Exenatide Benefits Hold Up Long Term in Type 2 Diabetes

By Nancy Walsh

New York — The glucose-lowering effects of the investigational agent exenatide were maintained for 80 weeks in an open-label extension study, Daniel J. Drucker, M.D., reported at a conference sponsored by the American Diabetes Association.

The reduction in hemoglobin A1c (HbA1c) remained at about 1%, which was initially seen in a 30-week randomized, blinded study. This reduction was accompanied by a mean weight loss of 10 pounds, said Dr. Drucker, director of the Banting and Best Diabetes Centre, University of Toronto.

Exenatide, the synthetic form of exendin-4, is the first of a new class of antidiabetic drugs known as incretin mimetics. Incretins are gut peptides that are secreted in response to nutrient ingestion, stimulating the secretion of insulin, inhibiting the secretion of glucagon, slowing gastric emptying, and reducing food intake. Mimicking their actions is aimed at restoring β-cell function, said Dr. Drucker, explained.

Exenatide is a potent agonist for glucagon-like peptide-1 (GLP-1). It is derived from the saliva of Heloderma suspectum, the Gila monster.

A total of 963 patients with type 2 diabetes that could not be controlled with metformin and/or a sulfonylurea drug participated in the open-label study, Dr. Drucker said.

The 1% decrease in HbA1c seen with twice-daily injections of exenatide is “fairly reasonable,” but “by no means can you say it normalizes blood glucose. It’s an other useful drug but type 2 diabetes is still a difficult disease to treat,” he said.

“So why would anybody want to inject themselves twice a day with a substance derived from the saliva of a lizard? Because of the 10-pound weight loss,” Dr. Drucker explained.

And despite the fact that 44% of patients in the placebo-controlled phase of the study complained of nausea, the dropout rate was quite low, he said.

Another observation that has emerged from the long-term study is that antibodies to the peptide do develop, but their presence does not appear to correlate with the magnitude of HbA1c reduction.

The drug also has pronounced effects on postprandial glucose. “Those of you who are following the debate about postprandial glucose and cardiovascular risk know that most of our drugs don’t do a very good job at controlling this,” he said. Recent reports have suggested that postprandial “hyperglycemic spikes” seen in diabetic patients may contribute to the onset of cardiovascular complications (Diabetes 2005;54:1-7).

Dr. Drucker disclosed that he is a board member of and consultant for Amylin Pharmaceuticals Inc., which has partnered with Eli Lilly & Co. to develop exenatide.

Impact of Support Groups

The third analysis, from Ute Schulz, Ph.D., focused on the impact of the group support component among the 440 participants in the earlier eight-site demonstration project. At 1 year, significant changes in coronary risk factors included reductions in weight from 85 to 80 kg and in LDL/HDL ratio from 4 to 3, along with increases in physical and mental functioning.

On average, participants attended 77% of all offered support group sessions during the year. The most support group sessions participants attended, the more time they spent practicing stress management and exercising.

That, in turn, was associated with better physical and mental functioning, weight loss, and decreased LDL/HDL ratios.

“Support group attendance may indirectly influence changes in coronary risk factors by fostering participants’ adherence to exercise and stress management. . . . These findings underline the importance of multicenter support programs in the ongoing prevention of CAD,” Dr. Schulz and her associates said.

Few in the medical community doubt the efficacy of the Ornish program—but what question is whether it can be implemented in the real world. Those who work at the PMRI — of which Dr. Ornish is founder, president, and director—hope that the final results from the MCLIP will encourage physicians to try harder to get patients into the program.

At a symposium held during the American Psychosomatic Society meeting, Gerödi Weidner, Ph.D., PMRI vice president and director of research, summarized the previously reported data on the Ornish program and offered this perspective when questioned about its real-world applicability: “Of course lifestyle changes are not for everyone, but open heart surgery’s not for everyone, either. Once you’ve been stented three times, the fourth time is not for [anybody].”

Traditional cardiac rehabilitation programs may increase their effectiveness by adding a stress management component.