

Push Diet, Exercise; Consider Glitazones for NASH

Patients who achieved greater than 9% weight loss had improvements in NASH activity scores.

BY SHARON WORCESTER
Southeast Bureau

MIAMI BEACH — All patients with non-alcoholic steatohepatitis, as well as those at risk for developing the condition, should be counseled about the importance of diet and exercise, while more aggressive therapy should be considered in those who fail to achieve 10% weight loss with diet and exercise alone, Dr. Stephen A. Harrison said at a meeting on hepatobiliary disease sponsored by the University of Miami.

Studies suggest that people who are overweight or obese have a substantially higher risk of nonalcoholic steatohepatitis (NASH). For example, about 3% of the general population has NASH, compared with 20%-40% of those with body mass index greater than 35 mg/kg², said Dr. Harrison, chief of hepatology at Brooke Army Medical Center, San Antonio. Female gender, Hispanic ethnicity, diabetes, metabolic syndrome, age over 50, and elevated aspartate transaminase level are among other factors that have been associated with NASH risk. (See box.)

Weight loss is the accepted standard for treatment, Dr. Harrison said. Studies consistently show that substantial weight loss results in improved histopathology. For example, in a recent randomized study evaluating the use of orlistat to augment weight loss, Dr. Harrison showed that patients in both the treatment and control groups who achieved greater than 9% weight loss

had improvements in insulin resistance, steatosis, and inflammation, as well as significant reductions in NASH activity scores.

Control patients who were treated with dietary restrictions and vitamin E lost a mean of 6% of their body weight, compared with 8% weight loss in those also treated with orlistat, and no differences were seen between the groups with regard to histopathologic outcomes. Orlistat can be considered a tool to help augment weight loss, but it is those patients who achieve greater than 9% weight loss who will benefit, Dr. Harrison noted.

Exercise has also been shown to be helpful in these patients. In one study of more than 1,500 individuals who exercised at a gym at least 1 day per week and who followed a diet low in processed carbohydrates, 6% of patients lost at least 5% of body weight, and nearly half of all patients with abnormal alanine transaminase (ALT) levels had ALT normalization at 1 year. Every 5% decrease in weight was associated with a 3.6-fold decrease in ALT, and participants also experienced reductions in triglycerides, blood pressure, and fasting glucose.

Weight loss surgery is also an option, particularly for morbidly obese patients and those who are not able to lose enough weight through diet and exercise alone.

Data on adjustable gastric banding are quite provocative in terms of its effects on NASH, Dr. Harrison said. In one study of 36 patients who lost an average of 75

Who's at Risk for a NASH Diagnosis?

A composite index based on clinical and laboratory findings can help identify patients at risk of having NASH, Dr. Harrison said.

A study of 80 patients with biopsy-proven nonalcoholic fatty liver disease, including 39 with simple steatosis and 41 with NASH, showed that the index—including three of five of the following factors—has 74% sensitivity and 66% specificity for identifying patients at risk of NASH. The factors are aspartate transaminase (AST) of 45 U/L or over, body mass index of 30 kg/m² or greater, AST:ALT ratio of 0.80 or greater, age of 50 or older, and female gender (*Liver Intern.* 2005;26:151-6).

“So for instance, if you have a fe-

male over age 50 that's obese, her probability of having steatohepatitis is certainly greater than 50%,” he said.

In addition, in a recent study of 97 severely obese patients undergoing bariatric surgery, insulin resistance was shown to be more severe in patients with NASH, compared with those without NASH, and both AST level and the presence of diabetes were independently associated with a NASH diagnosis (*Am. J. Gastroenterol.* 2007;102:399-408).

Other studies have also shown an association between metabolic syndrome and NASH; one study found that 88% of patients with NASH had metabolic syndrome, Dr. Harrison noted.

pounds by 25 months, 23 patients had NASH, and 82% of them had resolution of NASH.

Recent studies also appear to dispel the notion that the kind of rapid weight loss often associated with surgery can lead to worsening of steatohepatitis. Older data based on a single follow-up liver biopsy suggested that rapid weight loss was associated with increasing inflammation, but studies that are more recent have used serial biopsies, which showed an initial increase in inflammation, followed by resolution over time, he explained.

Pharmacotherapy is another option in those who can't or won't lose weight, Dr.

Harrison said. Thiazolidinediones (glitazones) will form the foundation of therapy in the future in these patients, he said.

Studies of pioglitazone and rosiglitazone, are promising in regard to their effects on plasma glucose, hepatic insulin sensitivity, adiponectin levels, hepatic fat content, inflammation, steatosis, and fibrosis.

Other drugs, such as metformin, show promise, but studies suggest that metformin is not associated with the histopathologic improvements seen with the glitazones. Combination therapy, however, may be beneficial; metformin appears to mitigate the weight gain that can occur with the glitazones, Dr. Harrison said. ■

More Techniques for Barrett's Ablation Are Now Available

BY DOUG BRUNK
San Diego Bureau

SAN DIEGO — Ablative therapies are a promising alternative to esophagectomy for treating patients with high-grade dysplasia associated with Barrett's esophagus, Dr. Kenneth K. Wang said at a meeting jointly sponsored by the AGA Institute and the Japanese Society of Gastroenterology.

One reason to consider ablation is that esophagectomy has high mortality. A study showed that the mortality is 20% in hospitals that perform fewer than two esophagectomies per year, compared with about 8% in hospitals that perform more than 19 esophagectomies per year (*N. Engl. J. Med.* 2002;346:1128-37). “There's a learning curve to esophagectomies,” said Dr. Wang, who directs the Barrett's Esophagus Unit at the Mayo Clinic in Rochester, Minn.

In addition, new Barrett's disease can occur after esophagectomy for high-grade dysplasia. One study of 40 patients who underwent esophagectomy found that 29% had erosive esophagitis and 40% had a columnar esophagus (*Br. J. Surg.* 2003;90:1120-8). “So you have to be aware that if you subject these patients to esophagectomy, it may not be the best thing, even if they're young,” he said.

One ablative option includes endoscopic mucosal resection using a cap-fitted endoscope. The most difficult part of this procedure is forming the snare around the loop of the cap, but this is improved with a newer band ligation device, Dr. Wang said.

Another option is circumferential endoscopic mucosal resection, which involves removing the index lesion as well as the Barrett's epithelium. “You can take out the whole Barrett's segment this way,” he said. “However, there is a bit of residual. It's very hard to take out the entire esophageal mucosa in a piecemeal fashion.”

One study of 35 Barrett's patients who underwent circumferential endoscopic mucosal resection found that 6% had residual high-grade dysplasia and 17% had residual intestinal metaplasia (*Gastrointest. Endosc.* 2003;57:854-9).

With this technique, “there's a lot of scarring, so you have to use repeated mucosal resection,” Dr. Wang said. In one study, treatment for 1 of 10 patients could not be completed because of scarring (*Gastrointest. Endosc.* 2006;63:847-52).

Overall, the results of endoscopic mucosal resection techniques “are pretty good,” he said. One study of 19 Barrett's patients with high-grade dysplasia and 96 with early cancers found a local remission rate of 98%. However, because the re-

searchers removed only high-grade dysplastic lesions, metachronous lesions occurred in 30% of patients over 34 months (*Euro. J. Gastroenterol. Hepatol.* 2002;14:1085-91). “Even though the treated area looks good and histology is improved, there are the same genetic defects in the areas around the treated site that must be dealt with,” Dr. Wang explained.

Complications occurred in 10% of the patients—mainly bleeding and stenosis.

Photodynamic therapy (PDT) is also being used to treat high-grade dysplasia and cancer associated with Barrett's. This technique “probably has the longest track record,” Dr. Wang said. “It's very easy to do and takes about 5 minutes of photoradiation time.”

In a trial presented at the 2006 Digestive Disease Week, researchers randomized 208 patients to either continued surveillance or PDT. At 24 months, 77% of those in the PDT group had elimination of high-grade dysplasia, compared with 39% of those in the surveillance arm.

The 5-year clinical response data showed that 52% of those in the PDT group had completely normal mucosa, compared with 7% in the surveillance arm.

Dr. Wang added that three Markov models have all shown “that PDT is more cost effective than surgery or surveillance.”

Other available techniques include multipolar electrocoagulation and argon plasma coagulation. Results from one randomized study of 52 patients suggest that the efficacy of these two techniques is about the same. The endoscopic and histologic ablation rates for patients who underwent multipolar electrocoagulation were 88% and 81%, respectively; the endoscopic and histologic ablation rates for patients who underwent argon plasma coagulation were 81% and 67%, respectively.

These techniques “are not perfect,” Dr. Wang said. “There are always bits of Barrett's left, and you still have to continue surveillance.”

New alternatives expected to hit the market soon include devices that use cryotherapy and radiofrequency to ablate Barrett's tissue.

Whether physicians implement ablative techniques into their practice or not “depends on a lot of factors,” he said. “It depends on your expertise and that of the surgeons in your institution. It depends on the patients, how long their longevity is, whether or not they're going to be willing to come back to you, and the length of the Barrett's segment.”

Dr. Wang disclosed that he has received research support from Axcan and BarRx and served as a paid consultant for InScope. ■