

# Hepatitis C

By Liz Highleyman

## **New Laboratory Model of HCV Replication**

The difficulty of culturing hepatitis C virus (HCV) in the laboratory has long hampered efforts to better understand the lifecycle of the virus and treat the disease. But now, researchers have found way to reproduce HCV in cell cultures. In the February 15 *Proceedings of the National Academy of Sciences*, Theo Heller, Satoru Saito, and colleagues from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) reported on a new model system that appears to replicate HCV in substantial quantities. The researchers constructed a replica of genotype 1b

HCV using a DNA copy of HCV RNA. The DNA copy was then inserted between two ribozymes, a type of RNA molecule that can cleave other RNA segments. This so-called “HCV-ribozyme expression construct” was composed only of HCV nucleic acids without an outer envelope. But when the researchers added the “naked” HCV genetic material to a human liver cell culture, they found that it replicated in the cells to produce what appeared to be complete HCV virions (virus particles). “Our model system produced viral particles that have all the properties of the whole virus,” said co-author T. Jake Liang, chief of the NIDDK’s Liver Disease Branch. The authors hope the new technique will allow researchers to screen drug candidates in the labo-

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ratory to determine if they inhibit HCV replication.

## **Noninvasive Measures of Fibrosis**

It is known that hepatitis C therapy is most crucial for patients with progressive liver damage. Liver biopsy is the “gold standard” for diagnosing fibrosis, but the procedure is expensive, uncomfortable, and can lead to complications, so it is not well suited to detecting advances in fibrosis over short intervals (less than about every 3-5 years). In addition, as demonstrated in a study by Marie-Christine Rousselet and colleagues published in the February issue of *Hepatology*, assessment of fibrosis severity on the basis of biopsy samples can vary considerably among different pathologists. As such, researchers have studied a number of noninvasive techniques to predict fibrosis.

In the December *Journal of Hepatology*, K. Patel and colleagues assessed the accuracy of a panel of serum markers known as extracellular matrix remodeling proteins (byproducts that

spill into the blood when fibrotic tissue builds up in the liver). The researchers evaluated a variety of markers in 294 subjects, then validated their accuracy in 402 additional patients. They found that a combination of three markers - hyaluronic acid, tissue inhibitor of metalloprotease-1 (TIMP-1), and alpha2-macroglobulin - best predicted moderate-to-severe fibrosis (METAVIR scores F2 to F4). Looking at all 696 subjects, the three markers together had an accuracy of 75%, a positive predictive value of 74.3%, and a negative predictive value of 75.8%. The authors concluded that the three-marker panel “may reliably differentiate” chronic hepatitis C patients with moderate-to-severe fibrosis (F2-F4) from those with mild or no fibrosis (F0-F1), although it could not delineate between stages within these categories.

In the January issue of *Hepatology*, Marianne Ziol and colleagues reported on a new method of assessing fibrosis using a transient elastography device, which measures liver stiffness. The researchers compared elastography and liver bi-

opsy results from 327 chronic hepatitis C patients. They found that liver stiffness was highly correlated with fibrosis stage - that is, the stiffer the liver, the more advanced the fibrosis. Agreement between elastography and biopsy results was better in patients with more advanced fibrosis and when larger biopsy tissue samples were used. The authors concluded that transient elastography appears to be “a reliable tool to detect significant fibrosis or cirrhosis in patients with chronic hepatitis C.”

Similar results were reported by L. Castera and colleagues in the February issue of *Gastroenterology*. The researchers analyzed data from 183 chronic hepatitis C patients with METAVIR fibrosis scores ranging from F1 to F4. They compared results from a transient elastography test called FibroScan (made by the French company Echo-sens) with results from liver biopsies and from three biochemical fibrosis tests (Fibrotest, Biopredictive, and the AST-to-platelets ratio index). They determined that a combination of FibroScan and FibroTest did the best job of predicting fibrosis. When the Fi-

broScan and FibroTest results agreed, they gave the same result as liver biopsies in 84% of cases with fibrosis scores of F2 or F3, and in 94% of cases with scores of F4. The authors concluded that using both FibroScan and FibroTest together “could avoid a biopsy procedure in most patients with chronic hepatitis C.”

## ***Hepatotoxicity of HIV Therapy***

It is known that certain anti-retroviral drugs used to treat HIV disease can cause liver toxicity. While some studies have suggested that HCV/HIV coinfecting patients are at higher risk of HAART-related hepatotoxicity, data have been inconsistent. In the February 15 *Clinical Infectious Diseases*, Lidia Aranzabal and colleagues from Madrid reported data from a study evaluating the impact of fibrosis on hepatotoxicity. The researchers studied 107 coinfecting patients who had undergone liver biopsy. Overall, 25% experienced liver toxicity, defined as an ALT/AST level greater than five times the upper limit of normal, or at least a 3.5-

fold increase in ALT/AST if levels were abnormal at baseline. However, rates differed dramatically based on liver disease severity: 38% of patients with severe fibrosis (stage F3 or F4) experienced hepatotoxicity, compared with 15% of subjects with mild-to-moderate liver damage (F1 or F2). The risk of liver toxicity was not associated with duration of HCV infection, HCV viral load, or HCV genotype. Among patients with severe fibrosis, non-nucleoside reverse-transcriptase inhibitor drugs (nevirapine [Viramune] or efavirenz [Sustiva]) were more likely to cause liver problems than non-NNRTIs, but this difference was not apparent in the mild-to-moderate fibrosis group.

In January, the Food and Drug Administration issued a public health advisory confirming that nevirapine (which is used alone to prevent mother-to-child HIV transmission in developing countries, as well as in combination regimens) can cause potentially life-threatening liver toxicity, especially in women and in patients with higher pre-treatment CD cell counts (above 250 for women and

above 400 for men); the drug’s product label was also recently changed to reflect this information.



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