

# Hepatitis C

## **Telaprevir for Hepatitis C Treatment**

Two articles in the September 2007 issue of *Hepatology* described studies of the experimental HCV protease inhibitor telaprevir (VX-950). In the first study, N. Forestier and colleagues evaluated the viral kinetics and safety of telaprevir administered alone and in combination with pegylated interferon alfa-2a (Pegasys). Twenty previously untreated patients with genotype 1 HCV were randomly assigned to receive Pegasys plus placebo, telaprevir monotherapy, or telaprevir plus Pegasys for 14 days. On Day 15, the median decreases in HCV RNA were 1.09 log, 3.99 logs, and 5.49 logs, respectively, in the three study arms. Four of the eight patients who received telaprevir plus Pegasys had undetectable HCV viral

load, compared with just one of eight in the telaprevir monotherapy arm and none in the Pegasys/placebo arm. No subjects who received telaprevir plus Pegasys – but half who took telaprevir alone – experienced HCV breakthrough during the initial dosing phase. Most side effects were mild, and no patients discontinued treatment due to serious adverse events. After the initial dosing phase, participants switched to standard therapy with Pegasys plus ribavirin. Twelve weeks after the switch, all eight patients in the original telaprevir/Pegasys arm, five of eight in the telaprevir monotherapy group, and one in the Pegasys/placebo group had undetectable HCV viral load. The researchers concluded that, “This study confirmed the substantial antiviral effects of telaprevir and showed an increased anti-

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## **Hepatitis Journal Review**

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ral effect of telaprevir combined with peginterferon alfa-2a.”

In the second study, T. Kieffer and colleagues used a sensitive genetic sequencing assay to identify mutations that conferred low-level (V36M/A, T54A, or R155K/T) or high-level (A156V/T and 36/155) resistance to telaprevir in a laboratory analysis. They sequenced HCV from the 16 participants who received either telaprevir monotherapy or telaprevir plus Pegasys in the previous study. Among the four patients who experienced viral rebound while on telaprevir alone, the R155K/T and A156V/T variants were detected during the initial steep decline in HCV RNA. After HCV rebound occurred, these were replaced by variants with the V36(M/A)/R155(K/T) double mutation. Among the four patients receiving telaprevir monotherapy and the eight receiving telaprevir plus Pegasys who did not experience viral breakthrough, the A156V/T variant was detected in some cases, but HCV RNA levels nevertheless continued to decline. These findings “suggest that the initial antiviral response to telaprevir is due to a sharp reduction in wild-type virus, which uncovers pre-existing telapre-

vir-resistant variants,” the investigators concluded. “In patients given telaprevir alone, viral rebound can result from the selection of variants with greater fitness.” But, they added, the combination of telaprevir plus Pegasys inhibited both wild-type and drug-resistant HCV strains.

### ***Occult HBV in People with Hepatitis C***

Occult, or hidden, hepatitis B virus (HBV) infection may worsen liver disease progression and reduce the effectiveness of hepatitis C treatment, researchers reported in the August 2007 *Journal of Medical Virology*. S. Mrani and colleagues collected data on 203 French patients with chronic hepatitis C. Despite the lack of detectable hepatitis B surface antigen (HBsAg), HBV DNA was detected in blood serum using a highly sensitive test. About one-quarter (23%) had occult HBV infection with a low HBV DNA level, but a significantly higher HCV RNA level. Patients with occult HBV had higher histological activity scores and more advanced liver fibrosis compared to those without detectable HBV DNA. Further, while 45% of patients with undetectable HBV DNA

achieved a sustained response to combination interferon-based treatment for hepatitis C, the response rate fell to 28% among those with occult HBV. The researchers concluded that, “occult HBV coinfection is associated with more severe liver disease, higher HCV viral load and decreased response to antiviral therapy irrespective of HCV genotypes.”

### ***Long-term Complications after HCV Clearance***

In the August 2007 *Journal of Viral Hepatitis*, P. Pradat and colleagues reported the results of a study looking at long-term liver disease complications in people who either spontaneously cleared HCV or achieved sustained response to antiviral treatment. The analysis included 1,641 hepatitis C patients in the HENCORE cohort who were recruited at eight centers in Europe in 1996-1997 and were re-analyzed five to seven years later. At that point, almost all patients (93%) who had cleared HCV spontaneously or after successful interferon-based therapy remained HCV RNA negative, and thus were considered “cured.” Among the participants who were sus-

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tained virological responders to treatment, only 2.3% developed severe liver complications (decompensated cirrhosis, hepatocellular carcinoma, or liver transplantation) compared with 31% of non-responders. Factors that appeared to predict decompensated cirrhosis included older age at the time of HCV infection, male sex, genotype 1 virus, and non-response to a prior attempt at treatment. Further, decompensated cirrhosis and hepatocellular carcinoma were associated with distinct variations in human leukocyte antigen genes, which play a role in immune response. The researchers concluded that, “Long-term follow up of HCV patients indicates that virological response persists over time and is associated with a very low incidence of liver complications.”

### **Genetic “Signature” Predicts Cirrhosis**

Demographic factors such as age, sex, and heavy alcohol use influence progression to advanced liver disease, but do not accurately predict which patients with chronic hepatitis C will go on to develop cirrhosis. As reported in the August 2007 issue of *Hepatology*, H. Huang and colleagues attempted to

identify a predictive genetic “signature” for cirrhosis. Based on data from a “training cohort” of 420 Caucasian hepatitis C patients, the researchers selected 361 genetic markers that appeared to be associated with cirrhosis. Using a machine learning approach, they then devised a signature consisting of seven markers that best predicted cirrhosis risk in this population. The performance of the resulting Cirrhosis Risk Score (CRS) was then tested in a separate “validation cohort” consisting of 154 Caucasian individuals. They found that the CRS predicted cirrhosis with 75% accuracy, compared with 53% using clinical factors alone. Based on these results, the researchers concluded that the CRS “is a better predictor than clinical factors in differentiating high-risk versus low-risk for cirrhosis in Caucasian chronic hepatitis C patients.”

### **Cognitive Impairment in Coinfected Patients**

Both HIV and HCV have been linked to neurocognitive impairment, but little is known about the effect of HCV in the brains of coinfecting individuals. In the August 1, 2007 *Journal of Infectious Diseases*, S. Letendre and colleagues reported

data from a study of the distribution of HCV in the brains of coinfecting patients. Using PCR testing, the researchers looked for HCV RNA in post-mortem (autopsy) brain tissue samples from 12 HIV/HCV coinfecting and 13 HIV mono-infected subjects, and compared the findings with retrospective data from patient medical records. They found that all of the coinfecting subjects had detectable HCV RNA in the brain. Specifically, HCV was found in the frontal cortex, basal ganglia, and white matter, but not in the cerebellum, brainstem, occipital cortex, or thalamus. The presence of HCV RNA in the central nervous system was associated with cognitive impairment prior to death, a history of methamphetamine use, and the excessive presence of astrocytes, a type of brain cell associated with neuron destruction. However, subjects with detectable HCV RNA in the brain had less severe HIV-related encephalitis (brain inflammation). The researchers concluded that, “The results support the hypothesis that HCV traffics into the HIV-infected brain, where it might lead to a productive coinfection associated with cognitive impairment.”