Research Article

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Hyporesponsiveness to PegIFNα2B plus ribavirin in patients with hepatitis C-related advanced fibrosis

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Background & Aims: The success of pegylated-interferon (PegIFN)/ribavirin (Rbv) therapy of chronic hepatitis C is compromised by liver fibrosis. Whether fibrosis equally affects the two PegIFNα-based therapies is unknown. To assess the response to the two PegIFN regimens in patients with different degree of liver fibrosis.

Methods: A sub-analysis of the MIST study: 431 consecutive naïve patients randomly assigned, based on HCV genotype, to receive either (A) PegIFNα2a 180 μg/wk plus daily Rbv 800–1200 mg or (B) PegIFNα2b 1.5 μg/kg/week plus daily Rbv 800–1200 mg, were stratified according to Ishak staging (S) into mild (S0–S2) or moderate (S3, S4) fibrosis and cirrhosis (S5, S6).

Results: In A the sustained virological response (SVR) rates were not significantly influenced by fibrosis stage (71% in S0–S2, 66% in S3, S4, 53% in S5, S6, $p = 0.12$), compared to B where the SVR rates differed according to fibrosis stage (65%, 46%, and 38%, $p = 0.004$, respectively). This was even more so in HCV-1/4 patients treated with PegIFNα2b where the SVR rates were twice as many in S0–S2 *vs.* S $\geqslant$3 (44% *vs.* 22%, $p = 0.02$), while in A the SVR rates were similar between the two fibrosis subgroups (S0–S2: 47% *vs.* S $\geqslant$3: 48%, $p = 0.8$). By logistic regression analysis genotype 1/4 and lack of rapid virological response were independent predictors of treatment failure in both treatment groups, while S $\geqslant$3 fibrosis was associated to PegIFNα2b treatment failure, only (OR 2.83, 95% CI 1.4–5.68, $p = 0.004$).

Conclusions: Liver fibrosis was an independent moderator of treatment outcome in patients receiving PegIFNα2b, not in those receiving PegIFNα2a.

Keywords: Hepatitis C virus; Liver fibrosis; Pegylated interferon; Ribavirin; Sustained virological response.

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Abbreviations: HCV, hepatitis C virus; PegIFN, pegylated-interferon; Rbv, ribavirin; Peg, polyethylene glycol; SVR, sustained virological response; RVR, rapid virological response; cEVR, complete early virological response; ETR, end of treatment response; S, Ishak fibrosis score; ITT, intention-to-treat.

Introduction

Infection with the hepatitis C virus (HCV) is a major cause of morbidity and anticipated liver-related mortality worldwide [1] and pegylated-interferon (PegIFN)/ribavirin (Rbv) is the only therapeutic approach to prevent these complications [2–4]. While liver fibrosis is of paramount importance in determining the risk of anticipated liver related death, unfortunately it represents one of the strongest independent moderators of treatment outcome to IFN based therapies [5–7]. As a consequence of this paradox, the success of treatment has long been dichotomized according to the presence or absence of advanced liver fibrosis in patients with chronic hepatitis C, even though the exact mechanism by which fibrosis conflicts with the antiviral effects of PegIFN and Rbv remains elusive. Indeed, the negative role of liver fibrosis could reflect the anatomical subversion of the liver architecture, which theoretically prevents optimal interaction between IFN and target liver cells as well as a long lasting duration of HCV infection in these patients. Moreover, the defective adherence to the optimal schedule of treatment due to cytopenia remains a challenge of IFN based therapy of HCV patients with advanced fibrosis, since it increases the chances of hypo-responsiveness [8]. In the light of these interactions between therapy of HCV and advanced liver fibrosis, we asked ourselves whether hepatic fibrosis affects the clinical activity of the two available PegIFN regimens used to treat HCV. Indeed, PegIFNalfa2a and PegIFNalfa2b, while sharing the same mechanisms of action, are markedly different in terms of pharmacokinetic and pharmacodynamic properties [9–14], which might relate to their clinical activity. The two drugs, in fact are characterized by significant differences in the pegylation process of the native IFN molecule that ultimately affect the volume of distribution, the serum half life and the *in vitro* antiviral activity of the two compounds. As a direct consequence of the different volume of distribution, the two drugs concentrate differently into the liver, a feature that, in theory, could translate into a different therapeutic activity of the two PegIFNs in the presence of advanced fibrosis. A sub-analysis of the MIST study [15] allowed us to compare the effectiveness of the two PegIFNα regimens according to the extent of liver fibrosis, histologically evaluated at the time of enrolment into the study.

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Materials and methods

Aim

This is a sub-analysis of the MIST study [15] that was originally designed to compare safety and effectiveness of PegIFNα2a and PegIFNα2b therapy associated with Rbv. In the present study, we assessed the outcome of PegIFN therapy according to the stage of liver fibrosis classified by the Ishak score system in liver biopsies, performed 2–20 months (median ± standard deviation: 12 ± 6) before the start of therapy.

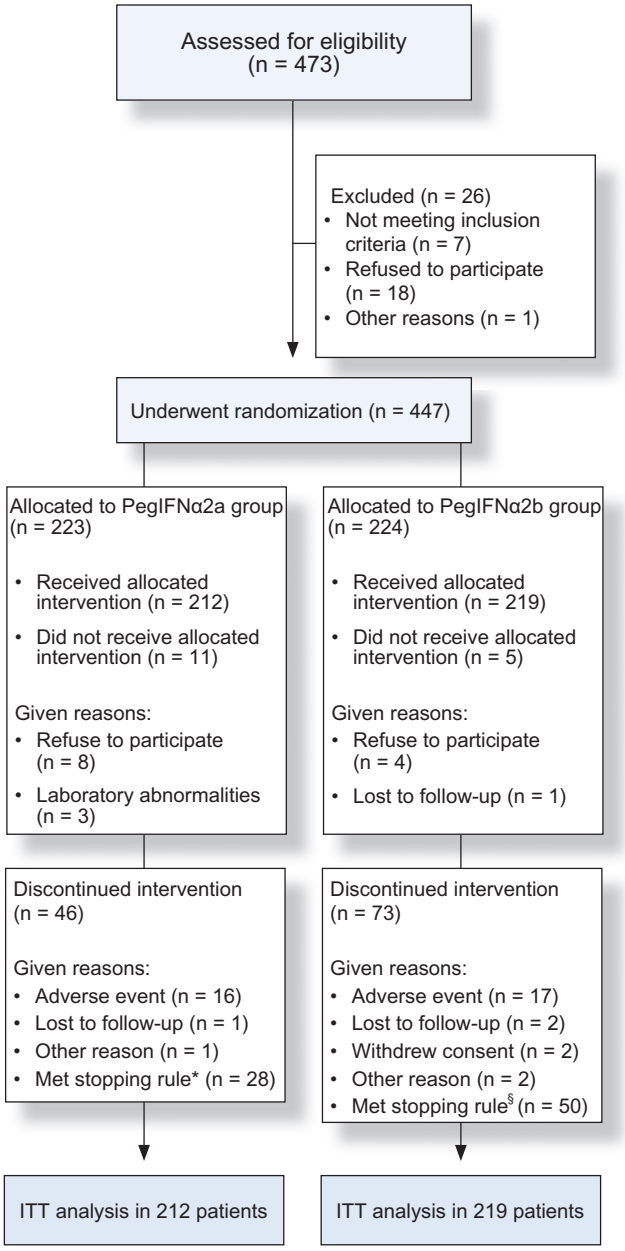

Fig. 1. Flow chart of the MIST study. Patients allocated to PegIFNα2a group: *19 patients met the week 12 stopping rule, 7 patients met the week 24 stopping rule and 2 patients had a virological breaktrough. Patients allocated to PegIFNα2b group: §32 patients met the week 12 stopping rule; 15 patients met the week 24 stopping rule and 3 patients had a virological breaktrough. ITT (intention-to-treat) analysis.

Patients

Patients enroled into the MIST study were randomized by a computer-generated allocation list stratified by HCV genotype, to receive a combination of PegIFNα2a (Pegasys, Roche, Basel Switzerland) 180 μg/week plus daily Rbv (Rebetol, Schering Plough corp, Kenilworth New Jersey USA) 800–1200 mg (A) or PegIFNα2b (PegIntron, Schering Plough corp) 1.5 μg/kg/week plus daily Rbv 800–1200 mg (B), for a standard duration based on HCV genotype. Patients with HCV-1 and HCV-4 were treated for 48 weeks: PegIFNα2a was associated with Rbv 1000–1200 mg day (<75 kg, ⩾75 kg); PegIFNα2b with Rbv 800 mg for patients of less than 65 kg body weight, 1000 mg for 65–85 kg and 1200 mg for ⩾85 kg. HCV-2 and HCV-3 patients were treated for 24 weeks: PegIFNα2a was associated with Rbv 800 mg day; PegIFNα2b with Rbv 800 mg for patients of less than 65 kg body weight, 1000 mg for 65–85 kg and 1200 mg for ⩾85 kg.

Measurements

Serum HCV-RNA was quantified by Versant HCV-RNA 3.0 assay (bDNA 3.0, Bayer Corporation, Emeryville, CA), with a sensitivity limit of 615 IU/ml and a dynamic range from 615 to 7700,000 IU/ml. Serum HCV-RNA was assessed by qualitative RT-PCR assay (COBAS Amplicor HCV test version 2.0, Roche Diagnostics) with a detection limit of 50 IU/ml, during treatment at weeks 4, 12, 24, and 48, and after therapy at weeks 4, 12, 24. HCV was genotyped by Line Probe Assay (INNO-LIPA HCV 2, Innogenetics, Zwijndrecht, Belgium).

Assessment of efficacy was SVR, defined as undetectable HCV-RNA by RT-PCR at week 24 of post-treatment follow up. Clearance of serum HCV-RNA by RT-PCR was assessed at week 4 (rapid virological response, RVR), at week 12 (complete early virological response, cEVR), at week 24, and at week 48 of treatment (end of treatment response, ETR). Patients with an ETR who tested HCV-RNA positive during follow-up were classified as relapsers. Patients who had a virological breakthrough were considered as non-responders. Therapy was discontinued in HCV-1 and HCV-4 patients if quantitative HCV-RNA testing at week 12 dropped by less than 2 log compared to baseline values (week 12 stopping rule), and at week 24 if HCV-RNA was still detectable in those patients in whom HCV-RNA dropped >2 log at week 12 (week 24 stopping rule).

All liver biopsies were performed with a 16 gauge Tru-Cut needle (Uro-Cut 16G, TSK, Tokyo, Japan) and read by a single pathologist (MFD), who was unaware of patient's identity and treatment regimen. The severity of hepatic inflammation was evaluated by the Ishak score [16] in separate reports for grading and staging. Patients were stratified according to the Ishak fibrosis score (S) on the baseline liver biopsy into mild (S0–S2) or moderate (S3, S4) fibrosis, and cirrhosis (S5, S6).

Statistical analysis

Comparisons between groups were made by using the Mann–Whitney *U* test or the Student *t* test for continuous variables and the χ^2 or Fisher exact probability test for categorical data. Intention-to-treat (ITT) analysis included all the 431 patients enroled: 212 of whom were treated with PegIFNα2a and 219 with PegIFNα2b (Fig 1). A probability value of p <0.05 was considered statistically significant. Logistic regression analysis was performed to identify variables associated with PegIFN/Rbv treatment failure. All variables with statistical significance at the univariate analysis were included in the final model and odds ratios (OR) and corresponding 95% confidence interval (95% CI) were computed. Calculations were done with Stata 10.0 statistical package (Stata 1944–2007, College Station, TX, USA).

Results

The clinical and demographic features of the two treatment groups stratified by fibrosis stage are shown in Table 1A and B. In both groups patients with S ⩾3 were more often male, older and had higher body mass index and serum ALT values than patients with S <3. The same was true for HCV-1, 4 patients (Supplementary Table 1A and B), while in HCV-2,3 patients, a similar prevalence of male gender was seen in S ⩾3 compared to S <3 patients (Supplementary Table 1C and D). Overall 10% (41/431) patients had to discontinue therapy for non virological reasons. Treatment discontinuation was not influenced by fibrosis stage being 9% (20/213) for S0–S2, 8% (11/136) for S3, S4