Pioglitazone: An Addition to Our Toolbox for Patients With Diabetes and Nonalcoholic Steatohepatitis?

Nonalcoholic fatty liver disease (NAFLD) is a growing global public health problem and is now recognized as the most common cause of chronic liver disease in the United States and other industrialized countries (1). The prevalence of NAFLD has increased in parallel with the dramatic increase in obesity and type 2 diabetes mellitus (T2DM), and it is now estimated to occur in more than 30% of the adult U.S. population (1). Although most patients with NAFLD have simple steatosis and a relatively benign clinical course, a smaller proportion develop nonalcoholic steatohepatitis (NASH), which may progress to cirrhosis and liver cancer and increases the risk for cardiovascular and chronic kidney disease (1). Moreover, the presence of NASH and significant fibrosis increases the likelihood of all-cause death, liver transplantation, and liver-related complications (2, 3). The presence of T2DM in patients with NASH is strongly associated with fibrosis severity and mortality risk (4). Therefore, patients with T2DM particularly need therapies that modify the natural history of NAFLD and NASH.

Currently, management of NASH is directed toward improving the metabolic parameters that may contribute to its pathogenesis, such as losing weight via lifestyle interventions, reducing insulin resistance, and improving diabetes control. Although weight loss of 5% or greater may improve NASH, most affected persons are unable to achieve or sustain this amount of weight loss. Thus, pharmacologic therapies targeting NASH would be welcome additions to the therapeutic toolbox (5).

Given that insulin resistance is a key factor in the development and progression of NASH, the insulin-sensitizing thiazolidinediones have been tested in several previous randomized, controlled trials (RCTs) (6, 7). The results of these studies have been promising, with observed improvements in steatosis, hepatocyte ballooning, and inflammation—the key histologic features of NASH. However, few studies have reported improvement in fibrosis, which is the dominant histologic feature that predicts liver morbidity and mortality, and none has established long-term efficacy in patients with T2DM.

Cusi and colleagues present the results of an RCT that enrolled 101 patients with histologically confirmed NASH and either prediabetes (49%) or T2DM (51%). Patients were randomly assigned to daily pioglitazone (initially 30 mg, later titrated to 45 mg) or placebo over 18 months, along with dietary counseling (8). Liver biopsies were performed at 0, 18, and 36 months to assess changes in predefined histologic outcomes. At 18 months, patients receiving pioglitazone and those receiving placebo who did not have histologic resolution of NASH were asked to continue or start use of pioglitazone for the next 18 months. The investigators acknowledged several discrepancies in the trial design as reported in ClinicalTrials.gov and in the current article.

Eighty-three (82%) patients completed the first 18 months, and 69 completed the open-label phase (36 months). At 18 months, those receiving pioglitazone were more likely to achieve the primary end point (58% vs. 17%; $P < 0.001$), with higher rates of improvement in the composite NAFLD activity score (NAS) without worsening of fibrosis. Each component of the NAS (steatosis, inflammation, and ballooning) also showed statistically significant improvement, and resolution of NASH was greater than with placebo (51% vs. 19%; $P < 0.001$). Although patients receiving pioglitazone were not statistically significantly more likely to show improvement in fibrosis (39% vs. 25%), a marginally significant change in the mean fibrosis score was observed with pioglitazone compared with placebo (−0.5 vs. 0.0; $P = 0.039$), and pioglitazone reduced fibrosis progression rates compared with placebo (12% vs. 28%; $P = 0.039$). Extending pioglitazone treatment to 36 months did not result in additional histologic improvement beyond that observed after the first 18 months. A similar finding has been reported in a previous rosiglitazone trial (9), suggesting that histologic improvement parallels the initial improvement in insulin sensitivity and plateaus when the insulin-sensitizing effects stabilize (probably in the first 6 months). Discontinuing pioglitazone treatment in patients with NASH, however, has been associated with worsening insulin sensitivity and liver histologic outcomes. Thus, a rationale for long-term treatment may be to reduce fibrosis progression rather than to normalize liver histologic parameters. Although an increase in plasma adiponectin level was correlated with histologic response, the investigators were unable to identify a clear profile of treatment responders. Because only half of the patients receiving pioglitazone had resolution of NASH, the early identification of factors predicting response remains a challenge for future trials.

Although this study aimed to provide recommendations for patients with T2DM, only half of all patients had diabetes at enrollment. Moreover, it did not include an analysis that compared outcomes among diabetic and prediabetic participants. Thus, whether efficacy differs according to the presence of prediabetes or diabetes remains uncertain. Of note, T2DM is associated with a higher risk for advanced fibrosis (bridging fibrosis or cirrhosis), which portends a greater risk for liver decompensation. In Cusi and colleagues' study, 12% of patients had advanced fibrosis; however, it remains unclear whether insulin sensitizers or other therapeutic agents are able to induce regression of fibrosis

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and subsequently improve long-term prognosis in this at-risk group.

Ultimately, patients with NAFLD are more likely to have cardiovascular morbidity than liver decompensation, so it is important to consider the effect of any pharmacologic intervention on cardiovascular risk. Pioglitazone induced significant improvements in most glucose- and lipid-related parameters, including insulin sensitivity, hemoglobin A_{1c} level, triglyceride level, and high-density lipoprotein cholesterol level, despite a modest increase in body weight (mean, 2.5 kg). Of note, no cardiovascular events or deaths were reported during the 3-year trial. Although pioglitazone has a black box warning from the U.S. Food and Drug Administration for cardiac failure, it seems to reduce vascular events in at-risk persons (10), making it appealing for patients with NAFLD.

The study by Cusi and colleagues extends previous observations of the therapeutic benefits of pioglitazone in NASH to include patients with impaired glucose regulation. Unfortunately, use of pioglitazone beyond 18 months did not provide significant additional resolution of fibrosis, but it may retard further progression. Whether physicians should include pioglitazone in the therapeutic arsenal for diabetic patients with NASH is unclear on the basis of this RCT. However, long-term confirmatory studies are unlikely to be performed given the impracticability and risk of serial liver biopsies. We believe that physicians should consider adding pioglitazone to their toolboxes when facing patients with NASH and diabetes, but the primary obstacle to the widespread use of pioglitazone remains its safety profile. Thus, treatment should be considered for patients at the greatest risk (those with NASH and fibrosis) and should be balanced against the common risk for weight gain and the uncommon risks for fracture and heart failure.

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