

Hepatitis C

Retreatment of Nonresponders

Many people with chronic hepatitis C – especially those with HCV genotype 1 – do not achieve a sustained response with their first course of treatment using pegylated interferon plus ribavirin. In the April 22, 2009 *Annals of Internal Medicine*, D.M. Jensen and colleagues reported results from the REPEAT trial, in which 950 patients who were nonresponders after 12 or more weeks of pegylated interferon alfa-2b (PegIntron) plus ribavirin were retreated with pegylated interferon alfa-2a (Pegasys). Participants were randomly assigned to receive treatment for 48 or 72 weeks; some used the standard 180 mcg/week dose the whole time, while others used a double 360 mcg/week dose for the first 12 weeks. Everyone also

took 1000-1200 mg/day weight-adjusted ribavirin.

Participants who received longer duration treatment were more likely to achieve sustained virological response (SVR) than those retreated for 48 weeks (16% vs. 8%). More patients who started with double-dose Pegasys had complete early virological response (EVR), or HCV RNA less than 50 IU/mL at week 12, than those who only used the standard dose (21% vs. 13%). About half (49%) of participants with complete EVR went on to achieve SVR, compared with just 4% of those without complete early response. The researchers concluded that retreatment for 72 weeks significantly increases the likelihood of sustained response. "The overall SVR rate was low," they stated, "but patients

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who are most likely to respond to retreatment can be identified at week 12."

Another recent study, reported in the May 2009 *Gastroenterology*, showed that retreatment using PegIntron is also effective. T. Poynard and the international Epic Study Group conducted a prospective trial to evaluate 1.5 mcg/kg/week PegIntron plus 800-1400 mg/day weight-adjusted ribavirin in 2333 chronic hepatitis C patients with significant fibrosis or cirrhosis who did not achieve a sustained response to prior conventional or pegylated interferon combination therapy. Participants with complete EVR were treated for 48 weeks; 188 patients with low but detectable HCV RNA at week 12 continued therapy at the investigators' request, and those with higher detectable HCV RNA could enter maintenance therapy studies.

Overall, 22% of the participants achieved SVR. Individuals with undetectable HCV RNA at week 12 were more likely to be sustained responders than those with low detectable viral load (56% vs. 12%). The SVR rate was higher in prior relapsers compared with those who never responded (38% vs. 14%), and patients previously

treated with conventional interferon did better than those with a prior attempt using pegylated interferon (25% vs. 17%). Predictors of sustained response in patients with undetectable HCV RNA at week 12 were HCV genotype 2 or 3 (vs. genotype 1), lower fibrosis scores, and low baseline viral load ($\leq 600,000$ IU/mL).

Racial Differences in Interferon Response

It is well known that people of African descent do not respond as well as whites to interferon-based therapy, but the reasons are poorly understood. The Virahep-C trial was designed to look at factors associated with differences in treatment response, with an emphasis on race. About 400 previously untreated genotype 1 chronic hepatitis C patients – half black and half white – were treated with 180 mcg/week Pegasys plus 1000-1200 mg/day weight-adjusted ribavirin, initially for 24 weeks; those who did not achieve undetectable HCV RNA at this point stopped therapy, while responders continued through 48 weeks. As reported in the April 15, 2009 *Journal of Infectious Diseases*, J. Hoofnagle and colleagues

analyzed early changes in HCV viral load in 341 study participants who completed the first four weeks of treatment without dose modification.

Viral load levels decreased in almost all participants, but declines varied widely among patients. At week 4, 22% of whites had rapid virological response (RVR), or undetectable HCV RNA, compared with 12% of blacks. Looking even earlier, racial differences in viral load decline reached statistical significance by the second day of treatment. Even blacks who experienced a decline in HCV RNA at week 4 comparable to that of whites still were less likely to achieve SVR. In addition to race, other factors associated with smaller viral load declines at week 4 were higher baseline HCV RNA level, more severe fibrosis, and higher body weight. These findings led the researchers to suggest that racial differences in response are probably related to "fundamentally biologic" differences in how the body responds to interferon.

In an accompanying editorial, A. Tai and R. Chung, noting that low SVR rates in blacks appear due in large part to impaired early

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viral kinetics, wrote that further studies are necessary "to uncover the relevant mechanisms that underlie this defect in interferon signaling" with the hope that "such mechanisms can be manipulated to restore interferon responsiveness."

Interferon-Signaling Genes

In a related study published in the April 2009 *Journal of Hepatology*, K. Kim and colleagues investigated how interferon response varies depending on viral and host factors. They measured expression of two genes that play a role in interferon signaling – STAT1 and SOCS3 – in pretreatment liver biopsy samples from 49 HCV monoinfected and 25 HIV/HCV coinfecting patients starting pegylated interferon plus ribavirin. Pretreatment SOCS3 expression was higher in nonresponders compared with responders. Among responders, SOCS3 expression did not differ according to HCV genotype. Blacks, however, had higher SOCS3 expression than other racial groups. In contrast, STAT1 expression in the liver did not differ between responders and nonresponders. "Our data indicate that hepatic SOCS3

is a stronger baseline predictor of antiviral response than viral genotype," the researchers concluded. "Poor response to antiviral therapy in African-Americans may be associated with higher hepatic SOCS3 expression."

Persistent HCV after SVR

Sustained virological response, or continued undetectable HCV viral load six months after completion of treatment, is widely considered a "cure." But active virus may persist at low levels, according to a study in the May 2009 *Hepatology*. In a laboratory study, S. MacParland and colleague assessed the infectivity of persistent HCV in cultured human T-cells. Naive lymphoid cells were exposed to plasma or supernatant material from cultured peripheral blood mononuclear cells from nine sustained responders to interferon-based therapy. The researchers looked for HCV RNA positive and negative strands, as well as the HCV nonstructural protein 5A (NS5A), mutant HCV variants, and release of newly produced virus particles.

The investigators found that 11 of the 12 established

cell cultures had detectable HCV RNA positive strands, and four also had evidence of negative strands produced during viral replication. NS5A was detected in the newly infected cells. Sequencing revealed HCV mutants not found in the original samples, another indicator of ongoing replication. Plasma from three patients elicited productive infection in culture cells. "HCV persisting at very low levels long after therapy-induced resolution of chronic hepatitis C can remain infectious," the researchers concluded.

HCV Sexual Transmission

Since the early 2000s, researchers in the U.K. and Europe have report clusters of apparently sexually transmitted acute hepatitis C, mostly among HIV positive men who have sex with men; more recently, similar outbreaks have also been seen in the U.S. (see "Sexual Transmission of HCV: An Emerging New Consensus?" in the April 2009 *HCV Advocate*). As reported in the May 2009 *Gastroenterology*, T. van de Laar and colleagues

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conducted a combined genetic analysis of more than 200 acute HCV case among gay/bisexual men in the U.K. (107), Netherlands (58), Germany (25), Australia (24), and France (12) diagnosed between 2000 and 2006. A majority of the men were on antiretroviral treatment for HIV and they had well-preserved immune function, with a median CD4 cell count of 518.

Using real-time PCR to amplify and compare the NS5B region of the HCV genome, the investigators found that 78% of the analyzed sequences (86% from Europe, 42% from Australia) fell into 11 clusters of closely related virus, each containing four to 37 sequences. The larger clusters encompassed multiple countries, and 85% of HCV transmissions occurred after 1996. While genotype 1 was most common (64%), nearly one-quarter (23%) of the men had genotype 4d, which is otherwise uncommon in Europe.

These findings, the researchers concluded, provide evidence for "a large international network of HCV transmission among HIV positive MSM" and "rapid spread of HCV among neighboring countries." The observed pattern "would imply occasional

introduction and transmission of HCV in the MSM population between 1975 and 1996, followed by a more rapid expansion of HCV transmission among HIV positive MSM since 1996," they wrote. "The reason for a change in HCV transmission pattern since the late 1990s remains unclear, but it probably relates to biologic and behavioral factors."



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