Exenatide Is Adjunctive Therapy in Type 2 Diabetes

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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 currently approved for use in combination with metformin, with or without a sulfonylurea.

Exenatide 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, who is professor of medicine and 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 A1c 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 versus 15% of the placebo group and resulting in withdrawal in 9% and 2%, respectively.

Mean baseline hemoglobin A1c was 7.9% in both groups. In the intent-to-treat analysis at week 16, mean A1c had dropped significantly to 7.1%, in the exenatide group, while rising slightly to 8.0% in the placebo group. Reductions in A1c were similar between the patients combining it with TZD and those taking it with both a TZD and metformin, he said.

Among the 86 exenatide and 96 placebo patients who completed the study, 62% of the exenatide group achieved the American Diabetes Association’s A1c target of 7% or less, compared with 16% of the placebo group. The proportions achieving the American Association of Clinical Endocrinologists’ target of 6.5% or less were 30% versus 8%, respectively. Both differences were significant.

Seven-point self-monitored glucose values, done at baseline and at the end of the study, 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, in contrast, showed essentially no differences in those measures from baseline to the end of the study, Dr. Zinman reported.

Mean body weight in the exenatide group dropped by 1.54 kg over the 16 weeks, compared with an insignificant 0.2 kg loss with placebo. Patients with the greatest decreases in A1c also lost the most weight, although even those who didn’t lose weight still had significantly better A1c values, he noted.