

Hepatitis C

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Shorter Treatment for Genotypes 2 & 3

Because patients with genotype 2 or 3 HCV typically respond well to interferon-based therapy, a Norwegian research team explored whether a shorter than usual treatment duration could still be beneficial. In a non-controlled trial, researchers studied 122 patients with genotype 2 or 3 HCV treated with pegylated interferon (Peg-Intron) plus ribavirin. Results were reported in the December 2004 issue of *Hepatology*. The 95 patients (78%) who experienced an early virological response (EVR; undetectable HCV RNA at weeks 4 and 8) received treatment for 14 weeks, while the remaining 27 (22%) were treated for the standard 24 weeks. Six months after the end of therapy, 90% of those in the

14-week arm (85 out of 95) and 56% in the 24-week arm (15 out of 27) achieved sustained virological response (SVR). In other words, a larger proportion of those treated for the shorter period had successful outcomes. Genotype 3a patients with lower pre-treatment HCV viral loads were more likely to achieve SVR after 14 weeks of therapy. If larger, randomized controlled trials confirm these results, a shorter course of therapy could become standard for early responders with genotype 2 or 3 HCV, thus shortening the duration of side effect and reducing the cost of treatment.

Treatment of Patients with Normal ALT

Experts have traditionally disagreed about the benefits of treating HCV-infected

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individuals with persistently normal alanine aminotransferase (ALT) levels, in part due to the belief that people with normal ALT are unlikely to experience liver fibrosis progression. Recent research has consistently shown that a proportion of patients with normal ALT do, in fact, develop progressive liver disease, but such individuals have typically been excluded from clinical trials of HCV therapies. Fortunately, two recent studies indicate that this population can benefit from HCV treatment. In the December 2004 issue of *Gastroenterology*, S. Zeuzem and colleagues reported on a study in which subjects with at least three normal ALT measurements over an 18-month period were randomized to receive pegylated interferon (Pegasys) plus ribavirin for 24 weeks (212 patients), the same combination for 48 weeks (210 patients), or no treatment (69 patients). After 72 weeks of follow-up, 30% of participants in the 24-week arm and 52% in the 48-week arm achieved SVR, while none in the untreated group cleared HCV; corresponding SVR rates were 13% and 40% for genotype 1, and 72% and 78% for genotypes 2 and 3. The re-

searchers concluded that “[t]he efficacy and safety of [Pegasys] and ribavirin combination therapy in patients with chronic hepatitis C and persistently normal ALT levels are similar to that in patients with elevated ALT levels,” and suggested that baseline ALT should not be used to determine whether or not patients should receive treatment.

In the second study, B. Kronenberger and colleagues found that HCV viral kinetics during treatment with Pegasys plus ribavirin were similar in subjects with persistently normal (n=20) and elevated (n=19) ALT levels. Results were reported in the December 2004 issue of *Hepatology*. While patients with normal ALT had slightly less death of HCV-infected liver cells before treatment, the ability of treatment to block HCV replications and loss of infected cells during therapy were similar in both groups. However, subjects with elevated gamma-glutamyl-transpeptidase (GGT) levels fared worse in terms of HCV suppression and liver cell death. The researchers suggested that GGT levels are a better predictor of response to therapy than ALT levels.

Interferon Stabilizes Fibrosis Progression

Interferon therapy (with or without ribavirin) can stabilize and potentially improve even severe liver fibrosis or cirrhosis, according to a report in the November 2004 issue of the *European Journal of Gastroenterology and Hepatology*. French researchers studied 96 patients treated with interferon plus ribavirin and 64 treated with interferon alone. In sustained responders, the fibrosis progression rate decreased from 0.26 to -0.67 MetaVir units. Even in nonresponders, the rate decreased from 0.25 units before treatment to 0 units during therapy. One-third of sustained responders (6 out of 18) and 9% of nonresponders (4 out of 43) experienced reversion from cirrhosis (stage F4) to severe fibrosis (stage F3); however, no patients with cirrhosis had a two-point decrease. Since interferon stabilized fibrosis progression even in nonresponders treated for 12 months, the researchers suggested that longer durations of therapy should be explored in these patients.

Promising Results for BILN-2061, but Studies Put on Hold

Given the side effects, cost, and frequent lack of efficacy of interferon-based therapy in patients with genotype 1 HCV, novel agents that work by different mechanisms are urgently needed. In the November 2004 issue of *Gastroenterology*, German researchers reported early results from a series of studies of BILN-2061, an experimental HCV serine protease inhibitor being developed by Boehringer Ingelheim. In the first placebo-controlled study, 31 patients with genotype 1 HCV and minimal liver fibrosis (Ishak score 1-2) received 25, 200, or 500 mg BILN-2061 twice daily for two days. In two subsequent studies, 10 patients with advanced fibrosis (Ishak score 3-4) and 10 with compensated cirrhosis (Ishak score 5-6) were treated with 200 mg BILN-2061, also for two days. Most patients achieved viral load reductions of 2-3 logs; in the first study, slightly more subjects receiving the highest dose experienced HCV RNA decreases of at least 3 logs. Good antiviral activity was seen in patients with and without cirrhosis, and the drug was well toler-

ated in all three studies. The researchers concluded that, "BILN-2061 is a well-tolerated and very active compound that reduced serum viral RNA concentrations after 2 days of treatment in patients infected with genotype 1 HCV independent of the degree of fibrosis."

However, further clinical trials of BILN-2061 have been put on hold "pending resolution of animal toxicity issues." Although the agent was well tolerated in preclinical toxicology studies and short-term clinical trials to date, cardiac problems seen in monkeys given high doses of the drug for four weeks have raised concerns that the company seeks to address before proceeding with further trials in humans.

Side Effect Management and Patient Support are Key to Good Adherence.

In the January 2005 *Journal of Clinical Gastroenterology*, B.P. Mulhall and Z. Younossi presented an overview of the importance of adherence in obtaining the best results from HCV therapy. "Evidence has accumulated over the past few years to indicate that close adherence to the optimal

antiviral regimen can enhance sustained virologic response," they write. "But optimal treatment outcomes require diligence and careful management of side effects related to combination therapy." Attempting to minimize side effects by reducing doses of pegylated interferon, ribavirin, or both is a potentially risky strategy, since doing so can lessen the chances of achieving a sustained response. Instead, Mulhall and Younossi suggest that use of growth factors to treat blood cell deficiencies (neutropenia due to interferon and hemolytic anemia caused by ribavirin) can eliminate the need for dose reductions while improving patients' quality of life. They also emphasize the need for support to help patients cope with treatment-related toxicities. "Effective side effect management is crucial for the success of this treatment because adherence is negatively affected by side effects related to the antiviral regimen," Mulhall and Younossi conclude. "By identifying and addressing the important side effects of combination therapy for HCV, adherence to treatment can be improved and optimal outcomes can be achieved."