9.6
Mean Knodell necroinflammatory score	7.4	7.3	7.3	7.6
Mean Ishak fibrosis score	2.1	2.2	2.3	2.5

* HBeAg denotes hepatitis B e antigen, and HBV hepatitis B virus. Plus-minus values are means ±SE.

† Race or ethnic group was self-assessed.

‡ The upper limit of normal for serum alanine aminotransferase was 48 IU per liter for men and 37 IU per liter for women.

§ The analysis included the 872 HBeAg-positive patients (94.7% of the total intention-to-treat population) with baseline liver-biopsy findings that could be evaluated. The Knodell Histologic Activity Index score can range from 0 to 22, with higher scores indicating more severe disease. The Knodell inflammatory score can range from 0 to 18, with higher scores indicating more severe chronic hepatitis. The Ishak fibrosis score is based on a scale of 0 to 6, where 0 indicates no fibrosis and 5 or higher indicates cirrhosis.

levels at week 52 was significantly greater in the telbivudine group than in the lamivudine group (Table 2). The difference was evident by week 12 in HBeAg-positive patients (reductions of 5.71 log₁₀ copies per milliliter for telbivudine and 5.42 log₁₀ copies per milliliter for lamivudine, P=0.01) and

by week 8 in HBeAg-negative patients (reductions of 4.36 log₁₀ copies per milliliter for telbivudine and 4.08 log₁₀ copies per milliliter for lamivudine, P=0.02), and it persisted through week 52 (Fig. 1A and 1B).

At week 52, the proportion of patients in whom

Table 2. Efficacy Results at Week 52.**

Variable	HBeAg-Positive Patients			HBeAg-Negative Patients				
	Telbivudine (N=458)	Lamivudine (N=463)	Difference (95% CI)	P Value	Telbivudine (N=222)	Lamivudine (N=224)	Difference (95% CI)	P Value
Therapeutic response (%)	75.3	67.0	8.3 (2.4 to 14.2)	0.005	75.2	77.2	-2.0 (-10.2 to 6.1)	0.62
Histologic response (%)	64.7	56.3	8.4 (2.0 to 14.7)	0.01	66.6	66.0	0.6 (-8.3 to 9.5)	0.90
Serum HBV DNA (mean change in log ₁₀ copies/ml from baseline)	-6.45	-5.54	-0.91 (-1.20 to -0.61)	<0.001	-5.23	-4.40	-0.83 (-1.20 to -0.45)	<0.001
Serum HBV DNA undetectable by PCR (%)	60.0	40.4	19.6 (13.3 to 25.8)	<0.001	88.3	71.4	16.9 (9.6 to 24.1)	<0.001
Alanine aminotransferase normalization (%)	77.2	74.9	2.3 (-3.3 to 7.9)	0.42	74.4	79.3	-4.9 (-13.0 to 3.2)	0.24
HBeAg loss (%)	25.7	23.3	2.4 (-3.2 to 8.1)	0.40	—	—	—	—
HBeAg seroconversion (%)	22.5	21.5	1.0 (-4.5 to 6.4)	0.73	—	—	—	—
Virologic response (%)†	25.7	22.8	2.9 (-2.8 to 8.5)	0.32	—	—	—	—
Viral breakthrough (%)‡	5.9	15.3	-9.4 (-13.4 to -5.5)	<0.001	2.3	12.5	-10.2 (-15.0 to -5.5)	<0.001
Viral resistance (%)§	5.0	11.0	-6.0 (-9.5 to -2.5)	<0.001	2.2	10.7	-8.5 (-12.9 to -4.0)	<0.001
Primary treatment failure (%)¶	4.7	13.4	-8.7 (-12.3 to -5.0)	<0.001	0.4	2.7	-2.3 (-4.6 to 0.1)	<0.06

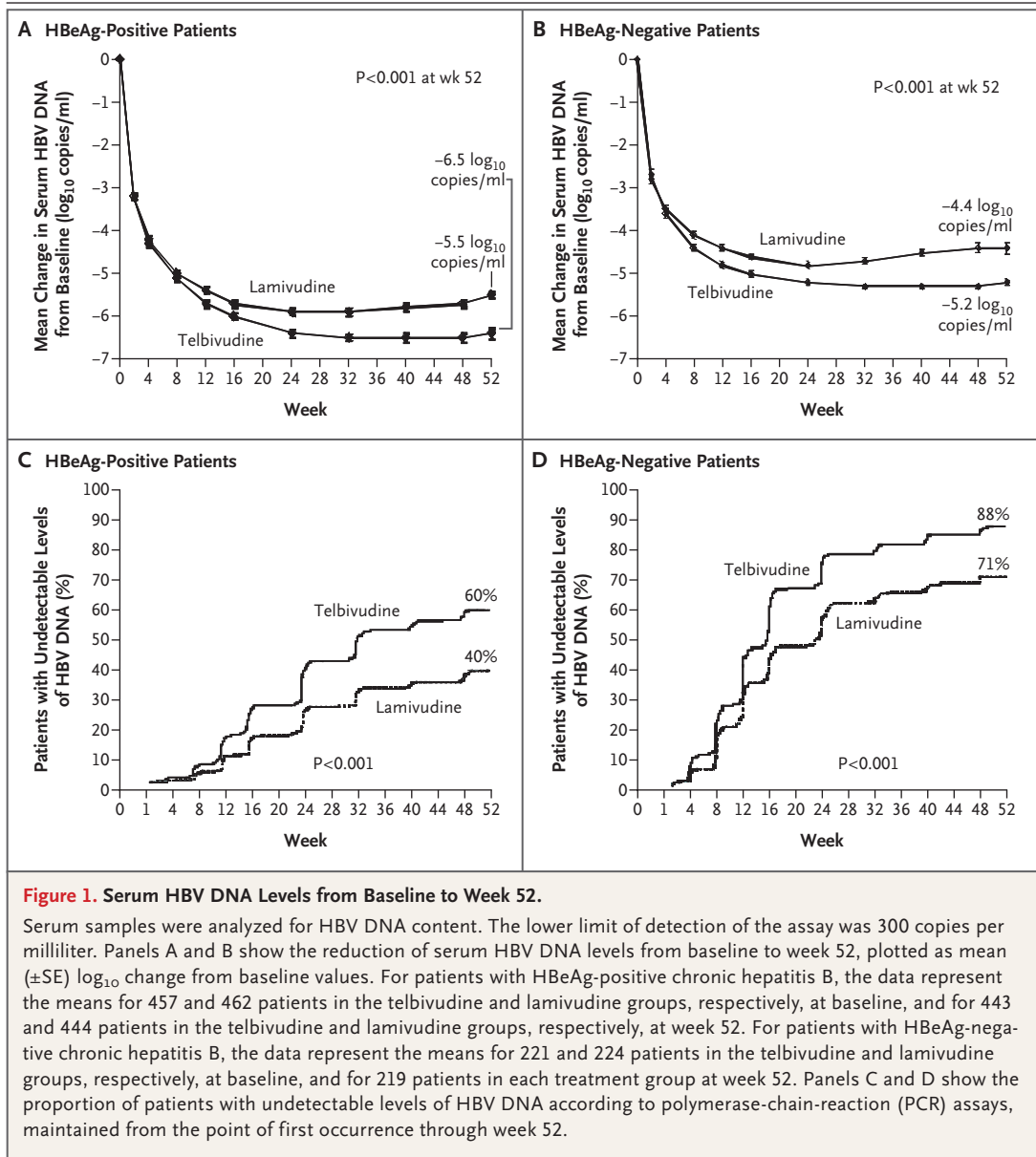
* HBeAg denotes hepatitis B e antigen, CI confidence interval, HBV hepatitis B virus, and PCR polymerase chain reaction.

† A virologic response is defined as a reduction in serum HBV DNA to less than 5 log₁₀ copies per milliliter, coupled with HBeAg loss.

‡ A viral breakthrough is defined as an increase in serum HBV DNA to at least 1 log above the nadir value on two successive visits, assessed at week 48.

§ Viral resistance is defined as breakthrough with treatment-emergent resistance mutations confirmed by genetic sequencing at week 48. In the study protocol, viral breakthrough was defined primarily as an increase in serum HBV DNA to at least 5 log₁₀ copies per milliliter after reduction to below that level. During the course of the study, this definition was superseded by the simpler and more widely accepted definition that pertains to the data reported above. Resistance rates per protocol were 3.0% for telbivudine and 8.2% for lamivudine in HBeAg-positive patients, and 2.1% for telbivudine and 8.5% for lamivudine (P<0.001) in HBeAg-negative patients.

¶ Primary treatment failure was considered to have occurred when serum HBV DNA levels remained above 5 log₁₀ copies per milliliter through week 52.



serum HBV DNA levels were undetectable by PCR assay was significantly greater in the telbivudine group than in the lamivudine group among HBeAg-positive patients (60.0% vs. 40.4%, P<0.001) and HBeAg-negative patients (88.3% vs. 71.4%, P<0.001) (Table 2). The mean time required for serum HBV DNA to become undetectable by PCR assay was significantly shorter in the telbivudine group than in the lamivudine group among HBeAg-positive patients (34 weeks vs. 39 weeks, P<0.001) and HBeAg-negative patients (20 weeks vs. 26 weeks, P<0.001) (Fig. 1C and 1D). Primary treatment failure was less frequent with telbivudine

than with lamivudine among both HBeAg-positive and HBeAg-negative patients, but the difference was significant only for HBeAg-positive patients (Table 2).

HBeAg AND HBsAg RESPONSES

Among HBeAg-positive patients, 25.7% of those in the telbivudine group and 23.3% of those in the lamivudine group had HBeAg loss (P=0.40) and 22.5% of those in the telbivudine group and 21.5% of those in the lamivudine group had HBeAg seroconversion (P=0.73) (Table 2). Among the 69% of patients with pretreatment alanine aminotrans-

ferase levels at least twice the upper limit of normal — a group generally considered the best candidates for treatment^{22,23} — HBeAg loss occurred in 30.8% and 26.2% of patients receiving telbivudine and lamivudine, respectively ($P=0.22$), and HBeAg seroconversion occurred in 26.6% and 24.1%, respectively ($P=0.49$). Less than 1% of patients in each treatment group had HBsAg seroconversion.

BIOCHEMICAL RESPONSE

The rates of normalization of serum alanine aminotransferase at week 52 were high (levels more than 70%) in both treatment groups, with results meeting noninferiority criteria in the HBeAg-positive and in the HBeAg-negative subgroups (Table 2).

ADDITIONAL HISTOLOGIC ANALYSES

Among HBeAg-positive patients, the mean Knodell Histologic Activity Index scores (range, 0 to 22, with higher scores indicating more severe disease) improved by 3.92 and 3.64 points in patients receiving telbivudine and in those receiving lamivudine, respectively (difference, 0.28; 95% confidence interval [CI], -0.23 to 0.79); among HBeAg-negative patients, the scores improved by 3.85 and 3.73 points, respectively (difference, 0.12; 95% CI, -0.59 to 0.82). Among HBeAg-positive patients with marked pretreatment bridging fibrosis or cirrhosis and who had Ishak fibrosis scores of 4 to 6 (where 0 indicates no fibrosis and 6 indicates cirrhosis), the Ishak fibrosis scores improved to between 0 and 3 in 68% of patients receiving telbivudine and 61% of patients receiving lamivudine (difference, 7%; 95% CI, -16 to 29); the corresponding figures for HBeAg-negative patients were 59% and 46% (difference, 13%; 95% CI, -14 to 40). In contrast, among patients with baseline Ishak fibrosis scores of 0 to 3, progression to a score greater than 3 by week 52 occurred in only 1% of patients in either HBeAg subgroup who were taking either telbivudine or lamivudine.

BREAKTHROUGH AND RESISTANCE

Viral breakthrough and genotypic resistance were significantly less common in patients receiving telbivudine than in those receiving lamivudine (Table 2). Resistance developed in 5.0% and 2.3% of HBeAg-positive and HBeAg-negative patients who received telbivudine, respectively, as compared with

11.0% and 10.7% of HBeAg-positive and HBeAg-negative patients who received lamivudine, respectively ($P<0.001$ for both comparisons).

Consistent with previous reports, M204I was the only signature mutation associated with telbivudine resistance; secondary mutations L80I/V and L80I/V+L180M accompanied M204I in 2.2% and 0.3%, respectively, of the patients who received telbivudine.^{14,38,39} Overall, the M204I mutation was detected in 46 of the 115 patients who received telbivudine and who had serum HBV DNA levels of at least 1000 copies per milliliter at week 52 (including patients with viral breakthrough), representing 6.8% of all telbivudine recipients in the study. Variants harboring mutations at the A181 and L229 codons were detected sporadically, with 16 and 6 occurrences, respectively, among the 115 telbivudine recipients with detectable HBV DNA, but these were not associated with viral breakthrough without concomitant detection of M204I. Lamivudine resistance was based on the signature mutations M204I and M204V; M204V was accompanied by the L180M secondary mutation, whereas M204I was seen alone or with the secondary mutation L80I/V.^{31,39}

EARLY VIRAL SUPPRESSION AND 1-YEAR EFFICACY OUTCOMES

The distribution of patients according to HBV DNA levels at week 24 (Fig. 2) is consistent with the greater viral suppression observed with telbivudine (Fig. 1). At week 24, more patients in the telbivudine group than in the lamivudine group were negative for HBV DNA according to PCR, whereas residual HBV DNA levels greater than $4 \log_{10}$ copies per milliliter were more frequent in patients in the lamivudine group than in those in the telbivudine group.

In the combined treatment groups, low HBV DNA levels at week 24 were associated with favorable 1-year efficacy outcomes (Fig. 3A). Of HBeAg-positive patients at week 24, 41% with undetectable levels of HBV DNA on PCR underwent seroconversion by week 52 as compared with 4% of patients with more than $4 \log_{10}$ copies of HBV DNA per milliliter. Similar correlations were observed between HBV DNA levels at week 24 and the proportion of patients with alanine transaminase normalization at week 52.

At week 24, in HBeAg-positive patients in both treatment groups combined, resistance occurred in only 2% of patients who were negative for HBV

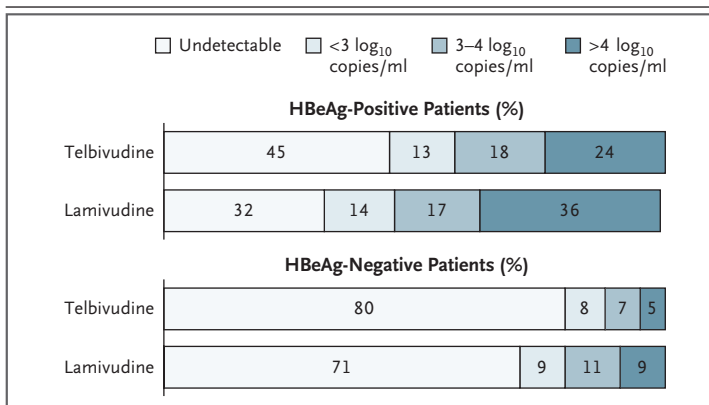


Figure 2. Serum HBV DNA Levels after 24 Weeks of Treatment.

The distribution of patients with HBeAg-positive chronic hepatitis B and those with HBeAg-negative chronic hepatitis B among four viral-load categories (in log₁₀ copies of HBV DNA per milliliter) is shown at week 24 according to treatment group. HBV DNA was classified as undetectable on the basis of PCR assays. Because of rounding, percentages may not total 100.

DNA on PCR, as compared with 15% of patients with viral loads above 4 log₁₀ copies per milliliter (Fig. 3A). A similar pattern was evident for HBeAg-negative patients. The pattern of relationships between HBV DNA levels at week 24 and subsequent resistance was similar for telbivudine and lamivudine. However, viral suppression was significantly greater and resistance was less frequent in the telbivudine group than in the lamivudine group within each viral-load category at week 24 (Fig. 3B). Multivariate regression analyses identified viral load at week 24 as the most significant predictor of 1-year efficacy outcomes and resistance.

SAFETY AND ADVERSE EVENTS

The frequencies of adverse events through week 52 were similar for patients who received telbivudine and for those who received lamivudine (Table 3). Serious adverse events (defined according to criteria adapted from the Division of AIDS, National Institute of Allergy and Infectious Diseases⁴⁰), regardless of attributability to study drug, were reported for 18 patients in the telbivudine group (2.6%) and 33 in the lamivudine group (4.8%).

Elevations in creatine kinase levels through week 52 were more common in recipients of telbivudine than in recipients of lamivudine (Table 3). Creatine kinase levels were elevated in 15% of study patients before treatment, a finding consistent with the frequent elevations in creatine kinase levels reported in patients who received placebo

in previous studies.^{32,34,41} Grade 3 or 4 elevations in creatine kinase levels (at least seven times the upper limit of normal), which were observed in 7.5% of patients in the telbivudine group and 3.1% of those in the lamivudine group, decreased spontaneously during drug treatment to grade 2 or lower by the next visit in 66.7% of the patients in the telbivudine group and 73.9% of those in the lamivudine group. Patterns of clinical adverse events, including infrequent muscle-related symptoms, correlated poorly with elevations in creatine kinase levels and were similar in the two study groups. Myopathy, characterized by muscle pain and weakness and moderately elevated creatine kinase levels before and during treatment, was reported in one patient 11 months after initiation of telbivudine. When telbivudine was discontinued, creatine kinase levels returned to normal within 1 month and symptoms resolved over a period of 9 to 12 months.

Grade 3 or 4 elevations in alanine aminotransferase and aspartate aminotransferase levels during treatment were less frequent in the telbivudine group than in the lamivudine group (Table 3). Grade 3 or 4 elevations in alanine aminotransferase levels were noted in 13.1% of patients receiving lamivudine and 12.5% of patients receiving telbivudine who had viral breakthrough. One patient with lamivudine resistance had liver failure and received a liver transplant. After week 24, alanine aminotransferase flares of at least 500 IU per liter and at least twice the baseline value were more common with lamivudine (2.2%) than telbivudine (0.4%).

DISCUSSION

In patients with HBeAg-positive chronic hepatitis B, telbivudine was superior to lamivudine for the primary and key secondary efficacy end points of therapeutic response and histologic response; in HBeAg-negative patients, telbivudine and lamivudine achieved similar rates of therapeutic and histologic response. In both HBeAg-positive and HBeAg-negative patients, telbivudine had greater antiviral efficacy than did lamivudine. The mechanism underlying the effect of pretreatment HBeAg status on therapeutic and histologic response is uncertain, but it may derive from the lower baseline HBV DNA levels and high viral clearance rates observed in HBeAg-negative patients. Results may differ with longer-term follow-up, as treatment-related differences in antiviral potency

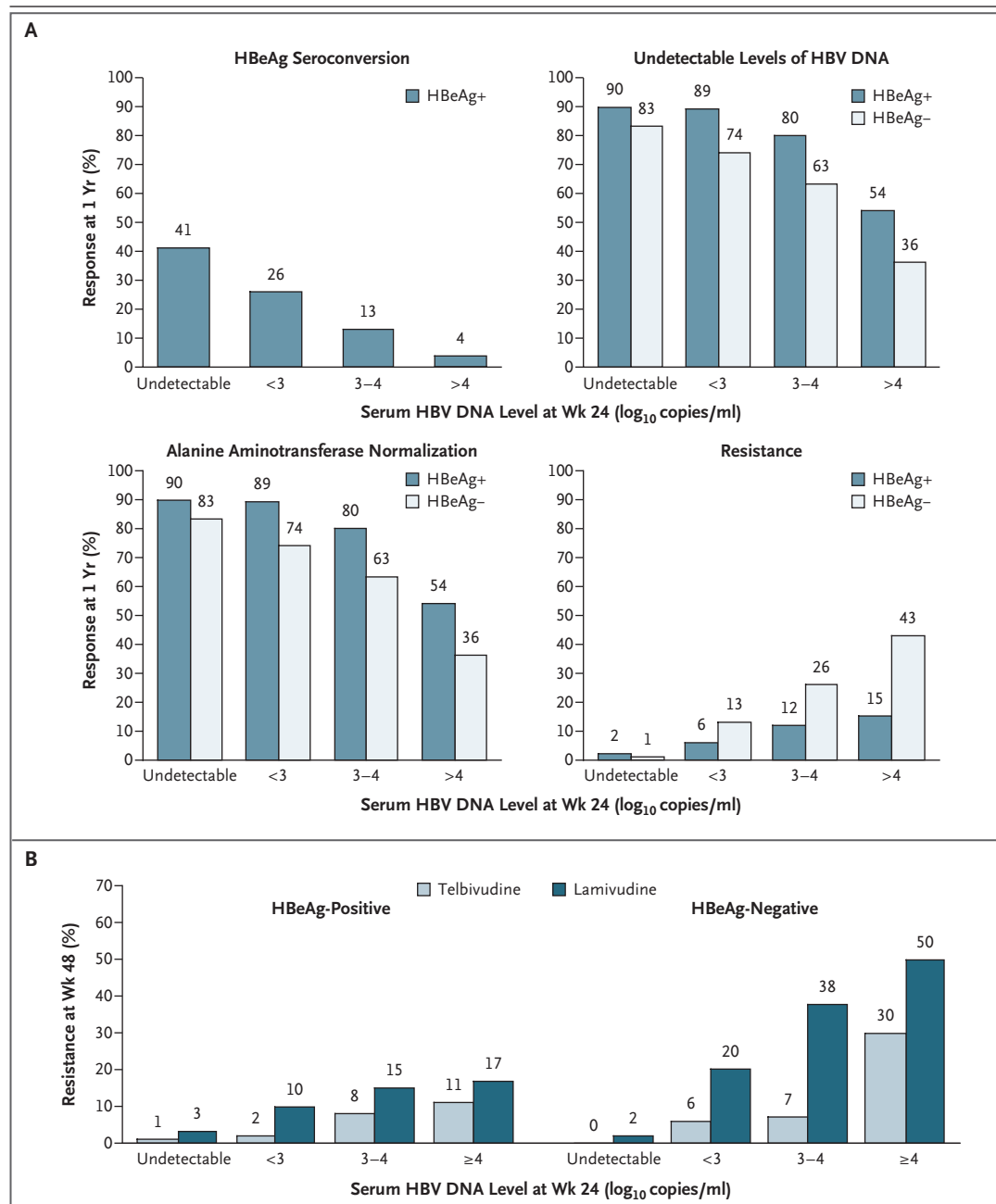


Figure 3. Effect of Early Viral Suppression on Treatment Outcomes.

The outcomes at week 48 (i.e., resistance) or week 52 (i.e., HBeAg seroconversion, alanine aminotransferase normalization, or undetectable levels of HBV DNA according to PCR assay) were assessed according to the category of residual viral load at week 24. Panel A shows the percentage of patients within each viral-load category at week 24 in whom the indicated efficacy end points were achieved at 1 year. Data are presented for the combined telbivudine and lamivudine treatment groups. Panel B shows the percentage of patients within each viral-load category at week 24 in whom resistance developed by 1 year, according to treatment group. HBV denotes hepatitis B virus, and HBeAg hepatitis B e antigen.

and resistance assume greater importance for determining therapeutic outcomes.

The lower resistance rates observed with telbivudine than with lamivudine are probably due in

part to the greater antiviral efficacy of telbivudine. Consistent with in vitro findings, data concerning clinical resistance confirm the M204I mutation as the primary basis for telbivudine re-

Table 3. Clinical Adverse Events and Laboratory Abnormalities to Week 52.

Event	Telbivudine (N = 680)	Lamivudine (N = 687)
Clinical adverse events — %*		
Any adverse event	73	69
Upper respiratory tract infection	12	12
Headache	10	12
Nasopharyngitis	10	10
Fatigue	10	9
Increased blood creatine kinase	8	6
Postprocedure pain	6	5
Cough	6	6
Upper abdominal pain	5	7
Influenza	5	5
Diarrhea	5	4
Nausea	5	4
Dizziness	4	5
Dyspepsia	2	5
Grade 3 or 4 laboratory abnormalities — no. (%)†		
Alanine aminotransferase	25 (3.7)	43 (6.3)
Aspartate aminotransferase	18 (2.6)	32 (4.7)
Creatine kinase	51 (7.5)	21 (3.1)
Lipase	12 (1.8)	22 (3.2)
Amylase	1 (0.1)	2 (0.3)
Absolute neutrophil count	13 (1.9)	9 (1.3)
Platelet count	5 (0.7)	4 (0.6)
Total bilirubin	0	2 (0.3)

* All clinical adverse events occurring in at least 5% of patients in either treatment group are listed, regardless of their attributability to the study drug.

† The severity of laboratory abnormalities was graded according to criteria adapted from the Division of AIDS, National Institute of Allergy and Infectious Diseases.⁴⁰ Grade 3 elevations in aminotransferase levels are those 3 to 10 times baseline; grade 4 elevations in aminotransferase levels are those at least 10 times baseline or accompanied by evidence of hepatic failure. Grades 3 and 4 elevations in creatine kinase levels are those at least 7 times the upper limit of normal.

sistance, in contrast to lamivudine resistance, which is associated with either the M204I or the M204V mutation.³⁸ HBV with either of these mutations is less susceptible to inhibition by nucleoside analogues but remains sensitive in vitro to the nucleotide analogues adefovir and tenofovir.³¹

This study confirms previously described associations between greater reductions in HBV DNA levels at week 24 and better subsequent therapeutic outcomes, including lower resistance.^{14,18,19} These relationships were similar for both study

drugs and may also apply to other agents for hepatitis B. The greater viral suppression achieved with more potent drugs predicts improved clinical outcomes overall.^{8,10} Future studies of patients with suboptimal responses may determine whether early treatment modification, using drugs with complementary resistance profiles, can improve subsequent outcomes.

The adverse event data in this trial were consistent with previous findings and preclinical toxicologic data^{12,14,42} and suggest that telbivudine and lamivudine have similar safety profiles. On-treatment aminotransferase flares after the first 6 months of treatment were less frequent with telbivudine, in accord with the lower incidence of viral breakthrough. Elevations in creatine kinase levels were more frequent with telbivudine but were not predictive of muscle-related adverse events. The occurrence of myopathy in a patient treated with telbivudine suggests that any persistent, unexplained muscle-related symptoms should be evaluated promptly.

As for all agents, the clinical role of telbivudine will be determined by efficacy, safety, and resistance considerations. Lamivudine was chosen as the comparator in this trial because it was the treatment of choice when the trial was initiated. Telbivudine has not been compared directly with other recently approved agents, such as entecavir. However, in separate trials, both telbivudine and entecavir have shown greater antiviral effects than have adefovir and lamivudine.^{33,35,43,44} One year of treatment with pegylated interferon has also been shown to be superior to 1 year of lamivudine when efficacy is assessed 24 weeks after both agents have been stopped.^{24,25} However, we are unaware of any trials that have compared the efficacy of 1 year of pegylated interferon with that of longer-term treatment with nucleoside or nucleotide analogues.

Maintaining safety and antiviral efficacy is critical with extended therapy. Loss of response due to cumulative resistance, treatment failure, or both has been observed with all nucleoside or nucleotide therapies for hepatitis B. Within 4 years after initiation of treatment, the cumulative incidence of lamivudine resistance approaches 70%.³⁹ Adefovir resistance was observed in 29% of HBeAg-negative patients after 5 years of treatment and in 16 of 38 HBeAg-positive patients with virologic failure after 110 to 279 weeks.⁴⁵ With entecavir, cumulative resistance was 0.8% at 4 years

according to an analysis of 120 of the 663 patients not previously treated with nucleosides from phase 3 trials.⁴⁶ Similarly, cumulative telbivudine resistance is likely to increase as therapy is extended. Long-term studies are needed to understand the cumulative prevalence and clinical effect of resistance to these agents.

The multiple therapeutic choices now available for hepatitis B will enhance the ability of clinicians to maintain long-term control of HBV replication, ultimately improving clinical outcomes for more patients. These results support telbivudine as an effective therapy for patients with chronic hepatitis B.

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APPENDIX

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