

# Push Diet, Exercise; Consider Glitazones for NASH

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/kg<sup>2</sup>, 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.

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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 histopathological 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.

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 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.

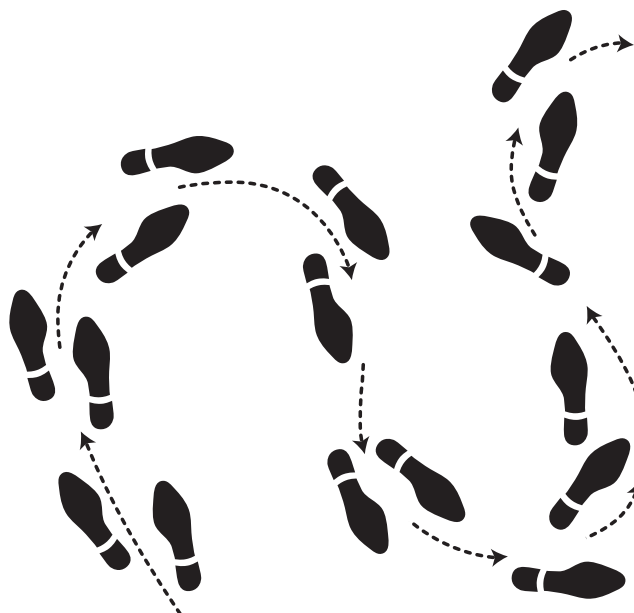
Studies of pioglitazone and rosiglitazone, for example, are very promising in regard to their effects on plasma glucose,

hepatic insulin sensitivity, adiponectin levels, hepatic fat content, inflammation, steatosis, and fibrosis.

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

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<sup>\*</sup>Results of a 12-week, placebo-controlled, randomized, double-blind, fixed-dose-treatment trial to assess the efficacy and safety of MIRAPEX vs placebo in the treatment of moderate to severe primary RLS (MIRAPEX n=254; placebo n=85). Measurement parameters included the International Restless Legs Syndrome Rating Scale (IRLS) and the Clinical Global Impressions-Improvement (CGI-I) scale. IRLS is an internationally validated scale that is the standard instrument for evaluation of severity of RLS. Total score ranges from 0 to 40, with 0 being absence of RLS symptoms and 40 the most severe symptoms. CGI-I is widely accepted for measuring improvement in RLS symptoms.

Reference: 1. Data on file, Boehringer Ingelheim Pharmaceuticals, Inc.



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