

Hepatitis C

Liz Highleyman

Hepatitis C Treatment

In the March 2004 issue of *Gastroenterology*, Jean-Michel Pawlotsky and colleagues reported on the antiviral action of ribavirin in patients with chronic hepatitis C. Combining ribavirin with interferon has been shown to improve virological response and prevent relapse. Dr. Pawlotsky's team studied 38 subjects with chronic genotype 1b hepatitis C receiving various schedules of standard interferon and/or ribavirin, plus seven untreated control subjects. Blood samples were assessed frequently (every 4-12 hours for the first four days) for HCV viral kinetics and ribavirin pharmacokinetics (how the drug is metabolized and distributed in the body). They found that four of the seven (57%) who received ribavirin monotherapy experienced a "significant, moderate, early, and transient" viral load decrease at days 2 and 3, an effect associated with

higher ribavirin blood concentrations and slower drug clearance. The effect disappeared after four days, and no patients who received ribavirin monotherapy completely cleared HCV.

In combination therapy, ribavirin improved the effectiveness of interferon, partially reducing viral load rebound between injections in patients receiving interferon three times weekly (this rebound was not seen in those receiving daily interferon, so ribavirin did not play such an important role). Patients receiving combination therapy went on to experience a further "second phase" decline in HCV viral load, which was not seen in those receiving ribavirin alone. The researchers concluded that "[r]ibavirin exerts a significant, moderate, and transient antiviral effect in a significant proportion of patients with chronic hepatitis C... and is partly responsible for the improved efficacy of the combination of standard [interferon] and ribavirin compared with [interferon] monotherapy."

In the March 2, 2004 issue of

Continued on page 2

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

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

www.hcvadvocate.org

© 2004
Hepatitis C Support Project

Continued from page 1

the *Annals of Internal Medicine*, Stephanos Hadziyannis and colleagues with the Pegasys International Study Group reported results of a trial of different doses and durations of combination therapy with pegylated interferon-alpha-2a (Pegasys) plus ribavirin. In this randomized study conducted at 99 international centers, 1311 chronic hepatitis C patients (90% white, 65% men, about 25% with compensated cirrhosis, all with elevated ALT) were treated with once-weekly Pegasys plus either low-dose (800 mg daily) or standard-dose (1000 or 1200 mg daily, depending on weight) ribavirin, for either 24 or 48 weeks. The authors found that among patients with HCV genotype 1, 48 weeks was superior to 24 weeks, and standard-dose ribavirin worked better than the lower dose. Among the genotype 1 subjects, sustained virological response (SVR) was seen in 52% treated for 48 weeks with standard-dose ribavirin, 41% treated for 48 weeks with low-dose ribavirin, 42% treated for 24 weeks with standard-dose ribavirin, and 29% treated for 24 weeks with low-dose ribavirin. In all groups, patients with lower initial HCV viral loads responded better than those with higher viral loads. Among patients with genotypes 2 or 3, however, SVR rates were not significantly different based on ribavirin dose, treatment duration, or

initial viral load (about 80% in all groups). Adverse side effects were more common in the longer-duration and higher-dose ribavirin arms, and early discontinuation due to insufficient response occurred more often in the lower-dose arms. "Treatment with [Pegasys] and ribavirin may be individualized by genotype," the authors concluded. "Patients with HCV genotype 1 require treatment for 48 weeks and a standard dose of ribavirin; those with HCV genotypes 2 or 3 seem to be adequately treated with a low dose of ribavirin for 24 weeks."

Some recent research indicates that certain "hard to treat" patients may benefit from a longer course of therapy. For example, HCV/HIV coinfecting individuals appear to clear HCV more slowly, and may require longer treatment—perhaps 72 weeks for those with genotype 1 and 48 weeks for those with genotypes 2 or 3. In the April 2004 issue of the *Journal of Hepatology*, Johannes Brouwer and colleagues from Belgium and the Netherlands reported on a study looking at whether prolonging therapy could reduce relapse rates in patients with chronic hepatitis C. Three hundred patients were randomly assigned to receive 6-month treatment with standard interferon plus ribavirin, 18-month treatment with interferon plus ribavirin, or 18-month interferon monother-

apy. At the end of treatment, HCV viral load was undetectable in 55% and 49% of those on 6-month and 18-month combination therapy, respectively, compared with 26% of those receiving monotherapy. Sustained response rates in the three groups were 34%, 43%, and 16%, respectively. Thus, the relapse rate was 38% for both the 6-month combination therapy and 18-month monotherapy arms, compared with just 13% for the 18-month combination therapy arm. While this study showed that six months of treatment is not adequate for many patients, it did not answer whether 18 months is superior to the typical 12-month course of therapy for genotype 1 HCV.

References:

- Pawlotsky, J. et al. Antiviral action of ribavirin in chronic hepatitis C. *Gastroenterology* 126: 703-14. March 2004.
- Hadziyannis, S. et al (PEGASYS International Study Group). Peginterferon-alpha2a (Pegasys) and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Annals of Internal Medicine* 140 (5): 346-355. March 2, 2004.
- Brouwer, J. et al. Reduction of relapse rates by 18-month treatment in chronic hepatitis C: A Benelux randomized trial in 300 patients. *Journal of Hepatology* 40 (4): 689-695. April 2004.

Continued on page 3

Continued from page 2

Interferon Improves Survival

A. Kasahara and colleagues from Japan reported in the March 2004 issue of the *Journal of Viral Hepatitis* that interferon improves survival in hepatitis C patients who respond well to therapy. In a long-term study of nearly 2954 patients with chronic hepatitis C patients (2698 treated with interferon and 256 untreated), death due to liver-related disease occurred in 68% of the treated patients and 81% of the untreated patients. In addition, the risk of death from all causes was lower for treated compared with untreated patients. Broken down by treatment response status, patients who achieved a sustained virological response had a significantly lower liver-related disease mortality rate than untreated patients, but this was not true for patients who achieved only a transient virological response. However, both sustained and transient biochemical responders (but not biochemical nonresponders) had a significantly lower liver-related death rate than untreated patients. The researchers concluded that “interferon treatment improved survival in chronic hepatitis C patients showing a biochemical as well as a virological response by preventing liver-related deaths.”

Reference:

Kasahara, A. et al. Interferon

treatment improves survival in chronic hepatitis C patients showing biochemical as well as virological responses by preventing liver-related death. *J. Viral Hepatitis* 11 (2): 148-156. March 2004.

HCV Screening Guidelines

The latest recommendations of the U.S. Preventive Services Task Force (USPSTF) concerning screening for HCV were published in the March 16, 2004 issue of the *Annals of Internal Medicine*. Although antibody tests can accurately identify people with HCV, infection rates are low among people without known risk factors (e.g., injection drug use, pre-1990 blood transfusion, occupational exposure), and most infected individuals never develop severe liver disease (although some 75% do become chronically infected). After reviewing available evidence, the USPSTF found no studies showing that the benefits of widespread screening of low-risk individuals outweigh the risks (including anxiety, possible complications of biopsies, and side effects and cost of treatment if a person is found to be infected). Therefore, the task force recommended against routine HCV screening of individuals with no known risk factors and no symptoms of liver disease. The task force declined to take a position either for or against routine screening even of adults with specific risk factors, again citing insufficient

evidence. In an accompanying article in the same issue, Roger Chou, Elizabeth Clark, and Mark Helfand reviewed the available evidence and concluded that “data are inadequate to accurately weigh the overall benefits and risks of screening in otherwise healthy asymptomatic adults.” The recommendations are controversial, and some studies suggest that limiting HCV screening to those with known risk factors will miss many infections. For example, a Scottish study published in the April 2004 issue of *Gut* found that risk-based screening identified only one-quarter of previously undetected infections among more than 30,000 pregnant women.

References:

U.S. Preventive Services Task Force. Screening for hepatitis C virus infection in adults: recommendation statement. *Annals of Internal Medicine* 140 (6): 462-464. March 16, 2004.
Chou, R. et al. Screening for hepatitis C virus infection: a review of the evidence for the U.S. preventive services task force. *Annals of Internal Medicine* 140 (6): 465-479. March 16, 2004.
Hutchinson, S. et al. Hepatitis C virus among childbearing women in Scotland: prevalence, deprivation, and diagnosis. *Gut* 53: 593-598. April 2004.

