Novel FFAR1 Agonist Reduced HbA_{1c} in Type 2

BY SHARON WORCESTER

FROM THE LANCET

The oral, highly potent, and selective free fatty acid receptor 1 agonist TAK-875 significantly improved glycemic control in patients with type 2 diabetes without increasing treatment-emergent hypoglycemic events in a phase II, randomized controlled trial comparing TAK-875, glimepiride, and placebo.

Activation of free fatty acid receptor 1 (FFAR1), also known as G-protein–coupled receptor 40, has been shown in preclinical studies to stimulate glucose-dependent beta-cell insulin secretion. The current findings show that it is a potential therapeutic target in the treatment of type 2 diabetes, Dr. Charles F. Burant of the University of Michigan, Ann Arbor, and his colleagues reported.

At weeks 4, 8, and 12 of treatment, all of the 303 patients who were randomized to receive treatment with TAK-875 at doses ranging from 6.25 to 200 mg once daily, as well as all of the 62 patients randomized to receive treatment with 4-mg glimepiride (a sulphonylurea that acts as an insulin secretagogue) once daily, achieved significant least-squares mean reductions from baseline in hemoglobin A_{1c}, compared with the 61 patients randomized to a placebo group. At 12 weeks, mean reductions in the TAK-875 group ranged from 0.65 percentage points with the 6.25-mg dose to roughly 1.0 percentage point with the 50-mg and higher doses; in the glimepiride group, the mean reduction was 1.05 percentage points, compared with 0.13 in the placebo group, the investigators said (Lancet 2012 Feb. 27 [doi:10.1016/S0140-6736(11)61879-5]).

Only the decrease in the 6.25-mg TAK-875 group was significantly smaller than that in the glimepiride group, they noted.

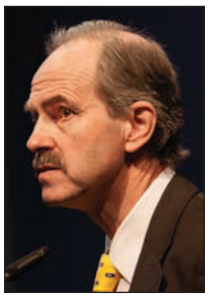
Additionally, the percentage of patients reaching the American Diabetes Association target of HbA_{1c} less than 7.0% by 12 weeks was generally similar in the 25- to 200-mg TAK-875 and glimepiride groups, and changes, relative to the placebo group, were significant, they said.

About 2% and 3% of the TAK-875 pa-

VIEW ON THE NEWS

Durability Questioned

The findings by Dr. Burant and colleagues promise to raise many questions about the potential of TAK-875 in the treatment of type 2 diabetes, according to Dr. Clifford J. Bailey.



FFAR1 agonists are "different and interesting" in that they may be capable of restricted initiation of insulin secretion, and "will mainly potentiate nutrient-induced insulin secretion, which will favor enhanced prandial insulin secretion and reduce the risk of interprandial hypoglycemia," Dr. Bailey wrote in an editorial accompanying the report.

However, among the varied matters that must be addressed are durability of stimulatory effects, impact on insulin resistance, and safety, he noted (Lancet 2012 Feb. 27 [doi: 10.106/S0140-6736(12)60165-2]).

"The question of durability looms large over insulin-releasing pharmacotherapies. The stimulatory effect of sulphonylureas seems to wear off and restrict long-term efficacy in many patients," he said.

DR. BAILEY *is with Aston University in Birmingham, England, and Birmingham Children's Hospital. He disclosed relationships with Bristol-Myers Squibb, AstraZeneca, Merck Sharp & Dohme, Novo Nordisk, GlaxoSmithKline, Sanofi-Aventis, and Prosidion.*

VITALS

Major Finding: At weeks 4, 8, and 12, all of the 303 patients randomized to receive treatment with TAK-875 at doses ranging from 6.25 to 200 mg once daily, as well as all of the 62 patients randomized to receive 4 mg of glimepiride once daily, achieved significant mean reductions from baseline in HbA_{1c}, compared with placebo.

Data Source: A phase II, randomized, double-blind, placebo- and active comparator–controlled trial.

Disclosures: The study was sponsored by Takeda Global Research and Development, for which Dr. Burant serves as an unpaid consultant and adviser. All other study authors are employed by the company.

tients and the placebo patients, respectively, experienced treatment-emergent hypoglycemic events during treatment, compared with 19% of the glimepiride patients, and the events were mild to moderate in intensity in all groups. This finding suggests a therapeutic advantage of agents targeting FFAR1, compared with sulphonylureas, which are associated with frequent occurrence of hypoglycemia.

The percentage of patients with treatment-emergent adverse events that were determined by the investigators to be related to the study drug was lowest in the TAK-875 patients (7%, compared with 11% in the placebo group and 23% in the glimepiride group).

Participants in this double-blind study were outpatient adults aged 18-80 with type 2 diabetes who had not responded to either an 8-week diet and exercise plan or to metformin treatment and who were enrolled during November 2009–September 2010 at 95 sites in the United States, Mexico, and Guatemala. Baseline characteristics were similar in all groups.

After a 2-week, single-blind, placebo run-in period, the patients were treated for 12 weeks, followed by a 2-week follow-up period.

The fact that a significant change in HbA_{1c}, as compared with placebo, was apparent at 4 weeks after treatment initiation with all doses of TAK-875 suggests a rapid onset of action. ■