

Consensus Interferon May Help Hepatitis C Patients Failing Initial Therapy

by Anthony J. Brown, MD

June 12, 2009 — Consensus interferon (CIFN) combined with ribavirin is a safe and effective treatment for some patients with chronic hepatitis C who did not respond to initial therapy with pegylated interferon and ribavirin, new research shows.

CIFN, also referred to as interferon alfacon-1 and by the brand name *Infergen*, is a wholly synthetic interferon.

Up to 50% of patients fail to respond to pegylated interferon and ribavirin as initial therapy for chronic hepatitis C, according to the report in the June issue of *Hepatology*. Failure to eliminate the virus places patients at risk for progression of their liver disease.

The best approach for patients who fail to respond to initial therapy is unclear, the report indicates. Some physicians have adopted a "watchful waiting" approach and "are anticipating new antiviral therapies with either protease inhibitors or polymerase inhibitors." The safety and efficacy of these new agents when combined with peginterferon and ribavirin in treating nonresponders, however, remain to be determined.

This study is the first to examine the use of CIFN in patients who have failed to respond to initial therapy, lead researcher Dr. Bruce R. Bacon, from Saint Louis University School of Medicine, told *Reuters Health*.

"The population of patients enrolled in the study was a very difficult-to-treat group, with a high proportion of patients who were prior null responders and about 60% of patients with advanced fibrosis/cirrhosis," he explained. "That any of these patients responded is good news."

The study involved 487 patients who failed initial therapy with peg-interferon and ribavirin and were treated with CIFN and ribavirin. Roughly half of the patients received CIFN at a dose of 9 mcg/day and half received CIFN at a dose of 15 mcg/day.

In the overall analysis, the sustained virologic response rates were 6.9% and 10.7% in the 9- and 15-microgram/day CIFN groups, respectively. When the analysis looked at patients with a $>2\text{-log}_{10}$ drop in hepatitis C virus RNA during initial therapy with peg-interferon, the corresponding rates jumped to 11% and 23%.

In patients with lower baseline fibrosis scores (F0 to F3), the sustained virologic response rates were 7.8% and 13.1% in the 9- and 15-mcg/day CIFN groups, respectively. Once again, the corresponding rates were higher when only patients with a $>2\text{-log}_{10}$ drop in hepatitis C virus RNA during initial therapy were considered: 10.7% and 31.6%.

Adverse events were common, although rarely a cause for treatment discontinuation. Neutropenia, fatigue, leucopenia, depression, and nausea were among the most common side effects.

"The current study shows the benefit CIFN holds for difficult-to-treat patients with chronic hepatitis C who have failed to respond to previous treatment with pegylated interferon and ribavirin," the researchers state. "The greatest sustained virologic response rate during retreatment in the present study was observed in F0-F3 patients who had a partial virologic response during their prior course of treatment."

Dr. Bacon added, "The take-home message is to select your patients carefully, and that this is an opportunity to try a new form of treatment in prior non-responders."

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Clinical Context

In patients with hepatitis C virus adherent to treatment the combination of peg-interferon and ribavirin produces a 50% to 60% sustained virologic response (SVR) rate but more than one third are classified as nonresponders and are at risk of chronic liver disease and may require live transplantation.

This is a phase 3 randomized, open-label safety and efficacy study of 2 doses of CIFN (9 and 15 µg/day) given with ribavirin in nonresponders to the peg-interferon with ribavirin combination. It was conducted at 44 sites in the United States and Puerto Rico.

Study Highlights

- The study was divided into 2 sections: DIRECT-001 and DIRECT-002, in which the first phase tested a no-treatment group that was randomized after 24-week observation.
- Patients were men and women chronically infected with hepatitis C virus by liver biopsy and based on being positive for serum antihepatitis C virus and/or hepatitis C virus RNA.
- The Metavir scoring system was used to classify hepatic fibrosis.
- Patients with advanced liver disease were included if they had normal liver function and no prior hepatic decompensation.
- Prior nonresponse to treatment was documented by chart review, and those noncompliant with prior treatment were excluded.
- Plasma hepatitis C virus RNA levels were determined by bDNA and transcription-mediated amplification (TMA) assays.
- Patients were randomized to 3 groups: CIFN 9 (n = 171) or CIFN 15 (n = 172) µg/day with ribavirin 1000 to 1200 mg/day based on body weight and no treatment (n = 173) in the 001 section.
- At 24 weeks, the no-treatment group was also randomized to one of the 2 treatments (DIRECT-002 section).
- Treatment continued to week 48, with follow-up at weeks 52, 60, 68, and 72.
- Primary outcome was proportion with SVR defined as undetectable hepatitis C virus RNA by both bDNA and TMA assays 24 weeks after the last dose of drug.
- Secondary outcomes were adverse effects, and SVR was explored for effect of demographic factors and cirrhosis.
- Mean age was 50 years, 70% were men, 63% were white, and 20% were African American.
- 95% had hepatitis C virus genotype 1, two thirds had high viral load at baseline, 25% had cirrhosis, 35% had bridging cirrhosis, and 52% had steatosis on liver biopsy.
- Mean body mass index was 29.5 kg/m².
- The intent-to-treat (ITT) population consisted of 487 patients who received 9 and 242 who received 15 µg/day of CIFN with ribavirin.
- By ITT analysis, pooled end-of-treatment response by TMA assay was 14.7% and 6.9% in the 9-µg/day and 18.5% and 10.7% in the 15-µg/day group for the 2 sections, respectively.
- Relapse rates pooled for both study sections were 52% and 42% for the 9- and 15-µg/day groups, respectively.
- In the no-treatment group, SVR rate was 0%.
- Overall SVR rates were 7% for the 9-µg/day and 17% for the 15-µg/day group.
- There were no statistically significant differences between the 9- and 15-µg/day groups for SVR rate.

- Patients with an early virologic response, defined as negativity at week 12 by TMA assay, were more likely to have SVR vs other patients.
- In these high responders, SVR rates were 81.3% and 63.6% for the 9- and 15- μ g/day groups, respectively.
- In slow responders, SVR rates were only 11.7% and 35.4% in the 9- and 15- μ g/day groups, respectively.
- In patients without cirrhosis, SVR rates were 7.8% and 13.1% for the 9- and 15- μ g/day groups, respectively.
- In patients with cirrhosis, SVR rates were 3.8% and 4.5%, respectively.
- Hepatitis C virus genotype 1 patients achieved an overall SVR rate of 23.1% and 88.8% in the 9- and 15- μ g/day groups, respectively.
- Patients with the best response to treatment were those with some prior response to peg-interferon/ribavirin treatment and those without cirrhosis.
- The most common reason for discontinuation was treatment failure.
- Adverse effects were similar to those reported for interferon including neutropenia, fatigue, depression, nausea, myalgia, and anemia.
- Ribavirin-induced hemolytic anemia occurred in 6.4% of patients.
- The authors concluded that the use of both doses of CIFN with ribavirin was associated with improved SVR in patients who did not respond to peg-interferon/ribavirin and best response rates were achieved in patients without cirrhosis.

Clinical Implications

- CIFN with ribavirin is associated with improved SVR in patients nonresponsive to peg-interferon with ribavirin.
- Better response to CIFN with ribavirin is achieved in those with early virologic response, in those who had some previous response to peg-interferon with ribavirin, and in those without cirrhosis.