Weekly Exenatide Topped Daily Insulin Glargine

In exenatide patients, 60% had an HbA1$_c$ of less than 7%, compared with 48% of glargine patients.

BY MIRIAM E. TUCKER

FROM THE LANCET

A once-weekly formulation of exenatide reduced hemoglobin A_{1c} level to a greater degree than did once-daily insulin glargine in DURATION-3, a phase III, 26-week open-label randomized trial of 456 patients with type 2 diabetes who had suboptimal control despite use of metformin with or without sulfonylureas.

The overall greater lowering of HbA_{1c} with exenatide was due to significantly lower postprandial glucose excursions, since fasting plasma glucose was actually lower among the patients randomized to insulin glargine. DURATION-3 (Efficacy of Once-Weekly Exenatide Long-Acting Release and Once-Daily Insulin Glargine in Patients With Type 2 Diabetes Treated With Metformin Alone or in Combination With Sulfonylurea) was conducted in 72 sites around the world, funded by Amylin Pharmaceuticals and Eli Lilly and Co. (Lancet 2010;375:2234-43).

Patients randomized to exenatide received a 2-mg dose injected once a week. Those in the insulin glargine group started with 10 IU per day injected at bedtime, and were instructed to adjust insulin doses to achieve target fasting glucose values of 72-99 mg/dL. Metformin doses were kept constant, but patients taking sulfonylureas were advised to reduce that dose. The study design did not allow for blinding, noted Dr. Michaela Diamant, of VU University, Amsterdam, and her associates.

Mean doses of insulin glargine rose from 10 IU to 31 IU per day, and nearly one in four patients reduced their sulfonylurea dose. Metformin doses were about 2,000 mg/day throughout the study.

At 26 weeks, hemoglobin A_{1c} in the exenatide group had dropped 1.5 percentage points, compared with 1.3 in those receiving glargine, and 60% of the exenatide patients achieved an HbA_{1c} of less than 7%, compared with 48% for the glargine group, both significant differences. The proportions achieving HbA_{1c} values less than 6.5% were 35% and 23%, respectively.

Mean fasting serum glucose concentrations were reduced in both groups, but to a significantly greater degree with insulin glargine (38 vs. 50 mg/dL), Dr. Diamant and her associates noted.

Whereas exenatide was associated with a progressive decrease in body weight, those taking insulin glargine had progressive increases. At 26 weeks, the exenatide group had lost an average of 2.6 kg, while the glargine group had gained 1.4 kg. In the exenatide group, reductions in body weight occurred in both those who reported nausea (3.5 kg) and those who did not (2.2 kg), they said.

Gastrointestinal events including nausea and diarrhea were among the most frequently reported adverse events in the exenatide group. Nausea was reported by 13% with exenatide vs. 1% with glargine, and diarrhea by 9% and 4%, respectively. All were mild or moderate in intensity. No serious adverse events were reported by more than one patient except for chest pain in two patients. No deaths occurred in either group. Discontinuations owing to adverse events were greater with exenatide (5% vs. 1%), due in part to injection-site reactions (2% vs. 0%).

At 26 weeks, five exenatide and no glargine patients had elevated amylase or lipase concentrations and one patient taking exenatide had edematous pancreatitis, an adverse event that has been reported previously with the currently available twice-daily exenatide. That patient was fully recovered by 2 months.

In an accompanying editorial, Dr. Anoop Misra and Dr. Shashank Joshi pointed out that the nausea, although less common with once-weekly exenatide versus the twice-daily formulation, could still be troublesome in patients who are taking multiple drugs, including metformin, and in those who have diabetic gastroparesis. They also noted that cardiovascular safety data are still needed for this drug, and strict monitoring of pancreatic effects will be necessary.

Both the long-acting and the twice-daily exenatide formulations have been linked to renal dysfunction, and to attenuation of the response among the 6%-9% who develop antibodies to the drug, Dr. Misra and Dr. Joshi said (Lancet 2010;375:2198-9).

Nonetheless, this or other drugs in the glucagon-like peptide-1 receptor analogue class might be suitable for patients with type 2 diabetes who are obese or those in whom hypoglycemia is a clinical concern. "Currently, there is more promise, few disadvantages, and some unknowns about treatment with long-acting exenatide for diabetes," they concluded.

Dr. Diamant is a consultant and speaker for Eli Lilly, Novo Nordisk, and Merck, Sharpe, and Dohme, and a consultant for Sanofi-Aventis. The VU University has also received research grants from those companies as well Amylin Pharmaceuticals, Novartis, and Takeda. Three of the coauthors are employees of Lilly, and one works for Amylin.

Dr. Misra has received lecture fees and research funding from Sanofi-Aventis, Merck, Novo Nordisk, and Eli Lilly. Dr. Joshi stated that he had no conflicts of interest. ■

VITALS

Major Finding: At 26 weeks, HbA_{1c} in patients treated with long-acting exenatide had dropped 1.5 percentage points, compared with a 1.3-point reduction in those treated with daily insulin glargine.

Data Source: DURATION-3, a phase III, 26-week open-label randomized trial of 456 patients with type 2 diabetes who had suboptimal control despite use of metformin with or without sulfonylureas.

Disclosures: The study was funded by Amylin Pharmaceuticals and Eli Lilly.

Intranasal Insulin Might Improve Mild Cognitive Impairment

BY MICHELE G. SULLIVAN

FROM THE INTERNATIONAL CONFERENCE ON ALZHEIMER'S DISEASE

Intranasal insulin boosted cognitive function and even brain activity in patients with mild cognitive impairment and early Alzheimer's disease in a 4-month, randomized, placebo-controlled trial.

The study, presented at the meeting, holds tantalizing hints of an Alzheimer's therapy that could be relatively inexpensive and easy to administer, but more research on a much larger scale is necessary before this science could move into the clinic.

Dr. Suzanne Craft of the University of Washington, Seattle, said growing evidence suggests that insulin may play a key role in cognition and that patients with Alzheimer's disease have significantly disrupted brain-insulin interactions.

"Insulin plays a number of important roles in the brain, and many are functions of great relevance to Alzheimer's disease," she said in an interview.

Insulin normally crosses the blood-brain barrier to bind with receptors in the hippocampus, frontal cortex, and other regions involved in cognition. "It also enhances memory, we believe through mediating glucose metabolism in the hippocampus, as well as by mediating levels of neurotransmitters, including acetylcholine," she said.

Insulin also improves blood flow to the brain and works to prevent beta-amyloid from aggregating on neurons. "It appears to help the beta-amyloid move from inside the brain cells to the interstitial space, where it can be cleared," she said. "It also increases the availability of a specific enzyme that breaks down amyloid."

In an extension of her previous work, Dr. Craft randomized 104 patients with mild cognitive impairment (MCI) or early Alzheimer's disease to placebo or to 20 or 40 IU daily of intranasal insulin. The compound is sprayed into the nose, where insulin bypasses the blood-brain barrier and travels directly into the brain along the perivascular channels around the olfactory and trigeminal nerves, allowing the drug to bind to brain receptors within 15-30 minutes of administration.

The patients' average age was 73 years. Their mean combined score on three baseline Mini-Mental State Examination tests was about 82. All patients took the Alzheimer's Disease Assessment Scale cognitive test for MCI (ADAS-cog/MCI), the Dementia Severity Rating Scale (DSRS), and the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) measures.

The 20-IU group experienced a significantly improved delayed story recall compared with the placebo group. The 20-IU group also showed significantly improved functional status on the DSRS. These improvements persisted for 2 months after insulin was ceased.

On the ADCS-ADL, placebo patients declined significantly more than 20-IU patients; 40-IU patients had no change in their score. On the ADAS-cog/MCI test, placebo patients scored significantly worse than both intervention groups, and the 40-IU group scored significantly better than did the 20-IU group.

Dr. Craft said that "it's hard to say for certain in a 4-month study that this would translate into clinical improvement, but on the ADAS-cog, we saw a 25% difference between the highest-dose insulin group and the placebo group. And we also saw improvements in a caregiver-rated functional scale. So I would say that these findings do suggest clinical improvement."

The fact that the improvements were maintained throughout the study and even after treatment stopped suggests that insulin has a cumulative effect in improving brain function, she added.

In a subgroup of 40 patients who underwent fluorodeoxyglucose PET scanning at baseline and during follow-up, those taking placebo showed a slowing of the cerebral metabolic rate for glucose utilization. This slowing was not seen in either the 20-IU or 40-IU subjects—a finding that Dr. Craft suggested may show slowing of disease progression.

"This is a new and very encouraging finding," she said. ■

VITALS

Major Finding: Intranasally delivered insulin boosted cognition and brain activity in patients with mild cognitive impairment and early Alzheimer's disease.

Data Source: A placebo-controlled trial that randomized 104 patients to placebo or to 20 IU or 40 IU of intranasal insulin every day for 4 months.

Disclosures: The study was sponsored by the National Institute on Aging and the Department of Veterans Affairs. Dr. Craft said she had no financial disclosures.