

### Hepatitis C

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#### Noninvasive Markers for Liver Disease

Liver biopsy remains the “gold standard” for determining the extent of liver damage, but the search is underway for less invasive techniques that can be used to monitor liver disease progression and the effectiveness of treatment without the need for repeated biopsies.

In the February 2004 issue of the *American Journal of Gastroenterology*, Vincent Leroy and colleagues looked at whether serum levels of several chemicals were related to METAVIR fibrosis scores in 194 hepatitis C patients and 194 healthy controls. The researchers found that levels of hyaluronate, procollagen type III N-terminal peptide (PIIINP), and tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-2 were

significantly higher in patients than controls. In a multivariate analysis, PIIINP and matrix metalloproteinase (MMP)-1 were independently associated with fibrosis. PIIINP is a marker for fibrogenesis (the production of fibrous tissue), while MMP-1 reflects fibrolysis (the breakdown of fibrous tissue). The authors concluded that combining the two markers “may provide a useful tool for evaluating liver fibrosis.”

Blood levels of gamma-glutamyl transpeptidase (GGT) are commonly measured along with ALT and AST to gauge liver disease status, and GGT levels are often elevated in people with chronic hepatitis C. But GGT is not a direct marker of liver damage, and its usefulness remains unclear. In the March 2004 issue of the *Journal of Gastroenterology and Hepatology*, Ivonete Silva and colleagues reported on a study designed to assess

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### Hepatitis Journal Review

*A publication of the Hepatitis C Support Project*

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the relationship between GGT and clinical, biochemical, and histological status in 201 chronic hepatitis C patients who underwent liver biopsy. Elevated GGT was seen in about half the patients. No association was seen between GGT levels and either bile duct damage or steatosis (fatty liver). But in a multivariate regression analysis, elevated GGT was associated with grade 3 or 4 inflammatory activity in the liver and stage 3 or 4 fibrosis. The authors concluded that GGT “seemed to be useful as an indirect marker of more advanced liver disease in chronic hepatitis C.”

### **Hepatocellular Carcinoma**

Hepatocellular carcinoma (HCC) is a type of liver cancer that develops in some people with chronic hepatitis C or B, usually after many years. It is the fifth most common cancer worldwide, and the third most common cause of cancer-related death. Several recent journal articles have focused on HCC, and the February 2004 issue of *Liver Transplantation* was

devoted to the topic. In the latter, Masao Omata and Haruhiko Yoshida presented an overview of the state of knowledge about HCC. Since hepatitis C and B are the predominant causes of HCC, better treatments for these diseases as well as widespread vaccination against hepatitis B can play a key role in reducing the incidence of liver cancer. For example, in the March 2004 issue of *Gut*, H. Yoshida and colleagues reported that interferon therapy delayed the development of HCC, especially in patients with advanced fibrosis.

Along with progress in therapy for hepatitis C and B, there have also been advances in HCC diagnosis and treatment. However, Omata and Haruhiko note, liver cancer recurrence is “extraordinarily frequent, since the remaining liver is still at a particularly high risk of HCC.” Also in *Liver Transplantation*, Josep Llovet and colleagues described the HCC diagnosis, staging, and treatment program used by the Barcelona Clinic Liver Cancer Group. Since HCC usually occurs in people with cirrhosis (whether due to

chronic viral hepatitis or some other cause), this group should be screened every six months for liver cancer using ultrasound and blood tests for alpha-fetoprotein. Other tests are under study; in the February 2004 issue of *Hepatology*, Jin Woo Kim and colleagues reported on a unique genetic pattern in tissue samples of patients with cirrhosis that may potentially be useful as a marker to help diagnose early onset HCC.

Surgical resection (removal of the tumor) is considered the best treatment option for patients with early HCC if they maintain reasonable liver function (e.g., normal bilirubin and no portal hypertension). As Lorenzo Capussotti and colleagues reported in *Liver Transplantation*, even large tumors (greater than 10 cm) and cancer that involves the portal vein can sometimes successfully be removed.

In patients with poor liver function, percutaneous ablation (destruction of the tumor in place), chemoembolization (delivery of drugs directly to the tumor), or liver transplantation are

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other possible options. As described by Riccardo Lencioni and colleagues, percutaneous ablation works best in people with early-stage HCC. Injection of ethanol (alcohol) into the tumor is the most common method, but recent studies show that thermal destruction using radiation (radiofrequency ablation) appears more effective and requires fewer treatment sessions. [Radiofrequency] ablation could therefore be considered as the percutaneous treatment of choice for patients with early-stage tumors,” the authors concluded. “Further investigation is warranted to clarify whether current [radiofrequency] technology could offer improved results in patients with intermediate-stage HCC.”

HCC survival rates depend on how early the cancer is detected and how large and extensive the cancer has grown. Kazuto Inoue and colleagues reported in *Liver Transplantation* that the 5-year survival rate was 93% among patients with early HCC (well-differentiated cancer, usually less than 2 cm, and not metastasized, or spread); however, cancer recurred after treatment in 53%. Masakazu Yamamoto

and colleagues reported in the March 2004 *Annals of Surgery* that the 5-year survival rate for early HCC was 85%, significantly better than the outcomes among patients with even small-sized advanced liver tumors. Tito Livraghi and colleagues reported, also in *Liver Transplantation*, that among 210 patients with early-stage HCC receiving treatment (radiofrequency ablation, ethanol injection, or chemoembolization) guided by ultrasound, 3- and 5-year survival rates were 69% and 49%. Among 164 patients with intermediate-stage HCC, the corresponding survival rates were 43% and 28%. Dr. Capussotti’s group reported that patients who underwent removal of large tumors had a 5-year survival rate of just 17%. Unfortunately, late-stage liver cancer is not considered treatable, although patients with advanced HCC may be eligible to join clinical trials of experimental therapies.

### **Promising Amantadine Results**

Amantadine (Symmetrel), a drug used to treat influenza and Parkinson’s disease, is also under study as a possible therapy for hepatitis C.

Research to date has been inconclusive, with several studies showing that amantadine did not appear particularly effective against HCV. But in the March 2004 issue of the *Journal of Hepatology*, Alessandra Mangia and colleagues from Italy reported on a study that produced more favorable results. The researchers conducted a meta-analysis of data from nearly 1,000 treatment-naive patients from six European centers. At the end of therapy, virological response was seen in 38.5% of subjects receiving interferon plus amantadine, compared with 29.5% of those using interferon alone. Sustained virological response (SVR; continued undetectable HCV viral load six months after the end of treatment) was seen in 23.1% and 17.3%, respectively. Addition of amantadine improved response rates in all subgroups except patients with low initial HCV viral load and those with genotypes 2 or 3. The researchers concluded that “therapy with amantadine and interferon is effective and may be an alternative to interferon and ribavirin in patients who cannot tolerate ribavirin.”