Peginterferon-α2a and Ribavirin Combination Therapy in Chronic Hepatitis C

A Randomized Study of Treatment Duration and Ribavirin Dose

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Background: **Treatment with pegylated interferon (peginterferon) and ribavirin for 48 weeks is more effective than conventional interferon and ribavirin in patients with chronic hepatitis C.**

Objective: **To assess the efficacy and safety of 24 or 48 weeks of treatment with peginterferon-α2a plus a low or standard dose of ribavirin.**

Design: **Randomized, double-blind trial.**

Setting: **99 international centers.**

Patients: **1311 patients with chronic hepatitis C.**

Intervention: **Peginterferon-α2a, 180 μg/wk, for 24 or 48 weeks plus a low-dose (800 mg/d) or standard weight-based dose (1000 or 1200 mg/d) of ribavirin.**

Measurement: **Sustained virologic response: undetectable HCV RNA concentration at the end of treatment and during 12 to 24 weeks of follow-up.**

Results: **Overall and in patients infected with HCV genotype 1, 48 weeks of treatment was statistically superior to 24 weeks and standard-dose ribavirin was statistically superior to low-dose ribavirin. In patients with HCV genotype 1, absolute differences in sustained virologic response rates between 48 and 24 weeks of treatment were 11.2% (95% CI, 3.6% to 18.9%) and 11.9% (CI, 4.7% to 18.9%), respectively, between standard- and low-dose ribavirin. Sustained virologic response rates for peginterferon-α2a and standard-dose ribavirin for 48 weeks were 63% (CI, 59% to 68%) overall and 52% (CI, 46% to 58%) in patients with HCV genotype 1. In patients with HCV genotypes 2 or 3, the sustained virologic response rates in the 4 treatment groups were not statistically significantly different.**

Conclusion: **Treatment with peginterferon-α2a and ribavirin may be individualized by genotype. Patients with HCV genotype 1 require treatment for 48 weeks and a standard dose of ribavirin; those with HCV genotypes 2 or 3 seem to be adequately treated with a low dose of ribavirin for 24 weeks.**

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See related article on pp 370-381.

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The combination of interferon-α and ribavirin for 48 weeks produces sustained virologic responses in approximately 40% of previously untreated patients with chronic hepatitis C (1–3). Two forms of pegylated interferon-α (peginterferon-α), a 12-KDa linear and a 40-KDa branched form, are widely approved for use with or without ribavirin. These products are pharmacologically distinct and are superior to conventional interferon when administered for 48 weeks (4–11).

The safety concerns inherent in using interferon and ribavirin mandate the need to balance exposure to therapy with efficacy considerations. The duration of treatment with conventional interferon-α2b and ribavirin can be reduced in certain patients from 48 to 24 weeks without loss of efficacy (1, 2, 12, 13). Similar data for peginterferon and ribavirin therapy are unavailable. Furthermore, no large randomized studies have examined different ribavirin dose regimens in this setting.

We investigated whether peginterferon-α2a (40 KDa) and ribavirin for 48 weeks is superior to 24 weeks of treatment and identified subgroups of patients in whom the treatment duration may be reduced. We also compared the efficacy and safety of 2 ribavirin dose regimens.

The ribavirin regimens evaluated in the study included a standard weight-based regimen (1000 or 1200 mg/d), which was approved for use in combination with interferon-α2b at the time the study was planned, and a fixed, low-dose regimen (800 mg/d). The low-dose regimen was evaluated because other authors had reported that reductions in dosage to as low as 600 mg/d to manage ribavirin-induced anemia did not seem to compromise sustained virologic response rates.

METHODS

Patient Selection

Treatment-naive adult patients with the following conditions were eligible for enrollment: a serum hepatitis C virus (HCV) RNA concentration greater than 2000 copies/mL (Cobas Amplicor HCV Monitor Test, version 2.0, Roche Diagnostics, Branchburg, New Jersey), an elevated serum alanine aminotransferase level documented on 2 or more occasions 14 days or more apart within the previous 6 months, compensated liver disease, and a liver biopsy specimen consistent with chronic hepatitis C obtained in the previous 15 months. Patients with compensated cirrhosis or transition to cirrhosis were classified as Child–Pugh class A. All women of childbearing potential were required to have a negative pregnancy test result 24 hours before the first dose of study medications. Patients were recruited ei-

ther directly from the investigators' practices or by referral from other practitioners.

Patients were excluded if they had one of the following conditions: neutropenia (neutrophil count $< 1.5 \times 10^9$ cells/L); thrombocytopenia (platelet count $< 90 \times 10^9$ cells/L); anemia (hemoglobin level < 120 g/L in women and < 130 g/L in men) or a medical condition that would be clinically significantly worsened by anemia; serum creatinine level more than 1.5 times the upper limit of normal; co-infection with hepatitis A or B virus or HIV; history of bleeding from esophageal varices or other conditions consistent with decompensated liver disease; organ transplant; severe or poorly controlled psychiatric disease, especially depression; malignant neoplastic disease; severe cardiac or chronic pulmonary disease; immunologically mediated disease (except controlled thyroid disease); seizure disorder; severe retinopathy; alcohol or drug dependence within 1 year of study entry; clinically significant comorbid medical conditions; pregnancy; or unwillingness to practice contraception.

Severe psychiatric disease was defined as treatment with an antidepressant medication or major tranquilizer for major depression or psychosis, respectively, for 3 months or more at any time or a history of a suicide attempt, hospitalization, or period of disability due to psychiatric disease.

Study Design

This phase III, randomized, double-blind clinical trial used a 2 × 2 factorial design to assess differences in sustained viral response rates in patients treated for 24 or 48 weeks with subcutaneous peginterferon-α2a (Pegasys, Roche, Basel, Switzerland) in combination with either a low dose or a standard weight-based dose of oral ribavirin (Copegus, Roche). The factorial design allows for the effects of 2 variables to be tested simultaneously: in this case, duration of treatment and ribavirin dose. All patients received peginterferon-α2a, 180 μg/wk, and ribavirin, 800 mg/d for 24 weeks (24-LD); 1000 mg/d (if their body weight was <75 kg) or 1200 mg/d (if their body weight was ≥75 kg) for 24 weeks (24-SD); 800 mg/d for 48 weeks (48-LD); or standard weight-based dose of ribavirin for 48 weeks (48-SD).

Investigators and patients were blinded to the ribavirin dose throughout the study and to treatment duration until week 24. A matching placebo tablet identical to the ribavirin tablets and packaged in identical bottles was provided through a central distribution process to maintain blinding. All patients received the same number of tablets per day (ribavirin or placebo).

Randomization was centralized, blocked, and stratified by geographic region. In each region, patients were stratified by HCV genotype (genotype 1 vs. non–genotype 1) and viral load (≤2×10^6 copies/mL vs. >2×10^6 copies/mL). Within each stratum, patients were randomly assigned to 1 of the 4 treatment groups. The computer-generated randomization list was prepared and managed by Applied Logic Associates, Houston, Texas. Randomization numbers were allocated sequentially in the order in which patients were enrolled.

The study was designed for an unequal, randomized allocation of patients to the 4 study groups based on genotype and baseline HCV titer. This unequal randomization was designed to reduce the number of patients with more difficult-to-treat characteristics (HCV genotype 1 and high baseline viral load) who would receive 24 weeks of treatment. This was done to ensure that, as dictated by statistical requirements, as few of these patients as possible received a course of treatment that was considered experimental at the time the study was initiated. After 3 months, it became apparent that the number of patients with a genotype other than genotype 1 and low baseline viral loads specified in the protocol could not be recruited within an acceptable time frame. The protocol was thus amended to allow for a revised randomization procedure. Patients with HCV genotype 1 and a low viral load (≤2×10^6 copies/mL) and those with a genotype other than genotype 1 were initially randomly assigned to groups 24-LD, 24-SD, 48-LD, and 48-SD in a 1:2:1:2 ratio. In the amended protocol, the randomization ratio was changed to 1:1:1:1 for subsequent patients. Patients with HCV genotype 1 and a high viral load (>2×10^6 copies/mL) were initially randomly assigned to groups 24-LD, 24-SD, 48-LD, and 48-SD in a 1:1:3:3 ratio. In the amended protocol, the randomization ratio was changed to 1:1:5:5 for subsequent patients.

The U.S. Food and Drug Administration and all institutional review boards approved the protocol amendment.

Context

Optimal treatment regimens of pegylated interferon (peginterferon) and ribavirin for chronic hepatitis C are undecided.

Contribution

This multicenter randomized trial found that, in patients with hepatitis C virus genotype 1, treatment for 48 weeks with peginterferon-α2a plus standard doses of ribavirin (1000 or 1200 mg/d) led to sustained virologic responses more often than did 24-week treatment and combination therapy with low-dose ribavirin. Longer treatment duration and higher ribavirin dose was not necessary in patients with genotype 2 or 3.

Implications

Patients with hepatitis C virus genotype 1 require higher ribavirin doses and longer treatment than do those with genotype 2 or 3.

–The Editors

Assessment and End Points

Serum HCV RNA concentration was determined at weeks 4, 12, 24, and 48 (only for groups 48-LD and 48-SD) during treatment and after 12 and 24 weeks of follow-up by a qualitative polymerase chain reaction assay (Cobas Amplicor HCV Test, version 2.0; limit of detection, 100 copies/mL [50 IU/mL]) in a central laboratory (UCTi, Farmingdale, New York, or London, United Kingdom, and ICON Laboratories, Farmingdale, New York). Patients in groups 48-LD and 48-SD with detectable HCV RNA and elevated alanine aminotransferase levels at week 24 were classified as nonresponders and discontinued further treatment.

All patients who received at least 1 dose of study drug were included in the efficacy analysis. The primary efficacy end point was sustained virologic response, defined as undetectable serum HCV RNA level at the end of treatment and during the 12- to 24-week follow-up. Patients without follow-up data were considered not to have achieved a sustained virologic response.

Hepatitis C virus genotyping was performed in a central laboratory by using an established method (14). Local pathologists evaluated pretreatment liver biopsy specimens by using standard criteria (15).

Safety Assessments

The safety sample comprised patients who received at least 1 dose of either study medication and had at least 1 postbaseline safety assessment. Safety was assessed by physical examination, laboratory tests, and spontaneous reports of clinical adverse events. All laboratory safety tests were performed at local laboratories. Investigators recorded adverse events on a standard form and rated the severity as mild, moderate, severe, or life threatening. Clinic visits to evaluate patients for adverse events and to conduct laboratory tests were scheduled at weeks 1, 2, 4, 6, 8, and 12 and at 6-week intervals thereafter. Dose modifications of peginterferon-α2a to 135, 90, or 45 μg/wk were permitted in patients who experienced clinically significant adverse events or laboratory abnormalities. The dose of ribavirin was reduced to 600 mg/d open-label if a patient experienced a clinically significant adverse event or laboratory abnormality, including decreases in hemoglobin level to less than 100 g/L in patients without heart disease or decreases of 20 g/L or more in patients with stable heart disease. Ribavirin therapy was discontinued in patients with hemoglobin levels less than 85 g/L. In the event of ribavirin dosage reductions, both the investigator and the patient remained blinded to the initial ribavirin dose. Patients could continue peginterferon-α2a if ribavirin therapy was discontinued, but ribavirin monotherapy was not allowed. The use of erythropoietin and granulocyte-stimulating growth factors was prohibited.

Statistical Analysis

On the basis of studies of interferon-α2b and ribavirin in patients with chronic hepatitis C (1, 2), we assumed that sustained virologic responses after 24 weeks of treatment with peginterferon-α2a plus ribavirin, 1000 or 1200 mg/d, would be 70% in patients with HCV non–genotype 1 regardless of viral titer, 40% in patients with HCV genotype 1 and low viral titer ($\leq 2 \times 10^6$ copies/mL), and 10% in patients with HCV genotype 1 and high viral titer. We required an improvement of 10% to 12% in sustained virologic response rate to justify extending the treatment duration to 48 weeks in these subgroups.

The study had 80% power to detect an improvement in sustained virologic response from 70% to 80% in patients with an HCV genotype other than genotype 1, 40% to 52% in patients with HCV genotype 1 and low viral load, and 10% to 30% in patients with HCV genotype 1 and high viral load, between the 24- and the 48-week treatment groups. The Cochran–Mantel–Haenszel test (16), stratified by a combination of geographic region, HCV genotype (1 and other than 1), HCV RNA level at baseline ($\leq 2 \times 10^6$ and $> 2 \times 10^6$ copies/mL), and ribavirin dose (800 and 1000 or 1200 mg/d), was used to compare treatment duration. We used this test (16), stratified by a combination of region, HCV genotype, viral load, and treatment duration, to compare ribavirin dose.

The Breslow–Day test assessed the homogeneity of the odds ratios over the strata formed by the combination of geographic region, HCV genotype, baseline viral load, and ribavirin dose. Because of the large number of strata (64 strata for the comparisons of treatment duration), the absence of heterogeneity across the strata (lack of treatment group by strata interaction) could have resulted from insufficient statistical power. For this reason, we used an alternative test for homogeneity suggested by Breslow and Day (16). With this test, strata are divided into groups so that the odds ratios are homogeneous within groups but not between them. The resulting statistic is a chi-square with degrees of freedom equaling the number of groups minus 1 under the homogeneity hypothesis and has enhanced power for detecting heterogeneity across groups, when the number of groups is much smaller than the number of strata.

Several logistic regression models were conducted to further explore the effect of the intervention variables (treatment duration and ribavirin dose) and several pretreatment factors on the likelihood of achieving a sustained virologic response. The following covariates were considered: age, weight, pretreatment alanine aminotransferase quotient, pretreatment HCV RNA levels, sex, race, HCV genotype, and fibrosis stage. Nine interaction terms with duration were tested in the model.

Study Conduct

The study was conducted in 99 centers in Europe, North and South America, Australia, New Zealand, and Taiwan. Institutional review boards of participating centers approved the protocol and all amendments, and all patients provided written informed consent. The study was

conducted according to the guidelines of the Declaration of Helsinki (as amended in Tokyo, Venice, and Hong Kong); under provisions of "Good Clinical Practices," as defined in the U.S. Code of Federal Regulations on the Protection of Human Subjects for the United States, or guidelines, by country; or within local laws and regulations of the country in which the research was conducted, whichever provided patients with the greatest protection.

Role of the Funding Source

Roche, Basel, Switzerland, sponsored the study and was responsible for the collection and statistical analysis of the data. The lead investigator had unlimited access to the data and interpreted the results. No limitations on publications were imposed. The first author made final decisions about all aspects of the manuscript, and all named authors participated in the interpretation of results and the writing of the manuscript.

RESULTS

Patient Demographic Characteristics

Enrollment began in November 1999 and the study ended in January 2002. A total of 1736 patients were screened, and 1311 patients were randomly assigned (**Figure 1**). Of the 27 patients randomly assigned but not treated, 13 declined treatment, 9 did not meet entry criteria, 3 did not return for follow-up, and 2 were not treated for administrative reasons. A total of 1014 patients completed the duration of treatment to which they had been randomly assigned. Follow-up data are available for 1045 patients at 12 weeks and for 1022 patients at 24 weeks after the end of treatment. Baseline characteristics of patients ($n = 1284$) across the 4 treatment groups were similar (**Table 1**). The between-group differences in HCV genotype and viral load reflect the unequal stratified randomization procedure (see earlier discussion). The differences in baseline HCV RNA levels between strata were minimal and not clinically meaningful.

Efficacy

With respect to the primary end point, patients treated for 48 weeks were more likely to achieve a sustained virologic response than patients treated for 24 weeks (48-LD or 48-SD vs. 24-LD or 24-SD; odds ratio, 1.53 [95% CI, 1.17 to 2.01]; $P = 0.002$). Similarly, the likelihood of achieving a sustained virologic response was greater among patients receiving a standard weight-based dose of ribavirin than among patients receiving a low dose of ribavirin (24-SD or 48-SD vs. 24-LD or 48-LD; odds ratio, 1.41 [CI, 1.10 to 1.81]; $P = 0.01$). Peginterferon-α2a and standard ribavirin for 48 weeks produced an overall sustained virologic response rate of 63% (CI, 59% to 68%).

Examination of the patterns of sustained virologic response rates across the study strata revealed distinct patterns of responses in patients with HCV genotype 1 and a genotype other than genotype 1. A revised homogeneity test identified a statistically significant ($P = 0.003$) interaction and confirmed that the differences between the 2 treatment durations varied statistically significantly according to genotype. Similar analyses were repeated for the secondary comparison of the 2 ribavirin dose groups. Once again, the results were primarily driven by genotype. Because of these findings, the study results are presented stratified by genotype.

These findings were confirmed by the results of the multiple logistic regression analysis, which showed that HCV genotype was the predominant predictor of response (odds ratio for a genotype other than genotype 1 vs. genotype 1 was 5.4 [CI, 4.1 to 7.1]; $P < 0.001$). In addition, the interaction between treatment duration and genotype was highly significant (odds ratio, 0.42 [CI, 0.24 to 0.75]; $P = 0.003$).

Because these findings indicate that the treatment effect was different depending on the HCV genotype, the study results are presented stratified by genotype.

Table 2 presents the measures of the treatment effect stratified by HCV genotype and viral load. **Figures 2** and **3** show the virologic response rates at the end of treatment and the end of follow-up.

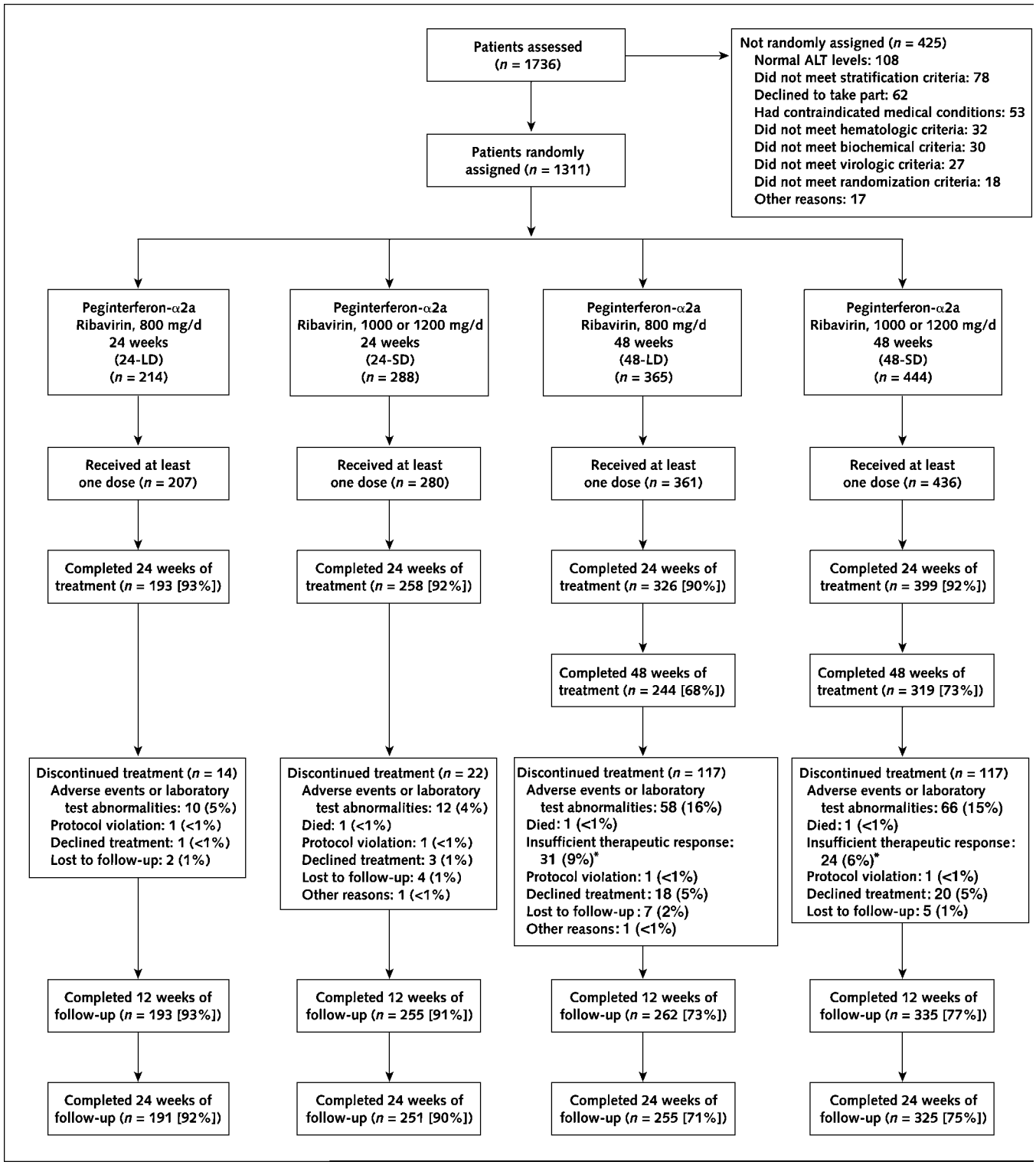
Among patients with HCV genotype 1 (**Table 2**) (**Figure 2B**), treatment for 48 weeks was more effective than 24 weeks in producing a sustained virologic response (odds ratio, 2.19 [CI, 1.52 to 3.16]; $P < 0.001$). Treatment with standard-dose ribavirin was also more effective than low-dose ribavirin in these patients (odds ratio, 1.55 [CI, 1.14 to 2.10]; $P = 0.005$). Group 48-SD had the highest sustained virologic response rate among patients infected with HCV genotype 1 (52% [CI, 46% to 58%]).

In patients with HCV genotypes 2 or 3, sustained virologic response rates were relatively uniform (**Table 2**) (**Figure 2D**). The highest sustained virologic response rate among patients with HCV genotypes 2 or 3 was in group 24-LD (84% [CI, 77% to 92%]) and the lowest was in group 48-LD (79% [CI, 71% to 87%]). The patient groups did not statistically significantly differ according to treatment duration or ribavirin dose regimen (**Table 2**). Similarly, viral load did not seem to influence sustained virologic response rates (**Figure 2**).

In patients with bridging fibrosis or cirrhosis, the effect of treatment duration and ribavirin dose seemed to follow the same pattern as in the overall sample (**Figure 3**, *bottom*), but this subgroup of patients is too small to allow us to draw definitive conclusions.

Thirty-six patients with HCV genotype 4 were included in the study. At the end of follow-up, sustained virologic responses were obtained in 0% (0 of 5 patients), 67% (8 of 12 patients), 63% (5 of 8 patients), and 82% (9 of 11 patients) of those randomly assigned to groups 24-LD, 24-SD, 48-LD, and 48-SD, respectively.

Figure 1. **Flow of participants through the study.**



Patients who withdrew from treatment after 12 weeks or more and had negative hepatitis C virus RNA levels were encouraged to return for follow-up. For this reason, the number of patients who completed follow-up is higher than the number of patients who completed treatment in 2 of the 4 groups (48 weeks of treatment with peginterferon-α2a and low-dose ribavirin [48-LD] and 48 weeks of treatment with peginterferon-α2a and standard weight-based dose of ribavirin [48-SD]). *According to the protocol, patients without a virologic or biochemical response after 24 weeks of treatment were classified as nonresponders and discontinued further treatment. 24-LD = 24 weeks of treatment with peginterferon-α2a and low-dose ribavirin; 24-SD = 24 weeks of treatment with peginterferon-α2a and standard weight-based ribavirin dose; ALT = alanine aminotransferase.

Table 1. **Patient Characteristics at Baseline***

Characteristic	Treatment Group			
	24-LD	24-SD	48-LD	48-SD
Duration of treatment, *wk*	24	24	48	48
Peginterferon-α2a dosage, *μg/wk*	180	180	180	180
Ribavirin dosage, *mg/d*	800	1000 or 1200	800	1000 or 1200
Total patients, *n*	207	280	361	436
Men/women, *n/n (% men)*	140/67 (68)	185/95 (66)	226/135 (63)	287/149 (66)
Mean age, *y*	41.2 ± 8.9	42.0 ± 9.2	42.6 ± 10.4	43.0 ± 10.1
Mean weight, *kg*	78.3 ± 16.7	77.1 ± 15.8	77.0 ± 17.0	77.3 ± 16.0
Mean body surface area, m^2	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2
Race or ethnicity, *n (%)*				
White	183 (88)	254 (91)	315 (87)	394 (90)
Black	7 (3)	9 (3)	11 (3)	11 (3)
Asian	14 (7)	16 (6)	31 (9)	26 (6)
Other	3 (1)	1 (<1)	4 (1)	5 (1)
Mode of infection, *n (%)*†				
Injection drug use	74 (36)	96 (34)	124 (34)	163 (37)
Transfusion	39 (19)	45 (16)	67 (19)	80 (18)
Unknown or other	72 (35)	97 (35)	127 (35)	131 (30)
ALT quotient, *n (%)*‡				
≤3	138 (67)	187 (67)	258 (71)	299 (69)
>3	69 (33)	93 (33)	103 (29)	137 (31)
Mean ALT level, *U/L*‡	88.3 ± 62.5	91.1 ± 67.5	81.3 ± 52.6	87.0 ± 60.9
Mean HCV RNA level, $\times 10^3$ *copies/mL*	5047 ± 5358	5513 ± 7002	7156 ± 8223	6059 ± 6847
HCV genotype, *n (%)*				
Type 1	101 (49)	118 (42)	250 (69)	271 (62)
Not type 1	106 (51)	162 (58)	111 (31)	165 (38)
Type 2	39 (19)	53 (19)	46 (13)	66 (15)
Type 3	57 (28)	91 (33)	53 (15)	87 (20)
Histologic diagnosis, *n (%)*				
Noncirrhosis	163 (79)	209 (75)	270 (75)	321 (74)
Cirrhosis	10 (5)	20 (7)	25 (7)	35 (8)
Bridging fibrosis	34 (16)	51 (18)	66 (18)	80 (18)

* All values expressed with a plus/minus sign are means ± SD. 24-LD = 24 weeks of treatment with peginterferon-α2a and low-dose ribavirin; 24-SD = 24 weeks of treatment with peginterferon-α2a and standard weight-based dose of ribavirin; 48-LD = 48 weeks of treatment with peginterferon-α2a and low-dose ribavirin; 48-SD = 48 weeks of treatment with peginterferon-α2a and standard weight-based dose of ribavirin; ALT = alanine aminotransferase; HCV = hepatitis C virus.
† Numbers do not add to 100% because of rounding.
‡ ALT value divided by the upper limit of normal for the local laboratory.

Safety

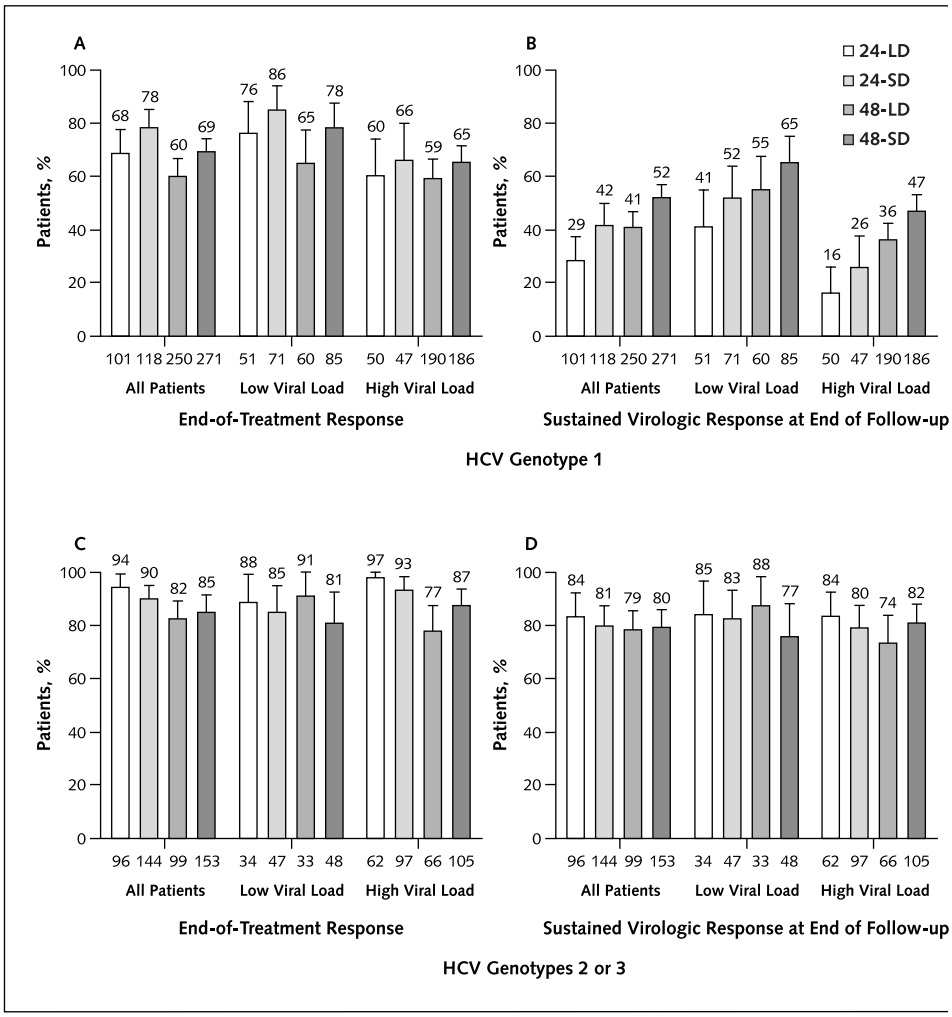
Most adverse events were mild to moderate in severity, and all adverse events were typical of those previously reported for interferon-α and ribavirin (**Table 3**). Severe and serious adverse events were less frequent in patients treated for 24 weeks than in those treated for 48 weeks (**Table 3**). Treatment-related serious adverse events occurred least frequently in group 24-SD. Two deaths (one opiate overdose

Table 2. **Treatment Effects by Hepatitis C Virus Genotype and Viral Load at Baseline***

Comparison or Stratum	Odds Ratio (95% CI)	*P* Value	Difference in Sustained Virologic Response Rate (95% CI), %
48 vs. 24 wks of treatment (48-LD and 48-SD vs. 24-LD and 24-SD)			
HCV genotype 1 (*n* = 740)	2.19 (1.52 to 3.16)†	<0.0001	11.2 (3.6 to 18.9)
High viral load (*n* = 473)	2.90 (1.66 to 5.07)†	0.0001	20.9 (11.4 to 30.3)
Low viral load (*n* = 267)	1.71 (1.05 to 2.80)‡	0.034	13.2 (1.2 to 25.1)
HCV genotype 2 or 3 (*n* = 492)	0.89 (0.56 to 1.42)‡	>0.2	−2.7 (−9.6 to 4.2)
Standard vs. low ribavirin dose (24-SD and 48-SD vs. 24-LD and 48-LD)			
HCV genotype 1 (*n* = 740)	1.55 (1.14 to 2.10)§	0.005	11.9 (4.7 to 18.9)
High viral load (*n* = 473)	1.56 (1.06 to 2.29)‖	0.025	10.4 (1.7 to 19.1)
Low viral load (*n* = 267)	1.53 (0.93 to 2.52)‖	0.101	10.4 (−1.8 to 22.4)
HCV genotype 2 or 3 (*n* = 492)	1.00 (0.63 to 1.61)§	>0.2	−0.7 (−7.8 to 6.3)

* 24-LD = 24 weeks of treatment with peginterferon-α2a and low-dose ribavirin; 24-SD = 24 weeks of treatment with peginterferon-α2a and standard weight-based dose of ribavirin; 48-LD = 48 weeks of treatment with peginterferon-α2a and low-dose ribavirin; 48-SD = 48 weeks of treatment with peginterferon-α2a and standard weight-based dose of ribavirin; HCV = hepatitis C virus.
† Adjusted for the effect of ribavirin dose, viral load, and study region.
‡ Adjusted for the effect of ribavirin dose and study region.
§ Adjusted for the effect of treatment duration, viral load, and study region.
‖ Adjusted for the effect of treatment duration and study region.

Figure 2. **End-of-treatment and sustained virologic response rates in patients randomly assigned to 24 or 48 weeks of treatment with peginterferon-α2a and either a low dose (800 mg/d) or standard weight-based dose of ribavirin (1000 or 1200 mg/d).**



Vertical bars represent 95% CIs. The total number of patients in each group is indicated at the base of each bar. HCV = hepatitis C virus.

and one multidrug toxicity and alcohol intoxication) were judged to be unrelated to study medications, while 2 events were considered to be related to study medications (one patient committed suicide, and one patient died of septicemia). Patients treated for 48 weeks had higher rates of premature withdrawal of therapy than those treated for 24 weeks. Dose modifications were most common in group 48-SD.

Hemoglobin concentrations decreased to less than 100 g/L in 3.4%, 10.0%, 6.4%, and 15.4% of patients in groups 24-LD, 24-SD, 48-LD, and 48-SD, respectively, and to less than 85 g/L in 4 patients (1%) in groups 24-SD and 48-SD. Among the patients in groups 24-LD and 48-LD, only 1 patient (<1%) had a hemoglobin concentration decrease to less than 85 g/L. Neutrophil counts decreased to less than 0.5×10^9 cells/L in 3% to 5% of patients in each group. Platelet counts less than 50×10^9 cells/L occurred in 3% to 5% of patients in the 4 groups. No patients developed platelet counts less than 20×10^9 cells/L.

DISCUSSION

The results of this study confirm the efficacy and safety of peginterferon-α2a and ribavirin therapy in patients with chronic hepatitis C (7). Treatment for 48 weeks with peginterferon-α2a in combination with a standard weight-based dose of ribavirin produced sustained virologic responses in 63% of patients.

Evidence from trials of conventional interferon-α2b and ribavirin suggests that patients with HCV genotype 1 require maximum treatment intensity, while patients with HCV genotypes 2 or 3 may be treated for a shorter duration (1, 2). Patients with HCV genotype 1 achieved the highest sustained virologic response rates when treated for 48 weeks with peginterferon-α2a and a standard dose of ribavirin. Decreasing the treatment duration, ribavirin

dose, or both markedly decreased sustained virologic response rates in this group. The absolute differences in sustained virologic response rates between 48 and 24 weeks of treatment were 11.2% (CI, 3.6% to 18.9%) and 11.9% (CI, 4.7% to 18.9%), respectively, between standard- and low-dose ribavirin.

This pattern was consistent in patients with HCV genotype 1 and with both high and low viral loads at baseline.

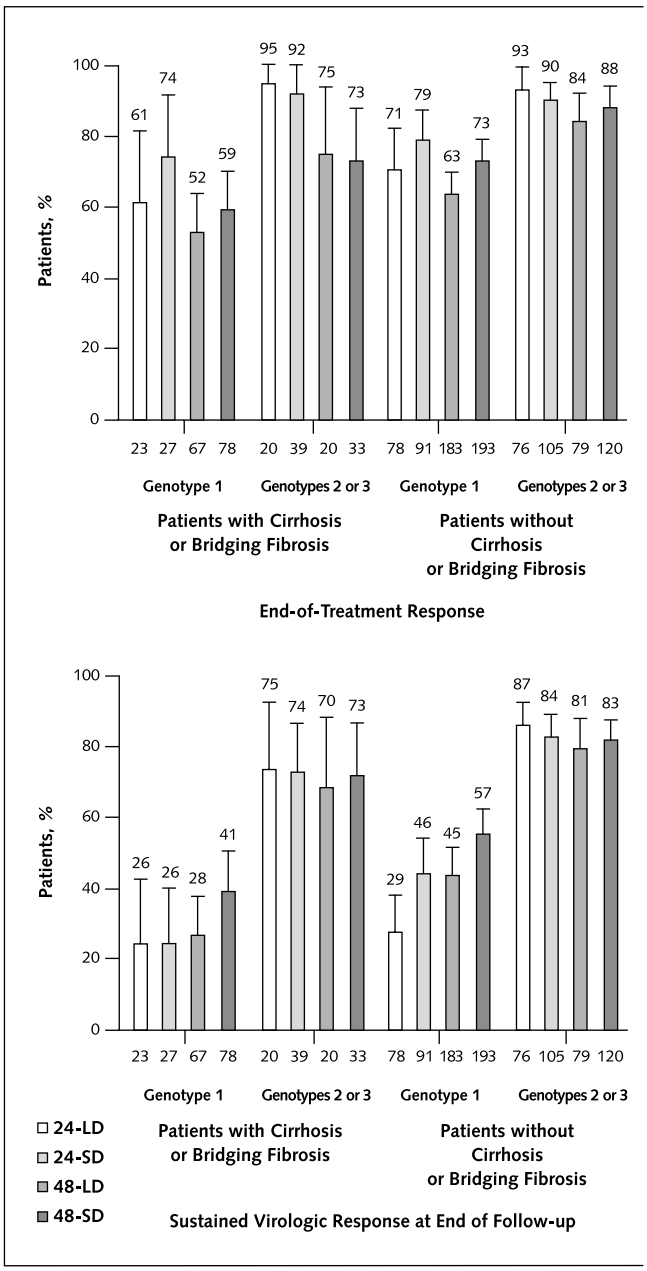
In contrast, sustained virologic response rates across the 4 treatment groups in patients with HCV genotypes 2 or 3 were of similar magnitude. No statistically significant differences in sustained virologic response rates were detected in patients treated for 24 or 48 weeks or in those treated with low- or standard-dose ribavirin. As the study had sufficient statistical power to detect differences in sustained virologic response rates in excess of 10% in this group, the observed lack of a greater effect with the higher ribavirin dose and longer treatment duration was probably not due to a type II error. Furthermore, our results are consistent with those obtained with conventional interferon and ribavirin (1, 2). Although there were relatively few patients, the data suggest that patients with HCV genotypes 2 or 3 with high viral loads or advanced liver fibrosis at baseline do not benefit from a more intensive treatment regimen. Because the less intensive regimens (24-LD and 24-SD) were better tolerated than the longer treatment regimens (48-LD and 48-SD), the reduced exposure will probably translate into a better benefit–risk ratio in patients with HCV genotypes 2 or 3.

The duration of follow-up was similar to that generally used in studies of interferon-based therapies for chronic HCV. A follow-up period of 24 weeks was used in patients treated for 24 and 48 weeks with interferon-α2b plus ribavirin (1, 2) and in those treated for 48 weeks with peginterferon-α2a, alone or in combination with ribavirin (7, 10, 11, 17). Patients with sustained virologic and biochemical responses 24 weeks after completing a 24-week course of interferon-α have remained without disease and have marked histologic improvement for more than 7 years (18).

In our study, the follow-up period was a 12- to 24-week period because most relapses occurred during the first 12 weeks of follow-up in other studies of peginterferon-α2a (19). Moreover, we obtained virologic measurements at both 12 and 24 weeks in 1022 of the 1045 patients (98%) with available follow-up data. Assuming that the 2% of patients with undetectable HCV RNA levels at week 12 and missing data at week 24 did not achieve a sustained virologic response, then sustained virologic response rates after 24 weeks of follow-up remain very similar to those presented in **Figure 2**, and the primary findings of the study are unchanged.

The percentage of patients achieving sustained virologic responses after treatment for 48 weeks with peginterferon-α2a and standard dose of ribavirin (63%) was similar to that reported by Fried and colleagues (7) with the identical regimen in a similar patient population (56%). Sustained virologic response rates in patients treated with this regimen in the 2 studies are also similar when grouped according to HCV genotype (52% and 46% in those with HCV genotype 1 and 80% and 76% in those with HCV

Figure 3. **End-of-treatment and sustained virologic response rates in patients randomly assigned to 24 or 48 weeks of treatment with peginterferon-α2a and a low-dose (800 mg/d) or standard weight-based dose of ribavirin (1000 to 1200 mg/d).**



Data are grouped according to the extent of fibrosis at baseline. Vertical bars represent 95% CIs. The total number of patients in each group is indicated at the base of each bar.

Table 3. **Incidence of Adverse Events, Premature Withdrawals, and Dose Reductions***

Variable	Treatment Group			
	24-LD (*n* = 207)	24-SD (*n* = 280)	48-LD (*n* = 361)	48-SD (*n* = 436)
	← *n (%)* →			
Severe adverse events	46 (22)	63 (23)	116 (32)	141 (32)
Serious adverse events	7 (3)	19 (7)	33 (9)	44 (10)
Treatment-related, serious adverse events†	3 (1)	8 (3)	15 (4)	14 (3)
Deaths	0 (<1)	1 (<1)	1 (<1)	2 (<1)
Specific adverse events‡				
Headache	102 (49)	136 (49)	187 (52)	239 (55)
Fatigue	98 (47)	135 (48)	182 (50)	211 (48)
Myalgia	91 (44)	120 (43)	154 (43)	163 (37)
Pyrexia	81 (39)	114 (41)	156 (43)	173 (40)
Insomnia	69 (33)	99 (35)	146 (40)	146 (33)
Nausea	64 (31)	91 (33)	107 (30)	151 (35)
Rigors	64 (31)	87 (31)	87 (24)	119 (27)
Irritability	59 (29)	76 (27)	96 (27)	112 (26)
Alopecia	53 (26)	74 (26)	106 (29)	92 (21)
Arthralgia	50 (24)	70 (25)	106 (29)	105 (24)
Pruritus	56 (27)	60 (21)	81 (22)	111 (25)
Depression	43 (21)	42 (15)	79 (22)	104 (24)
Diarrhea	44 (21)	46 (16)	65 (18)	96 (22)
Dermatitis	34 (16)	49 (18)	69 (19)	86 (20)
Decreased appetite	30 (14)	41 (15)	66 (18)	91 (21)
Premature withdrawal				
For adverse events or laboratory abnormalities	10 (5)	13 (5)	59 (16)	67 (15)
For insufficient response§	0 (<1)	0 (<1)	31 (9)	24 (6)
For any reason	14 (7)	22 (8)	117 (32)	117 (27)
Reduction or omission of ≥1 doses for adverse events or laboratory abnormalities				
Peginterferon-α2a	63 (30)	73 (26)	120 (33)	159 (36)
Ribavirin	39 (19)	76 (27)	101 (28)	166 (38)

* 24-LD = 24 weeks of treatment with peginterferon-α2a and low-dose ribavirin; 24-SD = 24 weeks of treatment with peginterferon-α2a and standard weight-based dose of ribavirin; 48-LD = 48 weeks of treatment with peginterferon-α2a and low-dose ribavirin; 48-SD = 48 weeks of treatment with peginterferon-α2a and standard weight-based dose of ribavirin.
† As judged by the investigator.
‡ Adverse events related to treatment, as judged by investigators, that occurred in at least 20% of the patients who received at least one dose of study medication and had at least one postbaseline safety assessment.
§ Patients in groups 48-LD and 48-SD who did not achieve either undetectable hepatitis C virus RNA or normalization of alanine aminotransferase levels at week 24 were considered nonresponders and discontinued further treatment.

genotypes 2 or 3) or the presence of bridging fibrosis or cirrhosis (52% and 43%). Whether these results can be generalized to treatment with peginterferon-α2b and ribavirin is unknown. The 2 molecular entities are pharmacokinetically distinct, and previous reports of the efficacy and safety profiles in monotherapy studies differ (6, 9–11, 20). In addition, no prospective data on the effect of different durations of treatment with peginterferon-α2b and ribavirin or different doses of ribavirin used in combination with pegylated interferon-α2b have been published.

The results of our study will help to refine treatment regimens in patients with chronic HCV who have elevated liver enzyme levels and compensated liver disease. However, our results do not apply to the large group of patients with persistently normal alanine aminotransferase levels or the growing number of patients with HIV or HCV coinfection. The results of ongoing studies in these patient populations are awaited with great interest.

Our data demonstrate that treatment response is primarily driven by the HCV genotype even in the presence of prognostic factors associated with a less favorable treatment outcome. Patients with HCV genotype 1 should be treated for 48 weeks and should receive a standard dose of ribavirin. Patients with HCV genotypes 2 or 3 may be treated for 24 weeks with a lower dose of ribavirin. Reducing treatment duration and ribavirin dose without loss of efficacy in a large subgroup of patients with chronic HCV should result in a clinically significant, positive shift in the therapeutic benefit–risk ratio. Predicting early virologic response (7, 21) and identifying baseline factors associated with positive outcomes should allow further refinement of this individualized patient treatment algorithm.

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