High Sustained Virologic Response Rates in Rapid Virologic Response Patients in the Large Real-World PROPHESYS Cohort Confirm Results From Randomized Clinical Trials

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The ability to predict which patients are most likely to achieve a sustained virologic response (SVR) with peginterferon/ribavirin would be useful in optimizing treatment for hepatitis C virus (HCV). The objective of this large international noninterventional cohort study was to investigate the predictive value (PV) of a virologic response (VR) by weeks 2, 4, and 12 of treatment on SVR. Treatment-naive HCV monoinfected patients (N = 7,163) age ≥18 years were prescribed peginterferon/ribavirin at the discretion of the treating physician according to country-specific requirements in accordance with the local label. The main outcome measure was the PV of a VR (HCV RNA <50 IU/mL) by weeks 2, 4, and 12 of treatment for SVR24 (HCV RNA <50 IU/mL after 24 weeks of untreated follow-up) by HCV genotype. The overall SVR24 rate was 49.4% (3,541/7,163; 95% confidence interval [CI]: 48.3-50.6%). SVR24 rates in patients with an HCV RNA titer <50 IU/mL by weeks 2, 4, and 12, respectively, were 66.2% (95% CI: 60.4-71.7%), 68.4% (95% CI: 65.7-71.0%), and 60.3% (95% CI: 58.5-62.1%) among genotype 1 patients; 82.0% (95% CI: 76.8-86.5%), 76.3% (95% CI: 73.3-79.1%), and 74.2% (95% CI: 71.3-76.9%) among genotype 2 patients; 67.3% (95% CI: 61.1-73.1%), 67.3% (95% CI: 64.2-70.3%), and 63.8% (95% CI: 61.0-66.6%) among genotype 3 patients; and 59.4% (95% CI: 40.6-76.3%), 63.3% (95% CI: 54.3-71.6%), and 54.3% (95% CI: 47.5-60.9%) among genotype 4 patients. The absence of a VR by week 12 had the highest negative PV across all genotypes. Conclusion: A VR by week 2 or 4 had the highest positive PV for SVR24 and differed according to HCV genotype. (HEPATOLOGY 2012;56:2039-2050)

Large randomized clinical trials report overall sustained virologic response (SVR) rates of 40% to 50% in treatment-naive chronic hepatitis C (CHC) patients treated with peginterferon/ribavirin.1-4 Thus, the ability to predict which patients are most likely to achieve SVR, at baseline or early during the course of treatment, would be clinically useful in targeting treatment to those most likely to respond. The absence of an early virologic response by week 12 of treatment is a well-established negative predictor...
of SVR and is recommended as a stopping rule in patients receiving peginterferon/ribavirin for almost a decade.\(^5\)\(^6\) Conversely, achievement of a rapid virologic response (RVR), defined as undetectable hepatitis C virus (HCV) RNA by week 4, is highly predictive of SVR.\(^7\)\(^8\) Indeed, a recent analysis of data from large randomized phase 3 studies showed that SVR rates were similar in patients with an RVR regardless of viral genotype.\(^9\) Measurement of viral kinetics during treatment with peginterferon/ribavirin is of practical value. In addition to the well-established predictive value of the response at weeks 4 and 12 for SVR, virologic responses at weeks 4 and 12 can be used to individualize the duration of treatment in an attempt to optimize treatment.\(^6\)

Although randomized trials are important in establishing the comparative efficacy of a drug, due to strict inclusion and exclusion criteria they produce results that are best-case scenarios. In contrast, in everyday clinical practice drugs are often perceived to be less effective. Large-cohort studies can play an important role in bridging gaps between the highly controlled environment of randomized trials and the reality of everyday practice. Cohort trials can enroll broader populations that include older patients and those with comorbidities, and can be used to model and disseminate best practices.

Given the importance of viral kinetics in the management of CHC patients, there is need for a cohort trial that can be used to help guide and optimize treatment of patients receiving peginterferon/ribavirin, and to inform the design of clinical trials of direct-acting antiviral agents. To address this need, we initiated a series of three large prospective international cohort studies with the objective of investigating the predictive value of virologic responses by week 2, 4, and 12 on SVR by week 24 (SVR24). Here, we present virologic response rates in treatment-naive HCV monoinfected patients and identify predictors of SVR24.

**Patients and Methods**

**Study Design.** This was a prospective, international noninterventional cohort study of CHC patients receiving treatment in accordance with country-specific legal and regulatory requirements. The study comprised three cohorts of patients enrolled in 19 countries (Supporting Table 1).

**Patients.** Eligible patients were age \(\geq 18\) years with serologically proven CHC who were prescribed peginterferon/ribavirin in accordance with local labels. For this analysis, hepatitis B virus (HBV) and human immunodeficiency virus (HIV) coinfected patients were excluded, as were those who received both peginterferon alfa-2a and peginterferon alfa-2b during PROPHESYS, or who had previously received any interferon-based treatment. The primary analysis population consisted of all patients who received \(\geq 1\) dose of peginterferon/ribavirin, had a baseline HCV RNA titer \(\geq 50\) IU/mL, and had \(\geq 1\) postbaseline HCV RNA test result. A subanalysis was performed among patients with sufficient follow-up data (n = 6,416). Patients were excluded from this population if they had HCV RNA <50 IU/mL at the end of treatment (EOT), had no relapse, and were missing an HCV RNA test \(\geq 140\) days after EOT for reasons not related to efficacy or safety.
All contraindications in the country-specific labeling for peginterferon/ribavirin were adhered to. Major exclusion criteria were autoimmune hepatitis, decompensated liver disease, and unstable or uncontrolled cardiac disease.

**Treatment.** The prescribed treatment was at the sole discretion of the physician and patients were included in PROPHESYS only after the choice of treatment had been made.

According to country-specific requirements, PROPHESYS 1 (www.clinicaltrials.gov NCT01070550) included patients prescribed peginterferon alfa-2a (40KD) (PEGASYS, Roche, Basel, Switzerland) plus ribavirin, whereas patients included in PROPHESYS 2 and 3 (www.clinicaltrials.gov NCT01066793, NCT01066819, respectively) received either peginterferon alfa-2a (40KD) or peginterferon alfa-2b (12KD) (PegIntron) plus ribavirin (Supporting Table 1).

**Outcomes.** Virologic response was defined as HCV RNA <50 IU/mL as determined by the local laboratory using TaqMan® or their routine HCV RNA assay. The primary outcome was the predictive value of the on-treatment virologic response by week 4 (RVR) and by week 12 for SVR24 by genotype. SVR12 and SVR24 were defined as last HCV RNA (RVR) and by week 12 for SVR24 by genotype.

**Virologic Response.** The overall SVR24 rate was 49.4% (3,541/7,163; 95% confidence interval [CI]: 48.3%-50.6%) across all genotypes combined, and 41.8%, 71.4%, 60.6%, and 41.0% in genotype 1, 2, 3, and 4 patients, respectively (Fig. 1A-D); SVR12 rates were slightly higher: 44.2%, 74.0%, 64.2%, and 41.0% in genotype 1, 2, 3, and 4 patients, respectively (Table 2). The mean durations of treatment for genotype 1, 2, 3, and 4 patients were 41.9, 23.7, 24.9, and 41.6 weeks, respectively (Supporting Table 2). Among study participants assigned to peginterferon alfa-2a (40KD), 72.6% and 70.8% of patients received ≥80% of the planned dose of peginterferon alfa-2a (40KD) and ribavirin, respectively, and among individuals assigned to peginterferon alfa-2b (12KD), 64.1% and 62.4% of patients received ≥80% of the planned dose of peginterferon alfa-2b (12KD) and ribavirin, respectively (Supporting Table 2).

In patients with sufficient follow-up data (n = 6,416), the overall SVR24 rate was 55.2% (3,541/6,416; 95% CI: 54.0%-56.4%) and 45.9%, 80.2%, 71.8%, and 46.1% for genotype 1 (n = 4,119), genotype 2 (n = 913), genotype 3 (n = 1,063), and genotype 4 (n = 282) patients, respectively.

The overall relapse rate was 21.8% (982/4,507; 95% CI: 20.6%-23.0%) and was highest among genotype 1 patients (27.0%; 95% CI: 25.3%-28.8%) and lowest among genotype 2 patients (10.9%; 95% CI: 8.8%-13.2%) (Fig. 1).
Among patients infected with HCV genotype 1 the SVR24 rate was 42.3% (1798/4247, 95% CI: 40.8%-43.8%) in those treated with peginterferon alfa-2a (40KD) and 34.1% (93/273, 95% CI: 28.5%-40.0%) in those treated with peginterferon alfa-2b (12KD).

Overall SVR24 rates in patients with HCV genotype 1 were 43.4% (1,709/3,942; 95% CI: 41.8%-44.9%) for White patients, 25.1% (57/227; 95% CI: 19.6%-31.3%) for Black patients, 55.6% (30/54; 95% CI: 41.4%-69.1%) for Asian patients, and 22.4% (32/143; 95% CI: 15.8%-30.1%) for Hispanic patients. For patients with sufficient follow-up data, SVR24 rates were 47.4% (1,709/3,606; 95% CI: 45.8%-49.0%) for White patients, 27.8% (57/205; 95% CI: 21.8%-34.5%) for Black patients, 62.5% (30/48; 95% CI: 47.4%-76.0%) for Asian patients, and 27.4% (32/117; 95% CI: 19.5%-36.4%) for Hispanic patients.

Genotype 1 patients had consistently lower rates of on-treatment virologic responses by weeks 2, 4, and 12 and the lowest SVR24 rates versus other genotypes; this was observed for both the overall population (Fig. 1A) and in the population of patients with sufficient follow-up data (Supporting Fig. 2A). Conversely, patients infected with HCV genotype 2 had the highest rates of on-treatment virologic responses and SVR24 (Fig. 1B; Supporting Fig. 2B). Not all study sites included a week 2 measurement.

Overall SVR24 rates were consistently high among patients with a virologic response by week 2, week 4, and week 12 (Fig. 2A). Among patients infected with HCV genotypes 1 or 4, a virologic response by week 4 had the highest PPV for SVR24 (Table 3). In contrast, a virologic response by week 2 had the highest PPV for SVR24 among genotype 2 patients and there was no difference in the PPV of a virologic response by
The absence of a virologic response by week 12 had the highest NPV across all genotypes. Interestingly, in patients with sufficient follow-up data, the PPV for patients with a virologic response by week 2 for SVR24 was 84.1%, 91.8%, 81.6%, and 70.4% for HCV genotypes 1, 2, 3, and 4, respectively, whereas the PPV for patients with a virologic response by week 4 for SVR24 was 80.9%, 86.2%, 80.9%, and 75.7%, respectively (Fig. 2B; Table 3).

**Efficacy by Fibrosis Status.** A total of 5,238 patients (73.1%) had a valid baseline assessment of hepatic fibrosis, of whom 1,491 (28.5%) were determined to have bridging fibrosis/cirrhosis. Numerically on-treatment virologic response rates and SVR24 rates were lower, and relapse rates higher, in these individuals compared with patients without bridging fibrosis/cirrhosis (Fig. 1A–D). Similar trends were observed among patients with sufficient follow-up data (Supporting Fig. 2A–D).

**Predictors of SVR.** In multiple logistic regression analysis, baseline factors that had a statistically significant positive association with SVR24 in genotype 1 patients included ethnicity (Asian versus White; White versus Black; and White versus Hispanic), absence of cirrhosis, higher platelet count, higher alanine aminotransferase (ALT) ratio, lower HCV RNA level, lower aspartate aminotransferase (AST) ratio, lower body mass index (BMI), younger age, and assignment to peginterferon alfa-2a treatment (40KD) (Fig. 3A).

When the analysis was restricted to genotype 1 patients with bridging fibrosis/cirrhosis, baseline factors that had a significant positive association with SVR included ethnicity (White versus Black and White versus Hispanic), lower HCV RNA level, and higher platelet count (Fig. 3B).

**Safety.** Peginterferon dosage was modified in 854 (11.9%) patients because of prespecified adverse events or laboratory abnormalities, the most common being neutropenia (n = 495, 6.9%) and thrombocytopenia (n = 219, 3.1%) (Table 4). Ribavirin dosage was modified in 1,030 (14.4%) patients because of anemia (Table 4). In general, rates of dosage modifications and discontinuations of peginterferon and ribavirin were not markedly different between patients with and without bridging fibrosis/cirrhosis. However, considerably more
<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>1 (4,520)</th>
<th>2 (1,025)</th>
<th>3 (1,259)</th>
<th>4 (317)</th>
<th>5/6 (28)</th>
<th>All Patients† (N = 7,163)</th>
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<tbody>
<tr>
<td>Mean age, yr ± SD</td>
<td>47.4 ± 11.8</td>
<td>52.4 ± 12.0</td>
<td>41.4 ± 10.1</td>
<td>44.5 ± 10.9</td>
<td>52.0 ± 12.7</td>
<td>47.0 ± 12.0</td>
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<td>Male, n (%)</td>
<td>2,363 (52.3)</td>
<td>528 (51.5)</td>
<td>845 (67.1)</td>
<td>214 (67.5)</td>
<td>19 (67.9)</td>
<td>3,979 (55.5)</td>
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<td>Race/ethnicity, n (%)</td>
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<tr>
<td>White</td>
<td>3,942 (87.3)</td>
<td>870 (84.9)</td>
<td>1,118 (89.2)</td>
<td>181 (57.3)</td>
<td>16 (57.1)</td>
<td>6,138 (85.8)</td>
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<td>Black</td>
<td>227 (5.0)</td>
<td>40 (3.9)</td>
<td>14 (11.1)</td>
<td>72 (22.8)</td>
<td>0</td>
<td>355 (5.0)</td>
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<td>Asian</td>
<td>54 (1.2)</td>
<td>12 (1.2)</td>
<td>38 (3.0)</td>
<td>7 (2.2)</td>
<td>10 (35.7)</td>
<td>122 (1.7)</td>
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<td>Hispanic</td>
<td>143 (3.2)</td>
<td>45 (4.4)</td>
<td>33 (2.6)</td>
<td>8 (2.5)</td>
<td>1 (3.6)</td>
<td>230 (3.2)</td>
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<td>Other</td>
<td>149 (3.3)</td>
<td>58 (5.7)</td>
<td>51 (4.1)</td>
<td>48 (15.2)</td>
<td>1 (3.6)</td>
<td>307 (4.3)</td>
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<td>Mean weight, kg ± SD</td>
<td>75.0 ± 15.6</td>
<td>75.3 ± 16.5</td>
<td>75.4 ± 15.8</td>
<td>76.1 ± 14.0</td>
<td>71.7 ± 12.5</td>
<td>75.1 ± 15.7</td>
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<tr>
<td>Mean BMI, kg/m² ± SD</td>
<td>26.2 ± 4.7</td>
<td>26.8 ± 5.4</td>
<td>25.4 ± 4.8</td>
<td>26.0 ± 4.5</td>
<td>25.2 ± 3.6</td>
<td>26.1 ± 4.8</td>
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<td>Method to assess liver fibrosis, n (%)</td>
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<tr>
<td>Biopsy</td>
<td>2,747 (60.8)</td>
<td>283 (27.6)</td>
<td>481 (38.2)</td>
<td>150 (47.5)</td>
<td>16 (57.1)</td>
<td>3,683 (51.4)</td>
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<td>Noninvasive</td>
<td>757 (16.8)</td>
<td>325 (31.7)</td>
<td>349 (27.7)</td>
<td>115 (36.4)</td>
<td>8 (28.6)</td>
<td>1,559 (21.8)</td>
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<tr>
<td>Not assessed</td>
<td>1,015 (22.5)</td>
<td>417 (40.7)</td>
<td>429 (34.1)</td>
<td>51 (16.1)</td>
<td>1 (3.6)</td>
<td>1,919 (26.8)</td>
</tr>
<tr>
<td>Median time from biopsy to start of treatment, days (Q1—Q3)</td>
<td>139 (68—298)</td>
<td>101 (52—289)</td>
<td>126 (58—295)</td>
<td>99 (61—256)</td>
<td>56 (42—133)</td>
<td>131 (64—294)</td>
</tr>
<tr>
<td>Patients with bridging fibrosis or cirrhosis, n/N (%)‡</td>
<td>1,117/3,501 (31.9)</td>
<td>124/607 (20.4)</td>
<td>187/830 (22.5)</td>
<td>51/265 (19.2)</td>
<td>8/24 (33.3)</td>
<td>1,491/5,238 (28.5)</td>
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<td>ALT quotient, n (%)</td>
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<tr>
<td>≤3</td>
<td>3,512 (79.2)</td>
<td>823 (82.1)</td>
<td>859 (70.4)</td>
<td>249 (80.1)</td>
<td>25 (92.6)</td>
<td>5,478 (78.2)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>923 (20.8)</td>
<td>179 (17.9)</td>
<td>362 (29.6)</td>
<td>62 (19.9)</td>
<td>2 (7.4)</td>
<td>1,530 (21.8)</td>
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<tr>
<td>Mean platelets, × 10⁹/L ± SD</td>
<td>213 ± 71</td>
<td>211 ± 68</td>
<td>213 ± 68</td>
<td>219 ± 75</td>
<td>210 ± 83</td>
<td>213 ± 70.2</td>
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<tr>
<td>Mean HCV RNA level, log₁₀ IU/mL ± SD</td>
<td>6.0 ± 0.8</td>
<td>5.9 ± 1.0</td>
<td>5.8 ± 0.9</td>
<td>5.3 ± 0.8</td>
<td>6.3 ± 0.7</td>
<td>5.9 ± 0.9</td>
</tr>
<tr>
<td>HCV RNA ≤400,000 IU/mL, n (%)</td>
<td>1,159 (4,475 (25.9)</td>
<td>321 (1,020 (31.5)</td>
<td>467 (1,242 (37.6)</td>
<td>182 (583 (31.3)</td>
<td>3 (10.7)</td>
<td>2,139 (7,090 (30.2)</td>
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<td>Intended treatment duration, weeks, n (%)</td>
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<tr>
<td>24§</td>
<td>56 (1.2)</td>
<td>982 (95.8)</td>
<td>1,193 (94.8)</td>
<td>7 (2.2)</td>
<td>4 (14.3)</td>
<td>2,244 (31.3)</td>
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<tr>
<td>48§</td>
<td>4,449 (98.4)</td>
<td>36 (3.5)</td>
<td>60 (4.8)</td>
<td>304 (95.8)</td>
<td>24 (85.7)</td>
<td>4,885 (68.2)</td>
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<tr>
<td>Other</td>
<td>15 (0.3)</td>
<td>7 (0.7)</td>
<td>6 (0.5)</td>
<td>6 (1.9)</td>
<td>—</td>
<td>34 (0.5)</td>
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<tr>
<td>Type of peginterferon prescribed, n (%)</td>
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<tr>
<td>alfa-2a (40KD)</td>
<td>4,247 (94.0)</td>
<td>880 (85.9)</td>
<td>1,159 (92.1)</td>
<td>302 (95.3)</td>
<td>25 (89.3)</td>
<td>6,625 (92.5)</td>
</tr>
<tr>
<td>alfa-2b (12KD)</td>
<td>273 (6.0)</td>
<td>145 (14.1)</td>
<td>100 (7.9)</td>
<td>15 (4.7)</td>
<td>3 (10.7)</td>
<td>538 (7.5)</td>
</tr>
</tbody>
</table>

*Some categories do not add up to the total number of patients because of missing values.
†The total number of patients includes 14 individuals with unknown genotypes.
‡Only patients with a valid result from a fibrosis assessment by biopsy or by a noninvasive method were included in the calculation.
§The intended treatment duration was categorized using time windows of ≤ 4 weeks.
ALT quotient, ALT value divided by the upper limit of the normal range of the local laboratory; BMI, body mass index.
patients with bridging fibrosis/cirrhosis had dose modifications (6.9% versus 1.7% in those without bridging fibrosis/cirrhosis) and premature withdrawal (1.1 versus 0.2, respectively) of peginterferon because of thrombocytopenia (Table 4).

Overall, 565 (7.9%) of patients withdrew from treatment prematurely for safety-related reasons. There were 21 deaths (0.3%) during study treatment.

**Discussion**

This is the largest report to date of efficacy data from patient cohorts that span several continents and include all HCV genotypes. Across diverse patient populations and treatment settings, 49.4% of patients achieved an SVR24 with peginterferon/ribavirin, a result that largely confirms the results of randomized controlled trials. Among genotype 1 patients with
sufficient follow-up data, the SVR24 rate was 81% in those who achieved an RVR (24.6%).

The overall SVR24 rate of 49.4% observed in PROPHESYS was very similar to SVR rates reported in large, well-controlled, randomized, multicenter clinical trials (44% to 63%).

SVR24 rates by individual genotypes in PROPHESYS are also similar to those reported in large well-controlled clinical trials. For example, among genotype 1 patients the SVR24 rate was 42% compared with 41% to 52% reported in other large clinical trials. Among patients with genotype 2 and 3 the SVR24 rates were 71% and 61% compared with 75% and 66%, respectively, in a large randomized trial. This clearly demonstrates that SVR rates achieved with peginterferon/ribavirin in the "real world" are indeed similar to those achieved in well-controlled clinical trials.

The SVR24 rates obtained in this trial are particularly good in light of the large proportion of patients with an EOT response (15%) who did not return for the final HCV RNA test and were imputed as treatment failures. However, the large number of patients lost to follow-up is a true reflection of real-world clinical practice in that patients are not compelled to return for all scheduled visits. Therefore, the analysis of the patient population with sufficient follow-up data is particularly valuable in cohort trials.

SVR24 rates in the present study also compare well with those obtained in randomized clinical studies, which generally have more restrictive inclusion and exclusion criteria. For this reason, patients treated in community-based practice may have a higher prevalence of "unfavorable" characteristics, such as advanced fibrosis or psychiatric disorders. For example, 28.5% of patients who had a valid result from a fibrosis assessment had bridging fibrosis/cirrhosis in the present study. In contrast, just 12% of patients in the pivotal trial by Fried et al. had bridging fibrosis/cirrhosis.

The comparatively high SVR rates in this study may result, in part, from greater overall skill and experience at participating clinics in treating patients with peginterferon/ribavirin. The high SVR rates in peginterferon/ribavirin control groups (>60%) in some recent studies of direct-acting antivirals may be further evidence of this "learning curve" phenomenon. Adherence with therapy is also a major determinant of SVR, as shown by Beinhardt et al. A recent report from New Mexico demonstrated that encouraging patients to adhere to treatment is more likely to be successful when experienced specialists are available to consult with less experienced physicians.
Achievement of SVR24 with peginterferon/ribavirin indicates that HCV infection has been eradicated.\textsuperscript{16} An analysis of data from more than 10,000 patients enrolled in 15 trials showed that there is a high degree of concordance between SVR12 and SVR24. The PPV between SVR12 and SVR24 was 98\% and the NPV was 99\%.\textsuperscript{17} For this reason, SVR12 is considered a suitable endpoint in efficacy trials. In PROPHESYS, SVR12 rates were 44.2\%, 74.0\%, 64.2\%, and 44.8\% in genotype 1, 2, 3, and 4 patients, respectively. Patients with undetectable HCV RNA after 12 weeks of follow-up may have been satisfied, or reassured that the outcome of treatment was successful and were not motivated to return for the week 24 follow-up visit.

The proportion of patients with HCV RNA <50 IU/mL by weeks 2, 4, and 12 varied widely by genotype. For example, the percentage of patients who had an HCV RNA titer <50 IU/mL by weeks 2, 4, and 12 was 6\%, 27\%, and 61\%, respectively, among genotype 1 patients, and 25\%, 85\%, and 95\%, respectively, among genotype 2 patients. The virologic response rates achieved by week 4 in this study are high compared with those obtained in genotype 1 (11\% to 27\%)\textsuperscript{4,18} and 2 (69\%)\textsuperscript{11} patients treated with peginterferon/ribavirin in large randomized studies.

Although on-treatment virologic response rates varied widely by genotype, SVR24 rates among patients with an on-treatment virologic response by weeks 2, 4,
or 12 were consistently high: 66%, 68%, and 60%, respectively, among genotype 1 patients, and 82%, 76%, and 74% among genotype 2 patients. It is noteworthy that among genotype 1 patients with complete follow-up data, the SVR24 rate in patients with an RVR was 81%, which is within the range reported among patients initiating boceprevir- or telaprevir-based triple therapy in phase 3 trials.19-22

The PPV of an on-treatment virologic response was maximized by week 2 for patients infected with HCV genotype 2 and by week 4 for patients infected with HCV genotypes 1 or 4. Conversely, the NPV of an on-treatment virologic response was maximized by week 12, regardless of genotype. These results suggest that prediction rules and decision points for treatment should be individualized by HCV genotype and should be of interest to experts who are developing guidelines for the treatment of CHC.

Few studies have measured virologic response rates at week 2 of treatment. Recent analyses have reported week 2 virologic response rates of 9% to 10% in HCV genotype 1 patients, and 18% in HCV genotype 3 patients,23,25 which compare well with the results of this study. Lee et al.25 observed considerably lower relapse rates in nongenotype 2/3 patients who became HCV RNA-negative by week 2 (5%) compared with those who became negative between weeks 2 and 4 (18%). In another large randomized study, all genotype 1 patients who had HCV RNA <43 IU/mL after 2 weeks of treatment with peginterferon alfa-2a (40KD)/ribavirin achieved an SVR.26

There are regional differences in RVR rates in genotype 1 patients, with the lowest rates originating from the U.S. and the highest from Asia.26,27 There are also statistically significant differences in viral response between ethnic and racial groups for all genotypes.10,11,26,28-31

These differences almost certainly reflect differences in the distribution of host IL28 genotypes in geographically distinct populations.32 This polymorphism is an especially important baseline predictor of SVR in the context of genotype 1 infection and appears to be less important in the context of HCV genotype 3 infection.24,32,33 It is now possible to determine the IL28B genotype before initiating peginterferon/ribavirin treatment.34 The absence of these data is a limitation of many studies including the present study. In future, the combination of IL28B genotype and RVR may be combined to select patients most likely to respond to peginterferon/ribavirin and those who might benefit the most from combination therapy with a protease inhibitor.

The MLR analysis identified a number of well-established baseline predictors of SVR that have been identified in previous randomized controlled trials. In addition, this analysis showed that assignment to peginterferon alfa-2a was significantly associated with achievement of an SVR24, which is consistent with the results of a comprehensive meta-analysis.35

Until recently, peginterferon/ribavirin was the treatment of choice for all patients with CHC. HCV protease inhibitors are now approved for use with peginterferon/ribavirin and, where available, protease inhibitor-based triple therapy is the new standard of care for patients infected with HCV genotype 1.34

Protease inhibitor-based triple therapy improves overall
SVR rates by increasing on-treatment virologic response rates at weeks 4 and 12, and by decreasing overall relapse rates.\textsuperscript{19,20}

From a global perspective this new standard of care will only be accessible to a minority of patients with CHC. Protease inhibitors are not yet available in many countries that lack the resources to pay for them, and may not be affordable for many patients in countries that lack publicly funded universal healthcare.\textsuperscript{36} Thus, peginterferon/ribavirin will continue to be used as the "standard of care" in many countries.

Moreover, among individuals who achieve a virologic response by week 4, SVR rates are similar in patients treated with triple therapy to those treated with dual therapy of peginterferon/ribavirin.\textsuperscript{19,20} Given the increased burden of adverse events associated with the addition of a protease inhibitor,\textsuperscript{19,20} it could be argued that these new agents should be reserved for individuals who do not achieve a virologic response by week 4 of treatment with peginterferon/ribavirin. This would amount to 73\% of the HCV genotype 1 patients in this trial. Currently available protease inhibitors are not approved for patients infected with HCV genotypes 2-6\textsuperscript{34}; thus, the dual combination of peginterferon/ribavirin remains the treatment of choice in these individuals.\textsuperscript{6,37} This means that peginterferon/ribavirin remains the only available treatment for a large proportion of patients.

In addition to the drawbacks associated with cohort studies, this trial has limitations. As noted above, a large proportion of patients failed to return for their final HCV RNA test, with the effect that the SVR rates were likely underestimated. This phenomenon emphasizes the need for strategies to maximize data collection efforts in cohort trials. Also, as noted previously, the \textit{IL28B} genotype was not determined in the present trial because its relevance to treatment outcome was not discovered until after this trial was initiated.\textsuperscript{32} Participants were enrolled only after the decision to initiate treatment with peginterferon/ribavirin. For these reasons it is not possible to state how many patients were considered for treatment, and which ones, ultimately, were either not recommended for treatment or declined treatment, and thus were not enrolled in the study. The dose and duration of treatment were left to the treating physician’s clinical judgment rather than a strictly enforced protocol. This reflects the situation in the “real world” but for this reason it is not possible to compare SVR rates between patients who received treatment for different durations on the basis of a strictly enforced study protocol. However, the intended duration of treatment for the majority of patients was consistent with that recommended in treatment guidelines in effect at the time the study was initiated.\textsuperscript{38}

In conclusion, the results of this large multinational trial demonstrate that, in the “real-world” setting, high SVR24 rates can be achieved with peginterferon plus ribavirin in patients with HCV genotypes 1-4 who achieve early virologic response. However, the data also indicate that there is no universal prediction rule for SVR24 that applies to all patients and that the best PPV for SVR24 differs by genotype. Future studies should examine the respective predictive values by host \textit{IL28B} genotype and viral genotype in an effort to further refine such prediction rules.

\textbf{References}


