Manage Lifestyle and Insulin Resistance in NAFLD Patients

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — With no specific treatment available for nonalcoholic fatty liver disease, the best current strategy centers on monitoring the patient's condition and managing the patient's lifestyle and metabolic syndrome, Dr. Nathan M. Bass said at the Third World Congress on Insulin Resistance Syndrome.

The patient's liver enzymes, liver function (bilirubin levels, albumin levels, prothrombin time), and platelet count should be monitored. Each patient also should undergo regular ultrasound exams. Patients should be instructed to avoid hepatotoxins—most notably, alcohol—and should be advised to pursue gradual weight loss with diet and exercise.

"Weight loss remains the simplest advice you can give," said Dr. Bass of the University of California, San Francisco, citing a study showing even modest weight loss (less than 10% of initial body weight) can reduce intrahepatic fat while leaving intramuscular fat unchanged. Such weight loss also improved basal and insulin-stimulated glucose metabolism (Diabetes 2005;54:603-8).

Bariatric surgery can be helpful for some patients with nonalcoholic fatty liver disease (NAFLD), but it should be the newer restrictive surgery involving gastric banding, which tends to decrease steatosis, fibrosis, and nonalcoholic steatohepatitis. Older malabsorptive surgical strategies can be dangerous; they can lead to increased steatosis, fibrosis, nonalcoholic steatohepatitis, and liver failure. The insulin-sensitizing agent metformin appears to be helpful in NAFLD; but the published studies tend to be small and open label, so the evidence base is not overwhelming. The thiazolidinediones pioglitazone and troglitazone seem to improve liver enzymes and fibrosis measured histologically, but again, the evidence is from open-label trials.

Dr. Bass noted some caveats with thiazolidinediones: They can cause weight gain and relapse upon discontinuation, and some patients experience serious side effects such as congestive heart failure and hepatotoxicity. ■

Biopsy Can Be Tricky in Fatty Liver Disease

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — The liver biopsy remains the preferred method for diagnosing nonalcoholic fatty liver disease, but biopsy candidates should be chosen with care. Not all patients with signs of the disease will require a biopsy, Dr. Nathan M. Bass said at the Third World Congress on Insulin Resistance Syndrome.

Patients who are eventually diagnosed with nonalcoholic fatty liver disease (NAFLD) present initially in a variety of ways, said Dr. Bass of the University of California, San Francisco.

For example, an insurance exam can turn up an incidental aminotransferase elevation or an enlarged liver. An abdominal imaging study may reveal a fatty liver. A patient may have a complication of cirrhosis. Or NAFLD patients may be identified by screening high-risk populations with liver enzyme tests or liver ultrasound. An increasing number of NAFLD patients are also being identified by liver biopsy during weight-reduction surgery, he said.

But it's not practical or desirable to screen all at-risk patients with a biopsy, and there are some good reasons not to do so. (See box.) About 25% of patients will experience significant pain during the biopsy, and 1%-3.5% of patients will have morbidities such as hypotension, pneumothorax, hemoperitoneum, hemobilia, and gall bladder penetration. About 0.1% of patients will die from the procedure.

There are five situations in which a liver biopsy is essential: when a patient's liver enzymes show an unusual pattern or are 3-5 times normal; when other liver disease cannot be excluded; when the patient does not have metabolic syndrome; to confirm a clinical suspicion of cirrhosis; and for qualifying a patient for entry into a clinical trial.

Although a definitive diagnosis still requires a biopsy, there are several alternatives for assessing the liver, Dr. Bass said.

Elevated liver enzymes can be suggestive of NAFLD, but in a phenomenon Dr. Bass called "The Silence of the Labs," some patients with NAFLD have normal liver enzymes. He cited one study of patients undergoing gastric bypass in which 68% had normal ALT and AST, but only 52% had a normal liver biopsy. In the remaining 48% with abnormal biopsy results, about 27% had nonalcoholic fatty liver, and the others had nonalcoholic steatohepatitis.

An NAFLD diagnosis is often made by exclusion—after alcoholic liver disease, drug-induced liver injury, iron overload, hepatitis B and C, and autoimmune hepatitis have been excluded.

It's difficult to exclude a significant contribution from alcohol, because patients are not always truthful. For inclusion in clinical trials, NIH defines "nonalcoholic" as less than 14 units of alcohol per week for men or less than 7 units per week for women. A unit is one can of beer, one glass of wine, or one shot of hard liquor.

Combining ultrasound evidence of fatty liver and liver enzyme elevation without markers for hepatitis C or B yields a 96% positive predictive value for NAFLD, according to one study. However, ultrasound is sensitive, but not very specific. CT imaging is somewhat more specific. In CT, a normal liver has about the same density as the spleen; in NAFLD, the spleen is brighter. But CT is too costly for routine screening. At least three serological tests for hepatic fibrosis are being developed, Dr. Bass said. Transient elastography, combining 5-MHz ultrasound and 50-Hz elastic waves, may also help diagnosis. ■

Biopsy's Pros And Cons

Pros

- ▶ Grade and stage of NAFLD are determined.
- ▶ Confidence in the diagnosis is 100%.
- ▶ Patients are motivated to lose weight.
- ▶ Biopsy is essential for enrollment in clinical trials of treatments.

Cons

- ▶ Risk of morbidity is increased with biopsy.
- ▶ Noninvasive diagnosis is quite accurate.
- ▶ Natural history of NAFLD is benign in most patients.
- ▶ NAFLD is a common disorder.
- ▶ There is no proven, specific treatment for NAFLD.

Source: Dr. Bass

Multidrug Approach Is Coming for Hepatitis B

BY BRUCE JANCIN
Denver Bureau

HONOLULU — The future of chronic hepatitis B therapy will look very much like HIV treatment today: multidrug combinations aimed at thwarting development of resistant viral strains, Dr. Paul J. Pockros predicted at the annual meeting of the American College of Gastroenterology.

"All of us in gastroenterology are going to have to deal with antiviral resistance. I think we're headed this way both for hepatitis B and hepatitis C. We're going to be akin to the HIV doctors. There are 21 HIV drugs available, and their resistance profiles dictate how they're used, with drugs in different classes being used together. That's really what many of us have started doing in dealing with hepatitis B," said Dr. Pockros, head of the gastroenterology/hepatology division at the Scripps Clinic in La Jolla, Calif.

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One major lesson hepatologists have learned from the HIV treatment experience is that sequential antiviral monotherapy is not the way to go. It results in creation of drug-resistant strains that can be transmitted to other individuals. That lesson was brought home by the experience with lamivudine, a nucleoside analog that was the first oral antiviral agent approved for chronic hepatitis B.

When lamivudine (Epivir) received marketing approval in 1998, it was quickly adopted as a first-line therapy because it is orally administered and has far fewer side effects than subcutaneous interferon-alfa-2b (Intron-A), then the only other treatment option. Unfortunately, as the years went by, the full scope of the lamivudine resistance problem became apparent. After 1 year, 20% of treated patients developed viral resistance to the drug. After 2 years, it was 38%. After 3 years, 49%. And after 4 years on lamivudine, 67% of treated patients had resistant virus. The clinical consequences include rebound of serum hepatitis B DNA, a reduced seroconversion rate, elevated serum liver enzymes, and reversal of histologic improvement.

Viral resistance has been much less of a problem with the two oral antiviral agents approved since lamivudine. The rate of resistance after 4 years on adefovir dipivoxil (Hepsera) monotherapy is 18%. The resistance rate after 1 year on the nucleoside analog entecavir (Baraclude) is 0% in lamivudine-naive patients and 7% in lamivudine-resistant individuals.

"My own view is that lamivudine will drop out of the picture because we have a better nucleoside analog now. It's not cheaper, but it's certainly better in its efficacy, and it causes less resistance," Dr. Pockros said.

With the 2005 marketing approval of pegylated interferon-alfa-2a, physicians can now choose from five agents for the treatment of hepatitis B. Many more are in the developmental pipeline.

"I think we'll end up with 10 drugs for hepatitis B, possibly even more, and we'll use combination therapy—either a combination of a nucleoside and a nucleotide analog, like adefovir and lamivudine, to minimize resistance, or a combination of one of those drugs and pegylated interferon," he predicted.

Four drugs are in or have finished phase III clinical trials for hepatitis B. Two, emtricitabine (Emtriva) and tenofovir (Viread), are already marketed for HIV. The others are the nucleotide analog telbivudine and pegylated interferon-alfa-2b. At least 11 agents are in phase II trials.

Although the preference of American patients and physicians is clearly for oral therapy even though the approved agents must often be prescribed indefinitely, pegylated interferon-alfa-2a has quickly become the leading first-line hepatitis B therapy in Europe.

"Many European countries have mandated it because pegylated interferon has a finite duration of therapy, it's relatively inexpensive because of that, and because they have a large hepatitis B e-antigen–negative population, where you're going to commit patients to lifetime therapy otherwise," Dr. Pockros said. He is on the speakers' bureaus for Gilead Corp., Bristol-Myers Squibb Co., Idenix Corp., and Roche. ■