

REVIEW

Efficacy of Chronic Hepatitis C Therapy in Community-Based Trials

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This article has an accompanying continuing medical education activity on page 1022. Learning Objectives—At the end of this activity the learner should recognize the different manner in which pivotal trials are conducted at academic medical centers as compared to trials in the community, appreciate the factors associated with a higher sustained virological response after therapy, and understand the importance of body weight dosing for ribavirin.

See CME exam on page 1022.

Prospective, randomized, controlled, phase 3 clinical trials establish pegylated interferon (PEG-IFN) alfa plus ribavirin as the standard of care for patients with chronic hepatitis C. Such clinical trials are conducted in a highly regimented manner; patients must meet strict inclusion/exclusion criteria, and treatment is administered under rigid protocols with close monitoring by study personnel. Whether the results of phase 3 trials can be generalized or achieved in everyday clinical practice is questioned in several therapeutic areas. The efficacy of PEG-IFN alfa plus ribavirin therapy observed in pivotal phase 3 trials has been confirmed in several community-based trials conducted in North America and Europe, demonstrating consistent overall rates of sustained virologic response across a wide range of patient populations. Sustained virologic response rates stratified by genotype, viral load, fibrosis score, age, and ethnicity, factors known to impact treatment outcome, are consistent between these trials and comparable to those reported in clinical trials. The United States-based WIN-R trial confirmed the value of combining weight-based ribavirin dosing with weight-based PEG-IFN alfa-2b dosing across a spectrum of patient body weights. Large Canadian trials (POWeR and EAP), a German trial (AWB), a French study (Hepatys), and an Italian study demonstrated that PEG-IFN alfa plus ribavirin produces excellent efficacy in difficult-to-treat patient populations. Collectively, these results confirm the efficacy of current standard treatment regimens in a wide range of community-based settings, affording clinicians confidence that they can attain results similar to those of rigidly controlled randomized trials.

Chronic infection with HCV is associated with a substantial global health burden. Chronic hepatitis C (CHC) is one of the most common causes of cirrhosis and hepatocellular carcinoma and appears to be a major reason for the increased mortality rate from hepatocellular carcinoma.^{1,2} As a result, CHC is the leading indication for liver transplantation in the United States and worldwide.^{2,3} Although the incidence of new HCV infections is declining, the health and economic burdens

associated with CHC are expected to increase during the next 20 years, given the slow development of disease-related complications in the course of chronic infection.⁴

Treatment guidelines for patients with CHC recommend combination therapy with pegylated interferon (PEG-IFN) alfa plus ribavirin (RBV).³ Two PEG-IFNs are approved and available, PEG-IFN alfa-2a (Pegasys; Roche, Geneva, Switzerland) and PEG-IFN alfa-2b (PegIntron; Schering-Plough, Kenilworth, NJ). Dosing schedules differ between these PEG-IFNs; PEG-IFN alfa-2a is administered as a fixed subcutaneous dosage of 180 $\mu\text{g}/\text{wk}$ and PEG-IFN alfa-2b as a weight-based dosage of 1.5 $\mu\text{g}/\text{kg}/\text{wk}$. In combination with PEG-IFN alfa-2a, the dosage of RBV is dependent on the patient's body weight, 1000 mg/day for patients weighing 75 kg or less and 1200 mg/day for patients weighing more than 75 kg. When combined with PEG-IFN alfa-2b, RBV doses are country-specific. In Canada, weight-based RBV dosages range from 800–1200 mg/day (800 mg/day for patients weighing <64 kg, 1000 mg/day for patients weighing 64 to <85 kg, and 1200 mg/day for patients weighing \geq 85 kg). In the United States, however, weight-based RBV dosages range from 800–1400 mg/day (800 mg/day for patients weighing \leq 65 kg, 1000 mg/day for patients weighing 66–85 kg, 1200 mg/day for patients weighing 86–105 kg, and 1400 mg/day for patients weighing >105 kg).⁵ RBV doses are also weight-based in most European countries, but doses and weight categories vary by country. The duration of PEG-IFN alfa plus RBV therapy is a function of HCV genotype; 24 weeks of combination therapy is recommended for genotype 2

Abbreviations used in this paper: AWB, Anwendungsbeobachtung; CHC, chronic hepatitis C; EAP, Canadian Pegasys Expanded Access Program; G, genotype; IFN, interferon; MU, million units; PEG-IFN, pegylated interferon; POWeR, PegIntron Prospective Optimal Weight Based Dosing Response Program; QW, once weekly; RBV, ribavirin; RCT, randomized controlled trial; SVR, sustained virologic response; TIW, three times weekly; ULN, upper limit of normal; WBD, weight-based dosing; WIN-R, weight-based dosing of peginterferon alfa-2b plus RBV.

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Table 1. Attributes of Phase 3 Randomized Controlled Clinical Trials and Community-Based Trials

Study type	Goals	Attributes	
		Pros	Cons
Phase 3 RCT	Establish efficacy/safety of a new therapy; gain marketing approval	Well-controlled; standard for establishing efficacy/safety; potential for greater access to resources for patients; potential for increased level of support for patients; compliance measured (ie, increased adherence); potential for greater patient motivation	Patient population not reflective of general population; possibly no translation of results to real-world setting; dosage regimen inflexible; management of adverse events might be predetermined
Community-based trial	Confirm efficacy/safety in routine clinical practice	Mimics everyday practice; improved patient retention	Variables not controlled; often no comparator (ie, placebo)

(G2)-infected and G3-infected patients, and 48 weeks is recommended for G1-infected patients.³

Regulatory approval for PEG-IFN alfa plus RBV combination therapy and support for guideline recommendations arose from 3 pivotal, phase 3, clinical registration trials that established the superiority of PEG-IFN alfa-based regimens over conventional IFN alfa-based regimens.⁶⁻⁸ In general, phase 3 trials are prospective, randomized, and controlled; hence, they are referred to as randomized controlled trials (RCTs) and are designed to establish the efficacy and safety of a new treatment modality. To that end, these trials are tightly controlled to limit patient variability and govern treatment regimens. The rigor of RCTs, however, is rarely attained in the community setting, leading many to question whether the results from phase 3 RCTs can be achieved in everyday clinical practice. Therefore, community-based clinical trials designed to examine the efficacy and safety of a treatment regimen in a real-world setting are important to confirm that the results of rigid phase 3 RCTs are generalizable and attainable and that they can be easily translated to routine clinical practice.

The goals and attributes of phase 3 RCTs and community-based trials are summarized in Table 1. These 2 trial types are distinguished by differences in study design, patient populations, access to resources, and other influential factors such as the timing of study conduct (ie, community-based trials are usually conducted after regulatory agency approval and marketing). Prospective, randomized, controlled, phase 3 trials are characterized by a strict a priori protocol with well-defined treatment durations and algorithms for dose modification or discontinuation. In contrast, community-based trials include a spectrum of treatment approaches; some have a very detailed, strict treatment protocol that is similar to a registration trial, whereas others leave many aspects of care to the discretion of the treating physician. Furthermore, community-based trials usually do not include a placebo arm. Phase 3 RCTs and community-based trials also differ with regard to patient selection. Phase 3 RCTs use strict inclusion/exclusion criteria, resulting in patient populations that represent only a small subset of those encountered in the community setting. These patient populations might not represent the overall population affected by the disease under study because the trial participants often have idealized characteristics. For example, patients with comorbid conditions or those receiving concomitant medications are often excluded from clinical registration trials because these attributes could complicate assessments or because of concerns about drug-drug interactions. In contrast, community-based trials usually include a larger spectrum of patients and, therefore, mimic clinical practice more closely.

Location and conduct also differ between phase 3 RCTs and community-based trials. Phase 3 RCTs are often conducted at academic/specialty centers, where patients have greater access to resources (eg, other specialists, laboratory assessments, experienced physicians, experienced research coordinators, close follow-up) than are available in the general community, although this distinction might be mitigated by the frequent involvement of academic centers in community trials and the level of experience and depth of the infrastructure available at some community sites. Compliance and treatment adherence are also usually closely monitored (eg, pill counts, medication diaries, direct observation of therapy, frequent visits by monitors from sponsors or clinical research organizations) in clinical registration trials, which might optimize these patient behaviors and ultimately influence treatment outcomes. Poor compliance/adherence and high dropout rates are more likely to be pitfalls of community-based trials. Last, participation in a clinical registration trial typically requires frequent travel to academic centers, which might cause a bias in favor of patients who are more compliant than average.

Herein we review the results of several community-based trials that evaluated the treatment of patients with PEG-IFN alfa plus RBV and compare the findings with those obtained in the large phase 3 RCTs.

Pegylated Interferon Alfa-2b Plus Ribavirin Registration Trial

The efficacy of PEG-IFN alfa-2b plus RBV therapy was established in a prospective, randomized, controlled, phase 3 clinical trial in patients with CHC that was completed in 2000.⁷ The trial included 1530 treatment-naïve patients with detectable HCV RNA levels, elevated alanine aminotransferase values, and liver biopsy findings consistent with CHC. Patients were randomly assigned to conventional IFN alfa-2b 3 million units (MU) 3 times weekly plus RBV 1000–1200 mg/day, PEG-IFN alfa-2b 1.5 μ g/kg/wk plus RBV 800 mg/day, or PEG-IFN alfa-2b 1.5 μ g/kg/wk for 4 weeks then 0.5 μ g/kg/wk plus RBV 1000–1200 mg/day. All regimens were administered for 48 weeks. Overall, 54% of patients receiving PEG-IFN alfa-2b (1.5 μ g/kg/wk) plus RBV 800 mg/day attained sustained virologic response (SVR) (Table 2). Logistic regression analysis found that the higher dose of PEG-IFN alfa-2b plus RBV was associated with higher SVR rates than the lower doses. Post hoc analysis revealed that PEG-IFN alfa-2b 1.5 μ g/kg/wk plus RBV >10.6 mg/kg, received by patients with body weight <75 kg, was associated with an SVR rate of 61%. As seen in other trials, several viral-related (eg, genotype, viral load) and host-related (eg, age, sex, histologic diagnosis)

Table 2. Trials Evaluating PEG-IFN Alfa-2b Plus RBV in the Treatment of CHC

Study	n ^a	Region	Study design	Patient characteristics	Regimen	SVR rate, %		
						Overall	G1	G2/3
Phase 3 trial								
Manns et al, ⁷ 2001	1530	Worldwide	Randomized, multicenter	Treatment naive; detectable HCV RNA; ALT >ULN; liver biopsy consistent with CHC	PEG-IFN alfa-2b 1.5 µg/kg QW + RBV 800 mg/day for 48 wk PEG-IFN alfa-2b 1.5 µg/kg QW for 4 wk, then 0.5 µg/kg for 44 wk + RBV 1000–1200 mg/day IFN alfa-2b 3 MU TIW + RBV 1000–1200 mg/day for 48 wk	54 47 47	42 34 33	82 80 79
Community-based trials								
WIN-R ⁹	4223	United States	Prospective, open-label, multicenter	Treatment naive; detectable HCV RNA; body weight <125 kg; age 18–70 y	PEG-IFN alfa-2b 1.5 µg/kg QW + RBV 800 mg/day	40.5	28.9	59.5
POWeR ^{14,15}	1800	Canada	Prospective, open-label, multicenter	Treatment-naive, CHC	PEG-IFN alfa-2b 1.5 µg/kg QW + WBD ^b RBV (800–1400 mg/day) PEG-IFN alfa-2b 1.5 µg/kg QW + WBD RBV 800–1200 mg/day for 24 (G2/3) or 48 (G1) wk	44.2 54.3	34.0 41.6	61.8 72–79
AWB ¹⁸	511	Germany	Open-label, multicenter	Treatment-naive or relapsed CHC	PEG-IFN alfa-2b 1.5 µg/kg QW + WBD RBV 800–1200 mg/day for 24 (G2/3) or 48 (G1) wk	66	53 ^c	76

QW, once weekly; TIW, 3 times weekly; ULN, upper limit of normal; WBD, weight-based dosing.

^aEvaluable patients included in efficacy analysis.

^b<65 kg, 800 mg; ≥65–85 kg, 1000 mg; >85–105 kg, 1200 mg; >105 kg, 1400 mg.

^cIncludes patients with G1, G4, G5, and G6 infection.

factors influenced response to treatment in this trial. For example, among patients in the high-dose PEG-IFN alfa-2b group, SVR was achieved in 42% of patients with HCV G1 infection versus 82% of those with G2 or G3.

Pegylated Interferon Alfa-2b Plus Ribavirin Community-Based Trials

Recently, several community-based trials have been conducted to establish whether the clinical efficacy and safety outcomes with PEG-IFN alfa-2b plus RBV therapy observed in the phase 3 RCT were achievable in general medical practice. These trials are summarized in Table 2 and are described in detail below.

Weight-Based Dosing of Peginterferon Alfa-2b Plus Ribavirin (WIN-R)

WIN-R was a prospective, randomized, multicenter, investigator-initiated, community-based, and academic-based study conducted in 5027 treatment-naive hepatitis C patients across 236 sites in the United States.⁹ The aim of the trial was to determine whether, when combined with PEG-IFN alfa-2b, weight-based dosing of RBV was more effective than fixed dosing of RBV. The chief impetus for the trial was the US Food and Drug Administration's initial approval of the 800-mg RBV dose for combination with PEG-IFN alfa-2b 1.5 µg/kg/wk, which was in contrast to the European approval of weight-based RBV dosing. This decision was based on the fact that 800

mg was the only RBV dose given in combination with this dose of PEG-IFN alfa-2b in patients who participated in the registration trial,⁷ even though logistic regression analysis demonstrated a positive relationship between SVR and RBV exposure (ie, milligrams of RBV per kilogram of body weight).

In WIN-R, patients were randomly assigned to receive PEG-IFN alfa-2b 1.5 µg/kg/wk plus RBV at a flat dose of 800 mg/day or at a weight-based dose of 800–1400 mg/day. In the latter arm, patients weighing less than 65 kg received 800 mg/day, patients weighing 65–85 kg received 1000 mg/day, patients weighing more than 85–105 kg received 1200 mg/day, and patients weighing more than 105 kg to less than 125 kg received 1400 mg/day. Initially, all patients were treated for 48 weeks. In 2001 shortly after the study began, the protocol was amended to offer randomization to 24 or 48 weeks' therapy for G2/3 patients. To maximize the number of G2/3 patients available for this randomization, enrollment of G2/3 patients was extended beyond the enrollment period of G1 patients for nearly 1 year, resulting in a higher proportion of patients (37%)⁹ with G2/3 than is characteristic of the US population (22%–24.8%).^{10,11}

In the protocol-defined primary efficacy analysis, SVR rates were significantly higher among patients receiving weight-based than those receiving flat-dose RBV (44.2% vs 40.5%; $P = .008$). This analysis included the 4223 evaluable patients weighing 65 kg or more who received different doses of RBV in each treatment arm (those weighing less than 65 kg received 800 mg

regardless of arm). Weight-based dosing proved superior to flat dosing in patients with HCV G1 infection (34.0% vs 28.9%; $P = .005$).⁹ Overall, SVR rates were consistent across weight groups for patients receiving weight-based dosing (42.0%–47.3%; $P = .973$), whereas SVR rates decreased with increased weight in the flat-dose group (43.8%–33.5%; $P = .001$).

For patients with HCV G2 or G3 infection, extending treatment duration from 24 to 48 weeks provided no additional benefit; SVR rates were 66.2% and 58.6%, respectively. More patients in the 48-week treatment group were prematurely discontinued from the study, which might explain the relatively lower SVR rate when compared with the 24-week treatment group. Overall, there was no significant difference in SVR rate among G2/3 patients who received flat-dose (59.5%) versus weight-based (61.8%; $P = .252$) RBV. However, SVR rates significantly decreased with increasing weight in the flat-dose group ($P = .034$) and were consistent across all weight categories in the weight-based group ($P = .356$).⁹

Overall, relapse rates were lower with weight-based dosing (15.3%) than with flat dosing (19.0%) and were highest for patients with G1 infection (23.0% vs 29.6%) and lowest for those with G2 (4.2% vs 5.9%) or G3 (10.6% vs 12.0%) infection. Adverse events reported in the WIN-R trial were consistent with those reported in clinical trials. Notably, the frequency of events (including serious adverse events) was similar between the weight-based and flat-dose groups, with the exception of more anemia (hemoglobin <10 g/dL) in the weight-based group (19.3% vs 12.5%). Furthermore, within the weight-based group including those who received the novel 1400-mg dose, there was no relationship between RBV dose and the frequency of adverse events, dose reductions for adverse events, serious adverse events, or hematologic abnormalities (including anemia).⁹

Data from subanalyses of the WIN-R study provided additional insight into the efficacy and safety of treatment in various subgroups. For example, one analysis confirmed differences in efficacy among ethnic groups. The impaired responsiveness of African Americans, suggested in several previous trials, was affirmed in the WIN-R study, which had the largest database of African Americans (nearly 400 patients) in a hepatitis C therapy trial. Of particular note was the finding of pronounced superiority of weight-based dosing of RBV in this group of patients; of 362 African American patients with HCV G1 who weighed ≥ 65 kg, SVR occurred in 21% of those receiving weight-based dosing but in only 10% of those receiving flat dosing ($P = .0006$).¹²

In summary, the WIN-R study demonstrated that SVR rates are equivalent across a wide spectrum of body weights when weight-based dosing of RBV and PEG-IFN alfa-2b are used. The study also found that weight-based dosing of RBV is superior to fixed dosing for patients with G1 and confirmed the equivalence of 24 and 48 weeks of therapy in G2/3 patients. In addition, the study suggested that weight-based dosing provides no overall benefit in patients with G2/3, although the trend toward lower efficacy of flat doses in heavier patients warrants further investigation. Because no increased risk for anemia was observed in patients receiving 1400 mg/day RBV, the investigators concluded that patients weighing more than 105 kg should receive this dose.

Of note, however, WIN-R, like all community-based trials, had some limitations. For example, the overall SVR rate reported for the flat-dose RBV group in WIN-R was lower than

that observed in the pivotal PEG-IFN alfa-2b trial (40.5% vs 54.0%, respectively).^{7,9}

Similarly, the 34% SVR rate in the WIN-R trial for G1 patients given weight-based RBV dosing was lower than the 40% SVR rate for G1 patients given the same regimen in the IDEAL study,¹³ a postmarketing US study conducted with the rigor of a registration trial. In the IDEAL trial, SVR was attained in 40% of patients receiving PEG-IFN alfa-2b 1.5 $\mu\text{g}/\text{kg}/\text{wk}$ plus RBV 800–1400 mg/day, in 38% of patients receiving PEG-IFN alfa-2b 1.0 $\mu\text{g}/\text{kg}/\text{wk}$ plus RBV 800–1400 mg/day, and in 41% of those receiving PEG-IFN alfa-2a 180 $\mu\text{g}/\text{wk}$ plus RBV 1000–1200 mg/day.¹³ The lower rates of SVR observed in the WIN-R trial compared with those in the pivotal and IDEAL trials might be attributed, in part, to the large number of patients lost to follow-up in WIN-R. For example, there were 329 patients (329/4223, 7.8%) across all genotypes who were responders at the end of treatment but who were categorized as nonresponders in the intent-to-treat analysis because of missing follow-up HCV RNA data.⁹ The pivotal trial included patients from Europe, Canada, Argentina, and the United States, whereas the WIN-R and IDEAL trials included only US patients; this might explain why SVR rates were lower in WIN-R and IDEAL than in the pivotal trial. In summary, results from WIN-R demonstrate the strengths and the limitations of investigator-initiated trials and underscore the importance of evaluating each trial within the context of its study design.

Pegetron Prospective Optimal Weight-Based Dosing Response Program (POWeR)

POWeR was a Canadian multicenter, open-label trial that included more than 1900 patients at 138 academic and community sites between 2002 and 2007.^{14–16} Patients did not conform to any prespecified inclusion/exclusion criteria and were treated at the discretion of individual physicians. Patients received PEG-IFN alfa-2b 1.5 $\mu\text{g}/\text{kg}/\text{wk}$ plus weight-based RBV 800–1200 mg/day for the recommended duration of 24 weeks for G2/3 patients and 48 weeks for G1 patients. RBV doses were 800 mg/day for patients weighing less than 64 kg, 1000 mg/day for those weighing 64 to less than 85 kg, and 1200 mg/day for those weighing 85 kg or more.¹⁶ The trial was primarily designed to determine the impact of body weight, HCV genotype, and fibrosis stage at baseline on treatment efficacy (SVR) in a real-life setting. The patient population included many patients with difficult-to-treat characteristics such as HCV G1 infection (60%), severe fibrosis or cirrhosis (40% among those who underwent liver biopsy), and high baseline viral load ($\geq 2 \times 10^6$ copies/mL or 600,000 IU/mL; 52%).¹⁴

In total, 1977 treatment-naïve patients initiated treatment; however, patients with undetectable HCV RNA at the end of treatment but no 6-month follow-up data, those with no treatment data, and those with HIV/HCV coinfection were excluded from the final analysis. Thus, 1800 patients had evaluable outcomes and were included in the prespecified per-protocol analysis.¹⁴ Patients who discontinued therapy for any reason (eg, adverse events, lack of response, personal reasons) were included in the analysis. In the per-protocol analysis, the overall SVR rate was 54.3%. SVR rates were 41.6%, 79.0%, and 72.0%, respectively, for patients with HCV G1, G2, and G3 infection, and relapse rates were higher for those with G1 infection than for those with G2 and G3 infection (17.2%, 7.6%, and 6.4%, respectively). In addition, SVR rates were higher in those with

minimal (METAVIR score, F2 or lower) fibrosis than in those with advanced (METAVIR scores, F3–F4) fibrosis/cirrhosis (60% vs 35%; $P = .001$) and in those with low ($\leq 600,000$ IU/mL) compared with high ($> 600,000$ IU/mL) viral load (57% vs 50%; $P = .009$).¹⁴ Furthermore, an analysis evaluating the effect of body weight on SVR rates showed no statistically significant difference in SVR rates across patient weight categories.¹⁵

SVR rates from the intent-to-treat analysis (excluding human immunodeficiency virus/HCV-coinfected patients [$n = 1950$]) were 50% overall, 39% in G1 patients, 73% in G2 patients, 65% in G3 patients, and 61% in other genotypes (P. Marotta, unpublished data, 2009).

In summary, the POWeR trial confirmed that in the community setting, therapy with weight-based PEG-IFN alfa-2b and weight-based RBV generates SVR rates comparable to those of phase 3 RCTs and is consistent across patient weight categories, including patients with HCV G1 infection.

Anwendungsbeobachtung (AWB): The German Experience

A German multicenter, open-label study evaluated the treatment of patients with PEG-IFN alfa-2b plus RBV in a real-life setting.^{17–20} This study was designed to obtain efficacy and safety data for treatment-naïve patients with CHC or those who experienced relapse to prior therapy. Patients were treated in hospitals and in medical practices, including practices that are members of the German Association of Gastroenterologists in Private Practice.¹⁹ Patients enrolled in the study received the European Agency for the Evaluation of Medicinal Products–approved weight-based dosing of PEG-IFN alfa-2b 1.5 $\mu\text{g}/\text{kg}/\text{wk}$ plus RBV (a dosage schedule of < 65 kg, 800 mg/day; 65–85 kg, 1000 mg/day; > 85 kg, 1200 mg/day was recommended) for 48 (G1/4/5/6 patients) or 24 (G2/3 patients) weeks. Ultimately, however, PEG-IFN alfa-2b and ribavirin doses used in AWB were at the discretion of the investigators, and at least 1 investigator chose to use 600 mg/day ribavirin for patients with low body weight.

To date, 4130 patients have been enrolled by 285 gastroenterologists in private practice or clinics.²⁰ Preliminary efficacy data, on the basis of 511 patients, revealed an overall SVR rate of 66% and a relapse rate of 17%.¹⁸ When stratified by genotype, SVR rates of 53% and 76%, respectively, were attained in patients with G1/4/5/6 and G2/3 infection.¹⁸ This analysis also found that the SVR rate was lower (56%) among patients who required PEG-IFN alfa-2b or RBV dose reductions than among those who did not (68%).¹⁸ Although preliminary, these results confirmed that treatment with PEG-IFN alfa-2b plus RBV leads to excellent SVR rates in a European community-based setting.

Pegylated-Interferon Alfa-2a Plus Ribavirin Community-Based Trials

Community-based trials evaluating the efficacy of PEG-IFN alfa-2a plus RBV combination therapy have reported virologic response rates similar to those observed in phase 3 trials.^{6,8} The overall SVR rate attained in the PEG-IFN alfa-2a/RBV registration trial was 56%, with SVR rates of 46% and 76%, respectively, for those with G1 or G2/3 HCV infection.⁶ SVR rates attained in community-based trials are summarized in Table 3 and described in detail below.

Canadian Pegasys Expanded Access Program

The Canadian Pegasys Expanded Access Program (EAP)^{21,22} was a prospective, multicenter, open-label, nonrandomized study in which patients received PEG-IFN alfa-2a 180 $\mu\text{g}/\text{wk}$ plus RBV (800 mg/day, then amended to 1000–1200 mg/day according to body weight). The study was designed and initiated before the optimal treatment regimens for G1 and G2/3 infection were established, and physicians could allocate patients to 24 or 48 weeks of treatment at their discretion. Consequently, some G2/3-infected patients were allocated to 48 weeks of treatment, but no G1-infected patients were allocated to 24 weeks of treatment.

Sixty-two percent of patients were infected with G1, and 34% had cirrhosis (F3–F4). Overall SVR rates were reported according to genotype and fibrosis stage, 41% for G1 patients without cirrhosis (F0–F2) and 34% for G1 patients with cirrhosis. SVR rates were higher in G2/3 patients without cirrhosis (72%–79%) than in those with cirrhosis (44%–66%), regardless of treatment duration.

A subanalysis of G1-infected patients revealed SVR rates of 45% and 54%, respectively, in the RBV 800 mg/day and 1000–1200 mg/day groups. Predictors of SVR in this study included the degree of RBV exposure during the first 12 weeks of therapy, body weight, baseline viral load, race, fibrosis stage, and age. It should be noted that the aforementioned SVR rates were from a per-protocol analysis, that the EAP program was conducted predominantly at academic sites, and that like the WIN-R trial, it had inclusion and exclusion criteria stricter than those of some other community-based trials.

The German Experience

Two PEG-IFN alfa-2a community-based trials have been conducted in Germany. The first was conducted in 2987 patients who were treated with PEG-IFN alfa-2a; most (96.2%) received treatment in combination with RBV.²³ Among the 738 patients for whom complete treatment data were available (a preliminary completers analysis), SVR was attained in 234 of 381 patients (61.4%) with HCV G1/4/5/6 and in 302 of 357 patients (84.6%) with HCV G2/3.²³ The second study, the German Open Safety Trial, was a phase 3 multicenter, open-label study of 317 patients in which allocation to the treatment groups was at the discretion of the investigator.²⁴ Treatment groups consisted of PEG-IFN alfa-2a plus ribavirin for either 24 or 48 weeks. SVR rates were 48.9% overall, 39.2% in G1 patients, and 65.7% in G2/3 patients. Most patients were treatment-naïve (85%), but 14% had previously experienced relapse.

The Hepatys Study

In addition, the French observational Hepatys study,²⁵ which consisted of 2101 patients who were treated with PEG-IFN alfa-2a plus RBV, reported an overall SVR rate of 57%. Most patients were treatment-naïve (70%) and infected with HCV G1, G4, or G5 (63%). Among treatment-naïve patients, SVR rates were 63% overall, 52% in G1 patients, 80% in G2 patients, and 74% in G3 patients. Multivariate analysis determined that age younger than 40, G2 or G3 infection, METAVIR fibrosis score lower than F2, and treatment-naïve status were independently associated with higher response rate. The authors concluded that these findings confirmed the efficacy of PEG-IFN alfa-2a plus RBV in the French clinical practice setting, which was comparable to that in the pivotal registration trial published by Fried et al.^{6,8}

Table 3. Trials Evaluating PEG-IFN Alfa-2a Plus RBV in the Treatment of CHC

Study	n ^a	Region	Study design	Patient characteristics	Regimen	SVR rate, %		
						Overall	G1	G2/3
Phase 3 trial Fried et al ⁶	1121	Worldwide	Randomized, multicenter	Treatment-naive; CHC; ≥ 2000 copies of HCV RNA/mL; ALT >ULN; liver biopsy consistent with CHC	PEG-IFN alfa-2a 180 μ g QW + RBV 1000–1200 mg/day for 48 wk	56	46	76
					PEG-IFN alfa-2a 180 μ g QW + daily placebo for 48 wk	29	21	45
					IFN alfa-2b 3 MU TIW + RBV 1000–1200 mg/day for 48 wk	44	36	61
Hadziyannis et al ⁸	1311	Worldwide	Randomized, double-blind, multicenter	Treatment-naive; CHC; >2000 copies of HCV RNA/mL; elevated ALT; liver biopsy results consistent with CHC	PEG-IFN alfa-2a 180 μ g QW + RBV 800 mg/d for 24 wk	—	29	84
					PEG-IFN alfa-2a 180 μ g QW + RBV 1000–1200 mg/d for 24 wk	—	42	81
					PEG-IFN alfa-2a 180 μ g QW + RBV 800 mg/d for 48 wk	—	41	79
					PEG-IFN alfa-2a 180 μ g QW + RBV 1000–1200 mg/d for 48 wk	—	52	80
Community-based trials Canadian Pegasys EAP ^{21,22}	508 ^d	Canada	Prospective, multicenter, open-label, nonrandomized	Treatment-naive; CHC; detectable HCV RNA; patients with METAVIR score F3–F4 must have had compensated liver disease	PEG-IFN alfa-2a 180 μ g/wk plus RBV (400 mg/day BID) for 48 wk	—	F0–2, 41; F3–4, 34	F0–2, 72; F3–4, 44
					PEG-IFN alfa-2a 180 μ g/wk plus RBV (400 mg/day BID) for 24 wk	—	—	F0–2, 79; F3–4, 66 ^e
					PEG-IFN alfa-2a 180 μ g/wk plus RBV (800 mg/day [n = 339], then amended to 1000–1200 mg/d [n = 552]) for 48 wk	—	800 mg, 45; 1000/1200 mg, 54	—
Germany ²³	2987	Germany	Prospective, multicenter	CHC patients treated with PEG-IFN alfa-2a	PEG-IFN alfa-2a (received by all patients) + RBV (received by 96.2% of patients) for 24–48 wk ^e	NR	61.4 ^b	84.6
Germany ²⁴	317	Germany	Phase 3, multicenter, open-label	CHC patients	PEG-IFN alfa-2a 180 μ g/wk plus RBV (400 mg/day BID) for 24 wk ^f	64.4	16.7	67.9
					PEG-IFN alfa-2a 180 μ g/wk plus RBV (400 mg/day BID) for 48 wk ^f	42.5	39.9	55.6
French Hepatys Study ²⁵	2101	France	Prospective, nationwide	CHC patients treated with PEG-IFN alfa-2a (70% were treatment-naive)	PEG-IFN alfa-2a plus RBV (doses/duration not given)	Overall, 57; treatment-naive, 63	Treatment-naive, G1 = 52	Treatment-naive, G2 = 80; G3 = 74

BID, twice a day; NR, not reported.

^aEvaluable patients included in efficacy analysis.

^bG1/4/5/6 infection.

^cAll treatment decisions, including PEG-IFN alfa-2a and RBV doses, were at the physician's discretion.

^dIntention-to-treat analysis.

^eP = NS vs 48 weeks of treatment.

^fAllocation to treatment group was at the discretion of the physician. PEG-IFN alfa-2a 180 μ g/wk plus 800 mg/d RBV in divided doses was recommended initially. Although weight-based RBV dosing for G1/4-infected patients was established during the study period, some physicians chose not to change the treatment regimen.

Pegylated-Interferon Alfa-2a and Pegylated-Interferon Alfa-2b in Real-World Italy

These observations are further supported by a retrospective study of 397 treatment-naive chronic hepatitis C patients from Italy who were treated with PEG-IFN alfa plus RBV.²⁶ Overall SVR rates attained in this population were similar to those observed in phase 3 trials: total population, 63.5%; G1 infection, 46.3%; G2/3 infection, 83.6%. In addition, the premature discontinuation rate (14.9%) was similar to that observed in phase 3 RCTs, but fewer dose reductions in PEG-IFN alfa, RBV, or both (26%) occurred. Most (78.6%) patients received PEG-IFN alfa-2b (the only PEG-IFN alfa available on the Italian market until August 2003).

Additional data are available from the PROBE study, an Italian prospective, observational, multicenter (N = 167) trial that evaluated the effectiveness of PEG-IFN alfa plus ribavirin in "real world" practice.²⁷ Patients were consecutively enrolled, including those older than 65 years and those with comorbidities (obesity, diabetes, psychiatric disorders, methadone use, thyroid disease, and markers of autoimmunity). Type and schedule/dosage of therapy were at the investigator's discretion. An interim analysis evaluated 2237 treatment-naive patients. SVR rates overall and for genotypes 1, 2, 3, and 4 were 50.7%, 34.0%, 73.0%, 59.3%, and 37.0%, respectively. SVR rates were lower in patients with F3/F4 liver disease (37.8%) or comorbidities (48.3%) but higher in those compliant ($\geq 80\%$) with therapy (68.1%). Suboptimal adherence to therapy and baseline characteristics might have influenced response rates; a large proportion of patients had G2 infection (30.8%, which reflects the epidemiology in Italy), advanced fibrosis (F3/F4; 24.9%), and obesity (50% had body mass index >25 kg/m²).

Discussion

Overall results from the US, Canadian, and European community-based trials suggest that treatment of CHC patients with PEG-IFN alfa plus RBV under real-life conditions is associated with SVR rates in the same range as those reported in the pivotal PEG-IFN alfa/RBV registration trials. Comparable SVR rates were obtained within the overall populations and in genotype-specific populations.

The goal of any clinical investigation is to determine the efficacy and safety of therapeutic interventions that could improve the lives of patients.²⁸⁻³⁰ To this end, phase 3 trials and community-based trials perform different but complementary roles. Phase 3 RCTs measure clinical efficacy and safety in a controlled setting for purposes of obtaining approval for a therapy, whereas community-based trials assess the efficacy and safety of treatments as they are actually used in everyday clinical practice. Community-based postmarketing trials are important because they represent the ultimate translation of research into clinical practice. They also provide unique insight into disease-management issues faced in the real-world setting. Because they more clearly represent the conditions observed by physicians in routine practice, findings from community-based trials can be generalized to the wider clinical population more readily and can enhance the capacity to formulate treatment guidelines.³¹ In addition to the CHC trials described here, trials from a variety of therapeutic areas such as hypertension, hypercholesterolemia, and dermatologic disorders have demonstrated that the efficacy and

safety results achieved in phase 3 RCTs can be duplicated in the community setting.³²⁻³⁴ Moreover, community-based trials provide the opportunity to address questions not resolved by pivotal trials, particularly when very large populations are required for adequate powering of the trial contemplated.

Community-based trials should maximize the use of available resources to make some provision for in-office monitoring, although it is unlikely to rival the depth and extent of monitoring that a clinical research organization provides for pivotal trials. The procurement of sufficient support for monitoring, database management, and statistical support yields substantial benefits and might appropriately be obtained from industry sources, even if the investigator is formally the sponsor of an investigator-initiated, community-based trial.

Results from community-based trials in patients with CHC have confirmed that the efficacy and safety attained with PEG-IFN alfa plus RBV regimens in real-world settings are consistent with those reported in phase 3 RCTs. In addition, data from community-based trials refine our understanding of how to optimize therapeutic regimens. Data from the WIN-R study demonstrate that weight-based RBV is superior to fixed-dose RBV and provide consistent SVR rates across body weight categories in a US population. Results from the Canadian POWeR trial and the EAP study demonstrate that excellent SVR rates can be attained in community practice among patient populations with large numbers of poor prognostic factors. Results from POWeR also suggest that as in the WIN-R trial, the likelihood of attaining SVR is equivalent across body weight categories with the use of weight-based dosing of both PEG-IFN alfa-2b and RBV. Data from the German and Italian PEG-IFN alfa-2a and -2b trials show encouraging community-based setting results. Collectively, the SVR rates observed in these trials suggest good treatment compliance among patients, despite the absence of factors known to increase adherence in clinical trials.

In conclusion, consistent results from community-based CHC trials are reassuring to physicians and patients. Such trials promote confidence that patients with CHC can be effectively treated in clinical practice and can attain SVR rates similar to those observed in phase 3 RCTs, ultimately diminishing barriers to treatment.

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