Saxagliptin Aids Type 2 Disease Glucose Control

BY MIRIAM E. TUCKER
Senior Writer

WASHINGTON — Once-daily saxagliptin added to metformin resulted in statistically significant reductions in hemoglobin A_{1c}, fasting plasma glucose, and postprandial glucose levels for up to 24 weeks in a placebo-controlled trial involving 743 patients with type 2 diabetes who were inadequately controlled with metformin alone.

Results of the multicenter phase III study were reported in a poster at the annual meeting of the American Association of Diabetes Educators by Dr. Shoba Ravichandran, an endocrinologist with Bristol-Myers Squibb, and Laureen MacEachern, director of scientific communications for the company. Saxagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor jointly developed by Bristol-Myers Squibb and AstraZeneca PLC, which cosponsored the study.

Significant reductions in HbA_{1c} and fasting plasma glucose were seen with all the saxagliptin doses, but the maximal benefit occurred at 5.0 mg/day.

At baseline, the patients had a mean diabetes duration of 6.5 years, mean hemoglobin A_{1c} of 8.0%, fasting plasma glucose of 176 mg/dL, and 2-hour postprandial glucose of 286 mg/dL.

All of the patients were on stable doses of metformin—between 1,500 and 2,550 mg/day—for at least 8 weeks prior to the study, and remained on the same dosage during the study. They were randomized to one of four groups: saxagliptin in daily doses of 2.5, 5, or 10 mg, or placebo.

The investigators found statistically significant reductions in both HbA_{1c} and fasting plasma glucose (FPG) were seen with all the saxagliptin doses, but the maximal benefit occurred with the 5.0-mg/day dose.

At week 24, placebo-corrected mean reductions from baseline in HbA_{1c} were 0.73, 0.83, and 0.72 percentage points for the 2.5-, 5-, and 10-mg/day doses, respectively. Placebo-corrected FPG was reduced from baseline by 16, 23, and 22 mg/dL, respectively.

Reductions in FPG were observed as early as week 2, Dr. Ravichandran and Ms. MacEachern said.

The investigators also reported significant placebo-adjusted reductions in 2-hour postprandial glucose levels from baseline—44, 40, and 32 mg/dL, for the 2.5- 5-, and 10-mg doses, respectively. Saxagliptin did not have a significant impact on body weight, with mean reductions from baseline at week 24 of 1.4, 0.9, and 0.5 kg, respectively, and of 0.9 kg in the placebo group.

Saxagliptin was generally well-tolerated. A total of 74% of patients in the three treatment groups and 65% of the placebo group reported at least one adverse event, including nasopharyngitis in 9% of the saxagliptin patients and 8% of the placebo group, headache in 8% vs. 7%, and diarrhea in 7% vs. 11%, respectively.

The incidence of hypoglycemia was similar in the saxagliptin plus metformin–treated patients (5.7%) and the placebo plus metformin patients (5.0%).

Events of hypoglycemia that were confirmed by a fingerstick glucose value of 50 mg/dL or less were 0.5% for the saxagliptin groups and 0.6% with placebo, the investigators reported.

In July, Bristol-Myers Squibb and AstraZeneca announced the submission of a New Drug Application to the U.S. Food and Drug Administration and validation of a Marketing Authorization Application to the European Medicines Agency for saxagliptin under the proposed trade name Onglyza. ■

One-Hour Glucose Concentration May Help Predict Type 2 Diabetes

BY NANCY WALSH
New York Bureau

A 1-hour plasma glucose concentration higher than 155 mg/dL measured during an oral glucose tolerance test, plus the presence of the metabolic syndrome, strongly predicts future risk for type 2 diabetes in subjects with normal glucose tolerance, according to the results of a large population-based epidemiologic study.

Reliable models for identifying people at risk for the development of type 2 diabetes are essential, because lifestyle changes and pharmacologic interventions can reduce the likelihood that the disease will develop, according to the study, which was published in Diabetes Care.

Models for identifying people at risk are essential because lifestyle changes and interventions can reduce the likelihood of the disease developing.

The researchers used a classification tree model that can stratify risk for nondiabetics with risk factors such as obesity, dyslipidemia, and hypertension based on their 1-hour glucose concentration. The model was previously demonstrated to be a better predictor for future type 2 diabetes than fasting plasma glucose or the 2-hour plasma glucose concentration, according to Dr. Muhammad A. Abdul-Ghani and colleagues in the divisions of diabetes and epidemiology, University of Texas Health Science Center at San Antonio.

They tested the model in a study population of 1,611 adults from the population-based San Antonio Heart Study. All patients had oral glucose tolerance tests at baseline and again at follow-up, 7-8 years later.

None had diabetes at baseline, but 90 had impaired fasting glucose (IFG), 220 had impaired glucose tolerance (IGT), and 51 of the 220 with IGT also had IFG and were designated as having combined glucose intolerance (CGI).

During the 7- to 8-year follow-up period, the conversion rate to diabetes was 5% for those who had normal glucose tolerance at baseline, 26.1% for those with IFG, 30.9% for those with IGT, and 82.3% for those with CGI.

Patients were partitioned in the classification tree according to whether their 1-hour plasma glucose concentration was above or below 155 mg/dL, and stratified as being at low risk for future diabetes, with an annual risk below 0.5%; at intermediate risk, with an annual risk of 1-2%; or at high risk, with an annual risk greater than 4%.

Analysis revealed that in patients with normal glucose tolerance, the annual risk for future type 2 diabetes was significantly higher, at 2.2%, in those whose 1-hour plasma glucose concentration was higher than 155 mg/dL, than for those with concentrations below this level, whose risk was 0.39% per year.

For those with normal glucose tolerance whose glucose concentration was higher than 155 mg/dL and who also had metabolic syndrome, the annual risk was very high, at 4.3%.

Their odds ratio for developing diabetes, at 15.2, is double that of patients with IGT whose 1-hour plasma glucose is below 155 mg/dL. "This group of high-risk individuals [with normal glucose tolerance] could benefit from an intervention program employing diet, exercise, and pharmacotherapy (metformin) to reduce future risk for diabetes," Dr. Abdul-Ghani and colleagues wrote (Diabetes Care 2008;31:1650-5).

The investigators also noted that their model is better at predicting risk than is the American Diabetes Association criteria of IGT or IFG. "About 17% of normal glucose–tolerant subjects, who have immediate and high risk for future type 2 diabetes and who were identified with the 1-h plasma glucose plus metabolic syndrome, would have been missed with the American Diabetes Association criteria alone," they wrote. ■

Hypoglycemia Can Induce Visual Disturbances in Diabetes

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

SAN FRANCISCO — Visual disturbances—including blurred vision, floaters, central scotoma, and even complete loss of vision—can be a symptom of hypoglycemia in some patients with diabetes, according to Dr. Mukhtar Khan.

Although not all those with diabetes experience visual disturbances during a hypoglycemic event, those who are susceptible might experience two or more, which resolve soon after blood glucose stabilizes, Dr. Khan wrote in a poster presented at the annual meeting of the Endocrine Society.

"Most clinicians are usually concerned about hyperglycemia and its effects," he said in an interview. "It is also important to keep the effects of hypoglycemia in mind, especially the visual effects, as these can have devastating consequences in diabetic patients in situations such as operating a motor vehicle."

His observational study enrolled 40 patients with diabetes (mean age 46 years) who had a history of visual symptoms during hypoglycemic episodes. Most of the patients (26) had type 1 diabetes; the rest had type 2 diabetes. Nineteen were on insulin pumps, while 21 were on various insulin regimens, including glargine, lispro, aspart, and mixed regimens.

For most of the patients (57%), visual symptoms occurred when blood glucose dropped to 30-50 mg/dL. For 25%, symptoms occurred at a glucose level of 51-65 mg/dL, while a minority (10%) experienced them at a level of 66-80 mg/dL. The remaining patients were unable to document their blood glucose level at the onset of visual symptoms.

Blurred vision was the most commonly reported symptom (77%). About half of the group (47%) reported seeing floaters. Dimming of vision occurred in 37%; central scotoma (a black spot or "hole" in the central visual field) in 32%; and double vision in 22%. A few patients (5%) reported a complete loss of vision during hypoglycemia. Most (67%) reported more than one symptom during the episode.

The visual disturbances resolved after blood glucose stabilized, Dr. Khan said. "After hypoglycemia correction, the symptoms resolved within 5-15 minutes in 16 subjects; 20-30 minutes in 17 subjects; and 35-90 minutes in three subjects. Two subjects, who experienced a complete loss of vision at a blood glucose level in the 30- to 40-mg/dL range, reported gradual resolution of visual symptoms in 180 minutes and 300 minutes after improvement in the glucose level."

Two patients did not report the time to resolution of their symptoms, noted Dr. Khan of the State University of New York, Syracuse.

"Patients with diabetes should be counseled about recognition and early management of visual effects of hypoglycemia," Dr. Khan said. "Prevention of hypoglycemia should be given as much importance as hyperglycemia during management of diabetes." ■

Pages 12a—12b