Liraglutide Improves Glucose Control in Type 1 Diabetes

BY KERRI WACHTER

FROM THE ANNUAL MEETING OF THE ENDOCRINE SOCIETY

BOSTON – Use of the type 2 medication liraglutide helped control glycemic oscillations in type 1 diabetes, significantly lowered hemoglobin A_{1c} levels, and was associated with weight loss, a small study has shown.

The net effect is not only an improvement in mean fasting and weekly glucose concentrations, but also "you have a remarkable effect on the oscillations of glucose," seen among type 1 diabetic patients, Dr. Paresh Dandona said at the meeting.

VITALS

Major Finding: Eight patients who continued liraglutide treatment for 24 weeks lost a significant amount of weight, down from a mean of 68 kg to 63.5 kg. Mean hemoglobin A_{1c} also dropped significantly from 6.5% to 6.1%. Mean basal insulin dropped by 48%, and mean bolus dropped by 42% as well.

Data Source: A prospective study of 14 patients with type 1 diabetes; eight patients were treated for a total of 24 weeks.

Disclosures: Two of the authors have significant financial relationships with several pharmaceutical companies, but not with Novo Nordisk, the makers of liraglutide. The remaining authors, including Dr. Varanasi, reported that they have no relevant financial disclosures.

Liraglutide (Vitoza), made by Novo Nordisk, is a glucagonlike peptide-1 (GLP-1) receptor agonist that is currently approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. As a GLP-1 analogue, liraglutide stimulates the release of insulin in response to elevated levels of blood sugar. It also inhibits the release of glucagon following meals, slowing the rate of food absorption from the gut into the bloodstream.

At the meeting, Dr. Ajay Varanasi reported the results of a prospective study in which 14 patients (9 male) with type 1 diabetes all used liraglutide.

Treatment for six of the patients involved a 1-week pretreatment period to optimize glycemic control, 1 week of liraglutide therapy, and 1 week post treatment. Eight additional patients also had a 1-week pretreatment period, followed by a 22-week period of liraglutide therapy, and a 1-week post-treatment period, for a total of 24 weeks.

During treatment, patients were instructed to inject 0.6 mg of liraglutide subcutaneously every day. At the onset of treatment, patients were advised to reduce their basal insulin by a quarter and bolus by a third. "This was to avoid hypoglycemia," explained Dr. Varanasi, the lead author, who is with the division of endocrinology and metabolism at the State University of New York at Buffalo. The eight patients treated for 24 weeks were advised to increase the daily dose of liraglutide to 1.2 mg after the first week and again to 1.8 mg after 2 weeks.

At baseline, the mean patient age was 40 years and the mean BMI was 24 kg/m^2. Patients had type 1 diabetes for an average of 24 years. The mean basal insulin was 24.5 U, the mean bolus was 22.5 U/day, and the mean HbA_{1c} level was 6.6%. All but one of the patients used insulin pumps, and the remaining patient was on four or more insulin injections per day. All patients used continuous glucose monitoring.

During the first week of treatment, despite the reduction in insulin, there was a significant reduction in mean fasting glucose and mean weekly blood glucose.

Most interestingly, said Dr. Varanasi, the mean weekly standard deviations in insulin concentrations were significantly reduced with treatment.

"Even in a reasonably well-controlled [type 1] diabetic with an HbA_{1c} of around 7% or less, there is [usually] a massive vacillation in insulin concentrations," observed Dr. Dandona, the principal investigator, who is chief of the division of endocrinology at the State University of New York at Buffalo.

The eight patients on longer-term therapy lost a significant amount of weight – down from a mean of 68 kg to 63.5 kg. The mean HbA_{1c} level dropped from 6.5% to 6.1%, which also was significant. Mean basal insulin dropped by 48%, and mean bolus dropped by 42%. The decrease in mean blood glucose was significantly reduced within the 24-48 hours. "This tells us that the response is pretty quick. And the mean standard deviation values were reduced within 48 hours," Dr. Varanasi noted.

Regarding the mechanism of action, Dr. Varanasi hypothesized that liraglutide may decrease the concentration of glucagon secreted after meals. Another theory is that the decrease in postprandial glucose excursion may be the result of slower gastric emptying, which is known to occur with liraglutide. The weight loss seen in patients on liraglutide may have also contributed to improved glycemic control. ■

Liraglutide Risks Revisited in Letter From Drug Maker

BY ELIZABETH MECHCATIE

FROM THE FOOD AND DRUG ADMINISTRATION

The manufacturer of liraglutide has issued a letter to health care professionals reminding them about the increased risk of pancreatitis associated with treatment in patients as well as informing them about the development of thyroid tumors in rodents exposed to clinically relevant doses of liraglutide, the Food and Drug Administration announced.

The information is not new, but the letter is being sent to clinicians because "a recent assessment of healthcare providers showed that some primary care providers are not fully aware of the serious risks associated with the use of Victoza," according to the FDA statement. Victoza is the trade name for liraglutide (rDNA origin) injection, which was approved by the FDA in 2010 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

The letter describes the "potential risk" of thyroid C-cell tumors, including medullary carcinoma, which may be associated with liraglutide. In rats and mice, liraglutide causes thyroid C-cell tumors at clinically relevant exposures, but the relevance to humans cannot be ruled out by clinical or nonclinical studies, according to the letter. In addition, pancreatitis was more common in patients treated with liraglutide, compared with comparators in clinical trials, so the drug may increase the risk of acute pancreatitis.

Because of these risks, liraglutide is not recommended as first-line therapy, and patients should be observed closely for signs and symptoms of pancreatitis after starting treatment and after dose increases. The company is monitoring cases of medullary thyroid cancer registry cases to determine whether there was an increase in cases associated with the availability of liraglutide in the United States.

More information including a link to the letter is available in the FDA statement at www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm258826.htm. Serious adverse events associated with liraglutide should be reported to MedWatch at 800-332-1088 or www.fda.gov/medwatch, or to Novo Nordisk at 877-484-2869.

Recombinant Hyaluronidase Speeds Insulin Absorption

BY MIRIAM E. TUCKER

FROM THE ANNUAL SCIENTIFIC SESSIONS OF THE AMERICAN DIABETES ASSOCIATION

SAN DIEGO – Recombinant human hyaluronidase combined with human regular insulin yielded comparable glycemic responses to lispro insulin in a study of 46 patients with well-controlled type 1 diabetes.

Recombinant human hyaluronidase (rHuPH20) is approved by the Food and Drug Administration to increase the dispersion and absorption of other injected drugs. This randomized, open-label, crossover study investigated whether a combination of rHuPH20 with human regular insulin (Halozyme Therapeutics' investigational Insulin-PH20) could produce glycemic control comparable to that of the currently available rapid-acting analogues. The ultimate aim is to combine it with those to make an even faster-acting analogue, Dr. Satish K. Garg said at the meeting.

"If we really want to achieve euglycemia in the postprandial phase, especially 1 and 2 hours after meals, we need an ultra–fast-acting insulin, and we don't have that," said Dr. Garg, professor of medicine and pediatrics at the University of Colorado, Denver.

The 46 patients had a mean age of 42 years, a mean body mass index of 26 kg/m^2, and a mean hemoglobin A_{1c} of 6.9%. They were randomized to either the Insulin-PH20 or insulin lispro for 2 consecutive 12-week periods, with twice-daily glargine as basal insulin in both groups. Forty-one of the 46 completed the trial.

The prespecified primary end point was a noninferiority margin of postprandial glucose values not exceeding 21.6 mg/dL for three meals over 3 days. The difference in glycemic excursions between the two insulin formulations was 2.4 mg/dL, clearly meeting the end point, Dr. Garg said.

HbA_{1c} was maintained for both groups in the trial, 7.0% for Insulin-PH20 and 6.9% for lispro, meeting the commonly applied noninferiority margin of 0.4%. Continuous glucose monitoring during the last 2 weeks of each treatment period showed similar mean glucose values (153 vs. 143 mg/dL), with similar amounts of time spent in the target range of 70-130 mg/dL (39% vs. 44%).

There were no significant differences in overall hypoglycemia, defined as blood glucose value of 70 mg/dL or below.

Dr. Garg has received grants and honoraria from Halozyme Therapeutics, Sanofi-Aventis, Novo-Nordisk, Dexcom, and Eli Lilly. ■

To view an interview with Dr. Garg, simply scan this QR code using your smartphone.