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PEGINTERFERON ALFA-2a PLUS RIBAVIRIN FOR CHRONIC HEPATITIS C VIRUS INFECTION

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ABSTRACT

Background Treatment with peginterferon alfa-2a alone produces significantly higher sustained virologic responses than treatment with interferon alfa-2a alone in patients with chronic hepatitis C virus (HCV) infection. We compared the efficacy and safety of peginterferon alfa-2a plus ribavirin, interferon alfa-2b plus ribavirin, and peginterferon alfa-2a alone in the initial treatment of chronic hepatitis C.

Methods A total of 1121 patients were randomly assigned to treatment and received at least one dose of study medication, consisting of 180 μg of peginterferon alfa-2a once weekly plus daily ribavirin (1000 or 1200 mg, depending on body weight), weekly peginterferon alfa-2a plus daily placebo, or 3 million units of interferon alfa-2b thrice weekly plus daily ribavirin for 48 weeks.

Results A significantly higher proportion of patients who received peginterferon alfa-2a plus ribavirin had a sustained virologic response (defined as the absence of detectable HCV RNA 24 weeks after cessation of therapy) than of patients who received interferon alfa-2b plus ribavirin (56 percent vs. 44 percent, $P<0.001$) or peginterferon alfa-2a alone (56 percent vs. 29 percent, $P<0.001$). The proportions of patients with HCV genotype 1 who had sustained virologic responses were 46 percent, 36 percent, and 21 percent, respectively, for the three regimens. Among patients with HCV genotype 1 and high base-line levels of HCV RNA, the proportions of those with sustained virologic responses were 41 percent, 33 percent, and 13 percent, respectively. The overall safety profiles of the three treatment regimens were similar; the incidence of influenza-like symptoms and depression was lower in the groups receiving peginterferon alfa-2a than in the group receiving interferon alfa-2b plus ribavirin.

Conclusions In patients with chronic hepatitis C, once-weekly peginterferon alfa-2a plus ribavirin was tolerated as well as interferon alfa-2b plus ribavirin and produced significant improvements in the rate of sustained virologic response, as compared with interferon alfa-2b plus ribavirin or peginterferon alfa-2a alone. (N Engl J Med 2002;347:975-82.)

ALTHOUGH the mechanism of action of ribavirin remains speculative,[1] the current standard of care for patients with chronic hepatitis C is the addition of ribavirin to interferon-based therapies.[2-7] Unfortunately, some patients, particularly those with more resistant hepatitis C virus (HCV) genotypes, do not respond to these agents.

Two types of pegylated interferon, which differ in their pharmacokinetic and chemical properties, have been developed. Both have demonstrated significantly superior efficacy to non-pegylated interferons in several controlled clinical trials.[8-12] Peginterferon alfa-2b (a 12-kD linear polyethylene glycol moiety) plus ribavirin produced significantly improved sustained virologic responses as compared with interferon alfa-2b plus ribavirin.[13] Peginterferon alfa-2a (a 40-kD branched polyethylene glycol moiety) has an extended serum half-life that provides constant viral suppression for seven days, thus allowing once-weekly dosing and enhanced clinical efficacy.[8-10,14-17] We undertook the present study to determine whether peginterferon alfa-2a plus ribavirin is more effective than interferon alfa-2b plus ribavirin or peginterferon alfa-2a alone for the treatment of chronic hepatitis C.

METHODS

Patient Selection

The study was conducted by the Pegasys International Study Group. Eligible subjects were adult patients who had never received interferon and who had at least 2000 copies of HCV RNA per milliliter of serum according to a polymerase-chain-reaction (PCR) assay (Cobas Amplicor HCV Monitor Test, version 2.0; Roche Diagnostics), serum alanine aminotransferase activity above the upper limit of normal within six months before entry into the study, and a liver-biopsy result consistent with the diagnosis of chronic hepatitis C. Serum HCV RNA levels above the linear

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*Other participants in the study are listed in the Appendix.

range of the PCR (more than 1 million copies per milliliter) were diluted to within the linear range. Patients were excluded from participation if they had neutropenia (fewer than 1500 neutrophils per cubic millimeter), thrombocytopenia (fewer than 90,000 platelets per cubic millimeter), anemia (less than 12 g of hemoglobin per deciliter in women and less than 13 g of hemoglobin per deciliter in men), human immunodeficiency virus (HIV) infection, decompensated liver disease, a serum creatinine level more than 1.5 times the upper limit of normal, poorly controlled psychiatric disease, alcohol or drug dependence within one year before entry into the study, or substantial coexisting medical conditions.

Study Design

This randomized, controlled clinical trial was conducted at 81 centers worldwide from February 1999 to April 2001. Patients were randomly assigned in a 2:1:2 ratio (with a block size of five) to receive subcutaneous, once-weekly injections of 180 μg of peginterferon alfa-2a (Pegasys, Hoffmann–LaRoche) plus daily ribavirin (Hoffmann–LaRoche) or placebo, or subcutaneous, thrice-weekly injections of 3 million units of interferon alfa-2b plus ribavirin (Rebetron, Schering-Plough) for 48 weeks. Ribavirin was given orally at a dose of 1000 mg per day for patients weighing 75 kg or less and 1200 mg per day for those weighing more than 75 kg. Randomization was stratified according to country and HCV genotype (HCV genotype 1 vs. other genotypes). Genotyping was performed by sequence analysis of a portion of the 5′ untranslated region of the HCV genome.[18] Participants were followed for 24 weeks after cessation of therapy. The sponsor, investigators, and patients who received peginterferon alfa-2a were unaware of who received ribavirin or placebo.

The institutional review boards of the participating centers approved the protocol, and all patients provided written informed consent. The study was designed by the sponsor in collaboration with expert hepatologists. Data were collected by the Pegasys International Study Group. Data analysis was performed by the sponsor and the authors of this report; the authors had full access to the data, and the decision to publish was not limited by the sponsor. The study was conducted according to the guidelines of the Declaration of Helsinki, the applicable provisions of Good Clinical Practices, or both.

Assessment of Efficacy

The primary efficacy end point was sustained virologic response, defined as the absence of detectable HCV RNA at the end of follow-up according to a PCR assay (Cobas Amplicor HCV Test, version 2.0; lower limit of detection, 100 copies [50 IU] per milliliter). For patients with at least 20 weeks of follow-up, the last observed HCV RNA level was used in assessments of efficacy. All patients with follow-up of less than 20 weeks were considered to have had no response to treatment.

Assessment of Safety

Safety was assessed by laboratory tests and evaluation of adverse events at weeks 1, 2, 4, 6, and 8; monthly thereafter during treatment; and at weeks 52, 60, and 72. Patients who discontinued therapy prematurely because of intolerance were encouraged to remain in the study. Stepwise reductions in the peginterferon alfa-2a dosages to 135, 90, or 45 μg per week and reductions in ribavirin dosages to 800 or 600 mg per day were allowed to manage adverse events or laboratory abnormalities that had reached predetermined thresholds of severity. If the adverse event resolved or improved, a return to initial dosing levels was permitted unless the patient had received the reduced dose for more than four weeks. Patients were withdrawn from treatment if they continued to have viremia at week 24, if they missed four consecutive doses, or at the discretion of the investigator.

Statistical Analysis

For the primary efficacy end point, a closed testing procedure was planned to allow for all possible pairwise comparisons among the three treatment groups.[19,20] The global hypothesis of no differences among the three treatment groups was tested at a significance level of 0.05; if there was a significant difference among the three treatment groups, each treatment comparison was then tested at a significance level of 0.05. The Cochran–Mantel–Haenszel test was used for both types of analysis and was stratified according to the combination of country and HCV genotype (HCV genotype 1 vs. other genotypes).[21] Because the simulated error rate (with the use of the Cochran–Mantel–Haenszel test for a single stratum) for each pairwise treatment comparison under this closed testing procedure was approximately 0.025, a two-sided 97.5 percent confidence interval for the odds ratios was reported for each pairwise treatment comparison. Stepwise, backward, and multiple logistic-regression models were used to explore base-line factors predicting a sustained virologic response. All patients who received at least one dose of study medication were included in all efficacy analyses, and if they had undergone at least one safety assessment after base line, they were included in the safety analysis.

RESULTS

Patient Demographics

Of the 1459 patients screened, 1149 were randomly assigned to treatment and 1121 were randomly assigned to treatment and received at least one dose of study medication. The patients who were excluded from the study did not have elevated alanine aminotransferase levels, refused to participate, or failed to meet other inclusion criteria. Twenty-eight patients were randomly assigned to treatment but did not receive at least one dose of study medication because they refused or did not come for treatment, because they did not meet inclusion criteria, or for other reasons, including administrative reasons that were identified after randomization. The pretreatment characteristics of patients in the treatment groups were similar (Table 1).

Virologic Response

Significantly more patients treated with peginterferon alfa-2a plus ribavirin had end-of-treatment virologic responses than patients treated with interferon alfa-2b plus ribavirin (69 percent vs. 52 percent, $P<0.001$) or peginterferon alfa-2a plus placebo (69 percent vs. 59 percent, $P=0.01$) (Fig. 1). Significantly more patients treated with peginterferon alfa-2a plus ribavirin had a sustained virologic response (i.e., no detectable HCV RNA 24 weeks after cessation of therapy) than those treated with interferon alfa-2b plus ribavirin (56 percent vs. 44 percent, $P<0.001$) or peginterferon alfa-2a plus placebo (56 percent vs. 29 percent, $P<0.001$) (Fig. 1).

Forty-six percent of patients with HCV genotype 1 who received peginterferon alfa-2a plus ribavirin had a sustained virologic response, as compared with 36 percent of those who received interferon alfa-2b plus ribavirin ($P=0.01$) and 21 percent of those who re-

TABLE 1. CHARACTERISTICS OF THE PATIENTS AT BASE LINE.*

CHARACTERISTIC	PEGINTERFERON ALFA-2a PLUS RIBAVIRIN (N=453)	INTERFERON ALFA-2b PLUS RIBAVIRIN (N=444)	PEGINTERFERON ALFA-2a PLUS PLACEBO (N=224)
Sex — M/F (% male)	324/129 (72)	325/119 (73)	151/73 (67)
Age — yr	42.8±10.1	42.3±9.6	42.4±8.9
Weight — kg	79.8±17.5	78.4±17.5	79.1±17.9
Body-mass index†	26.8±5.0	26.4±5.3	26.5±4.7
Body-surface area — m^2	1.9±0.2	1.9±0.2	1.9±0.2
Race — no. (%)			
White	372 (82)	385 (87)	186 (83)
Black	27 (6)	13 (3)	13 (6)
Asian	28 (6)	24 (5)	12 (5)
Other	26 (6)	22 (5)	13 (6)
Mode of infection — no. (%)			
Injection-drug use	190 (42)	180 (41)	80 (36)
Transfusion	85 (19)	97 (22)	47 (21)
Other	46 (10)	45 (10)	26 (12)
Unknown	132 (29)	122 (27)	71 (32)
Alanine aminotransferase quotient — no. (%)‡			
>1–1.5	95 (21)	81 (18)	46 (21)
>1.5–3	193 (43)	207 (47)	106 (47)
>3–7	142 (31)	136 (31)	63 (28)
>7	23 (5)	20 (4)	9 (4)
Alanine aminotransferase — U/liter§	90.2±65.2	90.7±61.3	87.3±55.7
Mean HCV RNA level — copies/ml $\times 10^{-6}$	6.0±7.3	6.0±7.3	5.9±7.4
HCV genotype — no. (%)			
1a	141 (31)	154 (35)	70 (31)
1b	155 (34)	122 (27)	68 (30)
1 other	2 (<1)	9 (2)	7 (3)
2	54 (12)	61 (14)	37 (17)
3	86 (19)	84 (19)	32 (14)
4	13 (3)	11 (2)	9 (4)
Other	2 (<1)	3 (<1)	1 (<1)
Histologic diagnosis — no. (%)			
No cirrhosis	397 (88)	390 (88)	190 (85)
Cirrhosis or bridging fibrosis	56 (12)	54 (12)	34 (15)

*Plus–minus values are means ±SD. Because of rounding, not all percentages total 100.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡The alanine aminotransferase quotient is the average of the two serum alanine aminotransferase values that qualified patients for participation, divided by the upper limit of normal.

§The average of two pretreatment values meeting the entry criteria was calculated.

ceived peginterferon alfa-2a plus placebo ($P<0.001$) (Table 2). Among the patients with HCV genotype 2 or 3, significantly more of those treated with peginterferon alfa-2a plus ribavirin had a sustained virologic response than of those treated with interferon alfa-2b plus ribavirin (76 percent vs. 61 percent, $P=0.005$) (Table 2). Among patients with HCV genotype 1 and high base-line viral RNA levels (more than 2 million copies per milliliter), 41 percent of those receiving peginterferon alfa-2a plus ribavirin had a sustained virologic response, as compared with 33 percent of those receiving interferon alfa-2b plus ribavirin (Table 2). Among patients with cirrhosis, 43 percent of those treated with peginterferon alfa-2a plus ribavirin and 33 percent of those treated with interferon alfa-2b plus ribavirin had a sustained virologic response (Table 2).

Independent Factors Associated with a Sustained Virologic Response

In multivariable analyses to identify predictors of sustained virologic response among patients who received peginterferon alfa-2a plus ribavirin, our final multiple logistic-regression model, including the following factors, was entered in the final stepwise regression analysis: sex, race (white vs. nonwhite), age (≤40 years vs. >40 years), body weight (≤75 kg vs. >75 kg), pretreatment viral load (≤2 million copies per milliliter vs. >2 million copies per milliliter), pretreatment alanine aminotransferase quotient (>3 vs. ≤3), pretreatment histologic diagnosis (cirrhosis vs. noncirrhosis), and HCV genotype (1 vs. non-1). Three factors independently and significantly increased the odds of achieving a sustained virologic response: an

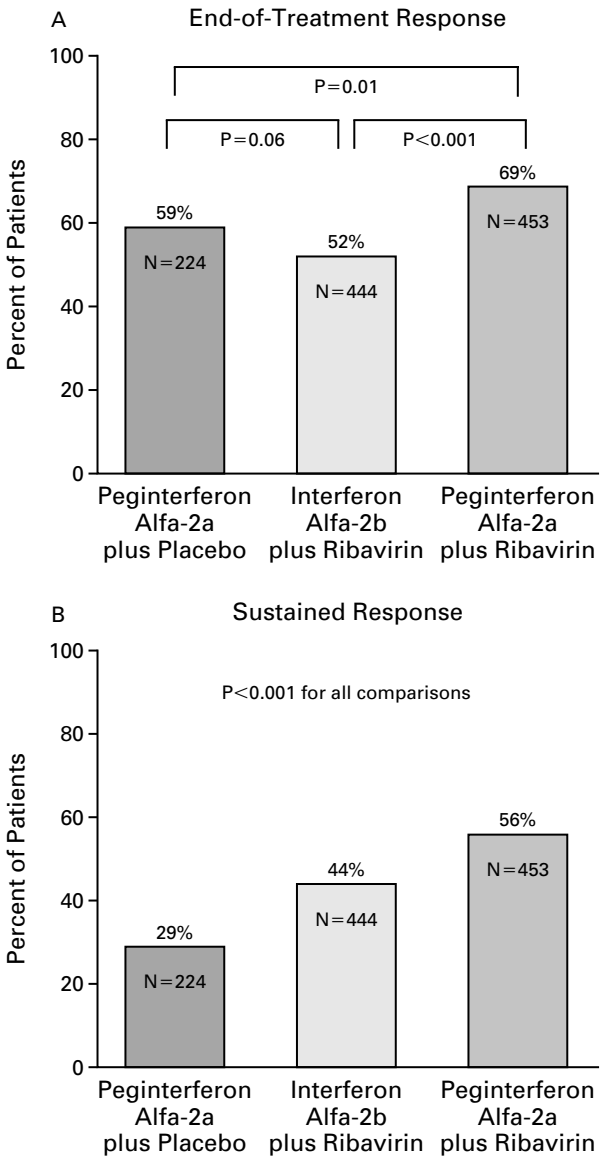

Figure 1. End-of-Treatment Virologic Response (Panel A) and Sustained Virologic Response (Panel B), According to Intention-to-Treat Analysis.

A virologic response was defined as an undetectable level of HCV RNA (<100 copies per milliliter). Differences were assessed by the Cochran–Mantel–Haenszel test stratified according to country and HCV genotype.

HCV genotype other than 1 (odds ratio, 3.25; 95 percent confidence interval, 2.09 to 5.12; P<0.001), an age of 40 years or less (odds ratio, 2.60; 95 percent confidence interval, 1.72 to 3.95; P<0.001), and a body weight of 75 kg or less (odds ratio, 1.91; 95 percent confidence interval, 1.27 to 2.89; P=0.002).

Predictive Value of Early Virologic Response

By week 12, 86 percent of patients (390 of 453) treated with peginterferon alfa-2a plus ribavirin had had a virologic response, defined as a 2-log decrease from base-line HCV RNA levels (97 patients) or no detectable serum HCV RNA (293 patients) (Fig. 2). The absence of an early virologic response was not associated with early treatment discontinuation (before week 12) or dose modification (data not shown). Of those with early virologic responses, 65 percent subsequently had a sustained virologic response. Those with no detectable HCV RNA by week 12 were more likely to have a sustained virologic response than those who had only a 2-log decrease in HCV RNA (221 of 293 vs. 32 of 97). In contrast, among the 63 patients who did not have an early virologic response, 61 (97 percent) did not have a sustained virologic response.

Safety

The proportions of patients withdrawn from treatment because of laboratory abnormalities or other adverse events were similar in the groups receiving peginterferon alfa-2a plus ribavirin (3 percent for laboratory abnormalities and 7 percent for other adverse events), peginterferon alfa-2a plus placebo (1 percent and 6 percent, respectively), and interferon alfa-2b plus ribavirin (1 percent and 10 percent) (Table 3). The most common types of events leading to discontinuation were psychiatric disorders (mainly depression-related events). The frequency and major causes of dose modifications are detailed in Table 3. Among patients who had an early virologic response with peginterferon alfa-2a plus ribavirin, the proportion with a sustained virologic response was similar among those who had a substantial dose reduction (to <80 percent of both study medications) and those who maintained the full dosing schedule (67 percent and 75 percent, respectively).[22] In contrast, discontinuation despite an early virologic response was associated with a decrease in efficacy in this treatment group (rate of sustained response, 12 percent).[22]

The median hemoglobin values decreased between weeks 1 and 8 in all treatment groups, then stabilized, and then returned to near base-line values after treatment was completed. The maximal decrease was greater in patients treated with peginterferon alfa-2a plus ribavirin (3.7 g per deciliter) or interferon alfa-2b plus ribavirin (3.6 g per deciliter) than in patients treated with peginterferon alfa-2a plus placebo (2.2 g per deciliter). There was no association between the incidence of serious cardiovascular events and the incidence of anemia.

The median neutrophil counts decreased from base line in all treatment groups, particularly during the first two weeks of treatment, and then stabilized for the remainder of the treatment period, increasing rap-

TABLE 2. PROPORTION OF PATIENTS WITH A SUSTAINED VIROLOGIC RESPONSE AS A FUNCTION OF HCV GENOTYPE AND HCV GENOTYPE PLUS BASE-LINE HCV RNA.*

VARIABLE	PEGINTERFERON ALFA-2a PLUS RIBAVIRIN (N=453)	INTERFERON ALFA-2b PLUS RIBAVIRIN (N=444)	PEGINTERFERON ALFA-2a PLUS PLACEBO (N=224)
	no./total no. (%)		
HCV genotype†			
All patients	255/453 (56)‡	197/444 (44)	66/224 (29)
Genotype 1	138/298 (46)§	103/285 (36)	30/145 (21)
Genotype 2 or 3	106/140 (76)¶	88/145 (61)	31/69 (45)
Genotype 4	10/13 (77)‖	4/11 (36)	4/9 (44)
Base-line HCV RNA**			
$\leq 2\times10^6$ copies/ml	99/159 (62)††	78/150 (52)	32/69 (46)
$>2\times10^6$ copies/ml	156/293 (53)‡‡	119/292 (41)	34/155 (22)
HCV genotype and base-line HCV RNA			
Genotype 1			
$\leq 2\times10^6$ copies/ml	64/115 (56)	40/94 (43)	17/44 (39)
$>2\times10^6$ copies/ml	74/182 (41)	63/189 (33)	13/101 (13)
Genotype 2 or 3			
$\leq 2\times10^6$ copies/ml	30/37 (81)	34/52 (65)	11/19 (58)
$>2\times10^6$ copies/ml	76/103 (74)	54/93 (58)	20/50 (40)
Histologic diagnosis			
Cirrhosis	24/56 (43)	18/54 (33)	7/34 (21)

*A sustained virologic response was defined as no detectable hepatitis C virus (HCV) RNA 24 weeks after the cessation of therapy.

†Six patients had other genotypes.

‡$P<0.001$ for the comparison between peginterferon alfa-2a plus ribavirin and interferon alfa-2b plus ribavirin.

§$P=0.01$ for the comparison between peginterferon alfa-2a plus ribavirin and interferon alfa-2b plus ribavirin.

¶$P=0.005$ for the comparison between peginterferon alfa-2a plus ribavirin and interferon alfa-2b plus ribavirin.

‖No P value was calculated, because of the small sample size.

**Base-line HCV RNA values were missing for three patients.

††$P=0.04$ for the comparison between peginterferon alfa-2a plus ribavirin and interferon alfa-2b plus ribavirin.

‡‡$P=0.003$ for the comparison between peginterferon alfa-2a plus ribavirin and interferon alfa-2b plus ribavirin.

idly to base-line values after the completion of treatment. Four patients (three receiving peginterferon alfa-2a plus ribavirin and one receiving interferon alfa-2b plus ribavirin) discontinued treatment because the neutrophil count was below 500 per cubic millimeter. The median platelet counts remained close to base-line values throughout treatment with interferon alfa-2b plus ribavirin but decreased progressively during the first eight weeks of treatment with peginterferon alfa-2a plus ribavirin or placebo, before stabilizing. After treatment was completed, the median platelet counts returned to normal within four weeks. Two patients with thrombocytopenia (one receiving peginterferon alfa-2a plus placebo and the other receiving interferon alfa-2b plus ribavirin) had serious bleeding. Five patients (four receiving peginterferon alfa-2a plus ribavirin and one receiving peginterferon alfa-2a plus placebo) discontinued treatment because of thrombocytopenia.

Most adverse events in all study groups were those commonly associated with interferon-based treatment (Table 3). Patients treated with peginterferon alfa-2a plus ribavirin or placebo had a lower incidence of influenza-like symptoms, such as pyrexia, myalgia, and rigors, than those treated with interferon alfa-2b plus ribavirin. Although few patients had a history of depression or active depression at base line (1 to 2 percent and 3 to 5 percent, respectively), a substantial minority reported depression during the study. Patients treated with peginterferon alfa-2a plus ribavirin or placebo had a lower incidence of depression than those treated with interferon alfa-2b plus ribavirin (22 percent and 20 percent vs. 30 percent). Three patients died after the end of treatment. One patient who had

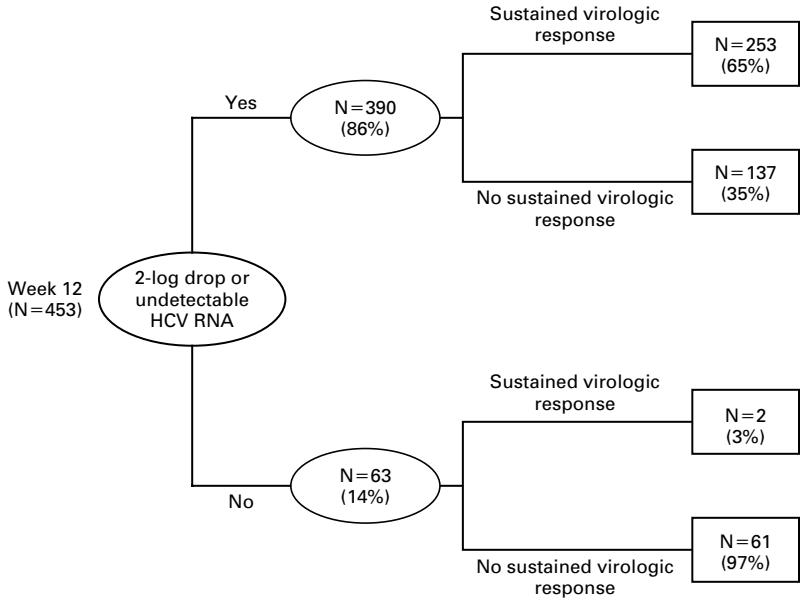

Figure 2. Predictability of Sustained Virologic Response.

At week 12, 86 percent (390 of 453) of the patients treated with peginterferon alfa-2a plus ribavirin either had a 2-log drop in HCV RNA levels or had undetectable levels of HCV RNA. Of these patients, 65 percent (253 of 390) went on to have a sustained virologic response. Of the 63 patients who did not have a 2-log drop or undetectable levels of HCV RNA at week 12, 61 (97 percent) did not have a sustained virologic response.

received interferon alfa-2b plus ribavirin died of hypertensive heart disease, and two who had received peginterferon alfa-2a plus placebo died, one from drowning and the other from liver cancer. None of the deaths were considered related to treatment.

DISCUSSION

Peginterferon alfa-2a plus ribavirin was significantly more effective than interferon alfa-2b plus ribavirin or peginterferon alfa-2a alone for the treatment of chronic hepatitis C. Overall, the rate of sustained virologic response was similar to that reported with peginterferon alfa-2b plus ribavirin.[13] In the current study, improved efficacy was seen in subgroups of patients with disease generally considered to have treatment-resistant characteristics.[13] In particular, patients with all HCV genotypes and those with high base-line levels of HCV RNA (more than 2 million copies per milliliter) were more likely to have a sustained virologic response when treated with peginterferon alfa-2a plus ribavirin than when treated with interferon alfa-2b plus ribavirin. Among patients considered to have the most treatment-resistant disease — that is, those with both HCV genotype 1 and high base-line viral levels — a substantially higher proportion of those treated with peginterferon alfa-2a plus ribavirin had a sustained virologic response than of those treated with interferon alfa-2b plus ribavirin.

Early prediction of virologic response to interferon-based therapy can help identify patients who are unlikely to have a sustained response and allow clinicians the option to discontinue treatment, saving patients the side effects and cost of additional therapy. In the current study, 97 percent of patients who did not have an early virologic response to peginterferon alfa-2a plus ribavirin by week 12 never had a sustained virologic response. The incremental benefit of continuing therapy beyond 12 weeks for patients who have not had an early virologic response must be considered for each patient individually.

This study was designed to treat patients for 48 weeks, regardless of HCV genotype. Therefore, we cannot comment on shorter treatment periods.

Several adverse events typically associated with the use of interferon (including influenza-like symptoms and depression) occurred less frequently with peginterferon alfa-2a, alone or in combination with ribavirin, than with interferon alfa-2b plus ribavirin. Monotherapy with peginterferon alfa-2a was generally better tolerated than the ribavirin-containing regimens. As is usual with interferon-based therapy, there were reductions in neutrophil and platelet counts with all treatments. Although these decreases were greater in patients treated with peginterferon alfa-2a plus ribavirin than in those treated with interferon alfa-2b plus ribavirin, they did not appear to be associated with se-

TABLE 3. INCIDENCE OF DISCONTINUATION, DOSE MODIFICATION, AND ADVERSE EVENTS.

VARIABLE	PEGINTERFERON ALFA-2a PLUS RIBAVIRIN	INTERFERON ALFA-2b PLUS RIBAVIRIN	PEGINTERFERON ALFA-2a PLUS PLACEBO
		number (percent)	
Discontinuation*			
Patients who withdrew during wk 1–48	100 (22)	140 (32)	72 (32)
Insufficient response	34	59	49
Adverse event	32	43	13
Laboratory abnormality†	12	4	2
Refusal of treatment	15	22	5
Violation of entry criteria	0	2	0
Failure to return	5	7	3
Other violation	2	3	0
Patients who withdrew during wk 49–72	19 (4)	14 (3)	6 (3)

	PEGINTERFERON ALFA-2a	RIBAVIRIN	INTERFERON ALFA-2b	RIBAVIRIN	PEGINTERFERON ALFA-2a	PLACEBO
Dose modification‡§						
Adverse event	48 (11)	95 (21)	47 (11)	97 (22)	14 (6)	39 (17)
Laboratory abnormality	111 (25)	108 (24)	36 (8)	84 (19)	54 (24)	9 (4)
Anemia	4 (1)	99 (22)	13 (3)	83 (19)	0	8 (4)
Neutropenia	91 (20)	6 (1)	24 (5)	1 (<1)	38 (17)	0
Thrombocytopenia	18 (4)	2 (<1)	1 (<1)	0	14 (6)	1 (<1)

Adverse events‡¶			
Fatigue‖	242 (54)	244 (55)	98 (44)
Headache‖	211 (47)	230 (52)	115 (51)
Pyrexia‖	195 (43)	247 (56)**	85 (38)
Myalgia‖	189 (42)	220 (50)††	94 (42)
Insomnia	168 (37)	174 (39)	52 (23)
Nausea	130 (29)	145 (33)	58 (26)
Alopecia	128 (28)	151 (34)	48 (21)
Arthralgia	121 (27)	112 (25)	64 (29)
Irritability	109 (24)	123 (28)	56 (25)
Rigors‖	106 (24)	157 (35)**	52 (23)
Pruritus	101 (22)	88 (20)	41 (18)
Depression	100 (22)	134 (30)‡‡	45 (20)
Decreased appetite	96 (21)	98 (22)	24 (11)
Dermatitis	95 (21)	80 (18)	29 (13)

*Values are based on patients randomly assigned to treatment who received at least one dose of study medication (453 who received peginterferon alfa-2a plus ribavirin, 444 who received interferon alfa-2b plus ribavirin, and 224 who received peginterferon alfa-2a plus placebo).

†Laboratory abnormalities included neutropenia, thrombocytopenia, and abnormal alanine aminotransferase levels.

‡Values are based on randomized patients who received at least one dose of study medication and had at least one post–base-line safety evaluation (451 who received peginterferon alfa-2a plus ribavirin, 443 who received interferon alfa-2b plus ribavirin, and 223 who received peginterferon alfa-2a plus placebo).

§Some patients who required dose modification had both an adverse event and a laboratory abnormality.

¶Patients may have had more than one adverse event. The adverse events listed are those that occurred in at least 20 percent of patients.

‖This symptom is one of the influenza-like symptoms often seen with interferon treatment.

** $P<0.001$ for the comparison with the group given peginterferon alfa-2a plus ribavirin by Fisher's exact test.

†† $P=0.02$ for the comparison with the group given peginterferon alfa-2a plus ribavirin by Fisher's exact test.

‡‡ $P=0.01$ for the comparison with the group given peginterferon alfa-2a plus ribavirin by Fisher's exact test.

rious sequelae and were effectively managed by dose modifications. Interestingly, for patients treated with peginterferon alfa-2a plus ribavirin who had an early virologic response, completion of therapy with dose reduction was not associated with a substantial decrease in efficacy.

Peginterferon alfa-2a offers significantly enhanced sustained virologic responses in all patients, regardless of HCV genotype and viral load, and a once-weekly dosing schedule. We think that the ability to predict the absence of sustained virologic response from HCV RNA levels at week 12 will be a useful clinical tool. The results of this study show that combination therapy with peginterferon alfa-2a plus ribavirin provides a considerable clinical advantage over therapy with interferon alfa-2b plus ribavirin.

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APPENDIX

In addition to the authors, the following members of the Pegasys International Study Group participated in this study: A. Abergel, Hôtel-Dieu Hospital, Clermont-Ferrand, France; A. Alberti, Università degli Studi di Padova, Padua, Italy; J. Areias, Hospital de Santo Antonio, Porto, Portugal; B.R. Bacon, Bethesda General Hospital, St. Louis; C. Berg, University of Virginia Health Systems, Charlottesville; F. Bianchi, Università degli Studi di Bologna, Bologna, Italy; M.-A. Bigard, Hôpitaux de Brabois, Vandoevreles-Nancy, France; F. Bonino, Azienda Ospedaliera Pisana, Pisa, Italy; H. Bonkovsky, University of Massachusetts Medical Center, Worcester; F. Bosques, Hospital Universitario Jose E. Gonzalez, Monterrey, Mexico; M. Bourlière, St. Joseph Hospital, Marseilles, France; J.P. Bronowicki, Centre Hospitalier Universitaire, Nancy, France; J.T. Brouwer, Academic Hospital Rotterdam, Rotterdam, the Netherlands; R. Brown, Columbia University College of Physicians and Surgeons, New York; M. Buhl, Marselisborg Hospital, Aarhus, Denmark; G. Cadeo, Università degli Studi di Brescia, Brescia, Italy; P. Cales, Hôpital Hôtel-Dieu, Angers, France; O. Campollo, Hospital Civil de Guadalajara, Guadalajara, Mexico; R. Carithers, University of Washington, Seattle; A. Carvalho, Hospitais da Universidade de Coimbra, Coimbra, Portugal; W.G.E. Cooksley, Royal Brisbane Hospital, Herston, Queensland, Australia; P. Couzigou, Haut-Leveque Hospital, Bordeaux, France; A. Craxì, University of Palermo, Palermo, Italy; P. Desmond, St. Vincent's Hospital, Fitzroy, Victoria, Australia; D. Dieterich, Cabrini Medical Center, New York; M. Farkkila, Helsinki University Central Hospital, Helsinki, Finland; K. Fawaz, New England Medical Center, Boston; P. Ferenci, Allgemeines Krankenhaus Wien, Vienna, Austria; J. Franco, Medical College of Wisconsin at Froedtert Hospital, Milwaukee; A. Gibas, Regional Gastroenterology Associates, Lancaster, Pa.; R. Gish, California Pacific Medical Center, San Francisco; E. Godofsky, Bach and Godofsky, Bradenton, Fla.; S. Hadziyannis, Evgenidion Hospital, Athens, Greece; T. Hassanein, University of California, San Diego; K.B. Hellum, Akershus Central Hospital, Nordbyhagen, Norway; Y. Horsmans, Cliniques Universitaires St. Luc, Brussels, Belgium; A. Horta E Vale, Clínica Diagnostics Medico Integral, Vila Nova de Gaia, Portugal; D. Jensen, Rush–Presbyterian–St. Luke's Medical Center, Chicago; M.-Y. Lai, National Taiwan University, Taipei, Taiwan; D. Larrey, Hôpital St.-Eloi, Montpellier, France; S.-D. Lee, Veterans General Hospital, Taipei, Taiwan; A.S. Lok, University of Michigan Medical Center, Ann Arbor; P. Marcellin, Hôpital Beaujon, Clichy, France; P. Martin, University of California, Los Angeles; D.K. Moonka, Henry Ford Health System, Detroit; R. Moreno, Hospital Universitario de la Princesa, Madrid; A. Mouro, Hospital Pulido Valente, Lisbon, Portugal; F. Nevens, University Hospital Gasthuisberg, Leuven, Belgium; G. Pastore, Policlinico di Bari, Bari, Italy; G.R. Piexe, Hospital Egas Moniz, Lisbon, Portugal; R. Poupon, Hôpital St.-Antoine, Paris; T. Poynard, Hôpital de la Salpétrière, Paris; F. Ramalho, Hospital Santa Maria, Lisbon, Portugal; H.W. Reesink, Academic Medical Center, Amsterdam; J. Reichen, Universität, Bern, Switzerland; S. Roberts, Alfred Hospital, Prahran, Victoria, Australia; J. Rodes, Clinico y Provincial, Barcelona, Spain; F.J. Salmeron, Hospital Clinico San Cecilio de Granada, Granada, Spain; D. Schulman, Digestive Health Consultants, Burbank, Calif.; H. Sette, Jr., Instituto de Infectologia Emílio Ribas, São Paulo, Brazil; S. Shedlofsky, University of Kentucky Medical Center, Lexington; K.E. Sherman, University of Cincinnati Medical Center, Cincinnati; F. Siddiqui, Harper Hospital, Detroit; M. Sulkowski, Johns Hopkins University, Baltimore; M.J. Tong, Huntington Medical Research Institutes, Pasadena, Calif.; R. Trejo, Centro Medico Nacional S. XXI, Mexico City, Mexico; C. Trepo, Hôpital Hôtel-Dieu, Lyons, France; D.J. van Leeuwen, University of Alabama, Birmingham; D. Vetter, Hôpital Civil, Strasbourg, France; T.L. Wright, University of California, San Francisco; J.-P. Zarski, Hôpital de la Tronche, Grenoble, France; S. Zeuzem, Klinikum der J.W. Goethe-Universität, Frankfurt, Germany. Safety Review Board: E. Krawitt, University of Vermont Medical Center, Burlington; V. Feinman, Mount Sinai Hospital, Toronto; V. Rustgi, Metropolitan Research, Fairfax, Va.

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