Microvesicular Steatosis Found in 10% NAFLD

BY SHERRY BOSCHERT

SAN DIEGO — Microvesicular steatosis may be more common in patients with nonalcoholic fatty liver disease than previously thought and is associated with markers of severe disease, a study of 1,022 biopsies suggests.

Ten percent of the liver biopsies from adult patients with nonalcoholic fatty liver disease (NAFLD) showed microvesicular steatosis when reviewed by a pathology committee for the study, Dr. Sweta R. Tandra and her associates reported at the annual meeting of the American College of Gastroenterology.

'Our data support a role for mitochondrial dysfunction in the pathogenesis of nonalcoholic steatohepatitis.'

DR. TANDRA

Previously, microvesicular steatosis was thought to be rare in patients with NAFLD, which is more typically associated with macrovesicular steatosis, said Dr. Tandra of Indiana University, Indianapolis. The significance of the presence of microvesicular steatosis has been unclear.

The investigators found microvesicular steatosis in 102 (10%) of the biopsies, which came from patients with an average age of 50 years and a mean body mass index of 35 kg/m^2. The patient cohort was 63% female and 82% white.

The presence of microvesicular steatosis was significantly associated with histologic indices that denote severe disease, including higher grades of macrovesicular steatosis, advanced fibrosis, ballooned hepatocytes, megamitochondria, higher NAFLD activity scores, and a diagnosis of nonalcoholic steatohepatitis. The findings were based on a multivariate analysis that adjusted for the influence of age, sex, race, body mass index, and the presence of diabetes.

The presence of macrovesicular steatosis increased the likelihood of finding microvesicular steatosis two- to sixfold. Also, patients with fibrosis were two to six times more likely to have microvesicular steatosis than were patients without fibrosis. Microvesicular steatosis was three to four times more likely in the presence of ballooning and five times more likely in the presence of megamitochondria, two markers of cell injury.

No associations were seen between microvesicular steatosis and lobular inflammation or levels of AST or ALT.

Biopsies were obtained from a consortium of eight clinical research centers and one data coordinating center sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases.

On histology, macrovesicular steatosis is defined by a single, large vacuole of fat that fills up the hepatocyte and displaces the nucleus to the periphery of the cell. In comparison, the presence of multiple small intracellular lipid droplets with an undisplaced nucleus generally defines microvesicular steatosis, which has been thought to result from impaired mitochondrial beta-oxidation of fatty acids.

"As microvesicular steatosis generally indicates mitochondrial dysfunction, our data support a role for mitochondrial dysfunction in the pathogenesis of nonalcoholic steatohepatitis," said Dr. Tandra, who reported having no conflicts of interest. ■

Gene Signature Appears to 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.

"The findings suggest that we might be able to identify patients who need preventive treatment for advanced cirrhosis and possibly hepatocellular carcinoma," Dr. Yujin Hoshida said at the annual meeting of the American Association for the Study of Liver Diseases.

Compensated cirrhotic patients at risk of poor prognosis can be identified via the 186-gene signature of nontumor liver tissue, Dr. Hoshida said.

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, Cambridge.

Dr. Hoshida 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 them to profile both nontumor and cancerous tissue obtained from 307 liver cancer patients participating in prospective surveillance studies.

The technique involved the use of a modified cDNA-mediated annealing, selection, extension, and ligation assay to interrogate approximately 6,000 genes expressed in the tumor and nontumor tissue. By partitioning samples into training and validation sets, the investigators 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. Approximately 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, he reported.

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.

Dr. Hoshida reported having no conflicts of interest. ■

Interferon Alpha-2a Trumps Alpha-2b for Chronic Hepatitis C

BY MARY ANN MOON

Pegylated interferon alpha-2a appears to induce a significantly better sustained virologic response than interferon alpha-2b, when combined with ribavirin in patients with chronic hepatitis C, Dr. Maria Grazia Rumi and her colleagues reported.

The two interferons differ in molecular size and structure, as well as in their pharmacokinetic and pharmacodynamic profiles. Interferon alpha-2a is administered in a fixed dose, while the dose of interferon alpha-2b is calculated according to body weight. Adverse effects differ as well. Interferon alpha-2b has been associated with lower rates of anemia, while interferon alpha-2a has been associated with lower rates of depression.

These distinctions "suggest that differences [also] may exist in safety and tolerability," wrote Dr. Rumi of the University of Milan and her associates.

Until now, there has been insufficient evidence to support choosing one of these agents over the other. Combined with ribavirin, either is considered to be a standard of care for eradicating chronic hepatitis C virus (HCV) infection. Studies that have directly compared interferon alpha-2a and interferon alpha-2b have been "limited in sample size or scope" and have arrived at disparate conclusions, the investigators said.

The new study was a randomized, head-to-head comparison of the safety and efficacy of the two drugs in 447 patients who had not received previous treatment for chronic hepatitis C. Overall, patients assigned to receive pegylated interferon alpha-2a for 48 weeks showed a higher rate of sustained virologic response (66%) than those assigned to receive interferon alpha-2b (54%).

Rapid virologic response was the strongest predictor of a sustained response, further supporting the idea that early suppression of HCV is crucial.

In the subgroup of patients with the highest levels of HCV RNA, rates of sustained virologic response were 62% with interferon alpha-2a and 48% with interferon alpha-2b. Similarly, in the subgroup of patients with cirrhosis, rates of sustained virologic response were 53% and 38%, respectively.

The researchers wrote that they were surprised that their analysis did not show cirrhosis to be a predictor of treatment failure, as it has been in previous studies of interferon. However, this study was statistically underpowered to assess the role of cirrhosis as a moderator of treatment outcome, they said.

Interferon alpha-2a also achieved higher rates of sustained virologic response (48%), compared with interferon alpha-2b (32%), in the subgroup of patients who had viral type HCV-1. Similarly, interferon alpha-2a achieved higher rates of sustained virologic response (96%) than interferon alpha-2b (82%) in the subgroup of patients who had viral type HCV-2

However, the two interferon formulations achieved similar rates of sustained virologic response in patients who had HCV-3 (65% and 69%, respectively) and in those who had HCV-4 (44% and 31%, respectively).

Rapid virologic response was the strongest predictor of a sustained response, "further supporting that early suppression of HCV is of crucial importance in the therapeutic resolution of chronic hepatitis C," they said. Dr. Rumi reported having no conflicts of interest. ■