

Hepatitis C

Shorter Therapy for Genotype 2 or 3

Given the side effects and expense of interferon-based therapy, considerable research has been devoted to finding ways to individualize treatment so patients can receive doses and durations of therapy sufficient to ensure optimal outcomes, but not more than is necessary.

In the August issue of *Gastroenterology*, M. von Wagner and colleagues studied whether shorter courses of therapy could be effective for patients with easier-to-treat HCV genotypes. In this study, 153 patients with chronic genotype 2 or 3 HCV were treated with pegylated interferon (Pegasys) plus ribavirin. Those with a rapid virological response (HCV RNA below 600 IU/mL) at week 4 were randomized to

continue treatment for a total of 16 weeks or for the standard course of 24 weeks; the 11 patients who did not experience rapid response were treated for 24 weeks. After treatment and follow-up, sustained virological response (SVR) was observed in 82% of the early response/short course patients, 80% of the early response/standard course group, and 36% among the patients without early response. Overall, the shorter 16-week course was as likely to produce SVR as the standard 24-week regimen. Looking just at patients with genotype 3 (about three-quarters of all subjects), the chances of achieving SVR were significantly higher among those with low HCV viral loads (85% SVR for HCV RNA 800,000 IU/mL or below vs 59% for HCV RNA above 800,000). The

Hepatitis Journal Review

A publication of the Hepatitis C Support Project

Executive Director
Editor-in-Chief,
HCSP Publications
Alan Franciscus

Contributor:
Liz Highleyman

Managing Editor, Webmaster
C.D. Mazoff, PhD

Design/Production
Alan Franciscus

Contact Information:
The Hepatitis C Support Project
PO Box 427037
San Francisco, CA 94142

www.hcvadvocate.org

© 2005
Hepatitis C Support Project

authors concluded that 16-week treatment was sufficient for patients with genotype 2 HCV or genotype 3 and low viral load, while those with genotype 3 and high viral load might need the longer standard course of therapy.

Higher Doses for “Difficult-to-Treat” Patients

Conversely, F. Lodato and colleagues reported in the September *Journal of Viral Hepatitis* that higher doses of pegylated interferon can improve SVR rates in “difficult-to-treat” patients^{3/4}including those with genotype 1 or 4, high viral load, previous non-response, or cirrhosis. In this pilot study, the researchers assigned 65 difficult-to-treat chronic hepatitis C patients to receive either a standard course of pegylated interferon (Peg-Intron) or higher doses of Peg-Intron twice weekly, both with ribavirin. Among patients never before treated, the likelihood of achieving SVR was significantly greater in the high-dose arm (72% vs 25%). Looking at treatment-naive patients with genotype 1 or 4 plus relapsers after prior therapy, 57% of the high-dose arm achieved SVR,

compared with 11% of the standard-dose group. Treatment discontinuation rates were 32% in the standard-dose and 19% in the high-dose arms (as more in the former group stopped early due to non-response). According to the authors, this study yielded the highest response rates yet reported for genotype 1 or 4 patients with high HCV viral load; they recommended larger randomized studies of high-dose interferon therapy.

Treatment of Non-Responders and Relapsers

Evidence continues to accumulate that some patients who did not respond or who relapsed after treatment with conventional interferon can achieve better outcomes when retreated with pegylated interferon plus ribavirin. As reported in the August *Journal of Hepatology*, E.L. Krawitt and colleagues administered Peg-Intron plus ribavirin for 48 weeks to 182 patients who did not achieve sustained HCV clearance after treatment with conventional interferon, with or without ribavirin. Overall, after a 24-week follow-up period, 20% of previous non-responders (23 of 116) and

55% of previous relapsers (36 of 66) achieved SVR. Among patients with genotype 1, the retreatment SVR rate for previous relapsers (53%) was much higher than for previous non-responders (17%)^{3/4}and was comparable to the response rate seen in treatment-naive genotype 1 patients. Among genotype 2 or 3 patients, however, retreatment SVR rates for previous relapsers and non-responders were similar (59% and 57%, respectively), but somewhat lower than rates observed in previously untreated patients.

Ondansetron for Fatigue

Fatigue is among the most common and potentially most disabling symptoms associated with both chronic C and its treatment. In the August 2005 issue of *Gut*, T. Piche and colleagues reported on a study of ondansetron, a receptor antagonist of the neurotransmitter serotonin that has been successfully used to treat chronic fatigue syndrome. The researchers randomly assigned 36 chronic hepatitis C patients with fatigue to receive either 4 mg ondansetron tablets twice daily or a placebo for one month. They found that

ondansetron significantly reduced fatigue scores, with more than 30% improvement on day 15, day 30, and day 60; significant improvement was not observed in the placebo group. Ondansetron reduced fatigue more than placebo both during the treatment period and during a one-month post-therapy follow-up period. Ondansetron also significantly reduced depression scores. The authors concluded that ondansetron “had a significant positive effect on fatigue” in chronic hepatitis C patients, which supports the hypothesis that fatigue involves serotonergic pathways in the brain.

Core Antigen Test to Monitor Treatment Response

Early virological response at 12 weeks has become the accepted standard for predicting whether hepatitis C patients are responding to therapy. If patients have not achieved substantial reductions in HCV RNA by 12 weeks, there is a low likelihood that they will go on to achieve SVR. In the September *Journal of Viral Hepatitis*, V. Gonzalez and colleagues reported on an alternative method for measuring early response to

therapy: total HCV core antigen. The researchers examined 290 blood serum samples from 58 treatment naive chronic hepatitis C patients to evaluate the correlation between HCV core antigen and HCV RNA, and whether HCV core antigen levels at baseline, 4 weeks, and 12 weeks after starting treatment could predict SVR. They found that baseline HCV core antigen was significantly associated with SVR, and that there “was a good correlation” between core antigen and HCV RNA during therapy. The negative predictive value (ability to predict non-response) of HCV core antigen testing was 75% at week 4 and 100% at week 12. The authors concluded that, “HCV core antigen detection is [a] quick and easy to perform alternative to HCV RNA, and could be used as a marker of HCV viraemia for monitoring the progress of therapy.”

Isatoribine for Hepatitis C

Many new therapies for hepatitis C are specific antiviral agents active against HCV, but immune-based therapies like interferon continue to play a crucial role. In the September issue of *Hepatology*, Y. Hors-

mans and colleagues reported on a small study of a selective “toll-like receptor” (TLR) agonist called isatoribine. TLRs are receptors that promote immune response to pathogens. Twelve subjects with chronic hepatitis C received once-daily administration of 800 mg intravenous isatoribine for seven days. Isatoribine led to a significant reduction in plasma HCV RNA (mean reduction of 0.76 log) among both genotype 1 and non-1 patients. Reduction in viral load was correlated with markers of heightened immune activation. Isatoribine was well tolerated, producing “a low frequency of mild to moderate adverse events.” The authors concluded that “systemic administration of the selective TLR7 agonist isatoribine resulted in dose-dependent changes in immunologic biomarkers and a statistically significant antiviral effect with relatively few and mild side effects.” Data from this pilot study suggest that larger, controlled studies are warranted.

