

# Hepatitis C

## **Pegasys Maintenance in HALT-C**

Nearly half of all people treated for chronic hepatitis C do not achieve a cure, and researchers are studying whether long-term low-dose pegylated interferon maintenance therapy can slow or prevent liver disease progression. Results from the largest such study, HALT-C, were published in the December 4, 2008 *New England Journal of Medicine*. A. DiBisceglie and colleagues initially treated chronic hepatitis C patients with advanced liver disease using standard-of-care 180 mcg/week pegylated interferon alfa-2a (Pegasys) plus weight-adjusted ribavirin. A total of 1,050 nonresponders and relapsers were then randomly assigned to receive either low-dose (90 mcg/week) Pegasys monotherapy or no ongoing therapy.

After 3.5 years, ALT levels, HCV viral load, and histological necroinflammatory scores decreased significantly in the treated patients. But there were no significant differences in rates of hepatocellular carcinoma, hepatic decompensation, fibrosis score increase of two or more points, or death (34.1% for the combined endpoint in the treatment arm vs. 33.8% in the untreated arm). Eight patients taking Pegasys maintenance therapy died, compared with two untreated participants. Percentages of patients with at least one serious adverse event were 38.6% and 31.8%, respectively (not quite statistically significant). The researchers concluded that, "Long-term therapy with peginterferon did not reduce the rate of disease progression in patients with chronic hepatitis

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### **Hepatitis Journal Review**

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C and advanced fibrosis, with or without cirrhosis, who had not had a response to initial treatment with peginterferon and ribavirin." Speaking to the media, Dr. DiBisceglie added, "To the extent there are still patients out there who are on this form of maintenance therapy, there is a real take-home message: It should be stopped."

The HALT-C findings were surprising to many because reduced ALT and histological necroinflammatory activity – as seen in an interim analysis – were presumed to be markers for improved liver health. Contrary to these results, a smaller German study presented by S. Kaiser at the recent AASLD Liver Meeting (*abstract 117*) found that low-dose monotherapy with 0.5 mcg/kg/week pegylated interferon alfa-2b (PegIntron) for three or six years led to a "significant and persistent" decrease in fibrosis. While the debate over pegylated interferon maintenance continues, nonresponders considering this approach should be aware that directly targeted "STAT-C" drugs, expected to become available in a couple years, may offer a better option.

## **HCV Treatment in Prisons**

HCV infection is common among prisoners, and it has been estimated that more than one-third of all people with hepatitis C in the U.S. pass through the correctional system each year. While some practitioners consider prisoners a "difficult to treat" population, two recent studies showed that treatment in prisons is feasible and cost-effective.

As reported in the October 1, 2008 *Clinical Infectious Diseases*, D. Maru and colleagues studied chronic hepatitis C patients in Connecticut Department of Correction facilities who were treated with pegylated interferon plus ribavirin during 2000-2006. Of 138 treatment-naïve patients referred for treatment, 49% were approved. The overall sustained virological response (SVR) rate was 47% (43% for HCV genotype 1, 59% for genotypes 2 or 3). Nine patients (13%) discontinued treatment due to adverse events. These SVR rates (especially for genotypes 2 and 3) were somewhat lower than those seen in non-incarcerated people; surprisingly, however, SVR was not significantly associated with black race, HIV coinfection, or high base-

line HCV viral load. "These results support the feasibility and clinical effectiveness of [pegylated interferon/ribavirin] for the treatment of chronic HCV infection in correctional facilities," the researchers concluded.

A related study by J. Tan and colleagues published in the November 2008 *Hepatology* looked at cost-effectiveness of treating prisoners with chronic hepatitis C. Assuming that genotype distribution, cirrhosis prevalence, and response rates were the same as in prior studies, their mathematical model showed that without pretreatment liver biopsy, treatment with pegylated interferon plus ribavirin was cost-effective for all ages and genotypes. If pretreatment liver biopsy was done, treatment was cost-saving for prisoners of all ages and genotypes with advanced fibrosis or compensated cirrhosis, but not for genotype 1 patients aged 40-49 years with no fibrosis. Treatment of chronic hepatitis C "results in both improved quality of life and savings in cost for almost all segments of the inmate population," the researchers stated.

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## **Hepatitis B and C Coinfection**

Due to overlapping transmission routes, many people are coinfecting with both hepatitis B and C viruses. A study published in the September 2008 *Journal of Viral Hepatitis* adds to the evidence that HBV and HCV seem to inhibit each other in the body. F. Tseng and colleagues enrolled 1,694 HBV/HCV coinfecting injection drug users in a cross-sectional study during 1998-2000. Within this population, hepatitis B surface antigen (HBsAg) prevalence decreased with increasing age among those who had detectable HCV RNA (from about 5% in those aged 18-29 years to 1% for those 50 or older), but stayed the same in those with undetectable HCV. Overall, chronic hepatitis B was less common among individuals with chronic hepatitis C, and this inverse relationship was most evident in the oldest participants. "Coinfection with HCV may enhance the resolution of HBsAg during the chronic phases of these infections," the researchers concluded.

In a related pilot study described in the November 2008 *Journal of Hepatology*, A. Potthoff and colleagues assessed the safety and effi-

cacy of hepatitis C treatment in 19 patients with chronic HBV/HCV coinfection. Ten participants had HCV genotype 1 and nine had genotypes 2 or 3; at baseline, 13 had undetectable HBV DNA, but were HBsAg positive. All patients received PegIntron plus weighted-adjusted ribavirin for 48 weeks, regardless of HCV genotype. In an intent-to-treat analysis, 14 participants (74%) achieved sustained HCV virological response and 12 (63%) experienced ALT normalization. Among 15 adherent patients who took the full course of treatment, 14 (93%) achieved SVR. Furthermore, two patients who were initially HBV DNA positive had undetectable HBV DNA at the end of follow-up, but four initially HBV DNA negative patients became HBV DNA positive after HCV clearance. The researchers concluded that, "Combination therapy with [Pegintron] and ribavirin is highly effective in inducing a virological response concerning HCV in patients with HBV/HCV coinfection." However, they added, "HBV replication may increase after the clearance of HCV, and thus close monitoring for both the viruses is recommended even in patients with initially undetectable HBV DNA."

## **HIV Treatment Interruption**

Because combination antiretroviral therapy for HIV will likely need to be lifelong and can involve long-term side effects, researchers have explored treatment interruption strategies in which patients stop therapy when their CD4 cell count is above a certain level. In the SMART trial – the largest and best known interruption study – participants randomly assigned to the treatment interruption arm stopped therapy when their CD4 cell count was above 350 and resumed when it fell to 250 (current U.S. guidelines recommend starting treatment under 350 cells); another arm received continuous therapy.

The study was halted ahead of schedule in January 2006 after interim results showed that patients in the treatment interruption arm not only had a higher rate of AIDS-related opportunistic disease or death due to any cause, but also were more likely to develop serious cardiovascular, kidney, and liver disease. Now, an ad hoc analysis by E. Tedaldi and colleagues in the December 1, 2008 *Clinical Infect-*

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*tious Diseases* suggests that treatment interruption may be especially risky for HIV positive people with hepatitis B or C coinfection.

Out of the total 5,472 participants enrolled in SMART, just 17% had HBV and/or HCV coinfection, but they accounted for nearly half the deaths not related to opportunistic disease. The rate of opportunistic disease or all-cause death was 3.9 events per 100 person-years for the coinfecting group compared with 2.0 for the HIV mono-infected patients. While the risk of opportunistic disease was similar in the two groups, the coinfecting group had an excess risk of death attributable to other causes. The main causes were substance abuse and non-AIDS-defining cancers (although liver cancer was not a major cause); there were also several suicides, and many deaths had an unknown cause. The coinfecting group included disproportionate number of injection drugs users, a group known to have an elevated risk of death due to various causes including overdose and violence. The SMART researchers concluded that, "Interruption of antiretroviral therapy is particularly unsafe in persons with hepatitis virus coinfection," but they added that, "Viral hepatitis was an unlikely cause of this excess risk."



## Increasing the Chance of Receiving Liver Transplantation by Multiple Listing



*Be sure to check out this article by Lorenzo Rossaro M.D., F.A.C.P. Professor of Medicine at the University of California Davis Medical Center is the latest addition to the HCV Advocate Medical Writers' Circle, a series of articles by doctors who specialize in the treatment of hepatitis C.*

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