ORIGINAL ARTICLE

Peginterferon Alfa-2a Alone, Lamivudine Alone, and the Two in Combination in Patients with HBeAg-Negative Chronic Hepatitis B

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ABSTRACT

BACKGROUND

Available treatments for hepatitis B e antigen (HBeAg)–negative chronic hepatitis B are associated with poor sustained responses. As a result, nucleoside and nucleotide analogues are typically continued indefinitely, a strategy associated with the risk of resistance and unknown long-term safety implications.

METHODS

We compared the efficacy and safety of peginterferon alfa-2a (180 μg once weekly) plus placebo, peginterferon alfa-2a plus lamivudine (100 mg daily), and lamivudine alone in 177, 179, and 181 patients with HBeAg-negative chronic hepatitis B, respectively. Patients were treated for 48 weeks and followed for an additional 24 weeks.

RESULTS

After 24 weeks of follow-up, the percentage of patients with normalization of alanine aminotransferase levels or hepatitis B virus (HBV) DNA levels below 20,000 copies per milliliter was significantly higher with peginterferon alfa-2a monotherapy (59 percent and 43 percent, respectively) and peginterferon alfa-2a plus lamivudine (60 percent and 44 percent) than with lamivudine monotherapy (44 percent, $P=0.004$ and $P=0.003$, respectively; and 29 percent, $P=0.007$ and $P=0.003$, respectively). Rates of sustained suppression of HBV DNA to below 400 copies per milliliter were 19 percent with peginterferon alfa-2a monotherapy, 20 percent with combination therapy, and 7 percent with lamivudine alone ($P<0.001$ for both comparisons with lamivudine alone). Loss of hepatitis B surface antigen occurred in 12 patients in the peginterferon groups, as compared with 0 patients in the group given lamivudine alone. Adverse events, including pyrexia, fatigue, myalgia, and headache, were less frequent with lamivudine monotherapy than with peginterferon alfa-2a monotherapy or combination therapy.

CONCLUSIONS

Patients with HBeAg-negative chronic hepatitis B had significantly higher rates of response, sustained for 24 weeks after the cessation of therapy, with peginterferon alfa-2a than with lamivudine. The addition of lamivudine to peginterferon alfa-2a did not improve post-therapy response rates.

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CHRONIC INFECTION WITH HEPATITIS B virus (HBV) is a major global health problem, affecting more than 400 million people worldwide.[1] Chronic hepatitis B is associated with serious complications, including liver failure, cirrhosis, and hepatocellular carcinoma. Hepatitis B e antigen (HBeAg)–negative chronic hepatitis B represents a late phase of the infection that is characterized by progressive liver damage[2,3] and viral variants with changes in the precore or core promoter region,[4,5] which abolish or suppress the expression of HBeAg. Spontaneous, sustained remissions are rare in HBeAg-negative chronic hepatitis B,[6] which has a poor prognosis. HBeAg-negative chronic hepatitis B occurs throughout the world, and its prevalence is increasing.[4,6]

HBeAg-negative chronic hepatitis B responds well to currently available therapies during treatment. However, relapse rates are high after treatment cessation, and the rates of sustained response are poor.[7-10] Current consensus guidelines recommend the use of interferon alfa or nucleoside or nucleotide analogues as first-line therapy for HBeAg-negative chronic hepatitis B.[6,11-13] However, conventional interferon alfa has suboptimal pharmacokinetics, necessitating an inconvenient dosing regimen. Lamivudine is associated with drug resistance, which increases with extended use.[14,15] Studies in patients with chronic hepatitis B have produced conflicting results regarding the benefits of combining interferon alfa and lamivudine,[16-18] and the role of such combinations in the treatment of chronic hepatitis B requires further clarification.

Peginterferon alfa-2a, created by attaching a large, branched, 40-kD polyethylene glycol molecule to interferon alfa-2a,[19] has better pharmacokinetics than conventional interferon alfa.[20] This allows for convenient once-weekly dosing, with effective serum levels maintained throughout the dosing interval.[20] Peginterferon alfa-2a, like conventional interferon alfa, has a dual immunomodulatory and antiviral mode of action but has yielded superior clinical outcomes in patients with chronic hepatitis C[21] and patients with HBeAg-positive chronic hepatitis B.[22] The current study was designed to assess the efficacy and safety of three regimens in patients with HBeAg-negative 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 54 sites in 13 countries, principally in Asia and Europe. 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, which comprised 48 weeks of treatment followed by 24 weeks of follow-up, was conducted according to the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. All patients gave written informed consent.

The study was designed by the sponsor (Roche) in collaboration with expert hepatologists. Clinical data were collected by the Peginterferon Alfa-2a HBeAg-Negative 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 were actively involved in the analysis and interpretation of the data and the drafting of the manuscript. All authors approved the final manuscript.

PATIENTS

Adult patients were eligible if they had been negative for HBeAg and positive for anti-HBe antibody and hepatitis B surface antigen (HBsAg) for at least six months, had an HBV DNA level of more than 100,000 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 24 months consistent with the presence of chronic hepatitis B, with evidence of prominent necroinflammatory activity (as assessed by a local pathologist). Exclusion criteria included decompensated liver disease, a coexisting serious medical or psychiatric illness, a neutrophil count of less than 1500 per cubic millimeter, a platelet 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 en-

try, treatment for chronic hepatitis B within the previous six months, and coinfection with hepatitis C virus (HCV) or hepatitis D virus or human immunodeficiency virus.

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 follow-up: the normalization of alanine aminotransferase levels and the suppression of HBV DNA levels to below 20,000 copies per milliliter. Alanine aminotransferase was measured at local laboratories in accordance with standard procedures. Serum HBV DNA was measured at one of three central laboratories with the use of the Cobas Amplicor HBV Monitor Test (Roche Diagnostics).

Secondary efficacy measures assessed after 24 weeks of follow-up included the proportion of patients with HBsAg loss, HBsAg seroconversion (defined by the loss of HBsAg and the presence of anti-HBs antibody), histologic response, and suppression of HBV DNA to below 400 copies per milliliter. A histologic response was defined as a reduction of at least two points in the modified Histologic 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).[23] Biopsy samples were scored by an independent histopathologist who was unaware of the timing of the biopsy or the patient's treatment assignment. Ranked assessments of necroinflammatory activity and fibrosis were also performed (and scored as improved, unchanged, or worse).

SAFETY ANALYSIS

Measures of safety included adverse events, hematologic measurements, clinical chemical measurements, and vital signs. Adverse events were 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 every four weeks during follow-up. Safety analyses included all randomized patients who received at least one dose of study medication and who underwent at least one safety assessment after baseline.

RESISTANCE ANALYSIS

At the end of treatment (week 48), HBV DNA was extracted from all available serum samples from patients in the two lamivudine groups. Mutations in the YMDD (tyrosine, methionine, aspartate, and aspartate) motif of the HBV polymerase gene were identified by means of the INNO-LiPA HBV DR assay (Innogenetics).[24]

STATISTICAL ANALYSIS

A sample size of 160 patients per treatment group provided the study with a statistical power of 80 percent at the 0.025 level of significance to detect a difference in response rates of 15 percent. The sample size was increased to 175 patients to allow for withdrawals. The goals of the study were considered to have been reached in the event of a significant result for either primary efficacy outcome. Therefore, a significance level of 0.025 was chosen for the two primary efficacy measures to maintain the overall significance level at 0.05. 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 their 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 values missing at week 72 were classified as having no response.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Of the 552 patients who underwent randomization, 537 were included in the analyses. Five patients randomly assigned to receive peginterferon alfa-2a monotherapy, seven assigned to peginterferon alfa-2a plus lamivudine, and three assigned to lamivudine monotherapy were excluded from analyses — six did not receive study medication, and all nine patients from a single center were ex-

cluded owing to irregularities in study conduct. Of the 537 patients included in the analyses, 26 receiving lamivudine, 17 receiving peginterferon alfa-2a plus lamivudine, and 12 receiving peginterferon alfa-2a monotherapy either did not complete treatment or did not enter or complete follow-up. Baseline demographic and other characteristics were similar among the three treatment groups (Table 1).

BIOCHEMICAL RESPONSE

At the end of treatment (week 48), the proportion of patients with normalized alanine aminotransferase levels was highest with lamivudine monotherapy (Table 2). After 24 weeks of follow-up (week 72), the percentage of patients with normalized alanine aminotransferase levels was significantly higher with peginterferon alfa-2a monotherapy (59 percent) and peginterferon alfa-2a plus lamivudine (60 percent) than with lamivudine monotherapy (44 percent; P=0.004 and P=0.003, respectively) (Table 2 and Fig. 1A). The patterns of alanine aminotransferase levels throughout the study are shown in Figure 2A.

During therapy, marked elevations in alanine aminotransferase (more than 10 times the upper limit of the normal range, or more than 300 IU per liter) were observed in a significantly higher percentage of patients receiving peginterferon alfa-2a

Table 1. Baseline Characteristics of the Patients.

Characteristic	Peginterferon Alfa-2a plus Placebo (N=177)	Peginterferon Alfa-2a plus Lamivudine (N=179)	Lamivudine (N=181)
Male sex — no. (%)	151 (85)	147 (82)	156 (86)
Race — no. (%)*			
White	66 (37)	65 (36)	69 (38)
Asian	107 (60)	111 (62)	111 (61)
Black	3 (2)	2 (1)	0
Other	1 (1)	1 (1)	1 (1)
Age — yr			
Mean ±SD	40±11.7	41±10.8	40±11.1
Median	41	40	40
Range	18–71	18–70	18–66
Weight — kg			
Mean ±SD	71±12.5	70±13.0	71±12.1
Median	70	68	70.5
Range	47–119	41–114	48–109
Alanine aminotransferase — IU/liter†			
Mean ±SD	94.4±85.9	90.8±76.2	105.7±128.2
Median	61.5	64.2	71.6
Range	10.2–507.8	11.3–513.8	9.8–1050.9
HBV DNA — log copies/ml			
Mean ±SD	7.14±1.84	7.35±2.00	7.24±1.78
Median	6.99	7.19	6.97
Range	2.3–13.1	2.7–16.9	2.8–13.0
Bridging fibrosis or cirrhosis — no. (%)‡	54 (31)	40 (22)	53 (29)
Prior use of lamivudine — no. (%)	7 (4)	15 (8)	9 (5)
Prior use of interferon alfa — no. (%)	11 (6)	18 (10)	14 (8)

* Race 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.

Table 2. Rates of Biochemical, Virologic, and Histologic Response.*

Response	End of Treatment (Week 48)			End of Follow-up (Week 72)		
	Peginterferon Alfa-2a plus Placebo (N=177)	Peginterferon Alfa-2a plus Lamivudine (N=179)	Lamivudine (N=181)	Peginterferon Alfa-2a plus Placebo (N=177)	Peginterferon Alfa-2a plus Lamivudine (N=179)	Lamivudine (N=181)
Biochemical response						
Normalization of alanine aminotransferase†						
No. of patients — %	67 (38)	87 (49)	132 (73)	105 (59)	107 (60)	80 (44)
95% CI — %	30.7 to 45.4	41.1 to 56.2	65.8 to 79.3	51.7 to 66.6	52.2 to 67.0	36.8 to 51.8
P value				0.004	0.003	
Odds ratio — 95% CI‡				1.9 (1.2 to 2.8)	1.9 (1.2 to 2.9)	
Virologic response						
HBV DNA <20,000 copies/ml§						
No. of patients — %	144 (81)	164 (92)	154 (85)	76 (43)	79 (44)	53 (29)
95% CI — %	74.8 to 86.8	86.6 to 95.2	79.0 to 89.9	35.5 to 50.6	36.7 to 51.7	22.8 to 36.5
P value				0.007	0.003	
Odds ratio — 95% CI‡				1.8 (1.2 to 2.9)	1.9 (1.2 to 3.0)	
HBV DNA <400 copies/ml						
No. of patients — %	112 (63)	156 (87)	133 (73)	34 (19)	35 (20)	12 (7)
95% CI — %	55.7 to 70.4	81.3 to 91.7	66.4 to 79.8	13.7 to 25.8	14.0 to 26.1	3.5 to 11.3
P value				<0.001	<0.001	
Change in HBV DNA						
Total no. of patients	166	165	174	165	170	154
Mean log copies/ml	−4.1	−5.0	−4.2	−2.3	−2.4	−1.6
95% CI — log copies/ml	−3.8 to −4.5	−4.7 to −5.3	−3.9 to −4.5	−1.9 to −2.7	−1.9 to −2.8	−1.2 to −2.0
Combined response						
Normalization of alanine aminotransferase and HBV DNA <20,000 copies/ml						
No. of patients — %	63 (36)	87 (49)	125 (69)	63 (36)	68 (38)	42 (23)
95% CI — %	28.6 to 43.1	41.1 to 56.2	61.8 to 75.7	28.6 to 43.1	30.9 to 45.5	17.3 to 30.0
P value				0.011	0.002	

monotherapy (12 percent) than peginterferon alfa-2a plus lamivudine (4 percent) or lamivudine monotherapy (6 percent; P=0.007 and P=0.038, respectively). In contrast, the percentage of patients with marked elevations in alanine aminotransferase levels after therapy was significantly higher with lamivudine monotherapy (14 percent) or peginterferon alfa-2a plus lamivudine (15 percent) than with peginterferon alfa-2a monotherapy (7 percent; P=0.03 and P=0.02, respectively). There was a significant association between a marked elevation in alanine aminotransferase during therapy and normalization of alanine aminotransferase levels at week 72 (P=0.01).

VIROLOGIC RESPONSE

At week 48, the percentage of patients with HBV DNA levels below 20,000 copies per milliliter was highest with the combination regimen (Table 2). At week 72, suppression of HBV DNA levels to below 20,000 copies per milliliter occurred in a significantly higher percentage of patients receiving peginterferon alfa-2a monotherapy (43 percent) or peginterferon alfa-2a plus lamivudine (44 percent) than lamivudine monotherapy (29 percent; P=0.007 and P=0.003, respectively) (Table 2 and Fig. 1B). Rates of suppression of HBV DNA to below 400 copies per milliliter at week 72 were 19 percent with peginterferon alfa-2a monotherapy, 20 percent with peginterferon alfa-2a plus lamivudine, and 7 percent with lamivudine alone (P<0.001 for both comparisons with lamivudine alone).

After 48 weeks, the extent of suppression of HBV DNA from baseline was greatest with peginterferon alfa-2a plus lamivudine (Table 2); the extent of HBV DNA suppression was similar with peginter-

Table 2. (Continued.)

Response	End of Treatment (Week 48)			End of Follow-up (Week 72)		
	Peginterferon Alfa-2a plus Placebo (N=177)	Peginterferon Alfa-2a plus Lamivudine (N=179)	Lamivudine (N=181)	Peginterferon Alfa-2a plus Placebo (N=177)	Peginterferon Alfa-2a plus Lamivudine (N=179)	Lamivudine (N=181)
Normalization of alanine aminotransferase and HBV DNA <400 copies/ml						
No. of patients — %	47 (27)	82 (46)	109 (60)	26 (15)	29 (16)	11 (6)
95% CI — %	20.2 to 33.7	38.4 to 53.4	52.7 to 67.4	9.8 to 20.8	11.1 to 22.4	3.1 to 10.6
P value				0.007	0.003	
Histologic response¶						
No. of patients‖				177	179	181
Improved — no. of patients (%)				85 (48)	68 (38)	72 (40)
95% CI — %				40.5 to 55.6	30.9 to 45.5	32.6 to 47.3
No. of patients with paired biopsy samples**				143	143	125
Improved — no. of patients (%)				85 (59)	68 (48)	72 (58)
95% CI — %				50.9 to 67.6	39.1 to 56.1	48.4 to 66.4
Ranked assessments of histologic response††						
Necroinflammatory activity						
Total no. of patients				143	143	125
Improved — no. of patients (%)				79 (55)	66 (46)	57 (46)
Worse — no. of patients (%)				16 (11)	23 (16)	21 (17)
Fibrosis						
Total no. of patients				143	143	125
Improved — no. of patients (%)				21 (15)	18 (13)	22 (18)
Worse — no. of patients (%)				11 (8)	15 (10)	6 (5)

* All P values are from the Cochran–Mantel–Haenszel test for the pairwise comparison of each peginterferon alfa-2a group with the lamivudine monotherapy group at week 72. CI denotes confidence interval.
† P=0.003 for the overall test of treatment effect.
‡ Odds ratios are given with 95 percent confidence intervals only for the two primary efficacy outcomes.
§ P=0.005 for the overall test of treatment effect.
¶ Histologic response was defined as a reduction of at least two points in the modified Histologic Activity Index score, as compared with the pretreatment score, according to criteria of Ishak et al.[23]
‖ Patients without paired biopsy samples were classified as having no response. P=0.144 for the overall test of treatment effect.
** Patients without paired biopsy samples were excluded. P=0.101 for the overall test of treatment effect.
†† Ranked assessments included patients with assessable liver-biopsy specimens at baseline and at week 72. "Improved" and "worse" were defined as a reduction of at least two points and an increase of at least two points in the modified Histologic Activity Index score, respectively.

feron alfa-2a monotherapy and lamivudine monotherapy. The patterns of HBV DNA levels throughout the study are shown in Figure 2B.

HBsAg RESPONSE

At week 72, HBsAg loss occurred in seven patients receiving peginterferon alfa-2a monotherapy (five Asian and two white patients) and in five receiving peginterferon alfa-2a plus lamivudine (four and one, respectively). HBsAg seroconversion (defined by the loss of HBsAg and the presence of anti-HBs antibody) occurred in five patients receiving peginterferon alfa-2a monotherapy and three receiving the combination regimen. At week 72, HBsAg loss or seroconversion was not identified in any patients receiving lamivudine monotherapy. Differences in HBsAg loss and seroconversion between peginterferon alfa-2a monotherapy and lamivudine monotherapy were significant (P=0.007 and P=0.029, respectively, 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 histo-

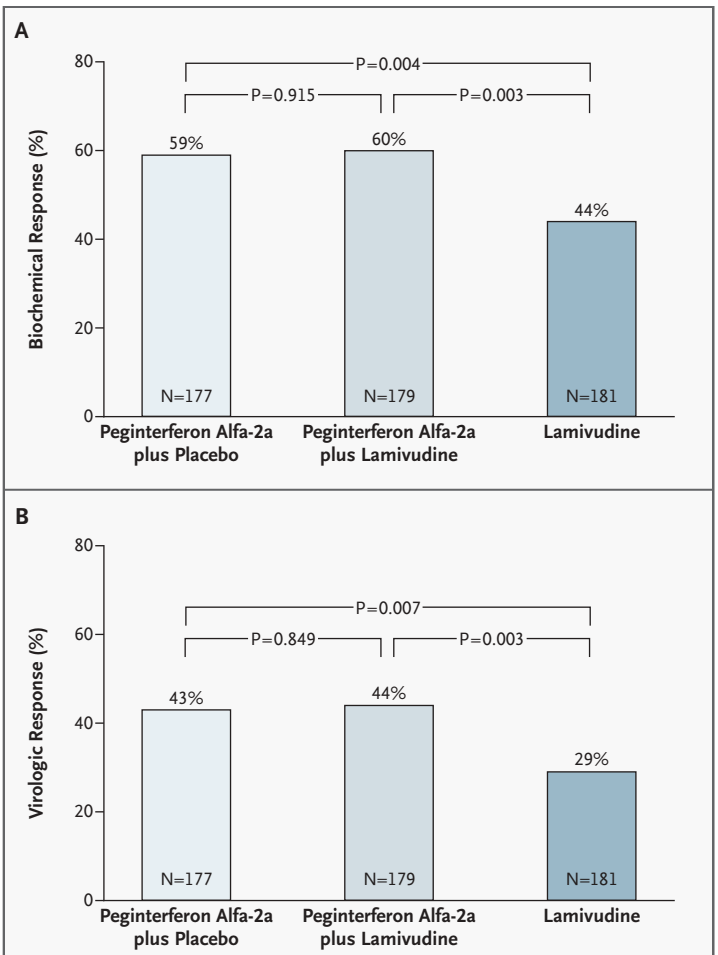


Figure 1. Rates of Biochemical Response (Panel A) and Virologic Response (Panel B) after 24 Weeks of Follow-up.

A biochemical response was defined as the normalization of alanine aminotransferase levels. A virologic response was defined as an HBV DNA level of less than 20,000 copies per milliliter. Differences were assessed by means of the Cochran–Mantel–Haenszel test, stratified according to geographic region and pretreatment alanine aminotransferase level. The number of patients in each group is shown in each bar, and the percentage of patients with a response in each group is shown above each bar.

logic activity and either a biochemical or virologic response at week 72, regardless of the treatment group (P<0.001). A histologic response occurred in 151 of 292 patients with a biochemical response (52 percent), as compared with 70 of 245 patients without a biochemical response (29 percent). A histologic response was seen in 116 of 208 patients with a virologic response (56 percent), as compared with 105 of 329 patients without a virologic response (32 percent).

RESISTANCE

At week 48, YMDD mutations were detected in 32 of 179 patients receiving lamivudine monotherapy (18 percent) and 1 of 173 patients receiving peginterferon alfa-2a plus lamivudine (1 percent, P<0.001 by Fisher's exact test).

SAFETY

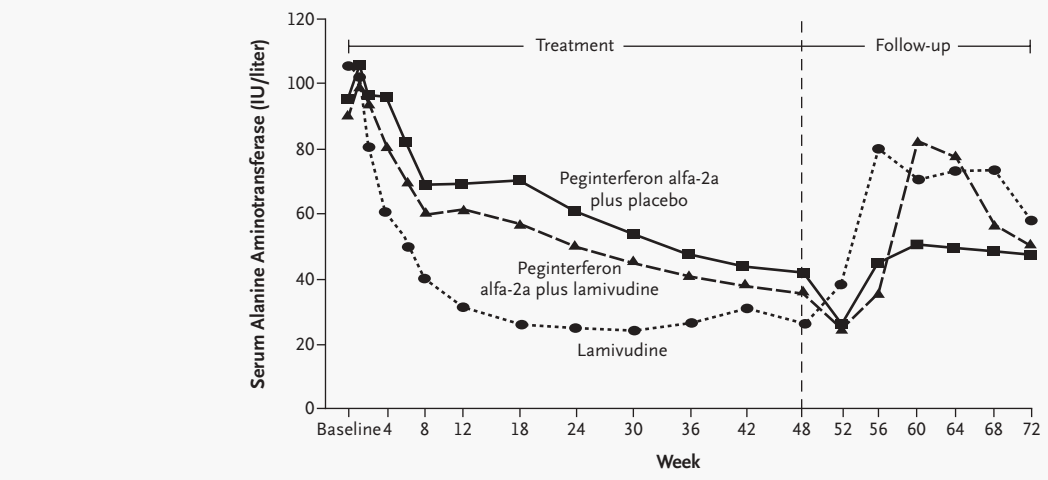
The rate of withdrawal from therapy was low in all three groups (Table 3). The rates of adverse events were similar in the peginterferon alfa-2a and combination-therapy groups but were significantly less frequent in the lamivudine group. The most common adverse events were those known to occur with conventional interferon alfa therapy, including pyrexia, fatigue, myalgia, and headache (Table 3). Depression was infrequent during the study and was reported by six patients (3 percent) receiving peginterferon alfa-2a monotherapy, eight patients (4 percent) receiving peginterferon alfa-2a plus lamivudine, and two patients (1 percent) receiving lamivudine monotherapy.

Twenty-six patients had a total of 27 serious adverse events: 9 (5 percent) patients receiving peginterferon alfa-2a monotherapy, 12 patients (7 percent) receiving peginterferon alfa-2a plus lamivudine, and 5 patients (3 percent) receiving lamivudine monotherapy (Table 3). Nine patients had serious infections; however, the incidence was similar in each treatment group (1 to 2 percent). There were two cases of serious thyroid disorders in the peginterferon alfa-2a group. All other serious adverse events were single cases in a variety of body systems. Hepatic decompensation was not reported in any patient during the study period, even though 27 percent of patients had bridging fibrosis or cirrhosis on pretreatment liver biopsy.

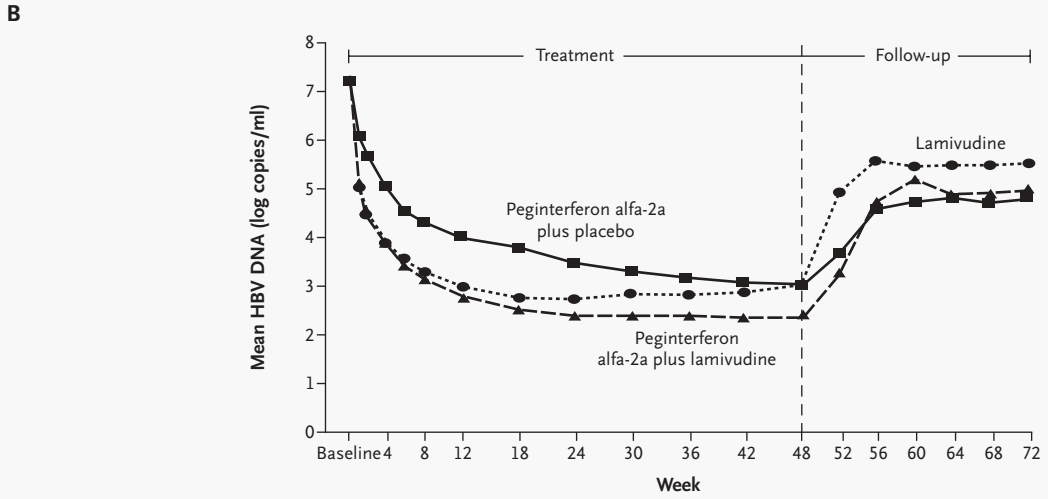
Mean neutrophil and platelet counts were reduced during treatment with peginterferon alfa-2a monotherapy and peginterferon alfa-2a plus lamivudine, yet returned to baseline levels shortly after treatment was stopped. Neutropenia and thrombocytopenia were the most common reasons for dose modification (Table 3).

DISCUSSION

We found that peginterferon alfa-2a alone or in combination with lamivudine resulted in higher rates of sustained response among patients with HBeAg-negative chronic hepatitis B than did lamivudine monotherapy, as reflected by the normaliza-



No. of patients																
Peginterferon alfa-2a plus placebo	177	176	176	175	176	175	173	173	167	167	167	161	164	160	147	167
Peginterferon alfa-2a plus lamivudine	179	174	176	176	175	174	172	171	171	166	169	164	168	167	153	171
Lamivudine	181	181	181	181	181	180	180	178	176	173	164	160	160	154	147	156



No. of patients																
Peginterferon alfa-2a plus placebo	177	175	174	176	176	174	174	170	164	166	165	158	162	158	145	165
Peginterferon alfa-2a plus lamivudine	179	174	176	176	175	173	171	170	168	165	169	161	163	164	152	170
Lamivudine	181	179	181	180	180	180	179	178	177	174	162	159	160	150	146	154

Figure 2. Mean Serum Alanine Aminotransferase Levels (Panel A) and HBV DNA Levels (Panel B) during the 72-Week Study Period.

tion of alanine aminotransferase levels, suppression of HBV DNA, and the loss or seroconversion of HBsAg. Previous studies have suggested that low levels of viremia may be compatible with the presence of minimally active hepatitis B.[12,25,26] In this study, over 40 percent of patients receiving peginterferon alfa-2a had HBV DNA levels below 20,000 copies per milliliter after 24 weeks of follow-up. This sustained suppression of HBV DNA (perhaps in combination with normalized alanine aminotransferase levels) might reduce the risk of end-stage liver disease or hepatocellular carcinoma. Longer follow-up is necessary to clarify the long-term benefits of peginterferon alfa-2a therapy.

Table 3. Incidence of Discontinuation of Treatment, Dose Modification, and Adverse Events.*

Variable	Peginterferon Alfa-2a plus Placebo (N=177)	Peginterferon Alfa-2a plus Lamivudine (N=179)	Lamivudine (N=181)
	number of patients (percent)		
Discontinuation			
For safety reasons†	13 (7)	7 (4)	0
For other reasons‡	2 (1)	3 (2)	4 (2)
Dose modification§			
Total	83 (47)	86 (48)	—
Adverse event	13 (7)	23 (13)	—
Laboratory abnormality	65 (37)	64 (36)	—
Alanine aminotransferase elevation	15 (8)	6 (3)	—
Neutropenia	30 (17)	44 (25)	—
Thrombocytopenia	34 (19)	22 (12)	—
Adverse events			
≥1 Reported serious adverse event¶	9 (5)	12 (7)	5 (3)
Death	1 (1)‖	0	0
≥1 Reported adverse event†	155 (88)	155 (87)	86 (48)
Most common adverse events**			
Pyrexia	105 (59)	98 (55)	8 (4)
Fatigue	74 (42)	75 (42)	33 (18)
Myalgia	47 (27)	49 (27)	11 (6)
Headache	42 (24)	34 (19)	14 (8)
Decreased appetite	31 (18)	26 (15)	6 (3)
Arthralgia	27 (15)	27 (15)	6 (3)
Alopecia	24 (14)	20 (11)	1 (1)
Diarrhea	20 (11)	10 (6)	5 (3)
Dizziness	15 (8)	12 (7)	8 (4)
Insomnia	15 (8)	15 (8)	5 (3)
Nausea	14 (8)	13 (7)	9 (5)
Irritability	12 (7)	8 (4)	4 (2)
Sore throat	11 (6)	5 (3)	8 (4)
Rigors	10 (6)	5 (3)	0
Injection-site reaction	10 (6)	21 (12)	0
Cough	10 (6)	5 (3)	2 (1)
Upper respiratory tract infection	9 (5)	4 (2)	7 (4)
Pruritus	9 (5)	11 (6)	4 (2)
Upper abdominal pain	9 (5)	12 (7)	14 (8)
Back pain	4 (2)	11 (6)	6 (3)

* Values are based on all randomized patients who received at least one dose of study medication and who underwent at least one safety assessment after baseline.
† $P<0.001$ for the overall test of treatment effect.
‡ $P=0.913$ for the overall test of treatment effect.
§ Some patients who required a dose modification had both an adverse event and a laboratory abnormality.
¶ A serious adverse event was one that presented a clinically significant hazard or resulted in a contraindication or side effect.
‖ Thrombotic thrombocytopenic purpura developed in this patient.
** Patients may have had more than one adverse event. The adverse events listed are those reported by at least 5 percent of patients in one of the peginterferon alfa-2a groups up to eight weeks after therapy.

In patients with HBeAg-positive chronic hepatitis B, alanine aminotransferase flares during therapy with interferon alfa have been indicated as a significant predictor of response.[27] However, this association is less clear in patients with HBeAg-negative chronic hepatitis B. The identification of a significant association between alanine aminotransferase flares during treatment and response in this study indicate that alanine aminotransferase flares may also be predictive of response in these patients.

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.[6,12,28] In this study, HBsAg loss was identified in 12 patients receiving peginterferon alfa-2a alone or in combination with lamivudine, 8 of whom underwent HBsAg seroconversion by the end of 24 weeks of follow-up, as compared with none receiving lamivudine alone. This observation concurs with those of previous studies showing that interferon alfa therapy is associated with an HBsAg response in patients with HBeAg-negative chronic hepatitis B.[29] However, the HBsAg response elicited by conventional interferon alfa tends to occur later than that observed with peginterferon alfa-2a in this study.[7,10,28] HBsAg loss or seroconversion was not reported in several clinical trials of lamivudine or adefovir in patients with HBeAg-negative chronic hepatitis B.[8,9,15,30] These results illustrate the importance of the dual immunomodulatory and antiviral effects of interferon-based therapies in the treatment of HBeAg-negative chronic hepatitis B.

No significant differences in efficacy were observed between the peginterferon alfa-2a monotherapy and combination groups after 24 weeks of follow-up. This finding extends those of other recent studies. For example, Santantonio and coworkers showed that adding conventional interferon alfa to lamivudine therapy did not increase response rates in patients with HBeAg-negative chronic hepatitis B when assessed 24 weeks after the end of treatment.[18] Similarly, recent preliminary data have suggested that after 24 weeks of follow-up, the combination of peginterferon alfa-2b and lamivudine is no more effective than peginterferon alfa-2b monotherapy in patients with HBeAg-positive chronic hepatitis B.[31]

Significantly fewer patients receiving combination therapy than lamivudine monotherapy had YMDD mutations at the end of treatment. This difference indicates that a more profound HBV DNA suppression, as seen during treatment with peginterferon alfa-2a in combination with lamivudine, may lead to a lower incidence of lamivudine resistance. This finding concurs with general theories on the development of antiviral drug resistance and confirms data reported in other studies of HBV.[32] Longer follow-up of patients in this study may clarify any additional benefits of combination therapy in the treatment of chronic hepatitis B.

The tolerability and safety profiles of peginterferon alfa-2a alone and in combination with lamivudine were satisfactory, and there were no unexpected adverse effects. Moreover, the addition of lamivudine did not substantially alter the safety profile of peginterferon alfa-2a. The safety profile of peginterferon alfa-2a also compares favorably with the profiles described in previous studies of conventional interferon alfa in patients with HBeAg-negative chronic hepatitis B.[7,33] It is noteworthy that no patient, including those with bridging fibrosis or cirrhosis, had hepatic decompensation during either treatment or follow-up.

The incidence of depression with peginterferon alfa-2a in this study (3 to 4 percent) was lower than previously observed among patients with chronic hepatitis C (16 to 20 percent).[21,34] This finding concurs with previous data showing that the rate of depression is lower among patients with chronic hepatitis B than among patients with chronic hepatitis C, both at baseline and during interferon alfa therapy.[35] The reasons for this remain unclear; however, virus-specific factors (e.g., HCV infection of the central nervous system) and host-susceptibility factors (e.g., the patient population and the presence of preexisting psychiatric disorders) may influence the rates of depression.[35,36]

The results of this large, multinational study demonstrate that peginterferon alfa-2a offers significantly improved efficacy over lamivudine in the treatment of HBeAg-negative chronic hepatitis B. The ability of this agent to improve and sustain biochemical, virologic, and HBsAg response rates constitutes a therapeutic advance over current treatments, which are associated with poor rates of sustained response after the cessation of therapy. Our data demonstrate the possibility of achieving HBsAg loss or seroconversion in patients with HBeAg-negative chronic hepatitis B with the use of peginterferon alfa-2a and therefore support the use of this agent as a first-line therapy for HBeAg-negative chronic hepatitis B.

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APPENDIX

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