

# Hepatitis C

## **Weight-Based Ribavirin**

Ribavirin is known to help prevent HCV relapse after interferon-based therapy. The original dose of ribavirin for chronic hepatitis C was 800 mg/day, but studies showed this was not adequate – especially for overweight patients – so weight-based dosing was approved: 1,000 mg/day if less than 75 kg (about 165 lb) or 1,200 mg/day if 75 kg or more. The latest data from the large WIN-R trial, reported by Ira Jacobson and colleagues in the October 2007 issue of *Hepatology*, indicate that more closely tailored dosing may work better.

In this randomized trial, 5,027 previously untreated participants received 1.5 mcg/kg/week pegylated interferon alpha 2-b (PegIntron) plus ribavirin

either as a flat 800 mg/day dose or with dosage adjusted according to body weight: less than 65 kg (about 140 lb): 800 mg/day; 65-84 kg (about 185 lb): 1,000 mg/day; 85-104 kg (about 225 lb): 1200 mg/day; 105-125 kg (about 275 lb): 1400 mg/day (no one weighed more than 125 kg). The ribavirin dose was reduced if patients developed anemia (though they could use erythropoietin). Participants with genotype 1 or 4 were treated for 48 weeks and those with genotype 2 or 3 were randomized to 24 or 48 weeks duration.

Among the study population as a whole, the sustained virological response (SVR) rate was significantly higher in patients who received weight-based compared with flat-dose ribavirin (44% vs 41%).

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## **Hepatitis Journal Review**

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End-of-treatment response rates were similar, indicating that the difference was due to less frequent relapse in the weight-based arm. For genotype 1 patients, the corresponding SVR rates were 34% vs 29%. However, for genotype 2 or 3 patients, weight-based dosing did not make a significant difference (SVR 62% vs 60%), and 48 weeks was no better than 24 weeks. Weight-based ribavirin dosing led to larger decreases in hemoglobin levels, but otherwise side effects were similar. The researchers concluded that, “Pegylated interferon alfa-2b plus weight-based ribavirin is more effective than flat-dose ribavirin, particularly in genotype 1 patients, providing equivalent efficacy across all weight groups.”

### ***Ribavirin for African Americans***

The WIN-R researchers also conducted a subgroup analysis of 362 African American participants with HCV genotype 1 in the study, since these patients do not respond as well as Caucasians to interferon-based therapy. Here again, the SVR rate was significantly higher among patients receiving weight-based rather than fixed-dose ribavirin (21% vs 10%),

and the relapse rate was lower (22% vs 30%). Side effects and drug discontinuations were similar in both arms. The researchers concluded that weight-based ribavirin “is more effective than flat dosing” in this population, but even with tailored dosing, response rates were lower for African Americans compared with other racial/ethnic groups. Inexplicably, response rates were better in heavier patients – even though the progressive doses were intended to give each weight category an equivalent ribavirin concentration – suggesting a potential role for therapeutic drug level monitoring.

### ***Hepatocellular Carcinoma***

Two recently published studies looked at the epidemiology and natural history of hepatocellular carcinoma (HCC), a form of liver cancer associated with chronic viral hepatitis. In the September 2007 issue of *Hepatology Research*, Hashem El-Serag presented an overview of HCC epidemiology in the U.S. While the overall incidence of HCC is increasing, there are striking differences with regard to age, sex, race/ethnicity, and geographic region, which reflect patterns of HBV and

HCV infection. Men are three times more likely than women to develop HCC, and there is a birth cohort effect with a cutoff after 1945. Asians are twice as likely to have HCC as African Americans or Hispanics, who in turn are affected twice as often as Caucasians. The higher rate among Asians is attributable to a high prevalence of HBV, and is not new. But the doubling of HCC incidence over the past two decades has disproportionately affected Caucasian, and to a lesser extent Hispanic, men between the ages of 45 and 65. HCV infection acquired two to four decades ago explains at least half this increase, and the rate is expected to continue rising for another 10 years. Interestingly, a significant proportion of HCC patients do not have either chronic viral hepatitis or a history of heavy alcohol use, and obesity and diabetes appear to be emerging risk factors. Despite a minor improvement in survival, people with HCC only live a median of eight months; the use of potentially curative therapy varies by region, but remains low overall.

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## **HCC in People with HIV**

A second study, reported in the October 2007 *Journal of Hepatology*, looked at HCC in HIV-positive individuals. Norbert Brau and colleagues conducted a retrospective analysis of patients at six centers in the U.S. and Canada between 1992 and 2005, identifying 63 cases of HCC in HIV-infected people. Compared with a control group of HIV-negative individuals with HCC, the HIV-positive patients were younger (52 vs 64 years), more likely to be coinfecting with HBV or HCV (97% vs 73%), and more likely to be symptomatic (51% vs 38%), but had similar average Child-Turcotte-Pugh and HCC staging scores. Overall, HIV/HCV coinfecting patients developed HCC sooner after HCV infection than HIV-negative people (mean 26 vs 34 years). HIV-positive patients were more likely than HIV-negative individuals to receive proven HCC therapy (48% vs 31%), but nevertheless had a similar median survival duration (6.9 vs 7.5 months). Among the 33 HIV-positive patients who did not receive HCC therapy, survival was longer (6.5 vs 2.6 months) in those with an undetectable HIV viral load (below 400 copies).

## **Biopsy Before HCC Surgery**

A third study looked at surgery (resection) to remove large HCC tumors. As reported in the September 2007 *Journal of the American College of Surgeons*, Alastair Young and colleagues conducted a retrospective analysis of all patients who had large HCC tumors removed at St. James's University in Leeds, U.K., over the past 12 years. Of these, 85 were classified as large (> 3 cm) and 42 were classified as giant (> 10 cm). Overall survival one year after surgery was 76%, falling to 51% at five years. Tumor size did not influence survival, although having multiple tumors predicted shorter survival. Pre-operative liver biopsy was associated with shorter survival times. Since HCC can usually be diagnosed using imaging and alpha-fetoprotein testing, the researchers concluded that pre-operative biopsies should be avoided since they are unnecessary and appear to worsen long-term outcomes.

## **HCV Progression in Coinfected Patients**

Past research suggests that HIV/HCV coinfecting people tend to experience more rapid liver disease progression than those with HCV alone, but

data from recent studies has been mixed. As reported in the September 2007 issue of *Hepatology*, Juan Pineda and colleagues analyzed mortality, hepatic decompensation (liver failure), and predictors of poor outcomes among 1,011 coinfecting Spanish patients starting combination anti-HIV therapy (HAART) for the first time. After a median follow-up period of just over five years, about 6% developed hepatic decompensation and about 7% died; 43% of these deaths were due to liver disease. Factors that predicted hepatic decompensation were age over 33 years, female sex, more advanced HIV disease, less CD4 cell recovery after starting HAART (less than 100 cells), and more follow-up time with a detectable HIV viral load. Factors associated with death due to liver failure were older age, smaller CD4 cell gains, hepatitis D coinfection, pre-existing cirrhosis at study entry, hepatic encephalopathy, and lack of hepatitis C treatment. The study authors concluded that, "End-stage liver disease is the primary cause of death in HIV/HCV coinfecting patients under HAART," but added that hepatitis C therapy can lead to better outcomes.

