

# Hepatitis C

## **Acute vs. Chronic HCV Diagnosis**

HCV viral load testing may help distinguish individuals with acute versus chronic infection, according to a report in the October 1, 2009 *Clinical Infectious Diseases*. Standard HCV antibody tests do not differentiate between acute and chronic infection. B. McGovern and colleagues conducted a study to determine whether virological parameters could provide more precise information about duration of infection.

Low-level HCV viremia (< 100,000 IU/mL) and large viral load fluctuations (> 1 log) were both found to be very common among a cohort of known acute seroconverters, or people who only recently developed antibodies against HCV (81% and 86%, respectively); in contrast, just 13% of patients with chronic infection had such

low virus levels. Next, looking at a group of injection drug users with suspected acute infection, 77% had low-level viremia and 36% experienced viral load fluctuations. "The diagnosis of acute infection in HCV-seropositive patients is strengthened by the use of virologic parameters that are uncommon in chronic disease," the researchers concluded.

## **Spontaneous HCV Clearance in Children**

Approximately 25% of adults exposed to HCV will spontaneously clear the virus without treatment, but it is not clear how often this occurs in children. As reported in the November 2009 *Journal of Viral Hepatitis*, S.T. Chen and colleagues conducted a long-term follow-up study of 42

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## **Hepatitis Journal Review**

*A publication of the Hepatitis C Support Project*

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children in Taiwan with chronic HCV infection. Participants were categorized as having high or low HCV viral load at the time of enrollment (above or below  $4.5 \times 10^4$  IU/mL). Overall, six children (14%) experienced spontaneous viral clearance during a median follow-up period of 10 years. Children who had low HCV RNA levels at enrollment and during the course of follow-up had a significantly higher likelihood of spontaneous viral clearance in the absence of therapy than those with higher viral loads.

### **Treatment Response in Older Patients**

Response to interferon-based therapy in older individuals is an important issue, as the average age of chronic hepatitis C patients is rising and the risk of advanced liver disease increases with longer duration of infection. In a study described in the October 2009 *Journal of Viral Hepatitis*, K.R. Reddy and colleagues analyzed data from 569 patients with chronic genotype 1 HCV infection enrolled in two randomized Phase III studies of 180 mcg/week pegylated interferon alfa-2a (Pegasys) plus 1000-1200 mg/day weight-adjusted ribavirin for 48

weeks.

The investigators found that patients older than 50 years had a significantly lower sustained virological response (SVR) rate 24 weeks after completing therapy compared with those age 50 or younger (39% vs. 52%, respectively;  $P = 0.0073$ ). However, older patients who achieved rapid virological response (undetectable HCV RNA at week 4 of treatment) or complete early virological response (detectable HCV RNA at week 4 but  $< 50$  IU/mL at week 12) had high SVR rates (83% and 61%, respectively).

Overall, the older group had a significantly higher relapse rate compared with the younger patients (41% vs. 25%, respectively;  $P = 0.0042$ ). Older patients were found to have lower cumulative pegylated interferon and ribavirin blood concentrations<sup>3/4</sup>despite being prescribed the same doses<sup>3/4</sup>and low drug levels predicted failure to achieve SVR. The researchers suggested that more frequent ribavirin dose reductions among the older patients likely contributed to the higher relapse rate. Higher baseline viral load, lower ALT ratio, and liver cirrhosis also predicted poorer response in older patients.

### **Retreatment of Nonresponders**

A significant proportion of people who receive interferon-based combination therapy for chronic hepatitis C do not achieve a sustained response to the first course of treatment. Numerous studies have evaluated the efficacy of retreatment, but results have been mixed. As reported in the October 2009 *Journal of Hepatology*, C. Cammà and colleagues from Italy conducted a meta-analysis of clinical trials using pegylated interferon plus ribavirin for retreatment of nonresponders to a prior course of either conventional or pegylated interferon plus ribavirin.

Using MEDLINE and a manual search, the researchers identified 14 published controlled or uncontrolled trials that met the inclusion criteria. In a pooled analysis of the data, the estimated overall SVR rate for retreatment was 16.3%. However, there was considerable variation in response based on several factors. Studies that included fewer patients with hard-to-treat HCV genotype 1, overweight participants, and patients with cirrhosis typically produced higher SVR rates. The use of a 24-

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week stopping rule during retreatment (discontinuing therapy if response is inadequate at 24 weeks) did not affect sustained response rates. "The overall modest efficacy argues against an indiscriminate retreatment with [pegylated interferon] and ribavirin of all non-responders," the investigators concluded. "Restricting retreatment to non-overweight patients or to those with genotype 2 or 3 infection, using a 24-week retreatment stopping rule, would optimize the potential benefit with a scarce likelihood of missing a curative response."

### **Response and Relapse in HIV/HCV Coinfected Patients**

HIV/HCV coinfecting individuals tend to experience faster liver disease progression and respond less well to interferon-based therapy than people with HCV alone, but there is little information about relapse after treatment in this population. As described in the November 1, 2009 *Clinical Infectious Diseases*, J. Medrano and colleagues retrospectively analyzed medical records from 604 chronic hepatitis C patients in Spain<sup>3/4</sup>including 386 who were also HIV positive<sup>3/4</sup>who were treated with pegylated interferon plus ribavirin.

HIV/HCV coinfecting patients achieved an end-of-treatment response less often than HCV monoinfected patients (37% vs. 61%, respectively) and were more likely to relapse after completion of therapy (33% vs. 22%, respectively). Furthermore, relapse occurred more often in patients with HCV genotypes 1 or 4 compared with 2 or 3. In both HIV positive and HIV negative participants, HCV relapse usually happened within 12 weeks after finishing treatment; three patients tested HCV positive after this point, but two of these cases appeared to be due to re-infection rather than relapse.

### **Coinfection with Advanced Immune Suppression**

HIV/HCV coinfecting patients with advanced immune suppression, indicated by low CD4 cell counts, are particularly prone to faster fibrosis progression and poorer response to interferon-based therapy, relative to those with better preserved immune function. J.A. Mira and colleagues, also from Spain, studied the safety and efficacy of pegylated interferon plus ribavirin in coinfecting patients with advanced immune suppression. Results were reported in the October 15, 2009 *Clinical Infectious Diseases*. The analysis included

542 HIV positive patients treated for hepatitis C between June 2001 and April 2007, stratified according to whether they had a CD4 count above or below 250 cells (under 350 is the current threshold for starting antiretroviral therapy for HIV, and under 200 qualifies as an AIDS diagnosis).

Patients with a CD4 count below 250 cells were somewhat less likely to achieve SVR than those with higher counts (26% vs. 39%, respectively), but the difference did not reach statistical significance ( $P = 0.09$ ). In a nested case-control study with matched patients, the difference in sustained response rates was smaller (26% vs. 32%, respectively) and further from statistical significance ( $P = 0.5$ ). Patients with CD4 counts below 250 cells had a trend toward greater likelihood of severe hematological toxicity (41% vs. 29%, respectively) and requiring interferon or ribavirin dose reductions (31% vs. 20%, respectively), but again these differences were not significant ( $P = 0.1$ ). "The efficacy of pegylated interferon plus ribavirin in HIV/HCV coinfecting patients with advanced immunosuppression is substantial and not significantly different [from] that observed in the overall coinfecting population," the researchers concluded.

