

Hepatitis C

Antiviral Effect of Telaprevir

Telaprevir (VX-950) is a promising oral HCV protease inhibitor being developed by Vertex. In the October 2006 issue of *Gastroenterology*, H. Reesink and colleagues reported data from a Phase I, placebo-controlled, double-blind trial of the safety and effectiveness of telaprevir in 34 patients with genotype 1 HCV, 27 of whom had failed prior interferon-based therapy. Trial participants were randomly assigned to receive placebo or one of three doses of telaprevir (450 or 750 mg every 8 hours or 1250 mg twice daily) for 14 days. HCV viral load decreased by at least 2 logs in all 28 patients treated with telaprevir, and by at least 3 logs in

26 subjects. The 750 mg group had the highest telaprevir trough concentrations between doses, and achieved a median HCV RNA reduction of 4.4 logs. In comparison, the median HCV reductions at Day 14 were 2.4 logs in the 450 mg group and 2.2 logs in the 1250 mg group. ALT levels decreased during therapy in all groups receiving telaprevir, and the drug was well-tolerated. However, telaprevir-resistant virus was observed in some patients. “[Telaprevir] was well-tolerated and demonstrated substantial antiviral activity,” the authors concluded. “Some patients had viral breakthrough during dosing, related to selection of variants with decreased sensitivity to [telaprevir].” Other ongoing studies have shown that anti-

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HCV activity is greater when telaprevir is combined with pegylated interferon, and combination therapy should delay the emergence of resistance mutations.

Integrating Medical and Mental Health Care

Psychiatric conditions and substance use are common among hepatitis C patients, and some studies have shown that individuals with a history of psychiatric conditions are more likely to experience depression during interferon-based therapy. In the October 2006 *American Journal of Gastroenterology*, A. Knott and colleagues reported on a retrospective evaluation of the effect of integrating psychiatric and medical care on initiation of antiviral treatment in 184 patients with chronic hepatitis C. Using various screening tests, the researchers found that most patients (81%) had evidence of mental health conditions, and 26% had a positive urine drug test. Among patients with psychiatric conditions, 38% had their own mental health providers, 47% had no provider and were referred to a psychiatric

clinical nurse specialist at the site where they received medical care, and 15% declined psychiatric referrals. Those with mental health conditions who received integrated care from a psychiatric nurse were significantly more likely to complete evaluation for and start anti-HCV therapy, at a rate similar to that of patients without psychiatric conditions. In addition, patients followed by a mental health provider (their own established provider or a nurse specialist) achieved significantly greater adherence to antiviral therapy. "Integrated care offers promise as an approach for addressing psychiatric comorbidity in this traditionally difficult to treat population," the authors concluded.

Impact of AZT on Anemia

Anemia is a common side effect during combination therapy for hepatitis C, since ribavirin can cause red blood cell destruction. Use of AZT (Retrovir) as part of an anti-HIV regimen may worsen anemia, since the drug is associated with bone marrow toxicity. In the October 2006 *Journal of Viral*

Hepatitis, D. Alvarez and colleagues reported on a retrospective study of the incidence of anemia, ribavirin dose reduction, and use of erythropoietin (EPO, Procrit) in 217 HIV/HCV coinfecting patients in two clinical trials of pegylated interferon plus weight-based ribavirin (800-1400 mg/day). Hemoglobin levels before anti-HCV therapy were similar in all patients, including the 29% who were taking AZT. After four weeks of pegylated interferon plus ribavirin, the mean hemoglobin decline was greater among AZT recipients (3.13 g/dL) compared with patients on other anti-HIV drugs (2.13 g/dL) and those not receiving antiretroviral therapy (1.47 g/dL). Consequently, ribavirin dose reduction and use of EPO were more common among patients taking AZT. However, discontinuation of anti-HCV therapy was not more likely among AZT recipients, and HCV early virological response rates at 12 weeks did not differ based on AZT use. These data show that anemia can be successfully managed, allowing the continuation of hepatitis C treatment in coinfecting patients taking AZT.

Coinfected Patients with Normal ALT

Studies have shown that HIV/HCV coinfecting individuals tend to experience more rapid liver disease progression than individuals with HCV alone. In HCV mono-infected patients, persistently normal ALT is associated with less disease progression, but this has not been extensively studied in the coinfecting population. As reported in the September 1, 2006 issue of *Clinical Infectious Diseases*, M. Sanchez-Conde and colleagues assessed ALT levels and their significance, as well as associated biopsy findings, in 256 coinfecting patients, about 9% of whom had normal ALT levels on two or more occasions within a six-month period. About one-third of the patients with elevated ALT – but none with persistently normal ALT – had evidence of advanced (stage F3 or F4) liver fibrosis. Among patients with persistently normal ALT, 96% had some grade of fibrosis, but this was usually mild; 29% had stage F2. Individuals with elevated ALT were more

likely than those with normal ALT to have genotype 3 HCV. “Histological abnormalities are significantly milder in patients coinfecting with HIV and HCV who have persistently normal ALT levels than those found in patients with high ALT levels,” the authors concluded. However, “a subgroup of patients with persistently normal ALT levels may have significant cases of fibrosis.” These findings suggest that it is advisable for coinfecting individuals with normal ALT to undergo biopsies to assess their need for treatment.

Real-Life Treatment of Coinfected Patients

For a variety of reasons, many HIV/HCV coinfecting patients do not receive treatment for hepatitis C. As described in the October 2006 *Journal of Viral Hepatitis*, P. Cacoub and colleagues analyzed barriers to anti-HCV therapy in coinfecting patients in France. The researchers surveyed physicians with a variety of specialties about the care offered to a total of 380 coinfecting patients, most of whom had well-controlled HIV (63% with

undetectable HIV viral load). They found that about half did not receive treatment for hepatitis C. Reasons for non-treatment reported by physicians included minimal liver fibrosis (i.e., no need for treatment), alcohol consumption, active drug use, no liver biopsy performed, treatment contraindicated (mainly due to psychiatric conditions), physician expectation of poor adherence to therapy, and patient refusal of treatment; physicians frequently gave more than one reason. Patients who received hepatitis C treatment were more often of European descent, had better controlled HIV, were more likely to be under the care of a hepatologist (as opposed to another specialty such as infectious diseases), were more likely to have received a liver biopsy, and more often had high HCV viral loads. Many of the reported barriers to treatment can be overcome; for example, depression can be managed with medication, and studies have shown that many patients with a history of substance use can achieve good adherence and sustained response to anti-HCV therapy.

