

# Hepatitis C

By Liz Highleyman

## **Genes Predict Interferon Response**

In the early May issue of *Gastroenterology*, Limin Chen and colleagues from the University of Toronto reported that a pattern of genes in the liver may help distinguish which individuals will or will not respond to interferon therapy for hepatitis C. The researchers used PCR tests to analyze gene expression in liver biopsy specimens from 16 HCV positive interferon responders, 15 HCV positive nonresponders, and 20 HCV negative subjects. Out of some 19,000 genes examined, they identified 18 “whose expression differed significantly between all responders and all nonresponders.” A subset of eight genes accurately predicted treatment response for 30 of the 31 HCV positive sub-

jects. Several of the genes in question are sensitive to interferon, indicating that some individuals may be naturally interferon-resistant. “Hepatic gene expression profiling identified consistent differences in patients who subsequently fail treatment with pegylated [interferon] plus ribavirin,” the authors concluded. In the future, a simple blood test may be developed to predict which individuals will respond to interferon, thus sparing nonresponders the side effects and expense of treatment. Further down the line, gene therapy might be used to transform nonresponders into responders.

## **Managing HCV-Related Depression**

Several recent journal articles have looked at the prevention and management of

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depression in HCV positive people being treated with interferon. Illustrating the increased attention to the problem, the April issue of *Psychiatric Times* featured an in-depth review of depression in people with chronic hepatitis C.

In the June issue of *Journal of Hepatology*, Martin Schaefer and colleagues from Berlin reported on a study of the effectiveness of pre-emptive antidepressant therapy in preventing depression during hepatitis C treatment. Before starting pegylated interferon plus ribavirin, 14 HCV positive patients with pre-existing psychiatric conditions received 20 mg daily of the selective serotonin reuptake inhibitor (SSRI) antidepressant citalopram (Celexa), which they continued to take during anti-HCV therapy. Depression was determined using DSM-IV, the most widely used diagnostic criteria. Subjects who received citalopram were significantly less likely to develop major depression during the first six months of anti-HCV treatment, compared with 11 HCV positive patients with psychiatric disorders who did not receive the antidepressant and 11 HCV positive subjects without psychiatric risk factors (14%, 64%, and

55%, respectively). Among those who did develop depression while taking interferon, citalopram was associated with improvement. Though this study was small and of short duration, the authors concluded that it “clearly indicates that [interferon]-induced depression in patients can be ameliorated by both the use of antidepressants as well as by intensive psychiatric care.”

As described in another article in the same issue, Wei Cai and colleagues examined the mechanism of interferon-induced depression, which remains poorly understood although previous research suggests the cytokine interferes with neurotransmitters. The researchers found that conventional interferon down-regulates (decreases the expression of) glucocorticoid receptors and a serotonin receptor called 5-HT<sub>1A</sub> by nearly 75% in laboratory cell lines; receptor levels recovered when interferon was removed. However, adding either the SSRI fluoxetine (Prozac) or the tricyclic antidepressant desipramine (Norpramin) to the cell cultures reduced the effect of interferon on the receptors. In addition, interferon’s effect on glucocorticoid receptors was

“abolished” when administered with tauroursodeoxycholic acid, an agent that protects against apoptosis (programmed cell death). While this study is preliminary, it suggests potential approaches to preventing neurological side effects caused by interferon.

In an editorial accompanying the latter two articles, Yves Horsmans concluded that new insights into the mechanisms and treatment of interferon-induced depression should allow more patients to be effectively treated for hepatitis C. Also, since Schaefer’s team found that the incidence of major interferon-related depression was similar in individuals with or without pre-existing psychiatric conditions, all patients may potentially benefit from prophylactic antidepressant therapy, not just those with pre-existing psychiatric risk factors.

### ***Treatment Would Reduce Societal Impact of HCV***

A prominent article in the *Wall Street Journal* in late May focused the attention of the general public on hepatitis C epidemic. While the incidence of new HCV infections has fallen by ap-

proximately 90% in the United States since the virus was discovered in 1989 – thanks to screening of donated blood and increased awareness and prevention efforts among injection drug users – the Centers for Disease Control and Prevention projects that the rate of severe liver disease and death related to HCV will triple over the next ten years. Because hepatitis C usually progresses slowly, many individuals infected decades ago are only now reaching the stage where severe liver damage begins to emerge.

A similar situation also exists in some European countries. In the May *Journal of Hepatology*, M. Buti and colleagues from Barcelona estimated the impact of future morbidity (illness), mortality, and costs related to chronic hepatitis C. The researchers used a mathematical model to project HCV-related complications and costs over the next 30 years in the approximately 420,000 HCV positive individuals in Spain. They predicted that by the year 2030, the proportion of patients with cirrhosis would increase by as much as 14% and overall HCV-related morbidity would rise by as much as

10%. However, providing anti-HCV treatment would dramatically reduce the impact of the disease.

“Treatment of the chronic HCV-infected population can eradicate the infection, increase patients’ survival, and reduce the need for liver transplantation,” the authors concluded, “making this a cost-effective strategy.”

### ***Cannabis Caution for People with HCV***

In other recent news, the Supreme Court’s June 7 ruling against medicinal use of cannabis (marijuana) put another medical story on the front pages. Patients use medical marijuana for indications such as relieving chronic pain, controlling nausea associated with cancer chemotherapy, and stimulating appetite to combat AIDS-related wasting. But a study reported in the May 12 online issue of *Hepatology* suggests that people with hepatitis C should be cautious about cannabis, since frequent use may promote liver fibrosis. C. Hezode and colleagues from France examined liver biopsy specimens from 270 HCV positive individuals who were not receiving hepatitis C treatment. They found that subjects who

used cannabis daily were more likely to have severe fibrosis and were at higher risk for rapid fibrosis progression compared with those who used marijuana only occasionally or did not use it at all. Other factors that predicted worse fibrosis progression in this study were older age (over 40) at the time of HCV infection, genotype 3, presence of steatosis (fatty liver), and heavy alcohol use. While correlation between cannabis use and rapid fibrosis progression does not necessarily imply causation, the researchers suggested that “[p]atients with ongoing [chronic hepatitis C] should be advised to refrain from regular cannabis use.”

