Exenatide Benefits Treatment-Refractory Diabetics

BY MIRIAM E. TUCKER
Senior Writer

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. 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, 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 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 versus 15% of the placebo group and resulting in withdrawal in 9% and 2%, respectively.

The nausea was generally mild to moderate. It 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 slightly to 8.0% in the placebo group. Reductions in A_{1c} with exenatide 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 A_{1c} 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 at the meeting.

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 A_{1c} also lost the most weight, although even those who didn't lose weight still had significantly better A_{1c} values, he noted. ■

Eye Exam Noninvasively Identifies Neuropathy

BY JEFF EVANS
Senior Writer

WASHINGTON — Corneal confocal microscopy provides a means for noninvasively diagnosing neuropathy early on in diabetic patients and for following the course of the disease during treatment, several speakers said at the annual scientific sessions of the American Diabetes Association.

By comparison, the clinical neurologic exam may be easier than corneal confocal microscopy but it lacks sensitivity, said Mitra Tavakoli, a doctoral student at the University of Manchester (England).

Nerve conduction studies are time-consuming and are reliable only in measuring the function of large nerve fibers. Quantitative sensory testing also is easier to do, but relies on the patient's response to take measurements. Skin nerve biopsies can provide much information, but are "highly invasive," she said.

Using a first-generation corneal confocal microscope, the ConfoScan P4 (Tomey Corp.), Ms. Tavakoli and her colleagues are able to obtain in vivo, real-time micrographs of the cornea at up to 680 times magnification without directly contacting the eye.

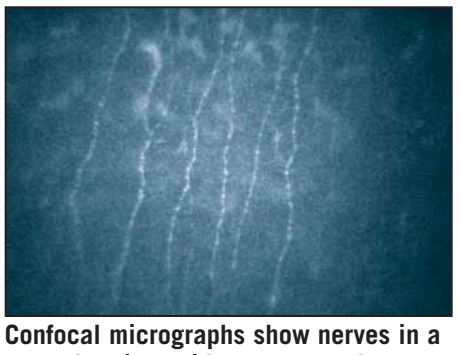
She and her coinvestigators studied 183 people including control patients without diabetes, diabetic patients without neuropathy, and diabetic patients with mild, moderate, or severe neuropathy.

They found that diabetic neuropathy was associated with progressive, significant reductions in corneal sensitivity (as measured by noncontact corneal aesthesiometry), nerve fiber density, nerve branch density, and nerve fiber length. Nerve fiber tortuosity also became progressively worse as the severity of neuropathy worsened.

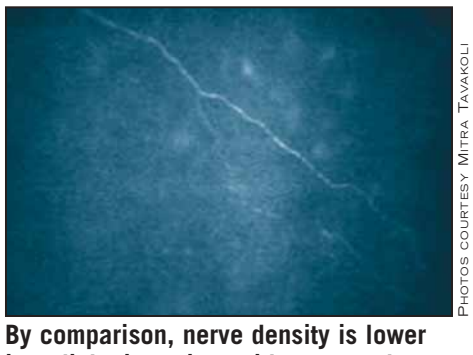
The measurements of corneal nerve morphology obtained with confocal microscopy correlated well with assessments of corneal sensitivity and neuropathy severity, as measured by the Neuropathy Disability Score.

In a poster presented at the meeting, Ms. Tavakoli and her colleagues used corneal confocal microscopy to show the effectiveness of pancreatic transplantation in improving neuropathy in 20 patients with type 1 diabetes who had an average age of 41 years.

Before transplantation, the diabetic patients had significantly reduced corneal sensitivity as well as significantly lower nerve fiber density, nerve branch density, and nerve fiber length on corneal confocal micrographs, compared with 18 individuals without neuropathy who had an average age of 55 years.



Confocal micrographs show nerves in a control patient without neuropathy.



By comparison, nerve density is lower in a diabetic patient with neuropathy.

PHOTOS COURTESY MITRA TAVAKOLI

At 6 months after transplantation, repeat scans in 11 of the patients who had neuropathy showed that nerve fiber density and length had improved significantly. Other posttransplantation studies that have employed electrophysiology and quantitative sensory testing have been able to detect improvements in large fiber function after 3-4 years, unlike the early detection of small fiber repair at 6 months in this study, Ms. Tavakoli reported.

In the laboratory of Nathan Efron, Ph.D.—one of Ms. Tavakoli's collaborators—the microscopy technique has proved to have sensitivity (71%) and specificity (77%) comparable with the histopathologic examination of skin punch biopsy specimens (59% and 90%, respectively) when both are compared with the "gold standard" Neuropathic Disability Score.

Dr. Efron has used confocal microscopy to monitor longitudinal changes in corneal morphology in patients who have received myopic laser in situ keratomileusis (LASIK), which involves cutting a flap of the cornea, irradiating the corneal stroma with a laser, and replacing the flap. The LASIK procedure severs corneal nerves in the subbasal nerve plexus where most of the corneal nerves reside. Several weeks after the surgery, confocal microscopy shows a "hazy image" devoid of any nerve fibers. At 3 months, a few nerve fragments can be seen, and at 6 months a few continuous nerves begin to appear (Optom. Vis. Sci. 2003;80:690-7).

"Certainly, this has implications with respect to diabetic patients who are having this LASIK procedure," said Dr. Efron, research professor at Queensland University of Technology, Brisbane, Australia. ■

HbA_{1c} Before Age 10 Predicts Complications

WASHINGTON — Hemoglobin A_{1c} levels during ages 11-19 years correlated with the risk of complications as adults among type 1 diabetes patients diagnosed before age 10, Dr. Emily J. Gallagher reported at the annual scientific sessions of the American Diabetes Association.

Medical records were reviewed for 57 men and 72 women who ranged in age from 15 to 69 years and had been diagnosed with type 1 diabetes before age 10. The mean duration of diabetes was 28 years, said Dr. Gallagher, of University College in Dublin. Mean HbA_{1c} values, available since 1983, were 7.5% for 30 of the patients at ages 0-10, rising to 9.4% for the 73 patients ages 11-19, then falling back to 8.5% after age 20 years in 108 patients.

Among the 129 study participants, 53% had developed at least one complication at a mean of 22 years after diagnosis. Retinopathy was present in 50% after a mean of 23 years, nephropathy in 23% after 28 years, and neuropathy in 18% after 27 years. Hypertension, HbA_{1c} levels, and fasting triglycerides were significant predictors for the development of nephropathy, while A_{1c} and hypertension predicted neuropathy.

For those with mean HbA_{1c} levels below 8%, there was a 50% probability of any complication at 33 years after diagnosis. For those with mean HbA_{1c} levels of 8%-10%, the time to a 50% probability of any complication was 26 years. For those with HbA_{1c} values above 10%, the time was 16 years. HbA_{1c} values during the 11- to 19-year age range correlated most strongly with time to development of complications, Dr. Gallagher reported.

—Miriam E. Tucker