Standard Hepatitis C Treatment Highly Effective

BY JOHN R. BELL
Associate Editor

WASHINGTON — Findings from the largest study of the standard treatment for hepatitis C infection, peginterferon and ribavirin, indicate that nearly all patients achieved a durable sustained virologic response—a cure, in the words of Dr. Mark G. Swain, who announced the results at the annual Digestive Disease Week.

The ongoing study, funded by Roche Pharmaceuticals, which manufactures both drugs, includes 997 patients from nine randomized multicenter phase III trials published since 2000. Patients from those trials were eligible for inclusion if they had achieved a sustained virologic response (SVR), defined as undetectable hepatitis C virus (HCV) RNA (fewer than 50 IU/mL) at 24 weeks' follow-up. The patients have been tested yearly for the presence of serum HCV RNA.

Of the total patient population, 163 were infected only with HCV and were treated with peginterferon alfa-2a monotherapy. Another 741 monoinfected patients were given both peginterferon alfa-2a and ribavirin, and 93 patients who were coinfected with HIV and HCV were treated with either monotherapy or combination therapy.

At a mean follow-up of 4.1 years (range 0.4-7.0 years), 989 of the 997 patients (99.2%) were free of HCV RNA. The other eight patients (0.8%) later became HCV RNA positive at a mean of 2 years after cessation of therapy. However, it is not known whether these patients (four men and four women) were reinfected during follow-up or experienced virologic relapse.

"There appear to be no risk factors associated with detectability of HCV RNA during follow-up," Dr. Swain noted. None of these eight patients had underlying cirrhosis, and "interestingly, only one patient actually received what we would now consider an adequate course of therapy, defined by current treatment paradigms," said Dr. Swain, professor of medicine, at the University of Calgary, Alta.

"These data suggest that clinical relapse is extremely rare in patients who achieve an SVR with peginterferon alfa-2a plus or minus ribavirin. And therefore, we suggest that patients who achieve an SVR may be deemed clinically cured of chronic hepatitis C," he concluded.

Dr. Jay Hoofnagle, director of the liver disease branch at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in Bethesda, Md., as an audience member questioned whether the eight patients who became positive for HCV RNA during follow-up were truly positive. He said that in his experience, polymerase chain reaction (PCR) testing can yield a false-positive rate of up to 1%, due to technical errors in the laboratory or other causes. "I think you need to bring those people back and make sure they have an infection," he suggested.

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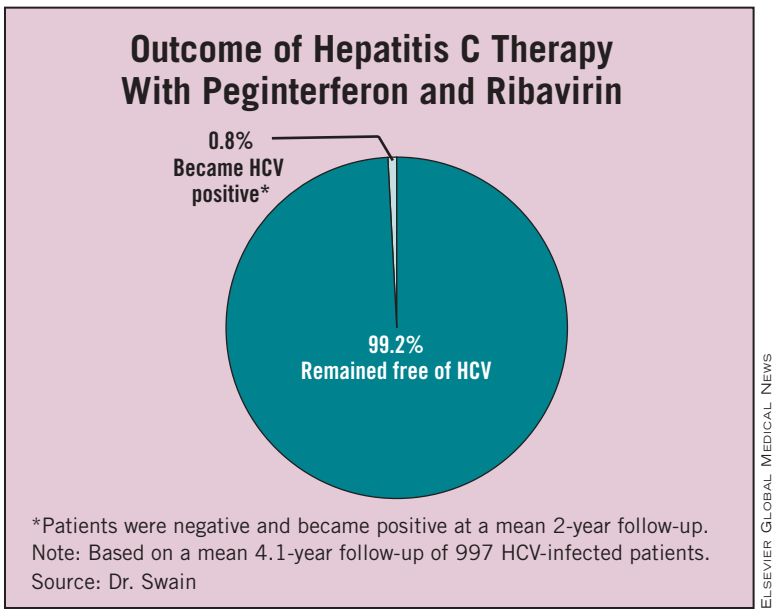
DR. SWAIN

Dr. Swain acknowledged that although false-positive results were possible, "0.8% is well within the numbers that people would normally report for reinfection, I think, in a population this size." He noted that one of these eight patients has been retested and is still positive for HCV RNA, and genotypic testing for this patient suggested that reinfection had occurred.

A false-positive rate of 1% would be considered high in commercial testing facilities such as the one used in his and his colleagues' study, Dr. Swain said in an interview. Moreover, "false positives would have to be a result of faulty technique—which would be unlikely to give just one false-positive result in a group of batched samples run at the same time—or contamination," he said. "I am very comfortable that these patients were not false positives," he said.

Prior studies have reported SVR rates of up to 66% in patients monoinfected with HCV, Dr. Swain noted, and in 40% of HIV coinfected patients.

"This is not the first study, but this is definitely the most compelling and the largest," Dr. John Vierling, professor of medicine and surgery at Baylor University, Houston, said in an interview. He noted that the first hint that an SVR might be possible with this treatment came in 1981, when one of the current study's component trials, led by Dr. Hoofnagle, ended up with normalization of the patients' liver tests. More recently, those patients were retested via PCR and liver biopsy, "and there was no evidence of virus in the liver cells … and those who had had some scarring reactions before they were treated some 20-some years ago—the scar was no longer present. The fibrosis that existed was now gone."



More recently, a European study found a high rate of SVR at the end of therapy and after 6 months' follow-up, which was eventually extended to 17 years. "What they found was that 98% of this large number of people had no detectable virus" in blood, white blood cells, or in the liver.

Dr. Vierling noted that the confluence of modern technology and a large study population account for the credence of Dr. Swain's and his colleagues' study.

"The beauty of this type of study is that these were studies in which we know everything about the patients. … They were able, [using] this mechanism, for the first time, to give us these 997 people that we're absolutely sure had a sustained virologic response," defined by blood testing. Unlike older studies that predated PCR testing, "you don't have the question of whether any of them got into that group who may have harbored virus, but nobody knew it." ■

Serum Markers May Help Diagnose Nonalcoholic Fatty Liver

BY HANNAH BROWN
Contributing Writer

GLASGOW, SCOTLAND — Serum fibrosis markers—currently used as a research tool—have high sensitivity and specificity for diagnosing more severe forms of nonalcoholic fatty liver disease, according to a presentation at the Diabetes U.K. Annual Professional Conference.

Diagnosis of the most severe forms of nonalcoholic fatty liver disease (NAFLD), which include the onset of steatohepatitis and subsequent fibrosis and cirrhosis, requires measurement of the extent of inflammation and the presence of fibrosis. Currently, only liver biopsy can identify patients with these symptoms; such patients must be managed more aggressively than patients with less severe forms of the disease, particularly with respect to cardiovascular risk factors. However, biopsy is an expensive diagnostic procedure and is dangerous for the patient.

Dr. Christopher Byrne, head of the endocrinology and metabolism unit at the University of Southampton (England), said he believes that "in future, noninvasive serum markers might be better. Research is beginning to suggest that within NAFLD, a scoring system such as that using ELF [enhanced liver fibrosis assay, which looks at several serum biomarkers of fibrosis] might prove useful." When combined with age as a risk factor, the three markers assessed by the ELF blood test—hyaluronic acid, procollagen III amino terminal peptide (PIIINP), and tissue inhibitor of metalloproteinase 1 (TIMP-1)—have around 85% specificity and sensitivity for moderate to severe NAFLD, he noted.

When combined with age as a risk factor, the markers assessed by the enhanced liver fibrosis assay have 85% specificity for moderate to severe disease.

Alanine aminotransferase (ALT) and GammaGT, plasma markers currently used to help guide diagnosis for NAFLD, are not very accurate, according to Dr. Byrne. "ALT is an extraordinarily poor proxy. Both GammaGT and ALT are in the normal range in patients who have quite extensive NAFLD when they get to biopsy," he said.

NAFLD is one of the most common forms of chronic liver disease in developed countries, affecting 10%-24% of the general population, and it is especially common in people with type 2 diabetes. Liver damage in this condition is caused by accumulation of lipids, oxidative stress, and inflammation caused by release of proinflammatory cytokines. The associated marked insulin resistance in NAFLD has led some scientists to propose that it might be a malignant form of metabolic syndrome.

"Even adjusting for obesity, patients with NAFLD have marked increases in nonesterified fatty acid accumulation," Dr. Byrne said. "So release of these from adipocyte depots into circulation is abnormal in these patients. But we don't know why [it is] associated with marked insulin resistance."

He presented research showing that a group of 1,974 type 2 diabetes patients with NAFLD had a significantly higher prevalence of coronary, cerebral, and peripheral cardiovascular disease than a group of 418 type 2 diabetics without fatty livers. "NAFLD is associated with increased mortality, especially at the more severe end," Dr. Byrne said. "In these patients, even adjusting for all conventional cardiovascular risk factors and features of the metabolic syndrome, NAFLD is an independent cardiovascular risk factor. If you find NAFLD, think accelerated cardiovascular risk and treat aggressively."

Treatment recommendations include initial weight loss in obese patients; limited evidence suggests that therapy with glitazones also can be used to increase insulin sensitivity and decrease liver fat content. "Glitazones show promise," Dr. Byrne said. "A new indication for glitazone therapy may prove to be NAFLD." ■