**<MAIN HEADER>EMERGING THERAPIES</>**

**Inhaled insulin pushing back**

**NO PHOTO**

Inhaled insulin may be returning to the US market.

That’s the hope at MannKind Corp, whose inhalation powder is featured in multiple presentations at the ADA’s Scientific Sessions this year. Research is showing that patients prefer inhaled insulin over subcutaneous injections for controlling postprandial glucose excursions; that the company’s whistle-sized, high-resistance inhaler produces consistent insulin delivery for a wide range of users; and that the produce suppresses endogenous glucose production more quickly than standard therapy with insulin lispro.

A joint ADA-<ital>*Lancet*</ital> symposium later today will detail data showing that Afrezza (insulin human [rDNA origin]) inhalation powder provides comparable glycemic control versus standard therapy, with less weight gain and less hypoglycemia. A Monday session will present 2-year data on hypoglycemia and weight gain.

Afrezza is an investigational, ultra-rapid-acting, mealtime insulin. It is typically combined with once-daily injected glargine, said Daniel Lorber, MD, coauthor of the <ital>*Lancet*</ital>study and medical director of the Diabetes Control Foundation, Diabetes Care and Information Center, Flushing, New York.

“Insulin therapy is often a delayed strategy in patients with type 2 diabetes because it is associated with weight gain, hypoglycemia, and the need for subcutaneous injections,” Lorber explained. “Our findings show that mealtime Afrezza with once-daily injected glargine provides equivalent glucose control with fewer injections, less hypoglycemia, and less weight gain than twice-a-day premixed insulin.”

A randomized study with 334 patients using Afrezza and 343 patients using premixed 70/30 insulin twice daily found similar glycemic control results. The Afrezza group had significantly less weight gain (0.9 kg vs 2.5 kg; <ital>*P*</ital>=.0002) over the study period. Patients using Afrezza also had significantly less mild to moderate hypoglycemia (48% vs 69%; <ital>*P*</ital><.001) and significantly less severe hypoglycemia (4% vs 10%; <ital>*P*</ital>=.0066). Pulmonary function test changes from baseline to week 52 were similar in the 2 groups.

Exubera (Pfizer), the first, and so far only, inhaled insulin to be approved by the FDA, was introduced in 2006 and withdrawn in 2007 because of poor sales. Novo Nordisk and Eli Lilly terminated their own inhaled insulin programs in 2008 and 2009, respectively. MannKind is currently preparing to resubmit its new drug application to FDA after a request for additional information earlier this year.

**<headline>Investigational insulin associated with less hypoglycemia, less weight gain</>**

**PLEASE USE PHOTO HELENA RODBARD.JPG**

**<photo caption>Helena Rodbard, MD</>**

A new form of human insulin (VIAject) that is absorbed more rapidly than insulin lispro or regular human insulin produces less hypoglycemia and less weight gain than regular human insulin in patients with type 2 diabetes, said Helena Rodbard, MD.

Hypoglycemia is common after administering rapid-acting insulin because larger doses are needed to control postprandial glycemia, she said.

VIAject is a very rapid-acting formulation of insulin that promotes rapid absorption that is said to mimic the effects of naturally produced insulin in nondiabetics.

Rodbard, an endocrinologist at Endocrine and Metabolic Consultants in Rockville, Maryland, presented the final analysis of a 6-month, open-label, parallel-group multinational (United States, Germany, India) study of 471 patients with type 2 diabetes who were randomized to either VIAject or regular human insulin when used in combination with previously prescribed insulin glargine, metformin, and/or thiazolidinedione therapy. To be included, patients had to have a hemoglobin (Hb) A<sub>1c</sub> level of 10.5% or less and be on a stable insulin regimen for at least 3 months.

The patients randomized to VIAject were advised to reduce premeal insulin to 50% of the pretrial prandial dose; those randomized to regular human insulin had dose initiation at the discretion of the investigator.

At 26 weeks, the reduction in levels of HBA<sub>1C</sub> was similar in both groups—by 0.56% in the VIAject group and 0.70% in the regular human insulin group. Fasting plasma glucose declined by a mean of about 25 mg/dL in each group.

There were a total of 1,919 hypoglycemic events (defined as glucose <70 mg/dL or symptomatic episodes resolving with treatment) in patients randomized to VIAject compared with 3,144 in those randomized to regular human insulin, a median subject event rate of 0.33 in the VIAject group versus 0.66 in the regular human insulin group (<ital>*P*</ital>=.018).

Patients taking VIAject gained 0.46 kg compared to a 1.35-kg weight gain in those taking regular human insulin (<ital>*P*</ital><.03).

The prevalence of injection site reactions (pain or irritation) was higher in the VIAject group, a difference that declined during the course of the study.

**<MAIN HEADER>NEW RESEARCH</>**

**<headline>Hypoglycemia raises risk of acute cardiovascular events</>**

**PLEASE USE PHOTO CHRISTOPHER CONNER.JPG**

**<photo caption>Christopher Conner, PharmD, PhD</>**

In adults with type 2 diabetes, hypoglycemic episodes increase the risk of adverse cardiovascular events, according to a retrospective analysis of a large healthcare claims database.

The data support similar findings from recent clinical trials, said the study’s lead investigator Christopher Conner, PharmD, PhD.

Conner and colleagues extracted healthcare claims from the Thomson Reuters MarketScan Research Databases, which include US individuals with employer-sponsored primary or Medicare supplemental insurance. They examined ICD-9-CM codes to look for an association between hypoglycemic events and acute cardiovascular events, including acute myocardial infarction, revascularization procedures, and new unstable angina in patients with type 2 diabetes who were 18 years old or older.

A baseline period (September 30, 2006, to September 30, 2007) was used to identify eligible patients and collect information on their clinical and demographic characteristics. An evaluation period (October 1, 2007, to October 30, 2008) was used to identify hypoglycemic events and adverse cardiovascular events.

Data were adjusted for important confounding variables such as age, sex, geography, insurance type, comorbidity scores, cardiovascular risk factors, diabetes complications, total baseline medical expenditures, and prior adverse cardiovascular events.

Of the 860,845 patients in the analysis set, 27,065 had hypoglycemic events during the evaluation period.

The adjusted odds of an adverse cardiovascular event was 79% higher in those with hypoglycemic episodes compared with those without hypoglycemic episodes, said Conner.

Age and prior cardiovascular events were the only 2 stronger predictors of an adverse cardiovascular event than hypoglycemic episodes among 17 significant variables examined. “Patients of all ages with temporally precedent [before the acute cardiovascular event] hypoglycemic events had a 27% higher regression-adjusted odds of adverse cardiovascular events than patients without temporally precedent hypoglycemic events,” he said.

Good glycemic control remains critically important, Conner said, and the analysis does not suggest a role of glycemic control in the relationship between hypoglycemic episodes and the risk of cardiovascular events.

**<headline>Diabetes exposure in utero increases risk of early ESRD</>**

**PLEASE USE PHOTO NELSON PORTRAIT.JPG**

**<photo caption>Robert G Nelson, MD</>**

Being exposed to diabetes in utero substantially increases the risk of premature end-stage renal disease (ESRD), found Robert G Nelson, MD.

The finding comes from a study of Pima Indians 5 to 44 years old with type 2 diabetes, 102 of whom were the offspring of diabetic mothers and 1,748 without diabetes exposure in utero.

“Pima Indians have the highest rate of type 2 diabetes in the world. We’ve been studying the population since 1965, so we have extensive longitudinal data that allows us to look not only at disease in the parents, but in the offspring, and follow them into adulthood,” said Nelson.

An earlier study by Nelson and colleagues showed that exposure to diabetes in utero caused a dramatic increase in the development of diabetes in youth. About one-third of cases of diabetes in young adulthood are attributable to diabetes exposure in utero, he said.

Genetic susceptibility from the mother can partially explain the early onset of diabetes in the offspring, Nelson said. Intrauterine exposure also is associated with higher birth weight and higher weight in childhood and adolescence compared with persons without such exposure.

In the current study, the participants were followed for a maximum of 40 years, from their onset of diabetes until either death, onset of ESRD, or age 45 years.

Fifty-seven of the participants who were exposed to diabetes in utero developed ESRD before age 45, which was 4 times the rate of ESRD compared with controls who were not exposed to diabetes in utero.

“Twenty percent of ESRD that occurs in the population before age 45 is attributable to exposure to diabetes in utero,” said Nelson. Assuming this relationship is causal, “if you delayed the development of diabetes until after the onset of childbearing years, you would reduce the incidence of diabetic ESRD by about 20%,” he said.

If the offspring are exposed to diabetes in utero, diabetes prevention efforts in the form of lifestyle modifications (diet and exercise) are needed to slow or prevent the development of diabetes and its complications, Nelson said.

**<headline>Hypoglycemia during hospitalization increases in-patient mortality risk</>**

**PLEASE USE PHOTO KIMBERLY G BRODOVICZ.JPG**

**<photo caption>Kimberly G Brodovicz, DrPH</>**

Hypoglycemia among insulin-treated hospitalized patients increases the risk of hospital mortality, according to findings from a retrospective cohort study.

Insulin is the standard in-hospital treatment for insulin-treated patients with diabetes, patients with diabetes treated with oral agents before their hospitalization, or those who develop stress-induced hyperglycemia during their hospitalization, said coinvestigator Samuel Engel, MD.

“Previously, the goal for treating patients in the hospital was to attempt to normalize their glucose levels and drop it below 110 mg/dL,” Engel said, but a large, randomized, controlled study called NICE SUGAR showed no clear benefit and a potential risk to aggressive versus conventional glucose management in patients admitted to the intensive care unit (ICU). This study led to a revision of glucose targets.

“Now, we’re looking at keeping blood glucose levels below the 140 to 150 mg/dL range,” said Engel. American Diabetes Association and American Association of Clinical Endocrinologists guidelines on goals for glycemic control released in 2009 call for a glucose target of 100 to 180 mg/dL for patients admitted to general medical wards (140 to 180 mg/dL in the ICU setting).

“The new target was chosen to be a level high enough so that even if there was unusual sensitivity to insulin, patients would still be above the hypoglycemia threshold,” said Engel, director in clinical research-metabolism, Merck Research Laboratories, North Wales, Pennsylvania.

In the study presented here, more than 107,000 general-ward and intensive-care admissions from 70 US hospitals were studied. Patients who were aged 30 years or older, who received insulin during their hospitalization and had valid glucose results available, and who were hospitalized from 24 hours to less than 30 days were included in the analysis.

Nonsevere hypoglycemia (blood glucose ≤70 mg/dL) occurred during 20% of admissions, and severe hypoglycemia (blood glucose ≤50 mg/dL) occurred in 7%.

Compared to the patients admitted who did not develop hypoglycemia, those with hypoglycemia had a 46% increased risk of in-patient mortality after adjusting for age, sex, hospital characteristics, and certain comorbidities. The group with severe hypoglycemia had an approximately 80% increased risk, and the group with nonsevere hypoglycemia had a 27% increased risk of in-patient mortality, said coinvestigator Kimberly G Brodovicz, DrPH, associate director in epidemiology at Merck Research Laboratories.

“This study highlights in perhaps a more relevant context the importance of avoiding hypoglycemia in this population,” said Engel.

Alternative therapies that could reduce blood glucose without causing hypoglycemia, such as incretin-based therapies or investigational agents, may potentially be of benefit in the in-patient setting, although the ability to use alternative agents in this setting has not yet been realized, the coinvestigators agree.

**<MAIN HEADER>PATIENT MANAGEMENT</>**

**<headline>Sulfonylureas not helpful in preventing type 2 diabetes</>**

**NO PHOTO**

Clinicians with patients who need oral drug therapy to prevent type 2 diabetes mellitus should stick to thiazolidinediones (TZDs), alpha-glucosidase inhibitors (AGIs), and biguanides. Sulfonylureas are not likely to help.

“The real message is that 3 agents work to prevent type 2 diabetes and 1 does not,” said Craig Coleman, PharmD, associate professor of pharmacy practice, University of Connecticut School of Pharmacy. “If all things are equal, go ahead and give a glitazone, but you should always make an individual decision with each patient.”

Although there are few head-to-head comparisons of oral antidiabetic agents, researchers conducted a meta-analysis of 19 randomized, controlled trials reported through May 2009. The trials included almost 14,000 participants at high risk for developing type 2 diabetes mellitus based on impaired glucose tolerance, impaired fasting glucose, history of gestational diabetes, or obesity.

Using a mixed treatment comparison, the team concluded that TZDs reduce the risk ratio of progressing to diabetes by 63%, AGIs by 40%, and biguanides by 27%. Metformin, a biguanide, is the only oral antidiabetic recommended under current ADA treatment guidelines to prevent the development of type 2 diabetes mellitus.

The current guidelines were developed largely based on data from the Diabetes Prevention Program (DPP) trial, Coleman noted. The guidelines emphasize diet and exercise over drug therapy, he continued, but several new agents have been developed since DPP was reported in 2002.

“We now have newer agents, particularly the glitazones,” he explained. “We wanted to compare these classes of agents. It appears that the glitazones have a superior efficacy than metformin.”

The meta-analysis found that TZDs significantly reduced the risk of developing type 2 diabetes mellitus by 50% compared with biguanides and trended toward a 40% risk reduction compared with AGIs. Sulfonylureas showed a 5% increase in risk compared to placebo.

“I’m not advocating that everyone get a glitazone,” Coleman said. “There are multiple agents that are efficacious.”

There are also concerns about cardiovascular disease and rosiglitazone. The ADA currently recognizes pioglitazone as the preferred agent in this class. Rosiglitazone is not mentioned because of data suggesting an increased risk of cardiovascular events in patients with advanced heart disease.

**<headline>Healthcare reform to boost diabetes care</>**

**PLEASE USE PHOTO RONALD ACKERMAN.JPG**

**<photo caption>Ronald Ackerman, MD, MPH</>**

**PLEASE USE PHOTO SHEREEN ARENT.JPG**

**<photo caption>Shereen Arent, JD</>**

**PLEASE USE PHOTO STEVEN WOOLF.JPG**

**<photo caption>Steven Woolf, MD, MPH</>**

**PLEASE USE PHOTO DENEEN VOJTA.JPG**

**<photo caption>Deneen Vojta, MD</>**

The bruising battle over healthcare reform has one clear winner, diabetes care. It may not be a total victory, but it is a major improvement.

“This is an exciting time, especially for patients,” said Ronald Ackerman, MD, MPH, assistant professor of internal medicine, Indiana University, Indianapolis. Ackerman moderated a Friday afternoon symposium on the implications of US healthcare reform for the prevention and care of diabetes. “Diabetes is a driving factor in the need for healthcare reform in the United States,” he said.

The Patient Protection and Affordable Care Act, also known as healthcare reform, will help patients access care.

“While the law is far from perfect, it is a watershed,” said Shereen Arent, JD, executive vice president, Government Affairs and Advocacy, American Diabetes Association. “Even if you have health coverage, without healthcare reform, you are one job loss away from being without healthcare.”

Diabetes and other preexisting conditions can no longer be used to deny or cancel coverage. Benefit caps must be reasonable, and state exchanges will make it easier to obtain coverage. The law also sets standards for prevention and wellness benefits. It creates both a national diabetes report card and a national diabetes prevention program.

However, reform doesn’t take full effect until 2014. There are also significant statutory gaps to be filled by regulatory language, and reform will involve multiple players.

“There is far greater success in modifying risk behaviors than anything we can do in clinical treatment,” said Steven Woolf, MD, MPH, professor of family medicine, epidemiology, and community health, Virginia Commonwealth University, Richmond. “There are larger social and environmental factors at work,” he said.

One insurer is using financial incentives to encourage lifestyle changes that will be a money saver.

“If we don’t reduce health risks, the cost trajectories will continue to accelerate,” said Deneen Vojta, MD, senior vice president, UnitedHealth Center for Health Reform and Modernization, Minnetonka, Minnesota. “We need to reach out to clinicians and patients to engage and transform their risk behaviors.”

UnitedHealth has 2 successful diabetes programs. The Diabetes Prevention Control Alliance is the Diabetes Prevention Program scaled up and rolled out nationwide, Vojta explained. UnitedHealth works with employers to identify employees at risk and entices them into a 20-week YMCA program. UnitedHealth pays for the program and saves money, because a 5% weight loss cuts the risk of progressing to diabetes by 58%, dramatically reducing future costs.

The insurer has a similar diabetes control partnership with Walgreen’s, based on the Asheville Project and Diabetes Ten City Challenge, using pharmacists to monitor, counsel, and care for patients. The program uses real-time reimbursement as an incentive for clinicians and pharmacists. Patients pay nothing for individual hands-on care from the healthcare professional they see most frequently and trust the most.