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ORIGINAL ARTICLE

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ABSTRACT

BACKGROUND

Treatment guidelines recommend the use of peginterferon alfa-2b or peginterferon alfa-2a in combination with ribavirin for chronic hepatitis C virus (HCV) infection. However, these regimens have not been adequately compared.

METHODS

At 118 sites, patients who had HCV genotype 1 infection and who had not previously been treated were randomly assigned to undergo 48 weeks of treatment with one of three regimens: peginterferon alfa-2b at a standard dose of 1.5 μg per kilogram of body weight per week or a low dose of 1.0 μg per kilogram per week, plus ribavirin at a dose of 800 to 1400 mg per day, or peginterferon alfa-2a at a dose of 180 μg per week plus ribavirin at a dose of 1000 to 1200 mg per day. We compared the rate of sustained virologic response and the safety and adverse-event profiles between the peginterferon alfa-2b regimens and between the standard-dose peginterferon alfa-2b regimen and the peginterferon alfa-2a regimen.

RESULTS

Among 3070 patients, rates of sustained virologic response were similar among the regimens: 39.8% with standard-dose peginterferon alfa-2b, 38.0% with low-dose peginterferon alfa-2b, and 40.9% with peginterferon alfa-2a ($P=0.20$ for standard-dose vs. low-dose peginterferon alfa-2b; $P=0.57$ for standard-dose peginterferon alfa-2b vs. peginterferon alfa-2a). Estimated differences in response rates were 1.8% (95% confidence interval [CI], –2.3 to 6.0) between standard-dose and low-dose peginterferon alfa-2b and –1.1% (95% CI, –5.3 to 3.0) between standard-dose peginterferon alfa-2b and peginterferon alfa-2a. Relapse rates were 23.5% (95% CI, 19.9 to 27.2) for standard-dose peginterferon alfa-2b, 20.0% (95% CI, 16.4 to 23.6) for low-dose peginterferon alfa-2b, and 31.5% (95% CI, 27.9 to 35.2) for peginterferon alfa-2a. The safety profile was similar among the three groups; serious adverse events were observed in 8.6 to 11.7% of patients. Among the patients with undetectable HCV RNA levels at treatment weeks 4 and 12, a sustained virologic response was achieved in 86.2% and 78.7%, respectively.

CONCLUSIONS

In patients infected with HCV genotype 1, the rates of sustained virologic response and tolerability did not differ significantly between the two available peginterferon–ribavirin regimens or between the two doses of peginterferon alfa-2b. (ClinicalTrials.gov number, NCT00081770.)

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Hepatitis C virus (HCV) chronically infects approximately 180 million people worldwide[1] and is a frequent cause of liver disease, including liver failure and hepatocellular carcinoma.[2] HCV treatment is recommended for persons at the greatest risk for progression of liver disease.[3] On the basis of noncomparative studies demonstrating similar safety and efficacy between the two treatments,[4,5] consensus guidelines recommend the use of either peginterferon alfa-2b or peginterferon alfa-2a in combination with ribavirin for the treatment of chronic hepatitis C. However, differences between the peginterferons with respect to structural modifications and dosing (weight-adjusted vs. fixed) may lead to important differences in clinical outcomes, and there is some evidence of such differences.[6-9] Randomized, comparative effectiveness trials are necessary to provide patients with evidence-based treatment options.

The Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) study was initiated to compare standard-dose and low-dose regimens of peginterferon alfa-2b, plus ribavirin, after it was observed that both dose levels yielded similar rates of sustained virologic response in the absence of ribavirin.[10] A third treatment group, peginterferon alfa-2a plus ribavirin, was added to the study because (in addition to standard-dose peginterferon alfa-2b plus ribavirin) it is the other approved regimen. The objective was to compare the safety and efficacy of the two standard regimens and the experimental low-dose peginterferon alfa-2b regimen.

METHODS

STUDY PATIENTS

We enrolled patients from 118 centers in the United States. Eligible patients were 18 years of age or older, had compensated liver disease due to chronic HCV genotype 1 infection and a detectable plasma HCV RNA level, and had not been previously treated for hepatitis C infection. The patients had an absolute neutrophil count of 1500 or more per cubic millimeter, a platelet count of 80,000 or more per cubic millimeter, and hemoglobin level of 12 g (for women) or 13 g (for men) or more per deciliter. Patients were excluded if they had coinfection with human immunodeficiency virus or hepatitis B, any other cause of liver disease, poorly controlled diabetes mellitus (glycated hemoglobin value >8.5%), morbid obesity (weight >125 kg), severe depression or a severe psychiatric disorder, or active substance abuse. All patients had undergone liver biopsy within 3 years before screening. A pathologist at the central site, who was unaware of the treatment assignments, reviewed all the biopsy specimens and determined the METAVIR fibrosis stage and inflammatory grade, as well as the percentage of the tissue containing hepatocytes with steatosis.[11]

STUDY OVERSIGHT

The study sponsor and the academic principal investigators were jointly responsible for the study design, protocol, statistical analysis plan, and data analysis. The principal investigators had unrestricted access to the data, wrote the manuscript, and vouch for the accuracy and integrity of the data and analyses. A publication committee comprising the academic principal investigators and three independent experts prepared the prespecified data-analysis plan and ensured the unbiased interpretation of the data.

STUDY DESIGN

Patients were randomly assigned, in a 1:1:1 ratio and with the use of an interactive voice system, to one of the three treatment groups and were stratified according to HCV RNA level (≤600,000 IU per milliliter or >600,000 IU per milliliter) and self-reported race (black or nonblack). The three treatment groups were as follows: peginterferon alfa-2b at the standard dose, 1.5 μg per kilogram of body weight per week, or at a lower dose, 1.0 μg per kilogram per week, both in combination with oral ribavirin at a dose according to body weight (40 to 65 kg, 800 mg per day; >65 to 85 kg, 1000 mg per day; >85 to 105 kg, 1200 mg per day; and >105 to 125 kg, 1400 mg per day); or peginterferon alfa-2a at a dose of 180 μg per week, plus oral ribavirin at a dose of 1000 to 1200 mg per day, according to body weight (<75 kg, 1000 mg per day; ≥75 kg, 1200 mg per day).

The study was double-blinded with regard to the dose of peginterferon alfa-2b. For patients receiving peginterferon alfa-2a, the dose of ribavirin was determined on the basis of prescribing information from the Food and Drug Administration (FDA). Because weight-based ribavirin dosing was not approved by the FDA for use with peginterferon alfa-2b when the study was initiated, the dose of ribavirin administered in the two groups receiving peginterferon alfa-2b was calculated to deliver a mean (±SD) of 13±2 mg per kilogram per

day, on the basis of data derived from previous trials and from the product information from the European Medicines Agency.[4,7,12] Patients underwent treatment for up to 48 weeks and follow-up for 24 weeks. The study was approved by each center's institutional review board and was conducted in accordance with provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

EFFICACY ASSESSMENTS

HCV RNA levels were measured with the use of the Cobas TaqMan assay (Roche), which has a lower limit of quantitation of 27 IU per milliliter. Measurements were obtained at screening visits 1 and 2 (baseline); weeks 2, 4, 12, 24, and 48 during the treatment period; and follow-up weeks 4, 12, and 24. Per established guidelines, patients with an insufficient virologic response at 12 weeks (a detectable HCV RNA level and a decrease of <2 $\log_{10}$ IU from the baseline level) or at 24 weeks (a detectable HCV RNA level) were considered to have treatment failure, and therapy was discontinued.

SAFETY ASSESSMENTS

Adverse events were graded by the investigators as mild, moderate, severe, or life-threatening, according to a modified World Health Organization grading system. Non–life-threatening adverse events were managed by reduction of the dose of peginterferon alfa or ribavirin (or both). The peginterferon-dose reduction was a two-step process: the dose was reduced if the neutrophil count was below 750 per cubic millimeter, and treatment with both drugs was permanently discontinued if the neutrophil count was below 500 per cubic millimeter. For patients receiving peginterferon alfa-2b, the ribavirin-dose reduction occurred in two steps, as established by Jacobson et al.[7] The first step was a reduction of either 200 mg (in patients receiving 800 to 1200 mg of ribavirin per day) or 400 mg (in patients receiving 1400 mg per day); the second step was reduction by another 200 mg, if required for resolution of the adverse event. For patients receiving peginterferon alfa-2a, ribavirin-dose reduction consisted of a reduction to 600 mg per day, on the basis of FDA-approved prescribing information. For all patients, ribavirin-dose reduction was required if the hemoglobin level was less than 10 g per deciliter; treatment with both drugs was permanently discontinued if the level was below 8.5 g per deciliter. In patients with a hemoglobin level less than 10 g per deciliter, use of erythrocyte-stimulating agents was permitted after ribavirin-dose reduction. Drug doses could be increased once the cytopenia resolved (i.e., the neutrophil count was ≥750 per cubic millimeter or the hemoglobin level was ≥10 g per deciliter).

END POINTS

Analyses included data from all patients who underwent randomization and who received at least one dose of study medication. The primary end point was a sustained virologic response, defined as undetectable HCV RNA levels 24 weeks after the completion of therapy. If the 24-week post-treatment HCV RNA measurement was missing, the 12-week post-treatment level was used. (This was done for 38, 21, and 25 patients receiving standard-dose and low-dose peginterferon alfa-2b and peginterferon alfa-2a, respectively, all of whom had had undetectable HCV RNA at 12 weeks after treatment.)

The study involved two primary comparisons: standard-dose versus low-dose peginterferon alfa-2b regimens and standard-dose peginterferon alfa-2b versus peginterferon alfa-2a. Secondary end points included the rates of virologic response during the treatment phase and relapse, defined as an undetectable HCV RNA level at the end of the treatment phase, with a detectable HCV RNA level during the follow-up period.

STATISTICAL ANALYSIS

For both primary comparisons, the trial was designed as a superiority study to detect clinically meaningful differences in the rates of sustained virologic response among the three regimens. The study had a statistical power of 80% to detect a significant absolute difference in rates of sustained virologic response of 6.5% between the standard-dose and low-dose peginterferon alfa-2b regimens and of 7% between the standard-dose peginterferon alfa-2b regimen and the peginterferon alfa-2a regimen. A one-sided test was used to compare the two peginterferon alfa-2b regimens, with an assumption that the standard-dose regimen would be at least as effective as the low-dose regimen. A two-sided test was used to compare standard-dose peginterferon alfa-2b and peginterferon alfa-2a. Because there were two primary treatment comparisons, the Holm–Bonferroni method was used to maintain the overall type 1 error rate at 0.05. According to this method, the lowest P value must

be below 0.025 to be considered to indicate statistical significance. If this criterion is met, then the higher P value must be below 0.05 to be considered to indicate statistical significance. If the lowest P value is greater than 0.025, no other tests are performed.

P values for the two primary treatment comparisons were calculated on the basis of a logistic-regression model controlling for the stratification factors (race and baseline HCV RNA level). Since neither of the two comparisons was significant, all P values are considered to be nominal and are labeled as such. Similarly, nominal two-sided 95% confidence intervals are reported, calculated for the two primary comparisons according to a Mantel–Haenszel approach controlling for the stratification factors. Summary statistics are reported for each of the three treatment regimens for subgroups of patients defined by prespecified baseline characteristics and one characteristic defined post hoc (baseline fasting glucose level). Multivariable logistic-regression analyses involving treatment regimen, prespecified baseline characteristics, and three post hoc factors (baseline fasting glucose level, hemoglobin value, and platelet count) were performed to study sustained virologic response and relapse. A stepwise procedure was used to identify independent predictors of sustained virologic response and relapse (with P=0.05 as the threshold level for variables to be entered into and retained in the final model). This type of approach was prespecified in the analysis plan for sustained virologic response but not for relapse. As was prespecified, we also explored the relationship between the magnitude and rapidity of virologic response during the treatment phase and the probability of achieving a sustained virologic response.

RESULTS

CHARACTERISTICS OF THE STUDY PATIENTS

Between March 2004 and June 2006, a total of 4469 patients were screened, and 3070 underwent randomization and treatment (Fig. 1). Baseline demographic characteristics were balanced among the three treatment groups (Table 1). The majority of patients were men in their 40s; 18.6% of the patients were black; and the mean body weight was 83.4 kg. After stratification on the basis of body weight, 1061 of 2035 patients (52.1%) receiving peginterferon alfa-2b were assigned to receive the same dose of ribavirin as the corresponding patients receiving peginterferon alfa-2a, whereas 773 of the 2035 patients (38.0%) were assigned a lower dose of ribavirin, and 201 of the 2035 (9.9%) were assigned a higher dose. During the treatment period, the mean and median daily ribavirin doses received were significantly higher among patients receiving peginterferon alfa-2a than those in either peginterferon alfa-2b group, regardless of ribavirin-dose reduction, use of erythrocyte-stimulating agents, or efficacy outcome (sustained virologic response, relapse, or nonresponse). The proportion of patients who received, on average, more than 13 mg of ribavirin per kilogram per day was greater in the peginterferon alfa-2a group (56.0%) than in either peginterferon alfa-2b group (29.1% in the standard-dose group and 32.6% in the low-dose group) (P<0.001 for each comparison).

EFFICACY

The rates of sustained virologic response did not differ significantly among the three treatment groups, with a rate of 39.8% (95% confidence interval [CI], 36.8 to 42.8) for standard-dose peginterferon alfa-2b, 38.0% (95% CI, 35.0 to 41.0) for low-dose peginterferon alfa-2b, and 40.9% (95% CI, 37.9 to 43.9%) for peginterferon alfa-2a, (P=0.20 for standard-dose vs. low-dose peginterferon alfa-2b; P=0.57 for standard-dose peginterferon alfa-2b vs. peginterferon alfa-2a) (Table 2). Estimated differences in response rates were 1.8% (95% CI, –2.3 to 6.0) between standard-dose and low-dose peginterferon alfa-2b and –1.1% (95% CI, –5.3 to 3.0) between standard-dose peginterferon alfa-2b and peginterferon alfa-2a. Therefore, the two primary trial end points of superiority were not met. Response rates at the end of the treatment phase were higher with peginterferon alfa-2a than with either peginterferon alfa-2b regimen, but the virologic relapse rate was also higher. In all three groups, HCV RNA suppression at treatment weeks 4 and 12 was strongly associated with achievement of sustained virologic response (Table 3). Fewer than 5% of patients who had a reduction from the baseline HCV RNA level of less than 1 $\log_{10}$ IU per milliliter at week 4 also had a sustained virologic response. A prolonged time (>12 weeks of therapy) to undetectable HCV RNA level was associated with a higher likelihood of relapse after treatment (Table 3). Stepwise multivariable logistic-regression analyses identified several baseline factors as independent predictors of sus-

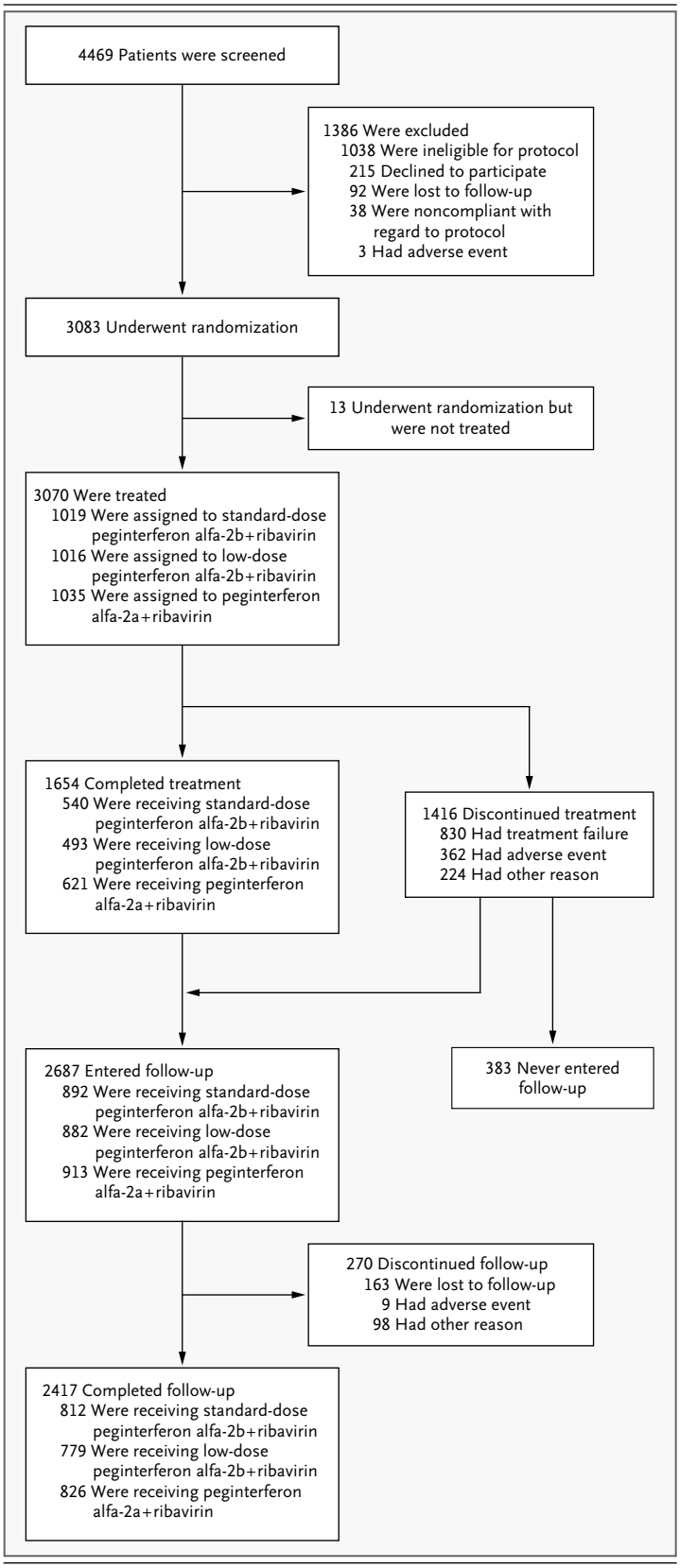

Figure 1. Screening, Treatment, and Follow-up of the Study Patients.

Patients with chronic hepatitis C virus (HCV) genotype 1 infection were randomly assigned to receive 48 weeks of treatment with either peginterferon alfa-2b at a standard dose (1.5 μg per kilogram of body weight per week) or a low dose (1.0 μg per kilogram per week), plus ribavirin at a dose of 800 to 1400 mg per day, or peginterferon alfa-2a at a dose of 180 μg per week plus ribavirin at a dose of 1000 to 1200 mg per day. Patients with an inadequate virologic response at 12 weeks (predefined as a $\log_{10}$ decrease of <2 from the baseline HCV RNA level) or at 24 weeks (predefined as detectable HCV RNA) were considered to have had treatment failure, and therapy was discontinued. All patients were eligible to undergo follow-up for up to 24 weeks after treatment.

tained virologic response: baseline HCV RNA level (≤600,000 IU per milliliter), race (nonblack), minimal fibrosis (METAVIR score of F0, F1, or F2), absence of steatosis, normal baseline fasting glucose level, and elevated baseline serum alanine aminotransferase level. Using the same method, we found that these factors were independently associated with relapse, as were age over 40 years and peginterferon alfa-2a treatment (Table 1 of the Supplementary Appendix, available with the full text of this article at NEJM.org).

RIBAVIRIN DOSING

Rates of sustained virologic response were similar among the three treatment groups, within the subgroups of patients receiving the same dose of ribavirin (those weighing >65 to <75 kg and those weighing >85 to 105 kg) (Table 2). The ribavirin dose was reduced, owing to an adverse event, in 30.2% of patients. The rate of sustained virologic response among these patients was 52.2% in the peginterferon alfa-2a, 51.8% in the standard-dose peginterferon-2b group, and 49.3% in the low-dose peginterferon alfa-2b group. In comparison, the rate of sustained virologic response was higher among patients who had a hemoglobin level that was less than 10 g per deciliter during the treatment phase but who required a ribavirin-dose reduction, as compared with those with levels of 10 g per deciliter or above: 48.8% (422 of 865 patients) versus 36.7% (793 of 2158 patients) (P<0.001).

SAFETY

The types and frequencies of adverse events were similar among the three groups (Table 4). The most common adverse events included influenza-

Table 1. Baseline Demographic and Disease Characteristics of the Study Patients, According to Treatment Group.*

Characteristic	Low-Dose Peginterferon Alfa-2b + Ribavirin (N = 1016)	Standard-Dose Peginterferon Alfa-2b + Ribavirin (N = 1019)	Peginterferon Alfa-2a + Ribavirin (N = 1035)
Age — yr	47.5±8.1	47.5±7.8	47.6±8.2
Weight — kg	83.4±15.8	84.0±16.5	82.8±16.6
Male sex — no. (%)	607 (59.7)	613 (60.2)	613 (59.2)
Race or ethnic group — no. (%)†			
White	724 (71.3)	732 (71.8)	733 (70.8)
Black	187 (18.4)	183 (18.0)	200 (19.3)
Hispanic	68 (6.7)	79 (7.8)	66 (6.4)
Asian-American	21 (2.1)	10 (1.0)	20 (1.9)
American Indian	5 (0.5)	3 (0.3)	3 (0.3)
Other	11 (1.1)	12 (1.2)	13 (1.3)
ALT above upper limit of the normal range — no. (%)	815 (80.2)	822 (80.7)	842 (81.4)
HCV RNA‡			
Log_{10} value (IU/ml)	6.32±0.70	6.32±0.69	6.34±0.64
>600,000 IU/ml — no. (%)	830 (81.7)	836 (82.0)	852 (82.3)
METAVIR fibrosis score of F3 or F4 — no. (%)§	107 (10.5)	111 (10.9)	110 (10.6)
Steatosis — no. (%)			
0	353 (34.7)	391 (38.4)	373 (36.0)
>0 to ≤5%	464 (45.7)	450 (44.2)	457 (44.2)
>5%	154 (15.2)	139 (13.6)	142 (13.7)
Missing data	45 (4.4)	39 (3.8)	63 (6.1)
HCV genotype 1 subtype — no. (%)			
1	2 (0.2)	2 (0.2)	4 (0.4)
1a	637 (62.7)	648 (63.6)	634 (61.3)
1b	358 (35.2)	353 (34.6)	374 (36.1)
1a and 1b	19 (1.9)	16 (1.6)	23 (2.2)

* Plus–minus values indicate means ±SD. There were no significant differences among the groups with regard to baseline characteristics. ALT denotes alanine aminotransferase, and HCV hepatitis C virus.
† Race or ethnic group was self-reported.
‡ Hepatitis C virus level was determined with the use of the Cobas TaqMan assay (Roche), for which the lower limit of quantitation is 27 IU per milliliter.
§ Percutaneous liver-biopsy specimens obtained before treatment were evaluated with regard to METAVIR fibrosis staging by a pathologist at the central site. The METAVIR scoring system classifies fibrosis according to a 5-point scale: F0 indicates no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa but without cirrhosis; and F4, portal fibrosis with cirrhosis.

like symptoms, depression, and the hematologic events of anemia and neutropenia. The proportions of patients with neutropenia who met the criterion for peginterferon-dose reduction (a neutrophil count of <750 and ≥500 per cubic millimeter were 21.1% receiving peginterferon alfa-2a, 19.4% receiving standard-dose peginterferon alfa-2b, and 12.5% receiving low-dose peginterferon alfa-2b. However, only 2.1 to 5.9% of patients met the discontinuation criterion based on neutropenia. The proportion of patients meeting the hemoglobin criterion for ribavirin-dose reduction (a hemoglobin level <10 and ≥8.5 g per deciliter) was somewhat higher with standard-dose peginterferon alfa-2b (28.2%) and peginterferon alfa-2a (25.8%) than with low-dose peginterferon alfa-2b (23.2%); only

Table 2. Virologic Response during and after Treatment, According to Treatment Group.*

Variable	Low-Dose Peginterferon Alfa-2b + Ribavirin (N = 1016)	Standard-Dose Peginterferon Alfa-2b + Ribavirin (N = 1019)	Peginterferon Alfa-2a + Ribavirin (N = 1035)	P Value†	
				Standard-Dose vs. Low-Dose Peginterferon Alfa-2b	Standard-Dose Peginterferon Alfa-2b vs. Peginterferon Alfa-2a
Virologic response — no. (%)					
According to treatment wk					
2	42 (4.1)	45 (4.4)	44 (4.3)	0.37	0.83
4	79 (7.8)	116 (11.4)	123 (11.9)	0.002	0.73
12	366 (36.0)	407 (39.9)	466 (45.0)	0.03	0.01
24	491 (48.3)	519 (50.9)	638 (61.6)	0.12	<0.001
48 (end of treatment)	500 (49.2)	542 (53.2)	667 (64.4)	0.04	<0.001
Relapse rate — no./total no. (%)‡	95/475 (20.0)	123/523 (23.5)	193/612 (31.5)		
Sustained virologic response — no. (%)§	386 (38.0)	406 (39.8)	423 (40.9)	0.20	0.57
Sustained virologic response according to baseline characteristics — no./total no. (%)¶					
Sex					
Female	147/409 (35.9)	180/406 (44.3)	177/422 (41.9)		
Male	239/607 (39.4)	226/613 (36.9)	246/613 (40.1)		
Age					
≤40 yr	72/154 (46.8)	74/140 (52.9)	91/163 (55.8)		
>40 yr	314/862 (36.4)	332/879 (37.8)	332/872 (38.1)		
Race‖					
Black	31/187 (16.6)	42/183 (23.0)	52/200 (26.0)		
White	316/724 (43.6)	319/732 (43.6)	324/733 (44.2)		
Weight — kg**					
40 to 65 kg	52/140 (37.1)	65/142 (45.8)	69/160 (43.1)		
>65 to <75 kg	66/165 (40.0)	55/150 (36.7)	72/175 (41.1)		
75 to 85 kg	93/250 (37.2)	99/272 (36.4)	123/270 (45.6)		
>85 to 105 kg	140/383 (36.6)	142/348 (40.8)	117/322 (36.3)		
>105 to 125 kg	35/78 (44.9)	45/107 (42.1)	42/108 (38.9)		
Fasting glucose					
<5.6 mmol/liter	302/720 (41.9)	323/739 (43.7)	322/730 (44.1)		
≥5.6 mmol/liter	84/296 (28.4)	83/279 (29.7)	100/304 (32.9)		

ALT			
Normal	73/201 (36.3)	64/197 (32.5)	72/193 (37.3)
Elevated	313/815 (38.4)	342/822 (41.6)	351/842 (41.7)
Hepatic steatosis††			
No	161/353 (45.6)	186/391 (47.6)	184/373 (49.3)
Yes	206/618 (33.3)	203/589 (34.5)	218/599 (36.4)
Virologic load			
>600,000 IU/ml	277/830 (33.4)	295/836 (35.3)	303/852 (35.6)
≤600,000 IU/ml	109/186 (58.6)	111/183 (60.7)	120/183 (65.6)
METAVIR fibrosis score††			
F0, F1, or F2	335/864 (38.8)	366/869 (42.1)	376/862 (43.6)
F3 or F4	32/107 (29.9)	23/111 (20.7)	26/110 (23.6)
Assigned ribavirin dose			
≤13 mg/kg/day	204/568 (35.9)	215/578 (37.2)	101/278 (36.3)
>13 mg/kg/day	182/448 (40.6)	191/441 (43.3)	322/757 (42.5)
Response rates in subgroups with ribavirin dose reduction — no./total no. (%)‡‡			
At end of treatment	160/268 (59.7)	224/338 (66.3)	238/322 (73.9)
Sustained virologic response	132/268 (49.3)	175/338 (51.8)	168/322 (52.2)
Relapse	23/155 (14.8)	43/216 (19.9)	63/227 (27.8)

* Virologic response was defined as an undetectable hepatitis C virus (HCV) RNA level (i.e., a level <27 IU per milliliter, as measured with the use of the Cobas TaqMan assay [Roche]). Percentages are based on the total number of patients in the group unless otherwise indicated. To convert the values for fasting glucose to milligrams per deciliter, divide by 0.05551. ALT denotes alanine aminotransferase.

† Nominal P values (one-sided for low-dose vs. standard-dose peginterferon alfa-2b and two-sided for standard-dose peginterferon alfa-2b vs. peginterferon alfa-2a) were obtained from a logistic-regression model with virologic response as the dependent variable and treatment group and the stratification factors (race and baseline virologic load) as independent variables. Since the two primary treatment comparisons for sustained virologic response are not significant (both P values >0.025), no other comparisons can be considered significant, on the basis of the multiplicity strategy prespecified in the trial design.

‡ Relapse was defined as undetectable HCV RNA levels at the end of treatment but detectable levels during the follow-up period. The 95% confidence intervals (CIs) for the rates of relapse were 19.9 to 27.2% for standard-dose peginterferon alfa-2b, 16.4 to 23.6% for low-dose peginterferon alfa-2b, and 27.9 to 35.2% for peginterferon alfa-2a. The difference in the rate of relapse between standard-dose peginterferon alfa-2b and peginterferon alfa-2a was –8.0% (95% CI, –13.2 to –2.8) and between standard-dose and low-dose peginterferon alfa-2b was 3.5% (95% CI, –1.6% to 8.6%).

§ Sustained virologic response was defined as undetectable HCV RNA levels at the end of the follow-up period. The 12-week post-treatment HCV RNA level was used if the 24-week post-treatment level was missing (as specified in the protocol). The numbers of patients who had undetectable HCV RNA levels 12 weeks after treatment but who missed the 24-week post-treatment visit were 21, 38, and 25 for low-dose peginterferon alfa-2b, standard-dose peginterferon alfa-2b, and peginterferon alfa-2a, respectively. The difference in the rate of response between standard-dose peginterferon alfa-2b and peginterferon alfa-2a was –1.1% (95% CI, –5.3 to 3.0) and the difference in the rate between standard-dose and low-dose peginterferon alfa-2b was 1.8% (95% CI, –2.3 to 6.0).

¶ All characteristics included in this table were identified in the subgroup-analysis section of the statistical-analysis plan, except for baseline fasting glucose level (a post hoc addition). P values for the interaction between treatment group and baseline characteristics are presented in Table 2 of the Supplementary Appendix, available with the full text of this article at NEJM.org.

‖ Race was self-reported.

** Patients in different weight categories received different doses of ribavirin, according to body weight and the assigned peginterferon regimen: those weighing 40 to 65 kg in the peginterferon alfa-2b groups received 800 mg of ribavirin daily and in the peginterferon alfa-2a group received 1000 mg of ribavirin daily, those weighing more than 65 and less than 75 kg in any of the three groups received 1000 mg of ribavirin daily, those weighing 75 to 85 kg in the peginterferon alfa-2b groups received 1000 mg of ribavirin daily and in the peginterferon alfa-2a group received 1200 mg daily, those weighing more than 85 kg and up to 105 kg received 1200 mg of ribavirin daily in any of the three groups, and those weighing more than 105 kg in the peginterferon alfa-2b groups received 1400 mg of ribavirin daily and in the peginterferon alfa-2a group received 1200 mg of ribavirin daily.

†† The total numbers of patients for whom we had data on histologic findings of hepatic steatosis and fibrosis scores are the subgroups of patients for whom the liver-biopsy specimen was deemed adequate for assessment by the pathologist at the central site.

‡‡ Response rates in subgroups with ribavirin dose reduction were calculated for all patients whose dose of ribavirin was reduced owing to an adverse event at any time or for any duration during the treatment phase of the study.

2.1 to 3.8% of patients met the discontinuation criterion (hemoglobin level <8.5 g per deciliter).

Most psychiatric adverse events were mild or moderate and were not treatment-limiting; however, 1.8 to 2.6% of patients did discontinue treatment. Twelve patients (0.4%) died during the study: seven during the treatment period and five during or after the follow-up period. Two of these deaths were considered by the investigator to be possibly related to study medications: a suicide at 6 months after the end of treatment with standard-dose peginterferon alfa-2b and a myocardial infarction during treatment with peginterferon alfa-2a.

DISCUSSION

Treatment with peginterferon alfa-2a or peginterferon alfa-2b, plus ribavirin, for 48 weeks is recommended for patients infected with HCV genotype 1, the most common variant in the United States and Europe.[13] Despite this recommendation, few data comparing these treatment regimens are available. Accordingly, several findings of our large, randomized comparative study affect the care of these patients.

The safety and adverse-event profiles and the efficacy data were similar among patients treated with low-dose or standard-dose peginterferon alfa-2b or peginterferon alfa-2a, in combination with differing ribavirin regimens. The finding that low-dose peginterferon alfa-2b resulted in a similar rate of sustained virologic response as the other regimens was unexpected. Since monotherapy with standard-dose peginterferon alfa-2b has been associated with higher rates of virologic response during the treatment period,[10] we aimed to test the hypothesis that use of standard-dose peginterferon alfa-2b with ribavirin would result in a higher rate of sustained virologic response than with the low-dose regimen. Although our data do not support this hypothesis, a significant interaction between treatment group and sex ($P=0.01$) (Table 2 in the Supplementary Appendix) suggests that women may have higher rates of sustained virologic response with standard-dose than with low-dose peginterferon alfa-2b. Although the interaction with race was not significant, blacks tended to have higher rates of sustained virologic response with the standard dose of peginterferon alfa-2b. Host, virologic, and treatment factors associated with eradication of HCV genotype 1 infection were identified. Consistent with previous observations,[14-20] a sustained virologic response was less frequent among blacks, persons with advanced hepatic fibrosis and steatosis, and those with high baseline HCV RNA levels. Although it was not a prespecified covariate, impaired fasting glucose was also associated with a lower likelihood of sustained virologic response. These data suggest a need for additional research to test the hypothesis that dietary and pharmacologic interventions to correct glucose intolerance can improve treatment response. The magnitude of HCV RNA suppression during the treatment phase was also closely linked to the likelihood of having a sustained virologic response. Among the 10% of patients with undetectable HCV RNA levels at treatment week 4, 86% had a sustained virologic response. The 24% of patients with a minimal decline in HCV RNA level (decline of <1 $\log_{10}$ IU from the baseline value) at treatment week 4 had a probability of sustained virologic response of less than 5%. Thus, virologic response at treatment week 4 is an important predictor of sustained virologic response; HCV RNA levels should be routinely assessed at this time point.

The time to the first undetectable HCV RNA level was associated with the probability of virologic relapse after the end of treatment. Approximately 50% of patients who had HCV suppression for the first time by treatment week 24 also had virologic relapse, as compared with less than 10% of patients who had HCV suppression at treatment week 4. After week 4, patients receiving peginterferon alfa-2a had a higher rate of HCV RNA suppression than did those who were receiving peginterferon alfa-2b; however, this difference was not sustained after the end of the treatment period. Thus, although the rates of sustained virologic response were similar among the three groups, patients treated with peginterferon alfa-2a were more likely to have a response while receiving therapy, followed by relapse after the completion of therapy, whereas patients treated with peginterferon alfa-2b were more likely to discontinue therapy at treatment week 12 or 24 because of an insufficient virologic response.

Increased ribavirin exposure during the treatment phase was associated with an increased likelihood of sustained virologic response among all treated patients. Ribavirin exposure was lower in patients who received peginterferon alfa-2b, which was administered according to four dosing categories (based on body weight), as compared with those who received peginterferon alfa-2a,

Table 3. Responses to Treatment, According to Treatment Group.*

Response	Low-Dose Peginterferon Alfa-2b + Ribavirin	Standard-Dose Peginterferon Alfa-2b + Ribavirin	Peginterferon Alfa-2a + Ribavirin
	number of patients/total number (percent)		
Change in HCV RNA between baseline and wk 4			
<1 $\log_{10}$ IU	10/304 (3.3)	10/220 (4.5)	11/226 (4.9)
1 to <2 $\log_{10}$ IU	66/249 (26.5)	51/243 (21.0)	67/232 (28.9)
2 to <3 $\log_{10}$ IU	85/151 (56.3)	80/149 (53.7)	72/158 (45.6)
3 to <4 $\log_{10}$ IU	86/113 (76.1)	78/126 (61.9)	91/147 (61.9)
≥4 $\log_{10}$ IU	69/88 (78.4)	76/96 (79.2)	81/124 (65.3)
Undetectable	69/79 (87.3)	107/116 (92.2)	98/123 (79.7)
Change in HCV RNA between baseline and wk 12			
<1 $\log_{10}$ IU†	1/142 (0.7)	1/91 (1.1)	3/75 (4.0)
1 to <2 $\log_{10}$ IU†	0/160	0/115	1/95 (1.1)
2 to <3 $\log_{10}$ IU	3/78 (3.8)	4/84 (4.8)	3/71 (4.2)
3 to <4 $\log_{10}$ IU	21/82 (25.6)	19/91 (20.9)	16/96 (16.7)
≥4 $\log_{10}$ IU	55/110 (50.0)	51/127 (40.2)	48/150 (32.0)
Undetectable	303/366 (82.8)	328/407 (80.6)	344/466 (73.8)
HCV RNA at wk 24			
≥2 $\log_{10}$ decline from baseline, detectable at wk 12, and undetectable at wk 24	75/154 (48.7)	70/157 (44.6)	66/193 (34.2)
Weeks to first undetectable HCV RNA level			
Sustained virologic response			
2	38/42 (90.5)	43/45 (95.6)	37/44 (84.1)
4	33/41 (80.5)	64/72 (88.9)	62/83 (74.7)
12	234/292 (80.1)	227/300 (75.7)	250/355 (70.4)
24	77/157 (49.0)	68/156 (43.6)	72/203 (35.5)
Relapse			
2	0/38	1/43 (2.3)	1/38 (2.6)
4	4/37 (10.8)	4/67 (6.0)	6/67 (9.0)
12	27/257 (10.5)	37/263 (14.1)	61/309 (19.7)
24	49/125 (39.2)	62/127 (48.8)	100/171 (58.5)

* The numbers of patients given are those with a sustained virologic response (as prespecified in the statistical analysis plan), except for weeks to first undetectable hepatitis C virus (HCV) RNA level, for which the number with relapse is also shown. Sustained virologic response was defined as an undetectable HCV RNA level (as measured with the Cobas TaqMan assay [Roche], with a lower limit of detection of 27 IU per milliliter) at the end of the follow-up period. Relapse was defined as an undetectable HCV RNA level at the end of the treatment period but a detectable level at the end of the follow-up period. Among the patients with the undetectable HCV RNA levels at treatment weeks 4 and 12, a sustained virologic response was achieved in 86.2% and 78.7%, respectively. The numbers of patients who had undetectable HCV RNA levels at 12 weeks after the end of treatment but who missed the 24-week post-treatment visit were 38, 21, and 25 for standard-dose peginterferon alfa-2b, low-dose peginterferon alfa-2b, and peginterferon alfa-2a, respectively. Patients with missing HCV RNA data at weeks 4, 12, or 24 were not included in the analyses.

† According to the protocol, therapy was discontinued in patients with a reduction in HCV RNA level at treatment week 12 that was detectable and was less than 2 $\log_{10}$ IU or with detectable HCV RNA at week 24; however, in some cases therapy was continued, on the basis of a request by an investigator. A total of 174 patients continued therapy beyond week 12 or 24 despite persistent low-level viremia. Of these patients, a sustained virologic response was achieved in only 14 (5 of 46 patients receiving low-dose peginterferon alfa-2b, 4 of 62 receiving standard-dose peginterferon alfa-2b, and 5 of 66 receiving peginterferon alfa-2a).

which was administered according to two. Patients weighing between 75 and 85 kg received 1000 mg of ribavirin per day if they were also receiving peginterferon alfa-2b, as compared with 1200 mg per day if they were also receiving peginterferon alfa-2a. In this large weight group (792 patients),

Table 4. Adverse Events, Discontinuations of Treatment, and Dose Reductions, According to Treatment Group.

Adverse Event	Low-Dose Peginterferon Alfa-2b + Ribavirin (N = 1016)	Standard-Dose Peginterferon Alfa-2b + Ribavirin (N = 1019)	Peginterferon Alfa-2a + Ribavirin (N = 1035)	P Value*		
				Low-Dose vs. Standard-Dose Peginterferon Alfa-2b	Standard-Dose Peginterferon Alfa-2b vs. Peginterferon Alfa-2a	Low-Dose Peginterferon Alfa-2b vs. Peginterferon Alfa-2a
Death — no.	1	5	6	0.10	0.78	0.06
Serious adverse event — no. (%)†						
Any	94 (9.3)	88 (8.6)	121 (11.7)	0.63	0.02	0.07
Treatment-related	45 (4.4)	40 (3.9)	46 (4.4)	0.57	0.56	0.99
According to clinical category						
Hematologic disorders	4 (0.4)	4 (0.4)	8 (0.8)	0.99	0.26	0.26
Cardiovascular disorders	7 (0.7)	8 (0.8)	9 (0.9)	0.80	0.83	0.64
Gastrointestinal and hepatobiliary disorders	18 (1.8)	23 (2.3)	22 (2.1)	0.44	0.84	0.56
Infections	21 (2.1)	16 (1.6)	30 (2.9)	0.40	0.04	0.23
Neoplasm	7 (0.7)	1 (0.1)	8 (0.8)	0.03	0.02	0.82
Nervous-system disorders	11 (1.1)	9 (0.9)	16 (1.5)	0.65	0.17	0.36
Psychiatric disorders	12 (1.2)	19 (1.9)	14 (1.4)	0.21	0.36	0.73
Respiratory disorders	9 (0.9)	7 (0.7)	10 (1.0)	0.61	0.49	0.85
Other disorders	54 (5.3)	40 (3.9)	52 (5.0)	0.14	0.23	0.77
Discontinuation of treatment — no. (%)						
For any reason	523 (51.5)	479 (47.0)	414 (40.0)	0.04	0.001	<0.001
For adverse event	98 (9.6)	129 (12.7)	135 (13.0)	0.03	0.80	0.02
For virologic nonresponse	357 (35.1)	262 (25.7)	211 (20.4)	<0.001	0.004	<0.001
Hematologic events — no./total no. (%)						
Reduced neutrophil count						
<750/mm^3	147/1008 (14.6)	222/1000 (22.2)	279/1034 (27.0)	<0.001	0.01	<0.001
<500/mm^3	21/1008 (2.1)	28/1000 (2.8)	61/1034 (5.9)	0.30	0.001	<0.001
Reduced hemoglobin						
<10 g/dl	255/1008 (25.3)	307/1000 (30.7)	306/1034 (29.6)	0.007	0.59	0.03
<8.5 g/dl	21/1008 (2.1)	25/1000 (2.5)	39/1034 (3.8)	0.53	0.10	0.02
Use of erythrocyte-stimulating agent	144 (14.2)	166 (16.3)	172 (16.6)	0.18	0.84	0.13

Dose modification — no. (%)						
Any	338 (33.3)	441 (43.3)	444 (42.9)	<0.001	0.86	<0.001
Of peginterferon alfa only	70 (6.9)	103 (10.1)	122 (11.8)	0.009	0.22	<0.001
Of ribavirin only	170 (16.7)	187 (18.4)	180 (17.4)	0.34	0.57	0.69
Of both	98 (9.6)	151 (14.8)	142 (13.7)	<0.001	0.48	0.004
Common adverse events (≥25% incidence) — no. (%)						
Fatigue	676 (66.5)	672 (65.9)	656 (63.4)	0.78	0.22	0.13
Headache	486 (47.8)	508 (49.9)	438 (42.3)	0.36	0.001	0.01
Nausea	377 (37.1)	433 (42.5)	377 (36.4)	0.01	0.005	0.75
Insomnia	389 (38.3)	401 (39.4)	428 (41.4)	0.62	0.36	0.16
Pyrexia	331 (32.6)	356 (34.9)	237 (22.9)	0.26	<0.001	<0.001
Anemia	293 (28.8)	345 (33.9)	348 (33.6)	0.02	0.91	0.02
Myalgia	270 (26.6)	274 (26.9)	233 (22.5)	0.87	0.02	0.03
Neutropenia	188 (18.5)	263 (25.8)	326 (31.5)	<0.001	0.004	<0.001
Depression	197 (19.4)	260 (25.5)	217 (21.0)	0.001	0.02	0.37
Irritability	262 (25.8)	256 (25.1)	262 (25.3)	0.73	0.92	0.81
Rash	223 (21.9)	225 (22.1)	290 (28.0)	0.94	0.002	0.002

* Nominal P values were calculated with the use of a two-sided chi-square test.
† Serious adverse events were classified according to the *Medical Dictionary for Regulatory Activities* (version 10.1) body-system organ classes.

the rate of sustained virologic response was higher by approximately 10 percentage points in the peginterferon alfa-2a group, suggesting that the ribavirin dose for persons who weigh between 75 and 85 kg should be 1200 mg per day in the peginterferon alfa-2b groups. Surprisingly, reducing the ribavirin dose because of treatment-related anemia (as was done in 30% of patients) did not appear to reduce the likelihood of sustained virologic response. Despite the reduction of ribavirin dose by as much as 50% in patients receiving peginterferon alfa-2a, patients with anemia had a higher rate of sustained virologic response than did those without anemia, suggesting that the magnitude of anemia may be a pharmacodynamic marker of drug exposure. The data indicate that the initial ribavirin dose should be at least 13 mg per kilogram per day and that the conservative management of anemia, involving a ribavirin-dose reduction in either one or two steps, appears to maintain safety and not to compromise efficacy.

The findings are subject to several limitations. Because the initial ribavirin dose varied among the patients, the study compares HCV treatment regimens and is not a direct comparison of the type of peginterferon. Nonetheless, more than 51% of patients received the same dose of ribavirin in combination with either peginterferon alfa-2a or peginterferon alfa-2b, and their rates of sustained virologic response were similar. Second, the procedure for ribavirin-dose reduction differed between the peginterferon alfa-2a group and the peginterferon alfa-2b groups. Yet, the rate of sustained virologic response was higher among patients who had the ribavirin dose reduced because of anemia than among those who did not. Third, since the study was conducted in the United States, these comparative data may not be generalizable to other regions or HCV genotypes. Fourth, owing to insurmountable differences in drug formulation (lyophilized powder in the case of peginterferon alfa-2b or solution in the case of peginterferon alfa-2a), patients and investigators were aware of the type of peginterferon being given. After careful inspection, however, no irregularity in data collection or reporting was detected.

In conclusion, the rates of sustained virologic response and the safety and adverse-event profiles were similar among patients infected with HCV genotype 1 who received standard-dose or low-dose peginterferon alfa-2b or peginterferon alfa-2a, in combination with ribavirin.

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