

Hepatitis C

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HCV/HIV Coinfection

A small Spanish study reported in the September 3 issue of *AIDS* produced the highest sustained virological response (SVR) yet seen in an HCV/HIV coinfecting cohort with genotype 1 HCV. Montserrat Laguno and colleagues from Barcelona randomly assigned 95 coinfecting subjects to receive either standard interferon three times weekly or pegylated interferon alfa-2b (Peg-Intron), both with weight-adjusted ribavirin. Subjects with genotypes 1 or 4 were treated for 48 weeks, while those with genotypes 2 or 3 were treated for 24 weeks. The overall SVR rates were 44% for Peg-Intron/ribavirin and 21% for standard interferon/ribavirin. Among those with genotypes 1 or 4, the corresponding SVR rates were 38% and 7%; among subjects with

genotypes 2 or 3, 53% and 47%, respectively, achieved SVR. In the recent APRI-COT study, which used pegylated interferon alpha-2a (Pegasys), the SVR rate for genotype 1 subjects was 29%. The recent RIBAVIC study, using Peg-Intron, found an SVR rate of just 15% among genotype 1 patients. (These two studies did not analyze genotypes 1 and 4 together; some recent research suggests genotype 4 may be easier to treat than previously believed.) Side effects were generally similar to those seen in other studies of interferon-based therapy; however, nine subjects developed signs of mitochondrial toxicity, a potential concern when ribavirin is used with certain nucleoside analog HIV drugs including d4T (Zerit) and ddI (Videx). The researchers recommended that concomitant use of ribavirin and these HIV medications

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“should be cautioned against or not recommended.”

In other coinfection news, a study reported in the September 2004 issue of *Human Pathology* confirms that fibrosis progression tends to be more severe in HCV/HIV coinfecting individuals than in those with HCV alone. A. Rullier and colleagues conducted a prospective study of 33 coinfecting patients and 33 control subjects with HCV alone. They found that while disease activity and HCV viral load were similar in the two groups, fibrosis was “more marked” in the coinfecting subjects. In addition, coinfecting patients had fewer CD4 white blood cells than those with HCV alone (although all of the HIV patients had at least 250 CD4 cells/mm³, indicating low-level immune suppression). “Our data confirm the need to treat [coinfecting] patients against HCV, and suggest that HIV infection could favor fibrosis via the modulation of the intrahepatic immune response,” the authors concluded.

HCV Liver Transplant Outcomes

Long-term transplant outcomes are similar in patients with hepatitis C and those with liver failure due to other causes, according to a study in the September issue of *Liver Transplantation*. Michael

Charlton, MD, from the Mayo Clinic and colleagues analyzed the medical records of 165 patients with HCV, part of the Liver Transplantation Database maintained by the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK). Subjects were followed for up to 12 years. The most common cause of transplant failure or death among these patients was recurrence of hepatitis C. HCV almost always infects the new liver after a transplant, and appears to progress more rapidly in patients taking immune-suppressing drugs to prevent organ rejection after the procedure. Nevertheless, in this study, 10-year outcomes in the hepatitis C patients were similar to those in patients undergoing liver transplants for other reasons. After 10 years, liver graft survival rates were 64% for HCV positive individuals, compared with 51% for patients without hepatitis C. Poor outcomes were associated with older age of both the recipient and the donor, high HCV viral load, and antibodies against cytomegalovirus (CMV), all of which, the research suggested, are indications of decreased immune function. “Long-term outcomes, specifically patient and liver graft survival, are as good for patients with hepatitis C as they are for patients with almost any other cause

of liver disease. This is contrary to the findings of less complete and rigorous data sets,” Charlton told *Reuters Health*.

Post-Transplant HCV Recurrence

Post-transplant hepatitis C recurrence is more severe and may follow a more aggressive course when using transplanted livers from living donors rather than cadavers, according to a Spanish study published in the September issue of *Hepatology*. Montserrat Garcia-Retortillo, Xavier Forns, and colleagues from Barcelona analyzed 116 consecutive patients undergoing liver transplantation for end-stage cirrhosis or hepatocellular carcinoma between March 2000 and August 2003. After a median follow-up of 22 months (range 3-44), severe hepatitis C recurrence (defined as the development of biopsy-proven cirrhosis or clinical symptoms of liver decompensation) occurred in 22% of patients overall. But the rate of severe recurrence differed significantly based on the source of the donated liver: 18% (17 of 95 cases) among those who received cadaver livers, compared with 41% (9 of 22 cases) among those who received livers from living donors. The researchers could not say with certainty what factors accounted for this difference,

but suggested that higher rates of biliary complications might contribute to fibrosis, or that liver regeneration when using a graft from a living donor might promote HCV replication in hepatocytes. In an accompanying editorial in the same issue, Mark Russo and Roshan Shrestha of the University of North Carolina note that other similar studies have not found the same difference between living donor and cadaver transplants. “The benefits of living donor liver transplantation should not be overlooked,” they wrote, arguing against making “a premature decision about the risk of recurrent hepatitis C with living donor liver transplantation.”

Hepatocellular Carcinoma News

Viral hepatitis, heavy alcohol consumption, and diabetes together increase the risk of developing hepatocellular carcinoma (HCC, a type of liver cancer) more than the separate factors alone, according to a study published in the September 1 issue of *Cancer*. Jian-Min Yuan from the University of Southern California and colleagues analyzed risk factors in 295 HCC patients and 435 cancer-free control subjects. As expected, hepatitis

C and B both increased the risk of developing HCC, but hepatitis C had a stronger effect. While heavy alcohol use significantly increased the risk of HCC, moderate drinkers, surprisingly, had a lower risk of liver cancer. Having diabetes increased the HCC risk three-fold. When considered together, subjects who were both heavy alcohol users and diabetic had a 17-fold greater risk of developing HCC. The combination of viral hepatitis plus either heavy drinking or diabetes increased liver cancer risk by about 48-fold.

In related news, Mindie Nguyen from Stanford university and colleagues reported in the September issue of *Clinical Gastroenterology and Hepatology* that Asians may have a four-fold greater risk, and African-American men a two-fold greater risk, of HCC compared with whites. The researchers analyzed medical records and pathology reports from 207 patients with chronic HCV and cirrhosis and 257 control subjects. After controlling for confounding factors, Asian men were 4.3 times as likely and Asian women were 4.6 times more likely to have HCC than whites. African-American men were 2.4 times as likely, but the risk was not significantly greater

for African-American women. The researchers said that their findings need to be confirmed in larger studies of racially varied populations.

In other HCC news, Monica Anzola presented an overview of how hepatitis C and B contribute to liver cancer in the September issue of the *Journal of Viral Hepatitis*. HBV is a DNA virus that integrates itself into the human host cell genome. This process is believed to be carcinogenic (cancer-causing), perhaps because the virus interferes with the cells’ normal growth and division. HBV also encodes a protein called HBx, which is known to contribute to the development of HCC. HCV, in contrast, is an RNA virus that does not integrate into the genetic material of the host cell. It likely promotes liver cancer “through host protein interactions or via the inflammatory response to the virus,” according to Anzola, since proteins encoded by HCV (including the core proteins NS3 and NS5A) interfere with cellular communication. A better understanding of how HCV and HBV proteins function, Anzola suggests, could lead to the development of strategies to reduce the carcinogenicity of these viruses.