

Hepatitis C

Antiviral Treatment for Cirrhotic Patients

Experts have traditionally cautioned against interferon-based therapy for people with liver cirrhosis due to side effects, but these patients can potentially benefit the most from treatment. As described in the July 2008 *Journal of Clinical Gastroenterology*, A. Floreani and colleagues evaluated the safety and efficacy of pegylated interferon alfa-2b (PegIntron) plus ribavirin in 365 previously untreated hepatitis C patients, of whom 87 had compensated cirrhosis and the rest had less severe fibrosis (Ishak stages F1-F4). After treatment, patients with cirrhosis had a significantly lower sustained virological response (SVR) rate compared with the non-cirrhotic patients (45.9% vs 65.8%); as expected, HCV genotypes 1 or 4 and high HCV viral load were associated with poorer response. However, the frequency of treatment-related side effects

was similar in the groups with and without cirrhosis. And while 13.2% of the cirrhotic patients who did not respond or relapsed after treatment went on to develop hepatocellular carcinoma (HCC), this occurred in none of the cirrhotic individuals who achieved SVR. "Cirrhotic patients with compensated disease have a reasonably good chance of virologic response and should be offered treatment, carefully monitoring any side effects," the researchers concluded.

EPO Safe for Managing Anemia

In recent years the U.S. Food and Drug Administration (FDA) has warned about an increased risk of cardiovascular complications, and faster tumor growth in people with some types of cancer, associated with use of erythropoiesis-stimulating agents (ESAs) such

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as erythropoietin (EPO or Procrit) that increase red blood cell production. Since many people with hepatitis C use these medications to manage ribavirin-induced anemia, C.T. Costiniuk and colleagues assessed whether such complications were also more frequent in this patient group. As reported in the July 15, 2008 issue of *Clinical Infectious Diseases*, the researchers identified all patients receiving interferon/ribavirin (174 total courses of therapy) at an Ottawa hospital between October 2003 and October 2006. Participants who were older and had lower body weight, lower baseline hemoglobin levels, and HCV genotypes 1 or 4 were more likely to use ESAs. Most patients who did so (88%) achieved a target hemoglobin level above 110 g/L. The SVR rate was slightly higher in ESA recipients compared with non-recipients (54% vs 45%), but the difference did not reach statistical significance. During the post-treatment follow-up period, none of the patients experienced myocardial infarction (heart attack), deep vein thrombosis (clotting), or pulmonary embolism. The frequencies of stroke and cancer were low overall, and the rate of adverse events was similar in both groups. The researchers concluded that, “ESA use is not associated with increased risk of cardiovascular events, malignancy, thrombosis, or death in HCV-infected patients during

receipt of HCV therapy or in the period after completion.”

Obesity and Diabetes Predict Liver Disease Progression

Research increasingly shows a link between metabolic abnormalities and liver disease progression in people with chronic hepatitis C. In the July 2008 issue of *Gastroenterology*, C.L. Chen and colleagues described a study exploring whether obesity, diabetes, and other metabolic factors are associated with HCC in people with hepatitis C or B. The study included 23,820 Taiwan residents followed for 14 years; 218 people who were positive for both HCV and HBV were excluded from the analysis. After controlling for other metabolic factors, obesity (body mass index of 30 kg/m² or greater) was associated with a 4.13-fold increased risk of HCC among hepatitis C patients, as well as a 2.36-fold higher risk in people with neither HCV or HBV; this association was not seen, however, in people with hepatitis B. Diabetes was associated with an increased risk of HCC in all 3 groups (HCV, HBV, and neither), with the largest increase (3.52-fold) seen in those with HCV. Hepatitis C and B patients who were both obese and diabetic had more than a 100-fold increased risk of HCC, indicating synergistic effects of metabolic factors and hepatitis.

“The finding that both obesity and diabetes are predictors of HCC risk, possibly differently depending on HBV and HCV infection status, may shed some light in preventing HCC,” the researchers concluded.

Sorafenib for Liver Cancer

HCC is a difficult cancer to treat, largely because it is often diagnosed late, but therapy has improved in recent years. As reported in the July 24, 2008 *New England Journal of Medicine*, J.M. Llovet and colleagues conducted a pivotal Phase III trial called SHARP (Sorafenib HCC Assessment Randomized Protocol) to assess the safety and effectiveness of sorafenib (Nexavar) as a treatment for HCC. In this multicenter trial, 602 participants with advanced HCC who had not received previous systemic treatment were randomly assigned to receive 400 mg twice-daily sorafenib or placebo. The study was stopped ahead of schedule after an interim analysis showed improved survival in the sorafenib group. The median overall survival duration was 10.7 months in the sorafenib arm compared with 7.9 months in the placebo arm. There was no significant difference between the two arms in the median time to symptomatic progression (4.1 vs 4.9 months), but the soraf-

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enib group had a shorter time to radiologic progression (5.5 vs 2.8 months). Seven patients in the sorafenib group (2%) and two in the placebo group (1%) experienced a partial response, but none in either group experienced a complete response. Diarrhea, weight loss, skin reactions, and elevated blood phosphate were more frequent in the sorafenib recipients. "In patients with advanced hepatocellular carcinoma, median survival and the time to radiologic progression were nearly three months longer for patients treated with sorafenib than for those given placebo," the researchers concluded. Based in part on these results, the FDA approved sorafenib for the treatment of unresectable (not curable by surgery) HCC in November 2007.

HIV/HCV Coinfection Does Not Impair CD4 Cell Recovery

Previous research has produced conflicting evidence about the effect of HCV on immunological response to combination antiretroviral therapy (HAART) in people with HIV. While several studies have shown that coinfecting patients experience slower or smaller CD4 cell increases, others have found no difference. As reported in the July 1, 2008 issue of *AIDS Research & Human Retroviruses*, K. Yacisin and colleagues per-

formed a retrospective analysis of CD4 cell restoration within three years after starting first-line HAART in 322 HIV positive patients, of whom 139 were HCV coinfecting; only individuals with sustained HIV suppression were included in the analysis. Older age, male sex, lower baseline CD4 count, use of only one class of anti-HIV drugs, and a history of injection drug use predicted smaller increases in absolute CD4 cell count or CD4 percentage after one to three years on HAART. No link was seen, however, with HCV coinfection, leading the researchers to conclude that "HCV replication *per se* does not impair the CD4 restoration in HIV-infected patients successfully treated with antiretroviral therapy."

Low Risk of Liver Mitochondrial Toxicity on HAART

Antiretroviral therapy for HIV has been linked to various types of liver toxicity in numerous studies. One type, characterized by liver steatosis and enlargement, is thought to be a manifestation of mitochondrial toxicity, or damage to energy-producing structures within cells. Some research indicates that HIV/HCV coinfecting patients are more prone to liver toxicity than those with HIV alone. As described in the June

19, 2008 issue of *AIDS*, M. Matsukura and colleagues performed a detailed electron microscope analysis of mitochondrial damage in liver biopsy samples taken between 2003 and 2006 from 14 HIV/HCV coinfecting men on stable HAART and nine who were not on HAART. They found that hepatocytes (liver cells) tended to be larger in patients on HAART compared with untreated individuals. However, mitochondrial volume, structure, lipid content, and mitochondrial DNA and RNA levels were similar in the two groups. "We found no evidence of increased mitochondrial toxicity in individuals currently on HAART, suggesting that concomitant HAART should not delay HCV therapy," the researchers concluded. "This is especially true as liver disease progression and not drug-induced hepatotoxicity is the most common cause of mortality in this population." One reason for these findings may be that this form of liver toxicity is less common since certain nucleoside reverse transcriptase inhibitors, in particular stavudine (d4T or Zerit) and didanosine (ddI or Videx), have fallen out of favor due to side effects.

