# Gene Signature Can Predict Cirrhosis Outcomes

BY DIANA MAHONEY

BOSTON — A gene signature that predicts survival after surgery for hepatocellular carcinoma also predicts the outcome of liver cirrhosis, a study has shown.

Compensated cirrhotic patients at risk of poor prognosis can be identified via the 186-gene signature of nontumor liver tissue, Dr. Yujin Hoshida reported at the annual meeting of the American Association for the Study of Liver Diseases.

The investigators performed whole-genome gene expression analysis of liver biopsy specimens obtained from 276 patients with compensated cirrhosis who were included in a prospective surveillance study for hepatocellular carcinoma, said Dr. Hoshida of the Broad Institute of Massachusetts Institute of Technology and Harvard University, Boston.

"The findings suggest that we might be able to identify patients who need preventive treatment for advanced cirrhosis and possibly hepatocellular carcinoma," Dr. Hoshida said.

He and his colleagues previously developed and reported (N. Engl. J. Med. 2008;359:1995-2004) a technique for globally profiling gene expression from formalin-fixed, paraffin-embedded (FFPE) tissues. The method enabled the researchers to profile both nontumor and cancerous tissue obtained from 307 liver cancer patients participating in prospective surveillance studies.

The technique involved a modified cDNA-mediated annealing, selection, extension, and ligation assay to interrogate about 6,000 genes expressed in the tumor and nontumor tissue. By partitioning samples into training and validation sets, the researchers were able to develop a 186-gene signature of nontumor tissues to predict hepatocellular carcinoma survival.

In the current study, the investigators used Cox regression modeling to evaluate the potential associations between the 186-gene signature and overall survival, hepatocellular carcinoma, and hepatic decompensation in patients with compensated cirrhosis.

Almost all (98%, or 270) of the 276 patients from whom biopsy specimens were obtained were classified as Child-Pugh A with respect to cirrhosis severity, Dr. Hoshida said. About 90% of the participants had hepatitis C infection, and the median baseline serum alpha-fetoprotein level was 6 mg/dL. Most patients (62%) were male.

During the prospective surveillance period (median follow-up of 9.8 years), 90 patients (33%) died, 81 (29%) developed hepatocellular carcinoma, and 88 (32%) developed hepatic decompensation.

In multivariate analyses, the 186-gene signature was associated with overall survival, with a hazard ratio (HR) of 2.2. It also was associated with hepatocellular carcinoma development (HR 1.6) and hepatic decompensation (HR 2.1). The association between the gene signature and each of the three outcomes remained significant after adjustment for bilirubin greater than 1.0 mg/dL and platelet count, Dr. Hoshida said.

Subsequent gene set enrichment analysis revealed enrichment of metabolic-related pathways in patients with a good prognosis and enrichment of pathways associated with inflammation (including those related to interferon and tumor necrosis factor–alpha signaling) in patients with a poorer prognosis, he noted.

Although additional clinical validation is required before the genetic signature is introduced into clinical practice, the findings are promising, said Dr. Hoshida, who noted that the prognostic prediction of early-stage cirrhosis will increase the opportunity for early medical intervention, including chemoprevention of advanced cirrhosis and hepatocellular carcinoma. ■

***Disclosures:*** *Dr. Hoshida reported having no relevant conflicts of interest.*

## Clinical Implications Not Yet Clear

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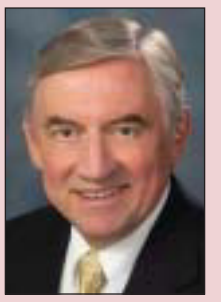

This study, largely involving hepatitis C patients, adds to our knowledge of factors that influence the course of hepatic cirrhosis. The ability to predict which patients with cirrhosis are likely to decompensate or develop hepatocellular carcinoma (HCC) should be helpful in clinical management.

The study shows that gene enrichment for metabolic-related pathways predicts a better outcome for patients with cirrhosis, compared with gene enrichment for inflammatory pathways—a finding that intuitively fits with existing clinical information related to prognosis. It also seems that a greater emphasis on following those patients at greatest risk for HCC could reduce the costs of screening, if we could reduce screening of patients with less risk. This genetic risk information also might permit earlier intervention for patients suspected of having an HCC, or those at risk of decompensation.

But would this information change how we deal with an individual patient? Would it benefit patients to know that they are in the group with a worse prognosis? We need further studies to see if this can truly change how we manage the individual patient with cirrhosis.

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# Telaprevir Useful as Adjunctive Agent in Refractory HCV

BY DIANA MAHONEY

BOSTON — The addition of the protease inhibitor telaprevir to antiviral therapy with pegylated interferon and ribavirin produced sustained virologic response in more than half of hepatitis C patients in a randomized trial who had previously failed the standard interferon/ribavirin protocol, Dr. John G. McHutchison reported at the annual meeting of the American Association for the Study of Liver Diseases.

The 453 patients with hepatitis C virus (HCV) genotype 1 enrolled in the multicenter PROVE3 trial—designed to assess the safety and efficacy of telaprevir plus pegylated interferon with or without ribavirin—were randomized to one of four regimens: telaprevir for 12 weeks and pegylated interferon plus ribavirin for 24 weeks (T12/PR24), telaprevir for 24 weeks and pegylated interferon plus ribavirin for 48 weeks (T24/PR48), telaprevir and pegylated interferon only for 24 weeks (T24/P24), or placebo and pegylated interferon plus ribavirin for 24 weeks followed by pegylated interferon and ribavirin for 24 weeks (PR48), said Dr. McHutchison of Duke University Medical Center, Durham, N.C.

The patients received the standard, subcutaneous 180 mcg/week of pegylated interferon, 1,000-1,200 mg of ribavirin according to body weight, and 1,250 mg of telaprevir on day 1 with 750 mg every 8 hours thereafter, he said.

Failure to respond to prior combination pegylated interferon/ribavirin treatment was defined as less than a 2-log decline in the serum HCV RNA level from baseline at 12 weeks. Virologic breakthrough was defined as the development of viremia during treatment of a patient whose HCV RNA had previously become undetectable during ongoing therapy. Relapse was defined as the reappearance of serum HCV RNA after the discontinuation of antiviral therapy and undetectable HCV RNA at the completion of therapy.

About 92% of the patients included in the intent-to-treat analysis had baseline HCV RNA levels of 800,000 IU/mL or higher, and 43% had cirrhosis or bridging fibrosis. The assigned treatment was completed by 235 of the patients, with discontinuation from protocol-defined stopping rules observed in 15% of the T12/PR 24 group, 23% of the T24/PR48 group, 37% in the T24/P24 group, and 59% in the PR48 group, Dr. McHutchison reported.

At 48 weeks after treatment completion, the sustained virologic response (SVR) rates across all three of the telaprevir-based regimens were significantly higher than in the interferon/ribavirin control arm. In the T12/PR24, the T24/PR48, and the T24/P24 groups, 51%, 53%, and 24% of the patients, respectively, achieved SVR, compared with 14% of the patients in the control group, he said.

Viral breakthrough rates during treatment were highest in the telaprevir/interferon-only group, at 21%, compared with 11%, 10%, and 3% in the T12/PR24, T24/PR48, and PR48 groups. Similarly, Dr. McHutchison noted, relapse rates 24 weeks after treatment were highest in the telaprevir/interferon-only group, at 53%, compared with 28%, 4%, and 52% in the T12/PR24, T24/PR48, and PR48 groups. "No late relapses occurred 48 weeks after treatment in the telaprevir groups," he said.

The telaprevir-based therapy was most successful in patients who had relapsed after the initial dual combination therapy. In the T12/PR24, T24/PR48, and T24/P24 groups, respectively, SVR was achieved by 69%, 76%, and 42% of patients who had previously relapsed, compared with 39%, 38%, and 11% of patients who had not responded to the initial treatment, Dr. McHutchison said.

"The general safety profile of all of the telaprevir regimens was similar to that seen in treatment-naive patients," Dr. McHutchison said. Grade 3 rash was observed in 5%, 4%, 3%, and 0% of the T12/PR24, T24/PR48, T24/P24, and PR48 groups, respectively, and grade 3 anemia was observed in 0%, 6%, 1%, and 1% of patients. And while 21 patients in the telaprevir groups discontinued treatment because of rash (18) or anemia (3), he said, "the number of withdrawals is not unusually high and is similar to the rates reported in prior phase II studies."

The findings of this phase IIb study have important clinical implications, Dr. McHutchison said. "The high rate of cure among previous treatment failures gives hope to a large segment of hepatitis C infected patients who do not respond to the current standard of care," he said, noting that the results still have to be confirmed in larger phase III clinical trials that are ongoing. ■

***Disclosures:*** *This study was funded by Vertex Pharmaceuticals and Tibotec, manufacturers of telaprevir. Dr. McHutchison disclosed relationships with multiple pharmaceutical firms, including Vertex.*