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Genotype-specific predictors of early viral clearance following treatment with peginterferon alfa-2a (40KD) (PegIFNα-2a) plus ribavirin (RBV): multiple logistic regression analysis from the large multinational PROPHESYS cohorts

D. Nelson,[1] P Ferenci,[2] M. Bourlière,[3] M. Curescu,[4] T. Hassanein,[5] A. Horban,[6] G. Lengyel,[7] S. Pol,[8] M. Puoti,[9] GF. Silva,[10] GM. Dusheiko,[11] M. Schmitz,[12] F. Tatsch,[13] A. Mangia[14]

[1]University of Florida, Gainesville, FL, United States, [2]Medical University of Vienna, Vienna, Austria, [3]Hôpital Saint Joseph, Marseille, France, [4]University of Medicine and Pharmacy Timisoara, Timisoara, Romania, [5]University of California San Diego, San Diego, CA, United States, [6]Medical University Clinic of Infectious Diseases, Warsaw, Poland, [7]Semmelweis University, 2nd Dept. of Medicine, Budapest, Hungary, [8]Université Paris Descartes and Hôpital Cochin, Paris, France, [9]University of Brescia, Brescia, Italy, [10]Botucatu School of Medicine, Botucatu, Brazil, [11]Royal Free and University College School of Medicine, London, United Kingdom, [12]IST GmbH, Mannheim, Germany, [13]Roche, Basel, Switzerland, [14]Hospital Casa Sollievo della Sofferenza, Rotondo, Italy

INTRODUCTION

The combination of pegylated interferon plus ribavirin is the standard of care for the treatment of chronic hepatitis C (CHC).[1,2] Randomized controlled trials have shown that this combination can eradicate hepatitis C virus (HCV) in more than 50% of patients.[3–5]

Analyses of data from such trials provide insight into the variety of patient- and treatment-related factors that modify the probability of achieving a cure.[6–8] Randomized controlled trials, however, typically enroll a homogeneous group of patients. Data from 'real-world' cohort studies can provide valuable additional information regarding demographics of patients currently under treatment and factors predictive of responses in a broader, more representative patient population.

PROPHESYS comprises three separate, country-specific noninterventional cohort studies of patients receiving treatment their physician has prescribed for CHC. Each cohort is run according to country-specific requirements for the design and conduct of noninterventional studies, and treatment of patients whose data are collected should be prescribed in accordance with the local label.

PROPHESYS 1 follows only patients prescribed ribavirin (COPEGUS®) with peginterferon alfa-2a (40KD) (PEGASYS®) while PROPHESYS 2 and 3 include those prescribed ribavirin with either peginterferon alfa-2a (40KD) or peginterferon alfa-2b.

OBJECTIVE

- The objective of this interim analysis of PROPHESYS was to identify baseline predictors of viral clearance during the first 12 weeks of treatment with peginterferon alfa-2a (40KD) plus ribavirin.

METHODS

- In addition to requiring that patient treatment and records of disease management be in accordance with local labels and clinical practice, PROPHESYS data are collected from CHC patients who:
  - Are males or non-pregnant females, aged 18 years or older
  - Have no previous treatment with peginterferon and/or ribavirin
  - Are not co-infected with hepatitis B virus
  - Have compensated liver disease
  - PROPHESYS study design is presented in **Figure 1**.

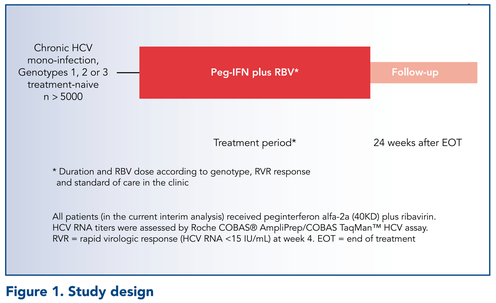

Figure 1. Study design

- Here, we present noncomparative results from patients prescribed only peginterferon alfa-2a (40KD) and ribavirin in PROPHESYS 1, 2, and 3.
- HCV mono-infected treatment-naive patients with HCV genotype 1, 2, or 3 infection who started therapy on or before October 31, 2009 and who had baseline HCV RNA results were included.
- Rapid virologic response (RVR) was defined as undetectable HCV RNA (<15 IU/mL) at week 4. Complete early virologic response (cEVR) was defined as undetectable HCV RNA (<15 IU/mL) at week 12 in patients without an RVR.
- A generalized additive model (GAM) and multiple logistic regression analysis (stepwise selection) were used to explore and identify baseline predictors associated with achievement of an RVR.

RESULTS

- In this interim analysis, a total of 5730 patients in PROPHESYS 1, 2, and 3 were prescribed peginterferon alfa-2a (40KD) plus ribavirin, the majority of whom (67%) had genotype 1 infection. The baseline characteristics of these patients are presented by HCV genotype in **Table 1**.

Table 1. Baseline characteristics of patients included in the interim analysis

	Genotype 1 n = 3867	Genotype 2 n = 825	Genotype 3 n = 1038
Male, n (%)	2044 (53)	427 (52)	689 (66.4)
Mean age, years	47	52	41
Race, n (%)			
White	3384 (87.5)	693 (84.0)	916 (88.2)
Black	199 (5.1)	30 (3.6)	11 (1.1)
Asian	46 (1.2)	8 (1.0)	31 (3.0)
Hispanic	119 (3.1)	42 (5.1)	28 (2.7)
Other	119 (3.1)	52 (6.3)	52 (5.0)
Mean weight, kg	75.2	75.7	75.9
Mean body mass index, kg/m²	26.2	27.0	25.6
ALT ratio, n (%)			
≤3	3062 (79.2)	686 (83.2)	736 (70.9)
>3	805 (20.8)	139 (16.8)	302 (29.1)
Cirrhotic (includes transition to cirrhosis), n (%)	962 (24.9)	105 (12.7)	146 (14.1)
Non-cirrhotic, n (%)	2004 (51.8)	387 (46.9)	527 (50.8)
Histology not assessed, n (%)	901 (23.3)	333 (40.4)	365 (35.2)
Mean HCV RNA, log_{10} IU/mL	6.0	5.9	5.8
Mean HCV RNA, IU/mL	3 291 485	3 220 624	2 322 783
Mean platelets, cells x10⁹ /L	214	210	213
Platelet count <140 cells x10⁹ /L, n (%)	547 (14.1)	116 (14.1)	126 (12.1)

- Virologic response rates at week 4 and 12 are presented by genotype in **Figure 2**. Patients infected with HCV genotype 1 had the lowest RVR rate (21%). Patients with HCV genotype 2 had the highest RVR rate (75%), so that considering also the cEVR rate (11%), 86% of them achieved virologic response by week 12.

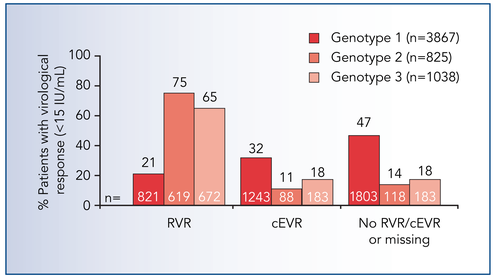

Figure 2. Virologic response rates (HCV RNA <15 IU/mL) by genotype at week 4 and 12 in patients prescribed peginterferon alfa-2a (40KD) in PROPHESYS 1, 2, and 3

- By GAM analysis in genotype 1 patients, baseline factors associated with RVR/cEVR showed generally monotone (e.g. age [**Figure 3a**] and body mass index [**Figure 3b**]) or non-monotone relationships, including one or more plateaus (e.g. HCV RNA [**Figure 3c**]) or reverse trends (e.g. alanine aminotransferase [ALT] ratio [**Figure 3d**]).

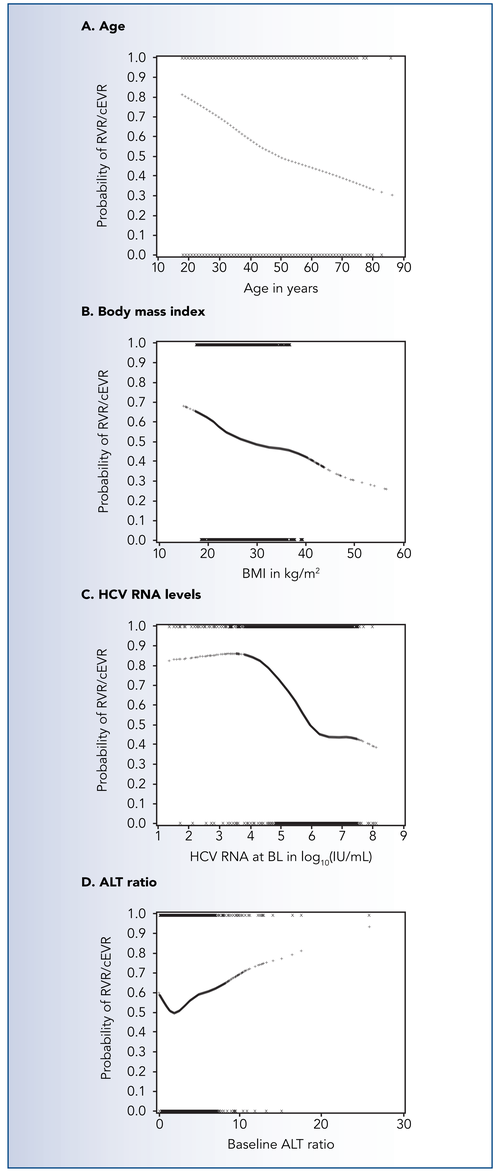

Figure 3. Relationship of baseline factors with RVR/cEVR in genotype 1 patients

- Multiple logistic regression analysis of potential baseline factors associated with an RVR at week 4 in genotype 1 patients showed that lower baseline HCV RNA level, absence of cirrhosis and histology not assessed, race (Asian race vs. White/Caucasian race and White/Caucasian race vs. Black race), higher platelet count and ALT ratio, male gender, younger age, and lower body weight were all positive predictors of RVR (all p<0.05) (**Figure 4a**).
- In genotype 2 patients, the only baseline factor associated with RVR was platelet count, while in genotype 3 patients, histology not assessed, lower HCV RNA and younger age were identified as positive predictors of RVR (**Figure 4b**).

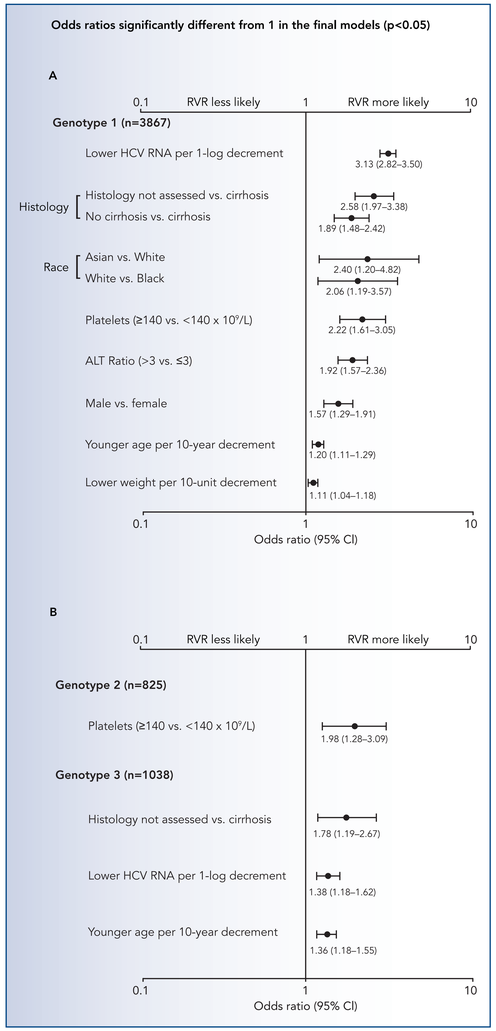

Figure 4. Significant baseline predictors of RVR in genotype 1 patients (panel a) and genotype 2 and 3 patients (panel b)

CONCLUSIONS

In this large cohort of patients from PROPHESYS, patient demographics differed markedly by HCV genotype, and rates of RVR and cEVR were similar to those reported in phase III clinical trials of peginterferon alfa-2a (40KD) plus ribavirin.[6,7]

There were also considerable variations in the baseline factors associated with RVR when patients were grouped by genotype, with only platelet count associated with RVR in genotype 2 patients.

Baseline factors strongly associated with viral clearance in this 'real-world' cohort are similar to those identified in previous randomized clinical trials.[9–10]

This interim analysis shows that clinicians should consider different factors when making treatment decisions for patients infected with different HCV genotypes, including patients most in need of direct-acting antivirals.

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