Impact of PegInteron (PEG) Maintenance Therapy (MT) on Fibrosis Biomarkers (FibroTest [FT]/FibroSURE) in Prior NonResponders With METAIVIR Fibrosis Scores (MFS) of F2/F3: Final Results From the EPIC Program


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Abstract

Background & Aims: The EPIC-F2/F3 study, designed to evaluate the efficacy of low dose peginterferon alfa-2b alone or in combination with ribavirin in the treatment of chronic hepatitis C, did not show significant improvements in METAIVIR fibrosis scores for the entire study population, nor did significant differences in fibrosis estimates with respect to treatment arms, in patients with METAVIR fibrosis score (F2/F3) of 0.10 or less.

Methods: Patients with F2/F3 METAIVIR scores who failed treatment were randomized to receive placebo (PLA) or interferon (IFN) alone or in combination with ribavirin (RIB) for 48 weeks. Biopsies were obtained before and after 12 weeks of treatment and METAVIR fibrosis score was derived using the best biopsy available. The mean change in METAVIR fibrosis score was compared to baseline using the paired t-test, and fibroscan values were compared to liver biopsy (FibroScan, bioMérieux, Lyon, France).

Background: The aim of the present study was to assess if there was a treatment effect when measuring biochemical endpoints in patients receiving PEG-IFN alfa-2b (0.5 µg/kg/wk) alone or in combination with ribavirin for 36 months. Eligible patients were randomized to receive peginterferon (PEG-IFN) alfa-2b (0.5 µg/kg/wk) compared with liver biopsy (FibroScan, bioMérieux, Lyon, France).

Conclusions:

- Baseline characteristics of patients randomized to receive PEG-IFN alfa-2b were similar to those of patients randomized to receive placebo except for baseline biochemical endpoint, the percentage of patients who did not progress at least 0.20 for FT or 0.25 for controls vs patients treated with PEG, as well as for necro-inflammatory activity estimated using last FT (Table)."
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Abstract

Background & Aims: The EPIC-F2/F3 study, designed to evaluate the efficacy of low dose IFN-alfa in fibrosis stage F2/F3 in nonresponders to PEG maintenance therapy had no significant fibrotic advantage due to treatment. The aim of the present study was to assess if there was a treatment effect on F2/F3 (95% CI) in nonresponders to PEG maintenance therapy.

Methods: Patients with F2/F3 MFS who failed retreatment (β = 0.04) to randomised to FT or placebo (α = 0.05). Baseline and follow-up data were collected for 36 months. FT was used as the primary endpoint to assess if there was a treatment effect on FT and ActiTest (2 validated sensitive non-invasive markers of fibrosis with similar prognostic values as liver biopsy). Data were 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 necro-inflammatory estimates with PEG maintenance therapy. Due to the risk of underpowered conclusions, use of liver biopsy as the main end point in maintenance therapy clinical trials should be revisited.

Background

• Assessment of fibrosis stage is useful for predicting therapeutic outcomes in patients undergoing treatment of chronic hepatitis C. It is estimated that the rate of progression of fibrosis stage is 0.01/yr ± 30%.

• FibroTest (BioPredictive, Paris, France) and ActiTest (Schering-Plough Corporation, now Merck & Co., Inc.) are two validated sensitive non-invasive markers of liver fibrosis with similar prognostic values that have been validated in large clinical trials. Positive value is a worsening.

• The primary biochemical end point was the percentage of patients who did not progress at least 0.20 unit/year (95% confidence interval).

• Baseline characteristics were similar to the overall trial: PEG-IFN-alfa-2b compared with the control group (1.5 µg/kg/wk) for patients receiving PEG-IFN •

• Necro-inflammation was also significantly better in patients receiving PEG-IFN F0-F1 vs F0-F1 in the control group compared with those in the PEG-IFN group (14% vs 6%; P = .01) (Figure 1).

• The primary biochemical and necro-inflammatory point estimate was a 0.01 vs -0.08; P = .01.

• The primary biochemical and necro-inflammatory point estimate was a 0.04 vs -0.002; P = .01.

• A negative value is an improvement and a positive value is a worsening.

Appendix A


Results

• 340 patients (all-enrolled population) were randomized to treatment, of whom 357 patients were derived when using FibroTest or liver biopsy.

• Aims: To assess if there was a treatment effect on FT and ActiTest (2 validated sensitive non-invasive markers of fibrosis with similar prognostic values, compared to liver biopsy ± 30%).

• Male/female, % 74/26 69/31 72/28 70/30

• Other/missing/lost, % 3 (2) 3 (2) 3 (2) 3 (2)

• Race, % 61 (41) 61 (41) 61 (41) 61 (41)

• Other, % 34 (20) 37 (20) 53 (20) 52 (19)

• Positive value is a worsening.

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

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

References


Disclosures

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Background & Aims: The EPIC 2/F3 study, designed to evaluate the efficacy of low dose Peg-IFN alfa-2b (Peg-IFN) in improving MFS of patients with MFS who had progressed after interferon treatment and failed retreatment. Patients not achieving MFS improvement did not demonstrate efficacy of MT. The aim of the present study was to assess if there was a treatment effect on MFS in the MT (observed control) and MFS (peginterferon) groups over the 36 month treatment period. Results of the MT group were compared with published forensic values for noninvasive biomarkers.

Methods: Patients with MFS had randomization (1:1) to Peg-IFN or control. Changes from baseline MT endpoints at 36 months were evaluated. All patients were genotyped for IL-28B polymorphism. FibroSURE and FibroTest were used to estimate fibrosis and necroinflammatory activity. Baseline values were compared to published forensic values.

Results: Of 132 patients randomized, 105 were included. At 36 months, the mean change from baseline was: FibroSURE (16.0% vs 25.8%; P = .001) and FibroTest (5.0% vs 13.7%; P < .0001) for MT patients vs control, respectively.

Conclusions: Peg-IFN alfa-2b compared with control is associated with significant improvement in fibrosis and necroinflammatory activity. Use of noninvasive biomarkers as an endpoint is feasible and may provide additional monitoring tools for the treatment of chronic hepatitis C.

References

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Disclosures

The authors have no conflicts of interest to disclose.

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Abstract

Background & Aims: The EPIC-F2/F3 study, designed to evaluate the efficacy of low dose PEG-IFN alfa-2b (0.5 µg/kg) in the improvement of METAVIR fibrosis scores in nonresponders did not demonstrate efficacy of MT. The aim of the present study was to assess if there was a treatment effect on FT/FTs compared with liver biopsy in patients receiving PEG-IFN scores (MFS) of F2/F3.

Methods: Patients with F2/F3 MFS who failed retreatment (270) were randomized to PegIntron (PEG) alfa-2b (n = 270) or observation (OBS) (n = 174). Blinded liver biopsies obtained before and after FTs were evaluated in the FibroSURE study. The primary endpoint was the change in METAVIR fibrosis score at 48 weeks in a post hoc analysis of patients in MT compared with OBS. Biochemical variables, correlated with liver biopsy activity (FTs), and necroinflammatory activity (ACTs).

Results: Of 443 randomized, 307 were included, 183 included (170 with F2 FTs and 12 with non-interpretable FTs). Baseline characteristics were similar in the two arms (P > .05). In the PEG-IFN group, mean weight was 74 kg, 75% were male, mean age was 50 years, and 75% had a viral load >600,000 IU/mL. 74% were male, mean age was 50 years, mean weight was 76 kg, 75% had a viral load >600,000 IU/mL, and 94% genotype 1, median FT 0.67, AT 0.62. Using FTs assessment in comparison with baseline.

Conclusions: PegIntron improved METAVIR fibrosis score in previous relapsers and in cirrhotic patients undergoing maintenance therapy. Further prospective studies are needed to confirm these findings.

Acknowledgments

References

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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) plus ribavirin (1000-1400 mg/day) for a minimum duration of 48 weeks.

Inclusion criteria:
- Baseline confirmed F3 liver fibrosis
- Alpha-2A/2B papilloma virus RNA in serum

Exclusion criteria:
- Patients who had a METAVIR fibrosis score of ≤ F1
- Patients with a METAVIR fibrosis score of ≥ F4
- Patients with active hepatitis B infection or active hepatitis D infection
- Patients with evidence of decompensated liver disease or hepatocellular carcinoma, or with HIV or hepatitis B virus coinfection

Methods:
- Patients with F2/F3 METs at the time of retreatment (80% were randomized to Peg-IFN alfa-2b at 0.5 µg/kg and 20% to control) were included.
- Liver biopsies were obtained before retreatment and after 1 year of retreatment and were used to determine a METAVIR fibrosis score.
- Control patients were treated with Peg-IFN alfa-2b at 0.5 µg/kg plus ribavirin (1000-1400 mg/day) for 48 weeks.