ORIGINAL ARTICLE

Peginterferon Alfa-2a, Lamivudine, and the Combination for HBeAg-Positive Chronic Hepatitis B

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ABSTRACT

BACKGROUND

Current treatments for chronic hepatitis B are suboptimal. In the search for improved therapies, we compared the efficacy and safety of pegylated interferon alfa plus lamivudine, pegylated interferon alfa without lamivudine, and lamivudine alone for the treatment of hepatitis B e antigen (HBeAg)–positive chronic hepatitis B.

METHODS

A total of 814 patients with HBeAg-positive chronic hepatitis B received either peginterferon alfa-2a (180 μg once weekly) plus oral placebo, peginterferon alfa-2a plus lamivudine (100 mg daily), or lamivudine alone. The majority of patients in the study were Asian (87 percent). Most patients were infected with hepatitis B virus (HBV) genotype B or C. Patients were treated for 48 weeks and followed for an additional 24 weeks.

RESULTS

After 24 weeks of follow-up, significantly more patients who received peginterferon alfa-2a monotherapy or peginterferon alfa-2a plus lamivudine than those who received lamivudine monotherapy had HBeAg seroconversion (32 percent vs. 19 percent [P<0.001] and 27 percent vs. 19 percent [P=0.02], respectively) or HBV DNA levels below 100,000 copies per milliliter (32 percent vs. 22 percent [P=0.01] and 34 percent vs. 22 percent [P=0.003], respectively). Sixteen patients receiving peginterferon alfa-2a (alone or in combination) had hepatitis B surface antigen (HBsAg) seroconversion, as compared with 0 in the group receiving lamivudine alone (P=0.001). The most common adverse events were those known to occur with therapies based on interferon alfa. Serious adverse events occurred in 4 percent, 6 percent, and 2 percent of patients receiving peginterferon alfa-2a monotherapy, combination therapy, and lamivudine monotherapy, respectively. Two patients receiving lamivudine monotherapy had irreversible liver failure after the cessation of treatment — one underwent liver transplantation, and the other died.

CONCLUSIONS

In patients with HBeAg-positive chronic hepatitis B, peginterferon alfa-2a offers superior efficacy over lamivudine, on the basis of HBeAg seroconversion, HBV DNA suppression, and HBsAg seroconversion.

More than 400 million people worldwide are chronically infected with hepatitis B virus (HBV).[1] Effective therapy is necessary to prevent the progression of chronic hepatitis B to cirrhosis, hepatocellular carcinoma, and death. Current consensus guidelines from Asia, Europe, and the United States recommend lamivudine, adefovir, or conventional interferon alfa for the treatment of chronic hepatitis B.[2-5] Lamivudine and adefovir suppress HBV replication and result in an improvement in liver architecture on microscopical evaluation during therapy. However, rates of hepatitis B e antigen (HBeAg) seroconversion, an end point that has been associated with improved long-term clinical outcomes,[6,7] are generally low with these agents.[8-10] Lamivudine and to a lesser extent adefovir are also associated with drug resistance,[8,9,11,12] which increases with prolonged use.[12,13] Although there have been very few direct comparisons, rates of HBeAg loss and seroconversion with conventional interferon alfa seem to be slightly higher than the rates with lamivudine or adefovir.[5] Conflicting data on the benefits of combining interferon-based therapies and lamivudine[11,14,15] indicate that the role of combination therapy in the treatment of chronic hepatitis B requires further clarification.

Conventional interferon alfa has suboptimal pharmacokinetics, resulting in an inconvenient dosing schedule and fluctuating drug exposure. Peginterferon alfa-2a, created by attaching a large, branched, 40-kD polyethylene glycol molecule to interferon alfa-2a,[16] has better pharmacokinetics than conventional interferon alfa. This allows for once-weekly dosing, with effective serum concentrations maintained throughout the dosing interval.[17] Peginterferon alfa-2a, like conventional interferon alfa, has a dual immunomodulatory and antiviral mode of action. In a phase 2, proof-of-concept study, peginterferon alfa-2a had better clinical outcomes than did conventional interferon alfa in patients with HBeAg-positive chronic hepatitis B.[18]

The current study was designed to assess the efficacy and safety of three regimens in patients with HBeAg-positive chronic hepatitis B: peginterferon alfa-2a monotherapy, peginterferon alfa-2a plus lamivudine, and lamivudine monotherapy.

METHODS

STUDY DESIGN

This multicenter, randomized, partially double-blind study was conducted at 67 sites in 16 countries in Asia, Australasia, Europe, and North and South America. The study was conducted in compliance with the Declaration of Helsinki and with the principles of Good Clinical Practice. All patients gave written informed consent.

Patients were randomly assigned in a 1:1:1 ratio to receive 180 μg of peginterferon alfa-2a (Pegasys, Roche) once weekly plus oral placebo once daily, 180 μg of peginterferon alfa-2a once weekly plus 100 mg of lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline) once daily, or 100 mg of lamivudine once daily. Randomization was centralized and stratified according to geographic region and alanine aminotransferase levels. The study comprised 48 weeks of treatment and 24 weeks of treatment-free follow-up.

The study was designed by the sponsor (Roche) in collaboration with expert hepatologists. Clinical data were collected by the Peginterferon Alfa-2a HBeAg-Positive Chronic Hepatitis B Study Group. The sponsor held the data and conducted the statistical analyses. The principal authors had full access to the data and vouch for the veracity and completeness of the data and data analysis. All authors made substantial contributions to the analysis and interpretation of the data and the drafting or revising of the manuscript. All authors approved the final manuscript.

PATIENTS

Adults were eligible if they had been positive for hepatitis B surface antigen (HBsAg) for at least 6 months, were negative for antibodies to HBsAg (anti-HBs antibodies) and positive for HBeAg, had an HBV DNA level of more than 500,000 copies per milliliter, had a serum alanine aminotransferase level that was greater than 1 but less than or equal to 10 times the upper limit of the normal range, and had had findings on a liver biopsy within the previous 12 months that were consistent with the presence of chronic hepatitis B. Exclusion criteria included decompensated liver disease, a coexisting serious medical or psychiatric illness, a neutrophil count of less than 1500 per cubic millimeter, a plate-

let count of less than 90,000 per cubic millimeter, a serum creatinine level that was more than 1.5 times the upper limit of the normal range, a history of alcohol or drug abuse within one year before entry, and coinfection with hepatitis C or D virus or human immunodeficiency virus. Previous treatment for chronic hepatitis B was permitted, but not within the six months before the study.

EFFICACY MEASURES

Efficacy analyses included all randomized patients who received at least one dose of study medication. The study had two predetermined primary measures of efficacy assessed after 24 weeks of treatment-free follow-up: HBeAg seroconversion (defined by the loss of HBeAg and the presence of anti-HBe antibody) and suppression of HBV DNA to levels below 100,000 copies per milliliter. HBeAg and serum HBV DNA were measured at a central laboratory with the use of the AxSYM test (Abbott) and the Cobas Amplicor HBV Monitor Test (Roche Diagnostics), respectively.

Secondary efficacy measures assessed after 24 weeks of treatment-free follow-up included the combined response (HBeAg seroconversion, the normalization of alanine aminotransferase levels, and the suppression of HBV DNA levels to below 100,000 copies per milliliter), HBsAg seroconversion (defined by the loss of HBsAg and the presence of anti-HBs antibody), and the histologic response. A histologic response was defined as a reduction of at least two points in the modified Histologic Activity Index score[19] as compared with the pretreatment score. Scores for this index can range from 0 to 24, with inflammation graded from 0 (none) to 18 (severe) and fibrosis graded from 0 (none) to 6 (cirrhosis). Biopsy samples were scored by an independent histopathologist who was unaware of the timing of the biopsy or the patient's treatment assignment.

SAFETY ANALYSIS

Measures of safety included adverse events, hematologic measurements, clinical chemical measurements, and vital signs. The severity of adverse events was graded on a three-point scale (mild, moderate, and severe), and causality was determined by the investigator. Safety was assessed at baseline; at weeks 1, 2, 4, 6, 8, and 12 and every six weeks thereafter throughout treatment; and as appropriate during follow-up. Safety analyses included all patients who underwent randomization and received at least one dose of study medication and who underwent at least one safety assessment after the baseline assessment.

RESISTANCE AND GENOTYPIC ANALYSES

HBV DNA was extracted from all available serum samples from patients in the two lamivudine groups at the end of treatment (week 48). Mutations in the tyrosine, methionine, aspartate, and aspartate (YMDD) motif of the HBV polymerase gene were identified by means of the INNO-LiPA HBV DR assay (Innogenetics).[20] Genotyping of HBV DNA was performed at baseline on serum samples from all patients by means of the INNO-LiPA HBV Genotyping assay (Innogenetics).

STATISTICAL ANALYSIS

A sample size of 231 patients per treatment group provided the study with a statistical power of at least 80 percent at the 0.0125 level of significance, with a two-sided test, to detect a difference in HBeAg seroconversion rates of 20 percent versus 34 percent or HBV DNA response rates (suppression below 100,000 copies per milliliter) of 30 percent versus 45 percent. The sample size was increased to 250 patients to allow for withdrawals. An overall significance level of 0.025 was chosen because of the two predetermined primary end points. This more stringent overall significance level was adopted for regulatory reasons. For secondary efficacy measures, the level of significance was set at 0.05.

The Cochran–Mantel–Haenszel test, stratified according to geographic region and pretreatment alanine aminotransferase level, was used to compare differences in response rates between the treatment groups. Only if the overall test of the treatment effect was significant were pairwise comparisons performed. Fisher's exact test was used when appropriate. For each treatment group, response rates were computed with corresponding 95 percent confidence intervals. No interim analyses were performed.

Response rates were calculated for all patients who received at least one dose of study drug, according to the intention-to-treat principle. Patients with missing values at week 72 were classified as having no response.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Of the 814 patients included in the analyses, 28 of the 271 patients randomly assigned to receive

peginterferon alfa-2a monotherapy, 25 of the 271 assigned to peginterferon alfa-2a plus lamivudine, and 42 of the 272 assigned to lamivudine monotherapy either did not complete treatment or did not enter or complete the follow-up phase. Baseline demographic and other characteristics were similar among the three treatment groups (Table 1).

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Peginterferon Alfa-2a plus Placebo (N=271)	Peginterferon Alfa-2a plus Lamivudine (N=271)	Lamivudine (N=272)
Male sex — no. (%)	214 (79)	208 (77)	215 (79)
Race or ethnic group — no. (%)†			
White	24 (9)	23 (8)	32 (12)
Asian	237 (87)	236 (87)	232 (85)
Black	4 (1)	4 (1)	3 (1)
Other	6 (2)	8 (3)	5 (2)
Age — yr			
Mean ±SD	32.5±9.6	31.7±10.3	31.6±9.7
Median	31	29	30
Range	18–77	18–66	17–65
Weight — kg			
Mean ±SD	66±13.0	66±14.8	67±14.4
Median	65	64	65
Range	35–128	41–135	40–160
Alanine aminotransferase — IU/liter‡			
Mean ±SD	114.6±114.3	114.9±94.1	102.3±78.4
Median	84.0	81.8	82.1
Range	11.4–1266.0	13.2–642.0	5.9–462.1
HBV DNA — log copies/ml¶			
Mean ±SD	9.9±2.1	10.1±1.9	10.1±2.0
Median	9.8	9.9	9.8
Range	4.4–16.1	3.1–17.9	3.0–16.0
Bridging fibrosis or cirrhosis — no. (%)§	49 (18)	40 (15)	47 (17)
Previous use of conventional interferon alfa — no. (%)	30 (11)	32 (12)	32 (12)
Previous use of lamivudine — no. (%)	31 (11)	24 (9)	42 (15)
Genotype distribution — no. (%)			
A	23 (8)	18 (7)	15 (6)
B	76 (28)	82 (30)	73 (27)
C	162 (60)	156 (58)	162 (60)
D	9 (3)	11 (4)	17 (6)
E, F, or H	0	3 (1)	4 (1)
Mixed	1 (<1)	1 (<1)	1 (<1)

* Percentages may not sum to 100 because of rounding.
† Race or ethnic group was generally assigned by the investigator, but in rare instances was clarified with the patient.
‡ The upper limit of the normal range is 30 IU per liter.
§ The presence or absence of bridging fibrosis and cirrhosis was assessed by local pathologists.
¶ Log to the base 10 was used.

Table 2. Rates of HBeAg, Virologic, Biochemical, Combined, and Histologic Responses.*

Response	End of Treatment (Week 48)			End of Follow-up (Week 72)		
	Peginterferon Alfa-2a plus Placebo (N=271)	Peginterferon Alfa-2a plus Lamivudine (N=271)	Lamivudine (N=272)	Peginterferon Alfa-2a plus Placebo (N=271)	Peginterferon Alfa-2a plus Lamivudine (N=271)	Lamivudine (N=272)
HBeAg response						
HBeAg seroconversion†						
Patients — no. (%)	72 (27)	64 (24)	55 (20)	87 (32)	74 (27)	52 (19)
95% CI — %	21.4 to 32.2	18.7 to 29.1	15.6 to 25.5	26.6 to 38.0	22.1 to 33.0	14.6 to 24.3
P value				<0.001	0.02	
Odds ratio (95% CI)‡				2.0 (1.3 to 3.0)	1.6 (1.1 to 2.4)	
HBeAg loss						
Patients — no. (%)	81 (30)	73 (27)	59 (22)	91 (34)	77 (28)	57 (21)
95% CI — %	24.5 to 35.7	21.7 to 32.6	16.9 to 27.1	28.0 to 39.5	23.1 to 34.2	16.3 to 26.3
P value				<0.001	0.04	
Virologic response						
HBV DNA <100,000 copies/ml§						
Patients — no. (%)	142 (52)	233 (86)	169 (62)	86 (32)	91 (34)	60 (22)
95% CI — %	46.3 to 58.5	81.3 to 89.9	56.1 to 67.9	26.2 to 37.6	28.0 to 39.5	17.3 to 27.5
P value				0.01	0.003	
Odds ratio (95% CI)‡				1.6 (1.1 to 2.4)	1.8 (1.2 to 2.6)	
HBV DNA <400 copies/ml						
Patients — no. (%)	68 (25)	186 (69)	108 (40)	39 (14)	37 (14)	14 (5)
95% CI — %	20.0 to 30.7	62.7 to 74.1	33.8 to 45.8	10.4 to 19.1	9.8 to 18.3	2.8 to 8.5
P value				<0.001	<0.001	
Change in HBV DNA						
Total no. of patients	248	249	249	248	254	241
Mean log copies/ml	−4.5	−7.2	−5.8	−2.4	−2.7	−1.9
95% CI — log copies/ml	−4.1 to −4.9	−6.9 to −7.5	−5.4 to −6.1	−2.0 to −2.8	−2.2 to −3.1	−1.5 to −2.3
Biochemical response						
Normalization of ALT						
Patients — no. (%)	105 (39)	126 (46)	168 (62)	111 (41)	106 (39)	76 (28)
95% CI — %	32.9 to 44.8	40.4 to 52.6	55.7 to 67.6	35.0 to 47.1	33.3 to 45.2	22.7 to 33.7
P value				0.002	0.006	

HBeAg RESPONSE

At the end of treatment (week 48), the percentage of patients with HBeAg seroconversion was highest with peginterferon alfa-2a monotherapy (Table 2 and Fig. 1A). The overall HBeAg seroconversion rates continued to rise during the entire study period in the two peginterferon alfa-2a groups but not in the lamivudine monotherapy group; seroreversion (loss of anti-HBe antibody and re-expression of HBeAg) was substantially less frequent with peginterferon alfa-2a monotherapy (occurring in 13 of 72 patients, or 18 percent) and with combination

Table 2. (Continued.)

Response	End of Treatment (Week 48)			End of Follow-up (Week 72)		
	Peginterferon Alfa-2a plus Placebo (N=271)	Peginterferon Alfa-2a plus Lamivudine (N=271)	Lamivudine (N=272)	Peginterferon Alfa-2a plus Placebo (N=271)	Peginterferon Alfa-2a plus Lamivudine (N=271)	Lamivudine (N=272)
Combined response						
HBeAg seroconversion, normalization of ALT, and HBV DNA <100,000 copies/ml						
Patients — no. (%)	27 (10)	42 (15)	50 (18)	62 (23)	56 (21)	28 (10)
95% CI — %	6.7 to 14.2	11.4 to 20.4	14.0 to 23.5	18.0 to 28.3	16.0 to 26.0	7.0 to 14.5
P value				<0.001	<0.001	
Histologic response¶						
All patients — no.‖				271	271	272
Improved — no. of patients (%)				102 (38)	112 (41)	93 (34)
95% CI — %				31.8 to 43.7	35.4 to 47.4	28.6 to 40.2
Patients with paired biopsy samples — no.**				207	215	184
Improved — no. of patients (%)				102 (49)	112 (52)	93 (51)
95% CI — %				42.3 to 56.3	45.2 to 58.9	43.1 to 58.0

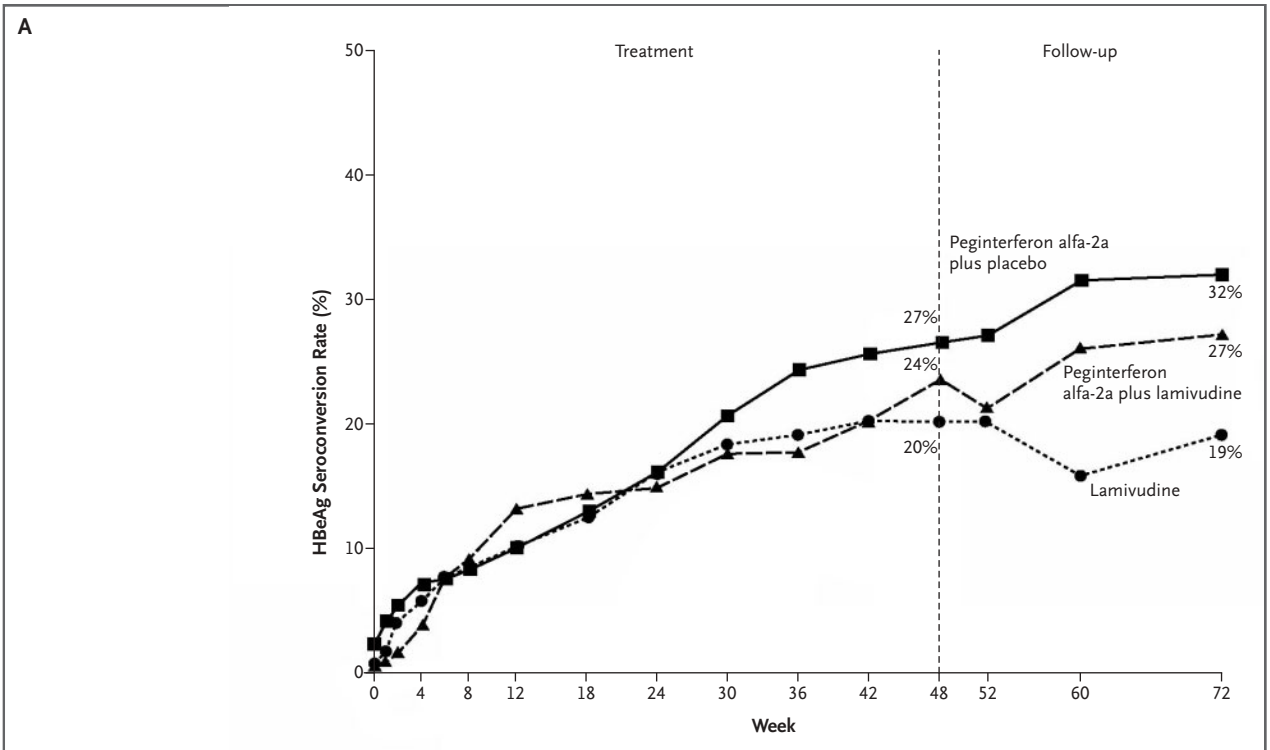
* All P values are from the Cochran–Mantel–Haenszel test for pairwise comparison of each peginterferon alfa-2a group with the lamivudine monotherapy group at week 72. CI denotes confidence interval, and ALT alanine aminotransferase.
† P=0.003 for the overall test of treatment effect, and P=0.23 for the comparison between peginterferon alfa-2a plus placebo and peginterferon alfa-2a plus lamivudine.
‡ Odds ratios are given with 95 percent confidence intervals only for the two primary efficacy outcomes.
§ P=0.007 for the overall test of treatment effect, and P=0.65 for the comparison between peginterferon alfa-2a plus placebo and peginterferon alfa-2a plus lamivudine.
¶ Histologic response was defined as a reduction of at least two points in the modified Histology Activity Index score as compared with the pretreatment score. Scores for this index can range from 0 to 24, with inflammation graded from 0 (none) to 18 (severe) and fibrosis graded from 0 (none) to 6 (cirrhosis).[19]
‖ Patients without paired biopsy samples were classified as having no response. P=0.23 for the overall test of treatment effect.
** Patients without paired biopsy samples were excluded. P=0.79 for the overall test of treatment effect.

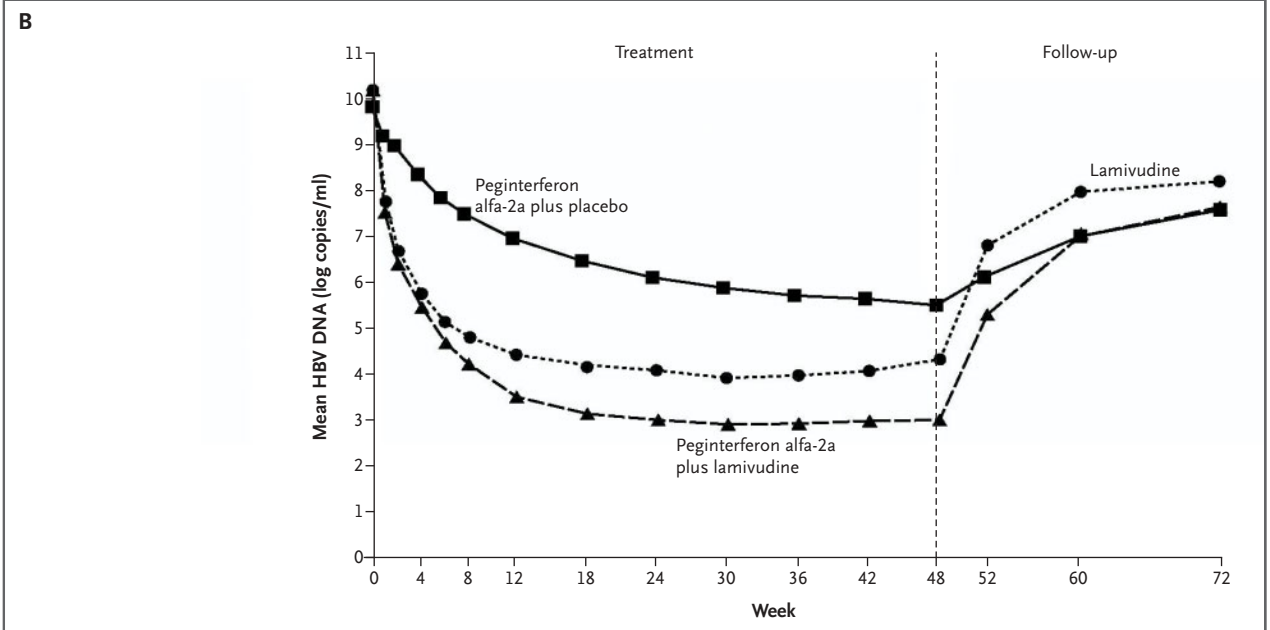
therapy (14 of 64 patients, or 22 percent) than with lamivudine monotherapy (23 of 55 patients, or 42 percent; P=0.005 and P=0.03, respectively, by Fisher's exact test). After 24 weeks of follow-up (week 72), the percentage of patients with HBeAg seroconversion was significantly higher with peginterferon alfa-2a monotherapy (32 percent) and combination therapy (27 percent) than with lamivudine monotherapy (19 percent; P<0.001 and P=0.02, respectively) (Table 2 and Fig. 2). At weeks 48 and 72, rates of HBeAg loss closely reflected rates of HBeAg seroconversion (Table 2).

HBeAg seroconversion rates in patients with and without previous exposure to lamivudine or conventional interferon were similar to rates in the overall study population (Table 3). Additional stratified analyses are detailed in Table 3.

VIROLOGIC RESPONSE

At week 48, the percentage of patients with suppression of HBV DNA was highest with combination therapy (Table 2). This changed during follow-up such that at week 72, suppression of HBV DNA levels to less than 100,000 copies per milliliter occurred in a significantly higher percentage of patients receiving peginterferon alfa-2a monotherapy (32 percent) or peginterferon alfa-2a plus lamivudine (34 percent) than in those receiving lamivudine monotherapy (22 percent; P=0.01 and P=0.003, respectively) (Table 2). Rates of suppression of HBV





No. of Patients													
Peginterferon alfa-2a plus placebo	271	269	265	265	262	263	259	258	255	248	254	241	248
Peginterferon alfa-2a plus lamivudine	271	268	268	267	268	263	259	254	255	249	254	244	254
Lamivudine	272	267	267	267	263	263	259	260	244	249	248	228	241

Figure 1. Rates of HBeAg Seroconversion (Panel A) and HBV DNA Levels (Panel B), from Baseline to Week 72.

HBeAg seroconversion was defined by the loss of HBeAg and the presence of anti-HBe antibody. Log to the base 10 was used. The information about the number of patients refers only to Panel B.

DNA levels to less than 400 copies per milliliter at week 72 were 14 percent with both peginterferon alfa-2a monotherapy and peginterferon alfa-2a plus lamivudine, and 5 percent with lamivudine alone (P<0.001 for both comparisons with lamivudine monotherapy). The patterns of HBV DNA levels throughout the study are shown in Figure 1B. Rates of normalization of alanine aminotransferase levels and combined response at week 72 closely reflected the virologic response rates (Table 2).

HBsAg RESPONSE

At week 72, HBsAg seroconversion was identified in eight patients receiving peginterferon alfa-2a monotherapy (three Asian and five white patients, five with HBV genotype A and three with genotype C) and in eight receiving peginterferon alfa-2a plus lamivudine (five Asian and three white patients; two with genotype A, one with genotype B, four with genotype C, and one with genotype H). HBsAg seroconversion was not identified in any patients receiving lamivudine monotherapy. The differences in HBsAg seroconversion between peginterferon alfa-2a monotherapy and lamivudine monotherapy, and between peginterferon alfa-2a plus lamivudine and lamivudine monotherapy, were significant (P=0.004 for both comparisons with lamivudine monotherapy, by Fisher's exact test).

HISTOLOGIC RESPONSE

The rate of histologic response was similar among the three treatment groups (Table 2). There was a significant association between improved histologic activity and either HBeAg seroconversion, a virologic response, or a biochemical response at week 72, regardless of the treatment group (P<0.001). Among patients with paired biopsy samples, a histologic response occurred in 133 of 179 patients (74 percent) who had HBeAg seroconversion as compared with 174 of 427 patients (41 percent) who did not have HBeAg seroconversion (P<0.001 by the log-likelihood ratio test).

ALANINE AMINOTRANSFERASE LEVELS

Alanine aminotransferase elevations, defined as a peak value at least five times as great as the baseline value, occurred in 14 patients receiving peginterferon alfa-2a monotherapy (5 percent), 16 receiving combination therapy (6 percent), and 12 receiving lamivudine monotherapy (4 percent). Rates of HBeAg seroconversion in these patients at week 72 were 43 percent, 38 percent, and 25 percent, respectively (Table 3).

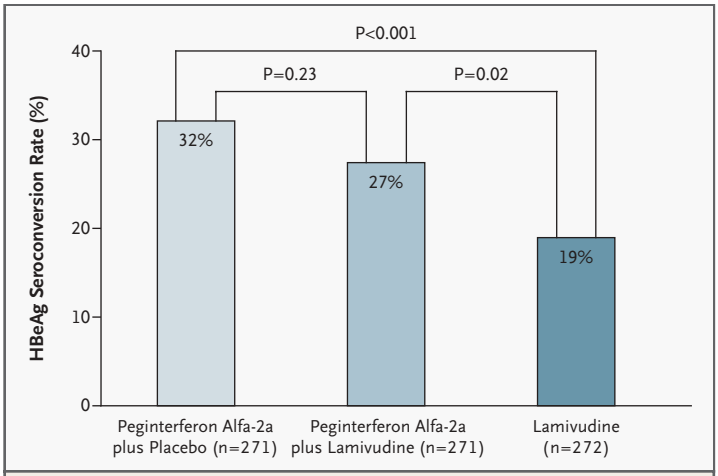


Figure 2. Rates of HBeAg Seroconversion after 24 Weeks of Follow-up.
The percentage of patients with seroconversion in each group is shown at the top of the corresponding bar.

RESISTANCE

At week 48, YMDD mutations were detected in 69 of 254 patients receiving lamivudine monotherapy (27 percent) and 9 of 256 patients receiving peginterferon alfa-2a plus lamivudine (4 percent, P<0.001).

SAFETY

The rate of withdrawal from therapy was low in all three groups (Table 4). The rates of adverse events were similar in the peginterferon alfa-2a and combination-therapy groups but were significantly less frequent in the lamivudine-only group (P<0.001 for the overall comparison). Among the three groups, the incidence of adverse events was similar between Asian and non-Asian patients (79 percent and 82 percent, respectively). The most common adverse events were those known to occur with interferon alfa therapy, including pyrexia, fatigue, headache, and myalgia (Table 4).

Depression, which is a potential concern with interferon-based therapy, was infrequent during the study and was reported by 13 patients (5 percent) receiving peginterferon alfa-2a monotherapy, 16 patients (6 percent) receiving peginterferon alfa-2a plus lamivudine, and 4 patients (1 percent) receiving lamivudine monotherapy.

Table 3. Effect of Baseline Factors and Alanine Aminotransferase Levels during Treatment on HBeAg Seroconversion Rates at Week 72.

Variable	Peginterferon Alfa-2a plus Placebo	Peginterferon Alfa-2a plus Lamivudine	Lamivudine
	no. of patients achieving HBeAg seroconversion/total no. of patients (%)		
Overall study population	87/271 (32)	74/271 (27)	52/272 (19)
Patients with no previous anti-HBV therapy*	66/214 (31)	59/221 (27)	42/208 (20)
Patients with previous exposure to lamivudine			
Yes	10/31 (32)	6/24 (25)	7/42 (17)
No	77/240 (32)	68/247 (28)	45/230 (20)
Patients with previous exposure to conventional interferon			
Yes	13/30 (43)	11/32 (34)	4/32 (12)
No	74/241 (31)	63/239 (26)	48/240 (20)
HBV genotype†			
A	12/23 (52)	4/18 (22)	3/15 (20)
B	23/76 (30)	24/82 (29)	17/73 (23)
C	50/162 (31)	43/156 (28)	29/162 (18)
D	2/9 (22)	2/11 (18)	3/17 (18)
Baseline HBV DNA levels (log copies/ml)			
≤9.07	37/70 (53)	20/56 (36)	24/78 (31)
>9.07–10.26	39/138 (28)	40/147 (27)	21/123 (17)
>10.26	11/63 (17)	14/68 (21)	7/71 (10)
Baseline alanine aminotransferase level (×ULN)‡			
≤2	27/92 (29)	19/93 (20)	19/96 (20)
>2 to 5	36/121 (30)	30/111 (27)	20/129 (16)
>5	24/58 (41)	25/67 (37)	13/47 (28)
Maximum alanine aminotransferase level during treatment (×ULN)‡			
≤5	39/149 (26)	35/150 (23)	33/177 (19)
>5 to 10	28/74 (38)	27/86 (31)	16/64 (25)
>10	20/48 (42)	12/35 (34)	3/31 (10)
Maximum alanine aminotransferase level during treatment (×baseline value)			
≤5	81/257 (32)	68/255 (27)	49/260 (19)
>5	6/14 (43)	6/16 (38)	3/12 (25)

* This group includes patients who had previously been treated with lamivudine, conventional interferon, and peginterferon only.
† This group includes only patients infected with HBV genotype A, B, C, or D.
‡ ULN denotes the upper limit of the normal range, which is 30 IU per liter.

Thirty-three patients had serious adverse events during treatment and up to eight weeks after therapy: 12 patients (4 percent) receiving peginterferon alfa-2a monotherapy, 16 patients (6 percent) receiving peginterferon alfa-2a plus lamivudine, and 5 patients (2 percent) receiving lamivudine monotherapy (Table 4). However, two patients receiving lamivudine monotherapy, neither of whom had cirrhosis or bridging fibrosis at baseline, had hepatic decompensation after the cessation of treatment. One patient required liver transplantation and made a full recovery, and one patient died.

Mean neutrophil and platelet counts were reduced during treatment with peginterferon alfa-2a monotherapy and peginterferon alfa-2a plus lamivudine, yet returned to baseline levels shortly after treatment was stopped. Laboratory abnormalities (alanine aminotransferase elevation, neutropenia, and thrombocytopenia) were the most common reason for dose modification (Table 4).

DISCUSSION

We found that peginterferon alfa-2a alone or in combination with lamivudine resulted in higher rates of sustained HBeAg, HBsAg, virologic, and biochemical response among patients with HBeAg-positive chronic hepatitis B than did lamivudine alone. HBeAg seroconversion is a key objective of therapy for HBeAg-positive chronic hepatitis B, since it is associated with improved long-term clinical outcomes, such as histologic improvement and increased complication-free and overall survival.[6,7]

In this study of patients, predominantly of Asian origin, who had previously been considered to have difficult-to-treat chronic hepatitis B,[21] HBeAg seroconversion rates were significantly higher after 24 weeks of treatment-free follow-up in patients receiving peginterferon alfa-2a alone or in combination with lamivudine than in those receiving lamivudine alone. Previous exposure to lamivudine did not affect the overall rates of HBeAg seroconversion. In accordance with previous findings with interferon alfa therapy,[22] marked elevations in alanine aminotransferase levels were more frequently associated with HBeAg response in patients receiving peginterferon alfa-2a alone or in combination with lamivudine than in those receiving lamivudine alone.

At present, it is not clear whether viral genotype is a predictor of treatment response in chronic hepatitis B, as it is in chronic hepatitis C. Responses to nucleoside or nucleotide analogues are generally consistent among all genotypes,[23,24] whereas higher responses to interferon alfa have been reported for HBV genotype A than for genotype D and for genotype B than for genotype C.[25] The results of our study indicate that HBeAg seroconversion was generally consistent across all genotypes. However, a recent study of peginterferon alfa-2b[26] reported a higher HBeAg seroconversion rate for genotype A. This trend was also observed in our study in the patients receiving peginterferon alfa-2a monotherapy. However, in our study, the number of patients infected with genotype A was very low.

Previous studies have shown that HBV DNA suppression is associated with HBeAg seroconversion.[8,10,27] At week 48 of our study, viral suppression was higher in patients receiving lamivudine monotherapy than in those receiving peginterferon alfa-2a monotherapy. However, despite this more potent suppression of HBV DNA with lamivudine, rates of HBeAg seroconversion at the end of treatment and after follow-up were highest with peginterferon alfa-2a monotherapy. These data indicate that a separate and probably immunomodulatory component influences HBeAg seroconversion with peginterferon alfa-2a. Similarly, among patients receiving peginterferon alfa-2a monotherapy or peginterferon alfa-2a plus lamivudine, who presumably had equivalent immunomodulation related to peginterferon alfa-2a, the increased antiviral activity in the group receiving combination therapy did not improve HBeAg seroconversion rates. Significantly fewer patients receiving combination therapy had YMDD mutants at the end of treatment than did patients receiving lamivudine alone. This suggests that more profound HBV DNA suppression, such as that seen during treatment with peginterferon alfa-2a plus lamivudine, leads to a lower incidence of lamivudine resistance, a finding that concurs with previous studies of HBV.[28,29]

HBsAg loss or seroconversion after therapy is considered the ultimate therapeutic goal of anti-HBV therapy, since it is associated with positive long-term clinical outcomes.[2,4,5,30] In this study, HBsAg seroconversion was identified in 8 of 473 Asian patients (2 percent) and 8 of 47 white patients (17 percent) receiving peginterferon alfa-2a alone or in combination with lamivudine, as compared with none receiving lamivudine alone. These HBsAg seroconversion rates with peginterferon

Table 4. Incidence of Discontinuation of Treatment, Dose Modification, and Adverse Events.*

Variable	Peginterferon Alfa-2a plus Placebo (N=271)	Peginterferon Alfa-2a plus Lamivudine (N=271)	Lamivudine (N=272)
	number of patients (percent)		
Discontinuation			
For safety reasons†	8 (3)	12 (4)	2 (1)
For other reasons‡	9 (3)	6 (2)	12 (4)
Dose modification§			
Total	124 (46)	127 (47)	—
Adverse event	20 (7)	23 (8)	—
Laboratory abnormality	99 (37)	102 (38)	—
Dose missed or dosage error	25 (9)	20 (7)	—
Other	2 (1)	2 (1)	—
Adverse events			
≥1 Reported serious adverse event (weeks 0 to 56)¶	12 (4)	16 (6)	5 (2)
Deaths			
Weeks 0 to 56	0	3 (1)‖	0
Weeks 57 to 72	0	0	1 (<1)**
≥1 Reported adverse event (weeks 0 to 56)††	240 (89)	240 (89)	152 (56)

alfa-2a compare favorably with rates of HBsAg response within 12 months of the cessation of treatment that were shown in studies of conventional interferon in Asian[31-33] and white[7,30] patients.

No statistically significant differences in efficacy were observed between the groups receiving peginterferon alfa-2a monotherapy and peginterferon alfa-2a plus lamivudine after 24 weeks of follow-up, a finding that concurs with a recent study of patients with HBeAg-negative chronic hepatitis B.[29] However, these results do not categorically rule out the possibility that combination therapy, including sequential therapy, may provide clinically relevant benefits.

The tolerability and safety profiles of peginterferon alfa-2a monotherapy and peginterferon alfa-2a plus lamivudine were similar to those reported in patients with HBeAg-negative chronic hepatitis B, and there were no unexpected adverse effects.[29] The safety profile of peginterferon alfa-2a in this study also compares favorably with the profiles described in previous studies of conventional interferon alfa in HBeAg-positive chronic hepatitis B.[11,18] As anticipated, peginterferon alfa-2a alone or in combination with lamivudine was not tolerated as well as lamivudine monotherapy. However, the rate of withdrawal from peginterferon alfa-2a therapy was less than 5 percent.

Depression was reported in 5 percent of patients receiving peginterferon alfa-2a in this study. This incidence is substantially lower than that observed among patients with chronic hepatitis C (16 to 20 percent).[34,35] This finding concurs with data from a recent study of peginterferon alfa-2a in HBeAg-negative chronic hepatitis B.[29]

In conclusion, the results of this large, multinational study show that peginterferon alfa-2a provides significantly improved efficacy over lamivudine in the treatment of HBeAg-positive chronic hepatitis B. Improvement in sustained HBeAg and HBsAg seroconversion rates, as well as sustained virologic and biochemical response rates, indicate that peginterferon alfa-2a offers a therapeutic advantage over available treatments for chronic hepatitis B. The ability to achieve HBeAg and HBsAg seroconversion after a defined period of peginter-

Table 4. (Continued.)

Variable	Peginterferon Alfa-2a plus Placebo (N=271)	Peginterferon Alfa-2a plus Lamivudine (N=271)	Lamivudine (N=272)
	number of patients (percent)		
Adverse events (continued)			
Most common adverse events (weeks 0 to 56)‡‡			
Pyrexia	133 (49)	148 (55)	12 (4)
Fatigue	108 (40)	101 (37)	37 (14)
Headache	76 (28)	81 (30)	27 (10)
Myalgia	70 (26)	77 (28)	8 (3)
Alopecia	55 (20)	78 (29)	6 (2)
Decreased appetite	40 (15)	34 (13)	5 (2)
Rash	27 (10)	22 (8)	10 (4)
Pruritus	26 (10)	26 (10)	5 (2)
Dizziness	25 (9)	32 (12)	11 (4)
Diarrhea	25 (9)	26 (10)	9 (3)
Nausea	24 (9)	27 (10)	6 (2)
Injection-site reaction	24 (9)	15 (6)	0
Arthralgia	24 (9)	24 (9)	7 (3)
Upper respiratory tract infection	21 (8)	15 (6)	29 (11)
Insomnia	20 (7)	23 (8)	10 (4)
Rigors	19 (7)	27 (10)	0
Upper abdominal pain	19 (7)	14 (5)	20 (7)
Sore throat	15 (6)	21 (8)	19 (7)
Gingival bleeding	15 (6)	15 (6)	1 (<1)
Cough	14 (5)	19 (7)	10 (4)
Dyspepsia	14 (5)	6 (2)	9 (3)
Depression	13 (5)	16 (6)	4 (1)

* Values are based on all randomized patients who received at least one dose of study medication and had at least one safety assessment after baseline. Dashes indicate no dose modifications in the group receiving lamivudine monotherapy.
† P=0.03 for the overall test of treatment effect. P=0.06 for the comparison between peginterferon alfa-2a plus placebo and lamivudine alone, and P=0.01 for the comparison between peginterferon alfa-2a plus lamivudine and lamivudine alone.
‡ P=0.36 for the overall test of treatment effect.
§ Some patients who required a dose modification had both an adverse event and a laboratory abnormality. Laboratory abnormalities include alanine aminotransferase elevation, neutropenia, and thrombocytopenia. Other includes circumstances related to patient compliance.
¶ A serious adverse event was one that presented a clinically significant hazard or resulted in a contraindication, side effect, or precaution. P=0.05 for the overall test of treatment effect, P=0.09 for the comparison between peginterferon alfa-2a plus placebo and lamivudine alone, and P=0.01 for the comparison between peginterferon alfa-2a plus lamivudine and lamivudine alone.
‖ All three deaths were accidental and were considered by the investigators to be unrelated to the study medication.
** Life-threatening hepatic encephalopathy developed in this patient, which was considered by the investigator to be related to discontinuation of lamivudine treatment.
†† P<0.001 for the overall test of treatment effect, P<0.001 for the comparison between peginterferon alfa-2a plus placebo and lamivudine alone, and P<0.001 for the comparison between peginterferon alfa-2a plus lamivudine and lamivudine alone.
‡‡ Patients may have had more than one adverse event. The adverse events listed are those reported by at least 5 percent of patients in any treatment group.

feron alfa-2a therapy supports the use of peginterferon alfa-2a as a first-line therapy for patients with HBeAg-positive chronic hepatitis B.

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APPENDIX

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