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An *a priori* prediction model of response to peginterferon plus ribavirin dual therapy in naïve patients with genotype 1 chronic hepatitis C

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ABSTRACT

Background: Aim was to select naïve patients with genotype 1 chronic hepatitis C having a high probability of response to Peg-interferon + ribavirin therapy.
Methods: In 1073 patients (derivation cohort), predictors of rapid and sustained virological response were identified by logistic analysis; regression coefficients were used to generate prediction models for sustained virological response. Probabilities at baseline and treatment week 4 were utilized to develop a decision rule to select patients with high likelihood of response. The model was then validated in 423 patients (validation cohort).
Results: In the derivation cohort, 257 achieved rapid virological response and 818 did not, with sustained virological response rates of 80.2% and 25.4%, respectively; interleukin-28B polymorphisms, fibrosis staging, gamma-glutamyl transferase, and viral load predicted sustained virological response. Assuming a <30% sustained virological response probability for not recommending Peg-interferon + ribavirin, 100 patients (25.6%) in the validation cohort were predicted *a priori* to fail this regimen. Assuming a ≥80% sustained virological response probability as a threshold to continue with Peg-interferon + ribavirin, 61 patients were predicted to obtain sustained virological response, and 55 of them (90.2%) eventually did.
Conclusions: This model uses easily determined variables for a personalized estimate of the probability of sustained virological response with Peg-interferon + ribavirin, allowing to identify patients who may benefit from conventional therapy.
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1. Introduction

For patients with hepatitis C virus genotype 1 (HCV-1) infection, triple therapy with peg-interferon and ribavirin (PEG/RBV) plus HCV NS3-NS4a protease inhibitors has boosted sustained virological response (SVR) to levels as high as 63–75% [1,2]. The arrival of novel therapies directed against specific viral targets holds promise of even greater success [3,4]. Eligibility for treatment will remain driven largely by efficacy, safety and affordability of antiviral therapies. Conventional dual therapy with PEG/RBV remains efficacious for about 40–50% of HCV-1 patients who have never been treated before [5,6]. Accordingly, the *a priori* estimation of the individual likelihood of response to PEG/RBV could effectively maximize treatment efficacy while containing health care costs. Indeed, this strategy may drive an individualized treatment algorithm.

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Patients who clear the virus after the initial 4 weeks of PEG/RBV therapy are the best candidates to obtain viral eradication [7]. By pooling data from several trials, we estimated that this condition may be achieved by 25–30% of naïve HCV-1 patients in Europe and in Australasia [8]. Several guidelines recommend for all previously untreated HCV-1 patients to commence therapy with a 4-week phase of PEG/RBV before the addition of a protease inhibitor [9–12]. Albeit this strategy would allow patients with rapid virological response (RVR) to obviate the use of a protease inhibitor [13] and could eventually be utilized to adjust treatment duration [5,14], it would expose naïve patients unlikely to obtain RVR to suboptimal therapy.

Some host and viral features at baseline that portend a low likelihood of obtaining SVR after PEG/RBV have been recognized [5,14–18]: the staging of liver fibrosis, serum gamma-glutamyl transferase (γGT) levels, HCV viral load, and the interleukin-28B polymorphisms (IL28B) have been concordantly recognized as impacting on the outcome of dual therapy. However, although useful, these predictors are only capable of identifying gross subclasses of patients. Indeed within each subclass, *i.e.* liver cirrhosis, some patients will and some others will not respond to PEG/RBV. What is currently lacking is a tool to assess the *a priori* probability of the therapeutic outcome before the patient actually undergoes PEG/RBV, in the same way as the MELD score estimates the probability of mortality for patients with end-stage liver disease [19].

We aimed to develop a prediction model capable of estimating probability of responding to dual therapy with PEG/RBV at presentation. The robustness of the model was validated in an independent cohort of naïve patients. Such a tool could assist physicians in counselling patients on the most appropriate antiviral therapy.

2. Materials and methods

2.1. Patients

This investigation refers to a retrospective analysis of a database of 1075 naïve HCV-1 patients with chronic hepatitis, who underwent PEG/RBV treatment at 15 Italian centres between 2005 and 2010. These patients were used as a model derivation cohort. Main characteristics of patients, as well as relevant inclusion and exclusion criteria, have been presented elsewhere [7]. Baseline features recorded included age, gender, serum levels of alanine-aminotransferase (ALT), and gamma-glutamyl transferase (γGT), blood platelet counts, HCV viraemia levels, genotypes of the IL28B locus, diabetes and the stage of liver fibrosis. The latter information was scored from 0 to 4, based on liver histology according to Metavir [20] or liver elastometry (Fibroscan) [21]. Patients with clinically evident cirrhosis, granted by concomitant laboratory abnormalities (such as platelet count <100,000 mL^{-1} and/or an APRI score >1.5) [22] and ultrasound evidence of portal hypertension (portal vein diameter >13 mm and spleen longitudinal diameter (>14 cm) [23] we scored as fibrosis stage 4.

In order to generalize the validity of the prediction model [24], an independent cohort of 423 naïve patients who received PEG/RBV treatment during the same time span was used as an external validation setting. These patients were recruited between 2003 and 2012 at 7 Italian centres who did not participate in the previous study [7].

2.2. Methods

Virological analyses and IL28B genotyping were conducted as previously reported [7]. Commercial assays were used to measure HCV RNA levels at local investigational sites, but real-time PCR based methods were used in all centres: levels below the lower limit of quantification at treatment week 4 or at week 24 of follow up off therapy were taken as indicative of RVR or SVR, respectively. All patients had given prior informed consent for use of data and serum for research purposes. The study was conducted in accordance with provisions of the Declaration of Helsinki and Good Clinical Practice Guidelines.

2.3. Statistical analysis

Continuous variables, *i.e.* age (in years), platelet counts ($\times 10^3$ cells/mL), HCV RNA levels (IU/mL), and serum ALT (expressed as times the upper normal limit) were summarized by median, first and third quartile because most of them showed a skew distribution which significantly departed from the normal density. All remaining variables were categorized as follows: diabetes (yes, no), γGT (normal, abnormal), fibrosis stage (F1, F2, F3, F4), HCV-1 subtype (1a, 1b), HBcAb status (positive, negative), genotype (1a, 1b) and described by absolute and relative frequencies. The genotype of the IL28B locus was given individually as CC, CT and TT. Associations between categorical variables were evaluated by χ^2-test; Fisher exact test was preferred in case of sparse tables. Continuous covariates were compared by *t*-test or Wilcoxon rank-sum test when a significant departure from normality was detected. Multivariate analysis was based on the logistic model [24]. The following covariates at baseline were considered as factors potentially affecting the probability of achieving RVR and SVR: age, gender, stage of liver fibrosis, ILB28 genotyping, HBcAb status, diabetes, γGT, platelet count, ALT, HCV viral load, and genotype. Variable selection was based on a non-automated backward selection, taking correlation structure among covariates and clinical interpretation of their effects into account. All numerical data were used as continuous variables in the multivariate analyses, except γGT that was recorded as normal *vs* abnormal levels. Since the distribution of HCV RNA levels was extremely skew, the $\log_{10}$ transformation of values was used. Of considered variables, the maximum percentage of missing data was 3% for ALT determination. No attempt was made to impute missing data, and incomplete observations were excluded from multivariable analysis. In the final logistic models only four patients had incomplete information on selected covariates. When a model to predict SVR was developed, in addition to baseline features, obtainment of RVR was also considered as an on-treatment predictor.

To evaluate the ability of the proposed models to predict RVR and SVR, receiver operating characteristic (ROC) curves were computed, and the area under the curve (*c*-statistic) reported. The Hosmer and Lemeshow test was performed to detect possible lack of fit of the final models to the observed data [25]. The confidence interval displacement diagnostic was used to measure the influence of individual observations on the regression estimates [26]. The change in deviance and in χ^2 statistic attributable to deleting the individual observation was considered as well. Poorly fitted observations were identified by the standardized deviance and Pearson residuals. All analyses were performed using SAS version 9.3.

3. Results

3.1. Model derivation cohort

The cohort included 414 (38.5%) subjects who obtained SVR and 661 (61.5%) who did not. Baseline characteristics in the two subgroups of patients are shown in Table 1. SVR patients were younger, had lower baseline viral load, more frequently had genotype CC of the IL28B polymorphism, and included fewer cirrhotics. In addition, they presented more frequently with normal γGT levels, and were less often diabetics. After treatment with PEG/RBV, 257

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