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PEGINTERFERON ALFA-2a IN PATIENTS WITH CHRONIC HEPATITIS C

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ABSTRACT

Background Covalent attachment of a 40-kd branched-chain polyethylene glycol moiety to interferon alfa-2a results in a compound (peginterferon alfa-2a) that has sustained absorption, a slower rate of clearance, and a longer half-life than unmodified interferon alfa-2a. We compared the clinical effects of a regimen of peginterferon alfa-2a with those of a regimen of interferon alfa-2a in the initial treatment of patients with chronic hepatitis C.

Methods We randomly assigned 531 patients with chronic hepatitis C to receive either 180 µg of peginterferon alfa-2a subcutaneously once per week for 48 weeks (267 patients) or 6 million units of interferon alfa-2a subcutaneously three times per week for 12 weeks, followed by 3 million units three times per week for 36 weeks (264 patients). All the patients were assessed at week 72 for a sustained virologic response, defined as an undetectable level of hepatitis C virus RNA (<100 copies per milliliter).

Results In the peginterferon group, 223 of the 267 patients completed treatment and 206 completed follow-up. In the interferon group, 161 of the 264 patients completed treatment and 154 completed follow-up. In an intention-to-treat analysis in which patients who missed the examination at the end of treatment or follow-up were considered not to have had a response at that point, peginterferon alfa-2a was associated with a higher rate of virologic response than was interferon alfa-2a at week 48 (69 percent vs. 28 percent, $P=0.001$) and at week 72 (39 percent vs. 19 percent, $P=0.001$). Sustained normalization of serum alanine aminotransferase concentrations at week 72 was also more common in the peginterferon group than in the interferon group (45 percent vs. 25 percent, $P=0.001$). The two groups were similar with respect to the frequency and severity of adverse events, which were typical of those associated with interferon alfa.

Conclusions In patients with chronic hepatitis C, a regimen of peginterferon alfa-2a given once weekly is more effective than a regimen of interferon alfa-2a given three times weekly. (N Engl J Med 2000;343:1666-72.)

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INTERFERON is an essential component of the treatment of chronic hepatitis C virus (HCV) infection. However, treatment with interferon alone is generally associated with a sustained virologic response in fewer than 20 percent of patients.¹⁻³ A 48-week combination regimen of interferon alfa and ribavirin is associated with a sustained virologic response in 38 to 43 percent of patients.^{4,5}

One of the reasons for the marginal response to interferon is its short half-life (approximately eight hours⁶), which leads to wide fluctuations in the plasma concentrations of the drug during the treatment period. Studies of viral kinetics indicate that HCV has a high rate of turnover and an in vivo half-life of only a few hours.^{7,8} Among patients treated with interferon alfa three times weekly, an intermittent increase in viral load can be observed on treatment-free days.⁹ Covalent attachment of a 40-kd branched-chain polyethylene glycol moiety to interferon alfa-2a produces peginterferon alfa-2a, a compound that has sustained absorption, a slower rate of clearance, and a longer half-life than unmodified interferon alfa.^{10,11} The sustained high concentrations of peginterferon alfa-2a in plasma¹² maintain an antiviral effect on HCV and make possible once-weekly administration. We compared the efficacy and safety of peginterferon alfa-2a administered once per week with the efficacy and safety of interferon alfa-2a administered three times per week for 48 weeks.

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*Other members of the study group are listed in the Appendix.

METHODS

Patients

Adult patients who had not previously taken interferon and who had the following characteristics were eligible for the study: a positive test for anti-HCV antibody, an HCV RNA level greater than 2000 copies per milliliter on polymerase-chain-reaction analysis (Cobas Amplicor HCV Monitor [version 2.0], Roche Diagnostics, Branchburg, N.J.), a serum alanine aminotransferase concentration above the upper limit of normal on two occasions during the preceding six months, and findings consistent with a diagnosis of chronic hepatitis C on liver biopsy performed during the preceding year, as determined by a single, study-designated pathologist.

Criteria for exclusion were neutropenia (neutrophil count, <1500 per cubic millimeter); thrombocytopenia (platelet count, <90,000 per cubic millimeter); a creatinine concentration more than 1.5 times the upper limit of normal; a serum alpha-fetoprotein concentration above 25 ng per milliliter (except in patients with no evidence of cancer on ultrasonography); coinfection with the hepatitis A virus, the hepatitis B virus, or the human immunodeficiency virus; decompensated liver disease; an organ transplant; neoplastic disease; severe cardiac or chronic pulmonary disease; autoimmune disease (except well-controlled thyroid disease); a psychiatric disorder; a seizure disorder; severe retinopathy; or unwillingness to practice contraception.

Study Design

This phase 3, open-label, parallel-dose, randomized trial was conducted by the Pegasys International Study Group between December 1997 and November 1999 at 36 centers in Australia, Canada, Germany, Mexico, New Zealand, Spain, Switzerland, Taiwan, and the United Kingdom. The study was approved by ethics committees at each center, and all the patients provided written informed consent. The study was designed by Hoffmann-LaRoche in collaboration with expert hepatologists. Data were collected by the investigators, and data analysis was performed by Hoffmann-LaRoche in conjunction with the authors.

Patients who met the criteria for entry were randomly assigned to receive subcutaneous treatment with either peginterferon alfa-2a (Pegasys, F. Hoffmann-LaRoche, Basel, Switzerland [the peginterferon group]) or interferon alfa-2a (Roferon-A, F. Hoffmann-LaRoche [the interferon group]). Patients in the peginterferon group received 180 μ g of the drug once a week for 48 weeks. Patients in the interferon group received 6 million units three times a week for 12 weeks and then 3 million units three times a week for the remaining 36 weeks of treatment. The patients and the investigators were unaware of the results of tests for HCV RNA, except at week 24 of treatment, according to international standards for practice. Patients were followed until week 72 to assess whether there was a sustained response to treatment.

Assessment and End Points

Hepatitis C virus genotyping was performed by sequence analysis of a portion of the 5' untranslated region of its genome. Efficacy was assessed by measuring plasma HCV RNA, measuring serum alanine aminotransferase, and examining the histologic features of pre- and post-treatment liver specimens. The primary efficacy end points were a virologic response (indicated by undetectable levels of HCV RNA on analysis with Cobas Amplicor HCV [version 2.0], which has a lower limit of detection of 100 copies per milliliter) at week 72 and a biochemical response (normalization of serum alanine aminotransferase concentrations to a value at or below the upper limit of normal) at week 72. After completion of the study, slides of liver-biopsy specimens obtained before the study and 24 weeks after discontinuation of treatment were coded and read by the study pathologist, who was unaware of the patients' identity and treatment and the date of biopsy. A histologic response was defined as a decrease of at least 2 points in the total score on the Histological Activity Index, where a score of 0 indicates no inflammatory changes and no fibrosis and a score of 22 indicates multilobular necro-

sis, marked intralobular degeneration and focal necrosis, marked portal inflammation, and cirrhosis.¹³

Adverse events were graded as mild, moderate, severe, or life-threatening, and their occurrence was assessed during treatment and for 56 days after the end of treatment. Laboratory values were assessed at the beginning of treatment (base line), at weeks 1, 2, 4, 6, and 8, and then every 4 weeks for the rest of the 72-week study period. Patients who discontinued their assigned treatment were encouraged to remain in the study for assessments through week 72. The protocol permitted dose modification (a 25 percent, 50 percent, or 75 percent reduction in the assigned dose) for patients who had clinically significant adverse events or important abnormalities in laboratory values. On resolution of the event or abnormality, doses could be restored to their original levels. Patients were withdrawn from the study if they missed four consecutive weeks of treatment or if an investigator was concerned about safety.

Statistical Analysis

All categorical variables were analyzed with use of the Cochran-Mantel-Haenszel test, with stratification according to center, and odds ratios and corresponding 95 percent confidence intervals were calculated.¹⁴ Two-sided *P* values were calculated for pairwise comparisons of the two treatment regimens. The first objective of the study was to establish that peginterferon alfa-2a was equivalent to interferon alfa-2a, with equivalence defined as a rate of sustained response in the peginterferon group that was no more than 5 percent less than the response rate in the interferon group.¹⁵ The second objective was to demonstrate that peginterferon alfa-2a was superior to interferon alfa-2a, as defined below. Peginterferon alfa-2a would be considered at least as efficacious as interferon alfa-2a if the lower limit of the two-sided 95 percent confidence interval for the true odds ratio (the ratio of the odds of having a sustained response to peginterferon alfa-2a to the odds of having a sustained response to interferon alfa-2a) was greater than 0.8. Peginterferon alfa-2a would be considered superior to interferon alfa-2a if the lower limit of the two-sided 95 percent confidence interval was greater than 1.

For this analysis, 456 patients were required (after adjustment for a dropout rate of 15 percent), assuming a sustained-response rate of 25 percent in the interferon group and of 35 percent in the peginterferon group. Intention-to-treat analysis was used for all measures of efficacy except for changes from base line in histologic findings. Patients who missed the examination at the end of the follow-up period (week 72) were considered not to have had a response at that point. A change from base line in the total Histological Activity Index score was analyzed only in patients who had undergone both pretreatment and post-treatment liver biopsies. Patients who received at least one dose of study medication were included in the analysis of safety.

RESULTS

Characteristics of the Patients

Of the 613 patients screened, 531 met the criteria for entry and underwent randomization. The main reasons for exclusion from the study were neutropenia, an HCV RNA level less than or equal to 2000 copies per milliliter, and a normal alanine aminotransferase concentration. Five patients (two in the peginterferon group and three in the interferon group) withdrew before receiving treatment but were included in the intention-to-treat analysis. The base-line characteristics of the patients in the two treatment groups were similar (Table 1). Of the 531 patients enrolled, 360 completed the study. Of the 267 patients assigned to receive peginterferon alfa-2a, 223 completed treatment and 206 completed follow-up. Of the 264 patients assigned to receive interferon alfa-2a, 161 completed

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

CHARACTERISTIC	PEGINTERFERON ALFA-2a (N=267)	INTERFERON ALFA-2a (N=264)
Male sex — no. (%)	178 (67)	176 (67)
Age — yr	40.6±10.3	41.0±9.2
Weight — kg	74.7±15.0	76.5±15.0
Body-surface area — m ²	1.9±0.2	1.9±0.2
Race — no. (%)		
White	230 (86)	224 (85)
Black	6 (2)	5 (2)
Asian	24 (9)	26 (10)
Other	7 (3)	9 (3)
Mode of infection — no. (%)		
Injection-drug use	102 (38)	97 (37)
Transfusion	54 (20)	67 (25)
Other	30 (11)	23 (9)
Unknown	81 (30)	77 (29)
Alanine aminotransferase quotient†		
≤3	161 (60)	166 (63)
>3	106 (40)	98 (37)
Mean no. of HCV RNA copies/ml — ×10 ⁻⁶	7.4±11.6	8.2±10.6
HCV genotype		
1a	80 (30)	83 (31)
1b	88 (33)	78 (30)
2	25 (9)	34 (13)
3	68 (25)	63 (24)
4	5 (2)	3 (1)
Other or unknown	1 (<1)	3 (1)
Total Histological Activity Index score‡	8.6±3.2	9.0±3.0
Histologic diagnosis — no. (%)		
No cirrhosis or bridging fibrosis	236 (88)	224 (85)
Bridging fibrosis	19 (7)	13 (5)
Cirrhosis	12 (4)	26 (10)
Not informative	0	1 (<1)

*Values include five patients (two in the peginterferon group and three in the interferon group) who withdrew from the study before the initiation of treatment. Plus-minus values are means ±SD. Because of rounding, not all percentages total 100.

†The alanine aminotransferase quotient is the average of the serum alanine aminotransferase values before treatment divided by the upper limit of normal.

‡On the 22-point Histological Activity Index, a score of 0 indicates no inflammatory changes and no fibrosis, and a score of 22 indicates multilobular necrosis, marked intralobular degeneration and focal necrosis, marked portal inflammation, and cirrhosis.

treatment and 154 completed follow-up. Patients were withdrawn for the following reasons: insufficient therapeutic response (13 in the peginterferon group and 53 in the interferon group), refusal of treatment (5 and 13, respectively), failure to return during treatment (4 and 8), laboratory abnormalities or adverse events (19 and 27), and other factors (3 and 2) (Table 2).

Efficacy

Therapy with peginterferon alfa-2a was associated with a higher rate of virologic response than was therapy with unmodified interferon alfa-2a (Table 3). At the end of treatment (week 48), 69 percent of the patients assigned to peginterferon alfa-2a, as compared

TABLE 2. RATES OF DISCONTINUATION OR DOSE REDUCTION DUE TO LABORATORY ABNORMALITIES OR ADVERSE EVENTS AND RATES OF ADVERSE EVENTS.*

VARIABLE	PEGINTERFERON ALFA-2a (N=265)	INTERFERON ALFA-2a (N=261)
	no. (%)	
Discontinuation	19 (7)	27 (10)
Dose modification†	51 (19)	47 (18)
Due to adverse event	21 (8)	30 (11)
Due to laboratory abnormality	37 (14)	24 (9)
Adverse events‡		
Headache	160 (60)	173 (66)
Fatigue	160 (60)	170 (65)
Pyrexia	99 (37)	135 (52)
Myalgia	110 (42)	111 (43)
Rigors	72 (27)	112 (43)
Alopecia	72 (27)	96 (37)
Nausea	55 (21)	91 (35)
Insomnia	48 (18)	62 (24)
Decreased appetite	53 (20)	55 (21)
Diarrhea	51 (19)	53 (20)
Depression	43 (16)	59 (23)
Dizziness	60 (23)	42 (16)
Pruritus	49 (18)	32 (12)
Upper abdominal pain	35 (13)	37 (14)
Cough	25 (9)	25 (10)
Nasopharyngitis	28 (11)	22 (8)
Vomiting	16 (6)	32 (12)
Inflammation at injection site	27 (10)	17 (7)
Impaired concentration	14 (5)	29 (11)

*Values are based on the patients who received at least one dose of study medication (265 in the peginterferon group and 261 in the interferon group). Laboratory abnormalities consisted of neutropenia, thrombocytopenia, abnormal alanine aminotransferase values, hypothyroidism, and hyperthyroidism.

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

‡Some patients had more than one adverse event.

with 28 percent of those assigned to interferon alfa-2a, had undetectable levels of HCV RNA (P=0.001). At the end of the follow-up period (week 72), 39 percent of the patients in the peginterferon group, as compared with 19 percent in the interferon group, had a sustained virologic response (P=0.001). All of the 103 patients in the peginterferon group who had a sustained virologic response had had base-line levels of HCV RNA of more than 10,000 copies per milliliter. Almost all (101) of these 103 patients had no detectable HCV RNA or the viral load decreased by a factor of 100 at week 12 (89 patients had no detectable HCV RNA, and 12 still had detectable HCV RNA). Similarly, in the interferon group, 98 percent of those

TABLE 3. VIROLOGIC AND BIOCHEMICAL RESPONSES AT WEEK 48 AND WEEK 72, ACCORDING TO INTENTION-TO-TREAT ANALYSIS.*

RESPONSE	PEGINTERFERON ALFA-2a (N=267)		INTERFERON ALFA-2a (N=264)	
	no.	% (95% CI)	no.	% (95% CI)
Completed treatment	223		161	
Completed follow-up	206		154	
Virologic response				
End of treatment (wk 48)	185	69 (63–75)†	73	28 (22–33)
End of follow-up (wk 72)	103	39 (33–45)†	50	19 (14–24)
Biochemical response				
End of treatment (wk 48)	123	46 (40–52)	104	39 (33–46)
End of follow-up (wk 72)	120	45 (39–51)†	65	25 (20–30)
Both virologic and biochemical response				
End of treatment (wk 48)	109	41 (35–47)†	65	25 (20–30)
End of follow-up (wk 72)	101	38 (32–44)†	46	17 (13–23)

*A virologic response was indicated by undetectable levels of HCV RNA (<100 copies per milliliter), and a biochemical response was indicated by normalization of serum alanine aminotransferase concentrations (to a value at or below the upper limit of normal). Patients who missed the follow-up examination at week 72 were considered not to have had a response at that point. CI denotes confidence interval (exact 95 percent confidence interval for binomial probabilities).

†P=0.001 for the comparison with the group assigned to interferon alfa-2a by the Cochran–Mantel–Haenszel test, with stratification according to center.

who had a sustained response had a decrease in viral titer of at least 2 log at week 12.

The rate of sustained biochemical response at week 72 was also significantly greater in the peginterferon group than in the interferon group (45 percent vs. 25 percent, P=0.001). The proportion of patients with both a sustained biochemical and a sustained virologic response was also higher in the peginterferon group than in the interferon group (38 percent vs. 17 percent, P=0.001). We found a high degree of correlation between sustained virologic response and biochemical response. Of the 153 patients in the two treatment groups who had a sustained virologic response, 147 (96 percent) also had a sustained biochemical response. Eighty-four percent of the patients in the peginterferon group who had a sustained biochemical response, as compared with 71 percent of such patients in the interferon group, also had a sustained virologic response. Of the 185 patients in the peginterferon group who had a virologic response at week 48, 76 did not have normal alanine aminotransferase concentrations. In 70 of these 76 patients (92 percent), however, alanine aminotransferase concentrations at week 48 were less than twice the upper limit of normal and were below base-line values. Of particular interest, there was a higher rate of sustained virologic response at week 72 among patients treated with peginterferon alfa-2a who had a virologic but not a biochemical response at week 48 than among those

TABLE 4. RATES OF HISTOLOGIC RESPONSE AT WEEK 72 AMONG PATIENTS WITH PAIRED BIOPSY SPECIMENS.*

PATIENT†	PEGINTERFERON ALFA-2a (N=184)		INTERFERON ALFA-2a (N=167)	
	PERCENT WITH HISTOLOGIC RESPONSE	MEAN CHANGE IN SCORE FROM BASE LINE	PERCENT WITH HISTOLOGIC RESPONSE	MEAN CHANGE IN SCORE FROM BASE LINE
All patients with paired specimens	63	-2.4	55	-2.0
Patients with a virologic response	82	-4.1	86	-4.9
Patients without a virologic response	47	-1.0	44	-1.0
Patients with a biochemical response	78	-3.8	77	-4.1
Patients without a biochemical response	46	-0.9	45	-1.1

*A histologic response was defined as a decrease of at least 2 points in the total score on the Histological Activity Index, where a score of 0 indicates no inflammatory changes and no fibrosis and a score of 22 indicates multilobular necrosis, marked intralobular degeneration and focal necrosis, marked portal inflammation, and cirrhosis.¹³ A virologic response was indicated by undetectable levels of HCV RNA (<100 copies per milliliter), and a biochemical response was indicated by normalization of serum alanine aminotransferase concentrations (to a value at or below the upper limit of normal). A minus sign denotes a decrease.

†Patients are classified according to whether they did or did not have a virologic or biochemical response at the end of the 72-week study period.

who had both a biochemical and a virologic response (64 percent vs. 50 percent), as well as a higher rate of sustained biochemical response (67 percent vs. 60 percent) and a higher rate of histologic response (79 percent vs. 64 percent).

The overall histologic response among the 351 patients with paired pre- and post-treatment biopsy specimens (66 percent of the 531 enrolled patients) is shown in Table 4. Histologic improvement was observed in 63 percent of the patients with paired specimens in the peginterferon group and 55 percent of those with paired specimens in the interferon group. In agreement with the results of other studies of interferon alfa,^{5,16} we found a histologic response in 44 percent to 47 percent of the patients who did not have a virologic response or a biochemical response at week 72, regardless of treatment group.

Multiple and stepwise logistic-regression models were used to explore the effects of various demographic and base-line characteristics on the probability of a sustained virologic response. Pretreatment factors considered were sex; race (white vs. nonwhite); age (>40 vs. ≤40 years); body-surface area (>2 vs. ≤2 m²); body weight (>85 vs. ≤85 kg); body-mass index, calculated as the weight in kilograms divided by the square of the height in meters (>28 vs. ≤28); HCV RNA level (>2 million vs. ≤2 million copies per milliliter); alanine aminotransferase quotient, calculated as the average of the serum alanine aminotransferase

values before treatment, divided by the upper limit of normal (>3 vs. ≤ 3); the Histological Activity Index score (>10 vs. ≤ 10); histologic diagnosis (cirrhosis or bridging fibrosis vs. no cirrhosis or bridging fibrosis); and HCV genotype (type 1 vs. other types). In the multiple logistic-regression model, all these factors, as well as the treatment assignment (peginterferon alfa-2a vs. interferon alfa-2a), were included simultaneously. The results demonstrated that treatment with peginterferon alfa-2a ($P<0.001$), a younger age ($P=0.003$), a smaller body-surface area ($P<0.001$), a lower level of HCV RNA ($P<0.001$), a higher alanine aminotransferase quotient ($P<0.001$), an absence of cirrhosis or bridging fibrosis ($P=0.03$), and an HCV genotype other than type 1 ($P<0.001$) independently and significantly increased the odds of a sustained virologic response. We also performed a multiple logistic-regression analysis that included only factors identified in the final, stepwise logistic-regression model (Fig. 1). The results were consistent with those of the initial multiple logistic-regression model.

Safety

The frequency and severity of adverse events were similar in the two treatment groups, and the adverse events were typical of those previously reported with standard therapy with unmodified interferon alfa (Table 2). Depression occurred in 16 percent of the patients treated with peginterferon alfa-2a and 23 percent of the patients treated with interferon alfa-2a. Psychiatric disorders, the most frequent serious adverse events, were reported in six patients in the peginterferon group (severe depression in four, psychosis in one, and personality disturbance in one) and in four

patients in the interferon group (severe depression in three and psychosis in one). One patient in the peginterferon group died of an accidental heroin overdose 10 days after completing 48 weeks of treatment; the patient had a history of injection-drug abuse, and the death was considered by the investigators to be unrelated to therapy.

In fewer than 1 percent of the patients in each group, therapy was discontinued because of laboratory abnormalities. Doses were modified because of neutropenia in 11 percent of the patients in the peginterferon group and in 7 percent of the patients in the interferon group. The neutrophil count during treatment decreased to less than 500 per cubic millimeter in 12 patients in the peginterferon group and in 4 in the interferon group. No serious infections were observed in patients with a neutrophil count below 500 per cubic millimeter, and in none of the patients was treatment discontinued because of neutropenia.

A platelet count of less than 50,000 per cubic millimeter during treatment was uncommon, occurring in only four patients in each treatment group. No patient in either group had a platelet count of less than 20,000 per cubic millimeter during treatment, and in none of the patients was treatment discontinued because of thrombocytopenia. Anemia was reported in three patients in the peginterferon group and in none in the interferon group. Treatment was discontinued in one patient in the peginterferon group because of anemia.

DISCUSSION

In patients with chronic hepatitis C, we found that once-weekly administration of 180 μg of peginterferon alfa-2a, a compound consisting of interferon alfa-2a

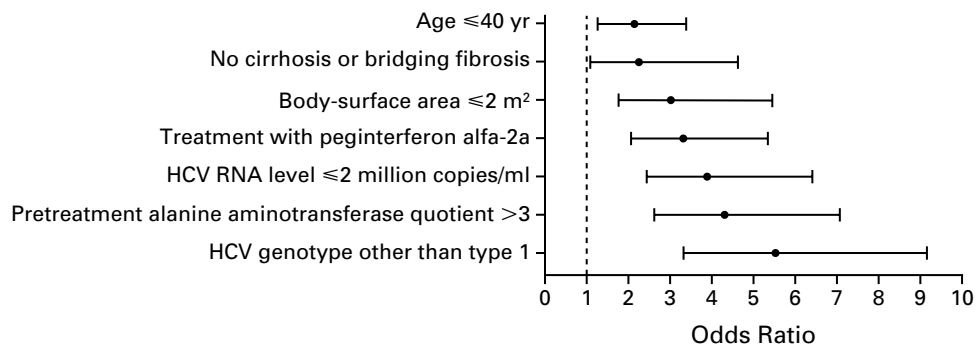


Figure 1. Independent Factors Associated with a Sustained Virologic Response, According to Multiple Logistic-Regression Analysis.

The independent factors used in this analysis were age (>40 vs. ≤ 40 years), histologic diagnosis (cirrhosis or bridging fibrosis vs. no cirrhosis or bridging fibrosis), body-surface area (>2 vs. ≤ 2 m²), treatment assignment (peginterferon alfa-2a vs. interferon alfa-2a), HCV RNA level (>2 million vs. ≤ 2 million copies per milliliter), the alanine aminotransferase quotient (the average of the serum alanine aminotransferase values before treatment divided by the upper limit of normal) (>3 vs. ≤ 3), and HCV genotype (type 1 vs. other types). An odds ratio equal to 1 (dashed line) indicates no difference between the subgroups defined according to the given factor. Bars indicate 95 percent confidence intervals.

with an attached 40-kd branched-chain polyethylene glycol moiety, was associated with a significantly higher rate of sustained virologic response than was a regimen of interferon alfa-2a given three times weekly. The improved efficacy of peginterferon alfa-2a may be due to the sustained antiviral effect associated with the enhanced pharmacokinetics of this molecule.¹¹ The virologic response to peginterferon alfa-2a was similar to that previously reported for combination therapy with interferon alfa and ribavirin, given for 48 weeks.^{4,5,17} The base-line characteristics of the two groups of patients in the present study are similar to those of patients in two large trials that compared interferon with a combination of interferon and ribavirin.^{4,5} However, the results of ongoing trials that directly compare these two treatments are needed before conclusions about relative efficacy and safety can be drawn.

In previous studies, combination therapy with interferon alfa and ribavirin was associated with a higher rate of response at the end of treatment and a smaller number of patients with subsequent relapse than was therapy with interferon alone.^{4,5,16,18} In our study, the rate of response at the end of treatment was higher in the group assigned to receive peginterferon alfa-2a than in the group assigned to receive unmodified interferon alfa-2a, but the rate of relapse between weeks 48 and 72 was also higher among the patients who had a response to peginterferon alfa-2a than among those who had a response to unmodified drug.

A discordance between the virologic and the biochemical responses at week 48 was observed in more of the patients assigned to receive peginterferon alfa-2a than of those assigned to receive unmodified interferon. Patients who had a virologic response at week 48 but who did not have a normal serum alanine aminotransferase concentration at this time had a better histologic response at week 72 than did the entire study cohort or the subgroup of patients who had both a virologic and a biochemical response at week 48. This finding indicates that peginterferon alfa-2a was not associated with long-term adverse effects on the liver. In addition, patients who had a virologic response but not a biochemical response at week 48 had better overall rates of virologic and biochemical responses at week 72 than patients who had both a virologic and a biochemical response at week 48. The reason for the better response in this subgroup of patients is not known, but it may be associated with a more pronounced immune response in the host and with the elimination of reservoirs of infected cells in these patients.

The beneficial effects of peginterferon alfa-2a were seen in patients in whom treatment has historically been unsuccessful. For example, therapy with interferon alfa alone results in a sustained virologic response in fewer than 10 percent of patients infected with HCV genotype 1.^{5,19} In the present study, peginterferon alfa-2a was associated with a 28 percent rate of sustained virologic response in patients infected with

HCV genotype 1, a rate that appears to be similar to that achieved with interferon alfa and ribavirin given as combination therapy for 48 weeks.⁵ No substantial differences in the rates of virologic response were observed between patients infected with HCV subtype 1a and those infected with HCV subtype 1b. In our study, 45 percent of patients with bridging fibrosis or cirrhosis had a sustained virologic response to peginterferon alfa-2a, a finding consistent with data from a large phase 2–3 study of the drug in patients with cirrhosis.²⁰

In general, peginterferon alfa-2a was well tolerated, and laboratory abnormalities and adverse events associated with its use were typical of those associated with unmodified interferon. In none of the patients in either treatment group was therapy discontinued because of neutropenia. Anemia and thrombocytopenia were rare in both treatment groups. In summary, peginterferon alfa-2a is a safe and effective treatment for HCV infection. Determination of its place in the treatment of this disorder awaits the results of studies in which it is compared with interferon–ribavirin combination therapy.

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APPENDIX

In addition to the authors, members of the study group who participated in this study included P. Mills, Gartnavel General Hospital, Glasgow, United Kingdom; G.M. Dusheiko, Royal Free Hospital, London; S. Ryder, Queens Medical Centre, Nottingham, United Kingdom; P. Buggisch, Universitätskrankenhaus Eppendorf, Hamburg, Germany; T. Göser, Universitätsklinik Köln, Cologne, Germany; D. Grandt, Universitätsklinikum der Gesamthochschule Essen, Essen, Germany; D. Häussinger, Heinrich Heine Universität, Düsseldorf, Germany; U. Hopf, Universitätsklinikum Rudolph Virchow, Berlin, Germany; M.P. Manns, Medizinische Hochschule Hannover, Hannover, Germany; G. Ramadori, Universität Göttingen, Göttingen, Germany; W. Schmidt, Christian Albrechts Universität, Kiel, Germany; G.R. Pape, Klinikum Grosshadern, Munich, Germany; S.-D. Lee, Veterans General Hospital Taipei, Taiwan; J. Rodes, Clinico y Provincial, Barcelona, Spain; R.E. Mur, Hospital Vall d'Hebron, Barcelona, Spain; J. Salmeron, Clinico San Cecilio, Granada, Spain; R. Moreno, Hospital La Princesa, Madrid; P. Adams, London Health Science Centre University, London, Ont., Canada; V. Bain, University of Alberta, Edmonton, Canada; W. DePew, Hotel Dieu Hospital, Kingston, Ont., Canada; S. Lee and M. Swain, Heritage Medical Research Clinic, Calgary, Alta., Canada; B. Rosser, Health Sciences Centre, Winnipeg, Man., Canada; S. Pedder, Hoffmann–LaRoche, Nutley, N.J.; M. Sherman, Toronto Hospital, Toronto; E. Yoshida, Vancouver Hospital and Health Science Centre, Vancouver, B.C., Canada; S. Roberts, Alfred Hospital, Prahran, Victoria, Australia; A. Juarez, Hospital de Especialidades, Mexico; and L. Munoz, Hospital Universitario J.E. Gonzalez, Monterrey, Mexico. Members of the Safety Review Board were H. Bonkovsky, University of Massachusetts Medical Center, Worcester; J. Dienstag, Massachusetts General Hospital, Boston; and O. Weiland, Karolinska Institute, Huddinge, Sweden.

REFERENCES

1. Carithers RL Jr, Emerson SS. Therapy of hepatitis C: meta-analysis of interferon alfa-2b trials. *Hepatology* 1997;26:Suppl 1:83S-88S.

2. Poynard T, Leroy V, Cohard M, et al. Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. *Hepatology* 1996;24:778-89.
3. Farrell GC. Therapy of hepatitis C: interferon alfa-n1 trials. *Hepatology* 1997;26:Suppl:1:96S-100S.
4. Poynard T, Marcellin P, Lee SS, et al. Randomized trial of interferon α 2b plus ribavirin for 48 weeks or for 24 weeks versus α 2b plus placebo for 48 weeks for treatment of chronic hepatitis C virus. *Lancet* 1998;352:1426-32.
5. McHutchison JG, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. *N Engl J Med* 1998;339:1485-92.
6. Wills RJ. Clinical pharmacokinetics of interferons. *Clin Pharmacokinet* 1990;19:390-9.
7. Zeuzem S, Schmidt JM, Lee J-H, Rüster B, Roth WK. Effect of interferon alfa on the dynamics of hepatitis C virus turnover in vivo. *Hepatology* 1996;23:366-71.
8. Neumann AU, Lam NP, Dahari H, et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon- α therapy. *Science* 1998;282:103-7.
9. Lam NP, Neumann AU, Gretsch DR, Wiley TE, Perelson AS, Layden TJ. Dose-dependent acute clearance of hepatitis C genotype 1 virus with interferon alfa. *Hepatology* 1997;26:226-31.
10. Nieforth KA, Nadeau R, Patel IH, Mould D. Use of an indirect pharmacodynamic stimulation model of MX protein induction to compare in vivo activity of interferon alfa-2a and a polyethylene glycol-modified derivative in healthy subjects. *Clin Pharmacol Ther* 1996;59:636-46.
11. Xu Z-X, Hoffman J, Patel I, Joubert P. Single-dose safety/tolerability and pharmacokinetic/pharmacodynamics (PK/PD) following administration of ascending subcutaneous doses of pegylated-interferon (PEG-IFN) and interferon α -2a (IFN α -2a) to healthy subjects. *Hepatology* 1998;28:Suppl:702A. abstract.
12. Algranati NE, Sy S, Modi M. A branched methoxy 40 kDa polyethylene glycol (PEG) moiety optimizes the pharmacokinetics (PK) of peginterferon α -2a (PEG-IFN) and may explain its enhanced efficacy in chronic hepatitis C (CHC). *Hepatology* 1999;30:Suppl:109A. abstract.
13. Knodell RG, Ishak KG, Black WC, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology* 1981;1:431-5.
14. Breslow NE, Day NE. Statistical methods in cancer research. Vol. 1. The analysis of case-control studies. Lyon, France: International Agency for Research on Cancer, 1980. (IARC scientific publications no. 32.)
15. Dunnett CW, Gent M. An alternative to the use of two-sided tests in clinical trials. *Stat Med* 1996;15:1729-38.
16. Davis GL, Esteban-Mur R, Rustgi V, et al. Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. *N Engl J Med* 1998;339:1493-9.
17. Lai MY, Kao JH, Yang PM, et al. Long-term efficacy of ribavirin plus interferon alfa in the treatment of chronic hepatitis C. *Gastroenterology* 1996;111:1307-12.
18. Reichard O, Norrkans G, Frydén A, Braconier JH, Sonnerborg A, Weiland O. Randomised, double-blind, placebo-controlled trial of interferon alfa-2b with and without ribavirin for chronic hepatitis C. *Lancet* 1998;351:83-7.
19. Martinot-Peignoux M, Marcellin P, Pouteau M, et al. Pretreatment serum hepatitis C virus RNA levels and hepatitis C virus genotype are the main and independent prognostic factors of sustained response to interferon alfa therapy in chronic hepatitis C. *Hepatology* 1995;22:1050-6.
20. Heathcote EJ, Shiffman ML, Cooksley WGE, et al. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. *N Engl J Med* 2000;343:1673-80.

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