

Hepatitis C

Relapsers and Nonresponders

Management of people with chronic hepatitis C who do not achieve sustained virological response (SVR) after their first course of interferon-based therapy – which includes at least half of patients with HCV genotype 1 – remains a challenge, according to a review in the December 2009 *Journal of Viral Hepatitis*. D. Dieterich and colleagues wrote that, "The probability of a previously treated patient responding to retreatment depends on the nature of the previous regimen, the magnitude of the response to previous treatment, and the patient's characteristics."

People who relapse after achieving undetectable viral load during therapy, and partial responders who experience a reduction but not clearance of HCV RNA, have better chances of retreatment success than complete nonresponders. In the EPIC-3 and REPEAT trials, retreating nonresponders

with a standard 48-week regimen of pegylated interferon plus ribavirin produced SVR rates of 6%-8%. However, in REPEAT the rate rose to 16% for those retreated for 72 weeks. "Based on available data, extended treatment is the best option for these individuals," the review authors wrote. However, they added, "Maintenance therapy with pegylated interferon is generally ineffective in nonresponders and cannot be recommended."

Pegylated Interferon Maintenance

The HALT-C trial was designed to test the benefits of low-dose pegylated interferon maintenance therapy. More than 1000 nonresponders with advanced liver disease (bridging fibrosis or cirrhosis, Ishak stages 3-6) who did not respond to pegylated interferon alfa-2a (Pegasys) or pegylated

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interferon alfa-2b (PegIntron) plus ribavirin were randomly assigned to receive either 90 mcg/week Pegasys monotherapy or no further treatment. After 3.5 years, patients who received maintenance therapy had lower liver enzyme (ALT and AST) and HCV RNA levels, but were not significantly less likely to progress to hepatocellular carcinoma, decompensated cirrhosis, a fibrosis score increase of two or more points, or death.

As described in the December 2009 *Gastroenterology*, M. Shiffman and colleagues analyzed a subset of 764 participants who received lead-in combination therapy in HALT-C (other patients enrolled directly into the maintenance phase) to determine whether HCV RNA suppression was associated with fewer negative outcomes. During the lead-in phase, 178 patients (23%) experienced at least a 4-log decrease in HCV RNA; 82% of this group achieved undetectable HCV RNA but later relapsed. These patients had significantly fewer clinical outcomes, regardless of whether they were randomized to receive interferon maintenance or no further treatment.

Following randomization, HCV RNA levels increased significantly in all participants receiving no further therapy and in 66% of those receiving maintenance therapy. Only 30 participants – 4% of the entire

subset or 17% of lead-in responders – had persistent HCV RNA suppression. Even among these patients, however, there was no significant reduction in clinical outcomes compared with those whose viral load rose. The researchers concluded that viral suppression during combination therapy is associated with fewer negative outcomes, but low-dose pegylated interferon maintenance therapy produced no additional benefit.

Fibrosis Progression in Nonresponders

Another HALT-C analysis, reported in the December 2009 *Hepatology*, looked at liver disease progression over time among study participants. Z. Goodman and colleagues used computer-assisted morphometric analysis to assess fibrosis progression in liver biopsy specimens obtained over 1.5 to 5 years from 346 nonresponders who still had detectable HCV RNA after 24 weeks of lead-in combination therapy, 78 patients who had undetectable HCV RNA at week 24 but either experienced viral breakthrough during the second 24 weeks of therapy or relapsed after completing treatment, and 111 people who enrolled directly into the maintenance phase.

The 346 nonresponders at week 24 had a mean 61% in-

crease in fibrosis after 24 months and an 80% increase after 48 months. The 78 viral breakthrough and relapse patients had a mean 48% increase in fibrosis at 36 months after starting treatment, but no further increase at 60 months. The 111 patients who enrolled in the monotherapy phase had significantly more fibrosis at baseline, but experienced an increase of only 21% after 21 months and had a slight decrease at 45 months. Pegylated interferon maintenance therapy had no effect on fibrosis progression in any of the groups. The investigators concluded that people without sustained response experience complex, non-linear (inconsistent over time) changes in fibrosis that vary widely among individual patients.

Sorafenib Inhibits HCV Replication

The liver cancer drug sorafenib (brand name Nexavar) may also have a direct effect on HCV, according to a study described in the December 2009 *Gut*. Prior research suggests that the HCV nonstructural protein NS5A interacts with a human cellular protein, c-Raf, that plays a role in cell signaling and may contribute to the development of cancer. (NS3/4A encodes HCV protease, NS5B encodes polymerase). K. Himmelsbach and colleagues

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assessed whether sorafenib – a c-Raf inhibitor – might also suppress HCV replication.

The researchers exposed HuH7.5 cells containing replicating HCV to sorafenib in a laboratory study. They found that in cells with replicating HCV particles, NS5A "recruited" c-Raf to the replicon complex, resulting in c-Raf activation. Adding sorafenib to the cell cultures blocked viral gene expression and replication. Sorafenib also decreased hyperphosphorylated forms of NS5A in HCV-replicating cells and led to increased production of hypophosphorylated forms. Furthermore, sorafenib caused rapid "dissociation" or destruction of lipid droplets, which play a key role in HCV replication. A different cancer drug, sunitinib (a tyrosine kinase inhibitor), in contrast, did not affect HCV replication. "Our data demonstrate that the well-characterized anti-tumour drug sorafenib efficiently blocks HCV replication *in vitro*," the researchers concluded. "This novel effect of sorafenib should be further explored as an antiviral strategy for patients with chronic HCV infection."

HCV and Sleep Disorders

In the January 2010 *Journal of Clinical Gastroenterology*, S. Sockalingam and colleagues presented a review of sleep disturbances in people with HCV. Up to 60% of patients with

chronic hepatitis C experience sleep problems, which are often related to existing psychiatric conditions such as depression. Neuropsychiatric side effects of interferon may also manifest as sleep problems, and up to 30% of interferon-treated patients have newly diagnosed sleep disturbances. Since insomnia in people with hepatitis C may be influenced by a variety of co-existing conditions – both psychiatric (such as depression) and medical (such as anemia or hypothyroidism) – screening to promptly recognize or exclude comorbid conditions can enhance treatment outcomes. In conclusion, the authors wrote, "Further research is needed to elucidate the efficacy of pharmacological and nonpharmacological treatments of sleep disorders in chronic hepatitis C patients."

Effect of CD4 Count in HIV/HCV Coinfection

Past research has shown that HIV/HCV coinfecting people tend to experience more rapid liver disease progression than HCV monoinfected individuals and do not respond as well to interferon-based therapy, but the influence of immune function (indicated by CD4+ T-cell count) is not fully understood. As reported in the December 2009 *Journal of Acquired Immune Deficiency Syndromes*, A. Neumann and colleagues

analyzed the influence of CD4 count on HCV viral kinetics and treatment outcomes in 32 HIV/HCV coinfecting patients and 12 participants with HCV alone who were treated with PegIntron plus weight-adjusted ribavirin for 48 weeks.

The investigators found that among people with HCV genotype 1, those with a pretreatment CD4 count of 450 or higher (normal is 500-1500; below 200 indicates AIDS) were significantly more likely to achieve SVR than those with greater immune deficiency. First-phase HCV RNA decline soon after starting treatment was significantly reduced among coinfecting patients with low compared with high CD4 counts, and also among HIV/HCV coinfecting patients overall compared with HCV monoinfected participants. Second-phase decline slope showed a similar trend for coinfecting patients. "Low baseline CD4+ T-cell count is associated with slower HCV viral kinetics and worse response to treatment among HIV coinfecting patients, suggesting HCV treatment response depends on immune status," the researchers concluded. "First phase viral decline (> 1.0 log) and second phase viral decline slope (> 0.3 log/week) are excellent predictors of SVR for coinfecting patients."

