

Insulin Sensitizer Effective, Less Edema

The side-effect profile is the main barrier with regard to thiazolidinedione therapy.

BY CONNI BERGMANN KOURY, EDITOR-IN-CHIEF

The non-thiazolidinedione (TZD) insulin sensitizer metaglidase significantly reduced HbA1c – comparable to that of TZD agents – and without weight gain or edema.

“If this profile is confirmed in phase 3 trials, metaglidase (Metabolex Inc) would represent a very useful addition to the diabetes armamentarium. I believe that further studies are clearly warranted,” said Julio Rosenstock, MD, at the American Diabetes Association 65th Annual Meeting and Scientific Sessions in San Diego. Dr. Rosenstock is a clinical professor of medicine at the University of Texas Southwestern Medical Center in Dallas.

Dr. Rosenstock presented data from a 3-month, multicenter, randomized phase 2 trial that evaluated 200- and 400-mg doses of the agent in type 2 diabetic patients who were already on insulin therapy. The primary objective was to assess metaglidase's effect on glycemic control. Fasting plasma glucose, lipid profiles, body weight and edema comparisons were secondary objectives.

BETTER SIDE-EFFECT PROFILE NEEDED

Glitazones have demonstrated efficacy both alone and in combination with oral agents or with insulin in type 2 diabetes. TZDs enhance insulin therapy and cause a reduction in HbA1c ranging from 0.8% to 12%. Often, the reduction is despite the reductions in insulin requirements. “However, weight gain and fluid retention remain the major side-effect barriers with the current TZDs,” he said. “These side effects are more prominent when used in combination with insulin therapy. Therefore, effective insulin sensitizers with better side-effect profiles on weight gain and edema remain an important, unmet need.”

Metaglidase has been shown to enhance insulin mediated GLUT4 translocation and lower glucose in diabetic models. It is a PPAR gamma partial agonist and mainly antagonist, without the PPAR alpha or delta activity, he said. In experimental models, it does not promote weight gain, fluid retention, cardiomegaly or lipogenesis.

The 217 patients studied were randomized to metaglidase 200 mg/day, 400 mg/day or placebo. Patients were sta-

bilized for between 2 to 4 weeks, with a maximum time in the trial of 4 months and a drug exposure of 3 months.

“The primary endpoint was HbA1c, and weight gain and edema were captured carefully throughout the study,” Dr. Rosenstock said. The two dosages were tested versus placebo, and the patients were seen every 2 weeks. Groups were well balanced in terms of baseline demographics including BMI, HbA1c, fasting plasma glucose and diabetes duration.

REDUCING HBA1C

Dr. Rosenstock reported a statistically significant HbA1c reduction in patients taking both doses of metaglidase compared with the placebo group taking only insulin (0.9% and 1.0% from baseline for metaglidase 200 mg and 400 mg, respectively, and 0.3% for placebo, $P=.002$).

There was a statistically significant dose-dependent decrease in fasting blood glucose. The decrease in patients taking 400 mg dose versus placebo was 41 mg/dL ($P=.005$).

Dr. Rosenstock reported a 21% reduction in triglyceride levels in patients taking the 400-mg dose of metaglidase versus placebo. There was also statistically significant dose-dependent increase in adiponectin levels in patients taking metaglidase 200 mg ($P=.018$) and 400 mg ($P<.001$) compared with placebo.

Weight gain was basically neutral, Dr. Rosenstock said and there was no increase in the incidence of edema associated with metaglidase (incidence of edema; 11.0% for 200 mg and 7.2% for 400 mg vs 20% for placebo group; $P=.037$; two-sided trend test).

“An effective medication with a better clinical safety profile would be a real advance for people with diabetes, helping them adhere to and benefit from their therapy,” Dr. Rosenstock said in a company news release. ■

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Rosenstock J, Flores-Lozano F, Schwartz S, et al. A novel non-TZD insulin sensitizer that improves glycemic control without causing edema or weight gain in patients with T2DM. Presented at the American Diabetes Association 65th Scientific Sessions, June 10-14, 2005, San Diego.