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Improved inflammatory activity with peginterferon alfa-2b maintenance therapy in non-cirrhotic prior non-responders: A randomized study☆

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Background & Aims: Therapeutic options for patients failing hepatitis C retreatment are limited. EPIC[3] included a prospective trial assessing long-term peginterferon alfa-2b (PegIFNα-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 PegIFNα-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 PegIFNα-2b and 11% of observation patients had improvement in MFS ($p = 0.32$). More PegIFNα-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 PegIFNα-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 PegIFNα-2b in terms of reduced fibrosis progression and improved activity score. The safety profile of PegIFNα-2b was similar to previous studies.
Conclusions: PegIFNα-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.
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Abbreviations: CHC, chronic hepatitis C; PegIFN, 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.

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 (PegIFN) 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 (EPIC[3]) study was a large, prospective, multiphase clinical program that evaluated the retreatment of patients with moderate to severe fibrosis/cirrhosis using PegIFNα-2b plus ribavirin [1,2]. In this study, retreatment of patients with CHC infection with PegIFNα-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 PegIFNα 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 PegIFNα does not delay development of HCC in patients with cirrhosis related to hepatitis C virus infection [2–4].

Here we describe the patients from EPIC^3, with METAVIR fibrosis scores (MFS) of F2 or F3, who failed retreatment with PegIFNα-2b plus ribavirin and enrolled in the maintenance study, to determine whether low-dose PegIFNα-2b (0.5 μg/kg/week) provides histologic benefit.

Materials and 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 EPIC^3 program. Detailed inclusion and exclusion criteria have been previously described [1].

In the EPIC^3 program, patients were initially retreated with PegIFNα-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 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 $\geqslant$750 cells/mm^3 and a platelet count $\geqslant$50,000 cells/mm^3 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 PegIFNα-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 ($\leqslant$50 *vs.* >50 years old) and MFS (F2 *vs.* 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) was used. The coefficient of variation of all assays was lower than 3%. GGT, ALT, and total bilirubin levels 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 ($\geqslant$1 unit decrease in MFS or activity scores), no change, or worsened ($\geqslant$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 μg/kg/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, $\leqslant$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 PegIFNα-2b (0.5 μg/kg/week) and 270 patients were randomized to observation (Fig. 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 PegIFNα-2b and observation groups (Table 1). Mean duration of treatment was 2.3 years and 2.4 years in the PegIFNα-2b and observation groups, respectively. Of the 540 patients enrolled, 348 (PegIFNα-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 PegIFNα-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 (Supplementary Table 1).

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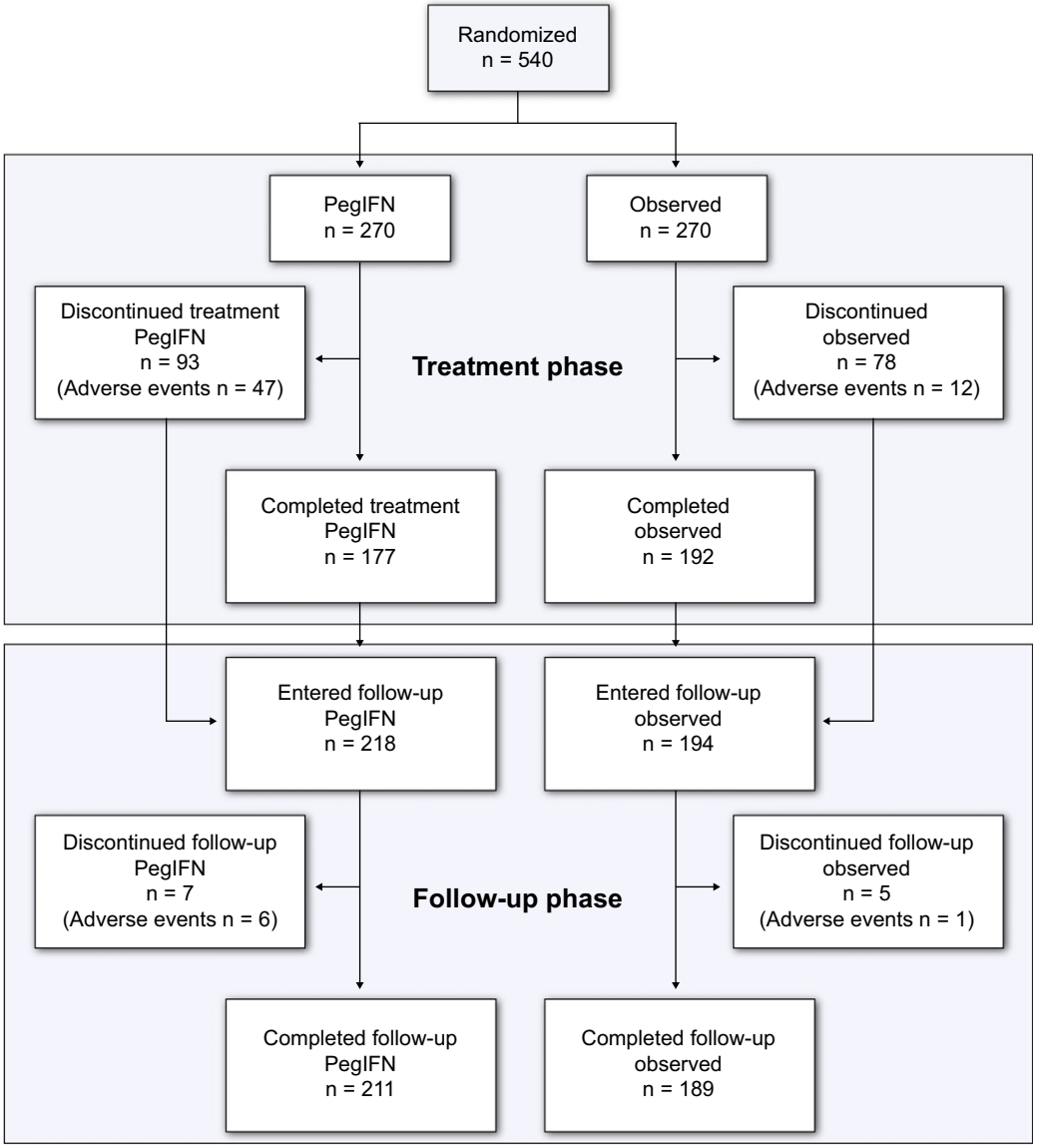

Fig. 1. Patients disposition.

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 PegIFNα-2b and 29 of 270 patients under observation achieved a ⩾1-unit improvement in MFS (16% *vs.* 11%, $p = 0.32$) (Fig. 2). Similar numbers of patients receiving PegIFNα-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 PegIFNα-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 PegIFNα-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 PegIFNα-2b recipients and 14% (28/197) of observation patients had ⩾1-unit improvement in MFS ($p = 0.08$) (Fig. 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 PegIFNα-2b, and 29 of 166 patients under observation (24.2% *vs.* 17.5%, $p = 0.195$).

Activity response

Significantly more patients receiving PegIFNα-2b had improvement in METAVIR activity score compared with patients in the observation group (20%, [54/270] *vs.* 9% [23/270], $p < 0.001$) (Fig. 3). Similar numbers of patients had no change in activity score between pre-treatment and end of maintenance (PegIFNα-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 PegIFNα-2b group and

Table 1. Patient demographics and disease and liver biopsy characteristics.

Characteristic	PegIFNα-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 (±SD), yr	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)	34 (20)[a]	15 (6)	8 (7)	7 (5)	37 (20)[a]
Hispanic	15 (6)	7 (6)	8 (5)		21 (8)	9 (7)	12 (8)	
Asian	9 (3)	1 (1)	8 (5)		2 (1)	1 (1)	1 (1)	
Others	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)
Others	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)	n.a.	27 (10)	10 (8)	17 (11)	n.a.
>0%-5%	132 (49)	65 (53)	67 (46)	n.a.	130 (48)	78 (64)	52 (35)	n.a.
>5%-30%	60 (22)	17 (14)	43 (29)	n.a.	55 (20)	20 (16)	35 (24)	n.a.
>30%-60%	21 (8)	10 (8)	11 (7)	n.a.	32 (12)	9 (7)	23 (16)	n.a.
>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 (± 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)	n.a.	238 (88)	108 (89)	130 (88)	n.a.
Marginal	24 (9)	8 (7)	16 (11)	n.a.	29 (11)	13 (11)	16 (11)	n.a.
Inadequate	6 (2)	1 (1)	5 (3)	n.a.	2 (1)	1 (1)	1 (1)	n.a.
Missing	0	0	0	n.a.	1 (<1)	0	1 (1)	n.a.
Mean length of post-maintenance therapy liver biopsy, mm[c]	17.8 (8.2)	17.7 (8.6)	17.8 (7.9)	n.a.	17.4 (7.8)	18.6 (7.4)	16.7 (8.1)	n.a.
Number of portal tracts of post-maintenance therapy liver biopsy, n (%)								
Adequate	166 (61)	72 (59)	94 (64)	n.a.	158 (59)	66 (54)	92 (62)	n.a.
Marginal	16 (6)	7 (6)	9 (6)	n.a.	8 (3)	0	8 (5)	n.a.
Inadequate	2 (1)	0	2 (1)	n.a.	2 (1)	1 (1)	1 (1)	n.a.
Missing	86 (32)	44 (36)	42 (29)	n.a.	102 (38)	55 (45)	47 (32)	n.a.
Mean time between pre-treatment and post-maintenance therapy liver biopsies (± SD), days	1325 (250)	1366 (174)	1294 (293)	n.a.	1414 (298)	1382 (273)	1436 (312)	n.a.

n.a., not available.

[a]Specific race among non-Caucasian patients in FibroTest populations was not collected.

[b]In the observation group, 1 patient was non-typable and 2 had missing genotype.

[c]Missing 86 in the PegIFNα-2b group and 102 in the observation group.

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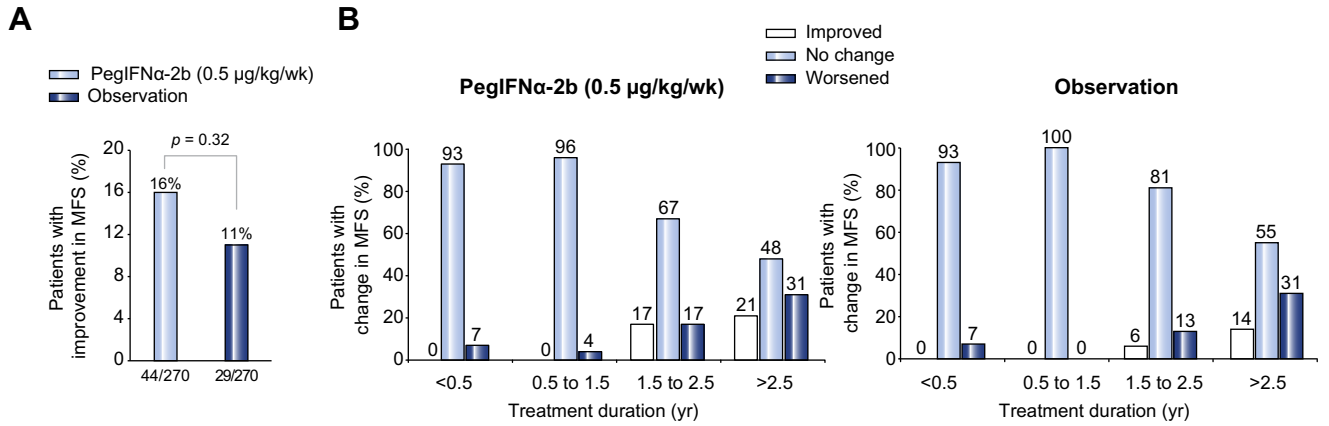

Fig. 2. METAVIR fibrosis score. (A) Improvement in METAVIR fibrosis score and (B) change in fibrosis score according to treatment duration. MFS, METAVIR fibrosis score; PegIFN, peginterferon.

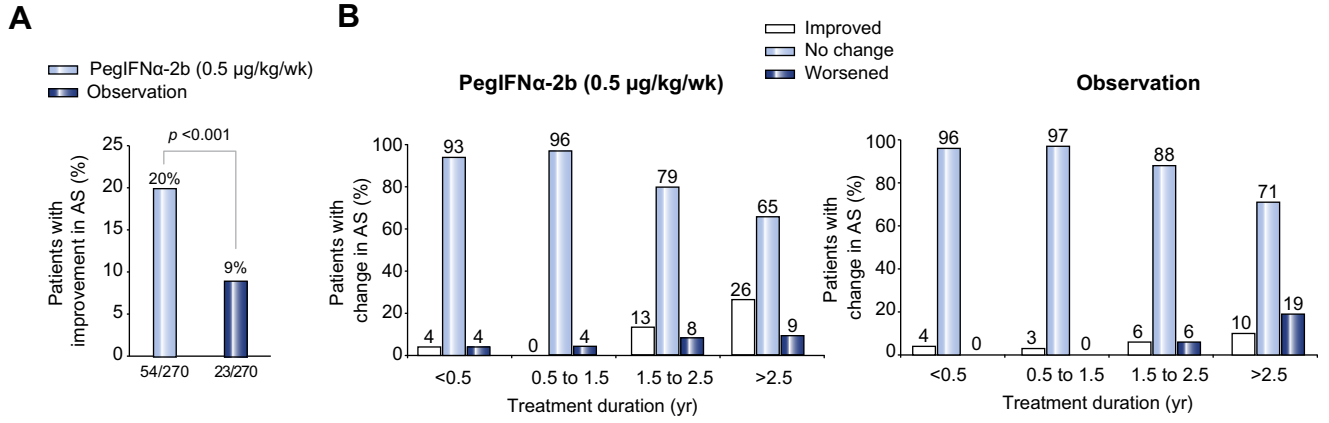

Fig. 3. METAVIR activity score. (A) Improvement in METAVIR activity score and (B) change in activity score according to treatment duration. AS, activity score; PegIFN, peginterferon.

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 PegIFNα-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 PegIFNα-2b group and 10% (20/197) in the observation group (p <0.0001) (Fig. 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 PegIFNα-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 PegIFNα-2b group than in the observation group (Supplementary Fig. 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 PegIFNα-2b than among those under observation (−0.90 × upper limit of normal [ULN] *vs.* −0.36 × 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 had uninterpretable FibroTest results. The remaining 357 patients (PegIFNα-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 PegIFNα-2b (14% *vs.* 6%; p = 0.02) (Fig. 4A) Similarly, using ActiTest equivalence, more patients receiving PegIFNα-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 PegIFNα-2b compared with the observation group (Fig. 4B). Based on the last FibroTest assessment, fibrosis score was significantly worse in observation patients than in patients receiving

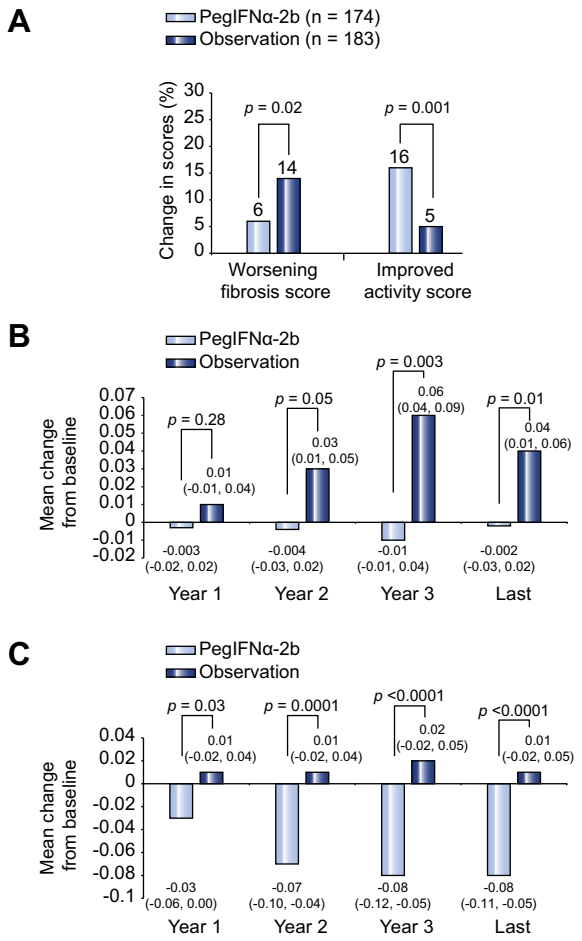

Fig. 4. FibroTest and ActiTest evaluations. (A) Change in fibrosis and necroinflammatory activity as assessed using FibroTest and ActiTest, and mean change from baseline in (B) fibrosis score, as measured using FibroTest, and (C) in necroinflammatory activity score, as measured using ActiTest. For panels 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. PegIFN, peginterferon.

PegIFNα-2b (0.04 *vs.* −0.002; $p = 0.01$). Similarly, necroinflammatory activity (as measured using ActiTest) was also significantly better in patients receiving PegIFNα-2b than in the observation group (Fig. 4C). ActiTest scores at the last clinic visit were significantly better in patients receiving PegIFNα-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 Fig. 2).

Safety

The safety profile of PegIFNα-2b was similar to that observed in previous studies of maintenance therapy (Table 2). AEs were reported by 95% (257/270) of patients in the PegIFNα-2b group and by 87% (234/270) of the observed patients. The type of AEs was similar between groups; however, frequency was higher in the PegIFNα-2b group. SAEs were reported by 20% of patients receiving PegIFNα-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 PegIFNα-2b group and depression (1% [3/270]) in the observation group. More patients discontinued PegIFNα-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 PegIFNα-2b group.

There were 3 deaths (cerebral hemorrhage, heart attack, and acute myeloid leukemia leading to septic shock) in the PegIFNα-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 PegIFNα-2b group occurred >1 month after the end of treatment/observation. There were no reports of HCC.

Table 2. Adverse events, discontinuations and dose reductions.

	PegIFNα-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)
PegIFNα-2b dose reduction due to adverse event, n (%)	19 (7)	n.a.
Neutrophil count (<0.75-0.5 ×10⁹/L/<0.5 ×10⁹/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)

n.a., not available.

Discussion

In the previous results of the EPIC[3] program, we observed that combining PegIFNα-2b and ribavirin permitted to obtain a 22% SVR in patients previously non-responders [1].

The results of the present study indicate that low-dose PegIFNα-2b for two years does not significantly improve MFS when

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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 PegIFNα-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 PegIFNα-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 PegIFNα 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 EPIC[3] and COPILOT focused solely on patients with cirrhotic liver disease, the primary publication from HALT-C reported a mixed population consisting of 40% of the patients with cirrhosis and 60% with bridging fibrosis [3]. Within the cohort of non-cirrhotic patients, progression of fibrosis was similar in observation and PegIFNα-2a groups (70% *vs.* 64%), and similar numbers of patients reached the primary composite outcome of death, hepatic decompensation, HCC, Child–Turcotte–Pugh score $\geqslant$7, or an increase in Ishak fibrosis score $\geqslant$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 were followed for an additional period [11]. The overall median duration of participation was 6 years. Among the 622 patients without cirrhosis, 109 progressed to cirrhosis at month 24 and a further 69 presented with cirrhosis at month 48. The annualized rate of progression to cirrhosis was 9.9%. There were not details between treatment groups but interestingly the factor mostly associated with the incidence of cirrhosis was the ALT level. These figures are compatible with the very slow progression rate in non-cirrhotic patients previously treated, as well as with the possible interest of reducing necrosis and inflammation.

Thus, data from the present study are consistent with those from HALT-C indicating no benefit of low-dose PegIFNα therapy in non-cirrhotic patients with CHC infection when treated for 2 years, and using liver biopsy as a reference. The review of long-term studies underlined that even in SVR, large population with paired biopsies are necessary [12] to see a benefit on fibrosis. The use of validated non-invasive biomarkers such as FibroTest should increase the power with repeated fibrosis estimates [13].

With no supporting data from EPIC[3], HALT-C, and COPILOT, PegIFNα 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 PegIFN plus ribavirin, and have shown efficacy in patients previously unresponsive to PegIFNα-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 PegIFNα-2b plus ribavirin, attained SVR, compared with 13% of those receiving PegIFNα-2b plus ribavirin [14]. Among patients with cirrhosis, SVR rates were 0% in patients receiving PegIFNα-2b plus ribavirin and 77% in those receiving boceprevir and PegIFNα-2b plus ribavirin. Similarly, in PROVE 3, 49% of patients with bridging fibrosis or cirrhosis receiving telaprevir and PegIFNα-2a plus ribavirin attained SVR compared with 11% of patients receiving PegIFNα-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 PegIFNα monotherapy.

End-of-maintenance biopsies were missing for 32% of patients who received PegIFNα-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 at assessing fibrosis levels using surrogate serum markers, have been reported [10,16–18], including FibroTest. In the treatment phase of the EPIC[3] 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 short-length biopsy samples [10]. Furthermore, FibroTest was validated using biopsy for assessing liver progression [19], and two prospective studies have demonstrated comparable prognostic values between FibroTest and biopsy in patients with CHC, suggesting its utility as a surrogate marker [20–21], including for discrimination of intermediate stages [22] .

The results of the present study may be influenced by carry-over effects from full-dose PegIFNα-2b plus weight-based ribavirin that patients received during the retreatment phase of the EPIC[3] 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 PegIFNα-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 also confirm that low-dose PegIFNα-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 PegIFNα-2b therapy would extend the trend toward improvement in MFS observed in patients treated for >2.5 years.

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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. E.R. 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, Medtronics, Novelos, 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. L.H. 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. C.A. Brass has stock ownership in and is a former employee of Merck Sharp & Dohme Corp. J.K. Albrecht is a former employee of Merck Sharp & Dohme Corp.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2012.11.001.

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