NASH Treatments Controversial, Unproven

BY DOUG BRUNK

SAN DIEGO — Treating nonalcoholic steatohepatitis is difficult territory for clinicians because no therapy has been proved effective, Dr. Arthur J. McCullough said at a meeting on chronic liver disease sponsored by Scripps Clinic.

"All therapies I consider emerging, because, at present, there are no proven therapies for this," said Dr. McCullough, chairman of the department of gastroenterology and hepatology at the Cleveland Clinic. "Not everyone with NASH [nonalcoholic steatohepatitis] progresses, but our current management is not adequate."

One practical approach is to advise patients to follow a Mediterranean diet, which has been shown to improve insulin resistance, compared with other diets. "There are controversies with whatever diet you use," he said. "Most of the studies say a high-fat diet is bad. For my patients, I recommend a low-fat diet emphasizing polyunsaturated fatty acids and a low glycemic diet, which means a fiber bread instead of white bread, fish and chicken, fruits and vegetables, no fructose, and no trans fat."

At least one study has demonstrated that use of polyunsaturated fatty acids (PUFAs) by NASH patients improved their alanine transaminase (ALT) and triglyceride levels (Aliment. Pharmacol. Ther. 2006;23:1143-51). PUFAs "work like fibrates," Dr. McCullough explained. "They upregulate peroxisome proliferator–activated receptor-alpha, which increases fatty acid oxidation from peroxisomes and mitochondria. But they also suppress a number of genes in the triglyceride synthesis pathway."

Another treatment approach involves weight loss and exercise. Between 2002 and 2007, there were 26 published studies on weight loss and exercise in patients with NASH, but the evidence is incomplete because only 3 of the trials were controlled and only 4 included liver biopsies before and after treatment. "Most of the trials were short term, so the intervention was mainly prescriptive," he said. "Only four included behavior therapy according to current guidelines."

Despite the paucity of robust studies, Dr. McCullough maintained that patients with NASH can improve their disease with small improvements in their body mass index. "It can be discouraging to tell people to lose 20% of their body weight, but I think you can achieve significant decreases in ALT and steatosis with as little as a 5% drop in body weight," he said. "We set targets of 5% at 3 months and 10% at 6 months."

Even so, only about 30% of patients at the Cleveland Clinic are able to sustain a weight loss of 10% over the long term, "and this is with behavior modification and counseling. We do the best we can, but this is very difficult to achieve."

Bariatric surgery is another treatment option. Dr. McCullough recommends this for patients with a body mass index (BMI) of 35 kg/m^2 or greater who have comorbidities. One study of 36 bariatric surgery patients—23 of whom had NASH—found that patients had lost a mean of 34 kg at 25 months after the procedure (Hepatology 2004;39:1647-54). Of the 23 patients with NASH, only 4 had residual disease at 25 months. There were improvements in steatosis, necroinflammation, and fibrosis.

Some clinicians have advocated the use of metformin in patients with NASH, but this is "a controversial area," Dr. McCullough said. The investigators looked at 200 patients, but only one of the studies was a controlled trial. That has prompted a movement toward use of the glitazones. "But the problem is, once you stop therapy with glitazones, the NASH comes back. If you're going to start people on this, it's lifelong therapy. Also, there is significant weight gain with the glitazones, an average of at least 3 kg."

Dr. McCullough prefers to use metformin because "it has [a] more direct effect on the liver," compared with the glitazones. For now, he said, clinicians should ask themselves two questions before recommending a specific therapy for NASH: "Once you start treatment, what then?" and "Do you feel good about using the treatment long term?"

Dr. McCullough had no conflicts to disclose. ■