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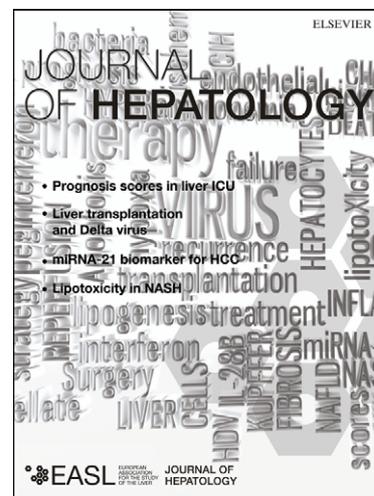
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**Improved Inflammatory Activity With Peginterferon Alfa-2b Maintenance Therapy in
Non-cirrhotic Prior Nonresponders: a Randomized Study**

Thierry Poynard,¹ Jordi Bruix,² Eugene R. Schiff,³ Moises Diago,⁴ Thomas Berg,⁵ Ricardo Moreno-Otero,⁶ Andre C. Lyra,⁷ Flair Carrilho,⁸ Louis H. Griffel,^{9*} Navdeep Boparai,^{9*} Ruiyun Jiang,⁹ Margaret Burroughs,⁹ Clifford A. Brass,^{9*} and Janice K. Albrecht^{9*}

¹Service d'Hepato-Gastroenterologie, APHP-UPMC Paris Liver Center, Paris, France;

²Centro de Investigación Biomédica en Red de Enfermedades Hepaticas y Digestivas, Liver Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain; ³Center for Liver Disease, University of Miami Miller School of Medicine, Miami, Florida, U.S.A.; ⁴Hospital General Universitario de Valencia, Valencia, Spain; ⁵Klinik und Poliklinik für Gastroenterologie & Rheumatologie, Sektion Hepatologie, Universitätsklinikum Leipzig, Leipzig, Germany;

⁶Hospital Universitario de la Princesa (IIS-IP) and Centro de Investigación Biomédica en Red de Enfermedades Hepaticas y Digestivas (Instituto de Salud Carlos III), Madrid, Spain;

⁷Hospital Sao Rafael and Federal University of Bahia, Salvador, Brazil; ⁸Gastroenterology, University of Sao Paulo School of Medicine, Sao Paulo, Brazil; ⁹Schering-Plough Corporation, now Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

*Former employee of Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA

Corresponding Author

Thierry Poynard, MD, PhD

Hôpital La Pitié Salpêtrière

Service d'Hépatologie

47-83 Boulevard de l'Hôpital

75651 Paris

CEDEX 13 France

Phone: 011-33-142-16-10-02;

Fax: 011-33-142-16-14-25;

E-mail: tpoynard@teaser.fr

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List of Abbreviations

CHC	chronic hepatitis C
PEG-IFN	peginterferon
SVR	sustained virologic response
HCC	hepatocellular carcinoma
MFS	METAVIR fibrosis score
HCV	hepatitis C virus
SAE	serious adverse event
GGT	gamma glutamyl transpeptidase
ALT	alanine aminotransferase

AE	adverse event
ULN	upper limit of normal

Conflict of Interest

T Poynard is on a speakers bureau for Merck Sharp & Dohme Corp. and has stock ownership or equity in BioPredictive. J Bruix has been a consultant for Bayer, Biocompatible, BMS, Glaxo, Kowa, Novartis, ArQule; has advisory arrangements with Bayer, Biocompatible, BMS; is on a speakers bureau for Bayer; and has received research and unrestricted grants from Bayer. ER Schiff has been a consultant for Gilead and Merck; has advisory arrangements with Bristol-Myers-Squibb, Gilead, and Vertex; and has received research grants from Abbott, Anadys, BMS, Gilead, Merck, Medtronic, Novartis, Orasure, Roche, Vertex, and Pharmasset. M Diago has nothing to disclose. T Berg is on a speakers bureau for Merck Sharp & Dohme Corp./Schering Plough. R Moreno-Otero has nothing to disclose. AC Lyra is an investigator for the study. F Carrilho has nothing to disclose. LH Griffel has stock ownership in and is a former employee of Merck Sharp & Dohme Corp. N Boparai is a former employee of Merck Sharp & Dohme Corp. R Jiang is an employee of Merck Sharp & Dohme Corp. M Burroughs has stock ownership in and is an employee of Merck Sharp & Dohme Corp. CA Brass has stock ownership in and is a former employee of Merck Sharp & Dohme Corp. JK Albrecht is a former employee of Merck Sharp & Dohme Corp.

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Abstract [250 limit; currently 250]

Background and Aims: Therapeutic options for patients failing hepatitis C retreatment are limited. EPIC³ included a prospective trial assessing long-term peginterferon alfa-2b (PEG-IFN alfa-2b) maintenance therapy in patients with METAVIR fibrosis scores (MFS) of F2 or F3 who previously failed hepatitis C retreatment. **Methods:** Patients with F2/F3 MFS who failed retreatment were randomized to PEG-IFN alfa-2b (0.5 µg/kg/week, n=270) or observation (n=270) for 36 months. Blinded liver biopsies obtained before retreatment and after maintenance therapy were evaluated using MFS and activity scores, and confirmatory testing was performed using FibroTest and ActiTest. **Results:** In total, 348 patients had paired biopsies: 192 patients had missing post-treatment biopsies and were considered as having no change in fibrosis/activity scores. In total, 16% of patients receiving PEG-IFN alfa-2b and 11% of observation patients had improvement in MFS ($p=0.32$). More PEG-IFN alfa-2b than observation patients had improvement in activity score (20% vs 9%; $p<0.001$). Among patients treated for >2.5 years, improvement in MFS or activity score was more common with PEG-IFN alfa-2b than observation (21% vs 14%, $p=0.08$ and 26% vs 10%, $p<0.001$). FibroTest and ActiTest evaluations indicated significant benefit associated with PEG-IFN alfa-2b in terms of reduced fibrosis progression and improved activity score. The safety profile of PEG-IFN alfa-2b was similar to previous studies. **Conclusions:** PEG-IFN alfa-2b did not significantly improve MFS estimated by biopsy compared with observation; however, activity scores were significantly improved and MFS trended toward increased improvement with treatment durations >2.5 years. Both FibroTest and ActiTest were significantly improved during maintenance therapy.

Keywords: Fibrosis; biomarkers; hepatitis C; liver; FibroTest

Introduction

Advancing liver disease is one of the most widely recognized factors affecting treatment outcomes for patients with chronic hepatitis C (CHC). Treatment of hepatitis C with peginterferon (PEG-IFN) plus ribavirin is contraindicated in patients with decompensated cirrhosis, and rates of sustained virologic response (SVR) are typically low in those with bridging fibrosis or compensated cirrhosis. Thus, many patients with advanced liver disease fail initial treatment and become candidates for retreatment. The Evaluation of PegIntron in Control of Hepatitis C Cirrhosis (EPIC³) study was a large, prospective, multiphase clinical program that evaluated the retreatment of patients with moderate to severe fibrosis/cirrhosis using PEG-IFN alfa-2b plus ribavirin [1, 2]. In this study, retreatment of patients with CHC infection with PEG-IFN alfa-2b plus ribavirin resulted in SVR rates of 21%, 16%, and 10% in genotype 1 patients with METAVIR F2, F3, and F4 disease, respectively [1].

Low rates of SVR among patients who fail repeated courses of PEG-IFN alfa plus ribavirin have led to the study of maintenance therapy as an approach to slow the histologic advancement of liver disease and delay the development of end-stage liver disease and hepatocellular carcinoma (HCC) [2-4]. Early studies suggest that interferon-based antiviral therapy may have a beneficial effect on liver fibrosis even in the absence of SVR, with as many as 19% of non-responders showing an improvement in fibrosis stage and an additional 62% experiencing stabilization of fibrosis [5]. However, despite these promising observations, results of 3 large studies indicate that long-term low-dose PEG-IFN alfa does not delay development of HCC in patients with cirrhosis related to hepatitis C virus infection [2-4].

Here we describe the patients from EPIC³ with METAVIR fibrosis scores (MFS) of F2 or F3 who failed retreatment with PEG-IFN alfa-2b plus ribavirin and enrolled in the maintenance study to determine whether low-dose PEG-IFN alfa-2b (0.5 µg/kg/week) provides histologic benefit.

Methods

Patients

Adult patients with CHC infection and biopsy-confirmed moderate to severe fibrosis (MFS, F2-F4) who failed at least 12 weeks of combination therapy with interferon (pegylated or non-pegylated) plus ribavirin were eligible for enrollment into the EPIC³ program. Detailed inclusion and exclusion criteria have been described previously [1].

In the EPIC³ program, patients were initially retreated with PEG-IFN alfa-2b 1.5 µg/kg/week plus ribavirin 800-1400 mg/day [1]. Patients with detectable HCV RNA levels after 12 weeks of retreatment were discontinued and became eligible for enrollment into the present maintenance study. Based upon results of the liver biopsies collected and read by a central pathologist before retreatment, patients with MFS of F2 or F3 were eligible for inclusion in this study. In addition, patients were required to have a neutrophil count ≥ 750 cells/mm³ and a platelet count $\geq 50,000$ cells/mm³ upon discontinuation of retreatment. Patients were excluded from this maintenance study if they had developed decompensated liver disease, experienced a treatment-related serious adverse event (SAE), or were abusing alcohol or other illegal drugs during the retreatment study.

Study design

This was a worldwide, multicenter, open-label, randomized study, conducted in accordance with the Declaration of Helsinki, current guidelines on Good Clinical Practices, and local ethical and legal requirements. All patients provided voluntary written informed consent prior to entry into the maintenance therapy phase of this trial.

Eligible patients were randomized to receive PEG-IFN alfa-2b 0.5 µg/kg/week or no treatment (observation) for up to 36 months with a subsequent 4-week follow-up period without treatment. Randomization was performed using a centralized system in a 1:1 ratio

according to a computer-generated code and stratified according to age (≤ 50 versus > 50 years old) and MFS (F2 versus F3).

Study assessments (physical exams, hematology, HCV RNA levels, and alpha-fetoprotein levels for patients with MFS F3) were performed monthly for 3 months and then every 3 months thereafter. A liver biopsy was performed 4 weeks before the final treatment or observation, and a follow-up visit was conducted 4 weeks after completing treatment or observation.

Serum samples and biochemical markers

FibroTest and ActiTest were measured at screening and yearly thereafter. Serum samples were collected and centrally stored, and blindly assessed according to recommended procedures [6-10]. FibroTest combines the following five markers: alpha-2-macroglobulin, haptoglobin, gamma glutamyl transpeptidase (GGT), total bilirubin, and apolipoprotein A1. ActiTest combines the same five markers as FibroTest plus alanine aminotransferase (ALT).

Apolipoprotein A1, alpha-2-macroglobulin, and haptoglobin were determined using serum samples stored at -80°C . An automatic nephelometer (Beckman Instruments, Brea, CA, USA) with reagents from Roche Diagnostics (Roche Diagnostics, Indianapolis, IN, USA), Siemens Healthcare Diagnostics (Siemens Healthcare Diagnostics, Deerfield, IL, USA), or Beckman Instruments (Beckman Instruments) were used. The coefficient of variation of all assays was lower than 3%. GGT, ALT, and total bilirubin were assessed prospectively during the trial period using Hitachi 747 or 911 (Boehringer Mannheim, Mannheim, Germany), or Roche modular analyzers (Roche Diagnostics).

Outcomes

The primary efficacy end point was histologic response based on improvement in MFS using blinded liver biopsies obtained before retreatment and at the end of maintenance therapy or

observation. Patients were categorized as improved (≥ 1 unit decrease in MFS or activity scores), no change, or worsened (≥ 1 unit increase in MFS or activity scores). For patients who discontinued early, a biopsy was performed at the last visit, and the fibrosis score from this biopsy was carried forward as the end-of-treatment score. Patients missing any post-treatment biopsy were classified as "no-change" for the primary efficacy analysis. The primary biochemical end point was the percentage of patients who did not progress at least 0.20 for FibroTest or 0.25 for ActiTest, corresponding to 1 MFS and 1 activity grade, respectively, at their last assay compared with baseline.

Safety evaluations included discontinuations or dose modifications because of adverse events (AEs) and SAEs. Dose reductions to 0.25 $\mu\text{g}/\text{kg}/\text{week}$ were permitted for patients experiencing an AE, and study medication could be interrupted for a maximum of 2 weeks if required. Guidelines for dose reductions and interruptions were pre-specified in the protocol.

Statistics

The statistical analysis was based on the intent-to-treat population, which included all randomized patients according to the treatment/observation actually received. With a planned enrollment of 350 subjects per group, a shift of 10% in the distribution of improved/no change/worsened between treatment groups would be detected with approximately 90% power (assuming the distribution in the observation group is 35%/45%/20% and the distribution in the PEG group is 45%/45%/10%). The proportion of patients in the improved, no-change, and worsened categories was summarized between the two treatment groups. The primary treatment comparison was based on a 2-sided Van Elteren extension of the Wilcoxon rank sum test for ordered categories ($\alpha=0.05$), taking into account the baseline stratification factors (MFS, F2 vs F3 and age, ≤ 50 vs >50 years old), using SAS PROC FREQ and modified ridit scores option. Pearson's Chi-Square test was used for all exploratory comparisons.

Results

Between March 2003 and October 2009, 540 patients were enrolled; 270 patients were randomized to PEG-IFN alfa-2b (0.5 µg/kg/week) and 270 patients were randomized to observation (**Figure 1**). Enrollment failed to reach the intended sample size due to a higher than expected rate of SVR in the retreatment phase [1] resulting in fewer patients being eligible for maintenance therapy.

Baseline characteristics were similar between PEG-IFN alfa-2b and observation groups (**Table 1**). Mean duration of treatment was 2.3 years and 2.4 years in the PEG-IFN alfa-2b and observation groups, respectively. Of the 540 patients enrolled, 348 (PEG-IFN alfa-2b, n = 182; observation, n = 166) had pre-retreatment and end-of-maintenance therapy biopsies. Almost 90% of baseline biopsy samples in both groups had adequate representation of portal tracts; whereas, approximately 60% of samples were considered adequate after maintenance therapy. The mean interval between pre-retreatment and end-of-maintenance therapy biopsies was 3.6 years in the PEG-IFN alfa-2b group and 3.9 years in the observation group. There was also no difference in patient characteristics between those with and without pre- and post-treatment biopsy (**Supplemental Table 1**).

Fibrosis response

Mean MFS at the end of the maintenance period did not differ from pre-retreatment MFS in either group. In total, 44 of 270 patients receiving PEG-IFN alfa-2b and 29 of 270 patients under observation achieved a ≥ 1 -unit improvement in MFS (16% vs 11%, $p = 0.32$) (**Figure 2**). Similar numbers of patients receiving PEG-IFN alfa-2b or observation had a ≥ 2 -unit improvement in MFS (3% [9/270] vs 2% [5/270]; $p = 0.28$). Most patients had no change in MFS between pre-retreatment and end-of-maintenance therapy (60% [162/270] vs 65% [176/270]), including 88 patients receiving PEG-IFN alfa-2b and 104 patients in the observation group who had missing post-maintenance biopsies. At the end of the maintenance period, 24% (64/270) of patients in the PEG-IFN alfa-2b group and 24%

(65/270) of those in the observation group had worsened MFS. In the subgroup of patients treated for >2.5 years, 21% (39/186) of PEG-IFN alfa-2b recipients and 14% (28/197) of observation patients had ≥ 1 -unit improvement in MFS ($p = 0.08$) (**Figure 2**). When the analysis was restricted to patients with pre- and post-treatment biopsy (excluding patients with missing post-treatment biopsies), ≥ 1 -unit improvement in MFS was seen in 44 of 182 patients receiving PEG-IFN alfa-2b, and 29 of 166 patients under observation (24.2% vs 17.5%, $p = 0.195$).

Activity response

Significantly more patients receiving PEG-IFN alfa-2b had improvement in METAVIR activity score compared with patients in the observation group (20%, [54/270] vs 9% [23/270], $p < 0.001$) (**Figure 3**). Similar numbers of patients had no change in activity score between pre-treatment and end of maintenance (PEG-IFN alfa-2b, 72% [195/270] vs observation, 77% [209/270]), including those with missing end-of-maintenance liver biopsies. Overall, 8% (21/270) of patients in the PEG-IFN alfa-2b group and 14% (38/270) of those in the observation group experienced deterioration in activity scores at end of maintenance compared with baseline. Activity score improved by ≥ 2 units in 1% of patients receiving PEG-IFN alfa-2b and 0% of the observation group. As seen with MFS, in the subgroup of patients treated for >2.5 years, the proportion of patients with an improvement in activity score was 26% (49/186) in the PEG-IFN alfa-2b group and 10% (20/197) in the observation group ($p < 0.0001$) (**Figure 3**). When this analysis was restricted to patients with pre- and post-treatment biopsy (excluding patients with missing post-treatment biopsies), ≥ 1 -unit improvement in activity score was seen in 54 of 182 patients receiving PEG-IFN alfa-2b, and 23 of 166 patients under observation (29.7% vs 13.9%, $p < 0.0001$).

Activity scores and ALT levels

In the subgroup of patients with improved or no change in METAVIR activity score, mean ALT levels at end of maintenance were lower in the PEG-IFN alfa-2b group than in the

observation group (**Supplementary Figure 1**). Similarly, among patients with improved METAVIR activity scores, decrease in mean ALT levels from pre-retreatment to end of maintenance was greater among patients receiving PEG-IFN alfa-2b than among those under observation ($-0.90 \times$ upper limit of normal [ULN] vs $-0.36 \times$ ULN).

Change in fibrosis/necroinflammatory activity when evaluated using FibroTest/ActiTest

Of the 540 patients enrolled, 182 were excluded from the FibroTest/ActiTest analyses: 171 patients had ≤ 1 FibroTest evaluation and 12 others had uninterpretable FibroTest results. The remaining 357 patients (PEG-IFN alfa-2b, $n = 174$; observation, $n = 183$) had a baseline FibroTest/ActiTest measurement plus ≥ 1 additional measurement during treatment/observation (**Table 1**). Baseline characteristics were generally comparable between the overall study population and those included in the FibroTest/ActiTest evaluations. At baseline, median FibroTest score was 0.67 and median ActiTest score was 0.62.

Using FibroTest equivalence to MFS, significantly more observed patients showed a worsening in fibrosis score compared with those receiving PEG-IFN alfa-2b (14% vs 6%; $p = 0.02$) (**Figure 4A**). Similarly, using ActiTest equivalence, more patients receiving PEG-IFN alfa-2b showed improvement in METAVIR activity grade compared with the observation group (16% vs 5%; $p = 0.001$). After 3 years of treatment, FibroTest data revealed a statistically significant improvement in fibrosis among patients receiving PEG-IFN alfa-2b compared with observation (**Figure 4B**). Based on the last FibroTest assessment, fibrosis score was significantly worse in observation patients than in patients receiving PEG-IFN alfa-2b (0.04 vs -0.002 ; $p = 0.01$). Similarly, necroinflammatory activity (as measured using ActiTest) was also significantly better in patients receiving PEG-IFN alfa-2b than in the observation group (**Figure 4C**). ActiTest scores at the last clinic visit were significantly better in patients receiving PEG-IFN alfa-2b than in observation patients (-0.08 vs. 0.01 ; $p < 0.0001$).

A total of 258 patients had both paired biopsies and paired ActiTest/FibroTest. As expected there was a significant ($p = 0.01$) association between the differences observed in activity grades estimated using the METAVIR scoring system and the differences between ActiTest values, and no significant association between differences observed between fibrosis stages and FibroTest values (Supplementary Figure 2).

Safety

The safety profile of PEG-IFN alfa-2b was similar to that seen in previous studies of maintenance therapy (**Table 2**). AEs were reported by 95% (257/270) of patients in the PEG-IFN alfa-2b group and by 87% (234/270) of observed patients. The type of AEs was similar between groups; however, frequency was higher in the PEG-IFN alfa-2b group. SAEs were reported by 20% of patients receiving PEG-IFN alfa-2b and by 11% of patients in the observation group; these events were not concentrated in any specific body system. The most common SAEs were chest pain (1% [3/270]) in the PEG-IFN alfa-2b group and depression (1% [3/270]) in the observation group. More patients discontinued PEG-IFN alfa-2b treatment than withdrew from observation because of AEs (17% vs 4%); more F3 patients than F2 patients (20% [30/147] vs 14% [17/123]) discontinued treatment in the PEG-IFN alfa-2b group.

There were 3 deaths (cerebral hemorrhage, heart attack, and acute myeloid leukemia leading to septic shock) in the PEG-IFN alfa-2b group and 1 (cardiac arrest secondary to multiple myeloma and cardiac amyloidosis) in the observation group; all were considered unlikely related to study drug by the investigators. The 3 deaths in the PEG-IFN alfa-2b group occurred >1 month after treatment/observation ended. There were no reports of HCC.

Discussion

In the EPIC³ study, treatment of previous non-responders with PEG-IFN alfa-2b and ribavirin resulted in an SVR rate of 22% [1]. The results of the present study indicate that low-dose PEG-IFN alfa-2b for two years does not significantly improve MFS when assessed by paired biopsies among patients with METAVIR F2 and F3 disease compared with observation. The number of patients who experienced an improvement in MFS did not differ between groups; however, significantly more patients receiving PEG-IFN alfa-2b experienced an improvement in necroinflammatory activity as assessed by paired biopsies. Furthermore, despite relatively small patient numbers, there appeared to be some benefit associated with PEG-IFN alfa-2b therapy, specifically within the population of patients treated for >2.5 years. As liver fibrosis progression is a slow process, a study of longer duration may be required to establish a clear benefit of active therapy versus observation or, alternatively, a more sensitive estimate of fibrosis progression.

Three studies indicate that maintenance therapy with low-dose PEG-IFN alfa fails to limit or delay the histologic advancement of liver disease when assessed by biopsy, or delay the development of end-stage liver disease and HCC in patients with advanced liver disease related to CHC infection [2-4]. While reports from EPIC³ and COPILOT focused solely on patients with cirrhotic liver disease, the primary publication from HALT-C reported a mixed population consisting of 40% patients with cirrhosis and 60% with bridging fibrosis [3]. Within the cohort of non-cirrhotic patients, progression of fibrosis was similar in observation and PEG-IFN alfa-2a groups (70% vs 64%), and similar numbers of patients reached the primary composite outcome of death, hepatic decompensation, HCC, Child–Turcotte–Pugh score ≥ 7 , or an increase in Ishak fibrosis score ≥ 2 (29.7% vs 31.7%) [3]. Furthermore, the rate of progression to cirrhosis was also similar in control and active groups (28.2% vs 31.9%, $p = 0.46$). After the randomization phase of the HALT-C trial, patients continued to be followed, with an overall median duration of participation of 6 years [11]. Of the 622 patients with baseline fibrosis, 109 progressed to cirrhosis at 2 years and a further 69 had developed cirrhosis at 4 years, resulting in an annualized rate of progression to cirrhosis of 9.9%.

Between-treatment-group comparisons were not reported, but interestingly the factor most strongly associated with the incidence of cirrhosis was the ALT level. These data are compatible with the very slow progression of liver disease in previously treated non-cirrhotic patients, as well as the possible impact of reduced necrosis and inflammation arising from interferon-based treatment. Thus, data from the present study are consistent with those from HALT-C indicating no benefit of low-dose PEG-IFN alfa therapy in non-cirrhotic patients with CHC infection when treated for 2 years and using liver biopsy as a reference. A review of other long-term studies emphasizes that large populations of patients are necessary to see a benefit of treatment on fibrosis when using paired biopsies, even within patient populations with SVR [12]. The use of validated non-invasive biomarkers such as FibroTest should increase the power with repeated fibrosis estimates [13].

With no supporting data from EPIC³, HALT-C, and COPILOT, PEG-IFN alfa maintenance therapy has now largely been surpassed by other recent advances in the treatment of CHC. Boceprevir and telaprevir are approved for the treatment of CHC in combination with PEG-IFN plus ribavirin, and have shown efficacy in patients previously unresponsive to PEG-IFN alfa-2b plus ribavirin [14, 15]. In the RESPOND-2 study, 68% of previous treatment failures with bridging fibrosis (F3) or cirrhosis (F4) receiving boceprevir and PEG-IFN alfa-2b plus ribavirin attained SVR, compared with 13% of those receiving PEG-IFN alfa-2b plus ribavirin [14]. Among patients with cirrhosis, SVR rates were 0% in patients receiving PEG-IFN alfa-2b plus ribavirin and 77% in those receiving boceprevir and PEG-IFN alfa-2b plus ribavirin. Similarly, in PROVE 3, 49% of patients with bridging fibrosis or cirrhosis receiving telaprevir and PEG-IFN alfa-2a plus ribavirin attained SVR compared with 11% of patients receiving PEG-IFN alfa-2a plus ribavirin [15]. However, despite the improvement in SVR rates with approved triple therapy, there will remain a substantial percentage of non-responders with advanced fibrosis who require alternative treatment options. For these patients, the debate regarding maintenance therapy is not closed, and because of the low power of the 3

published trials that used morbidity, mortality, and biopsy as end points, we as yet cannot exclude a beneficial effect of long-term PEG-IFN alfa monotherapy.

End-of-maintenance biopsies were missing for 32% of patients who received PEG-IFN alfa-2b and 38% of observation patients in the present study, and for the purposes of analysis, these patients were considered as having no change in fibrosis or necroinflammatory activity. Liver biopsy is the gold standard assessment for fibrosis, but it is an invasive test associated with rare clinical complications, sampling errors, and significant inter-observer variability [16]. Several alternatives to liver biopsy, which aim to assess fibrosis levels using surrogate serum markers, have been reported [10, 17, 18], including the FibroTest. In the treatment phase of the EPIC³ study, baseline FibroTest results had the same prognostic value for early and sustained virologic response as biopsy, and potentially may be a superior test compared with using short-length biopsy samples [10]. Furthermore, FibroTest was validated using biopsy for assessing liver progression [19] and two prospective studies have demonstrated comparable prognostic value between FibroTest and biopsy in patients with CHC suggesting its utility as a surrogate marker [20,21] including for discriminating intermediate stages [22].

The results of the present study may be influenced by carry-over effects from full-dose PEG-IFN alfa-2b plus weight-based ribavirin that patients received during the retreatment phase of the EPIC³ study [1]. These effects would be expected to equally affect both the treatment and observation groups, potentially obscuring an effect of active maintenance therapy, particularly during the early stages of the study. In addition, rates of discontinuation because of an AE were higher among treated than observation patients in the present study. However, discontinuation of an “observational” treatment clearly has limited clinical implications; therefore, the higher discontinuation rate in patients receiving PEG-IFN alfa-2b may at least in part reflect a tendency to retain observation patients within the study.

In conclusion, and as observed in other trials, a significant impact on MFS estimated by biopsy could not be demonstrated after 3 years of therapy. These data confirm also that low-dose PEG-IFN alfa-2b reduces hepatic inflammation. For patients with CHC and significant hepatic fibrosis who are unable to clear HCV, therapies to slow or reverse progression toward cirrhosis are still needed. However, some of these patients may also be candidates for triple therapy, and opportunities for viral eradication should be fully explored before considering maintenance treatment. It remains unclear whether longer periods of low-dose PEG-IFN alfa-2b therapy would extend the trend toward improvement in MFS seen in patients treated for >2.5 years.

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Acknowledgments

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Table 1. Patient Demographics and Disease and Liver Biopsy Characteristics

Characteristic	PEG-IFN alfa-2b				Observation			
	Total (N = 270)	F2 (n = 123)	F3 (n = 147)	F2/F3 FibroTest population (n = 174)	Total (N = 270)	F2 (n = 122)	F3 (n = 148)	F2/F3 FibroTest population (n = 183)
Male, n (%)	194 (72)	90 (73)	104 (71)	131 (75)	189 (70)	81 (66)	108 (73)	126 (69)
Mean age (\pm SD), yrs	49.8 (8.4)	49.3 (8.9)	50.2 (8.0)	50.1 (8.2)	49.2 (8.6)	47.9 (9.0)	50.3 (8.1)	49.6 (8.4)
Race, n (%)								
Caucasian	217 (80)	104 (85)	113 (77)	140 (80)	218 (81)	99 (81)	119 (80)	146 (80)
Black	16 (6)	7 (6)	9 (6)		15 (6)	8 (7)	7 (5)	
Hispanic	15 (6)	7 (6)	8 (5)		21 (8)	9 (7)	12 (8)	
Asian	9 (3)	1 (1)	8 (5)	34 (20) ^a	2 (1)	1 (1)	1 (1)	37 (20) ^a
Other	13 (5)	4 (3)	9 (6)		14 (5)	5 (4)	9 (6)	
Mean weight, kg	76.0 (14.4)	75.0 (12.9)	76.8 (15.5)	75.9 (14.1)	75.6 (14.0)	73.6 (13.4)	77.1 (14.3)	75.8 (14.5)
Baseline viral load, n (%) >600,000 IU/mL	193 (71)	88 (72)	105 (71)	130 (75)	183 (68)	78 (64)	105 (71)	125 (68)
Genotype, n (%) ^b								
1	248 (92)	114 (93)	134 (91)	163 (94)	249 (92)	113 (93)	136 (92)	169 (92)
2	4 (1)	2 (2)	2 (1)	2 (1)	1 (<1)	1 (1)	0	1 (1)
3	10 (4)	5 (4)	5 (3)	3 (2)	8 (3)	2 (2)	6 (4)	5 (3)
Other	8 (3)	2 (2)	6 (4)	6 (3)	9 (3)	5 (4)	4 (3)	8 (4)
Pre-treatment steatosis, n (%)								
Absent (0%)	44 (16)	26 (21)	18 (12)	NA	27 (10)	10 (8)	17 (11)	NA
>0%-5%	132 (49)	65 (53)	67 (46)	NA	130 (48)	78 (64)	52 (35)	NA
>5%-30%	60 (22)	17 (14)	43 (29)	NA	55 (20)	20 (16)	35 (24)	NA
>30%-60%	21 (8)	10 (8)	11 (7)	NA	32 (12)	9 (7)	23 (16)	NA
>60%	13 (5)	5 (4)	8 (5)		26 (10)	5 (4)	21 (14)	
Pre-treatment METAVIR activity score, n (%)								
0	19 (7)	14 (11)	5 (3)	12 (7)	14 (5)	6 (5)	8 (5)	8 (4)
1	203 (75)	95 (77)	108 (73)	132 (76)	216 (80)	104 (85)	112 (76)	151 (83)
2	45 (17)	14 (11)	31 (21)	27 (16)	38 (14)	12 (10)	26 (18)	23 (13)
3	3 (1)	0	3 (2)	3 (2)	2 (1)	0	2 (1)	1 (1)
Pre-treatment METAVIR fibrosis score, n (%)								
F2	123 (46)	123 (100)		84 (48)	122 (45)	122 (100)		88 (48)
F3	147 (54)		147 (100)	90 (52)	148 (55)		148 (100)	95 (52)
Mean (\pm SD) length of pre-treatment liver biopsy, mm	14.6 (7.1)	16.2 (6.9)	13.3 (7.0)		14.2 (6.9)	15.2 (7.4)	13.3 (6.3)	
Number of portal tracts of pre-treatment liver biopsy, n (%)								
Adequate	240 (89)	114 (93)	126 (86)	NA	238 (88)	108 (89)	130 (88)	NA
Marginal	24 (9)	8 (7)	16 (11)	NA	29 (11)	13 (11)	16 (11)	NA

Inadequate	6 (2)	1 (1)	5 (3)	NA	2 (1)	1 (1)	1 (1)	NA
Missing	0	0	0	NA	1 (<1)	0	1 (1)	NA
Mean length of post-maintenance therapy liver biopsy, mm ^c	17.8 (8.2)	17.7 (8.6)	17.8 (7.9)	NA	17.4 (7.8)	18.6 (7.4)	16.7 (8.1)	NA
Number of portal tracts of post-maintenance therapy liver biopsy, n (%)								
Adequate	166 (61)	72 (59)	94 (64)	NA	158 (59)	66 (54)	92 (62)	NA
Marginal	16 (6)	7 (6)	9 (6)	NA	8 (3)	0	8 (5)	NA
Inadequate	2 (1)	0	2 (1)	NA	2 (1)	1 (1)	1 (1)	NA
Missing	86 (32)	44 (36)	42 (29)	NA	102 (38)	55 (45)	47 (32)	NA
Mean time between pre-treatment and post-maintenance therapy liver biopsies (\pm SD), days	1325 (250)	1366 (174)	1294 (293)	NA	1414 (298)	1382 (273)	1436 (312)	NA

NA = not available

^aSpecific race among non-Caucasian patients in FibroTest populations was not collected.

^bIn the observation group, 1 patient was nontypeable and 2 had missing genotype.

^cMissing 86 in the PEG-IFN alfa-2b group and 102 in the observation group.

Table 2. Adverse Events, Discontinuations and Dose Reductions

	PEG-IFN alfa-2b (N = 270)	Observation (N = 270)
Death, n	3	1
Serious adverse events, n (%)	53 (20)	31 (11)
Discontinuation of treatment due to adverse event, n (%)	47 (17)	12 (4)
PEG-IFN alfa-2b dose reduction due to adverse event, n (%)	19 (7)	NA
Neutrophil count (<0.75-0.5 ×10 ⁹ /L / <0.5 ×10 ⁹ /L)	9 (3) / 3 (1)	1 (<1) / 2 (1)
Common adverse events (≥10% incidence), n (%)		
Headache	76 (28)	24 (9)
Fatigue	66 (24)	60 (22)
Insomnia	56 (21)	46 (17)
Arthralgia	50 (19)	40 (15)
Myalgia	46 (17)	20 (7)
Asthenia	46 (17)	31 (11)
Alopecia	38 (14)	21 (8)
Influenza-like Illness	34 (13)	4 (1)
Depression	34 (13)	25 (9)
Pruritus	36 (13)	16 (6)
Neutropenia	32 (12)	15 (6)
Irritability	32 (12)	13 (5)
Back pain	33 (12)	24 (9)
Pyrexia	30 (11)	13 (5)
Diarrhea	28 (10)	16 (6)
Dry skin	26 (10)	7 (3)
Hypertension	19 (7)	27 (10)

Figure Legends

Figure 1. Patient disposition.

Figure 2. METAVIR fibrosis score. Improvement in METAVIR fibrosis score (A) and change in fibrosis score according to treatment duration (B). MFS, METAVIR fibrosis score; PEG-IFN, peginterferon.

Figure 3. METAVIR activity score. Improvement in METAVIR activity score (A) and change in activity score according to treatment duration (B). AS, activity score; PEG-IFN, peginterferon.

Figure 4. FibroTest and ActiTest evaluations. Change in fibrosis and necroinflammatory activity as assessed using FibroTest and ActiTest (A), and mean change from baseline in fibrosis score as measured using FibroTest (B) and in necroinflammatory activity score as measured using ActiTest (C). For panels B and C, data are mean change from baseline (95% confidence interval). A negative value is an improvement and a positive value is a worsening. PEG-IFN, peginterferon

Supplemental Materials

Supplemental Table 1. Demographic Characteristics in Patients With and Without Pre- and Post-treatment Biopsy

	Subjects with pre-treatment and end-of-treatment biopsy		Subjects without pre-treatment and end-of-treatment biopsy	
	PEG-IFN (n = 182)	Observed (n = 166)	PEG-IFN (n = 88)	Observed (n = 104)
Sex, n (%)				
Male	45 (25)	43 (26)	31 (35)	38 (37)
Female	137 (75)	123 (74)	57 (65)	66 (63)
Race				
Caucasian	145 (80)	135 (81)	72 (82)	83 (80)
Non-Caucasian	37 (20)	31 (19)	16 (18)	21 (20)
Asian	8 (4)	0	1 (1)	2 (2)
Black	8 (4)	7 (4)	8 (9)	8 (8)
Hispanic	13 (7)	15 (9)	2 (2)	6 (6)
Other	8 (4)	9 (5)	5 (6)	5 (5)
Age				
Mean (SD)	49.5 (7.8)	49.2 (8.4)	50.4 (9.7)	49.2 (9.0)
Median	49.0	49.0	51.0	50.0
Range	26-65	28-66	21-66	23-66
≤50 yrs, n (%)	103 (57)	95 (57)	42 (48)	53 (51)
>50 yrs, n (%)	79 (43)	71 (43)	46 (52)	51 (49)
Weight (kg)				
Mean (SD)	76.38 (14.26)	76.60 (14.48)	75.08 (14.67)	73.88 (13.02)
Median	76.35	76.30	74.5	71.65
Range	46.5-123.5	39.6-124.7	42.0-130.2	48.0-105.0
Height				
Mean (SD)	170.29 (9.25)	170.82 (8.96)	169.33 (8.66)	169.53 (9.86)
Median	171.00	170.60	169.00	171.00
Range	145.0-190.0	147.0-190.0	148.0-190.0	148.0-196.0
Missing	4	2	4	4
BMI				
Mean (SD)	26.30 (4.2)	26.14 (3.88)	25.89 (3.98)	25.54 (3.69)
Median	25.75	26.00	25.4	24.7
Range	16.8-47.6	18.3-40.7	16.6-39.6	17.2-37.6
Missing	4	2	4	4
Viral load, n (%)				
≤600,000 IU/mL	51 (28)	49 (30)	26 (30)	37 (36)
>600,000 IU/mL	131 (72)	117 (70)	62 (70)	66 (63)
Missing			0	1 (1)
Genotype subtype				
1	0	1 (1)	0	0
1A	59 (32)	75 (45)	32 (36)	43 (41)
1A1B	3 (2)	1 (1)	1 (1)	1 (1)
1B	104 (57)	83 (50)	49 (56)	45 (43)
2A	2 (1)	0	0	0
2B	2 (1)	0	0	1 (1)
3A	5 (3)	2 (1)	5 (6)	6 (6)
4	7 (4)	3 (2)	1 (1)	6 (6)
Non-typeable	0	1 (1)	0	2 (2)
Genotype				
1	166 (91)	160 (96)	82 (93)	89 (86)
2	4 (2)	0	0	1 (1)
3	5 (3)	2 (1)	5 (6)	6 (6)
Other	7 (4)	3 (2)	1 (1)	6 (6)
Non-typeable	0	1 (1)	0	2 (2)
METAVIR activity, n (%)				
0	12 (7)	9 (5)	7 (8)	5 (5)
1	136 (75)	132 (80)	67 (76)	84 (81)
2	32 (18)	24 (14)	13 (15)	14 (13)

3	2 (1)	1 (1)	1 (1)	1 (1)
METAVIR fibrosis, n (%)				
2	79 (43)	66 (40)	44 (50)	56 (54)
3	103 (57)	100 (60)	44 (50)	48 (46)
Steatosis, n (%)				
0	30 (16)	20 (12)	14 (16)	7 (7)
1	88 (48)	79 (48)	44 (50)	51 (49)
2	46 (25)	35 (21)	14 (16)	20 (19)
3	9 (5)	16 (10)	12 (14)	16 (15)
4	9 (5)	16 (10)	4 (5)	10 (10)
Number of portal tracts				
Pre-treatment				
Adequate	159 (87)	147 (89)	81 (92)	91 (88)
Marginally	19 (10)	17 (10)	5 (6)	12 (12)
Inadequate	4 (2)	1 (1)	2 (2)	1 (1)
Missing	0	1 (1)	0	0
End of treatment				
Adequate	166 (91)	158 (95)	0	0
Marginally	16 (9)	8 (5)	0	0
Inadequate			2 (2)	2 (2)
Specimen length				
Pre-treatment				
Mean	14.96	13.45	13.86	15.32
SD	7.507	6.47	5.997	7.302
Minimum	1	2	2	2
Median	13	13	14	15
Maximum	40	30	30	40
Sum	2722	2233	1220	1593
End of treatment				
Mean	17.9	17.62	6.5	1.5
SD	8.129	7.68	0.707	2.121
Minimum	3	3	6	0
Median	16	16	6.5	1.5
Maximum	50	50	7	3
Sum	3257	2925	13	3

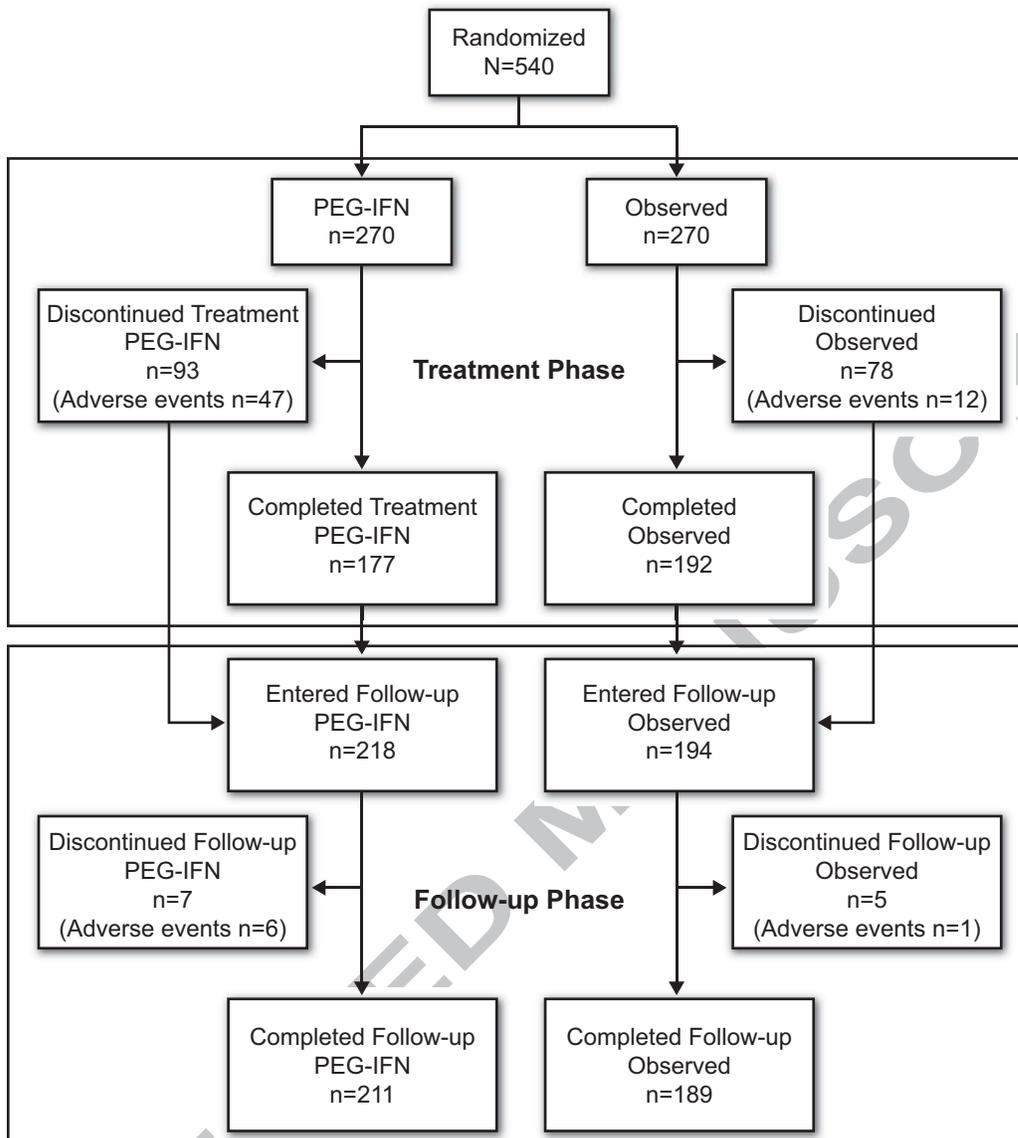
BMI, body mass index; PEG-IFN, peginterferon; SD, standard deviation.

Supplemental Figure 1. ALT levels (\times upper limit of normal) at end of treatment. ALT, alanine aminotransferase; PEG-IFN, peginterferon.

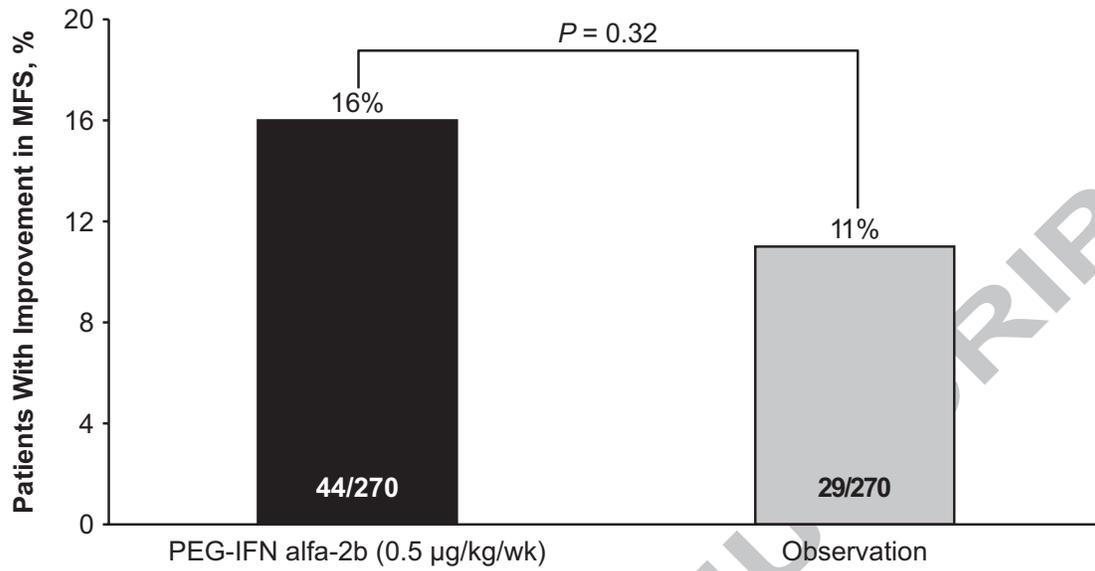
Supplemental Figure 2A. Changes in ActiTest and METAVIR grades.

Supplemental Figure 2B. Changes in FibroTest and METAVIR stage.

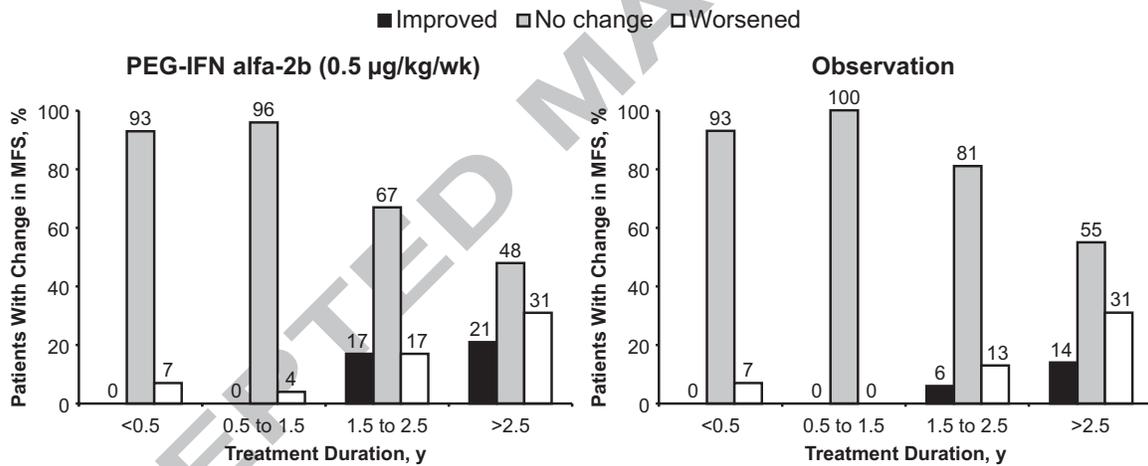
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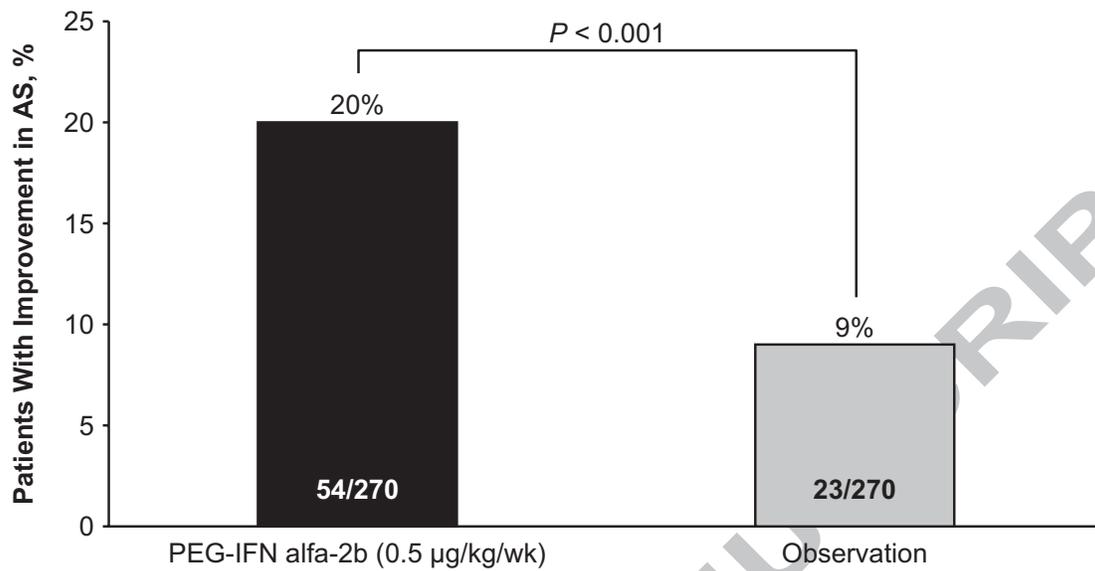
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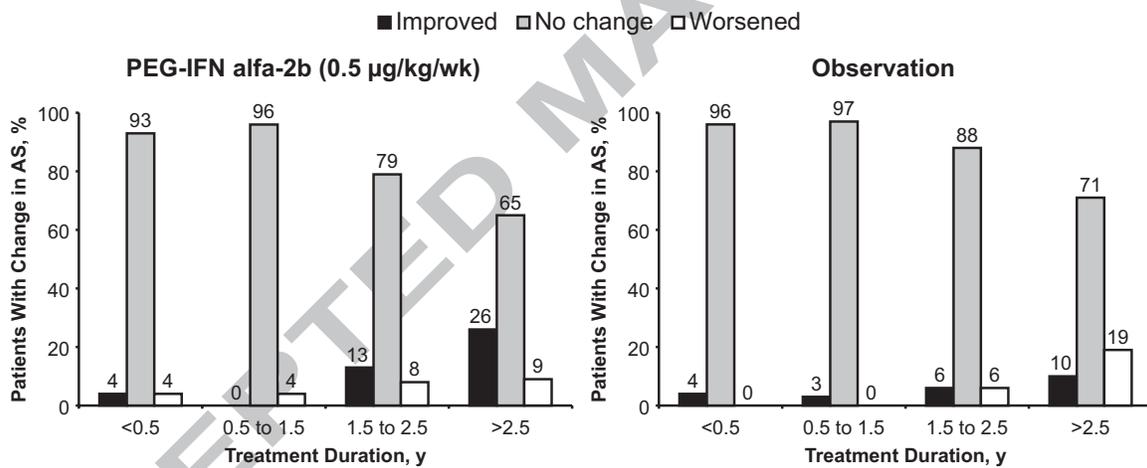
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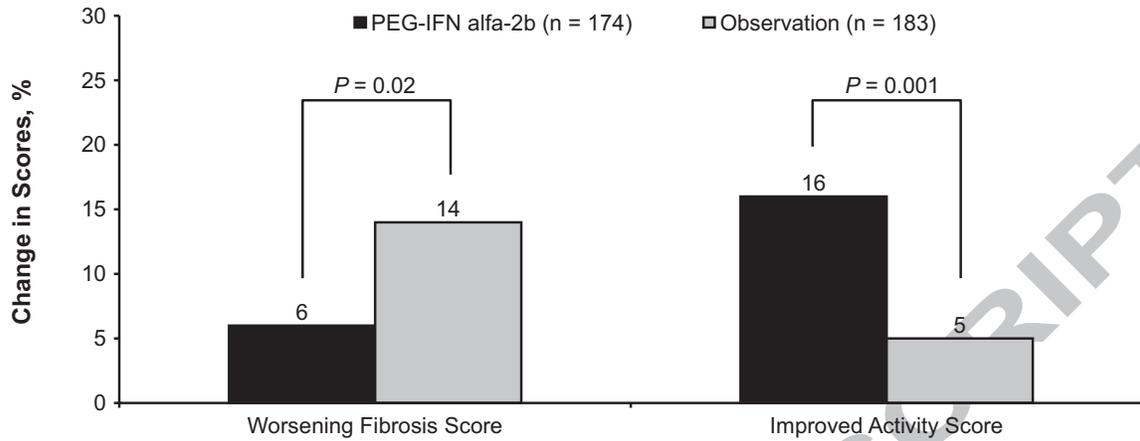
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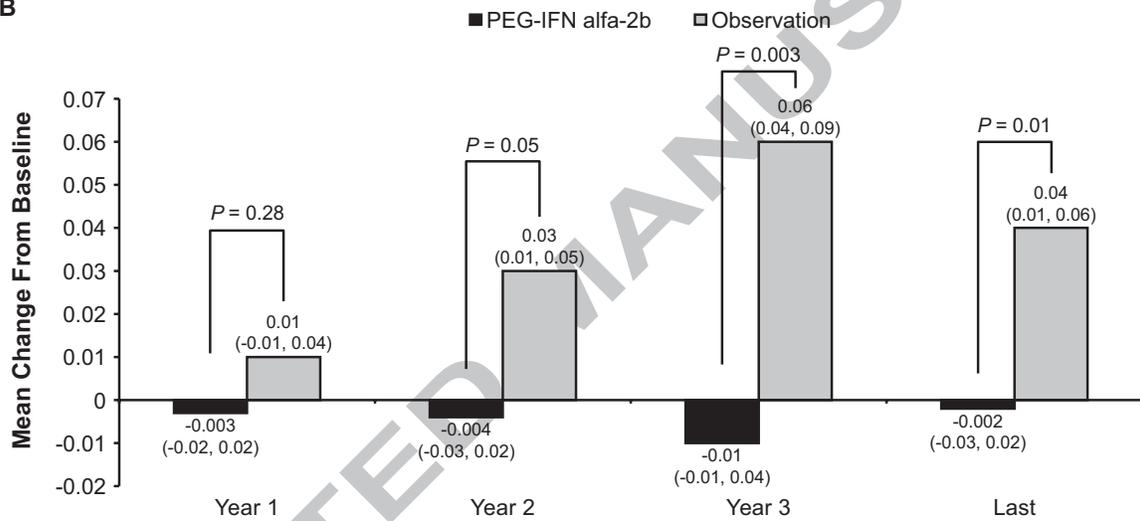
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A



B



C

