# CLINICAL ADVANCES IN LIVER, PANCREAS, AND BILIARY TRACT

## Randomized Study of Peginterferon-α2a Plus Ribavirin vs Peginterferon-α2b Plus Ribavirin in Chronic Hepatitis C

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**BACKGROUND & AIMS:** Ribavirin (RBV) combined with either pegylated interferon (PegIFN) α2a or PegIFNα2b is the standard of care for chronic hepatitis C virus (HCV) infection. Due to the lack of head-to-head studies, the 2 PegIFNs have not been directly compared. The endpoints of our study were safety and antiviral efficacy of the 2 regimens. **METHODS:** Treatment-naïve patients with chronic hepatitis C were randomly (1:1) assigned after stratification for HCV genotype to receive either 1.5 mcg/Kg/week PegIFNα2b plus RBV 800–1200 mg/day or 180 mcg/week PegIFNα2a plus RBV 800–1200 mg/day for 24 or 48 weeks according to HCV genotype. The study was powered to detect a difference of at least 10% in safety and efficacy of the 2 regimens. **RESULTS:** The 212 patients on PegIFNα2a and the 219 patients on PegIFNα2b had similar baseline characteristics, including cirrhosis (20% vs 18%, respectively). By intention to treat, the 2 groups showed similar rates of treatment-related serious adverse events (1% vs 1%, respectively) and drop out rates for adverse effects (7% vs 6%, respectively). Overall, sustained virologic response (SVR) rate was higher in PegIFNα2a than in PegIFNα2b patients (66% vs 54%, respectively, $P = .02$), being 48% vs 32% in the 222 HCV-1 and -4 patients ($P = .04$), and 96% vs 82%, respectively, in the 143 HCV-2 patients ($P = .01$). PegIFNα2a independently predicted SVR in the logistic regression analysis (odds ratio, 1.88; 95% confidence interval: 1.20–2.96). **CONCLUSIONS: Although the 2 regimens showed a similar safety profile, the PegIFNα2a-based treatment yielded significantly more SVR than PegIFNα2b.**

Pegylated interferon (PegIFN) α associated to ribavirin (RBV) is the standard of care for patients with chronic hepatitis C who meet criteria for treatment, virus eradication being the paradigm of therapy.[1,2] Currently, 2 PegIFNα are available that, however, differ in size and structure of the interferon and polyethylene-glycol molecules as well as in the pharmacokinetic and pharmacodynamic profiles and in vitro activity.[3–6] Because of different volumes of distribution and elimination half-life, the 2 PegIFNs have different approved dosing regimens, which is fixed for PegIFNα2a (180 μg per week) and based on body weight for PegIFNα2b (1.5 μg/kg per week). Whereas the registration trials of the 2 therapeutic regimens demonstrated the superiority of each PegIFN vs the common benchmark of standard IFNα2b, they could not provide any evidence for the superiority of one over the other regimen in terms of antiviral activity.[7,8] With all the caveats of an indirect comparison, in fact, those trials showed similar antiviral activity of both PegIFN-based treatments, whereas, compared with the PegIFNα2a, PegIFNα2b was associated with lower rates of anemia (9% vs 23%, respectively) and higher rates of depression (31% vs 22%, respectively), suggesting that differences might exist in safety and tolerability between treatments. However, the dilemma whether the 2 PegIFN-based regimens have different clinical activity can only be solved by a prospective head-to-head comparative study investigating the sustained virologic response (SVR). The only head-to-head studies available are limited in terms of either sample size or scope, ie, restricting response analysis to HCV-RNA status at week 12 of therapy, and provided discrepant results.[9–12] In 2003, we started an investigator initiated randomized head-to-head study aimed at comparing safety and antiviral efficacy of the 2 PegIFN/RBV regimens in previously untreated patients with chronic hepatitis C.

*Abbreviations used in this paper:* cEVR, complete early virologic response; ETR, end of treatment response; PegIFN, pegylated interferon; RBV, ribavirin; RVR, rapid virologic response; SVR, sustained virologic response.

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## Patients and Methods

### *Patients*

The study was conducted between September 2003 and June 2007 at the Liver Center Maggiore Hospital, University of Milan, Italy. Included were previously untreated patients 18 to 70 years of age, with serum HCV-RNA, higher than normal alanine aminotransferease (ALT) activity, and a diagnostic liver biopsy done in the previous 24 months. Excluded were patients with persistently normal ALT; hemoglobin ≤12 g/dL for women and ≤13 g/dL for men; white blood cell count $\leq 2.5 \times 10^3/mm^3$; neutrophil count $\leq 1.5 \times 10^3/mm^3$; platelet count $\leq 75 \times 10^3/mm^3$; serum creatinine level >1.5 times the upper limit of normal; any other liver disease; human immunodeficiency virus coinfection; autoimmune diseases; and general contraindications to the IFN and RBV.[1]

### *Study Design*

This is an independent, investigator-driven, single-center, open-label randomized trial devoid of any industrial support, designed to assess the safety and efficacy of RBV associated to either PegIFNα2a or PegIFNα2b as initial treatment of chronic hepatitis C. The study was approved by the Institutional Review Board of the Department of Internal Medicine. All patients gave their written informed consent to receive therapy and permission for use of their medical records. Patients were randomized using a computer-generated allocation list stratified by HCV genotype to receive RBV (Rebetol; Schering Plough Corp, Kenilworth, NJ) combined with either of the following: PegIFNα2a (Pegasys; Roche, Basel, Switzerland) 180 μg/week or PegIFNα2b 1.5 μg/kg/week (PegIntron; Schering Plough Corp). Patients with HCV-1 and HCV-4 were treated for 48 weeks: PegIFNα2a was associated with RBV 1000–1200 mg day (<75 kg; ≥75 kg); PegIFNα2b with RBV 800 mg for patients of less than 65-kg body weight, 1000 mg for 65–85 kg, and 1200 mg for ≥85 kg. HCV-2 and HCV-3 patients were treated for 24 weeks: PegIFNα2a was associated with RBV 800 mg day; PegIFNα2b with RBV 800 mg for patients of less than 65-kg body weight, 1000 mg for 65–85 kg, and 1200 mg for ≥85 kg.

### *Measurements*

Serum HCV-RNA was quantified by Versant HCV-RNA 3.0 assay (bDNA 3.0; Bayer Corporation, Emeryville, CA), with a sensitivity limit of 615 IU/mL and a dynamic range from 615 to 7,700,000 IU/mL. Serum HCV-RNA was assessed by qualitative reverse-transcription polymerase chain reaction (RT-PCR) assay (COBAS Amplicor HCV test version 2.0, Roche Diagnostics) with a detection limit of 50 IU/mL, during treatment at weeks 4, 12, 24, and 48 and after therapy at weeks 4, 12, 24. HCV was genotyped by Line Probe Assay (INNO-LIPA HCV 2, Innogenetics, Zwijndrecht, Belgium). Liver biopsies were performed with a 16-gauge Tru-Cut needle (Uro-Cut 16G; TSK, Tokyo, Japan) and read by a single pathologist (M.F.D.), who was unaware of the patient's identity and treatment regimen. The severity of hepatic inflammation was evaluated by the Ishak score in separate reports for grading and staging.[13] Disease duration was calculated by considering as the onset of infection the date of blood transfusion received prior to 1992 or the period of drug injection. In patients with unknown source of infection, the date of the first abnormal ALT test was arbitrarily taken as the start of infection.

### *End Points of the Study*

Safety assessment included red blood cells, white blood cells, and platelet count in response to therapy. PegIFNα2a was reduced to 135 μg and PegIFNα2b to 1.0 μg/kg per week in patients with $<0.75 \times 10^9$/L neutrophils at 2 consecutive tests, whereas it was withdrawn in patients with $<0.50 \times 10^9$/L. The same dose reductions were applied if platelets fell under 50,000 cells/mm³ with PegIFN being discontinued when reaching the 25,000 cells/mm³ threshold. In both treatment arms, RBV dose was tapered by 200 mg/day in patients with hemoglobin <10 g/dL, whereas it was discontinued in patients with <8.5 g/dL hemoglobin. Growth factors were allowed for the management of grade 2 anemia (erythropoietin alfa; 40,000 IU/week) and grade 3 neutropenia (granulocyte colony stimulating factor [GCSF], 30 MU/week) only in patients with advanced fibrosis starting from January 2006, as recommended by the Italian National Health System. Safety assessment included also treatment-related serious adverse events and psychologic depression evaluated by a psychiatrist who was blinded to the study treatment according to internationally accepted criteria.[14]

Assessment of efficacy was SVR, ie, undetectable HCV-RNA at week 24 of posttreatment. Clearance of serum HCV-RNA by RT-PCR was assessed at week 4 (rapid virologic response [RVR]), at week 12 (complete early virologic response [cEVR]), at week 24, and at week 48 of treatment (end of treatment response [ETR]). Patients with an ETR who tested HCV-RNA positive during follow-up were classified as relapsers. Patients who had a virologic breakthrough were considered as nonesponders. Therapy was discontinued in HCV-1 and HCV-4 patients if quantitative HCV-RNA testing at week 12 dropped by less than 2 log compared with baseline values and at week 24 if HCV-RNA was still detectable in those patients in whom HCV-RNA dropped >2 log at week 12.

### *Statistical Analysis*

A total of 210 subjects for each group was planned to achieve more than 80% power to detect a difference in the efficacy end point of 10%. The significance level of the 2-sided test was targeted at $P = .05$.

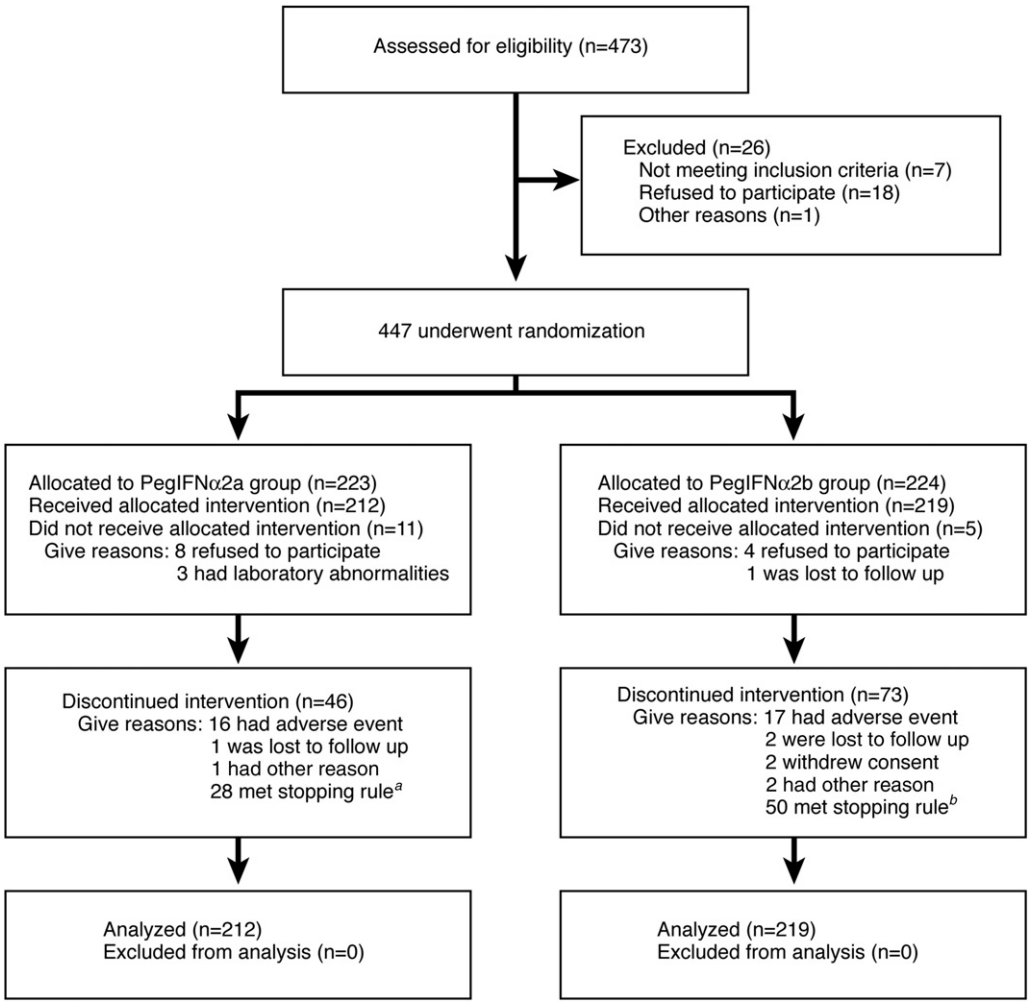


**Figure 1.** Flow chart of the MIST study. [a]Nineteen patients met the week 12 stopping rule, 7 patients met the week 24 stopping rule, and 2 patients had a virologic breakthrough. Twenty of 28 patients were HCV-1, and 8 were HCV-4. [b]Thirty-two patients met the week 12 stopping rule; 15 patients met the week 4 stopping rule; and 3 patients had a virologic breakthrough. Thirty-five of 50 patients were HCV-1, and 15 were HCV-4.

By intention-to-treat analysis, patients for whom HCV-RNA levels had not been measured by the end of the follow-up period as well as those who discontinued treatment for any reason were categorized as nonresponders. The distribution of individual characteristics was evaluated by simple descriptive statistics. Differences between distributions of covariates between randomization groups were evaluated by use of the Fisher exact test for categorical variables. The Wilcoxon rank-sum test or the median test was used in the statistical evaluation of the significant differences in the distributions of continuous variables across the treatments. When relevant, exact 95% confidence intervals (CIs) for the proportions were calculated.

Odds ratios (OR) and corresponding 95% CI were computed using multiple logistic regression models. All the regression equations included terms for age, sex, body mass index, viral load, duration of infection, cirrhosis, and alanine aminotransferase level at baseline. A stepwise regression discriminant analysis was performed to identify variables discriminated between subjects, using the overall sustained virologic response as dependent variable. Starting from a full model with all variables included, nonsignificant ones were progressively deleted with a step-down procedure based on a likelihood ratio test. The discriminatory accuracy of the model including all independent predictors of SVR was measured by the area under the receiver-operating characteristic curve.

## Results

### *Patient Characteristics*

A total of 447 patients were randomized, and 431 received at least 1 dose of the study medications (Figure 1). The 2 treatment groups showed similar demographic, clinical, and virologic features (Table 1). The distribution of selected variables across treatment and genotypes is presented in Table 2.

### *Safety and Tolerability*

The safety and tolerability profile of the 2 IFN regimens is shown in Table 3. A few serious adverse events occurred in the 2 groups (1% vs 1%, respectively). Eighteen PegIFNα2a patients and 23 PegIFNα2b patients discontinued treatment (8% vs 11%, respectively, $P = .6$; OR, 0.85; 95% CI: 0.34–1.65). The rates of grade 2 anemia (hemoglobin $<10$, $>8.5$ g/dL; 16% vs 23%,

**Table 1.** Baseline Characteristics of the 431 Patients With Chronic Hepatitis C Enrolled In the MIST Study

| | PegIFNα2a (n = 212) | PegIFNα2b (n = 219) | *P* value |
|---|---|---|---|
| Sex, n (%) | | | |
| Male | 128 (60.4) | 120 (54.8) | |
| Female | 84 (39.6) | 99 (45.2) | .2[a] |
| Age, *y* (mean ± SD) | 51.6 ± 12.0 | 52.8 ± 12.0 | .2[b] |
| Weight, *kg* (mean ± SD) | 72.2 ± 14.6 | 68.9 ± 12.0 | .08[b] |
| BMI, $kg/m^2$ (mean ± SD) | 25.5 ± 4.4 | 24.8 ± 3.7 | .4[b] |
| Mode of infection, n (%) | | | |
| Intravenous drug abuse | 27 (12.7) | 26 (11.9) | |
| Transfusion | 48 (22.6) | 40 (18.3) | |
| Sporadic | 136 (64.2) | 151 (68.9) | |
| Others | 1 (0.5) | 2 (0.9) | .6[a] |
| Duration of infection, *y* (mean ± SD) | 18.0 ± 13.6 | 16.1 ± 12.7 | .2[b] |
| Alanine aminotransferase, *IU/L* (mean ± SD) | 129.8 ± 104.6 | 129.0 ± 104.2 | .8[b] |
| ≥2-Fold increase at baseline, n (%) | 126 (59.4) | 130 (59.4) | 1.0[a] |
| HCV-RNA, $\times 10^6$ IU/L± | 2.6±5.8 | 2.2±4.7 | .7[b] |
| $<0.6 \times 10^6$ | 100 (47.2%) | 98 (44.7%) | .6[a] |
| $\geq 0.6 \times 10^6$ | 112 (52.8%) | 121 (55.3%) | |
| $\geq 0.8 \times 10^6$ | 102 (48.1%) | 103 (47.0%) | .8[a] |
| HCV genotype, n (%) | | | |
| 1 | 91 (42.9) | 87 (39.7) | |
| 2 | 69 (32.5) | 74 (33.8) | |
| 3 | 34 (16.0) | 32 (14.6) | |
| 4 | 18 (8.5) | 26 (11.9) | .6[a] |
| Ishak score S5, 6; n (%) | 43 (20.3) | 39 (17.8) | .5[a] |
| Hematologic values (mean ± SD) | | | |
| Hemoglobin, *g/dL* | 14.7 ± 1.3 | 14.6 ± 1.3 | .2[b] |
| WBC, $10^3$ cells | 6.3 ± 1.8 | 6.1 ± 1.9 | .2[b] |
| Platelets, $10^3$ cells | 194.1 ± 56.9 | 200.7 ± 75.8 | .5[b] |

[a]Fisher's exact test.
[b]Wilcoxon rank sum test.

respectively, $P = .1$) and grade 3 anemia (hemoglobin <8.5 g/dL; 1% vs 1%, respectively, $P = .6$) were similar in the 2 groups, and RBV dose reduction rates were 56% (119/212) in PegIFNα2a and 56% in PegIFNα2b patients ($P = 1.0$). Although grade 3 neutropenia occurred at similar rates in the 2 patients group (22% vs 16%, respectively, $P = .1$) however, PegIFNα2a dosing had to be reduced more often than PegIFNα2b to manage this adverse effect (9% vs 4%, respectively, $P = .04$). Treatment was discontinued because of neutropenia in 5 PegIFNα2a (2%) and in 3 PegIFNα2b patients (1%) ($P = .5$). Thrombocytopenia ($<75 \times 10^9$ cells/L) rarely occured (2% in PegIFNα2a and 1% in PegIFNα2b, $P = .5$), never reaching the threshold for treatment reduction or discontinuation. GCSF was equally administered in the 2 groups (10% vs 7%, respectively, $P = .3$) as was the use of erythropoietin (14% vs 12%, respectively, $P = .7$). Depression was diagnosed in similar proportion in the 2 treatment arms (9% vs 7%, respectively, $P = .6$). By univariate analysis, no demographic, clinical, or treatment-related predictors of safety were identified.

### *Virologic Response*

Overall, patients treated with PegIFNα2a showed higher rates of SVR than PegIFNα2b-treated patients (66% vs 54%, respectively, $P = .02$; OR, 1.71; 95% CI: 1.14–2.57) (Figure 2), in the presence of similar rates of posttreatment relapse (16% vs 18%, respectively, $P = .6$). In the multivariate logistic regression analysis including terms for age, sex, BMI as tertiles, viral load (cut-off, $6 \times 10^5$ IU/mL) genotypes (HCV-1 as reference), and cirrhosis (model fully adjusted), PegIFNα2a showed a significant 2-fold increase risk of SVR (OR, 1.95; 95% CI: 1.22–3.13). The rates of SVR were 62% with PegIFNα2a and 48% with PegIFNα2b ($P = .05$; fully adjusted OR, 1.87; 95% CI: 0.93–3.75) in patients with $>6 \times 10^5$ IU/mL HCV-RNA and 53% and 38%, respectively, in patients with cirrhosis ($P = .2$; fully adjusted OR, 1.82; 95% CI 0.69–4.79). The SVR rates achieved by PegIFNα2a were higher than those obtained with PegIFNα2b in HCV-1 (SVR: 48%, 95% CI: 38%–59% vs 32%, 95% CI: 23%–43%, respectively, $P = .04$) and HCV-2 patients (SVR: 96%, 95% CI: 88%–99% vs 82%, 95% CI: 73%–91%, respectively, $P = .01$). Conversely, the 2 regimens showed similar rates of SVR in patients with HCV-3 (SVR: 65%, 95% CI: 46%–80% vs 69%, 95% CI: 50%–84%, respectively, $P = .9$) and HCV-4 (SVR: 44%, 95% CI: 21%–69% vs 31%, 95% CI: 14%–51%, $P = .5$). In HCV-1 cirrhotic patients, the SVR rates were 50% with PegIFNα2a and 22% with PegIFNα2b ($P = .1$). Among patients with a RVR, a SVR was achieved in 83% of PegIFNα2a patients and 78% of PegIFNα2b patients. The corresponding figures for patients with a cEVR were 80% and 78%, respectively.

The median RBV intake per kilogram of body weight was similar in the overall population and in the HCV-1 and HCV-4 patients, independently of PegIFN type. The HCV-2 and HCV-3 patients treated with PegIFNα2a received less RBV than corresponding PegIFNα2b patients (Table 4). When analyzing RBV intake in terms of cumulative exposure to the drug, 83% (138/166) of patients in the PegIFNα2a arm and 82% (120/146) in the PegIFNα2b arm received >80% of the planned RBV dose ($P = .9$) The corresponding figures for the first 12 weeks of treatment were 94% (197/209) for the PegIFNα2a arm and 91% (198/217) for the PegIFNα2b arm ($P = .3$).

### *Independent Predictors of SVR*

Stepwise logistic regression analysis selected: age <40 years (OR, 3.20; 95% CI: 1.73–5.94), pretreatment HCV-RNA <600,000 IU/mL (OR, 1.49; 95% CI: 1.01–2.33), HCV genotypes 2 and 3 (OR, 7.9; 95% CI: 4.97–12.77), and PegIFNα2a (OR, 1.88; 95% CI: 1.20–2.96) as significant and independent pretreatment predictors of SVR (Table 5). The fully adjusted logistic regression model including only selected variables presents a high discriminatory accuracy (area under the receiver-operating characteristic curve = 0.79). In the analysis of both pretreatment and on-treatment variables, RVR was the strongest predictor of a SVR (OR, 5.1; 95% CI: 2.79–9.24).

**Table 2.** Baseline Characteristics of the 431 Patients With Chronic Hepatitis C Enrolled in the MIST Study, Stratified for HCV Genotype

| HCV-1 patients | PegIFN$\alpha$2a (n = 91) | PegIFN$\alpha$2b (n = 87) | *P* value |
|---|---|---|---|
| Sex, male, n (%) | 50 (55) | 43 (49) | .5[a] |
| Age, *y* (mean ± SD) | 54.8 ± 10.8 | 53.9 ± 12.6 | .9[b] |
| Weight, *kg* (mean ± SD) | 71.5 ± 13.2 | 68.2 ± 12.2 | .1[b] |
| BMI, $kg/m^2$ (mean ± SD) | 25.3 ± 4.0 | 24.8 ± 3.8 | .5[b] |
| Alanine aminotransferase, *IU/L* (mean ± SD) | 120 ± 68.6 | 115.9 ± 76 | .4[b] |
| ≥2-Fold increase at baseline, n (%) | 58 (64) | 49 (56) | .3[a] |
| HCV-RNA, n (%) | | | |
| $<0.6 \times 10^6$ IU/L | 35 (38) | 29 (33) | .5[a] |
| $\geq 0.6 \times 10^6$ IU/L | 56 (62) | 58 (67) | |
| $\geq 0.8 \times 10^6$ IU/L | 52 (57) | 46 (53) | .6[a] |
| Ishak score S5, 6; n (%) | 22 (24) | 18 (21) | .6[a] |
| **HCV-2 patients** | **PegIFN$\alpha$2a (n = 69)** | **PegIFN$\alpha$2b (n = 74)** | ***P* value** |
| Sex, male, n (%) | 40 (58) | 34 (46) | .2[a] |
| Age, *y* (mean ± SD) | 53.8 ± 13.5 | 58.7 ± 9.4 | .06[b] |
| Weight, *kg* (mean ± SD) | 70.9 ± 14.1 | 67.9 ± 11.2 | .3[b] |
| BMI, $kg/m^2$ (mean ± SD) | 25.3 ± 4.7 | 25.1 ± 3.9 | .7[b] |
| Alanine aminotransferase, *IU/L* (mean ± SD) | 154.1 ± 150.9 | 155.8 ± 141.5 | .8[b] |
| ≥2-Fold increase at baseline, n (%) | 38 (55) | 49 (66) | .2[a] |
| HCV RNA, n (%) | | | |
| $<0.6 \times 10^6$ IU/L | 37 (54) | 42 (57) | .7[a] |
| $\geq 0.6 \times 10^6$ IU/L | 32 (46) | 32 (43) | |
| $\geq 0.8 \times 10^6$ IU/L | 29 (42) | 29 (39) | .7[a] |
| Ishak score S5, 6; n (%) | 11 (16) | 10 (14) | .8[a] |
| **HCV-3 patients** | **PegIFN$\alpha$2a (n = 34)** | **PegIFN$\alpha$2b (n = 32)** | ***P* value** |
| Sex, male, n (%) | 23 (68) | 20 (63) | .8[a] |
| Age, *y* (mean ± SD) | 43.3 ± 7.5 | 44.2 ± 7.7 | .7[b] |
| Weight, *kg* (mean ± SD) | 73.8 ± 19 | 68 ± 13 | .4[b] |
| BMI, $kg/m^2$ (mean ± SD) | 25.5 ± 5 | 23.7 ± 3.2 | .1[b] |
| Alanine aminotransferase, *IU/L* (mean ± SD) | 126 ± 80.8 | 127.7 ± 81.1 | .8[b] |
| ≥2-Fold increase at baseline, n (%) | 22 (65) | 19 (59) | .8[a] |
| HCV-RNA, n (%) | | | |
| $<0.6 \times 10^6$ IU/L | 15 (44) | 13 (41) | 1.0[a] |
| $\geq 0.6 \times 10^6$ IU/L | 19 (56) | 19 (59) | |
| $\geq 0.8 \times 10^6$ IU/L | 17 (50) | 18 (56) | .8[a] |
| Ishak score S5, 6; n (%) | 5 (15) | 4 (13) | 1.0[a] |
| **HCV-4 patients** | **PegIFN$\alpha$2a (n = 18)** | **PegIFN$\alpha$2b (n = 26)** | ***P* value** |
| Sex, male, n (%) | 15 (83) | 23 (88) | .7[a] |
| Age, *y* (mean ± SD) | 43 ± 6.7 | 43 ± 8.9 | 1.0[b] |
| Weight, *kg* (mean ± SD) | 76.8 ± 13.4 | 75.5 ± 10.6 | .9[b] |
| BMI, $kg/m^2$ (mean ± SD) | 26.4 ± 3.6 | 25.6 ± 3.2 | .4[b] |
| Alanine aminotransferase, *IU/L* (mean ± SD) | 92.6 ± 52.3 | 98.1 ± 67 | .9[b] |
| ≥2-Fold increase at baseline, n (%) | 8 (44) | 13 (50) | .8[a] |
| HCV-RNA | | | |
| $<0.6 \times 10^6$ IU/L | 13 (72) | 14 (54) | .1[a] |
| $\geq 0.6 \times 10^6$ IU/L | 5 (28) | 12 (46) | |
| $\geq 0.8 \times 10^6$ IU/L | 4 (22) | 10 (38) | .2[a] |
| Ishak score S5, 6, n (%) | 5 (28) | 7 (27) | 1.0[a] |

[a]Fisher's exact test.
[b]Wilcoxon rank sum test.

## Discussion

Head-to-head trials comparing the 2 pegylated IFNs in combination with RBV in the treatment of patients with chronic hepatitis C are needed because there is insufficient evidence to support conclusions that one therapeutic regimen is superior to the other one.[1,2] Our study indicates the 2 therapeutic regimens to have a comparable profile of safety, whereas they substantially differ in terms of antiviral activity in the overall population of HCV-infected patients. The safety findings of our study are in line with the results of an adjusted, indirect meta-analysis of 16 randomized controlled studies reporting similar rates of withdrawal because of adverse events in patients receiving combination therapy with either PegIFN.[15] Our data also compare well with a large multicenter randomized study in the United States

**Table 3.** Rates of Safety and Tolerability in Patients With Chronic Hepatitis C Treated With RBV Combined With PegIFN-α2a or PegIFN-α2b

| Outcome | PegIFNα2a (n = 212), n (%) | PegIFNα2b (n = 219), n (%) | *P* value[a] |
|---|---|---|---|
| Endpoints of the study | | | |
| Serious adverse events | 2 (1) | 1 (1) | .2 |
| Treatment modification | | | |
| Discontinuation for safety reasons | 16 (7)[b] | 17 (8)[c] | .8 |
| Discontinuation for nonsafety reasons | 2 (1) | 6 (3) | .2 |
| PegIFN dose reduction | 22 (10) | 14 (6) | .2 |
| RBV dose reduction | 119 (56) | 123 (56) | 1.0 |
| Hematologic effect | | | |
| Grade 2 anemia | 35 (16) | 50 (23) | .1 |
| Grade 3 anemia | 2 (1) | 2 (1) | .6 |
| Grade 3 neutropenia | 46 (22) | 34 (16) | .1 |
| Grades 2 or 3 thrombocytopenia | 5 (2) | 3 (1) | .5 |
| Treated with GCSF | 21 (10) | 15 (7) | .3 |
| Treated with erythropoietin | 30 (14) | 27 (12) | .6 |
| Depression | 19 (9) | 15 (7) | .4 |
| Other adverse effects | | | |
| Influenza-like syndrome | 134 (63) | 136 (62) | .8 |
| Gastrointestinal symptoms | 8 (4) | 12 (5) | .5 |
| Psychiatric symptoms | 79 (37) | 70 (32) | .3 |
| Coughing and dyspnea | 22 (10) | 25 (11) | .8 |
| Dermatologic symptoms | 99 (47) | 91 (42) | .3 |

[a]Fisher's exact test.
[b]Reasons for treatment discontinuation: serious adverse events, n = 2; anemia and neutropenia, n = 7; depression, n = 2; and nonprotocol reasons, n = 5.
[c]Reasons for treatment discontinuation: serious adverse events, n = 1; anemia and neutropenia, n = 5; depression, n = 2; and nonprotocol reasons, n = 9.

originally designed to compare 2 dosing regimens of PegIFNα2b (1.0 μg/kg vs 1.5 μg/kg, respectively) with a third arm of PegIFNα2a in the treatment of HCV-1-infected patients, reporting similar rates of discontinuation of therapy because of adverse events with both pegylated IFNs.[16] As previously reported,[12] however, more patients receiving PegIFNα2a had to reduce treatment dosing compared with those receiving PegIFNα2b (9% vs 4%, respectively, $P = .04$) to manage grade 3 neutropenia in our study, thus confirming PegIFNα2a to have a more potent myelosuppressive effect.

The higher rates of SVR that we found in the overall patients receiving PegIFNα2a compared with those treated with PegIFNα2b (66% vs 54%, respectively, $P = .02$) indicate a difference in the antiviral activity between the therapeutic regimens. This was stressed by the multivariate analysis showing combination therapy with PegIFNα2a to be an independent pretreatment predictor of a SVR, with an OR of 1.88 (95% CI: 1.20–2.96). In the overall population, differences in the antiviral efficacy of the 2 therapeutic regimens were not related to a different distribution of pretreatment levels of HCV-RNA or cirrhosis nor were they dictated by differences in PegIFN dose reduction or daily RBV intake. In analogy with previous trials, patients age, HCV genotype, and baseline HCV-RNA were found to be independent pretreatment predictors of a SVR.[17] By the same token, RVR was the strongest independent on-therapy predictor of a SVR, further supporting that early suppression of HCV is of crucial importance in the therapeutic resolution of chronic hepatitis C.[18,19] Although the study was not powered to compare the therapeutic efficacy of the 2 regimens in each genotype stratum, PegIFNα2a achieved higher SVR rates in HCV-1- and HCV-2-infected patients compared with PegIFNα2b, whereas the 2 therapeutic regimens obtained similar SVR rates in HCV-3- and HCV-4-infected patients. Whereas, in HCV-4 patients, a sound comparison of treatment efficacy was compromised by the small sample size; in HCV-3 patients, comparison between treatments was biased by the inadequate RBV dosing (800 mg/day) of the PegIFNα2a arm, as previously suggested by us and others.[20,21] As a matter of fact, the non-SVR HCV-2 and HCV-3 patients in the PegIFNα2a arm had a median daily intake of 10 mg/kg RBV, which is significantly less than the daily dose received by the SVR patients with the same HCV genotype. Because of the 96% rates of SVR among HCV-2 patients, the issue of RBV dosing virtually impacted on HCV-3 patients only, who showed 30% posttreatment relapse rate, further supporting differences between HCV-2 and HCV-3 patients enrolled in our study. The remarkably high SVR rates achieved in HCV-2-infected patients with PegIFNα2a might reflect the favorable baseline characteristics of our population coupled with the extremely high RVR rates obtained, a finding that compares well with a previous report of 95% SVR rates following 16 or 24 weeks of PegIFNα2a plus RBV in HCV-2 patients with similar RVR rates and baseline demographics as our patients.[22]

In the overall patient population, the greater antiviral activity of PegIFNα2a was the direct consequence of higher ETR rates coupled with comparable rates of posttreatment relapse. With all the caveats of the limited sample size and the subanalysis approach, in HCV-2 patients the high SVR rates of PegIFNα2a were mainly associated to lower posttreatment relapse rates with respect to PegIFNα2b (0% vs 11%, respectively, $P = .006$). In HCV-1 patients, RBV dosing seemed to be instrumental in preventing posttreatment relapse, as a likely consequence of our choice of stepwise down-escalating RBV by 200 mg instead of the 1-step recommended dose of 600 mg, which allowed maintaining optimal therapeutic serum levels of RBV. This strategy likely impacted on the outcome of our study because 1 out of 2 patients in both therapeutic arms had to reduce RBV dosing because of either moderate or severe anemia.

We were puzzled with cirrhosis not emerging as an independent predictor of IFN-based treatment failure because this contradicted previous registration and field

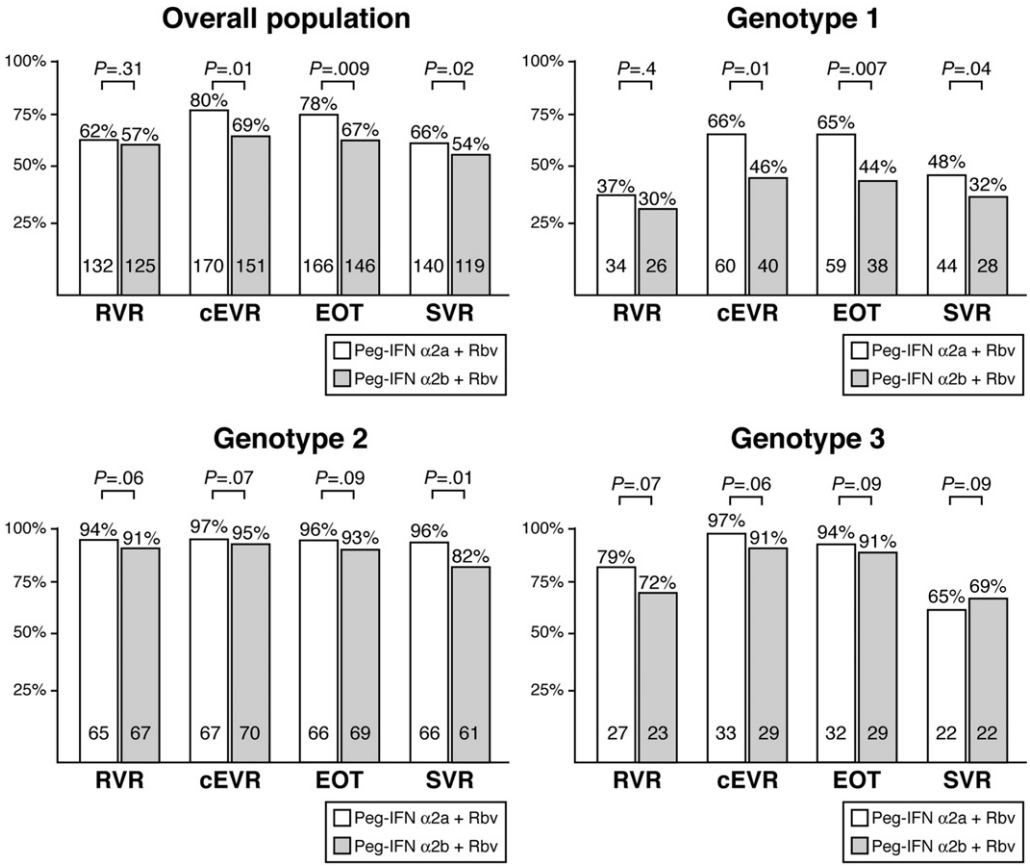


**Figure 2.** Rates of virologic response for the patients with chronic hepatitis C receiving RBV combined with PegIFN-α2a or PegIFN-α2b. *RVR,* rapid; *cEVR,* complete early; *EOT,* end of treatment; and *SVR,* sustained virologic.

practice studies with both PegIFNs.[7,17,23] Although our study was underpowered for assessing the role of cirrhosis as a moderator of treatment outcome, a trend was demonstrated for higher SVR rates in cirrhotic patients receiving PegIFNα2a compared with those treated with PegIFNα2b (53% vs 38%, respectively). Although we acknowledge that the 32% rate of SVR in our HCV-1 patients treated with PegIFNα2b is lower than that reported in patients enrolled in the registration trial,[7] we wish to point out that our study mimics the outcome of a field practice study in the United States: the Win-R study. In that study, HCV-1 patients treated with a similar PegIFNα2b/RBV schedule as ours showed 34% rates of SVR.[23]

A stronger antiviral activity of PegIFNα2a over PegIFNα2b was also reported by another investigator-initiated, single center study in Italy[24] and by the retrospective scrutiny of the field practice at Veterans Hospitals in the United States[25] and at several liver centers in Germany.[26] Whereas both our study and the individual dosing efficacy vs flat dosing to access optimal pegylated interferon therapy

**Table 4.** Median Actual Intake of RBV Expressed in Milligrams/Kilograms Body Weight per Day in the 2 Therapeutic Regimen Groups of Patients

| | PegIFNα2a | PegIFNα2b | *P* value[a] |
|---|---|---|---|
| Overall | 11.92 | 12.70 | .003 |
| SVR | 11.76 | 12.66 | .006 |
| Non-SVR | 12.23 | 12.94 | .1 |
| Genotypes 1/4 | 12.74 | 12.99 | .9 |
| SVR | 12.86 | 12.78 | .9 |
| Non-SVR | 12.63 | 13.01 | .9 |
| Genotype 2/3 | 11.11 | 12.50 | <.0001 |
| SVR | 11.29 | 12.58 | <.0001 |
| Non-SVR | 10.00 | 11.75 | .1 |

SVR, Sustained virologic response.
[a]Median test.

**Table 5.** Odds Ratio and Corresponding 95% Confidence Intervals From the Multivariate Logistic Regression Analysis Including All Independent Predictors of SVR

| | OR | 95% CI |
|---|---|---|
| Age, *y* | | |
| ≥40 | 1[a] | |
| <40 | 3.20 | 1.73–5.94 |
| HCV-RNA | | |
| ≥600,000 *IU/mL* | 1[a] | |
| <600,000 *IU/mL* | 1.49 | 1.01–2.33 |
| HCV genotype | | |
| 1 and 4 | 1[a] | |
| 2 and 3 | 7.97 | 4.97–12.77 |
| Treatment | | |
| PegIFNα2b | 1[a] | |
| PegIFNα2a | 1.88 | 1.20–2.96 |

[a]Reference category.

(IDEAL) study[16] similarly showed higher ETR rates following PegIFNα2a treatment compared with 1.5 μg/kg PegIFNα2b in HCV-1 patients, our study reported less post-treatment relapse rates in the PegIFNα2a patients than the IDEAL study, possibly as a consequence of different strategies of RBV down dosing. Whether our strategy of RBV dosing, which is at variance with the standard of care for PegIFNα2a treatment, is indeed cost-effective, needs to be prospectively assessed through a pharmaco-economy study.

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*Conflicts of interest*

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