Peginterferon Alfa-2a Plus Ribavirin Is More Effective Than Peginterferon Alfa-2b Plus Ribavirin for Treating Chronic Hepatitis C Virus Infection

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BACKGROUND & AIMS: Patients with chronic hepatitis C virus (HCV) infection are frequently treated with a combination of pegylated interferon (peginterferon) and ribavirin. This study compared the efficacy and safety of peginterferon alfa-2a and peginterferon alfa-2b, each in combination with ribavirin. **METHODS:** A total of 320 consecutive, treatment-naive, HCV RNA–positive patients with chronic hepatitis were randomly assigned to once-weekly peginterferon alfa-2a (180 μg, group A) or peginterferon alfa-2b (1.5 μg/kg, group B) plus ribavirin 1000 mg/day (body weight <75 kg) or 1200 mg/day (body weight ≥75 kg) for 48 weeks (genotype 1 or 4) or 24 weeks (genotype 2 or 3). The primary end point was sustained virological response (SVR) by intention-to-treat. **RESULTS:** More patients in group A than group B achieved an SVR (110/160 [68.8%] vs 87/160 [54.4%]; $P = .008$). Higher SVR rates were obtained in group A than group B among patients with genotype 1/4 (51/93 [54.8%] vs 37/93 [39.8%]; $P = .04$), with genotype 2/3 (59/67 [88.1%] vs 50/67 [74.6%]; $P = .046$), without cirrhosis (96/127 [75.6%] vs 75/134 [55.9%]; $P = .005$), and with baseline levels HCV RNA >500,000 IU/mL (58/84 [69%] vs 43/93 [46.2%]; $P = .002$). SVR rates in groups A and B were not statistically different among patients with baseline HCV RNA ≤500,000 IU/mL (52/76 [68.4%] vs 44/67 [65.7%]; $P = .727$) or in patients with cirrhosis (14/33 [42.4%] vs 12/26 [46.1%]; $P = .774$). **CONCLUSIONS: In patients with chronic HCV infection, peginterferon alfa-2a plus ribavirin produced a significantly higher SVR rate than peginterferon alfa-2b plus ribavirin.**

Pegylated interferon (peginterferon) plus ribavirin is the treatment of choice for chronic infection with hepatitis C virus (HCV). When administered in a pegylated formulation, the half-life of interferon is prolonged because of covalent binding of the polyethylene glycol molecule to the interferon moiety. Consequently, sustained virological response (SVR) rates have increased from <20% to >60% with the combination of peginterferon plus ribavirin in patients with chronic HCV infection.[1–4]

There are 2 commercially available peginterferons, and randomized controlled trials have shown that both peginterferon alfa-2a and peginterferon alfa-2b are effective and safe when administered in combination with ribavirin. Recently, data from 2 small clinical studies suggest that peginterferon alfa-2a produces a 14%–15% greater rate of early virological response (EVR) or SVR than peginterferon alfa-2b, although both studies failed to show a statistically significant difference because of insufficient sample sizes.[5,6] The present study aimed to compare the efficacy and safety of peginterferon alfa-2a versus peginterferon alfa-2b in combination with an identical dose of ribavirin in patients with chronic HCV infection.

Patients and Methods

Selection of Patients

Consecutive interferon-naive adults (aged 18 years or older) seen at the Liver Unit of Cardarelli Hospital (Napoli, Italy) who had chronic HCV infection were eligible for enrollment. Patients were required to have a detectable serum HCV RNA level, have an alanine aminotransferase (ALT) level >1.5 times the upper limit of normal for ≥6 months, have a liver biopsy performed within 12 months of starting treatment graded according to Scheuer's[7] criteria (unless not indicated or refused), have a negative pregnancy test result, use contraceptive methods during therapy and for 6 months after the end of treatment, and have abstained from alcohol use for at least 6 months. Cirrhosis was assessed on the basis of clinical and laboratory test results, liver-spleen ultrasonography, and upper gastrointestinal endoscopy in patients ineligible for and in those who refused a liver biopsy. Patients were excluded if they had a hemoglobin level <120 g/L; had a neutrophil count $<1.5 \times 10^9$/L or a platelet count $<70 \times 10^9$/L; had an abnormal serum creatinine level; were hepatitis B surface antigen positive or human immunodeficiency virus positive; had any other cause of liver disease; had a history of liver decom-

Abbreviations used in this paper: CI, confidence interval; ETR, end-of-treatment response; EVR, early virological response; peginterferon, pegylated interferon; SVR, sustained virological response.

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pensation; had clinically relevant depression or any other psychiatric disease; had cancer; had severe cardiac, pulmonary, or renal disease; or had uncontrolled diabetes or severe hypertension with vascular complications, including retinopathy.

Study Design

This prospective, randomized, open-label, single-center trial was conducted at the Liver Unit of Cardarelli Hospital. The study design was approved by the independent ethical committee of the institution, and all patients provided written informed consent to treatment. Patients who accepted the treatment were assigned to one of the 2 treatment arms on the basis of a computer-generated randomization list that was not available to the treating physician. The physician received the communication on the allocation of each patient from an independent researcher who did not know the patient or his or her characteristics except the genotype in order to use the list prepared for genotype 1 or 4 or the list for genotype 2 or 3. Patients at the end of the diagnostic process, if they accepted to be treated, were randomized.

Patients assigned to group A received subcutaneous peginterferon alfa-2a 180 μg once weekly (Pegasys; Hoffmann–LaRoche, Basel, Switzerland) plus ribavirin (Copegus; Hoffmann–LaRoche). Those assigned to group B received subcutaneous peginterferon alfa-2b 1.5 μg/kg body wt once weekly (PegIntron; Schering–Plough Corp, Kenilworth, NJ) plus ribavirin (Rebetol; Schering–Plough Corp). The dosage of ribavirin was determined by body weight (1000 mg/day in patients $<$75 kg; 1200 mg/day in patients $\geq$75 kg). Treatment was administered for 24 weeks in patients infected with HCV genotype 2 or 3 and for 48 weeks in patients infected with HCV genotype 1 or 4. Drug dosages and treatment durations were established according to recommendations of the Italian Association for the Study of the Liver (Associazione Italiana per lo Studio del Fegato), which were prepared in the autumn of 2003 and released in February 2004.

Adherence was measured according to the "80/80/80" rule,[8] which refers to the quantity of peginterferon and ribavirin administered (percentage of the planned total dose) and the total duration of treatment (percentage of the planned duration). Patients who took at least 80% of the 2 drugs for at least 80% of the scheduled time were considered to be adherent.

Serum HCV RNA was evaluated with a qualitative polymerase chain reaction assay (Cobas Amplicor HCV Test v2.0, Roche Diagnostics (Hoffmann-LaRoche, Basel, Switzerland); limit of detection, 50 IU/mL) before treatment (week 0); at study weeks 12, 24, and 48 in all patients; and at week 72 in patients infected with genotype 1 or 4. A quantitative HCV RNA test (Cobas Amplicor HCV Monitor Test v2.0, Roche Diagnostics; limit of quantization, 600 IU/mL) was performed at weeks 0, 12, and 24. HCV genotype was assessed by INNO-LiPA (Innogenetics NV, Gent, Belgium) HCV test.

Patients were assessed every 2 weeks during the first 2 months and every month thereafter during treatment as well as 3 and 6 months after the end of therapy. Complete blood counts and serum aminotransferase (aspartate aminotransferase/ALT) levels were assessed every 2 weeks for the first 2 months of therapy and monthly thereafter or more frequently if necessary. Serum creatinine level and routine laboratory test results were checked monthly. Thyroid function tests were performed at baseline and every 3 months thereafter or more frequently if necessary. Cardiac, chest, renal, and ocular assessment was performed before and at the end of therapy. Hepatobiliary ultrasonography was conducted at study entry and every 6 months during the study and follow-up periods.

Definition of Response and End Points

End-of-treatment response (ETR) and SVR were defined, respectively, as a negative qualitative HCV RNA level at the end of treatment and after 24 weeks of untreated follow-up. EVR was defined as qualitative HCV RNA negative (complete EVR) or a reduction from baseline HCV RNA level of >2 $\log_{10}$ IU/mL at week 12 (partial EVR). All patients with detectable HCV RNA at week 24 stopped treatment and were classified as nonresponders. Virological relapse was defined as reversion to HCV RNA–positive status in a patient who had an undetectable HCV RNA level ($<$50 IU/mL) at the end of treatment. Adverse events were recorded during each outpatient visit. No patient received treatment with erythropoietin or granulocyte colony–stimulating factor. The end point of the study was SVR.

Dose Modifications

The dosage of peginterferon was reduced by half if the neutrophil count decreased to $<0.75 \times 10^9$/L or the platelet count decreased to $<50 \times 10^9$/L. Peginterferon treatment was discontinued if the neutrophil count was $<0.50 \times 10^9$/L or the platelet count was $<25 \times 10^9$/L. Peginterferon dosages were reduced in 25% decrements or discontinued because of adverse events. The dosage of ribavirin was reduced in 200-mg decrements, as necessary, if hemoglobin level decreased to $<$100 g/L or by $\geq$30 g/L, or in the event of a severe cough or intolerable itching. Ribavirin treatment was discontinued if hemoglobin level decreased to $<$85 g/L.

Statistical Analysis

The study was designed to have 80% power to detect a difference of 15% or more in SVR rates between the 2 treatment groups. Based on this assumption, 160 patients were enrolled in each treatment group. Continuous variables are expressed as mean and SD or median and range. Frequencies were calculated for categorical variables, with the difference between groups reported with 95% confidence intervals (CIs). The Mann–Whitney rank sum test was used to compare continuous variables. The χ^2 test was used, with Yates' correction where appli-

Table 1. Baseline Characteristics

	Group A: peginterferon alfa-2a plus ribavirin (n = 160)	Group B: peginterferon alfa-2b plus ribavirin (n = 160)	Overall (n = 320)
Demography and anthropometry			
Mean (SD) age (*y*)	51.3 (10.3)	48.9 (11.3)	50.2 (10.9)
Sex, male/female (% male)	81/79 (50.6)	94/66 (58.8)	175/145 (54.7)
Mean (SD) body wt (*kg*)	70.4 (10.6)	69.9 (10.7)	70.0 (10.7)
Mean (SD) body mass index (kg/m^2)	25.5 (3.1)	25.3 (3.0)	25.4 (3.1)
Body wt <75 kg, n (%)	107 (66.9)	110 (68.8)	217 (67.8)
Body wt ≥75 kg, n (%)	53 (33.1)	50 (31.3)	103 (32.2)
Diagnosis, n (%)			
Chronic hepatitis	127 (79.4)	134 (83.7)	261 (81.6)
Cirrhosis	33 (20.6)	26 (16.3)	59 (18.4)
With biopsy	21 (13.1)	19 (11.9)	40 (12.5)
Without biopsy	12 (7.5)	7 (4.4)	19 (5.9)
HCV RNA level in serum			
Median (range) HCV RNA ($IU/mL \times 10^3$)	570 (0.37–8550)	604 (0.20–10,800)	600 (0.20–10,800)
No. (%) with ≤500 IU/mL × 10^3	76 (47.5)	67 (41.9)	143 (44.7)
No. (%) with >500 IU/mL × 10^3	84 (52.5)	93 (58.1)	177 (55.3)
Genotype 1/4, median (range)	600 (0.37–8550)	654 (0.86–10,800)	610 (0.37–10,800)
Genotype 2/3, median (range)	530 (11.9–8138)	600 (0.20–5170)	594 (0.20–8138)
Genotype, n (%)			
1	89 (55.6)	92 (57.5)	181 (56.6)
2	49 (30.6)	50 (31.2)	99 (30.9)
3	18 (11.3)	17 (10.6)	35 (10.9)
4	4 (2.50)	1 (0.62)	5 (1.6)
1/4	93 (66.3)	93 (66.3)	186 (58.1)
2/3	67 (33.7)	67 (33.7)	134 (41.9)
1/4, chronic hepatitis/cirrhosis	69 (74.2)/24 (25.8)	75 (88.1)/18 (11.9)	144 (77.4)/42 (22.6)
2/3, chronic hepatitis/cirrhosis	58 (86.6)/9 (13.4)	59 (88.1)/8 (11.9)	117 (87.3)/17 (12.7)
Mean (SD) ALT level (times upper limit of normal)	2.36 (1.44)	2.45 (1.82)	2.40 (1.64)

cable, to compare categorical variables. Multivariable logistic stepwise regression analysis was used to explore the independent effect of the treatment and the baseline factors (age, body weight, body mass index, sex, presence of cirrhosis, ALT level, HCV RNA level, HCV genotype) on the likelihood of achieving SVR. All *P* values were 2 sided with a .05 threshold for statistical significance. All statistical procedures were performed using SPSS version 13.0 for Windows (SPSS Inc, Chicago, IL). All patients who took at least one dose of the study medication were included in the efficacy analysis according to intention-to-treat principle. Patients who withdrew from the study for any reason were considered to be nonresponders in the efficacy assessment. Safety results are reported for the entire population and by HCV genotype because of the difference in treatment duration. In fact, patients treated for longer durations are at greater risk for adverse effects.

Results

Between March 2004 and December 2006, 408 patients were screened, of whom 320 (78%) were enrolled (Supplementary Figure 1). All patients were white, and the baseline characteristics of the 2 treatment groups were similar (Table 1).

A liver biopsy specimen was obtained in the chronic hepatitis group in 230 patients (88.1%), in whom the fibrosis grade was 2.13 (±1.03). Thirty-one patients (9.7%) refused to submit to the procedure. In this group, we used the criteria for diagnosis outlined in Patients and Methods because it was absolutely necessary to exclude cirrhosis. In patients with clear-cut signs of cirrhosis (19/320 [5.9%]), biopsy was not ethically justified because of the risk and no benefit for the patient. The criteria we used for clinical diagnosis of cirrhosis were presence of esophageal varices at endoscopy, low platelet count (<100 × 10^9/L), and ultrasound alterations typical for liver cirrhosis. The diagnosis was assumed as correct only if all 3 criteria were satisfied.

Efficacy

Overall, an EVR, as reported in Table 2, was obtained by 253 of 320 patients (79.1%): 136 (85%) in group A and 117 in group B (73%). This difference is statistically significant (difference, 12%; 95% CI, 2.9%–21%; $P = .009$). The majority of patients obtained a complete EVR, while the number of those who obtained a partial EVR was only 8.8%, with no difference between group A and group B.

An ETR was obtained in 237 patients (74.1%), 134 (83.8%) in group A versus 103 patients (64.4%) in group B (difference, 19.4%; 95% CI, 9.8%–28.5%; $P < .0001$), and an SVR was obtained in 197 patients (61.6%; 95% CI, 56.2%–66.9%), including 110 of 160 (68.8%; 95% CI, 61.6%–75.9%) in group A versus 87 of 160 (54.4%; 95% CI, 46.7%–62.1%) in group B. The difference between the 2

Table 2. Virological Response During Treatment and at the End of Follow-Up

	Group A: peginterferon alfa-2a plus ribavirin (n = 160)	Group B: peginterferon alfa-2b plus ribavirin (n = 160)	Overall (n = 320)	*P* value for the comparison with group A vs B
EVR, n (%)	136 (85)	117 (73.1)	253 (79.1)	.009
Complete	121 (75.6)	104 (65)	223 (69.7)	.037
Partial	15 (9.4)	13 (8.1)	28 (8.8)	.692
ETR, n (%)	134 (83.8)	103 (64.4)	237 (74.1)	<.0001
SVR, n (%)	110 (68.8)	87 (54.4)	197 (61.6)	.008
EVR by genotypes, no./total (%)				
1/4	72/93 (77.4)	62/93 (66.7)	134/186 (72.0)	.102
2/3	64/67 (95.5)	55/67 (82.1)	119/134 (88.8)	.028
2	47/49 (95.9)	41/50 (82.0)	88/99 (88.9)	.059
3	17/18 (94.4)	14/17 (82.4)	31/35 (88.6)	.554
SVR by genotypes, no./total (%)				
1/4	51/93 (54.8)	37/93 (39.8)	88/186 (47.3)	.04
2/3	59/67 (88.1)	50/67 (74.6)	109/134 (81.3)	.046
2	45/49 (91.8)	38/50 (76.0)	83/99 (83.8)	.062
3	14/18 (77.8)	12/17 (70.6)	26/35 (74.3)[a]	.92
SVR by diagnosis, no./total (%)				
Chronic hepatitis	96/127 (75.6)	75/134 (55.9)	171/261 (65.5)	.005
Cirrhosis	14/33 (42.4)	12/26 (46.1)	26/59 (44.1)	.774
SVR by baseline HCV RNA level in serum, no./total (%)				
≤500,000 IU/mL	52/76 (68.4)	44/67 (65.7)	96/143 (67.1)	.727
>500,000 IU/mL	58/84 (69.0)	43/93 (46.2)	101/177 (57.1)	.002

[a] $P = .21$ for the comparison between SVR in genotype 2 versus genotype 3.

groups is 14.4% (95% CI, 3.7%–24.6%; $P = .008$). The total number of patients who experienced a relapse during follow-up was 40 of 320 (12.5%), including 24 of 160 (15%) in group A versus 16 of 160 (10%) in group B (difference, 5%; 95% CI, −2.3% to 12.4%; $P = .176$). Among patients without cirrhosis, an SVR was achieved by 171 of 261 patients (65.5%), including 96 of 127 (75.6%) in group A and 75 of 134 (55.9%) in group B (difference, 19.7%; 95% CI, 8.11%–30.4%; $P = .005$). Among the 59 patients with cirrhosis, 26 obtained an SVR (44.1%), including 14 of 33 (42.4%) in group A versus 12 of 26 (46.1%) in group B (difference, 3.7%; 95% CI, −20.4% to 27.6%; $P = .774$). An SVR was obtained in 96 of 143 patients (67.1%) with a baseline HCV RNA level ≤500,000 IU/mL, including 52 of 76 (68.4%) in group A and 44 of 67 (65.7%) in group B (difference, 2.7%; 95% CI, −12.4% to 17.9%; $P = .727$). In 177 patients with a baseline HCV RNA level >500,000 IU/mL, 101 achieved an SVR (57.1%), including 58 of 84 (69%) in group A and 43 of 93 (46.2%) in group B (difference, 22.8%; 95% CI, 8.2%–36.0%; $P = .002$). An ETR was obtained in 116 of 186 patients (62.4%) infected with genotype 1 or 4, including 70 of 93 (75.3%) in group A versus 46 of 93 (49.5%) in group B (difference, 25.8%; 95% CI, 11.9%–38.4%; $P = .0003$), and an SVR was obtained in 88 of 186 patients (47.3%), including 51 of 93 (54.8%) in group A and 37 of 93 (39.8%) in group B (difference, 15%; 95% CI, 0.72%–28.5%; $P = .040$). Relapse during follow-up occurred in 28 patients (15.1%) overall, including 19 of 93 (20.4%) in group A and 9 of 93 (9.7%) in group B (difference, 10.7%; 95% CI, 0.38%–21.1%; $P = .040$). Among 134 patients infected with genotype 2 or 3, 121 (90.3%) achieved an ETR, including 64 of 67 (95.5%) in group A and 57 of 67 (85.1%) in group B (difference, 10.4%; 95% CI, 0.16%–21.3%; $P = .80$), and an SVR was obtained by 109 of 134 patients (81.3%), including 59 of 67 (88.1%) in group A and 50 of 67 (74.6%) in group B (difference, 13.5%; 95% CI, 0.14%–26.4%; $P = .046$). A total of 12 of 134 patients with genotype 2 or 3 experienced a relapse during follow-up (8.9%), including 5 of 67 (7.5%) in group A and 7 of 67 (10.4%) in group B (difference, 2.9%; 95% CI, −7.32% to 13.5%; $P = .54$). Patients infected with genotype 2 had a higher overall SVR rate (83/99; 83.8%) than those infected with genotype 3 (26/35; 74.3%), although the difference was not statistically significant ($P = .21$). Among those with genotype 2 infection, 45 of 49 patients (91.8%) in group A and 38 of 50 (76%) in group B ($P = .06$) obtained an SVR. Among those infected with genotype 3, an SVR was obtained by 14 of 18 patients (77.8%) in group A and 12 of 17 (70.6%) in group B ($P = .92$).

Factors Related to SVR

According to multivariate stepwise analysis, we included in the model the following preselected variables: age, body weight, body mass index, sex, absence of cirrhosis, ALT level, HCV RNA level, HCV genotype, and schedule of treatment. Male gender (odds ratio, 1.93; 95% CI, 1.17–3.20; $P = .011$), absence of cirrhosis (odds ratio, 2.36; 95% CI, 1.28–4.41; $P = .007$), treatment with peginterferon alfa-2a (odds ratio, 2.32; 95% CI, 1.39–3.88; $P = .001$), and infection with genotype 2 or 3 (odds ratio,

4.83; 95% CI, 2.81–8.31; $P < .0001$) were all independently associated with SVR.

Adverse Events and Dose Reductions

The dosage of peginterferon and/or ribavirin was reduced in most patients, and only 30 of 320 patients (9.4%) reported no adverse events. The type and incidence of adverse events were very similar in the 2 treatment groups. Twenty-six patients (8.1%) were classified as nonresponders because of interruption of therapy due to any type of adverse event, including 4 of 26 (15.4%) in group A and 22 of 26 (84.6%) in group B ($P = .0005$). In detail, for adverse events, the causes for stopping therapy in group A were dermatitis (1), severe depression (1), pruritus (1), and hyperthyroidism (1). In group B, the causes were fatigue (2), myalgia (2), severe depression (3), nausea (1), pruritus (2), alopecia (1), irritability (1), hyperthyroidism (1), decreased appetite (2), dermatitis (1), and cough (1). Of the 5 patients with laboratory abnormalities, one patient discontinued because of a high decrease in platelet count, 2 patients discontinued because of neutropenia, and the other 2 patients discontinued because of anemia. The use of erythropoietin and granulocyte-stimulating growth factors was prohibited by regulation of the National Health System at time of the planning of the study. Only recently the National Health System has allowed the use of the 2 drugs, but only for responders, to avoid the loss of therapeutic response; however, this was done when it was no longer necessary for our patients because the trial was at the end.

More than 50% of patients were unable to comply with the 80/80/80 rule, especially those infected with genotype 1 or 4 (Table 3). No patient was lost to follow-up. No serious adverse events were reported. Serious adverse events were defined as follows: death, any kind of life-threatening event, and any kind of adverse effect requiring hospitalization.

Discussion

In this study, peginterferon alfa-2a produced a significantly greater SVR rate than peginterferon alfa-2b in patients with chronic HCV infection. Previous comparative studies have investigated the antiviral activity and pharmacokinetic properties of the 2 formulations.[9–11] A pharmacokinetic analysis in 22 patients showed that peginterferon alfa-2a was still detectable 168 hours after administration at a dosage of 180 μg/wk but

Table 3. Adverse Events Included Are Those Reported With a Frequency More Than 5%

	Group A peginterferon alfa-2a plus ribavirin (#93) genotypes 1 and 4	Group B peginterferon alfa-2b plus ribavirin (#93) genotypes 1 and 4	Group A peginterferon alfa-2a plus ribavirin (#67) genotypes 2 and 3	Group B peginterferon alfa-2b plus ribavirin (#67) genotypes 2 and 3	Overall
Discontinuation	3 (3.2)	13 (14)	1 (1.5)	9 (13.4)	26 (8.1)
Laboratory abnormalities	0	5 (5.4)	0	0	5 (1.6)
Adverse events	3 (3.2)	8 (8.6)	1 (1.5)	9 (13.4)	21 (6.6)
Dose modification					
Anemia	17 (18.3)	20 (21.5)	13 (19.4)	10 (14.9)	60 (18.7)
Neutropenia	3 (3.2)	3 (3.2)	1 (1.5)	1 (1.5)	8 (2.5)
Thrombocytopenia	4 (4.3)	3 (3.2)	3 (4.5)	3 (4.5)	13 (4.1)
Adverse events	33 (35.5)	33 (35.5)	19 (28.4)	23 (34.3)	108 (33.7)
The 80/80/80 rule[a]	43 (46.2)	20 (21.5)[b]	48 (71.6)	42 (62.7)[c]	153 (47.8)
No adverse events	9 (9.7)	7 (7.5)	7 (10.4)	7 (10.4)	30 (9.4)
Any adverse events					
Fatigue	54 (58.1)	55 (59.1)	39 (58.2)	31 (46.3)	
Arthralgia	34 (36.6)	42 (45.2)	14 (20.9)	24 (35.8)	
Irritability	30 (32.3)	30 (32.3)	23 (34.3)	19 (28.4)	
Decreased appetite	23 (24.7)	21 (22.6)	7 (10.4)	13 (19.4)	
Fever	22 (23.7)	44 (47.3)	8 (11.9)	31 (46.3)	
Pruritus	15 (16.1)	16 (17.2)	12 (17.9)	8 (11.9)	
Headache	14 (15.1)	18 (19.4)	11 (16.4)	10 (14.9)	
Cough	14 (15.1)	15 (16.1)	6 (9.0)	5 (7.5)	
Myalgia	14 (15.1)	16 (17.2)	9 (13.4)	14 (20.9)	
Dermatitis	13 (14.0)	7 (7.5)	6 (9.0)	2 (3.0)	
Nausea	10 (10.8)	12 (12.9)	4 (6.0)	3 (4.5)	
Dyspnea	11 (11.8)	13 (14.0)	2 (3.0)	6 (9.0)	
Thyroid abnormalities	10 (10.8)	9 (9.7)	2 (3.0)	0	
Insomnia	7 (7.5)	8 (8.6)	4 (6.0)	9 (13.4)	
Alopecia	6 (6.5)	13 (14.0)	3 (4.5)	9 (13.4)	
Depression	5 (5.4)	6 (6.5)	6 (9.0)	3 (4.5)	

NOTE. All values are expressed as n (%).

[a]Patients who took at least 80% of the 2 drugs for at least 80% of the scheduled time.

[b]$P = .0004$ for the comparison between peginterferon alfa-2a and peginterferon alfa-2b in genotypes 1 and 4.

[c]$P = .27$ for the comparison between peginterferon alfa-2a and peginterferon alfa-2b in genotypes 2 and 3.

that peginterferon alfa-2b administered at a dosage of 1.0 $\mu g \cdot kg^{-1} \cdot wk^{-1}$ (ie, lower than in the present study) was undetectable in 92% of patients at the same time point.[9] At week 12, mean serum HCV RNA levels were significantly lower in patients treated with peginterferon alfa-2a than peginterferon alfa-2b ($P < .01$). In contrast, the pharmacodynamic profile (induction of 2′-5′-oligoadenylate synthetase, neopterin, and β_2 -microglobulin activity) of the 2 peginterferons was similar in the same patients.[10] In another study[11] in 36 patients with genotype 1, those receiving peginterferon alfa-2b 1.5 $\mu g \cdot kg^{-1} \cdot wk^{-1}$ had significantly greater up-regulation of interferon alfa response genes than those receiving peginterferon alfa-2a 180 μg/wk (ribavirin 13 $mg \cdot kg^{-1} \cdot day^{-1}$ was administered after week 4). Patients treated with peginterferon alfa-2b also had greater $\log_{10}$ maximum and $\log_{10}$ time-weighted average decreases in serum HCV RNA levels, and a correspondingly greater proportion of peginterferon alfa-2b–treated patients achieved ≥ 2 $\log_{10}$ reduction in serum HCV RNA levels by week 8 (72% vs 44% of peginterferon alfa-2a–treated patients; $P = .09$). Although these data suggest that peginterferon alfa-2b has better biological activity, the between-group differences were not statistically significant.

To date, only 2 randomized clinical studies have compared the efficacy of the peginterferon formulations, neither of which was sufficiently powered to detect a statistically significant difference in SVR rates.[5,6] Despite a difference of 15% in the EVR rate between patients treated with peginterferon alfa-2a 180 μg/wk plus ribavirin (n = 58) and peginterferon alfa-2b 1.5 $\mu g \cdot kg^{-1} \cdot wk^{-1}$ plus ribavirin (n = 58) in one study, the difference was not statistically significant (82% vs 67%, respectively; $P = .08$).[5] An SVR rate of 48.6% was obtained in patients with genotype 1 who received peginterferon alfa-2a 180 μg/wk plus ribavirin (n = 37) and 35.1% in those treated with peginterferon alfa-2b 1.5 $\mu g \cdot kg^{-1} \cdot wk^{-1}$ plus ribavirin (n = 37) in a second study, but the sample size was too small to show a statistically significant difference.[6] The 14.4% difference in SVR rate in favor of peginterferon alfa-2a in the present study is consistent with the between-group differences of 14%–15% in rates of EVR and SVR in these 2 trials.

In the retrospective phase of the large (n = 2149) PROBE study (sponsored by Hoffmann–La Roche),[12] the rate of SVR was higher in genotype 1 patients treated with peginterferon alfa-2a than with peginterferon alfa-2b (45% vs 38.4%; $P = .04$). The prospective phase of this study is yet to be completed.

Similar to the PROBE study, a recently published observational retrospective study of a large cohort (N = 9544) of US veterans[13] reported that treatment of genotype 1 patients with peginterferon alfa-2a was associated with a higher likelihood of SVR than treatment with peginterferon alfa-2b.

In the present study, the 2 peginterferons were administered at dosages recommended in treatment guidelines with a sample size adequate to draw reliable conclusions concerning efficacy and safety. Ribavirin was administered at weight-based dosages that were stable during the study, so the only independent variable was the type of peginterferon. An SVR was achieved in 68.8% of patients randomized to peginterferon alfa-2a and 54.4% of those randomized to peginterferon alfa-2b (difference, 14.4%; 95% CI, 3.7%–24.6%; $P = .008$). The apparently high SVR rates may be due to the low number of patients with cirrhosis enrolled in the study (n = 59; 18.4%).

In subgroup analyses, the SVR rate was 47.3% in patients with genotype 1/4 (54.8% in recipients of peginterferon alfa-2a and 39.8% in recipients of peginterferon alfa-2b; difference, 15%; $P = .040$). Genotype 4 is very uncommon in southern Italy. Table 1 shows that the number of these patients is only 5 (1.6% of the total) not equally distributed because they were randomized together with genotype 1. For this reason, 4 patients were treated with peginterferon alfa-2a and one with peginterferon alfa-2b. Only one of them responded, and she was in the peginterferon alfa-2b arm.

Among those infected with genotype 2/3, the overall SVR rate was much higher (81.3%). The SVR rate was considerably higher in patients infected with genotype 2 than genotype 3 (83.8% vs 74.3%, respectively). Although this difference is not statistically significant ($P = .21$), we believe that these genotypes should no longer be considered to be a homogeneous group.

In patients without cirrhosis, the SVR rate was 75.6% in peginterferon alfa-2a recipients and 55.9% in peginterferon alfa-2b recipients ($P = .005$); in patients with cirrhosis, the SVR rates were 42.4% and 46.1%, respectively ($P = .77$).

Another interesting finding of this study is the relationship between SVR and the baseline HCV RNA level. In the 143 patients with an HCV RNA level ≤500,000 IU/mL, the 2 treatments were not statistically different (SVR of 68.4% in patients treated with peginterferon alfa-2a and 65.7% in patients treated with peginterferon alfa-2b; $P = .727$). In patients with baseline serum HCV RNA levels >500,000 IU/mL, the SVR rate was 69.0% in those treated with peginterferon alfa-2a and 46.2% in those treated with peginterferon alfa-2b ($P = .002$).

However, it is important to note that our subgroup analyses are post hoc and thus the results should be regarded with caution. Our subgroup results should be verified with a prospective trial that is specifically designed and powered to confirm or not confirm our results.

A multivariate analysis showed that male gender, absence of cirrhosis, use of peginterferon alfa-2a, and infection with genotype 2/3 were independently associated with SVR.

Only 30 of 320 patients (9.4%) did not experience adverse events, with no difference between group A and group B.

The results of a very large randomized trial comparing 2 regimens of peginterferon therapy in patients with genotype 1 in the United States were recently reported (IDEAL trial).[14] The IDEAL trial showed no difference in

SVR rates between patients treated with peginterferon alfa-2a plus ribavirin and those treated with peginterferon alfa-2b plus ribavirin. There was a number of fundamental differences between the IDEAL trial and the current study that may help to explain the different outcomes: (1) a multicenter postapproval industry-sponsored trial versus an investigator-initiated single-center trial, (2) a US population with higher body mass index and more black/Latino patients versus a European population, (3) 2 different ribavirin regimens with different starting doses and dose reduction rules versus equal ribavirin doses in all patients, (4) a genotype 1–only study vs all genotypes, and (5) different laboratories for testing the main indicator of response (HCV RNA by polymerase chain reaction). In fact, using a fixed dose of ribavirin in all the genotypes treated and in the 2 groups treated with peginterferons might have given a better indication of the different performance of the 2 peginterferons themselves without a confounding effect of differing ribavirin doses and dose reductions. The results of the 2 studies, when analyzed together, may indeed be quite compatible with closer inspection of end-of-treatment and relapse results in the IDEAL trial. However, because these trials were designed so differently and conducted in very different populations with HCV infection, we do not believe they can be directly compared. The reader should not draw conclusions across populations from either study.

In conclusion, this single-center, randomized, head-to-head study indicates that (1) the safety profile of the 2 preparations is similar and (2) in the populations studied, the rate of SVR obtained with peginterferon alfa-2a plus ribavirin is higher than that achieved with peginterferon alfa-2b plus ribavirin.

Supplementary Data

Note: To access the supplementary material accompanying this article visit the online version of *Gastroenterology* at www.gastrojournal.org and at doi: 10.1053/j.gastro.2009.10.005.

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Conflicts of interest

The authors disclose the following: Dr Ascione has received lecture fees from Bayer Healthcare, Bristol-Myers Squibb, Gilead, Grifols, Novartis, Schering-Plough, Roche, and Roche Diagnostics. The remaining authors discloses no conflicts.

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