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CORRESPONDENCE

Pioglitazone in Nonalcoholic Steatohepatitis

TO THE EDITOR: Belfort and colleagues (Nov. 30 issue)[1] report on the efficacy of 6 months of treatment with pioglitazone with respect to the histologic severity of nonalcoholic steatohepatitis. I agree with the authors' conclusion that the results serve as "proof of concept" that pioglitazone leads to histologic improvement in patients with this condition.

These results apply to nonalcoholic steatohepatitis in patients with type 2 diabetes mellitus or impaired glucose tolerance; however, they may not apply to the general population of patients with nonalcoholic steatohepatitis. Indeed, although this condition is frequently associated with obesity and type 2 diabetes, only one third of people with nonalcoholic steatohepatitis have type 2 diabetes.[2-4]

Moreover, it would be interesting to know whether pioglitazone is equally effective in improving the hepatic histologic findings in patients with type 2 diabetes and in those with impaired glucose tolerance. In the study by Belfort and colleagues, information on the exact proportion of patients with type 2 diabetes and of those with impaired glucose tolerance is lacking. Patients with type 2 diabetes have a higher risk of fibrosis and cirrhosis than do patients who do not have diabetes.[2-4] Thus, the efficacy of pioglitazone in reducing the severity of nonalcoholic steatohepatitis might be different among patients with type 2 diabetes than among those with impaired glucose tolerance.

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TO THE EDITOR: The study by Belfort et al. shows a significant effect of pioglitazone, as compared with placebo, for the treatment of nonalcoholic steatohepatitis. However, the average weight reduction was only 0.5 kg over a 6-month period in subjects in the placebo group; this may explain the lack of improvement in indicators of nonalcoholic steatohepatitis in these subjects. Thus, the ineffective diet and exercise program could have led to an overestimation of the effect of pioglitazone. Belfort and colleagues attempt to address this limitation by showing that there was no hepatic histologic improvement in 12 subjects who were assigned to placebo and who lost a mean (±SD) of 3.2±0.5 kg. This sample size may lack the power to detect differences. Also, the authors cite a meta-analysis that reported the variable ef-

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fects of weight reduction in patients with nonalcoholic steatohepatitis; however, the analysis showed consistent improvement in liver measurements after weight reduction.[1] The standard treatment for nonalcoholic steatohepatitis and other obesity-related diseases is weight reduction, achieved through concurrent diet and exercise.[2,3] It is impossible to predict what the real difference would have been if the subjects in the placebo group had lost weight. Future research regarding nonalcoholic steatohepatitis will require comprehensive programs of diet and exercise to estimate accurately the effects of drugs over standard treatment.

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TO THE EDITOR: In their placebo-controlled trial, Belfort et al. show that pioglitazone leads to improvement in subjects with nonalcoholic steatohepatitis by reducing insulin resistance and suppressing cytokine-mediated inflammation. However, it is not clear whether the beneficial effect of pioglitazone occurs through improved insulin sensitivity or its direct antiinflammatory effect on the liver.

Recently we established an animal model of steatohepatitis in which the pathological abnormalities are exacerbated by insulin resistance and obesity-related diabetes.[1] In this model, pioglitazone inhibits the activation of stellate cells, which play a central role in hepatic fibrosis, probably by down-regulating the hepatic expression of transforming growth factor β and inflammatory cytokines. The improvement in the pathological findings as a result of the antiinflammatory effects of pioglitazone on the liver were more striking in obese animals with diabetes than in nonobese animals without diabetes, indicating that the effect of pioglitazone occurs mainly through improved insulin resistance.

Therefore, a larger clinical trial is needed to clarify whether pioglitazone ameliorates the pathological features of nonalcoholic steatohepatitis in patients with and in those without insulin resistance. This point is especially relevant if made-to-order pioglitazone therapy is anticipated for patients with nonalcoholic steatohepatitis.

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THE AUTHORS REPLY: Targher asks about the proportions of patients with type 2 diabetes and of those with impaired glucose tolerance in our study. In the pioglitazone group, 13 patients had impaired glucose tolerance, and 14 had type 2 diabetes. In the placebo group, 12 patients had impaired glucose tolerance, and 9 had type 2 diabetes. We think that the proportion of patients with nonalcoholic steatohepatitis and undiagnosed impaired glucose tolerance or type 2 diabetes is much higher than previously appreciated. In our study, all patients underwent a screening oral glucose tolerance test, and 8 of 23 patients received a new diagnosis of type 2 diabetes this way. Among the other 25 patients with a diagnosis of impaired glucose tolerance ("prediabetes"), none were suspected of having this condition. The histologic scores at baseline and the response to pioglitazone were similar, regardless of whether patients had impaired glucose tolerance or type 2 diabetes. Reducing plasma glucose levels with pioglitazone may be important in order to ameliorate hepatic lipogenesis (i.e., to reduce the activity of hepatic carbohydrate response-element–binding protein[1]). Future studies may determine whether pioglitazone is of greater benefit in patients with impaired glucose tolerance or type 2 diabetes.

We agree with Chavez-Tapia et al. that lifestyle modification and weight reduction are the cornerstones of treatment for both type 2 diabetes and nonalcoholic steatohepatitis. However, we did not compare the effect of weight reduction (in the

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placebo group) with the effect of pioglitazone treatment. The two groups received identical nutritional counseling to reflect the current standards of care. Against this background, we compared placebo with pioglitazone. Our results match those of the clinical-practice and lifestyle-intervention studies that show the difficulties of achieving and maintaining weight loss in patients with nonalcoholic steatohepatitis. In the meta-analysis of 13 trials by Wang et al.,[2] the studies were typically small (only 3 had >50 patients) and uncontrolled (10 were case series), and they frequently used a surrogate primary end point (i.e., liver aminotransferase levels in 8 of the 13 trials); steatosis was the only histologic improvement. As in our placebo group, improvement in aminotransferase levels does not necessarily translate into improved liver histologic scores. Recently, Huang et al.[3] reported a trend toward a histologic benefit but not a significant benefit of a year-long, intense nutritional counseling program in patients with nonalcoholic steatohepatitis. Weight reduction in their study (–2.9 kg) was similar to that in our patients in the diet-plus-placebo group who had a response to the study treatment (–3.2 kg). Moderate weight loss may improve liver histologic results, but long-term controlled trials using histologic results as the primary end point are needed.

As suggested by Ota et al., pioglitazone not only may improve insulin resistance but may have direct antiinflammatory effects on the liver. In our study, pioglitazone ameliorated systemic inflammation by lowering plasma C-reactive protein, tumor necrosis factor α, transforming growth factor β, and intracellular adhesion molecule and vascular-cell adhesion molecule concentrations (unpublished data). Obesity and high-fat diets may activate the hepatic inhibitor of κB kinase β and nuclear factor-κB inflammatory pathways and promote insulin resistance.[4] As Ota and colleagues suggest, more work is needed in this area.

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Bivalirudin in Acute Coronary Syndromes

TO THE EDITOR: The main message of the study of bivalirudin in patients with acute coronary syndromes, reported by Stone et al. (Nov. 23 issue)[1] is that, as compared with heparin or enoxaparin plus a glycoprotein IIb/IIIa inhibitor, bivalirudin alone offers a similar degree of protection against ischemic events and a significant reduction in bleeding complications. Most of the benefit of bivalirudin alone was associated with the lower rate of catheterization-related hemorrhage (0.8% with bivalirudin alone vs. 2.5% in the other two groups). Given the importance of bleeding complications for the interpretation of the results, it is surprising that no details on the arterial access used during the trial were provided, although the numbers reported suggest a predominant use of the transfemoral approach. If this is true, considering that severe local arterial complications are rare when the radial artery is used for diagnostic or interventional procedures,[2,3] probably little or no benefit should be expected from bivalirudin in the setting of transradial catheterization. We still need better antithrombotic strategies for high-risk acute coronary syndromes, but the reduction of vascular complications is best accomplished by a wider application of the transradial technique.

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