

# Hepatitis C

## ***HCV in the Young and the Old***

Two recent journal articles discussed the natural history of hepatitis C in children and in older adults. Raffaele Iorio and colleagues from Italy evaluated the long-term outcome of chronic hepatitis C in 125 children followed from 1986 through 2004. As reported in the November 15 issue of *Clinical Infectious Diseases*, all remained free of clinical symptoms throughout the observation period. Within a year of testing positive for HCV antibodies, 100 children developed elevated aminotransferase (ALT and AST) levels and detectable HCV RNA; 25 had persistently normal aminotransferase, and among these, 16 had detectable HCV RNA. Interferon-based therapy produced sustained virological response (SVR) in 38% of treated children (24% for genotype 1 and 65% for other genotypes), while 12% cleared HCV

spontaneously with no treatment. Among the 64 children who underwent liver biopsy, liver damage was mild; among the 21 who had serial biopsies, only one developed cirrhosis. The researchers concluded that, "Children with [chronic hepatitis C] were symptom free and had a morphologically mild liver disease." While SVR rates in this study were low – other research suggests children respond better than adults – many did not receive optimal combination therapy with pegylated interferon plus ribavirin. "The real impact of therapy on long-term outcome remains to be established," the authors stated.

In the December 1 *Clinical Infectious Diseases*, Esther-Lee Marcus and Ran Tur-Kaspa presented an overview of hepatitis C in older adults. Most older patients with chronic HCV acquired the infection earlier in life and are now beginning to present with

## **Hepatitis Journal Review**

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long-term complications of liver disease, including cirrhosis and hepatocellular carcinoma. The authors note that the burden of chronic hepatitis C in elderly persons “is expected to increase significantly in the United States during the next two decades,” as people infected in the 1960s and 1970s reach their senior years. Since interferon-based therapy does not work as well in older individuals, and since elderly patients may be less able to tolerate side effects, Marcus and Turkaspa recommend that “the risk-benefit of combination antiviral therapy consisting of pegylated interferon and ribavirin should be assessed on an individual basis.” They hopefully suggest that new antiviral agents with fewer side effects may provide potential alternatives, and recommend that elderly patients (up to age 75) should be included in clinical trials of hepatitis C treatments.

### ***Do Coinfected Patients Need Transplants Sooner?***

Several studies have shown that HIV/HCV coinfecting patients experience more rapid liver fibrosis progression. Now, a new study by Margaret Ragni and colleagues, reported in the November issue of *Liver Trans-*

*plantation, indicates that coinfecting individuals are more likely to die while waiting for liver transplants.* The researchers prospectively enrolled 58 HIV-positive patients with end-stage liver disease (mostly due to HCV) between September 1997 and December 2002. In this group, 30% received transplants and 36% died while waiting for new livers, compared with 63% transplants and 16% deaths in a comparison group of 1,359 HIV-negative patients. In this study, coinfecting patients did not have more severe liver failure or worse HIV disease, so the reason for the increased mortality rate was unclear and it was “difficult to predict a poor outcome or prevent it.” In particular, MELD score (an index used to rate severity of liver failure), HIV viral load, CD4 cell count, and ability to tolerate antiretroviral therapy did not predict which HIV-positive patients would die while on the waiting list. Since the primary cause of death among the coinfecting patients was infection (57%), the authors suggested immune deficiency may be a contributing factor. They concluded that, “pretransplant survival appears shorter in HIV-positive [liver transplant] candidates and is unrelated to severity of liver or HIV disease.” In an accompanying editorial, transplant surgeon

Peter Stock suggested that coinfecting patients with advanced liver disease should be evaluated sooner for transplant eligibility.

### ***Opiate Withdrawal Encourages HCV Activity***

Withdrawal from opiates may worsen hepatitis C progression, according to a study in the November *American Journal of Pathology*. In a laboratory study, Chuan-Qing Wang and colleagues looked at the effect of morphine on an HCV “replicon” model in human liver cells. These researchers previously showed that addition of morphine to cell cultures enhanced HCV replication; now they report that removal of morphine after four days of exposure has much the same effect. Blocking opiate receptors using naloxone (Narcan) – which produces immediate and sudden withdrawal – induced even greater HCV replicon expression (a model of HCV virus replication) than simple morphine cessation. Morphine withdrawal suppressed natural interferon production in liver cells, and also inhibited the antiviral effect of recombinant interferon used to treat hepatitis C. These findings may shed further light on some past research suggesting injection drug users are prone

to more severe HCV-related liver disease, since withdrawal occurs not only when drug users attempt to quit, but also repeatedly between “fixes.”

## **Herbal Therapies for Liver Disease**

In the October 2005 *Journal of Hepatology*, Felix Stickela and colleagues, from the U.S. and Germany, presented a review of herbal therapies used to treat liver conditions. Among the herbs that have shown promise in treating liver disease are milk thistle, licorice root (glycyrrhizin), and various Chinese and Japanese preparations. But many herbal remedies have also been implicated in liver toxicity, including the Chinese medicine preparations Jin Bu Huan and Ma-Huang (Ephedra), pyrrolizidine alkaloids (found in certain types of herbal tea), comfrey, germander, greater celandine, kava root, chaparral, pennyroyal, sassafras, and certain Ayurvedic preparations. Interestingly, a majority of herbal hepatotoxicity is seen in women, even though they are not more likely to use such remedies. While symptoms of liver toxicity often resolve when an herb is discontinued, in some cases fulminant liver failure and irreversible liver damage can occur. The au-

thors concluded that, “So far, the evidence supporting the use of herbals to treat chronic liver diseases is insufficient and herbs should not be recommended outside clinical trials.” Controlled clinical trials of herbal preparations are scarce, but more are needed, given that an estimated 20-30% or more of people with liver disease have used herbal therapies.

Milk thistle (*Silybum marianum*) – and its active ingredients known as silymarin – is among the most commonly used herbs for liver conditions. Two recent journal articles present systemic reviews of research to date. Andrea Rambaldi and colleagues with the Cochrane Hepato-Biliary Group conducted a review and meta-analysis of trials studying milk thistle for viral hepatitis B or C or alcoholic hepatitis; results were reported in the November *American Journal of Gastroenterology*. The authors reviewed 13 randomized clinical trials with a total of 915 participants conducted through December 2003. They found that, on the whole, milk thistle or its components had no significant effect on all-cause mortality, liver disease complications, or liver histology, compared with placebo or no intervention. However, “liver-related mortality was significantly reduced by [milk thistle] in all

trials,” and the herb was not linked to increased risk of adverse side effects. The authors concluded that milk thistle “does not seem to significantly influence the course of patients with alcoholic and/or hepatitis B or C liver diseases,” but “could potentially affect liver injury.” As reported in the November *Journal of Viral Hepatitis*, K.E. Mayer and colleagues analyzed data from 148 papers in the medical literature discussing studies of silymarin and liver disease (four focused on hepatitis C, one included subjects with hepatitis B, and two included people with unspecified chronic viral hepatitis); none of the studies looked at silymarin in combination with interferon, ribavirin, or other standard hepatitis B or C therapies. The authors found that silymarin treatment led to decreased aminotransferase levels in four studies, and performed better than placebo in one study. However, they concluded that, “There is no evidence that silymarin affects viral load or improves liver histology in hepatitis B or C.” Both research teams recommended that further controlled studies be conducted.

