**Meeting Highlights**

**American Diabetes Association**

**Reuben B. David**

A simpler dosing regimen may bring the benefits of rapid-acting insulin tailored to mealtime carbohydrates to a wider population; a lipid-lowering agent offers a glycemic control bonus, and a new oral agent targeting pancreatic islet dysfunction demonstrates broad efficacy. These innovations were presented at key clinical sessions at this year’s American Diabetes Association’s (ADA’s) 66th Annual Scientific Sessions, which took place from June 9 to 13, 2006.

**Intensive Insulin Therapy**

To help patients meet their glycosylated hemoglobin (HbA1c) goals, more of them should be using basal–bolus, or “intensive,” insulin. With intensive insulin treatment, patients give themselves an injection of short-acting insulin before each meal and an injection of longer-acting insulin before going to bed.

What holds them back, according to Richard Bergenstal, MD, Clinical Professor at the University of Minnesota Medical School in Minneapolis, is that counting carbohydrates at meals for matching up their rapid-acting insulin on top of “background” 24-hour insulin is perceived as too complicated. The solution—a simple mealtime insulin-dosing algorithm—appears to be safe, feasible, and effective, based on study results that he presented.

“This new dosing approach relies on a simple algorithm that allows patients to start with a fixed dose of mealtime [insulin] glulisine and then adjust to target based on pre-meal glucose patterns,” Dr. Bergenstal explained.

When weekly blood sugar records show glucose to be out of range for a meal, insulin doses for the prior meal are adjusted upward or downward by 1 to 3 units accordingly.

The strategy was tested in a randomized clinical trial that compared the simplified fixed-dose method with carbohydrate counting among 273 patients with type-2 diabetes. The mean age of the patients was 55 years.

The patients received 24-hour insulin glargine (Lantus, Sanofi-Aventis) and rapid-acting insulin glulisine (Apidra, Sanofi-Aventis). The baseline adjusted mean HbA1c was 8.16% in both groups.

After 24 weeks, patients in the algorithm and carbohydrate-counting groups achieved similar mean HbA1c values (6.70 for the algorithm, 6.54 for carbohydrate counting), with most patients achieving HbA1c targets of below 7%. Furthermore, rates of hypoglycemia (indicated by a blood glucose level below 50 mg/dl) were lower in the algorithm group (4.9 vs. eight events per patient-year [P = .02]); however, these patients gained more weight (3.7 kg) than the carbohydrate-counting group (2.4 kg) (P = .06).

Body mass index (BMI) increased significantly in both groups, compared with baseline levels (P = .0001). The BMI increase was significantly greater in the algorithm group (1.3 kg/m²) than in the carbohydrate-counting group (0.8 kg/m²) (P = .03).

“When you drive blood sugar down, people start retaining the calories they eat,” Dr. Bergenstal explained. He said that the reduction in risk accompanying the HbA1c decreases was far beyond the risk added with extra weight gain. With tight glucose control, instead of excreting sugar in urine, the body converts the glucose to fat.

“We hope to help them take that off,” he said.

Dr. Bergenstal commented, “Some people just don’t want their whole life to be about their diabetes. So if they know, ‘I just take 10 units every breakfast and I take 12 at lunch—and 18 at supper’—that’s simple enough.”

**Colesevelam**

It has been known for some time that colesevelam (Wel-Chol, Sankyo), a bile acid–binding resin indicated for lowering low-density lipoprotein-cholesterol (LDL-C) levels, reduces glucose levels in individuals with type-2 diabetes. Given that a proportion of this population cannot use metformin (Glucophage, Bristol-Myers Squibb) because of elevated creatinine values, and given that another group with congestive heart failure cannot use a thiazolidinedione (TZD) because of the potential for edema, a randomized clinical trial was conducted to quantify colesevelam’s potential for helping with glycemic control, according to investigators analyzing the phase 2 study.

Sherwyn L. Schwartz, MD, Professor of Medicine at the University of Texas in San Antonio, reported that 65 patients, with a mean age of about 56 years, were already taking a sulfonylurea, metformin, or a combination. These patients were randomly selected to receive colesevelam 3.75 g/day or placebo. Enrolled patients had not been able to control their glucose levels at the time of randomization; HbA1c values ranged from 7% to 10%. The participants were instructed to continue their prior antidiabetic regimens.

The primary endpoint was a mean change in HbA1c levels from the baseline evaluation to week 12.

The analysis showed a significantly greater reduction in HbA1c (in percent) from baseline to 12 weeks with the colesevelam group (from 7.9% to 7.7%), compared with a slight rise in the placebo group (from 8.1% to 8.3%) (P = .007). The difference was more pronounced among patients with higher baseline HbA1c values (8% or higher)—namely a reduction from 8.7% to 8% with colesevelam and a slight elevation from 9% to 9.2% with placebo (P = .002).

Franklin Zieve, MD, at Hunter Holmes McGuire Veterans Affairs Medical Center in Richmond, Virginia, conducted a secondary endpoint analysis. He evaluated changes in post-prandial glucose levels over a period of 12 weeks in the same clinical trial. Plasma glucose was measured in the fasting state and at one hour after consumption of a test meal consisting of continued on page 461
two eight-ounce cans of Ensure with fiber at baseline and at 12 weeks. Subjects took three tablets of the study medication five minutes before the test meal.

Dr. Zieve said that changes in postprandial glucose concentrations from baseline to week 12 were significantly greater than the changes observed with placebo (with colesevelam, a decrease from 269 to 251.2 mg/dl; with placebo, a rise from 285 to 287.7 mg/dl) ($P = .026$).

Colesevelam was well tolerated, and treatment-emergent adverse drug events during the study treatment period were similar in the colesevelam and placebo groups of patients.

Commenting on the findings, Dr. Schwartz pointed out that about 10% to 15% of patients cannot take statins because of muscle aches.

“There is a group of patients with glucose out of control and elevated lipids who are candidates for these benefits.”

Dr. Zieve noted that the 0.5% decline in HbA$_{lc}$ with colesevelam meets the usual FDA standard for glycemic control agents. He said also that colesevelam would most likely be used not as monotherapy for patients with diabetes but as an add-on therapy.

“It has the side benefit of lowering LDL—which you want to do in diabetics anyway.”

**Vildagliptin**

In a presentation of late-breaking trial results, about two thirds (65%) of patients with type-2 diabetes receiving the investigational oral agent vildagliptin (VGP) (Galvus, Novartis) achieved ADA targets of below 7% for HbA$_{lc}$. The effects of VGP, a dipeptidyl peptidase IV (DPP-4) inhibitor and the first in a new therapeutic class, were examined in a news conference summarizing about a dozen studies. Overall, more than 5,400 patients have been enrolled in the VGP studies, and pivotal trials were conducted in 25 countries, according to Ameet Nathwani, MD, of Novartis Pharma AG. Some of the outcomes were as follows:

- Among patients receiving the combination of VGP 100 mg daily and the TZD pioglitazone 30 mg daily (Actos, Takeda/Eli Lilly) over 24 weeks, the mean HbA$_{lc}$ reduction from a baseline of 8.7% was 1.9% ($P < .001$) versus pioglitazone 30 mg alone.
- Among patients with high baseline HbA$_{lc}$ values (above 9%), the reduction was greater, at 2.8%.
- Among elderly patients, the mean reduction was 2.3%.
- Among obese patients with a BMI of 35 or higher, the mean reduction was 2.2%.
- Among treatment-naïve patients and those not achieving their goals with metformin, HbA$_{lc}$ was lowered by 1.1% with VGP monotherapy.

Weight change was not significant, and tolerability was “placebo-like,” according to Dr. Nathwani. He added:

“The fact that patients receiving VGP have a five-fold increase in beta-cell function plus enhanced insulin sensitivity suggests potential for long-term disease modification.”

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**Meeting Highlights: ADA**

*continued from page 452*