Poster #817

Impact of PegIntron (PEG) Maintenance Therapy (MT) on Fibrosis Biomarkers (FibroTest [FT]/FibroSURE) in Prior Nonresponders With METAVIR Fibrosis Scores (MFS) of F2/F3: Final Results From the EPIC³ Program

T. Poynard,[1] M. Munteanu,[2] J. Bruix,[3] E. R. Schiff,[4] M. Diago,[5] T. Berg,[6] R. Moreno-Otero,[7] L. G. Lyra,[8] N. Boparai,[9] L. H. Griffel,[10] M. Burroughs,[9] C. A. Brass,[9] J. K. Albrecht[9]

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Abstract

Background & Aims: The EPIC³ F2/3 study, designed to evaluate the efficacy of low dose PEG-2b (0.5 mcg/kg/week) MT vs observation (OBS) on improvement of MFS in previous nonresponders did not demonstrate efficacy of MT. The aim of the present study was to assess if there was a treatment effect on FT and Actitest (AT), two validated sensitive non-invasive markers of fibrosis with similar prognostic values, compared to liver biopsy (LBx) (FT: FibroTest, AT: necroinflammatory activity).

Methods: Patients with F2/F3 MFS who failed retreatment (ReRx) were randomized to PEG or OBS for 36 months. Blinded LBx obtained before ReRx and after MT were evaluated using MFS and MAS. FT-AT were blindly assessed using predetermined cutoffs. The primary biochemical endpoint was the percentage of patients who did not progress at least 0.20 for FT or 0.25 for AT corresponding to 1 MFS and 1 activity grade respectively, at the last assay in comparison with baseline.

Results: Of 539 randomized, 357 were included, 182 not included (170 with < 2 FT and 12 with not interpretable FT). Baseline characteristics were similar to the overall trial: PEG (n=174) and OBS patients (n=183): 75% male, mean age 50 years, mean weight 76kg, 74% viral load >600,000IU/mL, and 94% genotype 1, median FT 0.67, AT 0.62. Using FT equivalence of MFS, significantly more patients worsened in OBS vs PEG (14% vs 6%; *P* = .02) and using AT equivalence more PEG patients improved in activity METAVIR grade AS vs OBS (16% vs 5%; *P* =.001). There was significant worsening in fibrosis estimated using last FT, in controls vs patients treated with PEG, as well as for necro-inflammatory activity estimated using last AT (table). Impact by time is in Table.

Conclusions: Using biomarkers this randomized trial demonstrated improvement of both fibrosis and necroinflammatory estimates with PEG maintenance therapy. Due to the risk of under powered conclusions, using biopsy as the main endpoint in maintenance therapy clinical trials should be revisited.

Table. Fibrotest and Actitest over Time (mean change from baseline; 95%CI)

	FIBROTEST				ACTITEST			
	1 year	2 years	3 years	Last	1 year	2 years	3 years	Last
PEG-IFN	-0.003 (-0.02 : 0.02)	-0.004 (-0.03 : 0.02)	-0.01 (-0.01 : 0.04)	-0.002 (-0.03 : 0.02)	-0.03 (-0.06 : -0.00)	-0.07 (-0.10 : -0.04)	-0.09 (-0.12 : -0.05)	-0.08 (-0.12 : -0.05)
Control	0.01 (-0.01 : 0.04)	0.03 (0.01 : 0.05)	0.06 (0.04 : 0.09)	0.04 (0.01 : 0.06)	0.01 (-0.02 : 0.04)	0.01 (-0.02 : 0.04)	0.02 (-0.01 : 0.05)	0.02 (-0.02 : 0.05)
Signifi-cance	0.28	0.05	0.003	0.01	0.03	0.0001	<0.0001	<0.0001

Negative value is an improvement. Positive value is a worsening.

Note: This abstract has been modified since submission.

Background

- Assessment of fibrosis stage is useful for predicting therapeutic outcomes in patients undergoing treatment for chronic hepatitis C
  - Because of the limitations of liver biopsy, several noninvasive methods have been developed as alternatives
- FibroTest (BioPredictive, Paris, France) and Actitest are validated sensitive noninvasive markers of liver fibrosis with similar prognostic values that have been validated in patients with chronic hepatitis C[1,2]
- Diagnostic and prognostic values of FibroTest have similar accuracy to those of a biopsy specimen 25 mm in length, at baseline and in longitudinal studies[3,4]
  - In a recent meta-analysis of patients with hepatitis B and C from 12 published studies, similar estimates of the effect of treatment on liver fibrosis progression were derived when using FibroTest or liver biopsy[4]
  - FibroTest is approved in France for first-line assessment of fibrosis and cirrhosis in patients with chronic hepatitis C[5]
- FibroTest has been extensively studied during retreatment of previous nonresponders or relapsers and in cirrhotic patients undergoing maintenance therapy[6,7]

Aim

- The aim of the present study was to assess if there was a treatment effect when measuring with FibroTest and ActiTest compared with liver biopsy in patients with METAVIR F2/F3 score

Patients and Methods

Study Design

- The EPIC³ F2/F3 study was a multicenter, open-label, randomized study
- Eligible patients were randomized to receive peginterferon (PEG-IFN) alfa-2b (0.5 µg/kg/wk) or no treatment (observational control) for 36 months
  - Randomization was stratified according to METAVIR score (F2 vs F3) and patient age (≤50 years vs >50 years)

Patients

- Adult patients aged 18-65 years with chronic hepatitis C who failed to respond to retreatment with PEG-IFN alfa-2b (1.5 µg/kg/wk) plus ribavirin (800-1400 mg/day) for a minimum duration of 12 weeks in the EPIC³ retreatment study[7]
- Inclusion criteria:
  - Biopsy-confirmed F2 or F3 liver fibrosis
  - Alpha-fetoprotein ≤200 ng/mL for patients who had a METAVIR fibrosis score of F2 or ≤100 ng/mL for patients who had a METAVIR fibrosis score of F3
  - Patients who had a METAVIR fibrosis score of F3 must have had an abdominal ultrasound showing no evidence of focal mass suggestive of hepatoma and/or ascites
- Patients with evidence of decompensated liver disease or hepatocellular carcinoma, or with HIV or hepatitis B virus coinfection were excluded

Assessments

- Blinded liver biopsies obtained before retreatment and after maintenance therapy were evaluated using METAVIR fibrosis score
  - The change in fibrosis was expressed as improved or worsened by 1 or more units, or no change
- FibroTest and ActiTest were blindly assessed using predetermined cutoffs
- 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 METAVIR fibrosis score and 1 activity grade, respectively, at their last assay compared with baseline

Results

- 540 patients (all-enrolled population) were randomized to treatment, of whom 357 (FibroTest study population) were included in the present analysis
- 182 randomized patients were not included
  - 170 patients had <2 FibroTest results
  - 12 patients had FibroTest results that were not interpretable
- Baseline characteristics were similar between the all-enrolled population and patients with FibroTest evaluations (**Table 1**):
  - 74% were male, mean age was 50 years, mean weight was 76 kg, 75% had a viral load >600,000 IU/mL, and 94% were infected with genotype 1
  - Median FibroTest score was 0.67
  - Median ActiTest score was 0.62

Table 1. Patient Baseline Characteristics

	Fibrotest Study Population (n = 357)		All Enrolled (n = 540)	
	PEG-IFN alfa-2b (0.5 µg/kg/wk) (n = 174)	Control (n = 183)	PEG-IFN alfa-2b (0.5 µg/kg/wk) (n = 270)	Control (n = 270)
Male/female, %	74/26	69/31	72/28	70/30
Age, mean (SD), y	50.1 (8.2)	49.6 (8.4)	49.8 (8.4)	49.2 (8.6)
Body weight, mean (SD), kg	75.9 (14.1)	75.8 (14.5)	76.0 (14.4)	75.4 (14.0)
Race, n (%)				
White	140 (80)	146 (80)	217 (80)	218 (81)
Nonwhite	34 (20)	37 (20)	53 (20)	52 (19)
Genotype, n (%)				
1	163 (94)	169 (92)	248 (92)	249 (92)
2/3	5 (3)	6 (3)	14 (5)	9 (3)
Other/missing/ nontypable	6 (3)	8 (4)	8 (3)	12 (4)
Viral load, n (%)				
>600,000 IU/mL	130 (75)	125 (68)	193 (71)	183 (68)
≤600,000 IU/mL	44 (25)	57 (31)	77 (29)	86 (32)
METAVIR fibrosis score, n (%)				
2	84 (48)	88 (48)	123 (46)	122 (45)
3	90 (52)	95 (52)	147 (54)	148 (55)
METAVIR activity score, n (%)				
0	12 (7)	8 (4)	19 (7)	14 (5)
1	132 (76)	151 (83)	203 (75)	216 (80)
2	27 (16)	23 (13)	45 (17)	38 (14)
3	3 (2)	1 (1)	3 (1)	2 (1)

Primary Efficacy Outcomes From the EPIC³ F2/F3 Study

- In the all-enrolled population, there was no significant difference in fibrosis score response between patients receiving PEG-IFN alfa-2b or control (**Table 2**)

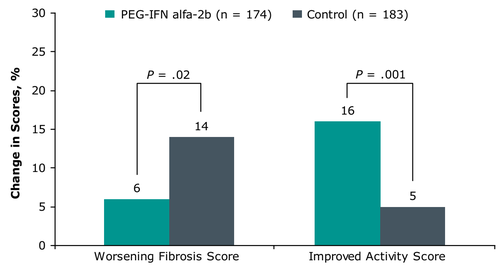
Table 2. Primary Efficacy Outcomes of the EPIC³ F2/F3 Study

	PEG-IFN alfa-2b (0.5 µg/kg/wk) (n = 270)	Control (n = 270)	*P*
Improved, n (%)	44 (16)	29 (11)	
No change, n (%)	162 (60)	176 (65)	.3192
Worsened, n (%)	64 (24)	65 (24)	

FibroTest/ActiTest Results

- Using FibroTest equivalence to METAVIR fibrosis score, significantly more patients worsened in the control group compared with those in the PEG-IFN alfa-2b arm (14% vs 6%; *P* = .02) (**Figure 1**)
  - Similarly, using ActiTest equivalence, more patients receiving PEG-IFN alfa-2b showed improvement in METAVIR activity grade compared with those in the control group (16% vs 5%; *P* = .001)

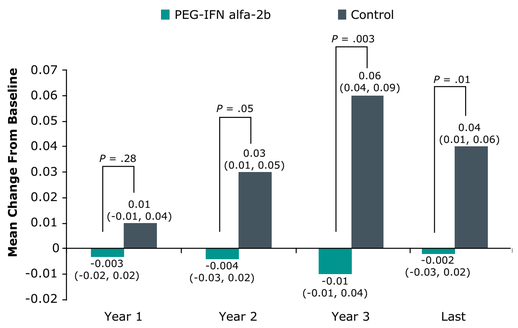
Figure 1. Change in fibrosis and necroinflammatory activity as assessed using FibroTest and ActiTest.



PEG-IFN = peginterferon.

- After 3 years of treatment, FibroTest data revealed a statistically significant improvement in fibrosis (**Figure 2**)
  - Fibrosis score, estimated using last FibroTest assessment, was significantly worse in control patients compared with patients receiving PEG-IFN alfa-2b (0.04 vs -0.002; *P* = .01)

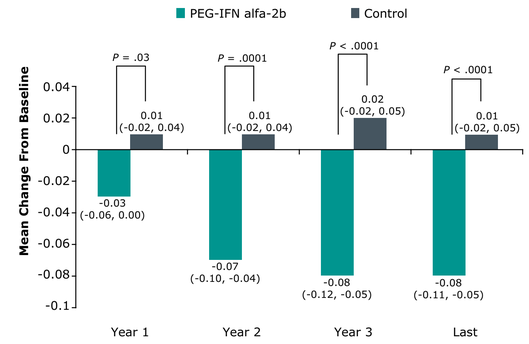
Figure 2. Mean change from baseline in fibrosis score as measured using FibroTest. Data are mean change from baseline (95% confidence interval). A negative value is an improvement and a positive value is a worsening.



PEG-IFN = peginterferon.

- Necroinflammatory activity was also significantly better in patients receiving PEG-IFN alfa-2b compared with the control group (**Figure 3**)
  - At the last clinic visit, necroinflammatory activity was significantly worse in control patients compared with patients receiving PEG-IFN alfa-2b (0.01 vs -0.08; *P* < .0001)

Figure 3. Mean change from baseline in necroinflammatory activity score as measured using ActiTest. Data are mean change from baseline (95% confidence interval). A negative value is an improvement and a positive value is a worsening.



Conclusions

- Using biomarkers, this randomized trial demonstrated improvement of both fibrosis and necroinflammatory estimates with PEG-IFN alfa-2b maintenance therapy
- Due to the risk of underpowered conclusions, use of biopsy as the main end point in maintenance therapy clinical trials should be revisited

Acknowledgments

L. Colombato, J. Curciarello, H. Fainboim, A. Gadano, M. Silva, H. Tanno, R. Terg, W. Cheng, D. Crawford, J. George, G. Jeffrey, B. Leggett, L. Mollison, M. Ngu, S. Roberts, D. Routley, W. Sievert, H. Brunner, A. Maieron, J. Delwaide, Y. Horsmans, H. Van Vlierberghe, A. Barone, H. S. M. Coelho, M. L. G. Ferraz, R. P. F. Filho, R. Focaccia, F. L. Goncales, A. Mattos, M. Mauad, C. Brandao Mello, D. A. Muzzillo, H. Rosa, R. Teixeira, F. Anderson, K. W. Burak, R. Enns, V. Feinman, K. S. Gutfreund, E. J. Heathcote, N. Hilzenrat, K. Kaita, P. Marotta, K. Peltekian, F. Wong, A. Varon, K. Barange, M. Bourliere, J.-P. Bronowicki, X. Causse, P. Marcellin, R. Poupon, A. Tran, C. Trepo, P. Buggisch, W. Caselmann, D. Haeussinger, H. Hinrichsen, M. Manns, R. Guenther, C. Niederau, W. Schmidt, U. Spengler, R. Zachoval, S. Zeuzem, E. Manesis, A. Alberti, M. Colombo, A. Picciotto, M. Podda, M. Rizzetto, E. Villa, A. L. Zignego, A. Craxi, J.-L. Poo-Ramirez, A. Carvalho, A. M. Vale, A. Reymunde, J. Sanchez-Tapias, D. Toro-Lugo, E. Torres, R. P. Alvarez, J. L. Calleja, M. A. Serra Desfilis, R. Esteban-Mur, M. Ramos, G. Castellano, R. Planas Vila, R. Hultcrantz, B. Muellhaupt, J. Reichen, M.-Y. Lai, G. Dusheiko, W. Rosenberg, L. Balart, H. Bodenheimer, S. Flamm, S. Gordon, I. Jacobson, P. King, P. Kwo, L. Marsano, A. J. McCullough, T. McGarrity, J. McHutchison, M. P. Pauly, R. Perrillo, F. Poordad, R. Reindollar, V. Rustgi, W. Schmidt, O. Shaikh, K. Sherman, C. Smith, M. Sulkowski, N. Tsai. Editing assistance was provided by T. Ibbotson, PhD, and C. Knight, PharmD. This assistance was funded by Schering-Plough Corporation, now Merck & Co., Inc., Whitehouse Station, NJ, USA.

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Disclosures

T. Poynard has a capital interest in BioPredictive, the company marketing FibroTest, and M. Munteanu is a full-time employee of BioPredictive. T. Poynard, T. Berg, and E. R. Schiff are members of the speaker bureau for Schering-Plough Corporation, now Merck & Co., Inc.; T. Poynard, E. R. Schiff, M. Diago, and T. Berg receive research support from Schering-Plough Corporation, now Merck & Co., Inc.; E. R. Schiff and J. Bruix are consultants for Schering-Plough Corporation, now Merck & Co., Inc.; L. G. Lyra is an investigator for this study; N. Boparai, M. Burroughs, C. A. Brass, and J. K. Albrecht are employees of Schering-Plough Research Institute, now Merck Research Institute and stockholders of Schering-Plough Corporation, now Merck & Co., Inc.; L. H. Griffel is a former employee of Schering-Plough Corporation, now Merck & Co., Inc.; R. Moreno-Otero has nothing to disclose.

Presented at the 61st Annual Meeting of the American Association for the Study of Liver Diseases, October 29–November 2, 2010, Boston, MA.

Supported by Schering-Plough Corporation, now Merck & Co. Inc., Whitehouse Station, NJ, USA.

Poster #817

Impact of PegIntron (P
Prior Nonresponders W

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Abstract

Background & Aims: The EPIC[3] F2/3 study, designed to evaluate the efficacy of low dose PEG-2b (0.5 mcg/kg/week) MT vs observation (OBS) on improvement of MFS in previous nonresponders did not demonstrate efficacy of MT. The aim of the present study was to assess if there was a treatment effect on FT and Actitest (AT), two validated sensitive non-invasive markers of fibrosis with similar prognostic values, compared to liver biopsy (LBx) (FT: FibroTest, AT: necroinflammatory activity).

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Presented at the 61st Annual Meeting of the American Association for the Study of Liver Diseases, Oc

PEG) Maintenance Therapy (MT) With METAVIR Fibrosis Scores (

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on Fibrosis Biomarkers (FibroT
MFS) of F2/F3: Final Results Fr

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a, Spain; [4]University of Miami School of Medicine, Miami, FL, USA; [5]Hosp Rafael, Salvador, Brazil; [9]Schering-Plough Corporation, now Merck & Co., now Merck & Co., Inc., Whitehouse Station, NJ, USA

Primary Efficacy Outcomes From the EPIC[3] F2/F3 Study

- In the all-enrolled population, there was no significant difference in fibrosis score response between patients receiving PEG-IFN alfa-2b or control (**Table 2**)

Table 2. Primary Efficacy Outcomes of the EPIC[3] F2/F3 Study

	PEG-IFN alfa-2b (0.5 µg/kg/wk) (n = 270)	Control (n = 270)	*P*
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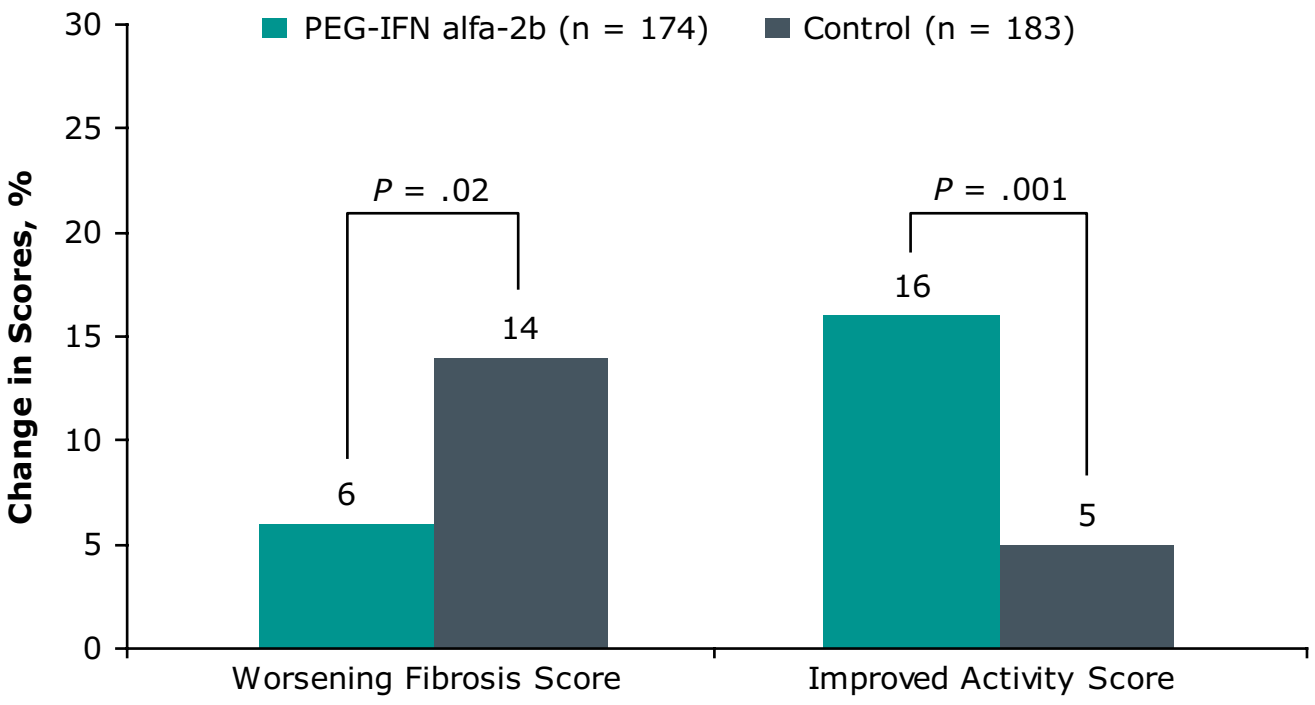
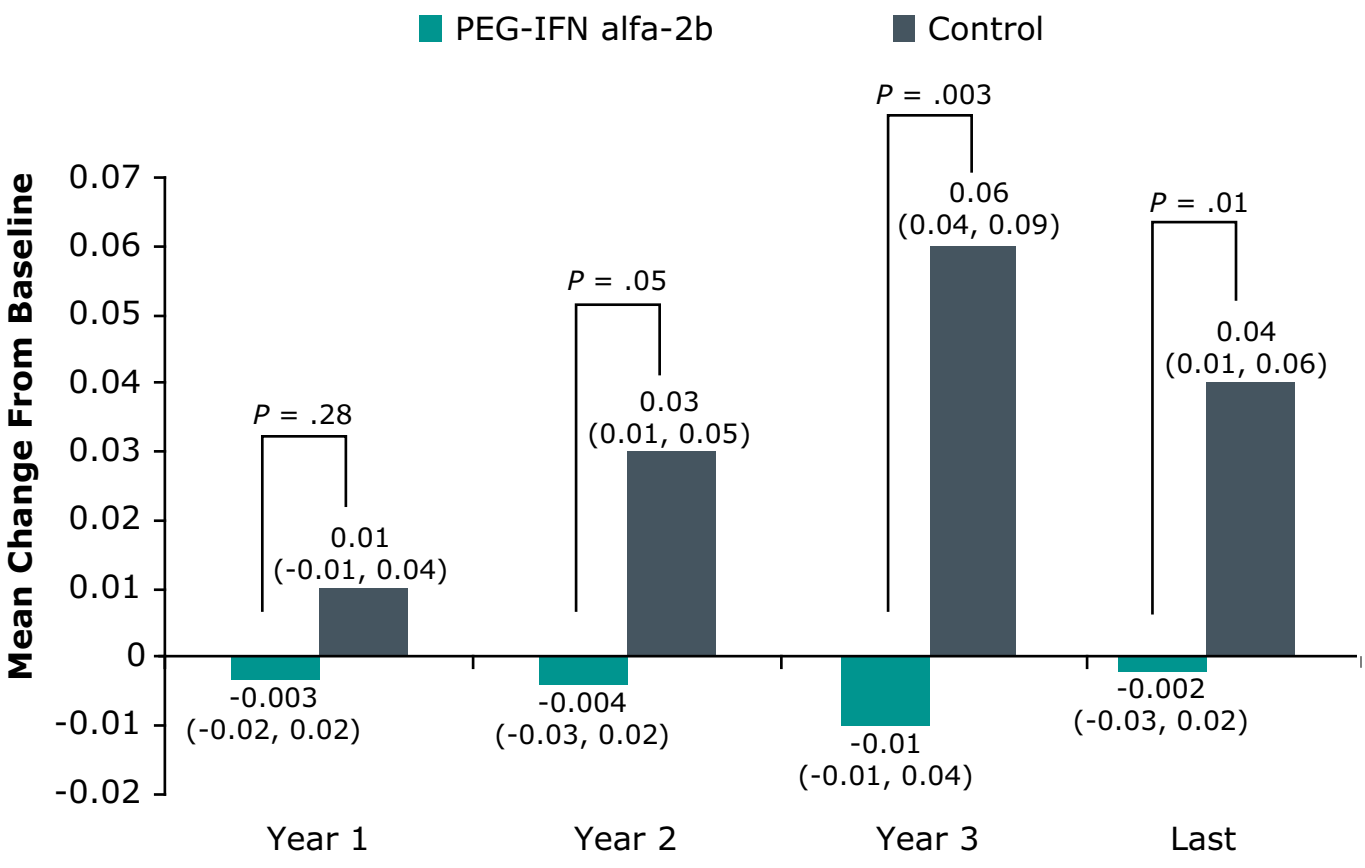


PEG-IFN = peginterferon.

- After 3 years of treatment, FibroTest data revealed a statistically significant improvement in fibrosis (**Figure 2**)
  - Fibrosis score, estimated using last FibroTest assessment, was significantly worse in control patients compared with patients receiving PEG-IFN alfa-2b (0.04 vs -0.002; *P* = .01)

Figure 2. Mean change from baseline in fibrosis score as measured using FibroTest. 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.

- Necroinflammatory activity was also significantly better in patients receiving PEG-IFN alfa-2b compared with the control group (**Figure 3**)
  - At the last clinic visit, necroinflammatory activity was significantly worse in control patients compared with patients receiving PEG-IFN alfa-2b (0.01 vs -0.08; *P* < .0001)

Test [FT]/FibroSURE) in rom the EPIC³ Program

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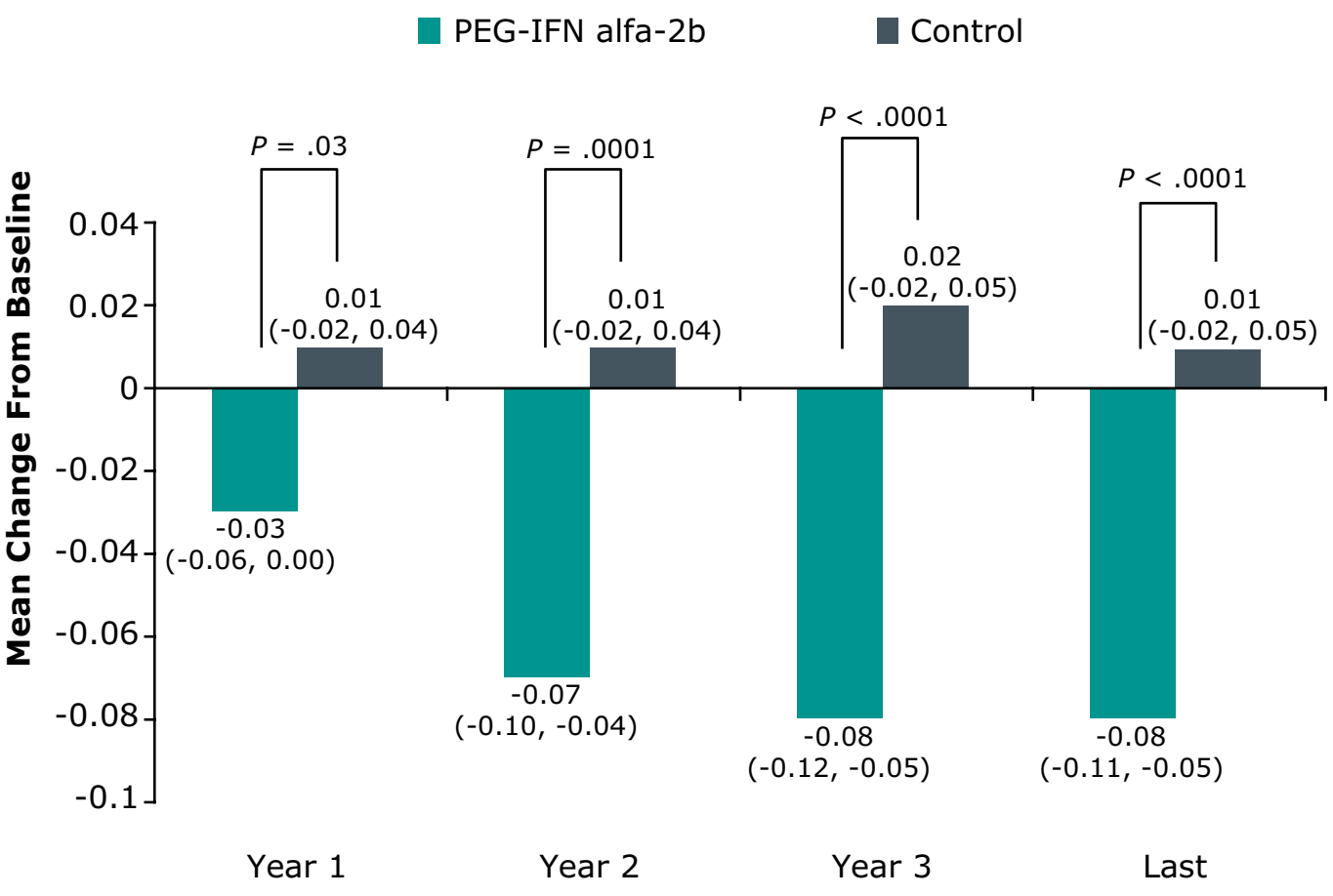
Figure 3. Mean change from baseline in necroinflammatory activity score as measured using ActiTest. Data are mean change from baseline (95% confidence interval). A negative value is an improvement and a positive value is a worsening.



Conclusions

- Using biomarkers, this randomized trial demonstrated improvement of both fibrosis and necroinflammatory estimates with PEG-IFN alfa-2b maintenance therapy
- Due to the risk of underpowered conclusions, use of biopsy as the main end point in maintenance therapy clinical trials should be revisited

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Disclosures

T. Poynard has a capital interest in BioPredictive, the company marketing FibroTest, and M. Munteanu is a full-time employee of BioPredictive. T. Poynard, T. Berg, and E. R. Schiff are members of the speaker bureau for Schering-Plough Corporation, now Merck & Co., Inc.; T. Poynard, E. R. Schiff, M. Diago, and T. Berg receive research support from Schering-Plough Corporation, now Merck & Co., Inc.; E. R. Schiff and J. Bruix are consultants for Schering-Plough Corporation, now Merck & Co., Inc.; L. G. Lyra is an investigator for this study; N. Boparai, M. Burroughs, C. A. Brass, and J. K. Albrecht are employees of Schering-Plough Research Institute, now Merck Research Institute and stockholders of Schering-Plough Corporation, now Merck & Co., Inc.; L. H. Griffel is a former employee of Schering-Plough Corporation, now Merck & Co., Inc.; R. Moreno-Otero has nothing to disclose.

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