

Hepatitis C

By Liz Highleyman

12-Week Therapy for Early Responders with Genotype 2 or 3

The late May journal review reported on a small study by A. Tabaru and colleagues (published in the April *American Journal of Gastroenterology*) showing that a six-week course of treatment with conventional interferon monotherapy worked about as well as the standard 24-week course for people with genotype 2a HCV. Now, a new, larger study published in the June 23 *New England Journal of Medicine* confirms the effectiveness of shorter-term therapy for selected patients. A. Mangia and colleagues from Italy studied 283 subjects with chronic genotype 2 or 3 HCV treated with pegylated interferon-alfa-2b (Peg-Intron) plus ribavirin. Seventy patients were randomly assigned to receive the standard 24-week course of therapy (group 1); among the

remaining subjects (group 2), those that had an early response, or undetectable HCV viral load at week 4 (133 patients), stopped treatment after 12 weeks, while the rest (80 patients) continued therapy for a full 24 weeks.

Overall, about 60% of the subjects had undetectable HCV RNA after four weeks of therapy. The researchers found that 76% of subjects in group 1 (the standard-duration arm) achieved sustained virological response (SVR) 24 weeks after the end of treatment, compared with 77% in group 2. The overall SVR rates differed by genotype: 80% for genotype 2 and 66% for genotype 3. The rate of relapse (undetectable HCV at the end of treatment followed by detectable viral load at the end of the 24-week post-treatment follow-up period) was higher in group 2 compared with group 1 (8.9% vs 3.6%); early-response patients treated for 12 weeks

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were about as likely to experience relapse as patients without early response treated for the full 24 weeks (90% of the relapsed patients treated for 12 weeks later achieved SVR after being retreated for 24 additional weeks). Patients receiving therapy for 12 weeks had a lower rate of adverse side effects, were less likely to require interferon or ribavirin dose reduction, and fewer withdrew prematurely from treatment compared with those treated for 24 weeks. “A shorter course of therapy over 12 weeks with peginterferon alfa-2b and ribavirin is as effective as a 24-week course for patients with HCV genotype 2 or 3 who have a response to treatment at four weeks,” the researchers concluded. “Tailoring treatment so that those with an early response are given a shorter course may make therapy more appealing to patients, without adversely affecting outcomes.”

New Initiative to Study Silymarin (Milk Thistle)

Due to the less-than-optimal response rate and high probability of side effects associated with interferon-based treatment, many people with chronic hepatitis C are interested in complementary and alternative therapies. Among the most promising is milk

thistle (*Silybum Marianum*) and its derivative, silymarin. Milk thistle has been used for centuries in various healing traditions as a liver disease remedy, and studies have shown that silymarin protects animals from liver damage due to exposure to toxins. In the July issue of *Hepatology*, Jay Hoofnagle, director of the National Institute of Diabetes and Digestive and Kidney Diseases Liver Disease Research Branch, described a new initiative by the National Institutes of Health (NIH) to study silymarin in clinical trials. Although herbal products containing milk thistle are widely used—by 10-15% of patients with liver disease, according to surveys—silymarin has not yet been subject to rigorous, controlled studies. While the exact mechanisms by which silymarin works are not fully understood, it may exert a combination of antioxidant, antifibrotic, anti-inflammatory, and immunomodulatory effects. Researchers plan to develop a standardized formulation of silymarin (since available products vary widely), which will be studied in Phase I/II trials in subjects with chronic hepatitis C and nonalcoholic steatohepatitis (NASH)—especially those who have not responded to standard treatments. In March, the NIH’s National Center for Complementary and Alternative Medicine (NCCAM) announced

that it is seeking industry partnerships to carry out this initiative. In June, NIH invited applicants for a new Silymarin Clinical Research Consortium, which will consist of about four collaborating research centers. For more information, see

<http://grants.nih.gov/grants/guide/rfa-files/RFA-AT-05-006.html>.

Noninvasive Fibrosis Tests

The search continues for noninvasive methods of measuring of liver disease progression that could reduce the need for liver biopsy. In the June issue of *Hepatology*, Carolin Lackner and colleagues from Austria assessed the accuracy of several noninvasive tests for predicting fibrosis. The researchers examined how the AST/ALT ratio (AAR), AST-to-platelet ratio index (APRI), cirrhosis discriminant score (CDS), age-platelet index (AP), Pohl score, and platelet count alone compared with liver biopsy results in 194 treatment-naive individuals with chronic hepatitis C. They found that APRI, CDS, AP, and platelet count were comparably accurate in diagnosing significant fibrosis (Ishak stages F3 through F6) and predicting cirrhosis. The AAR test, which looks only at liver enzyme levels, was not as ac-

curate as APRI, which also considers platelet count. But elevated APRI and decreased platelet count were able to diagnose significant fibrosis and exclude cirrhosis only about 75-80% of the time. The authors concluded that, “simple fibrosis tests may render liver biopsy unnecessary only in a minority of patients with chronic HCV,” and said that, “Improved serum fibrosis markers with greater sensitivity for severe fibrosis or cirrhosis are needed.”

In a study published in the July *Journal of Hepatology*, Thomas Kelleherb and colleagues evaluated another method of fibrosis prediction in 95 HIV/HCV coinfecting subjects in the Johns Hopkins HIV Clinic cohort. The researchers measured ALT and AST levels, APRI, albumin, total bilirubin, hyaluronic acid (HA), and YKL-40 (a glycoprotein thought to be associated with tissue regeneration). Comparing these serum values and biopsy results, the researchers found that fibrosis scores of F3 or higher were 27 times more common in subjects with high HA levels (above 86 ng/mL). Advanced fibrosis was less strongly associated with decreased albumin and elevated AST levels. All 35 subjects who had normal or near-normal HA, albumin, and AST levels also had minimal fibrosis. The authors con-

cluded that serum testing for HA, albumin, and AST—the SHASTA index—could “accurately stage mild and advanced fibrosis.”

In an editorial in the same issue, Marija Zeremski and Andrew Talal presented an overview of the current state of noninvasive markers of liver fibrosis and asked, “Are they ready for prime time?” Assessment of liver health is an important aspect of hepatitis C management and can show when treatment is needed; frequent fibrosis assessment using noninvasive tests may be particularly important in HIV/HCV coinfecting individuals, in whom fibrosis progression tends to be more rapid. Although liver biopsy remains the “gold standard” for fibrosis assessment, it is not without its disadvantages, including cost, discomfort, a small risk of complications, and variability of specimens depending on where in the liver they are obtained. Several noninvasive markers are based on blood tests routinely done in hepatitis C patients (e.g., ALT, AST, platelet count). Because fibrosis is essentially an extension of the body’s normal wound-healing mechanisms—including accumulation of collagen and other extracellular matrix proteins—serum markers of this activity may reflect fibrosis progression. General markers of inflammation (e.g., apolipoprotein A1,

haptoglobin) may also be useful. In general, an index or combination of serum markers—such as APRI, SHASTA, or Fibrotest—predicts fibrosis better than single markers alone. Current noninvasive tests are best at diagnosing either mild or advanced fibrosis, but are less effective at distinguishing intermediate stages. According to Zeremski and Talal, prospective comparative studies of various noninvasive markers are needed, in both coinfecting individuals and those with HCV alone. Such studies, they said, “could also enhance our understanding of the rate of fibrosis progression” in different populations, and “assess the improvement in these markers” in patients who successfully resolve HCV infection with treatment. “The ease with which noninvasive markers can be obtained holds tremendous promise for longitudinal evaluation of fibrosis in patients with chronic liver disease,” the authors concluded.

