

Hepatitis C

Retreatment Benefits Relapsers, Patients with Genotypes 2 or 3

A study in the August *Journal of Hepatology* added to the evidence that patients previously treated unsuccessfully with conventional interferon with or without ribavirin may respond better to subsequent treatment using pegylated interferon. Edward Krawitad and colleagues treated 182 previous nonresponders or relapsers with Peg-Intron/ribavirin for 48 weeks. SVR was achieved by 20% of previous nonresponders and 55% of previous relapsers. Among the previous nonresponders, the SVR rate for genotype 1 was 17%, compared with 57% for genotypes 2 or 3; for the previous relapsers, the respective rates were 53% and 59%. The re-

searchers concluded that “[t]he response to pegylated interferon and ribavirin in previous nonresponders with genotypes 2 and 3 and in prior relapsers with chronic hepatitis C is comparable to overall sustained viral response rates seen in previously untreated patients.”

In an attempt to improve treatment outcomes for patients with chronic hepatitis C, researchers are studying different forms of interferon, a natural immunomodulating chemical produced by the immune system. In a pilot study reported in the July *Journal of Hepatology*, A. Soza and colleagues used interferon-gamma to treat 14 patients with chronic genotype 1 hepatitis C who had not responded or had relapsed after therapy with conventional interferon alpha (the type usually used) plus ri-

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

Design/Production
Alan Franciscus

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

www.hcvadvocate.org

© 2005
Hepatitis C Support Project

bavirin; doses were 100, 200, or 400 mcg three times weekly for four weeks. The researchers found that mean HCV viral load did not decrease and serum aminotransferase (ALT and AST) levels also did not change. Low-grade fever and malaise were common, although no serious side effects were seen. They concluded that while interferon-gamma was “relatively well-tolerated,” it “had no effect on HCV RNA levels” in patients who had failed to achieve SVR with interferon-alpha-based therapies.

Treatment of Genotype 4 HCV

Studies continue to yield conflicting data on the treatment of genotype 4 HCV, which is the most prevalent type in the Middle East and parts of Africa. While some have shown that genotype 4 is resistant to treatment (like genotype 1), others suggest it may be easier to treat (like genotypes 2 and 3). In the July *Journal of Viral Hepatitis*, M. Derbala and colleagues reported on a study of 61 patients with chronic genotype 4 HCV in Egypt. Subjects received either conventional interferon plus ribavirin or Peg-Intron plus

ribavirin. End-of-treatment response rates were 35% in the conventional interferon group and 43% in the Peg-Intron group. SVR rates were 26% and 33%, respectively – closer to those seen for genotype 1 than for genotypes 2/3 in other studies. In contrast to past research, however, end-of-treatment and sustained response rates did not differ significantly between conventional and pegylated interferon. The authors concluded that, “the poor response of genotype 4 in Egypt (genotype 4a) to different forms of interferons may be related to an intrinsic resistance to the direct antiviral effect of interferon.”

In related news, S. Kamal and colleagues reported on a study of treatment duration and viral kinetics in patients with genotype 4 HCV in the June issue of *Gut*. In this trial, 287 subjects were randomly assigned to received Peg-Intron plus ribavirin for 24, 36, or 48 weeks. Using an intent-to-treat analysis (all randomized patients were included in the analysis), SVR rates were 29%, 66%, and 69%, respectively. Subjects who went on to achieve SVR showed greater antiviral efficacy and rapid viral load decline from baseline to week 4.

There was no significant difference in efficacy when comparing 36 and 48 weeks of therapy, but the incidence of adverse side effects was higher in the group treated longer. It is unclear why SVR rates in Kamal’s study were about twice as high as those obtained by Derbala, especially since both trials were conducted in Egypt, and thus patients could be expected to have similar demographic factors with respect to HCV variants.

siRNAs Inhibit HCV Replication

In order to reproduce, HCV must take over the host cell’s replicative machinery – the ribosomes – to synthesize its own proteins. HCV messenger RNA acts as a “blueprint” for the translation of these proteins. Researchers are studying various gene therapy techniques to inhibit HCV replication, among them the use of small interfering RNA sequences (siRNAs) that bind to viral RNA and target it for destruction. Mortimer Korfa and colleagues tested siRNAs targeting either conserved sequences of HCV genetic material or else cellular cofactors – proteasome α -subunit 7 (PSMA7) and Hu antigen R

(HuR) – that are thought to promote HCV replication; results were reported in the August *Journal of Hepatology*. They found that siRNAs directed against PSMA7 and HuR inhibited expression of host cell genes, and that “silencing” of PSMA7 and HuR significantly reduced HCV proteins levels in a “replicon” (laboratory model of HCV). Further, siRNAs directed against HCV itself also substantially inhibited translation of viral proteins. Combining the HCV-targeted and cofactor-targeted siRNA sequences produced an additive inhibitory effect. The authors concluded that, “A dual approach of direct- and cofactor-mediated inhibition of HCV replication might avoid selection of mutants and thereby become a powerful strategy against HCV.” These agents are at the early stages of preclinical development, however, and are not likely to be commercially available for several years.

HIV/HCV Coinfection in IDUs

Following up on the journal’s April 15 supplement devoted to “Hepatitis C Virus Infection and Substance Abuse,” the July 1 supple-

ment of *Clinical Infectious Diseases* looked at medical management of HIV/HCV coinfection in injection drug users (IDUs). Articles included discussions of acute HCV infection, mechanisms of hepatic injury, neuropsychological aspects of HIV/HCV coinfection and neurocognitive function, outcomes of end-stage liver disease in the coinfecting population, delivering therapy to incarcerated coinfecting individuals, clinical trials, optimal therapeutic interventions, integrated care for HIV/HCV and substance use, effects of alcohol use, and interactions between opioid drugs and antiretroviral medications.

Diana Sylvestre from the university of California at San Francisco presented an overview of hepatitis C treatment in substance users. While this population comprises the majority of existing and new HCV cases, many substance users have been excluded from treatment and clinical trials. Sylvestre’s group obtained promising results treating patients on methadone maintenance therapy with conventional interferon. Subjects who had no coexisting mental illness, had abstained from illicit drugs for at least six months before starting hepatitis C

treatment, and did not start using drugs again during treatment achieved outcomes similar to those seen in large trials of non-drug-using patients: 40% SVR and 15% discontinuation. Preliminary data from a second study using pegylated interferon show an SVR rate of about 50%. Shorter duration of pretreatment abstinence and illicit drug use during therapy did not significantly affect treatment outcomes, but having a pre-existing psychiatric condition was associated with lower response rates. Notably, 16% of subjects reported that injecting interferon made them crave drugs. “These results show that patients undergoing maintenance therapy with methadone can successfully undergo treatment for HCV infection in an outpatient setting that can address their special needs, even in the presence of comorbid mental illness, intervening drug use, and short duration of pretreatment drug abstinence,” Sylvestre concluded. “Providing integrated treatment for HCV infection in settings closely associated with substance abuse treatment services may minimize the effect of drug use on outcomes of treatment for HCV.”