Poster #1216

Impact of Advanced Fibrosis and Cirrhosis on Sustained Virologic Response of HCV G1-Infected Patients: Results of The Canadian POWeR Program

THE POWER STUDY

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Abstract

Aim: To evaluate the impact of advanced fibrosis/cirrhosis on SVR rates in treatment-naive genotype (G) 1-infected chronic hepatitis C patients treated with weight-based PEG-IFN alfa-2b and weight-based ribavirin (RBV) in "real-life" clinical settings.

Methods: The POWeR program was a prospective, noninterventional, observational study conducted at 138 community and academic centers in Canada. HCV G1-infected patients were treated for up to 48 weeks with PEG-IFN alfa-2b (1.5 µg/kg/wk) plus weight-based RBV (800-1200 mg/d). This ITT analysis includes G1 patients with a liver biopsy result (assigned METAVIR score of F1-F4) who received at least one treatment dose; HIV/HCV coinfected patients were excluded. SVR was defined as undetectable HCV RNA 24 weeks post-treatment. Statistical analysis was performed with Fisher exact test.

Results: This ITT analysis involved 718 G1-infected HCV patients with liver biopsy specimens, 60% (432/718) with mild to moderate fibrosis (F1-F2), and 40% (286/718) with advanced fibrosis/cirrhosis (F3-F4). Baseline viral load results were available for 651/718 (91%) patients, revealing high viral load (HVL, >600,000 IU/mL) in 356/651 (55%) patients. In this ITT analysis, the SVR rate was 38% (272/718). SVR rates in patients with F1, F2, F3, and F4 fibrosis were 52%, 46%, 26%, and 18%, respectively. End-of-treatment (EOT) responses were significantly higher in patients with F1-F2 fibrosis than in those with F3-F4 advanced fibrosis/cirrhosis (59% vs 34%, $P < 0.0001$); corresponding SVR rates were 48% and 22% ($P < 0.0001$). Relapse after EOT response was higher in patients with F3-F4 than F1-F2 fibrosis (35% vs 18%, $P = 0.0009$). Patients with F1-F2 fibrosis and low viral load (LVL, ≤600,000 IU/mL; n = 172) achieved significantly higher SVR rates than those with F1-F2 and HVL (n = 219) (58% vs 41%, $P = 0.0008$); however, the effect of HVL on SVR was not apparent among patients with F3-F4 advanced fibrosis or cirrhosis (20% LVL vs 21% HVL, P = ns; n = 123 and 137, respectively).

Conclusions: Advanced hepatic fibrosis clearly diminished SVR rates in treatment-naive G1 HCV patients treated with PEG-IFN alfa-2b plus weight-based RBV therapy. Advanced fibrosis/cirrhosis superseded the impact of viral load, as HVL reduced SVR rates in patients with mild/moderate fibrosis but not those with advanced disease. These results suggest that G1 patients with advanced fibrosis require additional therapeutic approaches, including modified dose and/or duration of treatment, to optimize outcomes.

Note: Abstract has been updated since submission.

Background

- In randomized controlled trials (RCTs), a sustained virologic response (SVR) was attained by 54% to 63% of patients with chronic hepatitis C who receive pegylated interferon (PEG-IFN) alfa plus ribavirin[1-3]
  - — However, patients with hepatitis C virus (HCV) genotype 1 (G1) infection are particularly difficult to treat, and SVR rates in this population ranged from 42% to 52%[1-3]
- In G1-infected patients, baseline viral load and stage of fibrosis are important predictors of treatment outcome[3]
  - — SVR rates were greater in G1 patients with low baseline viral loads than in those with high baseline viral loads (65% vs 47%)[3]
  - — SVR rates were lower in G1 patients with bridging fibrosis or cirrhosis than in those with milder liver disease (41% vs 57%)[3]
- However, these RCTs were tightly controlled to limit patient variability and to govern treatment regimens
  - — The rigor of RCTs is rarely attained in the community setting, leading many to question whether the results from phase 3 RCTs can be achieved in everyday clinical practice
- The Pegetron® (PEG-IFN alfa-2b; Schering-Plough) Prospective Optimal Weight-Based Dosing Response (POWeR) study was a Canadian, prospective, open-label, noninterventional, phase 4, community- and academic-based therapeutic outcomes study that enrolled patients with chronic hepatitis C who were previously naive to treatment

Aim

- To determine the influence of liver fibrosis and viral load on SVR rates in patients with chronic hepatitis C caused by HCV G1 infection who were treated with weight-based PEG-IFN alfa-2b and weight-based ribavirin in a "real-life" clinical setting

Patients and Methods

Patients

- The POWeR study was a multicenter program conducted at 138 community and academic centers in Canada between 2002 and 2007
- Patients were treated, followed up, and managed according to the Canadian product monograph, current treatment guidelines, and standard of care at each site, with no study-related intervention beyond collection of data
- Patient characteristics collected at baseline included:
  - — Genotype
  - — Liver histology: determined by liver biopsy and given a METAVIR score of F1 (mild), F2, F3, or F4 (cirrhosis)
  - — Viral load: defined as low (≤600,000 IU/mL) or high (>600,000 IU/mL)

Treatment

- Patients were treated with a weight-based dosing regimen of PEG-IFN alfa-2b (1.5 µg/kg/wk) plus ribavirin (800-1200 mg/d)
  - — Ribavirin dosing
    - <64 kg = 800 mg/d
    - 64 to <85 kg = 1000 mg/d
    - ≥85 kg = 1200 mg/d
- Recommended standard-of-care treatment duration was 48 weeks

Efficacy Assessments

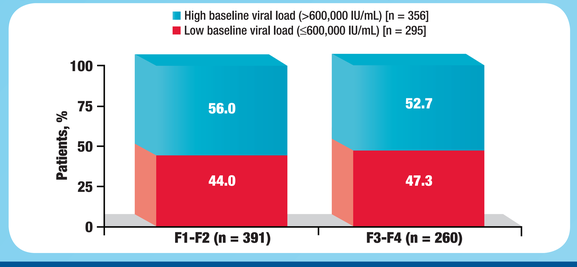
- The primary end point was SVR, defined as undetectable HCV-RNA (<50 or <600 IU/mL, depending on study site) 24 weeks after the completion of treatment
- Secondary end points were:
  - — End of treatment (EOT) response and relapse rates
  - — EOT response was defined as undetectable serum HCV RNA immediately after the completion of therapy
  - — Relapse was defined as attainment of EOT response but with recurrence of viremia during the 24-week posttreatment follow-up period
- This intent-to-treat (ITT) analysis included all G1 patients who had liver biopsy results and who received at least 1 treatment dose
- Statistical analysis was performed using the two-tailed Fisher exact test

Results

Patient Characteristics

- In total, 1950 HCV-monoinfected patients were enrolled and treated: 60% (n = 1161) had HCV G1 infection; 15% (n = 298) had HCV G2 infection; 22% (n = 431) had HCV G3 infection; 2% (n = 44) were infected with other genotypes; and 16 (<1%) had missing genotype data
- This ITT subanalysis is based on 718 HCV G1-infected patients who had pretreatment METAVIR fibrosis scores from F1 to F4, based on liver biopsy specimen analysis
- Overall, 432 of 718 (60%) patients had mild to moderate fibrosis scores (F1-F2), and the remaining 286 (40%) patients had bridging fibrosis or cirrhosis (F3-F4)
- Baseline viral load data were available for 651 of 718 (91%) patients
  - — 356 (55%) patients had high baseline viral loads (>600,000 IU/mL), and 295 (45%) patients had low baseline viral loads (≤600,000 IU/mL)
- Combined fibrosis and baseline viral load distributions are shown in **Figure 1**

Figure 1. Patient fibrosis and baseline viral load characteristics (n = 651).

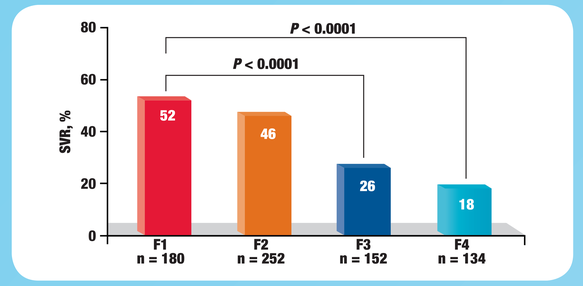


Response Rates

SVR Rates According to Fibrosis Score

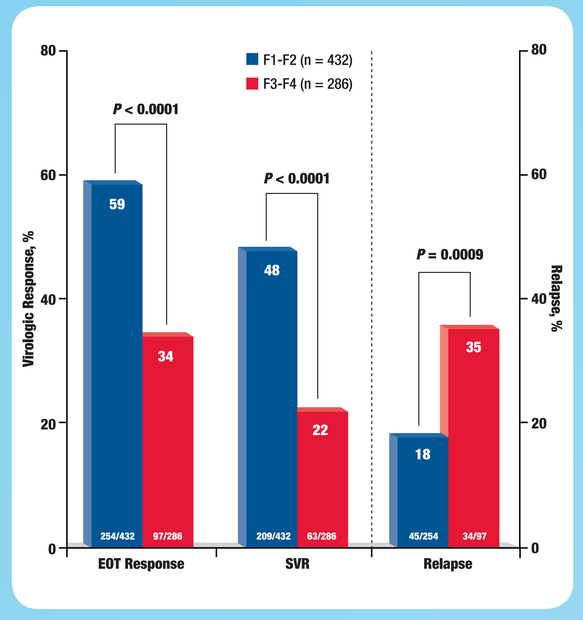
- Based on ITT analysis, the SVR rate in this treatment-naive G1 population was 38%
- SVR rates were highest in patients with F1 fibrosis and lowest in patients with cirrhosis (**Figure 2**)

Figure 2. SVR rates according to METAVIR fibrosis score. F# = fibrosis score; SVR = sustained virologic response.



- EOT response and SVR rates were significantly higher in patients with mild to moderate fibrosis (F1-F2) than in those with bridging fibrosis or cirrhosis (F3-F4) ($P < 0.0001$; **Figure 3**)
- Relapse rates were significantly higher in patients with F3-F4 than with F1-F2 fibrosis scores (35% vs 18%; $P = 0.0009$; **Figure 3**)

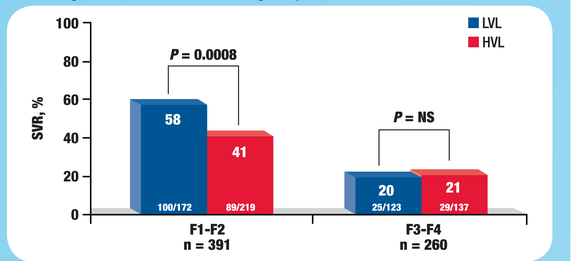
Figure 3. Virologic outcomes according to METAVIR fibrosis score. EOT = end of treatment; SVR = sustained virologic response.



Virologic Response Rates According to Viral Load

- Among patients with mild to moderate fibrosis (F1-F2), SVR rates were significantly higher in those with low baseline viral loads than in those with high baseline viral loads (58% vs 41%; $P = 0.0008$; **Figure 4**)
- However, among patients with bridging fibrosis or cirrhosis (F3-F4), there was no significant difference in SVR rates in patients with high or low baseline viral loads (21% vs 20%; **Figure 4**)

Figure 4. SVR according to METAVIR fibrosis score and viral load. F# = fibrosis score; HVL = high baseline viral load (>600,000 IU/mL); LVL = low baseline viral load (≤600,000 IU/mL); NS = not significant; SVR = sustained virologic response.



Summary

- HCV G1-infected patients with bridging fibrosis or cirrhosis attained significantly lower SVR rates than patients with less advanced liver disease
  - — In patients with bridging fibrosis or cirrhosis, baseline viral load was not a significant predictor of SVR
  - — The effect of viral load on SVR rates was only apparent in HCV G1-infected patients with minimal fibrosis (F1-F2)
- In HCV G1-infected patients, fibrosis score was the most clinically relevant baseline indicator of SVR and relapse
- Future investigations should focus on measures that may reduce relapse, such as maximizing ribavirin dose, increasing treatment duration, and using combination therapy with STAT-C molecules

Conclusions

- Treating HCV G1-infected patients early, before the onset of advanced liver disease, should help improve HCV antiviral treatment outcomes
- HCV G1-infected patients with F3-F4 bridging fibrosis/cirrhosis require additional therapeutic approaches, which may include modified dosing, modified duration of treatment, or both, to optimize outcomes

Acknowledgments

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References

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Disclosures

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