Liver Biopsy May Become Ancillary Prognostic Test

BY MIRIAM E. TUCKER
Senior Writer

PHILADELPHIA — Liver biopsy is losing its appeal as a diagnostic tool for chronic liver disease, Dr. K. Rajender Reddy said at the annual meeting of the American College of Physicians.

Problems associated with liver biopsy such as sampling error, inadequate specimens, and interobserver variability have become increasingly apparent in recent years, while noninvasive markers of fibrosis and inflammation are showing more promise as diagnostic tools.

Liver biopsy is assuming a role more as a prognostic test than as a diagnostic test. At the very least, it should not be used "as a knee-jerk response to hepatic biochemical test abnormalities," said Dr. Reddy, professor of medicine and surgery and director of hepatology at the University of Pennsylvania, Philadelphia.

Recent studies suggest that because liver biopsy samples less than 1/50,000 of the liver, cirrhosis may be missed in up to 20% of patients. Moreover, grades of inflammation and stage of fibrosis may be underscored in short, narrow specimens. Obtaining an adequate specimen—ideally more than 2.5 cm long, more than 1.4 mm wide, and with 11 or more portal triads—is often a challenge.

Panels of noninvasive markers of fibrosis and inflammation may be validated in the near future. Indirect markers include the aspartate transaminase:alanine transaminase (AST:ALT) ratio, AST-platelet ratio index, the Fibro Test, and ActiTest. Direct markers such as hyaluronic acid and YKL-40 may prove useful as well. Also, an ultrasonographic tool called FibroScan is being evaluated in Europe.

The pros and cons of doing a liver biopsy depend on the condition. With hepatitis C, biopsy may help determine the extent of fibrosis and inflammation, which are the best predictors of disease progression. But noninvasive markers may also accurately stage and grade disease.

In hepatitis C patients with genotype 1, which has the lowest treatment response rate, biopsy may help identify patients most in need of treatment. But patients with more responsive genotypes 2 and 3 may be more motivated for therapy anyway and may forego biopsy. Biopsy can help determine the need for treatment in patients with side effects or in those who were previously treated and therefore less likely to respond to retreatment.

With hepatitis B, the decision to treat is generally made with hepatitis B serologies, viral DNA, and ALT, although biopsy might be considered in patients with fluctuating ALT levels. And, although biopsy might prompt screening for varices and hepatocellular carcinoma (HCC) in a patient with hepatitis B, surveillance for HCC is recommended in these patients whether cirrhosis is present or not, Dr. Reddy noted.

For patients with elevated ALT levels, a biopsy can help confirm a diagnosis. But a cause for abnormal hepatic biochemical tests is accurately identified clinically in more than 90% of cases without a biopsy. Similarly, diagnosis of alcoholic liver disease (NAFLD) is also usually made clinically, although not all patients have classic risk factors. Currently, only biopsy can distinguish simple steatosis from steatohepatitis, but noninvasive markers may accomplish this in the future.

The presence of steatohepatitis or fibrosis might motivate a patient with NAFLD to undertake risk-factor modification, but there is no proven therapy for NAFLD. Absence of steatohepatitis or fibrosis might remove that motivation. ■

Nonalcoholic Fatty Liver Emerging as Major Problem

BY MIRIAM E. TUCKER
Senior Writer

PHILADELPHIA — Nonalcoholic fatty liver disease is emerging as a major health burden in the United States, Dr. K. Rajender Reddy said at the annual meeting of the American College of Physicians.

Often associated with obesity and underlying insulin resistance, nonalcoholic fatty liver disease (NAFLD) is believed to affect as much as 20%-30% of the U.S. population, said Dr. Reddy, professor of medicine and surgery and director of hepatology at the University of Pennsylvania, Philadelphia.

Overall, about 10% of patients with nonalcoholic fatty liver disease have nonalcoholic steatohepatitis.

DR. REDDY

There is some debate about the amount of alcohol ingestion permitted to make the distinction between alcoholic steatosis and NAFLD, which is defined as increased liver weight by 5%-10% as a result of fat accumulation (steatosis), in the absence of excessive alcohol consumption.

Most experts agree, however, that overall alcohol consumption of less than 20 g per day is well below that which would be associated with significant alcoholic liver disease, noted Dr. Reddy, who is also medical director of liver transplantation at the university.

Classification of NAFLD falls into four types: Type 1 (fatty liver alone) and type 2 (fat accumulation and lobular inflammation) are considered to be NAFLD alone. The more serious types 3 (fat accumulation and ballooning degeneration) and 4 (fat accumulation, ballooning degeneration, and either Mallory hyaline and/or fibrosis) are characterized as nonalcoholic steatohepatitis (NASH).

"There is a tendency to use the term NASH loosely in everyone who has nonalcoholic fatty liver disease. You should use the general term NAFLD and reserve NASH only for those who have histologic evidence of steatohepatitis," Dr. Reddy advised.

Overall, about 10% of patients with NAFLD have NASH. Limited data on the natural history of these conditions suggest that about 15%-20% of patients with steatosis will progress to steatohepatitis at some point. Of those, smaller numbers will go on to develop fibrosis, cirrhosis, and hepatocellular carcinoma. The exact percentages have varied widely in different studies.

Factors that predict progression from NAFLD to NASH include age greater than 45 years, type 2 diabetes, body mass index greater than 35 kg/m2, hypertension, and liver enzyme abnormalities. Overall, the 1- and 5-year survival rates for NASH have been reported to be 67% and 59%, respectively. But the mortality is not always liver-related and could be due to comorbid conditions such as hypertension, dyslipidemia, and diabetes. In one recent study of 420 NAFLD patients in Minnesota who were followed for a mean of 7.6 years, mortality was 34% greater than expected for the general Minnesota population. Liver disease was the third-leading cause of death, versus number 13 in the population (Gastroenterology 2005;129:113-21).

Data pertaining to treatment of NAFLD are also limited, but weight management is considered a major priority for all patients because of proven benefits in cardiovascular risk profile. ■

Single-Center Study Shows Rifaximin Best for Hepatic Encephalopathy

BY BRUCE JANCIN
Denver Bureau

HONOLULU — Rifaximin is the new treatment of choice for patients with hepatic encephalopathy, Dr. Carroll B. Leevy said at the annual meeting of the American College of Gastroenterology.

Rifaximin (Xifaxan), a nonabsorbable antibiotic with gastrointestinal specificity approved by the Food and Drug Administration for treating travelers' diarrhea, is approved in 17 other countries for management of hepatic encephalopathy.

Rifaximin proved superior to lactulose, the current standard therapy, in a single-center retrospective crossover study. Rifaximin resulted in less hospitalization and lower hospital costs than lactulose, and maintained patients at less severe grades of hepatic encephalopathy, said Dr. Leevy, clinical affairs director at the New Jersey Medical School Liver Center, Newark.

Hepatic encephalopathy is characterized by altered mental status. Hospitalizations for the disease tend to be prolonged, lasting a mean of 5-7 days and costing $23,000 per episode.

The disorder is due to systemic accumulation of ammonia, which is not detoxified in the cirrhotic liver. Rifaximin is thought to reduce ammoniagenic bacteria in the gut. Neomycin and other antibiotics also have been reported to be effective in hepatic encephalopathy, but with more toxicity due to systemic absorption.

Dr. Leevy reported on 145 patients with hepatic encephalopathy who received 30 cc b.i.d. of lactulose for 6 months or longer, then were switched to rifaximin at 400 mg t.i.d. for at least 6 months. He compared end points during the patients' last 6 months on lactulose with those during their first 6 months on rifaximin. All key end points were significantly better in the rifaximin group. (See box below.)

Most patients on lactulose were in hepatic encephalopathy grade 2 (lethargy, obvious personality changes, and/or inappropriate behavior) or grade 3 (disoriented as to time and place, and with incomprehensible speech) versus grade 1 or 2 while on rifaximin.

Rifaximin vs. Lactulose in Hepatic Encephalopathy

	Rifaximin	Lactulose
Mean number of weeks hospitalized during 6 months on drug	0.4	1.8
Mean days per hospitalization	2.5	7.3
Average hospitalization cost during 6-month period	$14,222	$56,635
Incidence of asterixis	63%	93%
Incidence of diarrhea	37%	92%
Incidence of flatulence	2%	74%

Source: Dr. Leevy

Compliance was significantly better with rifaximin as well. Most patients took 50%-75% of their doses of lactulose, as compared with 75%-100% of their three times daily doses of rifaximin, he added.

One audience member defended lactulose as a trusted drug and said he wasn't about to discard it based on a single-center retrospective study. Dr. Leevy said that the problem with lactulose isn't whether it can be efficacious but "that it's hard to tolerate and few people will take it." Most patients experience diarrhea or constipation as a side effect, which worsens their hepatic encephalopathy, he said.

Dr. Leevy said that Salix Pharmaceuticals Inc., rifaximin's maker, paid for the statistical analysis; the study itself was initiated and funded by the hospital. ■

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