Sitagliptin Performs Well in Early Studies

Novel compound significantly reduces glucose and is well tolerated in patients with type 2 diabetes.

BY MIRIAM E. TUCKER
Senior Writer

SAN DIEGO — The novel investigational compound sitagliptin significantly lowers glucose levels and is well tolerated in patients with type 2 diabetes, three investigators reported in separate presentations at the annual scientific sessions of the American Diabetes Association.

Sitagliptin, manufactured by Merck & Co., appears to work by inhibiting the enzyme dipeptidyl peptidase IV (DPP-IV), which inactivates the incretin gut hormones glucagonlike peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The two peptides, normally released by the gut after a meal, enhance insulin secretion, while GLP-1 also inhibits glucagon secretion. Inhibition of DPP-IV activity increases the active concentration of these hormones, thereby enhancing their glucose-lowering action.

Unlike some of the new agents that mimic the action of GLP-1, sitagliptin is orally active and in these trials did not appear to be associated with increased gastrointestinal side effects, said Ronald L. Brazg, M.D., of Rainier Clinical Research Center, Renton, Wash.

Russell Scott, M.D., Ph.D., reported data from the largest of three randomized, double-blind, placebo-controlled phase II studies presented at the meeting. In the dose-finding study, 743 patients with type 2 diabetes aged 21-76 years were taken off all other medications and randomized to 5 mg, 12.5 mg, 25 mg, or 50 mg of sitagliptin twice daily; glipizide 5-20 mg twice daily; or placebo. At baseline, the subjects had a mean hemoglobin A_{1c} level of 7.9%, with 21% having an A_{1c} level of 7.0% or lower.

At week 12, there were statistically significant dose-dependent reductions in A_{1c} level, compared with the placebo group, in all sitagliptin dose groups, ranging from a 0.38 percentage point drop with 5 mg twice daily to a 0.77-point drop with 50 mg twice daily. The reduction in the glipizide group—the dose was titrated up every 2 weeks as needed—was 1.0 percentage point. Similarly, 2-hour fasting plasma glucose (FPG) levels fell in a dose-dependent manner, with reductions ranging from 35.0 mg/dL to 54.2 mg/dL in the four sitagliptin groups. Glipizide reduced FPG level by 72.1 mg/dL, reported Dr. Scott, professor of medicine and director of the lipid and diabetes research group at Christchurch Hospital and School of Medicine, New Zealand.

There were no changes in weight with sitagliptin or placebo, compared with a mean 1.1-kg weight gain at week 12 with glipizide. Hypoglycemia occurred in 0%-4% of the sitagliptin groups and 2% of the placebo group, compared with 17% of those taking glipizide. Gastrointestinal adverse events occurred in 8%-17% with sitagliptin, 12% with placebo, and 14% with glipizide.

In a small second study, 28 patients who were already taking 1,500 mg/day or more of metformin were randomized to receive 50 mg of sitagliptin twice daily or placebo. The study was originally designed to have two 4-week crossover periods. However, because the patients who received sitagliptin during the first 4 weeks didn't return to baseline after the end of the second 4 weeks in which they received placebo, Dr. Brazg presented only the results from the first 4 weeks.

Over a 24-hour period, the weighted mean glucose level in the sitagliptin plus metformin group was 125 mg/dL, compared with 158 mg/dL for placebo plus metformin, a mean reduction of 33 mg/dL. The difference in FPG levels—128 vs. 149 mg/dL—also was highly significant, even though those values were not markedly elevated to begin with.

There were no clinically meaningful changes in body weight, in hepatic or muscle enzymes, or in any laboratory parameters, he said.

The third study was presented in a poster by Gary Herman, M.D., of Merck Research Laboratories, Rahway, N.J., and his associates. Here, 552 patients aged 30-74 years with a mean baseline A_{1c} level of 5.8%-10.4% (29% had levels of 7% or less) and mean FPG level of 130 mg/dL or higher were randomized to sitagliptin 25 mg, 50 mg, or 100 mg once daily; sitagliptin 50 mg twice daily; or placebo. Patients who had been taking other oral hypoglycemics underwent a washout period.

At week 12, there were significant mean reductions in A_{1c} level in all treatment groups, compared with the placebo group, ranging from 0.39 percentage points for 25 mg twice daily to 0.56 points for 100 mg once daily.

In an analysis with the last observation carried forward, the differences were greatest in those with the highest A_{1c} levels at baseline, with a reduction of 0.82 percentage points with the 100 mg/day dose for those with baseline A_{1c} values of 8.5% or higher, compared with a 0.37-point drop among those who started out at less than 7%. Similarly, reductions in FPG level, compared with placebo, ranged from 11.0 mg/dL with 25 mg twice daily to 17.2 mg/dL with 100 mg once daily, Dr. Herman and his associates reported.

There were no clinically significant treatment-related trends in clinical or laboratory adverse events or test abnormalities, nor any differences in vital signs or other physical findings. One hypoglycemic event occurred in each sitagliptin group, with none reported in the placebo group.

Phase III trials of sitagliptin are underway, according to a Merck statement. ■

Lipid Levels Flag Future Risk of Type 2 Diabetes in Heart Patients

BY MITCHEL L. ZOLER
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NEW YORK — Three lipid measures were strong predictors of the future risk of type 2 diabetes in a study of 362 patients who were assessed prior to undergoing coronary angiography.

High serum levels of triglycerides, low levels of HDL cholesterol, and a small size of LDL cholesterol particles all identified patients who had an increased risk of developing type 2 diabetes during 4 years of follow-up, Christoph H. Saely, M.D., reported at an international symposium on triglycerides and HDL.

High serum levels of triglycerides, low levels of HDL cholesterol, and a high level of small LDL cholesterol particles identified an increased diabetes risk.

Because of this link with a bad clinical outcome, these lipid markers may be useful for identifying patients who stand to gain the most from lifestyle modifications, said Dr. Saely, a physician at the Vorarlberg Institute for Vascular Intervention and Treatment in Feldkirch, Austria. The lipid markers may also be able to flag patients who warrant frequent surveillance of their glucose tolerance.

The study involved patients without diabetes who were scheduled for coronary angiography because of suspected coronary artery disease. At baseline, 172 of the patients had a normal fasting glucose level of less than 100 mg/dL; the remaining 190 patients had impaired fasting glucose, defined as a level of at least 100 mg/dL.

During 4 years of follow-up, incident type 2 diabetes was diagnosed in 15 patients. Thirteen of these cases had impaired fasting glucose at baseline. In a multivariate analysis, patients with impaired fasting glucose had a 5.5-fold increased risk of developing type 2 diabetes compared with those who had normal fasting glucose levels.

An additional multivariate analysis showed that patients who had an elevated level of serum triglycerides at baseline had a 2.5-fold increased risk of developing type 2 diabetes, compared with those who did not have elevated triglycerides. Patients with a low level of HDL cholesterol at baseline also had a 2.5-fold increased risk of developing type 2 diabetes, and patients with a high level of small, dense LDL particles also had a 2.5-fold higher risk of developing type 2 diabetes.

All three analyses evaluated these lipid measures as continuous variables. As a result, the study was unable to identify a particular cutoff value that defined high triglyceride level, low HDL cholesterol level, or a high level of small LDL particles, Dr. Saely said at the symposium, sponsored by the Giovanni Lorenzini Medical Foundation.

These lipid measures probably flag patients at high risk of developing type 2 diabetes because they identify patients who either have or soon develop metabolic syndrome, Dr. Saely told this newspaper. But he cautioned that the epidemiologic relationships seen in this study can only be applied with confidence to similar groups of patients: those who are suspected of having coronary artery disease and are scheduled to undergo coronary angiography. ■

GERD Symptoms Highly Prevalent In Patients With Type 2 Diabetes

SAN DIEGO — The prevalence of gastroesophageal reflux disease symptoms in patients with type 2 diabetes is more than twice what is seen in the normal adult population, and appears to be especially high in patients with diabetic neuropathy.

Khushbu Chandrarana, M.D., and her associates conducted a prospective study of 150 patients aged 18 to 82 years with type 2 diabetes. The participants had not been diagnosed with other conditions, such as angina, that might explain gastroesophageal reflux disease (GERD)–type symptoms.

Patients with a GERD diagnosis prior to onset of their diabetes were not included in the study, which was presented as a poster at the annual meeting of the Endocrine Society.

A questionnaire given to eligible consecutive patients targeted the five most common symptoms of GERD: heartburn at least once a week, hoarseness, chronic cough, chest pain, and regurgitation.

A total of 40% of patients reported at least 1 GERD symptom and 30% reported having heartburn at least weekly. The prevalence of weekly heartburn in U.S. adults is 14%, said Dr. Chandrarana, a resident in the divisions of endocrinology and gastrointestinal medicine at Saint Peter's University Hospital, New Brunswick, N.J.

Among 46 patients with neuropathy, 27 (59%) reported GERD symptoms, compared with 34 of 104 diabetic patients (33%) who did not have neuropathy.

"Since experience of heartburn is likely to be blunted by neuropathy, the actual incidence of GERD may be even higher," Dr. Chandrarana noted.

She encouraged physicians to be sensitive to the possibility that their patients with diabetes might also have GERD, a treatable disease.

The connection makes sense, she said, since the pathophysiology of GERD involves delayed gastric emptying, which is also a common complication of diabetes with neuropathy.

—Betsy Bates

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