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The PROPHESYS Cohorts Evaluated Standard Treatment with Peginterferon Alfa/Ribavirin for Chronic Hepatitis C

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Abstract

Dual peginterferon/ribavirin therapy remains a viable option for patients with chronic hepatitis C, because of the high cost of Direct-acting Antiviral Agents (DAA). We assessed real-life practice and treatment outcomes in Hungarian treatment-naive HCV genotype 1-infected patients who received peginterferon alfa-2a/ ribavirin treatment.

Keywords: Hungary; Peginterferon alfa-2a/Ribavirin; Predictive value; PROPHESYS; Real-world; Virologic response

Introduction

By examining treatment patterns and outcomes in routine clinical practice, observational cohort studies have certain advantages over randomized clinical trials [1]. As such, they generally have a broader scope than that of randomized trials. Moreover, cohort studies enroll diverse populations rather than the homogenous, strictly selected study populations typical of randomized trials. Thus, the results of cohort studies indicate how well the results of randomized trials can be translated into meaningful outcomes in the "real world".

Methods

The study design and primary results of the prospective, international PROPHESYS cohorts are reported elsewhere [2]. Briefly, a total of 7,163 treatment-naive patients with HCV mono-infection from 19 countries who were treated with peginterferon alfa/ribavirin were enrolled into three cohorts (PROPHESYS 1, 2, or 3). Patients eligible for enrollment were HCV RNA-positive adults aged 18 years or older who had been prescribed peginterferon alfa/ribavirin in accordance with the local summary of product characteristics [2].

Data was captured on an electronic Case Report Form (eCRF). In addition to baseline factors and treatment outcomes, treating physicians recorded details of treatment such as the planned treatment regimen, the actual treatment regimen, and the reasons for modifying the treatment regimen.

Cumulative exposure to peginterferon alfa-2a and ribavirin was expressed as percentage of the planned dose received by a patient (i.e. 100 × actual cumulative dose/(dose × intended treatment duration recorded at the start of treatment). If for a patient the treatment duration was shorter than the intended treatment duration, the reason for premature discontinuation was recorded (e.g. adverse events, insufficient viral response, etc.)

SVR24 was defined as last HCV RNA < 50 IU/mL 24 weeks after EOT (≥ 140 days after the last dose), respectively.

Relapse was defined as serum HCV RNA ≥ 50 IU/mL during follow-up in a patient with an EOT response. Only patients with an EOT response (HCV < 50 IU/mL) and at least one post-treatment HCV RNA result were included in the calculation of the relapse rate. Positive Predictive Value (PPV) was defined as the probability that a patient with a specific on-treatment virologic response would achieve an SVR24. Associations between baseline factors and SVR24 were examined by Multiple Logistic Regression (MLR) analysis. All statistical tests are performed two-sided and a p-value of < 0.05 is considered statistically significant. However, all statistical tests are of exploratory nature and a significant difference should be interpreted cautiously.

Results

A total of 654 HCV genotype 1 patients from 32 sites in Hungary received at least one dose of peginterferon alfa-2a/ribavirin and were included in the analysis. Patients were enrolled, treated, and tested for their HCV RNA levels between June 2007 and March 2011.

Of 654 patients included in the analysis, a total of 235 individuals (35.9%) stopped treatment prematurely (Table 3). The most common reason for premature withdrawal from treatment was insufficient virologic response. Within the PROPHESYS database, a higher proportion of Hungarian than non-Hungarian patients withdrew prematurely due to insufficient virologic response (20.2% [132/654] vs 12.4% [447/3,593]) (Chi-Square test, p < 0.0001; unpublished data). Only five patients with an EOT response had missing follow-up results for assessment of SVR24. Adverse events or laboratory abnormalities that led to premature withdrawal from treatment with peginterferon included neutropenia (n = 6), flu-like symptoms (n = 4), thrombocytopenia (n = 4), depression (n = 2), and other events (n = 40). In addition, treatment with ribavirin was withdrawn prematurely in 14 patients because of anemia.

On-treatment prediction of SVR24: A total of 529 (80.9%) patients achieved at least a 2-log drop in HCV RNA level during the first 12 weeks of treatment (20.3%, 34.9%, and 25.7% achieved an

Treatment extension: Overall treatment was prolonged in a total of 122 of 651 (18.7%) patients who had a virologic response documented within the first 12 weeks (Table 4). Among these individuals, physicians cited efficacy-related reasons as the reason for treatment prolongation in 105 of 651 (16.1%) patients. In comparison, treatment was prolonged for efficacy-related reasons in 8.4% of corresponding patients (303/3,593) who were enrolled at non-Hungarian study sites within PROPHESYS (Chi-Square test, p < 0.0001; unpublished data).

Discussion

The relatively high SVR24 rates observed in this study may be attributed, in part at least, to a combination of high rates of treatment completion and follow-up (i.e. few patients were lost post-treatment) and the use of Response Guided Therapy (RGT). Other factors that may have contributed to this difference in SVR24 rates include the higher proportion of Caucasian patients and the lower proportion of patients with advanced fibrosis at Hungarian study sites. However, a considerably lower proportion of patients had a fibrosis assessment performed at Hungarian than non-Hungarian study sites, and the proportion of patients with low platelet counts, typical of patients with cirrhosis, was similar in these two populations. Thus, one must be cautious before concluding that the true prevalence of advanced fibrosis was lower in

patients enrolled at Hungarian sites.

Among Hungarian patients included in this analysis, 68% (444/654) completed at least 80% of the planned duration of treatment, among whom 87% received at least 80% of the planned ribavirin dose. Analyses of data from large randomized clinical trials have shown that exposure to at least 60% of the target dose of ribavirin is associated with higher SVR24 rates [4].

Adherence to national guidelines and the use of RGT may have contributed to the comparatively high SVR24 rates. Hungarian guidelines for the treatment of chronic hepatitis C recommend monitoring the virologic response at Weeks 4 and 12 and modifying the treatment regimen accordingly [3]. Among treatment-naive genotype 1 patients in PROPHESYS, the rate of treatment prolongation for efficacy-related reasons was approximately two-fold higher in Hungarian patients than in patients enrolled at non-Hungarian sites (16% vs 8%, $p < 0.0001$).

The results of this study are of practical value and can be used to inform treatment decisions with the approved HCV protease inhibitors, boceprevir and telaprevir, which became available and financed for a segment of Hungarian patients in 2013. Furthermore simeprevir will also be available from 2015. These protease inhibitors have the potential to significantly increase overall SVR rates and decrease the duration of treatment in treatment-naive patients with HCV genotype 1 infection [5,6]. However, protease inhibitors must be used in combination with peginterferon alfa/ribavirin, thus increasing the adverse event burden and the potential cost of treatment. This is particularly problematic in countries with limited resources for the treatment of chronic hepatitis C. If such countries adopt a policy to use protease inhibitors universally for patients with HCV genotype 1 infection, fewer patients might be treated overall.

Conclusion

In conclusion, this subanalysis from the large PROPHESYS database shows that comparatively high SVR24 rates were achieved with the combination of peginterferon alfa-2a/ribavirin in Hungarian patients with HCV genotype 1 infection.

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