

# Hepatitis C

## **Ribavirin Prevents Relapse**

The IDEAL trial compared pegylated interferon alfa-2a (Pegasys) versus pegylated interferon alfa-2b (PegIntron), both with weight-adjusted ribavirin, in more than 3,000 treatment-naive HCV genotype 1 patients. Participants who received Pegasys had a higher end-of-treatment response rate, but PegIntron recipients were less likely to relapse, so sustained virological response (SVR) rates after completion of treatment were similar. Some experts, however, suggested that the trial was not a true head-to-head comparison because the Pegasys arm received 1,000-1,200 mg/day ribavirin while the PegIntron arm received 800-1,400 mg/day – that is, the heaviest patients received more ribavirin in the latter arm.

In a retrospective follow-up analysis reported in the April 2009 *Scandinavian Journal of Gastroenterology*, S. Zopf and colleagues took a closer look at ribavirin dosing in the Pegasys arm of the trial. In IDEAL, participants weighing more than 105 kg reached a maximum ribavirin dose of 13.2 mg/kg in the PegIntron arm versus 11.3 mg/kg in the Pegasys arm. In the present analysis, the researchers found that Pegasys recipients whose ribavirin dose was at least 13.2 mg/kg had a relapse rate of 19%, while those whose dose was below 13.2 mg/kg had a 71% likelihood of relapse. Consequently, the SVR rate was significantly greater in the higher ribavirin dose group (60% vs 29%, respectively), demonstrating the need for adequate dosing according to weight.

(Continued on page 2)

## **Hepatitis Journal Review**

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## Telaprevir

Among several experimental directly-targeted antiviral agents for hepatitis C, the Vertex HCV protease inhibitor telaprevir (formerly VX-950) is furthest along in development. Final results from a pair of Phase 2b clinical trials – PROVE 1 and PROVE 2 – were published in the April 30, 2009 *New England Journal of Medicine*. PROVE 1, conducted in the U.S., included 250 previously untreated genotype 1 chronic hepatitis C patients (77% white), while PROVE 2, conducted in Europe, included 334 participants (94% white). Participants were randomly assigned to receive standard therapy with 180 mcg/week Pegasys plus 1000-1200 mg/day ribavirin for 48 weeks or various regimens containing telaprevir (1250 mg on day 1 then 750 mg every 8 hours) plus Pegasys, with or without ribavirin.

In PROVE 1, SVR rates were significantly higher in patients who received telaprevir/Pegasys/ribavirin for 24 or 48 weeks, but those who took the three-drug regimen for only 12 weeks did no better than those on standard dual therapy (SVR 61%, 67%, 35%, and 41%, respectively). Only 7% of

patients taking telaprevir experienced viral breakthrough. In the small subgroup of African-American patients (a population that responds more poorly to interferon-based therapy), those taking telaprevir had a four-fold higher SVR rate compared with standard therapy (44% vs. 11%). Discontinuation due to adverse events was about twice as likely in the telaprevir arms compared with standard therapy (21% vs. 11%), with skin rash being the most common reason for stopping. In PROVE 2, the 12- and 24-week triple regimens performed better than standard dual therapy, which in turn worked better than the 12-week telaprevir/Pegasys regimen without ribavirin (SVR 60%, 69%, 46%, and 36%, respectively). Again, rash, itching, and anemia were more common in the telaprevir arms.

In an accompanying editorial, J. Hoofnagle wrote that these trials "suggest that the addition of telaprevir to the combination of peginterferon and ribavirin will increase rates of sustained virologic response in patients with chronic hepatitis C due to infection with HCV genotype 1 from approximately 45% to as high as 65% and will permit therapy to be limited to 24

weeks, thus avoiding the expense and side effects of prolonged therapy."

Telaprevir has also been studied in prior pegylated interferon/ribavirin nonresponders and relapsers in the PROVE 3 trial. As reported at the 2009 European Association for the Study of the Liver (EASL) meeting in April, patients receiving telaprevir/Pegasys/ribavirin had significantly higher SVR rates than those taking standard dual therapy, but the 24-week arm had a higher relapse rate than the 48-week arm, indicating that longer treatment may be better for treatment-experienced patients.

## Sorafenib for Cirrhosis

The drug sorafenib (Nexavar), which has been shown to be an effective treatment for hepatocellular carcinoma (HCC), may also help prevent complications of liver cirrhosis, according to a report in the April 2009 *Hepatology*. M. Mejias and colleagues designed a study in rats to determine whether sorafenib – an angiogenesis inhibitor that suppresses blood vessel proliferation – could slow the progression of portal hypertension,

*(Continued on page 3)*

characterized by increased blood pressure and use of alternative circulation channels when the portal vein supplying the liver becomes blocked by scar tissue. In rats with portal hypertension and cirrhosis (caused by blocking the portal vein and bile ducts), twice-daily sorafenib inhibited chemical signaling pathways (e.g., VEGF) necessary for blood vessel growth.

Compared with untreated rats, the sorafenib-treated rats had an 80% decrease in visceral (splanchnic) blood vessel proliferation, an 18% reduction in development of portosystemic collateral blood vessels, a 17%-28% decrease in superior mesenteric artery blood flow, a 24%-31% decline in cardiac output, and as much as a 25% reduction in portal pressure. In cirrhotic rats, sorafenib also produced "remarkable improvement" in liver fibrosis and inflammation. In an accompanying editorial, V. Shah and J. Bruix noted that the cancer drugs imatinib (Gleevec) and sunitinib (Sutent) also decreased portal hypertension in preclinical studies, and suggested that these types of agents might one day be used to slow or prevent fibrosis before it progresses to cirrhosis and HCC.

## **CD4 Recovery in Coinfected Patients**

While HIV infection tends to accelerate liver disease progression in people with hepatitis C, the effect of HCV on HIV disease progression is less clear. Some research suggests that HIV/HCV coinfecting people have slower CD4 T-cell recovery on antiretroviral treatment, but other studies disagree. As reported in the April 2009 the *Journal of Acquired Immune Deficiency Syndromes*, L. Peters and colleagues looked at CD4 cell gains among 4,208 participants in the large EuroSIDA cohort who had at least two undetectable HIV viral load measurements (< 50 copies/ml) after starting combination antiretroviral therapy.

Unadjusted annual changes in CD4 counts were similar for HIV/HCV coinfecting patients and HCV seronegative participants (36 vs. 38 cells/mm<sup>3</sup>). After adjusting for potentially confounding factors, annual CD4 changes did not differ significantly according to HCV antibody serostatus, HCV genotype, detectable versus undetectable HCV viral load, HCV RNA level, or use of interferon-based hepatitis C treatment. The researchers concluded that coinfection

with HCV did not affect CD4 cell recovery in individuals with durable maximum suppression of HIV.

## **Injection Drug Use**

Sharing needles and other drug injection equipment is an efficient route for transmission of HCV, HIV, and other blood-borne diseases. In the April 10, 2009 *Morbidity and Mortality Weekly Report*, researchers with the Centers for Disease Control and Prevention (CDC) published an overview of HIV transmission risk among more than 10,000 injection drug users (IDUs) in 23 U.S. cities. The report compiled data from the National HIV Behavioral Surveillance System collected between May 2005 and February 2006, but the findings are also relevant to HCV; because the study focused on people at risk for HIV, those who were already HIV positive were excluded. About two-thirds of the survey respondents were men and almost half were African-American.

Nearly one-third of respondents (32%) said they shared needles or syringes during the survey period; a similar percentage also

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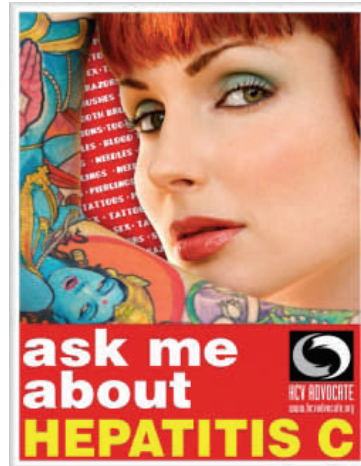
reported sharing other injection equipment (such as "cookers"). White IDUs (40%) and those 25-34 years old (39%) were most likely to report needle sharing. Almost two-thirds (63%) said they engaged in unprotected vaginal sex, and 47% reported multiple opposite-sex partners. A large majority – 72% – said they had been tested for HIV and HCV; however, while younger IDUs (age 18-24) were most likely to be tested for HIV, they were least likely to be tested for HCV. The researchers recommended integrated health services that provide prevention counseling, screening, and vaccination (if available) for hepatitis, sexually transmitted diseases, tuberculosis, and HIV. "Providing comprehensive services to IDUs can help reduce the spread of bloodborne infections and increase access to health care, providing an effective approach to the spread of disease for the entire population," they concluded.

In a related report in the March 1, 2009 issue of *Drug and Alcohol Dependence*, V.A. Gyarmathy and colleagues looked at associations between HCV infection and types of syringes and syringe cleaning among 215 IDUs in Buda-

pest, Hungary. Although 37% of the study participants tested HCV positive, only 14% of the total (39% of those who tested positive) knew they were infected. Use of two-piece syringes was a significant risk factor for HCV infection. Among participants who only used one-piece syringes, those who shared previously used syringes without always cleaning them were significantly more likely to have HCV, but this was not the case for those who said they always cleaned used syringes before reusing them. In comparison with some past research, this study did not find an association between HCV infection and sharing cookers or transferring drugs from one syringe into another (e.g., "back-loading").



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