Exenatide Benefits Treatment-Refractory Diabetics

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WASHINGTON — Exenatide appears beneficial as adjunctive therapy in patients with type 2 diabetes who have not achieved target glucose levels with a thiazolidinedione alone or in combination with metformin, Dr. Bernard Zinman reported at the annual scientific sessions of the American Diabetes Association.

The incretin mimetic exenatide (Byetta) is approved for use in combination with metformin, with or without a sulfonylurea. It works by several mechanisms, including enhancement of glucose-dependent insulin secretion, suppression of glucagon secretion, slowing of gastric emptying, and improvement in beta-cell function. Thiazolidinediones (TZDs), on the other hand, work primarily by reducing peripheral insulin resistance.

"Given the pathophysiology of type 2 diabetes and the actions of exenatide and [TZDs], this combination therapy may be especially useful in long-term management," said Dr. Zinman, a professor of medicine who holds the Sam and Judy Pencer Chair in Diabetes at the University of Toronto.

In a placebo-controlled, double-blind trial involving 233 patients with hemoglobin A_{1c} levels of 7.1-10% despite use of a TZD alone (20%) or a TZD plus metformin (80%), 121 were randomized to receive two daily injections of exenatide for 16 weeks (5-mg doses in the first 4 weeks, 10 mg thereafter), while the other 112 received placebo injections. The study was conducted in 49 centers, including 37 in the United States, 7 in Spain, and 5 in Canada.

Of 35 patients from the exenatide group who withdrew prior to the end of the study, 19 (15.7% of the whole exenatide group) did so because of adverse events, compared with 2 of 16 controls (1.8% of the whole control group) who withdrew.

Nausea was the most common adverse event, occurring overall in 40% of the exenatide group and 15% of the placebo group. The nausea, generally mild to moderate, tended to occur most often at weeks 4-8 while the exenatide dose was being increased from 5 mg to 10 mg, and to decline thereafter. Hypoglycemia occurred in 11% of the exenatide group and 7% with placebo, an insignificant difference, said Dr. Zinman, who is also director of the Leadership Sinai Centre for Diabetes and senior scientist, Lunenfeld Research Institute at Mount Sinai Hospital, Toronto.

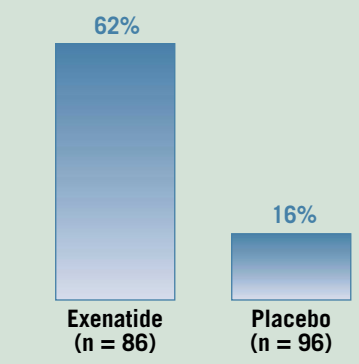
Mean baseline hemoglobin A_{1c} was 7.9% in both groups. In the intent-to-treat analysis at week 16, mean A_{1c} had dropped significantly to 7.1% in the exenatide group, while rising to 8.0% in the placebo group. Reductions in A_{1c} with exenatide were similar between patients combining it with TZD and those taking it with both a TZD and metformin, he said.

Among 86 exenatide and 96 placebo patients who completed the study, 62% of the exenatide group achieved the American Diabetes Association's A_{1c} target of 7% or less, vs. 16% of the placebo group. The proportions achieving the American Association of Clinical Endocrinologists' target of 6.5% or less were 30% and 8%, respectively. Both differences were significant.

Self-monitored glucose values showed that patients taking exenatide had significantly lower fasting glucose levels and postprandial glucose excursions at the end of the study, compared with baseline. The mean postprandial drop was 27 mg/dL, and was greatest after breakfast and dinner (mean drop of 34 mg/dL for both meals). The placebo group showed essentially no differences in those measures from baseline to the end of the study.

Mean body weight in the exenatide group fell by 1.54 kg over the 16 weeks, compared with an insignificant 0.2-kg loss with placebo, Dr. Zinman reported. ■

Exenatide Helps Patients Meet Hemoglobin A_{1c} Targets of ≤7%



Source: Dr. Zinman