

## ORIGINAL ARTICLE

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

George K.K. Lau, M.D., Teerha Piratvisuth, M.D., Kang Xian Luo, M.D., Patrick Marcellin, M.D., Satawat Thongsawat, M.D., Graham Cooksley, M.D., Edward Gane, M.D., Michael W. Fried, M.D., Wan Cheng Chow, M.D., Seung Woon Paik, M.D., Wen Yu Chang, M.D., Thomas Berg, M.D., Robert Flisiak, M.D., Philip McCloud, Ph.D., and Nigel Pluck, M.D., for the Peginterferon Alfa-2a HBeAg-Positive Chronic Hepatitis B Study Group\*

## ABSTRACT

From the Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong SAR, China (G.K.K.L.); the Department of Medicine, Songklanakarin Hospital, Songkla, Thailand (T.P.); the Department of Infectious Diseases, Nangfang Hospital, Guangzhou, China (K.X.L.); the Service d'Hépatologie, INSERM Unité 481, and Centre de Recherches Claude Bernard sur les Hépatites Virales, Hôpital Beaujon, Clichy, France (P. Marcellin); the Department of Internal Medicine, Chiang Mai University, Chiang Mai, Thailand (S.T.); the Clinical Research Department, Royal Brisbane Hospital, Herston, Australia (G.C.); the Gastroenterology Department, Middlemore Hospital, Otahuhu, New Zealand (E.G.); the University of North Carolina Liver Program, University of North Carolina, Chapel Hill (M.W.F.); the Gastroenterology Department, Singapore General Hospital, Singapore (W.C.C.); the Division of Gastroenterology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea (S.W.P.); the Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan (W.Y.C.); Medizinische Klinik mit Schwerpunkt Hepatologie und Gastroenterologie, Charité, Universitätsmedizin Berlin, Campus Virchow-Klinikum, Berlin (T.B.); the Department of Infectious Diseases, Medical University of Białystok, Białystok, Poland (R.F.); Roche, Dee Why, Australia (P. McCloud); and Roche, Welwyn, United Kingdom (N.P.). Address reprint requests to Dr. Lau at Rm. 1838, Block K, Queen Mary Hospital, University of Hong Kong, Hong Kong SAR, China, or at gkklau@netvigator.com.

\*Other members of the Peginterferon Alfa-2a HBeAg-Positive Chronic Hepatitis B Study Group are listed in the Appendix.

N Engl J Med 2005;352:2682-95.

Copyright © 2005 Massachusetts Medical Society.

**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.

**M**ORE THAN 400 MILLION PEOPLE worldwide are chronically infected with hepatitis B virus (HBV).<sup>1</sup> 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.<sup>2-5</sup> 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,<sup>6,7</sup> are generally low with these agents.<sup>8-10</sup> Lamivudine and to a lesser extent adefovir are also associated with drug resistance,<sup>8,9,11,12</sup> which increases with prolonged use.<sup>12,13</sup> 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.<sup>5</sup> Conflicting data on the benefits of combining interferon-based therapies and lamivudine<sup>11,14,15</sup> 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,<sup>16</sup> has better pharmacokinetics than conventional interferon alfa. This allows for once-weekly dosing, with effective serum concentrations maintained throughout the dosing interval.<sup>17</sup> 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.<sup>18</sup>

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, Glaxo-SmithKline) 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<sup>19</sup> 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).<sup>20</sup> 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).

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)
<b>HBeAg response</b>						
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	
<b>Virologic response</b>						
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
<b>Biochemical response</b>						
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 peri-

od 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)
<b>Combined response</b>						
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	
<b>Histologic response¶</b>						
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).<sup>19</sup>

|| 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.

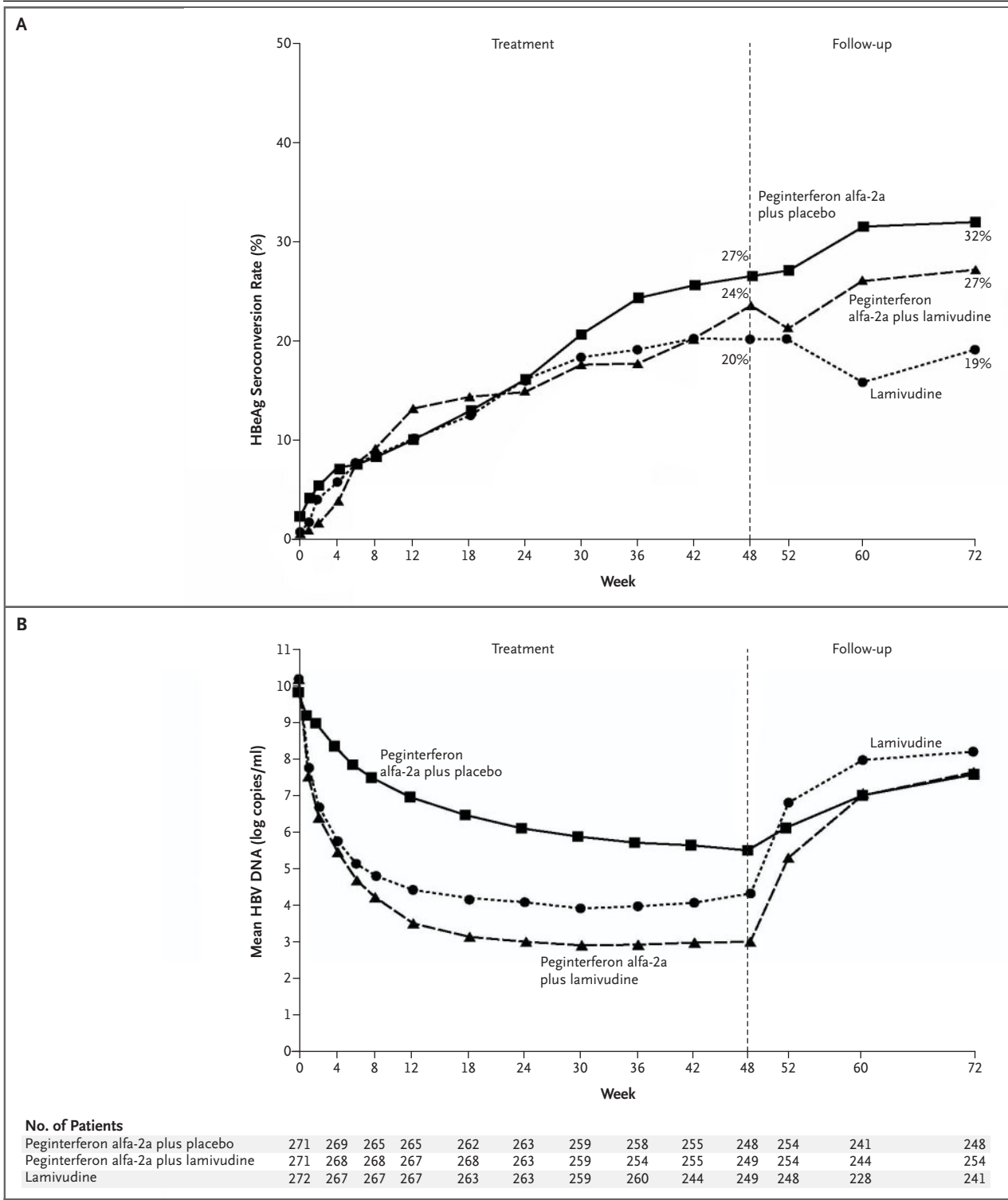
therapy (14 of 64 patients, or 22 percent) than with lamivudine monotherapy (23 of 55 patients, or 42 percent; P=0.005 and P=0.03, respectively, by Fisher's exact test). After 24 weeks of follow-up (week 72), the percentage of patients with HBeAg seroconversion was significantly higher with peginterferon 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



**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

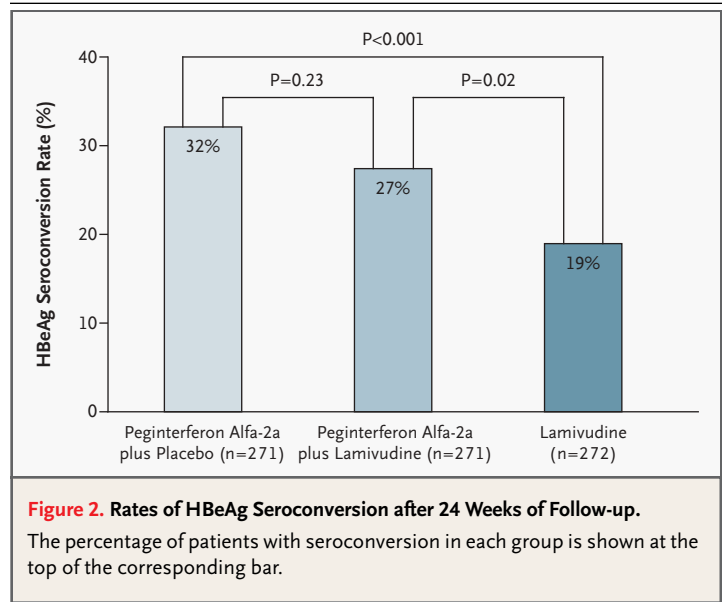
At week 72, HBsAg seroconversion was identified in eight patients receiving peginterferon alfa-2a monotherapy (three Asian and five white patients, five with HBV genotype A and three with genotype C) and in eight receiving peginterferon alfa-2a plus lamivudine (five Asian and three white patients; two 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 HBsAg 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 HBsAg seroconversion as compared with 174 of 427 patients (41 percent) who did not have HBsAg 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 HBsAg seroconversion in these patients at week 72



were 43 percent, 38 percent, and 25 percent, respectively (Table 3).

#### 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
	<i>no. of patients achieving HBeAg seroconversion/total no. of patients (%)</i>		
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.<sup>6,7</sup>

In this study of patients, predominantly of Asian origin, who had previously been considered to have difficult-to-treat chronic hepatitis B,<sup>21</sup> 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,<sup>22</sup> 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 hep-

atitis B, as it is in chronic hepatitis C. Responses to nucleoside or nucleotide analogues are generally consistent among all genotypes,<sup>23,24</sup> 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.<sup>25</sup> The results of our study indicate that HBeAg seroconversion was generally consistent across all genotypes. However, a recent study of peginterferon alfa-2b<sup>26</sup> 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.<sup>8,10,27</sup> 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.<sup>28,29</sup>

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.<sup>2,4,5,30</sup> 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)
	<i>number of patients (percent)</i>		
<b>Discontinuation</b>			
For safety reasons†	8 (3)	12 (4)	2 (1)
For other reasons‡	9 (3)	6 (2)	12 (4)
<b>Dose modification§</b>			
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)	—
<b>Adverse events</b>			
≥1 Reported serious adverse event (weeks 0 to 56)¶	12 (4)	16 (6)	5 (2)
<b>Deaths</b>			
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<sup>31-33</sup> and white<sup>7,30</sup> 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.<sup>29</sup> 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.<sup>29</sup> 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.<sup>11,18</sup> As anti-

ated, 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).<sup>34,35</sup> This finding concurs with data from a recent study of peginterferon alfa-2a in HBeAg-negative chronic hepatitis B.<sup>29</sup>

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)
	<i>number of patients (percent)</i>		
<b>Adverse events (continued)</b>			
Most common adverse events (weeks 0 to 56) <sup>‡‡</sup>			
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.

Supported by a research grant from Roche, Basel, Switzerland.

Drs. McCloud and Pluck are employees of Roche. Drs. Lau and Piratvisuth are consultants and lecturers for Roche. Dr. Marcellin reports having served as a consultant and lecturer for Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Gilead Sciences, Roche, Schering-Plough, Valeant Pharmaceuticals, and Vertex Pharmaceuticals and as a consultant for Novartis. Dr. Cooksley reports having served as a consultant and lecturer for Roche and having received grant support from Bristol-Myers Squibb, GlaxoSmithKline, Gilead Sciences,

Roche, and Schering-Plough. Dr. Gane reports having served as a consultant for Roche and as a lecturer for GlaxoSmithKline. Dr. Fried reports having received research grant support from Roche and partial funding from the University of North Carolina General Clinical Research Center (RR000046) and having served as a consultant and lecturer for Roche and as a member of the advisory board for Idenix Pharmaceuticals.

We are indebted to Drs. Friederike Zahm and Matei Popescu (Roche, Basel, Switzerland), to Ms. Julie-Ann Quayle and Mr. Balu Ramakrishnan (Roche, Dee Why, Australia), and to Ms. Sally Ellis (Roche, United Kingdom), for their critical analysis of the study data; and to Professor Yun-Fan Liaw (Chang Gung Memorial Hospital and University, Taipei, Taiwan) for his critical review of the article.

### APPENDIX

In addition to the authors, the Peginterferon Alfa-2a HBeAg-Positive Chronic Hepatitis B Study Group includes the following persons: V. Balan (Mayo Clinic, Scottsdale, Ariz.); Y. Baruch (Rambam Medical Center, Haifa, Israel); N. Boyer (Hôpital Beaujon, Clichy, France); T. Box (Mountain West Gastroenterology, Salt Lake City); K. Burak (Heritage Medical Research Clinic, Calgary, Alta., Canada); Y.-C. Chao (Tri-Serice General Hospital, Taipei, Taiwan); H. Cheinquer (Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil); K.-W. Chung (Catholic University of Korea, St. Mary's Hospital, Seoul, Republic of Korea); Y.-H. Chung (Ulsan University College of Medicine, Asan Medical Centre, Seoul, Republic of Korea); A. Chutaputti (Pramongkutklao Hospital, Bangkok, Thailand); K. Fawaz (New England Medical Center Hospital, Boston); V. Feinman (Mount Sinai Hospital, Toronto); N. Girgrah (University Health Network, Toronto Hospital-General Division, Toronto); R. Gish (California Pacific Medical Center, San Francisco); N. Gitlin (Atlanta Gastroenterology Associates, Crawford Long Hospital and Medical Tower, Atlanta); T. Goeser (University of Cologne, Cologne, Germany); F. Gonçalves Jr. (Universidade Estadual de Campinas, Campinas, Brazil); R. Guan (Mount Elizabeth Medical Center, Singapore); D. Haeussinger (University of Düsseldorf, Düsseldorf, Germany); W. Halota (Medical Academy, Bydgoszcz, Poland); K.-H. Han (Yonsei University College of Medicine, Severance Hospital, Seoul, Republic of Korea); M. Heim (Canton Hospital of Basel, Basel, Switzerland); A. Horban (Hospital for Infectious Diseases, Warsaw, Poland); J.-D. Jia (Beijing Friendship Hospital, Liver Research Center, Beijing); R. Jin (Beijing You An Hospital, Beijing); M.-C. Jung (University Clinic, Grosshadern, Munich, Germany); M.-Y. Lai (National Taiwan University Hospital, Taipei, Taiwan); A. Lee (Concord Repatriation General Hospital, Concord, Australia); S.-D. Lee (Taipei Veterans General Hospital, Taipei, Taiwan); B.-J. Lei (First Affiliated Hospital, Western China Medical University, Chengdu, China); Y.-F. Liaw (Chang Gung Memorial Hospital and University, Taipei, Taiwan); A. Lok (University of Michigan Health System, Ann Arbor); Z.-M. Lu (Ruijin Hospital, Shanghai, China); P. Luengrojjanakul (Siriraj Hospital, Bangkok, Thailand); Y. Lurie (Tel Aviv Sourasky Medical Center, Tel Aviv, Israel); V. Mahachai (Chulalongkorn Hospital, Bangkok, Thailand); M. Manns (Medical School, Hanover, Germany); P. Martin (Cedars Sinai Medical Center, Los Angeles); R. Parana (Hospital Universitario Professor Edgard Santos, Bahia, Brazil); M. Pawlowska (Medical Academy, Bydgoszcz, Poland); W. Schmidt (University Clinic I, St. Josef Hospital, Bochum, Germany); H. Sette, Jr. (Instituto de Infectologia Emilio Ribas, São Paulo); C. Smith (Minnesota Clinical Research Center, St. Paul); C. Trepo (Hotel Dieu, Lyon, France); N. Tsai (St. Francis Medical Center, Honolulu); B. Tung (University of Washington, Seattle); R. Tur-Kaspa (Rabin Medical Center, Petah Tikva, Israel); M.-B. Wan (Changhai Hospital, Shanghai, China); Q.-H. Wang (First Affiliated Hospital of Peking University, Beijing); D.-Z. Xu (Beijing Ditan Hospital, Beijing); G.-B. Yao (Shanghai Jing An Central Hospital, Shanghai, China); J.-L. Yao (Third Affiliated Hospital of Sun Yat-Sen, Medical Science University, Guangzhou, Guangdong, China); Y.-K. Yin (Shanghai Huashan Hospital, Shanghai, China); Y. Yu (First Affiliated Hospital, College of Medical Science, Zhejiang University, Hangzhou, China); H.-F. Zhang (Beijing 302 Hospital, Beijing); Y.-R. Zhao (Second Affiliated Hospital, Chongqing Medical College, Chongqing, China).

### REFERENCES

- Lai CL, Ratzliff V, Yuen MF, Poynard T. Viral hepatitis B. *Lancet* 2003;362:2089-94.
- de Franchis R, Hadengue A, Lau G, et al. EASL International Consensus Conference on Hepatitis B, 13-14 September, 2002 Geneva, Switzerland: consensus statement (long version). *J Hepatol* 2003;39:Suppl 1: S3-S25.
- Liaw YF, Leung N, Guan R, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2005 update. *Liver Int* 2005;25:472-89.
- Lok AS, McMahon BJ. Chronic hepatitis B: update of recommendations. *Hepatology* 2004;39:857-61.
- Lok AS, McMahon BJ. AASLD practice guidelines 2003: chronic hepatitis B. (Accessed June 3, 2005, at [http://www.aasld.org/netFORUMAASLD/eweb/docs/chronic hep\\_B.pdf](http://www.aasld.org/netFORUMAASLD/eweb/docs/chronic hep_B.pdf)).
- Fattovich G, Rugge M, Brollo L, et al. Clinical, virologic and histologic outcome following seroconversion from HBeAg to anti-HBe in chronic hepatitis type B. *Hepatology* 1986;6:167-72.
- Niederer C, Heintges T, Lange S, et al. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *N Engl J Med* 1996;334:1422-7.
- Lai CL, Chien RN, Leung NW, et al. A one-year trial of lamivudine for chronic hepatitis B. *N Engl J Med* 1998;339:61-8.
- Dienstag JL, Schiff ER, Wright TL, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med* 1999;341:1256-63.
- Marcellin P, Chang TT, Lim SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003;348:808-16.
- Schalm SW, Heathcote J, Cianciara J, et al. Lamivudine and alpha interferon combination treatment of patients with chronic hepatitis B infection: a randomized trial. *Gut* 2000;46:562-8.
- Qi X, Snow A, Thibault V, et al. Long-term incidence of adefovir dipivoxil (ADV) resistance in chronic hepatitis B (CHB) patients after 144 weeks of therapy. *J Hepatol* 2004;40:Suppl 1:A57. abstract.
- Liaw YF. Results of lamivudine trials in Asia. *J Hepatol* 2003;39:Suppl 1:S111-S115.
- Barbaro G, Zechini F, Pellicelli AM, et al. Long-term efficacy of interferon alpha-2b and lamivudine in combination compared to lamivudine monotherapy in patients with chronic hepatitis B: an Italian multicenter, randomized trial. *J Hepatol* 2001;35:406-11.
- Santantonio T, Niro GA, Sinisi E, et al. Lamivudine/interferon combination therapy in anti-HBe positive chronic hepatitis B patients: a controlled pilot study. *J Hepatol* 2002;36:799-804.

16. Bailon P, Palleroni A, Schaffer CA, et al. Rational design of a potent, long-lasting form of interferon: a 40 kDa branched polyethylene glycol-conjugated interferon alpha-2a for the treatment of hepatitis C. *Bioconjug Chem* 2001;12:195-202.
17. Perry CM, Jarvis B. Peginterferon-alpha-2a (40 kD): a review of its use in the management of chronic hepatitis C. *Drugs* 2001;61:2263-88.
18. Cooksley WG, Piratvisuth T, Lee S-D, et al. Peginterferon  $\alpha$ -2a (40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. *J Viral Hepat* 2003;10:298-305.
19. Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. *J Hepatol* 1995;22:696-9.
20. Lok AS, Zoulim F, Locarnini S, et al. Monitoring drug resistance in chronic hepatitis B virus (HBV)-infected patients during lamivudine therapy: evaluation of performance of INNO-LiPA HBV DR assay. *J Clin Microbiol* 2002;40:3729-34.
21. Craxi A, Di Bona D, Cammà C. Interferon- $\alpha$  for HBeAg-positive chronic hepatitis B. *J Hepatol* 2003;39:S99-S105.
22. Liaw YF. Hepatitis flares and hepatitis B e antigen seroconversion: implication in anti-hepatitis B virus therapy. *J Gastroenterol Hepatol* 2003;18:246-52.
23. Yuen MF, Wong DK, Sablon E, et al. Hepatitis B virus genotypes B and C do not affect the antiviral response to lamivudine. *Antivir Ther* 2003;8:531-4.
24. Westland C, Delaney W IV, Yang H, et al. Hepatitis B virus genotypes and virologic response in 694 patients in phase III studies of adefovir dipivoxil. *Gastroenterology* 2003;125:107-16.
25. Kao JH. Hepatitis B viral genotypes: clinical relevance and molecular characteristics. *J Gastroenterol Hepatol* 2002;17:643-50.
26. Janssen HL, van Zonneveld M, Senturk H, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. *Lancet* 2005;365:123-9.
27. Perrillo RP, Schiff ER, Davis GL, et al. A randomized, controlled trial of interferon alfa-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. *N Engl J Med* 1990;323:295-301.
28. Richman DD. The impact of drug resistance on the effectiveness of chemotherapy for chronic hepatitis B. *Hepatology* 2000;32:866-7.
29. Marcellin P, Lau GKK, Bonino F, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2004;351:1206-17.
30. Fattovich G, Giustina G, Sanchez-Tapias J, et al. Delayed clearance of serum HBsAg in compensated cirrhosis B: relation to interferon alpha therapy and disease prognosis. *Am J Gastroenterol* 1998;93:896-900.
31. Lok AS, Lai CL, Wu PC, Leung EK. Long-term follow-up in a randomised controlled trial of recombinant alpha 2-interferon in Chinese patients with chronic hepatitis B infection. *Lancet* 1988;2:298-302.
32. Lok AS, Chung HT, Liu VW, Ma OC. Long-term follow-up of chronic hepatitis B patients treated with interferon alfa. *Gastroenterology* 1993;105:1833-8.
33. Tangkijvanich P, Thong-ngam D, Mahachai V, Kladchareon N, Suwangool P, Kullavanijaya P. Long-term effect of interferon therapy on incidence of cirrhosis and hepatocellular carcinoma in Thai patients with chronic hepatitis B. *Southeast Asian J Trop Med Public Health* 2001;32:452-8.
34. Zeuzem S, Feinman SV, Rasenack J, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med* 2000;343:1666-72.
35. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;347:975-82.

Copyright © 2005 Massachusetts Medical Society.

#### PHYSICIAN-JOURNALIST

The *Journal* is seeking a physician with substantial reporting experience to write occasional articles on timely topics in medicine and society for the Perspective section. Send curriculum vitae and writing samples to Perspective Editor, *New England Journal of Medicine*, 10 Shattuck St., Boston, MA 02115, or at [writer@nejm.org](mailto:writer@nejm.org).