Glucagon Receptor Blockers Eyed for Type 2

BY MIRIAM E. TUCKER

FROM THE ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES

LISBON – New data on two investigational glucagon receptor antagonists suggest that this novel class of drugs has potential to be an effective treatment for type 2 diabetes, but only if safety can be established, according to two presentations at the meeting.

Both Merck's MK-0893 and Lilly's LY2409021 work by suppressing glucagon action via receptor blockade. Dr. Samuel S. Engel, senior director of clinical research, diabetes, and endocrinology, at Merck presented phase II study data on the efficacy and safety of MK-0893 in combination with metformin or sitagliptin in 146 patients with type 2 diabetes, and Dr. Melvin J. Prince, senior director of medical diabetes and endocrinology at Lilly, presented phase I dose-finding data on LY2409021 in 47 patients.

Both agents produced statistically significant reductions in hemoglobin A_{1c}. However, both also produced small but significant elevations in liver enzymes, and both carry the theoretical potential for hypoglycemia and hyperglucagonemia. "There is definitely potential for the glucagon receptor antagonists in diabetes, but there is also a risk of hypoglycemia associated with them. Also, it has been noted in the past that the hyperglucagonemia that results when the alpha cells overproduce glucagon has led to pancreas tumors in animal studies, so that's a risk," session moderator Dr. Finbarr O'Harte, professor of endocrinology and metabolism at the University of Ulster, Derry (Northern Ireland), said in an interview.

In June at the American Diabetes Association's annual scientific sessions, Dr. Engel presented data from a phase II study in which 342 type 2 diabetes patients were randomized to once-daily MK-0893 in four different dosages, metformin 1,000 mg twice daily, or placebo. At 12 weeks, treatment with MK-0893 resulted in significant, dose-dependent reductions in fasting plasma glucose, ranging from 32 mg/dL with a 20-mg dose to 63 mg/dL with 80 mg, from a baseline of 180-193 mg/dL. Metformin reduced FPG by 37 mg/dL, and placebo by just 2 mg/dL from baseline. For HbA_{1c}, reductions at 12 weeks ranged from 0.6-1.5 percentage points, versus 0.8 percentage points with metformin and 0.5 with placebo.

The current study evaluated 40 mg/day MK-0893 in combination with 2,000 mg/day metformin or 100 mg/day sitagliptin, as well as 100 mg of sitagliptin plus 2,000 mg of metformin. The 146 patients had a mean age of 53 years, HbA_{1c} of 8.6%, and mean diabetes duration of 7 years. The MK-0893/metformin combination was superior to sitagliptin/metformin in lowering 24-hour weighted mean glucose, with a reduction of 117 mg/dL compared with 85 mg/dL. However, MK-0893/sitagliptin was significantly less effective than sitagliptin/metformin, which produced a 24-hour WMG reduction of 100 mg/dL. This could be because sitagliptin, a DPP-4 inhibitor, also suppresses glucagon and so there could be a threshold effect, Dr. Engel noted.

All treatments were equally well tolerated. However, there was a significantly higher incidence of diarrhea in the two MK-0893 groups (10% vs. 0%). Also, the liver enzymes alanine transaminase (ALT) and aspartate aminotransferase (AST) were elevated in the MK-0893/metformin group, and total cholesterol and LDL cholesterol were increased from baseline with MK-0893/sitagliptin, relative to reductions with MK-0893/metformin and sitagliptin/metformin, he reported.

In the phase I dose-ranging study of LY-2409021, 47 patients were randomized to one of four doses or metformin. Patients had a mean baseline fasting blood glucose of 148 mg/dL, and a baseline HbA_{1c} of 8.0%. By day 28, mean reductions in HbA_{1c} were statistically significant compared with baseline in all treatment groups, ranging from 1.02 percentage points with 60 mg to 0.69 percentage points with 5 mg. In the placebo group, HbA_{1c} dropped by 0.49 percentage points, Dr. Prince reported.

Fasting glucagon significantly increased by 0.6- to 4.2-fold compared with baseline across the LY dose levels, and fasting active glucagon-like peptide-1 (GLP-1) rose by 59% at the highest dose. Glucagon and GLP-1 returned to baseline levels during follow-up, he said.

The agent was generally well tolerated. Reversible elevations in hepatic transaminases were seen in five of nine patients in the highest-dose group, with no clinical signs or significant elevations in bilirubin or alkaline phosphatase, he reported. In the interview, Dr. O'Harte said that these two agents seem to have already exceeded expectations. "We need toxicity studies, but there's a possibility for a breakthrough, I hope."

Dr. Engel is an employee of Merck, and Dr. Prince is an employee of Lilly. Dr. O'Harte stated that he had no disclosures. ■

Device Mimics Bariatric Surgery's Antidiabetic Effects

BY SARA FREEMAN

FROM THE ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES

LISBON – Improved glucose parameters, substantial weight loss, and increased incretin hormone levels can be achieved by the insertion of a novel, minimally invasive, intestinal device in obese patients with type 2 diabetes.

The use of a duodenal-jejunal bypass liner (DJBL) not only improves hemoglobin A_{1c} and aids weight loss, but also appears to increase levels of glucagon-like peptide (GLP)-1 and peptide YY while in place, according to the findings of a small study presented at the meeting.

Although the effects may be temporary, they could offer patients a reversible alternative to bariatric surgery that helps to kick-start weight loss and self-management of diabetes, said study author Dr. Charlotte de Jonge of Maastricht University in the Netherlands. "Not all patients want [bariatric] surgery, as it is permanent."

She added that the DJBL was perhaps "an easy first step" and that patients could perhaps still opt for weight-loss surgery later on or be retreated with the device to the point that medication was again sufficient to help manage their diabetes.

The DJBL (EndoBarrier) is a 60-cm impermeable sleeve that is inserted and removed endoscopically, and which effectively blocks the duodenum and proximal jejunum in a manner similar to the Roux-en-Y-gastric bypass procedure. It is thought to work by creating a physical barrier between ingested food and the intestinal wall, and perhaps alters the activation of incretin hormones in the gut. On average, the device can be inserted in 20 minutes and removed in 10 minutes, under conscious sedation, which allows the patient to go home the same day as the procedure.

The aim of the 17-patient study was to investigate the possible mechanisms for the improvement in diabetic parameters after insertion of the DJBL seen in previous studies. Fourteen men and three women participated, all of whom had type 2 diabetes and a body mass index in excess of 30 kg/m^2. All ate a low-calorie diet during the study, which restricted their intake to 1,200-1,500 kcal per day. Participants consulted a nutritionist every month, but the diet was not prescriptive.

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The EndoBarrier is a 60-cm sleeve that blocks the duodenum and proximal jejunum.

Before implantation of the device, subjects underwent a meal tolerance test that involved a 12-hour fast, then ingestion of a 500-kcal liquid meal and blood sampling at baseline and at 10-, 20-, 30-, 60-, 90-, and 120-minute intervals. HbA_{1c}, glucose, insulin, GLP-1, and PYY concentrations were measured. Measurements were repeated before removal of the device, and again 1 week after removal of the device.

The DJBL was left in place for 24 weeks, although Dr. de Jonge noted that the device could be used for up to 2 years in some patients. About 500 patients have received the device in clinical studies, she said in an interview. It has received approval for use in a few European countries and Australia. It remains investigational in the United States.

Within 1 week after implantation, fasting and area under the curve (AUC) glucose concentrations were improved (11.4±0.5 mmol/L vs. 8.9±0.4 mmol/L and 1,999±88 vs. 1,535±53), respectively. In addition, AUC concentrations of GLP-1 increased from 2,584 at baseline to 4,112 at removal and PYY from 4,440 to 6,448. All differences were statistically significant.

When the device was removed at 6 months, a significant mean weight loss of 13 kg had been recorded, with a mean loss of excess weight of 30%, said Dr. de Jonge. Importantly, mean HbA_{1c} decreased from 8.4% at baseline to 7.0% at removal and there was a reduction in the use of antidiabetic medication in all but one of the study participants. All these difference were highly significant.

"Interestingly, GLP-1 and GIP [glucose-dependent insulinotropic peptide] not only have an effect on insulin, but they also affect glucagon as well," Dr. de Jonge reported during her presentation. There was a normalization of the glucagon response during treatment with the DJBL to a more physiological response.

Almost all patients reported increased satiety, she added.

Commenting on the presentation, Dr. Roy Taylor, professor of medicine and metabolism at the University of Newcastle (U.K.), noted that it would be useful to know what the effects of diet alone were and to see the relationship to the other changes in parameters shown.

In an interview, Dr. de Jonge noted that other data had suggested the weight loss achieved by diet alone was around 4-5 kg, so there did appear to be a greater weight loss effect when the DJBL was inserted.

With regard to side effects, the most common adverse events were abdominal discomfort, including epigastric pain and nausea. Such events were more common in the first 1-2 weeks, but tended to resolve with longer duration of use. There was no withdrawal of the device, and Dr. de Jonge noted that even when patients reported side effects, they were loath to have it removed.

"What we hope is that we can encourage lifestyle changes and we can motivate patients to remain at a lower weight," Dr. de Jonge observed.

GI Dynamics funded the study. Dr. de Jonge and Dr. Taylor reported having no conflicts of interest. ■