Tight Glycemic Control Achieved Mixed Results

BY MIRIAM E. TUCKER

FROM THE ANNUAL SCIENTIFIC SESSIONS OF THE AMERICAN DIABETES ASSOCIATION

ORLANDO — Intensive glycemic control did not reduce the risk for developing advanced measures of microvascular outcomes, although it did delay the onset of albuminuria and some measures of eye complications and neuropathy among patients with longstanding type 2 diabetes at high cardiovascular risk.

The mixed results, from a subanalysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, suggest that the microvascular benefits of intensive therapy should be weighed against the increase in total disease-related mortality, increased weight gain, and high risk for severe hypoglycemia that emerged with the main findings of the trial 2 years ago, Dr. Faramarz Ismail-Beigi said.

"Caution should be exercised in pursuit of a strategy of intensive glycemic control for prevention of microvascular complications in patients with established type 2 diabetes and characteristics similar to those in the ACCORD trial," Dr. Ismail-Beigi of Case Western Reserve University, Cleveland, said. The findings were released simultaneously online in the Lancet (doi:10.1016/S0140-6736(10)60576-4).

The ACCORD trial randomized 10,251 adults with type 2 diabetes to either intensive glycemic control with a target hemoglobin A_{1c} of less than 6.0%, or standard therapy aiming for HbA_{1c} values of 7.0%-7.9%. The intensive arm was stopped early in February 2008—after a median follow-up of 3.7 years—because of a 22% higher all-cause mortality in the intensive group. They were then transitioned to standard therapy for the rest of the trial, which also included blood pressure and lipid control arms (N. Engl. J. Med. 2008;358:2545-59).

At the time of that transition and at study end, the two groups did not differ in the prespecified primary composite outcome of advanced nephropathy and diabetic eye complications (development of renal failure or retinal photocoagulation or vitrectomy to treat retinopathy), or in a second composite end point that added a peripheral neuropathy outcome (score of greater than 2.0 on the Michigan neuropathy screening instrument or the first composite outcome). At the end of the study, 10.9% of the intensive group and 11.5% of the standard treatment group met the first composite end point, and 38.2% and 40.0%, respectively, met the second.

However, microvascular renal outcomes based on urinary measures were significantly reduced in the intensive glycemic therapy group. Intensive glycemia therapy led to a 21% reduction in the development of microalbuminuria at the time of transition. This effect was attenuated to 15% at study end, but remained statistically significant, Dr. Ismail-Beigi reported.

For diabetes-related eye events, three-line worsening of visual acuity was more common in the standard group than in the intensive group at both transition and study end (20.7% vs. 19.1%).

'Caution should be exercised in pursuit of a strategy of intensive glycemic control for prevention of microvascular complications in patients with established type 2 diabetes.'

Cataract extraction was also significantly reduced, by 21%, in the intensive group, compared with the standard group at study end. Other diabetes-related eye outcomes did not differ between the two groups, he said.

Peripheral neuropathy (MNSI greater than 2.0) was less common in the intensive group than in the standard group at study end (55.6% vs. 58.6%). Loss of ankle jerk reflex and light touch (10-g monofilament) perception were both rarer in the intensive vs. standard therapy groups at study end, but loss of vibratory sensation did not differ between the two groups.

In an accompanying editorial in the Lancet, Dr. Ronald Klein pointed out that the American Diabetes Association's recommendation of a hemoglobin value of less than 7.0% was based on the findings of the United Kingdom Prospective Diabetes Study (UKPDS), which showed that intensive glycemic therapy in newly diagnosed type 2 diabetes patients did reduce the risk for the same composite microvascular end points as the ones used in ACCORD (Lancet 1998;352:837-53).

However, the follow-up period of ACCORD was much shorter than that of the UKPDS, in which it took about 10 years to show efficacy of intensive glycemic control for the same advanced end points, noted Dr. Klein, of the department of ophthalmology and visual sciences at the University of Wisconsin, Madison.

"I do not believe the ACCORD experience will (or should) cause clinicians to doubt the importance of glycemic control in preventing microvascular complications," Dr. Klein concluded.

The ACCORD trial was funded by the National Heart Lung and Blood Institute, with contributions of medications, equipment, or supplies from several manufacturers. Dr. Ismail-Beigi has received travel support from NHLBI and did not disclose any other relationships. However, several coauthors declared financial relationships with many manufacturers of diabetes-related products. Dr. Klein has worked as a consultant for AstraZeneca, Eli Lilly, GlaxoSmithKline, Takeda, Pfizer, and Novartis. ■

Study Favors Once-Weekly Exenatide for Lowering HbA_{1c}

BY MIRIAM E. TUCKER

FROM THE LANCET

Once-weekly exenatide reduced hemoglobin A_{1c} to a significantly greater degree than did either sitagliptin or pioglitazone in DURATION-2, a 26-week randomized, double-blind trial of 491 patients with type 2 diabetes who had baseline HbA_{1c} levels of 8.5% or higher despite metformin treatment.

The study, funded by Amylin Pharmaceuticals and Eli Lilly, was published online to coincide with a presentation of its results by lead author Dr. Richard M. Bergenstal at the annual scientific sessions of the American Diabetes Association (Lancet 2010 June 26 [doi:10.1016/S0140-6736(10)60590-9]).

Patients received treatment in 72 sites in the United States, India, and Mexico. All had been treated with a stable metformin regimen for at least 2 months before screening and continued to take metformin throughout the study. The patients were randomized to one of three regimens: 2-mg exenatide injection once weekly plus oral placebo once daily, 100 mg oral sitagliptin once daily plus placebo injection once weekly, and 45 mg oral pioglitazone once daily with placebo injections once weekly.

Patients and staff in DURATION-2 (A Study to Compare the Glycemic Effects, Safety, and Tolerability of Exenatide Once Weekly to Those of Sitagliptin and a Thiazolidinedione in Subjects With Type 2 Diabetes Treated With Metformin) were all blinded to treatment allocation during the 26 weeks of treatment, said Dr. Bergenstal of the International Diabetes Center at Park Nicollet, Minneapolis, and his associates.

Of the 514 participants randomized to treatment, those who received at least one treatment (491) were included in the intention-to-treat analysis. Fewer patients withdrew from treatment with sitagliptin (13%) than did those receiving exenatide once weekly (21%) or pioglitazone (21%).

At 26 weeks, mean HbA_{1c} values were 7.2% for exenatide, 7.7% for sitagliptin, and 7.4% for pioglitazone. From baseline to week 26, reduction in HbA_{1c} with once-weekly exenatide was significantly greater than with the other two drugs, at 1.5 percentage points, compared with 0.9 and 1.2 percentage points with sitagliptin and pioglitazone, respectively.

When the data were stratified by baseline HbA_{1c}, once-weekly exenatide was associated with a significantly greater reduction in HbA_{1c} than was sitagliptin in all patients, but for exenatide versus pioglitazone the difference was significant only in patients with baseline HbA_{1c} of 9% or higher, the investigators reported.

All three treatments improved fasting plasma glucose, but once-weekly exenatide resulted in a significantly greater reduction than did sitagliptin—32 vs. 16 mg/dL—but not pioglitazone, which produced a reduction in fasting plasma glucose of 27 mg/dL. Fasting insulin was significantly increased at week 26 with once-weekly exenatide compared with both sitagliptin and pioglitazone, they said.

Weight loss at 26 weeks was significantly greater with exenatide than with sitagliptin, 2.3 vs. 0.8 kg, while the pioglitazone group gained an average of 2.8 kg. Over 75% of the patients on once-weekly exenatide lost body weight, compared with 61% of those on sitagliptin and 21% of those on pioglitazone.

Reductions in systolic blood pressure were significantly greater with once-weekly exenatide than with sitagliptin, but did not differ from those seen with pioglitazone. Change in diastolic pressure at week 26 did not differ between the three groups. Significant improvement in HDL cholesterol was recorded with all treatments, and improvement was significantly greater with pioglitazone than with exenatide. Pioglitazone was the only treatment associated with a significant reduction in triglycerides and total cholesterol, Dr. Bergenstal and his associates noted.

The most common treatment-emergent adverse events for patients on exenatide and sitagliptin were nausea and diarrhea, whereas pioglitazone patients' most common adverse events were upper respiratory tract infection and peripheral edema. Vomiting was more common with exenatide than with sitagliptin or pioglitazone.

Adverse events leading to withdrawal from the study drug occurred in 10 patients on exenatide, 5 on sitagliptin, and 6 on pioglitazone. Of the 26 serious adverse events during treatment, one was fatal but the others resolved.

Dr. Bergenstal's institution has received consultancy fees or research grant support, or both, with receipt of travel and accommodation expenses in some cases, from Abbott Diabetes Care, Amylin, Bayer, Eli Lilly, Intuity Medical, Hygieia Medical, LifeScan, Mannkind, Medtronic-Minimed, National Institutes of Health, Novo Nordisk, ResMed, Roche, Sanofi-Aventis, United Health Group, and Valeritas; all research activity, and advisory or consultancy services were done under contract with the nonprofit International Diabetes Center at Park Nicollet. Dr. Bergenstal also owns stock in Merck. One coauthor has similar disclosures, six are employees of Amylin Pharmaceuticals, and one is an employee of Eli Lilly. ■