

Hepatitis C

Liz Highleyman

Hepatitis C Treatment in Nonresponders

In the April 2004 issue of *Gastroenterology*, Mitchell Shiffman and colleagues reported the first results from the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial, ongoing at 10 centers in the U.S. The study evaluated 604 patients with chronic hepatitis who did not respond to previous treatment with standard interferon, with or without ribavirin; all subjects had bridging fibrosis or cirrhosis—the most difficult population to treat. The primary endpoint of the study was whether therapy delayed or stopped the progression of cirrhosis. Participants were retreated with pegylated interferon-alpha-2a (Pegasys) 180 µg/week plus ribavirin 1000–1200 mg/day (depending on weight). Patients who showed an

early response (undetectable HCV viral load at 20 weeks) continued treatment for 48 weeks and were followed for an additional 24 weeks.

At 20 weeks, 35% of patients had undetectable HCV viral load. At the end of treatment the response rate was 32%, and at the end of follow-up (72 weeks) 18% achieved sustained virological response (SVR). Among those who achieved an early virological response (EVR) by 12 weeks, 34% went on to achieve SVR, but only three patients (1%) who did not achieve EVR later achieved SVR. The SVR rate was 14% for patients with genotype 1, 65% for genotype 2, and 54% for genotype 3. Consistent with other studies, African-Americans had lower sustained response rates (6% compared with 20% for whites), as did patients over age 60. Other predictors of sustained response were a lower AST to ALT ratio and absence of cirrhosis. Patients

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

previously treated with standard interferon monotherapy were more likely to respond to the new regimen than those who previously received standard interferon plus ribavirin. Subjects who received a lower initial dose of ribavirin during the first 20 weeks (due to intolerance) were less likely to achieve SVR, confirming other research showing that ribavirin helps prevent relapse. However, when the dose of Pegasys or ribavirin was reduced after 20 weeks (when HCV viral load was already undetectable) the SVR was not significantly different. The researchers concluded that “[s]elected nonresponders to previous interferon-based therapy can achieve SVR following retreatment with [Pegasys] and ribavirin.” The patients who still did not respond will enter a maintenance phase of the trial to see whether lower-dose, long-term (3.5 years) interferon therapy can help delay or prevent liver disease progression even in the absence of virological response.

Fibrosis

Progression

In the March 2004 issue of *Gut*, S.D. Ryder and colleagues from the Trent

Hepatitis C Study Group reported data from a study of fibrosis progression in patients with chronic hepatitis C. The researchers prospectively studied the rate of fibrosis progression by looking at the results of repeat liver biopsies in patients who did not receive treatment between the two procedures. The study included more than 200 HCV-infected patients (about 60% men; median age 36 years), most with mild liver disease. The median interval between biopsies was 2.5 years. One-third of the patients showed progression of at least 1 point in their Ishak fibrosis scores, while about 25% had increases of two or more points. Patients who were older at the time of the first biopsy and those who showed some fibrosis on the earlier biopsy were more likely to progress. In contrast to some previous studies, fibrosis progression was not independently associated with duration of HCV infection, alcohol consumption, ALT level, coinfection with hepatitis B virus (HBV), HCV genotype, iron levels, steatosis (fatty liver), or degree of necroinflammation (liver inflammation and cell death). These data indicate that even mild fibrosis can progress significantly over

30 months in patients with untreated hepatitis C. The researchers concluded that their results “suggest that HCV infection will place an increasing burden on health care services in the next 20 years,” making a case for early treatment to prevent or retard fibrosis progression.

In other fibrosis news, Armelle Poujol-Robert and colleagues reported in the March 2004 issue of the *American Journal of Gastroenterology* that fibrosis and cirrhosis are associated with several factors that promote blood clotting, or thrombosis (deficiency of protein C and elevated levels of factor VIII and homocysteine), possibly because these factors affect microcirculation in the liver. And in the April 2004 issue of the *Journal of Hepatology* (which contained several reports on mechanisms of liver damage), Pedro Lorenzo Majano and colleagues reported that in a laboratory study of human hepatocytes (liver cells), the antioxidant N-acetylcysteine (NAC) altered NF-kappa-B activity and reduced levels of an enzyme that generates nitric oxide, suggesting that it may help

Continued on page 3

Continued from page 2

protect the liver from inflammatory damage. NAC has been touted as a complementary therapy for fibrosis, and is used to prevent liver damage due to acetaminophen overdose.

HCV/HBV Coinfection

Although coinfection with hepatitis C and HIV has received a great deal of attention in recent years, HCV/ HBV coinfection has been less studied—even though it appears to be quite common. In the April 2004 issue of *Gastroenterology*, Yun-fan Liaw and colleagues from Taiwan (where hepatitis B is endemic and usually acquired perinatally or by age 2) looked at the impact of HCV superinfection in patients with HBV. (Strictly speaking, “coinfection” refers to simultaneous infection with more than one pathogen, while “superinfection” refers to

infection with a second pathogen at a later time; however, “coinfection” is often used to refer to both).

The study showed that among patients already infected with HBV, HCV superinfection can cause acute icteric (characterized by jaundice) hepatitis, similar to that seen in patients with HBV/HDV (hepatitis D, which only occurs in conjunction with hepatitis B). In this study, 34% of 93 HCV superinfected patients rapidly developed hepatic decompensation (e.g., blood clotting problems, ascites, encephalopathy), 11% experienced liver failure, and 10% died. The long-term effects of superinfection with HCV are worse than those of HDV. About half of the untreated HBV/HCV coinfecting patients in this study developed cirrhosis after 10 years of follow-up, higher than the rates seen in people with chronic hepatitis C alone, chronic active hepatitis B alone, or HBV/HDV coinfection. Rates of

hepatocellular carcinoma (HCC, a type of liver cancer) were also higher among the HBV/HCV patients: 14% at 10 years, 21% at 15 years, and 32% at 20 years. Interestingly, clearance of HBV surface antigen (HbsAg) occurred earlier and more often in those superinfected with HCV, a phenomenon the researchers called “HBV displacement”; past research has shown that HBV superinfection also seems to suppress HCV. The researchers concluded that “the long-term prognosis following acute HCV superinfection is much worse in terms of cirrhosis or HCC development and associated mortality than that following acute HDV superinfection or active hepatitis B.” Hepatitis B or A superinfection in patients who already have hepatitis C can also cause severe liver disease; for this reason, all HCV-infected people should consider hepatitis A and B vaccination.

