

# Hepatitis C

## ***Ribavirin Causes HCV Mutation***

Research shows that ribavirin enhances the efficacy of interferon treatment for hepatitis C, though why it does so is unclear. As reported in the October 2005 *Journal of Hepatology*, Y. Asahina and colleagues evaluated HCV mutations before starting of treatment and during a 4-week ribavirin monotherapy phase before starting interferon in 34 patients. A significantly higher rate of mutation in the NS5A and NS5B regions of HCV occurred during ribavirin monotherapy compared with the pre-treatment observation period. While on ribavirin, there were more than four times as many mutations per site per year. Further, after interferon was added, the rate of mutation was greater in patients who achieved sustained virological response (SVR) compared with non-responders

– 23 times higher in the case of NS5A; certain types of NS5A mutations were only seen in sustained responders. In an accompanying editorial, A. Perelson and R. Ribeiro reviewed several of ribavirin's proposed mechanisms of action. Because other inosine monophosphate dehydrogenase (IMPDH) inhibitors besides ribavirin do not have a significant anti-HCV effect, this is probably not major mode of action. Because ribavirin alone decreases HCV levels only slightly, it is probably not a potent inhibitor of HCV polymerase. But when mutation is enhanced, the resulting virus may be less "fit"; it may fail to replicate or may produce progeny that are less infectious. Some mysteries remain – such as why only a minority of the 34 subjects experienced increased HCV mutation (10 for NS5A and 8 for NS5B). Perelson and Ribeiro speculated that some

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patients' HCV may be more tolerant of mutations; host factors may also play a role. "Although this mechanism is not yet fully elucidated," they concluded, "the current report brings us closer to an understanding of ribavirin's mode of action, which will be crucial for designing improved therapies for HCV."

### **Interferon and Liver Cancer**

Looking at another type of mutation study, M. Nishikawa and colleagues examined mutation of mitochondrial DNA (mtDNA) in liver tissue; results were reported in the September 2005 *Journal of Viral Hepatitis*. The researchers obtained liver biopsy specimens from 26 chronic hepatitis C patients before and after interferon therapy. They found that the mtDNA mutation rate was four times higher in HCV positive patients compared to HCV negative controls. They also found that interferon therapy decreased the rate of mtDNA mutation. Decreased mutation was associated with lower histological activity scores. Because liver cell mutations can give rise to liver cancer, these findings may help explain why interferon lowers the risk of hepatocellular carcinoma. The authors concluded that, "mtDNA could provide a new criterion for the therapeutic evaluation

of the effect of [interferon], and may be useful for the prediction of risk of carcinogenesis." In a related study reported in the same issue, M.F. Donato and colleagues found that HCV patients treated with interferon had significantly reduced liver cell proliferation, another harbinger of liver cancer. While the reduction was greater in virological responders, non-responders, too, also showed decreased cell proliferation.

### **Biomarkers for Liver Damage and Treatment Response**

The search continues for non-invasive tests to help monitor disease progression and treatment response in patients with hepatitis C. A.M. DiBisceglie and colleagues examined levels of alpha-fetoprotein (AFP) – traditionally considered a biomarker for hepatocellular carcinoma (HCC) – in 1,145 participants in the HALT-C trial; results were reported in the September 2005 *Journal of Hepatology*. They found that about 17% patients had baseline AFP levels of 20 ng/mL or greater. AFP levels were significantly higher among patients with cirrhosis than among those with bridging fibrosis. Elevated serum AFP in patients with cirrhosis was independently correlated with female sex, black race, de-

creased platelet count, and increased AST/ALT ratio. HCC was detected in six patients, but only half of these had elevated AFP. Levels of AFP decreased significantly during treatment with pegylated interferon (Pegasys) plus ribavirin.

Looking at alternative biomarkers, S. Horiike and colleagues evaluated levels of 8-nitroguanine and 8-hydroxy-2'-deoxyguanosine (8-OHdG) – two markers of nucleic acid damage – in the livers of HCV patients before and after interferon-based therapy (also reported in the September 2005 *Journal of Hepatology*). The researchers found that these markers were both present in the livers of chronic hepatitis C patients, but not in HCV negative controls. Accumulation of 8-nitroguanine and 8-OHdG increased with severity of inflammation, and markedly decreased in sustained responders after treatment. The authors concluded that, "8-Nitroguanine is a useful biomarker to evaluate the severity of HCV-induced chronic inflammation in relation to hepatocellular carcinoma."

Gamma-glutamyl transferase (GGT) is a bile duct enzyme that is included in the liver function test panel, but typically does not receive as much attention as ALT and AST. As reported in the September 2005 *Journal of Clinical Gastroenterology*, C.A. Villela-Nogueira and colleagues ana-

lyzed 211 chronic hepatitis C patients during the 6-month follow-up period after completion of interferon plus ribavirin therapy. Pretreatment GGT levels were elevated in 63% of patients, and 40% achieved SVR. In a regression analysis, having a normal GGT level was associated with SVR, while elevated GGT predicted poorer treatment response.

### ***Ribavirin Plus ddI a Risky Combo***

Firouze Bani-Sadr and colleagues reported in the September 1, 2005, *Journal of Acquired Immune Deficiency Syndromes* that use of the anti-HIV drug ddI (didanosine or Videx) in combination with ribavirin increases the risk of mitochondrial toxicity (damage to energy-producing structures in cells). Mitochondrial toxicity can lead to pancreatitis (inflamed pancreas) and lactic acidosis (elevated lactic acid levels), characterized by symptoms such as nausea, abdominal pain, muscle weakness, and shortness of breath. The researchers reviewed data from 283 HIV/HCV coinfecting patients in a clinical trial of interferon plus ribavirin. Overall, 11 developed symptomatic mitochondrial toxicity, for an incidence rate of 48 per 1,000 person-years (PY). Among patients taking ddI, however, the incidence rate was more than

four times higher: 200 per 1,000 PY. In an adjusted analysis, ddI was 46 times more likely to cause symptomatic mitochondrial toxicity than anti-HIV regimens without ddI. No increase in mitochondrial toxicity was observed in coinfecting patients taking anti-HIV drugs other than ddI – including d4T (stavudine or Zerit), which has previously been linked to mitochondrial toxicity. The researchers recommended that ddI should be avoided in patients taking ribavirin. If the drugs must be used together, patients should be monitored closely for signs of mitochondrial damage. Because some of the signs of mitochondrial damage resemble common interferon side effects, the authors recommended testing lactic acid and lipase (an enzyme produced by the pancreas) levels in patients with these symptoms.

### ***Anti-HIV Therapy and Liver Toxicity***

In a related study reported in the October 15, 2005, *Clinical Infectious Diseases* K.E. Sherman and colleagues analyzed liver toxicity in 70 HIV/HCV coinfecting individuals in a larger study of HIV positive patients treated for the first time with nelfinavir (Viracept) or lopinavir/ritonavir (Kaletra) plus

3TC (lamivudine or Epivir) and d4T. HCV viral load initially rose when patients started anti-HIV therapy, increasing by 6.1% and 9.6%, respectively, in the two arms by week 24. By week 48, however, HCV levels returned to close to baseline levels in the Kaletra arm. Among immunocompromised patients with fewer than 100 CD4 cells, half in the nelfinavir group, but none in the Kaletra arm, experienced HCV viral load increases of .5 log IU or more. ALT levels fell by 5.5% in the Kaletra arm and rose by 111.4% in the nelfinavir arm at week 24; 6.9% in the Kaletra arm and 19.5% in the nelfinavir arm had grade 3 or 4 (severe or life-threatening) ALT abnormalities. By week 48, however, ALT had returned to close to baseline levels in both groups. These results suggest that current coinfection treatment guidelines recommending that anti-HIV therapy should be stopped if serious ALT elevations develop may be too conservative. Rather than stopping anti-HIV treatment when hepatitis “flares” are detected, patients should perhaps instead be closely monitored and kept on anti-HIV therapy, in order to benefit from decreased HIV viral load and improved immune function.