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High predictive value of early viral kinetics in retreatment with peginterferon and ribavirin of chronic hepatitis C patients non-responders to standard combination therapy☆

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***Background/Aims*: To evaluate the efficacy of peginterferon alfa-2b and ribavirin in unselected consecutive patients with chronic hepatitis C, treated outside of trials, who were relapsers or non-responders to interferon and ribavirin combination.**

***Methods*: One hundred and fifty-four patients were evaluated. There were 101 non-responders and 53 relapsers to standard combination therapy. Patients were retreated with peginterferon alfa-2b 1.5 μg/kg/wk plus ribavirin 1000–1200 mg/day during 48 weeks.**

***Results*: Forty-four patients (28.6%) achieved sustained virological response (SVR). Rapid (week 4) and early (week 12) virological response had high negative predictive values of SVR (94% and 97%, respectively); however positive predictive values were relatively low (52% and 49%, respectively). Relapsers had higher SVR rates (58.5%) than non-responders (13%) $p < 0.0001$. In non-responders, SVR raised to 50% in patients with genotype non-1 and mild or moderate fibrosis. In multivariate analysis, predictors of SVR were: relapse after interferon plus ribavirin combination, mild or moderate fibrosis, genotype non-1 and baseline viral load <2 million copies/ml.**

***Conclusions*: Relapsers to interferon plus ribavirin therapy, and non-responders with genotype non-1 and mild or moderate fibrosis, achieved a relatively high SVR rate following retreatment with peginterferon plus ribavirin. Early viral kinetics had a high negative predictive value of SVR.**

***Keywords*: Predictive factors; Genotype 1; Early virological response; Cirrhosis; Side effects**

1. Introduction

The current optimal therapy for patients with chronic hepatitis C (CHC) is the combination of peginterferon (PEG-IFN) and ribavirin (RBV) [1]. Data from four large, randomized controlled trials have shown that PEG-IFN alfa-2a or PEG-IFN alfa-2b, with or without ribavirin, achieved significantly higher sustained virological response (SVR) rates in comparison with standard IFN, with or without RBV in naïve patients [2–5]. As the treatment of CHC has improved, the question

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Abbreviations: CHC, chronic hepatitis C; PEG-IFN, peginterferon; RBV, ribavirin; RVR, rapid virological response; EVR, early virological response; EOT, end of treatment; SVR, sustained virological response; BMI, body mass index.

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has arisen as to whether patients who failed previous treatment regimens should be retreated. A large randomized controlled trial has shown that retreatment with IFN and RBV of relapsers to IFN monotherapy allowed to achieve a 49% SVR rate [6]. Several studies have established that a small but significant increase in SVR resulted when non-responders to IFN monotherapy were retreated with IFN and RBV [7–9]. Given the superior results observed with PEG-IFN and RBV in naïve population, it is now appropriate to consider whether retreating previous relapsers and non-responders to standard IFN and RBV will be more effective with this strategy. Recent trials have shown that PEG-IFN and RBV combination was effective in a substantial number of these patients [10–13]. Of note, these studies included selected patients and different populations of non-responders (IFN monotherapy, IFN plus RBV) and did not systematically assess the predictive value of early viral kinetics. This study describes the effects of retreatment, outside of trials, with PEG-IFN alfa-2b and RBV, and the factors associated with SVR, in a population of unselected consecutive patients who have failed to achieve SVR with standard combination therapy. Influence of early viral kinetics on SVR has been particularly assessed.

2. Patients and methods

2.1. Patient population

Patients, consecutively included in the study, were relapsers or non-responders to standard IFN+RBV. Non-response was defined as having detectable HCV RNA in serum at the end of treatment, with a minimal duration of 12 weeks. Relapse was defined as recurrence of viremia after undetectable HCV RNA in serum at the end of treatment.

2.2. Study design

Patients were treated with PEG-IFN alfa-2b (Pegintron®, Schering-Plough Corp.) at a dose of 1.5 μg/kg/week and RBV (Rebetol®, Schering-Plough Corp.) either 1000 mg/day (body weight $\leqslant$75 kg) or 1200 mg/day (body weight >75 kg) for a duration of 48 weeks. While on therapy, patients were evaluated at monthly intervals to monitor side effects and changes in complete blood count and serum liver chemistries.

2.3. Definitions of response

Rapid virological response (RVR) and early virological response (EVR) were defined as $\geqslant$2 log decline in HCV RNA level from pre-treatment baseline or undetectable HCV RNA in serum at treatment week 4 and 12, respectively. End of treatment (EOT) virological response was defined as undetectable HCV RNA in serum at treatment week 48. SVR was defined as undetectable serum HCV RNA at week 72, 24 weeks after treatment was discontinued.

2.4. Dose reduction

The dose of PEG-IFN alfa-2b was reduced stepwise from 1.5 μg/kg/week to 1–0.75 and then to 0.5 μg/kg/week if neutrophil count declined to less than 750 mm^{-3} or platelet count to less than 40.000 mm^{-3}. RBV was reduced to 600 mg/day if hemoglobin level declined to 10 g/dl. Further dose reductions or discontinuation of these drugs was performed for ongoing hematologic adverse effects or severe flu-like or neuropsychiatric symptoms.

2.5. Liver histology

All patients had a liver biopsy performed within 12 months before initiation of retreatment. Necroinflammation activity was graded and fibrosis was staged according to the Metavir score [14,15]. Steatosis was classified as absent, mild (<30%), moderate (30–50%) or severe (>50%).

2.6. Assessment of HCV RNA load, viral kinetics and genotypes

Serum HCV RNA level was quantified at treatment starting, and then at weeks 4, 8, 12, 48 and 72, using the Bayer VERSANT® HCV RNA 3.0 Assay (bDNA, sensitivity of 3200 copies/ml). HCV RNA was qualitatively detected using the Bayer transcription-mediated amplification (TMA) assay (sensitivity 50 copies/ml) when it was undetectable using bDNA. HCV genotype was determined with the INNO-LiPA HCV II kit (Bayer Diagnostics, Emeryville, CA).

2.7. Statistical analyses

Predictors of virological response were assessed with χ^2-test and Fisher exact test for categorical variables and with *t*-test and Mann–Whitney test for continuous variables. Predictors, significantly related to response in univariate analyses, were entered in a multivariate logistic regression to assess their relative importance. Analyses were performed using the SPSS version 12.0.

3. Results

3.1. Patient population

The study population consisted of 154 consecutive patients, followed up in the hepatology departments of Beaujon hospital (Clichy) and Saint Joseph hospital (Marseille) in France between January 2001 and December 2003. Clinical characteristics of these patients are summarized in Table 1. There were 101 non-responders and 53 relapsers to standard IFN+RBV. Mean age of patients was 49.6 years; 64.9% were male. Mean BMI was 26.1 kg/m^2. Intravenous drug use and blood transfusion were the principal mode of infection with an estimated duration of infection of 23.8 years. Serum ALT values averaged 2.7 times the upper limit of the normal range. Mean baseline viral load was 10 million copies/ml and 64% had an HCV RNA level >2 million copies/ml. Seventy-one percent were infected with genotype 1. Steatosis was absent ($n = 44$, 28.6%), mild ($n = 70$, 45.4%), and moderate or severe ($n = 40$, 26%). Necroinflammation was mild ($n = 53$, 34.4%), moderate ($n = 87$, 56.5%) and severe ($n = 14$, 9.1%). Fibrosis was mild ($n = 27$, 17.5%), moderate ($n = 55$, 35.7%), bridging ($n = 33$, 21.4%), and 39 patients (25.3%) had cirrhosis.