Novel Drug Lowers Liver Enzymes in NASH

BY BRUCE JANCIN

VIENNA — A novel antiapoptotic drug has reduced markers of liver damage in patients with nonalcoholic steatohepatitis in a phase II trial.

Four weeks of therapy at the highest studied dose of the once-daily hepatoselective oral agent GS-9450 resulted in normalization of serum alanine aminotransferase levels in 35% of patients with NASH, compared with 9% in the placebo arm of the double-blind randomized multicenter trial, said Dr. Vlad Ratziu.

Based on the favorable safety and efficacy demonstrated in this study, the next step for GS-9450 will be a larger clinical trial with histologic end points, added Dr. Ratziu of Pierre and Marie Curie University, Paris.

GS-9450 is a potent inhibitor of caspases 1, 8, and 9. These enzymes modulate apoptosis, identified as one of the major mechanisms of liver injury in NASH. The drug has a liver-to-blood-concentration ratio of 100:1. GS-9450 also is being developed for a separate indication in the treatment of liver injury in patients with chronic hepatitis C.

The phase II dose-ranging study involved 124 patients with biopsy-confirmed NASH treated at 6 French and 35 U.S. centers. They were randomized to 4 weeks of GS-9450 at 1, 5, 10, or 40 mg or placebo once daily. From a mean baseline alanine aminotransferase (ALT) of 106 IU/L, levels of the liver enzyme dropped by 43% following 4 weeks of GS-9450 at 40 mg/day and by 30% with 10 mg/day, vs. 2% with placebo. Levels of serum aspartate aminotransferase followed suit.

Serum levels of CK-18 caspase cleavage fragments, thought to be a marker of apoptotic liver disease, declined in the 10- and 40-mg treatment arms. No severe adverse events occurred. Mild to moderate nausea, fatigue, and arthalgia were more common in GS-9450-treated patients than with placebo.

One audience member voiced concern that an apoptosis-blocking agent could have a carcinogenic effect.

Dr. Ratziu replied that animal studies actually suggest GS-9450 has the opposite effect, but more clinical data are needed to provide definitive reassurance.

"One possible explanation for the decrease in neoplastic risk seen in animal models is that this is a selective caspase inhibitor, not a pan-caspase irreversible inhibitor," the gastroenterologist added.

Dr. Peter Ferenci called this GS-9450 study one of the meeting highlights. GS-9450 represents a novel therapeutic approach in NASH, an important disease for which there is a clear unmet need for better treatments. There are no drugs of established efficacy.

"Treatment today centers on weight loss and recommendations for increased mobility, which are very hard for many patients to follow," said Dr. Ferenci, professor of medicine at the Medical University of Vienna.

NASH is an advanced form of nonalcoholic fatty liver disease (NAFLD). It's estimated that up to 5% of Americans have NASH, which often leads to cirrhosis. Up to 20% of Americans have NAFLD.

The prevalences of both NASH and NAFLD are rising in parallel with the obesity epidemic. Both conditions are increasingly being diagnosed in heavy children.

Elsewhere at the meeting, Dr. Ulrich Leuschner reported that high-dose ursodeoxycholic acid proved no more effective than placebo for the treatment of NASH in a randomized trial. This finding is a disappointment in light of several earlier open-label studies suggesting a beneficial effect, noted Dr. Leuschner of J.W. Goethe University, Frankfurt, Germany.

He reported on 186 patients with histologically confirmed NASH who were randomized to 23-28 mg/kg per day of ursodeoxycholic acid or placebo for 18 months. Posttreatment liver biopsies were obtained in 135 patients. They showed no significant differences in rates of improved liver histology between the ursodeoxycholic and placebo groups; nor were there any overall significant differences in liver function tests.

The study's only hope was the finding of significant improvements in intra-acinar inflammation and gamma glutamyltransferase in a relatively small but specific patient subgroup of younger mildly overweight men.

Dr. Ratziu is a consultant to Gilead Sciences, which sponsored his study. Dr. Leuschner is a consultant to Dr. Falk Pharma GmbH, which supported the ursodeoxycholic acid trial. ■

VITALS

Major Finding: From a mean baseline ALT of 106 IU/L, levels dropped by 43% following 4 weeks of the investigational drug GS-9450 at 40 mg/day and by 30% with 10 mg/day, compared with 2% with placebo.

Data Source: A phase II dose-ranging study involved 124 patients with biopsy-confirmed NASH treated at 6 French and 35 U.S. centers.

Disclosures: The study was sponsored by Gilead Sciences. Dr. Ratziu is a consultant to the company.

Sleeve Gastrectomy Is Option for High-Risk Patients

BY MICHELE G. SULLIVAN

NATIONAL HARBOR, MD. — Although sleeve gastrectomy has a higher rate of complications compared with other bariatric procedures, 2-year weight loss was similar to that seen after gastric bypass in a study of 446 patients.

"Gastric staple line leaks are the main concern in this procedure," Dr. Philippe Topart said at the annual meeting of the Society of American Gastrointestinal and Endoscopic Surgeons. "Twenty-three of the major complications were gastric leaks."

But at 2 years, his patients had lost a mean of 55% of their excess body weight, said Dr. Topart of the Clinique D'Anjou, Angers, France.

His series included procedures in 14 facilities in France and Switzerland. The patients' mean age was 43 years; 25% had failed a prior gastric banding. Most (83%) were female. Body mass index was more than 50 kg/m^2 in 31%, 45-50 kg/m^2 in 21%, 40-44 kg/m^2 in 27%, and up to 40 kg/m^2 in 21%.

Most patients (65%) had at least one comorbid condition, including metabolic syndrome (52%) hypertension (38%), dyslipidemia (24%), diabetes (23%), and nonalcoholic steatohepatitis (1%).

The majority of cases (99%) were performed laparoscopically. Mean length of hospital stay was 7 days. There were no postoperative deaths. The overall complication rate of 17% was attributable to dysphagia in 23 patents, postoperative bleeding in 1, and obstruction in 1, along with minor complications in 23 patients.

Gastric leaks occurred in 23 patients (5%). The leak rate was reduced in patients with staple line reinforcement (0% vs. 4.5% in nonreinforced staple lines) and in patients with oversewing (35% vs. 6%), Dr. Topart said.

"However, this was not a significant difference and the only prognostic factor was the operation duration," he said.

Patients with a lower BMI (35-49 kg/m^2) lost significantly more weight than did those with a BMI of 50-70 kg/m^2 (67% vs. 46%).

Males and patients with multiple comorbidities lost significantly less weight than did women or patients with no comorbidities. Prior gastric banding did not significantly affect weight loss.

"Sleeve gastrectomy appears to be a reasonable option as a primary bariatric surgical treatment, although the complication rate—especially gastric leaks—is far from being negligible," Dr. Topart said in an interview.

Since 2008, 150 sleeve gastrectomies have been performed in his practice, with a complication rate slightly higher than that seen in the 400 Roux-en-Y gastric bypasses performed.

"However, as reported in the multicenter retrospective study, there were no postoperative deaths, while with our gastric bypass we had a 0.25% 90-day death rate."

Evidence in favor of sleeve gastrectomy has mounted to the point that two major U.S. insurance companies—Aetna Inc. and UnitedHealthcare—announced that they will cover the procedure. Aetna began coverage in April. UnitedHealthcare began coverage in October 2009 when sleeve gastrectomy was was done as part of other related procedures, but now covers it as a stand-alone procedure, according to spokeswoman Cheryl Randolph.

The major concern is still the long-term weight-loss outcomes, Dr. Topart said. But a 2009 position statement by the American Society for Metabolic and Bariatric Surgery (ASMBS) appeared to be the tipping point for Aetna to decide to cover the surgery. "ASMBS determined that sleeve gastrectomy is an 'approved bariatric surgical procedure,' despite finding only 'limited' intermediate-term data and a lack of long-term data on the effectiveness of the procedure," the Aetna policy states.

ASMBS accepted sleeve gastrectomy as an approved procedure because of its potential value for high-risk patients, primarily those with an average BMI of 60 kg/m^2, according to its November 2009 position statement.

"Although the published intermediate-term 3- to 5-year follow-up data after sleeve gastrectomy are increasing, the data remain limited. The ASMBS has accepted sleeve gastrectomy as an approved bariatric surgical procedure primarily because of its potential value as a first-stage operation for high-risk patients, with the full realization that successful long-term weight reduction in an individual patient after the procedure would obviate the need for a second-stage procedure," the statement said.

It is unclear how often sleeve gastrectomy patients will require a different bariatric procedure.

The ASMBS paper noted that long-term data "might or might not ultimately confirm that the procedure should remain in the category of a staged treatment intervention." Sleeve gastrectomy can cause long-term nutritional deficits because the resected stomach absorbs some vitamins and nutrients less readily than it did before surgery, the paper stated. ■

VITALS

Major Finding: Weight loss at 2 years in patients undergoing sleeve gastrectomy was similar to that achieved by gastric bypass surgery.

Data Source: A review of 446 consecutive cases.

Disclosures: Dr. Topart disclosed that he has received travel support and research grants from Ethicon Endo-Surgery and W.L. Gore, and research grants from Santinov.