Induction Pegylated Interferon Alfa-2a and High Dose Ribavirin Do Not Increase SVR in Heavy Patients With HCV Genotype 1 and High Viral Loads

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BACKGROUND & AIMS: Patients infected with hepatitis C virus (HCV) genotype 1, body weight ≥85 kg, and high baseline viral load respond poorly to standard doses of pegylated interferon (peginterferon) and ribavirin. We evaluated intensified therapy with peginterferon alfa-2a plus pegylated interferon (peginterferon) and ribavirin. METHODS: This double-blind randomized trial included HCV genotype 1-infected outpatients from hepatology clinics with body weight ≥85 kg and HCV RNA titer ≥400,000 IU/mL. Patients were randomized to 180 µg/wk peginterferon alfa-2a for 48 weeks plus 1200 mg/day ribavirin (standard of care) (group A, n = 191) or 1400/1600 mg/day ribavirin (group B, n = 189). Additional groups included 360 µg/wk peginterferon alfa-2a for 12 weeks then 180 µg/wk peginterferon alfa-2a for 36 weeks plus 1200 mg/day ribavirin (group C, n = 382) or 1400/1600 mg/day ribavirin (group D, n = 383). Follow-up lasted 24 weeks after treatment. RESULTS: Sustained virologic response rates (HCV RNA level <15 IU/mL at end of follow-up) in groups A, B, C, and D were 38%, 43%, 44%, and 41%, respectively. There were no significant differences among the 4 groups or between pooled peginterferon alfa-2a regimens (A + B vs C + D; odds ratio [OR], 1.08; 95% confidence interval [CI], 0.83–1.39; P = .584) or pooled ribavirin regimens (A + C vs B + D; OR, 1.00; 95% CI, 0.79–1.28; P = .974). CONCLUSIONS: In patients infected with HCV genotype 1 who are difficult to treat (high viral load, body weight ≥85 kg), a 12-week induction regimen of peginterferon alfa-2a and/or higher-dose ribavirin is not more effective than the standard regimen.

Keywords: Chronic Hepatitis C; Tolerance of High-Dose Pegylated Interferon; Steatosis and Response to HCV Therapy; Tolerance of High-Dose Ribavirin.

PEGylated interferon (peginterferon) alfa plus ribavirin is currently the standard of care for treating chronic hepatitis C infection, with approximately 40% to 50% of patients achieving a sustained virologic response (SVR). The likelihood that any given patient will achieve an SVR varies and is influenced by patient and viral characteristics. For example, SVR rates are higher in white patients than in black and Hispanic patients and higher in those infected with hepatitis C virus (HCV) genotype 2 or 3. It has been shown in one study that high viral load is significantly associated with lower SVR rates, even when a direct-acting antiviral agent is combined with peginterferon and ribavirin. Obesity, hepatic steatosis, and insulin resistance are some of the host characteristics that have been associated with lower SVR rates in patients with chronic hepatitis C. More recently, host genetic polymorphisms have been shown to strongly influence the rate of SVR. Improved treatment strategies for patients with “difficult-to-cure” characteristics are needed.

The use of higher doses of peginterferon alfa-2a, either as a fixed-dose induction or for the full treatment duration, as well as higher doses of ribavirin have been shown to increase the likelihood of achieving an SVR in small pilot studies. A 12-week high-dose (360 µg/wk) peginterferon alfa-2a induction regimen produced higher SVR rates than the standard 180-µg/wk regimen in a study of nonresponders to conventional interferon therapy (38% vs 18%). The objective of this large, randomized, international study was to determine whether a 12-week fixed-dose induction regimen of peginterferon alfa-2a and/or a high-dose weight-based ribavirin dose regimen could increase SVR rates in patients weighing ≥85 kg with HCV genotype 1 infection and a baseline HCV RNA level ≥400,000 IU/mL.

Abbreviations used in this paper: cEVR, complete early virologic response; CI, confidence interval; HOMA-IR, homeostasis model of assessment-insulin resistance; NAS, nonalcoholic fatty liver disease activity score; OR, odds ratio; peginterferon, pegylated interferon; RVR, rapid virologic response; SVR, sustained virologic response.
Patients and Methods

Patient Selection

Eligible patients were aged 18 years or older and had a body weight ≥85 kg, HCV genotype 1 infection, and an HCV RNA titer ≥400,000 IU/mL. Patients were required to have a liver biopsy result within 24 months of receiving study medication consistent with the diagnosis of chronic hepatitis C. Up to 20% of enrolled patients could have had a histologic diagnosis of transition to cirrhosis or cirrhosis provided that they had compensated liver disease (Child–Pugh grade A), a serum α-fetoprotein level <100 ng/mL, and no evidence of hepatocellular carcinoma on ultrasonography, computed tomography, or magnetic resonance imaging scan performed within the previous 2 months. Liver biopsy specimens were evaluated by a central pathologist blinded to treatment assignment using the Ishak-modified histologic activity index scoring system and, in addition, were graded for the degree of steatosis and nonalcoholic steatohepatitis using the nonalcoholic fatty liver disease activity score (NAS).13,14

Patients were ineligible if they had previously received treatment with interferon, ribavirin, or an investigational agent for treatment of HCV infection; were infected with hepatitis A or B virus or human immunodeficiency virus; had a history or evidence of a chronic liver disease other than chronic hepatitis C, a current or past history of chronic systemic disease including severe psychiatric disease, or an increased baseline risk of anemia; and/or had an absolute neutrophil count <1500 cells/mm³, a platelet count <90,000 cells/mm³, a hemoglobin concentration <12 g/dL if female or <13 g/dL if male, or a serum creatinine level >1.5 times the upper limit of normal. Pregnant or breastfeeding women and male partners of pregnant women were ineligible.

Study Design

Patients eligible for this trial were randomized (stratified by country) in a 1:1:2:2 ratio to 48 weeks of double-blind treatment with (A) subcutaneous peginterferon alfa-2a (40KD) (Pegasys; Roche, Basel, Switzerland) 180 μg/wk plus oral ribavirin (Copegus; Roche) 1200 mg/day; (B) peginterferon alfa-2a 180 μg/wk plus ribavirin 1400 mg/day (body weight <95 kg) or 1600 mg/day (body weight ≥95 kg); (C) peginterferon alfa-2a 360 μg/wk for 12 weeks and then 180 μg/wk for 36 weeks plus ribavirin 1200 mg/day; or (D) peginterferon alfa-2a 360 μg/wk for 12 weeks and then 180 μg/wk for 36 weeks plus ribavirin 1400 mg/day (body weight <95 kg) or 1600 mg/day (body weight ≥95 kg). The computerized randomization list was generated by the sponsor, was maintained in a central repository, and incorporated double-blind labeling of medication boxes. Medication box numbers were communicated to study sites by telephone.

Blinding of the dose of peginterferon alfa-2a during the first 12 weeks of treatment was maintained by the provision of an identical volume of solution in all vials (180 μg/mL for patients in groups A and B and 360 μg/mL in groups C and D) and by achieving dose reductions through changes in volume administered. Thus, a 25% dose reduction from 180 μg/wk to 135 μg/wk in groups A or B, or from 360 μg/wk to 270 μg/wk in groups C or D, was achieved by an identical reduction in the administered volume from 1.0 mL to 0.75 mL. Blinding of the dose of ribavirin was maintained by providing 2 bottles of tablets containing placebo and drug and having each patient take the same number of tablets each day.

In the event of laboratory abnormalities or adverse events, the dose of either study drug could be reduced in a stepwise manner that maintained blinding. Treatment with peginterferon alfa-2a monotherapy could be continued if ribavirin therapy was interrupted; however, ribavirin monotherapy was not allowed. In addition to dose reductions, use of hematopoietic growth factors (granulocyte-colony stimulating factor or erythropoiesis-stimulating agents) was allowed during treatment at the discretion of the investigator.

The study was conducted in accordance with the Declaration of Helsinki, the protocol was approved by institutional review boards at each center, and each patient provided written informed consent.

Assessment of Efficacy

Serum HCV RNA level was measured by real-time polymerase chain reaction assay (Cobas Ampliprep/Cobas TaqMan HCV test; detection limit, 15 IU/mL; Roche Diagnostics North America, Indianapolis, IN).

Rapid virologic response (RVR) and complete early virologic response (cEVR) were defined as undetectable HCV RNA (<15 IU/mL) by weeks 4 and 12 of treatment, respectively. SVR was defined as undetectable HCV RNA (<15 IU/mL) at the end of untreated follow-up (study week 72).

The positive predictive value of an RVR or a cEVR was calculated as the proportion of patients with an RVR or a cEVR who achieved an SVR. Conversely, the negative predictive value of an RVR or a cEVR was calculated as the proportion of patients without an RVR or a cEVR who did not achieve an SVR.

Patients who withdrew prematurely and who were HCV RNA negative at their last assessment were expected to return for HCV RNA testing 12 and 24 weeks after their last dose and at study weeks 48 and 72 for determination of their HCV RNA status.

Assessment of Safety

Safety assessments were performed throughout treatment and follow-up and included physical examinations, laboratory tests, documentation of clinical adverse
events and dose adjustments or withdrawals for safety reasons or intolerance, and completion of the Beck Depression Inventory.

**Statistical Analysis**

The primary efficacy end point was SVR at the end of untreated follow-up (study week 72). Patients with missing serum HCV RNA results at the end of follow-up were considered nonresponders in the intention-to-treat analysis.

A target enrollment of 1140 patients was established under the modeled assumption that an SVR would be obtained in 28%, 32%, 36%, and 43% of patients, respectively, in groups A, B, C, and D. Significance testing was conducted with the Cochran–Mantel–Haenszel test stratified by country and dose of ribavirin (high vs standard). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

The Breslow–Day test was used to assess the homogeneity of ORs across the strata. A test for a potential interaction between the dose of peginterferon alfa-2a and ribavirin was first conducted with a 2-sided significance level of 0.2. If the P value was >.2, then a prospectively planned pooled analysis of the 2 induction vs noninduction groups was to be conducted (A + D vs A + B). If the P value was ≤.2, then the comparison was to be conducted separately for each ribavirin dose level (C vs A and D vs B). A 2-sided significance level of 0.025 was established for pooled and nonpooled hypothesis testing.

On this basis, the study had 86% power to detect a statistically significant difference in the number of patients with an SVR between the induction and noninduction groups.

The intention-to-treat population included all patients who received at least one dose of study medication according to the treatment group. The safety population included all patients who received at least one dose of study medication and had at least one postbaseline safety assessment.

The secondary exploratory analyses were as follows. SVR rates by treatment group were calculated for subgroups of patients according to baseline steatosis (<5% vs ≥5%), NAS (0–2 vs ≥3), homeostasis model of assessment-insulin resistance (HOMA-IR) (<2 vs ≥2), body weight (<95 kg vs ≥95 kg), exposure to peginterferon alfa-2a (>98% vs >80%–98% of planned doses), and exposure to ribavirin (>98% vs >80%–98% of planned doses).

Various multiple logistic regression analyses were performed to explore the effects of dose and baseline factors on the probability of SVR in patients who received >80% of the planned dose of both study drugs.

**Results**

The study was conducted across 156 centers in 14 countries, with the first patient enrolled on November 1, 2006, and the last patient completing follow-up on April 22, 2009. A total of 1175 patients were randomized, and 1145 patients received at least one dose of study medication and comprised the intention-to-treat population (Figure 1).

**Patient Demographics**

Baseline characteristics were well balanced across the study groups (Table 1). The majority of patients in each treatment group were male (76%–81%) and white (81%–87%) with a mean age of 45 to 46 years, a mean body mass index of 32 kg/m², and a mean baseline viral load ≥800,000 IU/mL (82%–86%). Overall, 119 patients (10%) enrolled in the trial had bridging fibrosis or cirrhosis and 306 (27%) had hepatic steatosis.

**Virologic Response**

The rate of SVR at the end of untreated follow-up (week 72), the primary efficacy outcome in the trial, is shown in Figure 2. SVR rates in groups A, B, C, and D were 38%, 43%, 44%, and 41%, respectively.

There were no statistically significant differences in the SVR rates among the 4 treatment groups or between the pooled standard-dose (A + B) and induction-dose (C + D) peginterferon alfa-2a regimens (OR, 1.08; 95% CI, 0.83–1.39; P = .584) or for the pooled standard-dose (A + C) and high-dose (B + D) ribavirin regimens (OR, 1.00; 95% CI, 0.79–1.28; P = .974).

There was no statistical difference in relapse rates among groups A (33%), B (30%), C (29%), and D (32%) or between pooled standard-dose (A + C) and high-dose (B + D) ribavirin regimens (OR, 1.036; 95% CI, 0.742–1.447; P = .836) (Figure 2).

The rates of RVR by week 4 in groups A, B, C, and D were 12%, 12%, 17%, and 16%, respectively, and rates of cEVR by week 12 were 53%, 55%, 58%, and 61%, respectively (Figure 2).

The positive predictive value of an RVR in groups A, B, C, and D was 77% (17/22), 78% (18/23), 89% (62/70), and 77% (51/66), respectively, and the negative predictive value of an RVR was 67% (113/168), 62% (102/165), 66% (196/297), and 66% (204/307), respectively.

The positive predictive value of a cEVR in groups A, B, C, and D was 68% (69/101), 67% (70/104), 69% (153/222), and 61% (143/233), respectively, and the negative predictive value of a cEVR was 97% (87/90), 87% (74/85), 92% (147/160), and 91% (137/150), respectively.

Exploratory analyses showed that intensification of therapy in groups B, C, and D produced numerically higher SVR rates in patients with steatosis affecting ≥5% of hepatocytes, NAS ≥3, and body weight ≥95 kg and in a smaller subset of patients with HOMA-IR ≥2 (Figure 3). The reason for the relatively small number of patients with HOMA-IR scores that this baseline measurement was only collected for some patients following a protocol amendment on February 7, 2007.
Numerically higher SVR rates were also obtained with intensified regimens when the analysis was restricted to patients with at least 80% exposure to either drug, suggesting that this strategy may be successful among those patients able to tolerate higher doses for the duration of treatment (Figure 3).

The results of the multiple logistic regression analysis in 767 patients who received at least 80% of the planned doses of both study drugs, which included steatosis, NAS, and other baseline factors as potential explanatory factors, showed that a histologic diagnosis of cirrhosis, steatosis affecting 5% or more of hepatocytes, and age older than 40 years were significant negative predictors of SVR (Figure 4).

**Safety**

A total of 126 patients (11%) withdrew from treatment for safety reasons (Figure 1) and with similar proportions across the 4 treatment groups (9%–12%). The proportion of patients experiencing serious adverse events was similar across the 4 treatment groups (Table 2). One of 8 deaths during treatment and follow-up (suicide) was considered possibly related to treatment (Table 2).

The incidence of individual adverse events was generally similar across the 4 treatment groups, although the incidence of fatigue, chills, and dizziness was higher in patients in groups B, C, and D compared with group A, and the incidence of myalgia, nausea, and alopecia was higher in patients in groups C and D than groups A and B (Table 2). Recently, pulmonary adverse events with interferon-based therapies have received particular focus. In the present study, the incidence of pneumonia (<1%, 2%, <1%, and 1% in groups A, B, C, and D, respectively) and respiratory, thoracic, and mediastinal disorders (<1%, <1%, 0%, and <1% in groups A, B, C, and D, respectively) were low in all treatment groups.

The incidence of reductions in hemoglobin level to <10 g/dL and <8.5 g/dL was greatest in patients receiving the higher dose of ribavirin (groups B and D), and the incidence of reductions in neutrophil counts to <1.0 × 10⁹/L was greatest in patients receiving the fixed-dose induction regimens of peginterferon alfa-2a (groups C and D). The use of colony-stimulating factors in the 4 treatment arms ranged from 4% to 8%.

The relative mean exposure to peginterferon alfa-2a (range, 83%–85%) and ribavirin (range, 80%–84%) was
Table 1. Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment group</th>
<th>A</th>
<th>Peginterferon alfa-2a 180 µg/wk and ribavirin 1200 mg/day (n = 191)</th>
<th>B</th>
<th>Peginterferon alfa-2a 180 µg/wk and ribavirin 1400/1600 mg/day (n = 189)</th>
<th>C</th>
<th>Peginterferon alfa-2a 360/180 µg/wk and ribavirin 1200 mg/day (n = 382)</th>
<th>D</th>
<th>Peginterferon alfa-2a 360/180 µg/wk and ribavirin 1400/1600 mg/day (n = 383)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>154 (81)</td>
<td>148 (78)</td>
<td>292 (76)</td>
<td>310 (81)</td>
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<td>Age, mean ± SD (y)</td>
<td>46.1 ± 9.9</td>
<td>45.1 ± 9.5</td>
<td>45.7 ± 9.6</td>
<td>46.0 ± 10.2</td>
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<tr>
<td>Body wt Mean ± SD (kg)</td>
<td>100.3 ± 13.2</td>
<td>98.6 ± 13.0</td>
<td>98.7 ± 14.8</td>
<td>98.3 ± 12.5</td>
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<td>&lt;95 kg, n (%)</td>
<td>82 (43)</td>
<td>91 (48)</td>
<td>188 (49)</td>
<td>182 (47)</td>
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<td>≥95 kg, n (%)</td>
<td>109 (57)</td>
<td>97 (51)</td>
<td>191 (50)</td>
<td>200 (52)</td>
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<td>Body mass index Mean ± SD (kg/m²)</td>
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<td>32 ± 5.9</td>
<td>32 ± 5.6</td>
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<td>2&lt;40, n (%)</td>
<td>13 (7)</td>
<td>17 (9)</td>
<td>31 (8)</td>
<td>25 (7)</td>
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<td>35 to&lt;40, n (%)</td>
<td>30 (16)</td>
<td>29 (15)</td>
<td>57 (15)</td>
<td>52 (14)</td>
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<td>30 to&lt;35, n (%)</td>
<td>72 (38)</td>
<td>56 (30)</td>
<td>131 (34)</td>
<td>143 (37)</td>
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<td>25 to&lt;30, n (%)</td>
<td>68 (36)</td>
<td>79 (42)</td>
<td>149 (39)</td>
<td>152 (40)</td>
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<td>&lt;25, n (%)</td>
<td>8 (4)</td>
<td>7 (4)</td>
<td>11 (3)</td>
<td>10 (3)</td>
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<td>3 (&lt;1)</td>
<td>1 (&lt;1)</td>
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<td>Race and ethnicity, n (%)</td>
<td>166 (87)</td>
<td>154 (81)</td>
<td>333 (87)</td>
<td>329 (86)</td>
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<td>White</td>
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<td>29 (15)</td>
<td>38 (10)</td>
<td>43 (11)</td>
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<td>11 (3)</td>
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<td>Latino (Hispanic)</td>
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<td>18 (10)</td>
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<td>64 ± 46.3</td>
<td>62 ± 47.6</td>
<td>62 ± 42.1</td>
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<td>ALT quotient, n (%)</td>
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<td>38 (20)</td>
<td>73 (19)</td>
<td>61 (16)</td>
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<td>1–3</td>
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<td>116 (61)</td>
<td>242 (63)</td>
<td>256 (67)</td>
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<tr>
<td>Steatosis, n (%)a</td>
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<td>132 (70)</td>
<td>290 (76)</td>
<td>274 (72)</td>
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<td>&lt;5%</td>
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<td>50 (13)</td>
<td>65 (17)</td>
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<tr>
<td>5%–33%</td>
<td>14 (7)</td>
<td>17 (9)</td>
<td>38 (10)</td>
<td>37 (10)</td>
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<tr>
<td>33%–66%</td>
<td>5 (3)</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
<td>6 (2)</td>
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<tr>
<td>Mean NAS, n (%)</td>
<td>129 (68)</td>
<td>132 (70)</td>
<td>284 (74)</td>
<td>265 (69)</td>
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<td>0–2</td>
<td>51 (27)</td>
<td>43 (23)</td>
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<td>93 (24)</td>
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<td>3–4</td>
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<td>HOMA-IR score, n (%)b</td>
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<td>9 (5)</td>
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<td>23 (6)</td>
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<td>&lt;2</td>
<td>12 (6)</td>
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<td>32 (8)</td>
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<td>2–4</td>
<td>25 (13)</td>
<td>22 (12)</td>
<td>46 (12)</td>
<td>37 (10)</td>
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<tr>
<td>Missing</td>
<td>146 (76)</td>
<td>148 (78)</td>
<td>291 (76)</td>
<td>291 (76)</td>
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<tr>
<td>Histologic diagnosis of bridging fibrosis/ cirrhosis, n (%)</td>
<td>23 (12)</td>
<td>19 (10)</td>
<td>31 (8)</td>
<td>46 (12)</td>
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<tr>
<td>Mean Ishak HAI score ± SD</td>
<td>8.9 ± 2.6</td>
<td>8.7 ± 2.5</td>
<td>8.5 ± 2.6</td>
<td>8.7 ± 2.6</td>
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<tr>
<td>HCV genotype</td>
<td>85 (45)</td>
<td>93 (49)</td>
<td>184 (48)</td>
<td>184 (48)</td>
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<td></td>
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<tr>
<td>1a</td>
<td>103 (54)</td>
<td>94 (50)</td>
<td>195 (51)</td>
<td>197 (52)</td>
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<td></td>
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<tr>
<td>1b</td>
<td>1 (&lt;1)</td>
<td>2 (1)</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
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<tr>
<td>Mean HCV RNA level x 10⁶ ± SD (IU/mL)</td>
<td>5.66 ± 7.32</td>
<td>6.35 ± 8.49</td>
<td>6.38 ± 8.64</td>
<td>6.82 ± 8.60</td>
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<tr>
<td>HCV RNA level, n (%)</td>
<td>15 (8)</td>
<td>13 (7)</td>
<td>24 (6)</td>
<td>11 (3)</td>
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<td></td>
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<tr>
<td>&lt;400,000 IU/mLc</td>
<td>18 (9)</td>
<td>17 (9)</td>
<td>41 (11)</td>
<td>43 (11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>400,000 to &lt;800,000 IU/mL</td>
<td>157 (82)</td>
<td>159 (84)</td>
<td>317 (83)</td>
<td>326 (86)</td>
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</table>

NOTE. NAS comprises 3 histologic features that are scored semiquantitatively: steatosis (0–3), lobular inflammation (0–3), and hepatocellular ballooning (0–2).

ALT, alanine aminotransferase; ALT quotient, baseline ALT level divided by the upper limit of normal for the local laboratory; HAI, histologic activity index.

aSteatosis in liver biopsy specimens was defined as the percentage of cells with fatty changes per high-powered field.

bHOMA-IR assessed in a subset of patients.

cPatients had HCV RNA <400,000 IU/mL on the first day of treatment but had previously met inclusion criteria at screening.
similar in the 4 treatment groups, and the median administered dose of both peginterferon alfa-2a and ribavirin was close to 100% in each treatment group (Table 2).

Discussion

Large, randomized, international trials have shown that SVR rates of 46% to 52% can be achieved in treatment-naive patients with genotype 1 with the standard 48-week regimen of peginterferon alfa-2a 180 μg/wk plus ribavirin 1000/1200 mg/day.2,3,15

The PROGRESS trial is the first large, randomized, international study to evaluate peginterferon plus ribavirin in a population comprised exclusively of heavier patients with high baseline HCV RNA levels and genotype 1 infection. The SVR rates (38%–44%) were slightly lower when compared with earlier studies in unselected patients with genotype 1 and were not increased by a fixed-dose induction regimen of peginterferon alfa-2a and/or a high-dose weight-based ribavirin regimen. The lack of an effect of the fixed-dose induction regimen of peginterferon alfa-2a or high-dose weight-based ribavirin was not expected based on the results of a prior study that examined higher doses of peginterferon alfa-2a and/or ribavirin in this population. In this pilot study, a 28% SVR rate was achieved with standard doses of peginterferon alfa-2a and ribavirin.16 However, a higher-dose regimen of peginterferon alfa-2a (270 μg/wk) plus ribavirin (1600 mg/day) did produce numerically higher SVR rates (47%), with the higher dose of peginterferon alfa-2a administered for the full treatment duration compared with the present study, which used an induction regimen.16

There have now been 3 large, randomized, multicenter trials, including the present study, in which a 12-week induction dose regimen of 360 μg/wk peginterferon alfa-2a has not significantly increased SVR rates in the overall population beyond that obtained with the standard-dose regimen.15,17 The populations selected for these trials differed and represented a broad spectrum of patients who can be considered difficult to treat. In a trial of treatment-naive patients with genotype 1 with unselected body weights and viral loads, the SVR rates after 48 weeks of treatment were 53% with high-dose induction dosing and 50% with the standard regimen; at the other extreme, in a trial of nonresponders to previous treatment with pegylated interferon alfa-2b plus ribavirin, the final SVR rates were 7% with high-dose induction dosing with a total treatment duration of 48 weeks but...
14% with 72 weeks of treatment with the standard regimen.17

In the single multicenter trial that evaluated induction dosing with peginterferon alfa-2b plus ribavirin, there was also no statistically significant difference in the SVR rate in patients randomized to a double-dose of peginterferon alfa-2b for 12 weeks (32%) or a control group that received the standard regimen (29%).18

Exploratory analyses in this study showed that the standard dose regimen was as effective as the intensified regimens in patients with steatosis scores <5%, NAS <2, and body weight <95 kg. Importantly, SVR rates achieved with the standard of care in these subgroups (47%–49%) were in line with the SVR rates achieved in unselected patients with genotype 1 in other large randomized studies.2,3,15,19 In contrast, the standard-dose regimen was considerably less effective in patients with steatosis scores ≥5%, NAS ≥3, or body weight ≥95 kg and produced SVR rates of 13% to 29%. The same trends are apparent between patients with HOMA-IR scores <2 and those with HOMA-IR scores ≥2, although the number of patients in these groups is considerably smaller. Some, but not all, available evidence suggests that metabolic factors (steatosis, nonalcoholic steatohepatitis, insulin resistance) and obesity adversely affect SVR rates in patients with chronic hepatitis C7,8,20–23; however, there are few data that provide insight into how to overcome these barriers to treatment success. Thus, one of the key

Figure 3. SVR according to (A) baseline steatosis score, (B) baseline NAS, (C) baseline HOMA-IR score, (D) baseline body weight, (E) exposure to peginterferon alfa-2a, and (F) exposure to ribavirin. Treatment exposure was calculated as the percentage of the total target dose administered after physician-initiated dose reductions for laboratory abnormalities and adverse events.
insights of this study is that intensification of therapy with peginterferon alfa-2a and ribavirin may still be beneficial in patients with genotype 1 who have steatosis, elevated NAS, body weight of at least 95 kg, and, possibly, insulin resistance, and these clinical factors may be worthy of consideration in future study designs or treatment algorithms. The multiple logistic regression analysis shows that absence of cirrhosis, younger age, and absence of steatosis were associated with an SVR in compliant patients and indicates that there is a trend toward better response rates with intensified therapy. Future studies, including those investigating direct-acting antiviral agents, should take these findings into consideration.

In the present study, intensification of treatment did not result in a substantial increase in the safety burden. The proportion of patients with serious adverse events was similar across the 4 groups in the trial. However, the incidence of dose reductions for peginterferon alfa-2a and ribavirin was higher in the intensified than the standard-dose regimens, and the incidence of reductions in hemoglobin concentration and neutrophil count was higher in the high-dose regimens. The pattern of laboratory abnormalities reflects the dose-dependent action of the 2 drugs, with more anemia in the high-dose ribavirin groups and more neutropenia in the high-dose peginterferon alfa-2a induction therapy groups. However, the incidence of treatment discontinuations for safety was similar across the 4 groups. Other trials of high-dose peginterferon alfa-2a therapy have reported similar rates of withdrawal for adverse events in patients receiving a 360-μg/wk induction regimen and in those receiving the standard-dose regimen. An exception is the small trial by Fried et al in which a higher withdrawal rate was reported in patients randomized to 48 weeks of treatment with peginterferon alfa-2a 270 μg/wk than 180 μg/wk (19% vs 11%, respectively). The similar rates of treatment discontinuations across treatment groups may be interpreted as suggesting that dose reductions and/or use of growth factors were effective in mitigating any potential additional safety burden associated with the high-dose regimens in this study. Dose modifications of peginterferon alfa-2a for adverse events and laboratory abnormalities and use of colony-stimulating factors were more frequent in patients in group B than in group A. This suggests that some physicians may reduce the dose of peginterferon alfa-2a in response to laboratory abnormalities other than neutropenia, the incidence of which was similar in groups A and B. Despite these reductions, 70% to 74% of patients had more than 80% exposure to peginterferon alfa-2a and 67% to 72% of patients had more than 80% exposure to ribavirin.

It is well established that patients who achieve undetectable HCV RNA by week 12 (cEVR) typically achieve an SVR. In the present study, intensified dosing did not significantly impact the rates of undetectable HCV RNA up to week 12 and did not change the positive predictive value of these responses, although one could speculate that if the 360-μg/wk dose of peginterferon alfa-2a was

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**Figure 4.** Multiple logistic regression analysis of baseline host and viral factors associated with SVR. Only adherent patients (n = 767), defined as those who received ≥80% of the planned doses of both study drugs, were included. ALT, alanine aminotransferase; NAFLD, nonalcoholic fatty liver disease.
Table 2. Adverse Events and Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon</td>
<td>Peginterferon</td>
<td>Peginterferon</td>
<td>Peginterferon</td>
<td>Peginterferon</td>
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<tr>
<td>alfa-2a 180 µg</td>
<td>alfa-2a 180 µg</td>
<td>alfa-2a 360/180 µg</td>
<td>alfa-2a 360/180 µg</td>
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</tr>
<tr>
<td>wk and ribavirin</td>
<td>wk and ribavirin</td>
<td>wk and ribavirin</td>
<td>wk and ribavirin</td>
<td></td>
</tr>
<tr>
<td>1200 mg/day</td>
<td>1400/1600 mg/day</td>
<td>1200 mg/day</td>
<td>1400/1600 mg/day</td>
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</tr>
<tr>
<td>(n = 191)</td>
<td>(n = 189)</td>
<td>(n = 382)</td>
<td>(n = 383)</td>
<td></td>
</tr>
</tbody>
</table>

- Total serious AEs, n 25 28 47 52
- Patients with ≥1 serious AE, n (%) 22 (12) 20 (11) 36 (9) 39 (10)
- Deaths, n (%) 1^a (1%) 2^b (1%) 2^c (1%) 2^d (1%)
- Specific AEs, n (%)a
  - Pyrexia 83 (43) 78 (41) 176 (46) 205 (54)
  - Fatigue 66 (35) 102 (54) 185 (48) 182 (48)
  - Headache 75 (39) 76 (40) 152 (40) 168 (44)
  - Chills 42 (22) 55 (29) 122 (32) 132 (34)
  - Myalgia 46 (24) 44 (23) 111 (29) 118 (31)
  - Insomnia 46 (24) 45 (24) 98 (26) 113 (30)
  - Nausea 41 (21) 42 (22) 112 (29) 104 (27)
  - Arthralgia 50 (26) 49 (26) 88 (23) 89 (23)
  - Asthenia 28 (15) 35 (19) 84 (22) 81 (21)
  - Decreased appetite 30 (16) 31 (16) 73 (19) 85 (22)
  - Rash 38 (20) 40 (21) 65 (17) 78 (20)
  - Pruritus 34 (18) 27 (14) 76 (20) 59 (15)
  - Irritability 34 (18) 29 (15) 64 (17) 66 (17)
  - Cough 27 (14) 35 (19) 59 (15) 69 (18)
  - Alopecia 23 (12) 20 (11) 71 (19) 71 (19)
  - Decreased weight 31 (16) 31 (16) 54 (14) 67 (17)
  - Diarrhea 25 (13) 27 (14) 62 (16) 62 (16)
  - Dizziness 14 (7) 27 (14) 44 (12) 59 (15)
  - Anemia 23 (12) 24 (13) 39 (10) 57 (15)
- Depression, n (%) Patients with depression 32 (17) 36 (19) 72 (19) 58 (15)
- Treatment for depression 24 (13) 29 (15) 52 (14) 49 (13)
- Dose modified for depression 2 (1) 2 (1) 6 (2) 4 (1)
- Premature withdrawal for depression-related events 3 (2) 4 (2) 6 (2) 5 (1)

Specific laboratory abnormalities, n (%)
- Hemoglobin 8.5–10.0 g/dL 25 (13) 35 (19) 51 (13) 79 (21)
- Hemoglobin <8.5 g/dL 6 (3) 12 (6) 9 (2) 22 (6)
- Neutrophils 0.5–1.0 x 10^9/L 61 (32) 64 (34) 159 (41) 171 (45)
- Neutrophils <0.5 x 10^9/L 9 (5) 10 (5) 25 (7) 26 (7)
- Platelets 20,000 to <50,000 x 10^9/L 7 (4) 9 (5) 18 (5) 20 (5)
- Platelets <20,000 x 10^9/L 3 (2) 0 0 3 (1)

Dosage reductions for adverse events, n (%) 
- Peginterferon alfa-2a (4) (10) (7) (7)
- Ribavirin (11) (13) (12) (13)

Dosage reductions for laboratory abnormalities, n (%) 
- Peginterferon alfa-2a (10) (21) (19) (22)
- Ribavirin (16) (21) (13) (22)

Premature withdrawal from treatment, n (%) 
- Peginterferon alfa-2a 52 (27) 53 (28) 107 (28) 112 (29)
- Ribavirin 54 (28) 53 (28) 109 (29) 117 (31)

Premature withdrawal for laboratory abnormalities, n (%) 
- Peginterferon alfa-2a 2 (1) 0 2 (<1) 6 (2)
- Ribavirin 3 (2) 0 2 (<1) 8 (2)

Premature withdrawal for adverse events, n (%) 
- Peginterferon alfa-2a 17 (9) 15 (8) 35 (9) 35 (9)
- Ribavirin 18 (9) 15 (8) 37 (10) 37 (10)

Interventions to manage hematologic abnormalities, n (%) 
- Use of hematopoietic stimulants 17 (9) 22 (12) 36 (9) 51 (13)
continued beyond 12 weeks, the positive predictive value might have been impacted. Interestingly, if groups A and B are combined and groups C and D are combined, the difference in RVR becomes significant and the difference in cEVR almost reaches significance (data not shown). Recent data suggest that the ability to clear HCV RNA early during treatment and achieve an SVR is dependent on host genetic polymorphisms located close to the IL-28B gene. The haplotype of the IL-28B gene was not assessed in this study but, assuming similar distribution of the favorable haplotype across the 4 treatment groups in the present study, it is apparent that induction dosing with peginterferon alfa-2a and/or higher doses of ribavirin does not affect the phenotype response. Genetic variants that lead to a deficiency of inosine triphosphatase have been shown to exert a protective effect against ribavirin-induced anemia in patients with chronic hepatitis C. These variants are likely to have a significant impact on the incidence of anemia and ribavirin dose reductions and may indirectly influence the probability of SVR but unfortunately were not included in the protocol for this study. For the reasons outlined previously, genotypic analyses should be included in future clinical studies.

These data do not mean that higher doses of peginterferon and/or ribavirin should be completely abandoned as a potential treatment of chronic HCV. Although speculative, consideration should be given to exploring dose escalation strategies among patients who do not achieve an early clearance of HCV RNA. In these patients, increased doses of peginterferon and/or ribavirin may be beneficial, possibly when combined with longer treatment duration to reduce rates of relapse, as was shown for non-RVR patients with genotype 1 or 4 HCV who achieved an EVR (defined as undetectable serum HCV RNA [600 IU/mL] by quantitative polymerase chain reaction or a 2-log10 decrease or greater from baseline in serum HCV RNA level by quantitative polymerase chain reaction) and were treated for 72 weeks compared with 48 weeks with peginterferon alfa-2a plus ribavirin.

Furthermore, future analyses may also allow pretreatment assessment for IL-28B to identify a subgroup of patients with a low chance for SVR and who could potentially benefit from the higher-dose induction strategy and/or a longer treatment duration.

In conclusion, in a large study exclusively designed to assess response rates in those with HCV genotype 1, high viral load, and higher body weight, intensification of

Table 2. Continued

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>A Peginterferon alfa-2a 180 μg/wk and ribavirin 1200 mg/day (n = 191)</th>
<th>B Peginterferon alfa-2a 180 μg/wk and ribavirin 1400/1600 mg/day (n = 189)</th>
<th>C Peginterferon alfa-2a 360/180 μg/wk and ribavirin 1200 mg/day (n = 382)</th>
<th>D Peginterferon alfa-2a 360/180 μg/wk and ribavirin 1400/1600 mg/day (n = 383)</th>
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</thead>
<tbody>
<tr>
<td>Use of colony-stimulating factors*</td>
<td>8 (4)</td>
<td>15 (8)</td>
<td>29 (8)</td>
<td>30 (8)</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>4 (2)</td>
<td>3 (2)</td>
<td>8 (2)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Platelet transfusion</td>
<td>2 (1)</td>
<td>0</td>
<td>0</td>
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<td>Exposure to treatment (expressed as a percentage of the planned dose)</td>
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<tr>
<td>Peginterferon alfa-2a Mean ± SD</td>
<td>84.8 ± 25.7</td>
<td>85.2 ± 23.2</td>
<td>84.8 ± 24.0</td>
<td>83.3 ± 26.0</td>
</tr>
<tr>
<td>Median</td>
<td>100</td>
<td>100</td>
<td>99.6</td>
<td>98.8</td>
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<tr>
<td>Patients receiving ≥80% of the planned dose, n (%)</td>
<td>142 (74)</td>
<td>139 (74)</td>
<td>276 (72)</td>
<td>270 (70)</td>
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<tr>
<td>Ribavirin Mean ± SD</td>
<td>84.0 ± 22.9</td>
<td>81.8 ± 28.0</td>
<td>79.7 ± 29.4</td>
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<tr>
<td>Median</td>
<td>98.2</td>
<td>99.4</td>
<td>97.8</td>
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<tr>
<td>Patients receiving ≥80% of the planned dose, n (%)</td>
<td>131 (69)</td>
<td>268 (70)</td>
<td>255 (67)</td>
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therapy with a 12-week induction regimen of peginterferon alfa-2a and/or a weight-based ribavirin regimen was safe and well tolerated but did not significantly increase SVR rates compared with standard dosing. Retrospective subgroup analyses suggest that dose intensification was numerically beneficial compared with the standard regimen in patients with steatosis, elevated NAS, body weight ≥95 kg, and, possibly, insulin resistance. An exploratory multiple logistic regression analysis supported the finding that steatosis was a negative predictor of SVR, but neither elevated NAS nor body weight was significantly associated with SVR in this analysis. These findings should be evaluated further in well-designed clinical studies, including those involving direct-acting antiviral agents.

References


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Conflicts of interest

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