

# Hepatitis C

## **Individualized Treatment Duration**

Tailoring the duration of interferon-based therapy according to early viral kinetics did not lead to improved outcomes, according to a study in the August 2009 *Hepatology*. T. Berg and colleagues from Germany compared individualized versus standard duration therapy among 433 genotype 1 chronic hepatitis C patients. Participants were randomly assigned to receive either 1.5 mcg/kg/week pegylated interferon alfa-2b (PegIntron) plus 800-1,400 mg/day weight-adjusted ribavirin for 48 weeks, or an individually tailored duration ranging from 18 to 48 weeks, calculated as the time it took to reach undetectable HCV RNA using a bDNA assay (limit of detection 615 IU/mL)

multiplied by six.

Sustained virological response (SVR) rates, assessed 24 weeks after completing therapy, were significantly lower in the tailored duration group compared with the standard duration group (35% vs. 48%). The difference reflected a higher relapse rate in the variable duration group (33% vs. 14%). Baseline viral load and time to reach undetectable HCV RNA using a more sensitive TMA assay (limit of detection 5.3 IU/mL) were significant predictors of sustained response. Looking just at patients with both low baseline viral load (< 800,000 IU/mL) and a negative TMA test within the first four weeks of treatment, SVR rates were comparable in the standard and

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## **Hepatitis Journal Review**

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variable duration groups, and even patients treated for only 18 or 24 weeks had a sustained response rate above 80%. The researchers suggested that the inferiority of the individualized protocol might be attributable to use of the less sensitive test and not taking baseline viral load into account.

### **Ribavirin Dose Reduction and Relapse**

Reducing the dose of ribavirin decreases the effectiveness of interferon-based therapy, according to a report in the August 2009 *Journal of Viral Hepatitis*. N. Hiramatsu and colleagues from Japan analyzed the effect of ribavirin dosage on viral relapse in 984 genotype 1 chronic hepatitis C patients treated with pegylated interferon alfa-2b combination therapy. Among the 472 study participants with undetectable viral load at weeks 24 and 48, the mean dose of ribavirin was a significant predictor of virological relapse, along with degree of fibrosis and time when HCV RNA became undetectable. Greater reductions in ribavirin exposure were associated with stepwise increases in the

relapse rate, ranging from 11% with the highest doses to 60% with the lowest doses. Doses of pegylated interferon, however, were not significantly linked to relapse. Among participants with complete early virologic response (EVR, defined as undetectable HCV RNA at week 12), only 4% of those who received at least 12 mg/kg/day of ribavirin experienced relapse. Reducing ribavirin levels – even after week 12 – increased the risk of relapse, while the dose of pegylated interferon could be reduced to 0.6 mcg/kg/week after week 12 without decreasing the likelihood of sustained response. "Maintaining as high a ribavirin dose as possible (³ 12 mg/kg/day) during the full treatment period" can suppress virological relapse in genotype 1 patients, the researchers concluded, especially those with complete EVR.

### **Weight, Insulin Resistance, and Fatty Liver**

Factors associated with being overweight appear to worsen liver disease progression in people

with chronic hepatitis C, according to a study in the August 2009 *Gastroenterology*. J. Everhart and colleagues examined the effects of weight-related conditions on disease outcomes among approximately 1,000 participants in the HALT-C trial, which studied long-term pegylated interferon alfa-2a (Pegasys) maintenance therapy in patients who did not achieve sustained response to pegylated interferon/ribavirin combination therapy. At the time of study entry, participants had a high median body mass index (29.2 kg/m<sup>2</sup>) and waist circumference, as well as high rates of diabetes (25%) and insulin resistance.

Of the various noninvasive measures evaluated, insulin resistance (according to the HOMA2-IR method) was most strongly associated with disease outcomes. Presence of steatosis (fat accumulation) in the baseline liver biopsy sample was associated with an increased likelihood of poor outcomes among patients with bridging fibrosis, but a decreased rate among patients with cir-

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rhosis. Weight gain of 5% or more during the first year of follow-up was also linked to poor outcomes. "Insulin resistance, histologic features of fatty liver disease, and weight change were associated with outcomes of chronic hepatitis C," the researchers concluded, suggesting that "[i]mprovement in these weight-related factors might modify disease progression."

### **Hepatitis C in Children and Adolescents**

Children and adolescents with chronic hepatitis C frequently develop symptoms related to liver disease progression, according to a study in the August 2009 *Pediatric Infectious Disease Journal*. W. Henderson from the National Institutes of Health and colleagues analyzed symptoms and pathophysiology among 62 pediatric outpatients aged 3 months to 19 years. Nearly two-thirds (60%) had clinical symptoms such as fatigue, joint pain, abdominal pain, and easy bruising or bleeding. Boys were significantly more likely than girls to be symptomatic (58% vs. 42%), and children with symptoms were significantly older on average than those without (14 vs. 9

years). Surprisingly, patients with low HCV viral load (< 2 million copies/mL) were five times more likely to experience symptoms than those with higher viral load. Liver biopsies revealed that 80% of participants had evidence of liver inflammation, 57% had fibrosis, and 9% had steatosis; all participants with steatosis or cirrhosis reported symptoms. However, there was no significant relationship between symptom status and race/ethnicity, HCV genotype, coexisting conditions, or liver enzyme (ALT, AST, or GGT) levels. The researchers concluded that "Pediatric patients with HCV can have significant symptoms and physiologic liver changes related to HCV."

### **SVR Reduces Complications in HIV/HCV Coinfection**

HIV/HCV coinfecting individuals who achieve a sustained response to interferon-based therapy have a lower risk of liver-related complications and death, according to a study in the August 2009 *Hepatology*. J. Berenguer and colleagues from Spain analyzed the association between sustained HCV clearance and improved clinical outcomes in 711 coinfecting patients at 11 HIV clinics who were treated with conventional or

pegylated interferon plus ribavirin. Most (84%) were on combination antiretroviral therapy, about half had undetectable HIV viral load, and the median baseline CD4 cell count was relatively high at 544, but 21% had a history of past AIDS-defining illnesses.

Nearly one-third (31%) of the patients achieved SVR. During an average follow-up period of 21 months, the risk of death and liver-related complications (decompensation, hepatocellular carcinoma, and liver transplantation) was significantly lower among sustained responders compared to non-responders and relapsers. The overall mortality rate was 0.46 per 100 person-years (PY) in the SVR group compared with 3.12 per 100 PY in the non-SVR group. Rates of death due to liver-related causes were 0.23 vs 1.65 per 100 PY, respectively. None of the sustained responders developed liver cancer or required a liver transplant. These results, the researchers concluded, "suggest that the achievement of an SVR after interferon/ribavirin therapy in patients coinfecting with HIV/HCV reduces liver-related complications and mortality."

