

Hepatitis C

Liz Highleyman

Ribavirin and Anemia

Hemolytic anemia related to ribavirin is a common reason for discontinuation or modification of HCV therapy. In the May issue of the *Journal of Viral Hepatitis*, Sulkowski and colleagues reported on an analysis of 677 HCV patients (not coinfecting) receiving standard interferon plus ribavirin (1000-2000 mg/day) in two separate studies. More than half experienced a 30 g/L or greater decrease in hemoglobin (Hb—an indication of anemia). Women were more likely to experience Hb levels below 100 g/L, but men were more likely to see a 30 g/L or greater drop. Ribavirin dose reduction led to increases in Hb concentration of about 10 g/L.

However, lowering the dose or delaying initiation of ri-

bavirin does not seem to be a good strategy for reducing anemia, since a full course of standard-dose ribavirin appears to play an important role in preventing HCV relapse. In fact, Bräu suggested that patients' inability to tolerate a full course of ribavirin might help account for the low SVR rates seen in his study. Instead, use of erythropoietin (EPO, Procrit) to stimulate red blood cell production may allow patients to remain on ribavirin for the recommended 24-48 weeks. In the May 2004 issue of *Gastroenterology*, Nezam Afdhal and colleagues reported results of a controlled study of 185 HCV patients who developed anemia while taking ribavirin. Patients received 40,000 IU of EPO or placebo once weekly. After eight weeks, Hb levels rose and quality of life improved in the patients receiving EPO. Use of EPO enabled 88% of patients in this arm to

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stay on full-dose ribavirin, compared with 60% in the placebo group.

Treatment Response in African Americans

Several studies have shown that African Americans respond less well to HCV treatment than whites, although the reason for this difference is not clear. In the May issue of the *American Journal of Gastroenterology*, Richard Sterling and colleagues reported data from a retrospective analysis of 59 inmates (83% male, 55% Caucasian, 73% with genotype 1 HCV, 41% with advanced fibrosis) at prisons run by the Virginia Department of Corrections. Subjects were treated with standard interferon plus ribavirin. Overall sustained virological response (SVR) rates were 41% in Caucasians and 28% in African Americans. Looking only at those with genotype 1 HCV, however, the corresponding SVR rates were 33% and 29— not a statistically significant difference. The authors concluded, “HCV can be effectively treated in the correctional setting with response rates similar to, if not better than the published literature.” They suggested that in the setting of

directly observed therapy, which ensures excellent adherence, similar SVR rates may be achieved regardless of race.

HIV/HCV Coinfection

Impact of HAART

Several recent reports have discussed the management of hepatitis C in patients coinfecting with HIV. The January 2 issue of *AIDS* contained several articles on this topic, including an overview by Vincent Soriano and colleagues of care of coinfecting patients. In the May 2004 issue of *Clinical Gastroenterology and Hepatology*, Sterling and colleagues examined the impact of highly active antiretroviral therapy for HIV (HAART) on liver disease in coinfecting individuals. Based on a retrospective analysis of 101 coinfecting patients and 302 with HCV alone, the researchers found no significant differences in biochemical (e.g., ALT level) or histological (liver tissue health) parameters between the coinfecting and HCV-monoinfecting subjects. They also observed no impact on liver disease due to protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors

(NNRTIs), although some drugs in both classes are known to be hard on the liver. On the whole, the patients had well controlled HIV disease and high CD4 cell counts, suggesting that effective HAART may help slow liver disease progression.

HAART Boosts HCV Diversity

But HAART may also have negative effects that are not yet well understood. According to a report in the April 15 issue of the *Journal of Infectious Diseases*, anti-HIV therapy appears to increase HCV genetic diversity. Jason Blackyard, Raymond Chung, and colleagues assessed HCV quasispecies (viral variants) in 11 coinfecting patients in study ACTG 383. They found that several HCV genetic sequences became more variable after patients started HAART. For some sequences, diversity was greater in subjects whose HCV viral load increased after starting anti-HIV therapy (which happens about 25% of the time), compared with those whose HCV levels remained stable. The post-HAART increase in HCV viral load was not due to the emergence of a dominant strain. The researchers suggested that as HAART

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improves immunological function, the immune system exerts greater selection pressure on HCV, causing it to mutate more rapidly in an effort to evade the body's stronger immune defenses. It is not known how increases in HCV viral load and genetic diversity might impact clinical disease progression. But Chung sounded a note of caution: "We need to be mindful that HCV RNA can actually increase in some patients who are treated with HAART," he told Reuters Health News. "While we may be improving HIV disease with HAART, we may unwittingly be [contributing to] HCV-related liver disease."

Coinfection Treatment

In the April issue of *Hepatology*, Norbert Bräu and colleagues reported on a study of standard interferon plus either full-course or delayed ribavirin in 107 HCV/HIV coinfecting patients. SVR rates were poor in both groups (about 11% with full-course ribavirin and about 6% with delayed ribavirin), and more than half discontinued therapy prematurely. Anemia occurred more often in the full-course group, and was

more common in patients who were also taking AZT (Retrovir). As Mark Sulkowski noted in the same issue, standard interferon is now considered substandard therapy; recent studies have shown better SVR rates in coinfecting patients receiving pegylated interferon plus ribavirin (about 40% in the APRI-COT study). Indeed, in the January 2 *AIDS*, Robert Myers and colleagues reported that coinfecting patients who had previously failed to respond or relapsed after treatment with standard interferon (with or without ribavirin) had a SVR rate of 16% (9% for genotype 1) when retreated with Peg-Intron plus ribavirin, demonstrating that at least a portion of this hard-to-treat population can be successfully treated with the best current therapy.

Angel Luis Ballesteros and colleagues reported in the same issue that coinfecting patients who ultimately achieved SVR experienced a very early decline in HCV viral load, starting 24 hours after beginning treatment with pegylated interferon plus ribavirin. A similar decline was not seen in non-responders, suggesting that a lack of virological response as early as week 4 might be used as an indica-

tor of treatment failure, allowing treatment discontinued and sparing patients the side effects and cost of continued therapy.

HCV Associated with Lower Blood Lipids

While anemia may be a greater concern for coinfecting patients using AZT, another side effect associated with anti-HIV therapy—elevated blood lipid (fat) level—seems to be less common in people with hepatitis C. In a letter to the editor in the May 1, 2004 issue of the *Journal of Acquired Immune Deficiency Syndromes*, Simona Di Giambenedetto and colleagues reported that HCV coinfection was associated with a lower probability of increased total cholesterol levels in patients treated with PIs or NNRTIs; triglyceride levels, however, did not differ by HCV status. Blood fat abnormalities are a growing concern for people using HAART because they are associated with increased risk of cardiovascular disease. It is not known why cholesterol levels do not rise as much in coinfecting individuals treated with HAART, nor whether this effect will persist in patients who achieve a sustained response to anti-HCV therapy.

