Results After 3 Months

Pioglitazone *from page 1*

zone group by the end of the study, compared with 28% on placebo.

"It's a very impressive study. Those are numbers you don't see very often," Dr. Paul Jellinger commented in a phone interview.

The findings are likely to increase the off-label treatment of prediabetes with thiazolidinediones (TZDs) as monotherapy or in combination with metformin, according to Dr. Jellinger, professor of medicine on the voluntary faculty at the University of Miami and a past president of both the American College of Endocrinology and the American Association of Clinical Endocrinologists. Dr. Jellinger is on the speakers bureau of Takeda Pharmaceutical Co., which makes pioglitazone, as well as the speakers bureaus for Merck, Novo Nordisk, Eli Lilly & Co., Amylin Pharmaceutical, and GlaxoSmithKline.

There are no medications approved for the treatment of prediabetes to prevent progression to diabetes. Metformin probably is the most common off-label treatment used for this purpose, Dr. Jellinger said, because a previous study showed similar—though not as striking—benefits. Adding metformin may modulate some of the weight gain associated with TZDs, he noted.

In Dr. DeFronzo's trial, called the Actos Now for Prevention of Diabetes (ACT NOW) study, patients started with an average body mass index of 34 kg/m^2 and gained a mean of 3.5 kg (about 8 pounds) in the pioglitazone group and 0.7 kg (less than 2 pounds) in the placebo group over a mean 2.6-year follow-up.

Patients had a mean age of 52 years and were recruited in eight medical centers over a 2-year period, then followed for at least 2 more years or until a diabetes diagnosis. All had 2-hour glucose values of 140-199 mg/dL on oral glucose tolerance test, a fasting plasma glucose concentration of 95-125 mg/dL, and one or more other high-risk characteristics (at least one component of the metabolic syndrome, a family history of type 2 diabetes, a history of gestational diabetes, the presence of polycystic ovary syndrome, or minority ethnic background).

A combination of impaired glucose tolerance and impaired fasting glucose was present in 68% of patients, and the rest had isolated impaired glucose tolerance. Compared with 102 healthy matched controls, patients in the study showed a 48% reduction in insulin sensitivity and a 78% decrease in the insulin secretion/insulin resistance index.

Patients were randomized to treatment with placebo or 30 mg/day pioglitazone. If the drug was tolerated after 1 month, the dose could be increased up to 45 mg/day.

"What was quite surprising was how quickly pioglitazone dropped the fasting glucose," Dr. DeFronzo said. "Within the first 3 months of initiating pioglitazone, there was a defined decrease in glucose" separating the two groups that was maintained to the end.

One new case of diabetes could be avoided per year for every 3.5 patients treated with pioglitazone.

DR. DEFRONZO

The study had 90% power to detect at least a 50% reduction in progression to diabetes in the treatment group vs. placebo.

Future long-term research should examine whether treating prediabetes with TZDs or metformin delays or actually prevents progression to diabetes, and whether these drugs reduce cardiovascular events in these patients, Dr. Jellinger suggested.

Dr. DeFronzo is an adviser and speaker for Takeda, which funded the study. He also is a consultant, adviser, or speaker for, or has received research support from, Bristol-Myers Squibb Co., Amylin Pharmaceuticals Inc., Eli Lilly & Co., Novartis, Pfizer Inc., Roche Diagnostics, AstraZeneca Pharmaceuticals LP, Johnson & Johnson, and Isis Pharmaceuticals Inc. ■

Same Heart Effects With Basal, Prandial Insulin Following MI

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — Basal or mealtime insulin worked equally well to treat patients with type 2 diabetes after a myocardial infarction, but the mealtime group needed more insulin in a randomized, open-label study of 1,112 patients.

Previous epidemiological studies have shown an association between postprandial hyperglycemia and acute MI or death in people with diabetes. Every 1-mmol/L decrease in postprandial hyperglycemia after glucose challenge was thought to be associated with a 9% reduction in risk for MI or death in patients with diabetes.

Postprandial glucose levels in the current study were significantly higher in patients who used basal insulin therapy than in those on prandial insulin therapy, but there was no significant difference between groups in the primary end point of cardiovascular outcomes including cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for acute coronary syndromes, Dr. Itamar Raz and his associates reported.

The planned 3-year study was stopped early because of the lack of difference after a mean of 2.6 years. In the basal insulin group, 32% of patients had at least one cardiovascular event, compared with 31% in the prandial insulin group, he said at the annual scientific sessions of the American Diabetes Association.

Hemoglobin A_{1c} (HbA_{1c}) levels ended up being similar between groups, according to a preliminary intent-to-treat analysis of data from the HEART2D (Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Type 2 Diabetes Mellitus) trial.

Approximately half of patients in each group reached group-specific blood glucose targets, but patients in the prandial insulin group needed more insulin to reach them, said Dr. Raz of the Hadassah University Medical Center, Jerusalem.

Insulin-naive patients were randomized within 21 days of an acute MI to diabetes therapy with either prandial insulin (lispro t.i.d.) or basal insulin (twice-daily NPH insulin or once-daily glargine). The prandial group aimed for a 2-hour postprandial glucose level less than 7.5 mmol/L, and the basal group target was a fasting and plasma blood glucose level less than 6.7 mmol/L.

Both groups aimed for an HbA_{1c} level below 7%, and rescue therapy was started if the HbA_{1c} level was higher than 8% on two consecutive visits. For rescue, the prandial group added bedtime NPH, and the basal group converted to 70% human insulin isophane suspensions with 30% human insulin injection (Humulin 70-30).

Eli Lilly & Co., which makes insulin lispro and Humulin 70-30, sponsored the study, and some of Dr. Raz's coinvestigators were Lilly employees. Dr. Raz has been an adviser or consultant to Sanofi-Aventis, which makes insulin glargine, and to other companies including Merck & Co., the American Type Culture Collection, Keryx Biopharmaceuticals Inc., Johnson & Johnson, Pfizer Inc., and Oramed Pharmaceuticals.

Concomitant cardiovascular medications were used by 95% of patients in each group.

Patients had a mean age of 61 years, and just over a third in each group were older than 65 years. All had diabetes for at least 3 months at enrollment, no clinical signs of heart failure, and a left ventricular ejection fraction of 30% or greater.

There were 51 deaths in each group during the trial, mainly because of cardiovascular causes. Stroke killed 3 patients in the prandial insulin group and 2 in the basal group, and cardiovascular events killed 44 patients in the prandial group and 42 in the basal group. ■

Metformin May Improve Response in Breast Cancer

BY FRAN LOWRY
Orlando Bureau

CHICAGO — The widely used diabetes drug metformin may have an antitumor effect, according to data from a retrospective study of more than 2,500 breast cancer patients, including 155 women with diabetes.

Patients taking metformin for diabetes had a threefold higher pathologic complete response (pCR) rate after neoadjuvant chemotherapy, compared with those who had diabetes but were not on metformin (24% vs. 8%, $P = .007$), Dr. Sao Jiralerspong of the University of Texas M.D. Anderson Cancer Center in Houston reported in a poster at the annual meeting of the American Society of Clinical Oncology.

The rate of pCR, defined as no residual disease in the breast or lymph nodes, also was higher in the cohort of patients taking metformin than in patients without diabetes, who had a pCR rate of 16% after neoadjuvant chemotherapy ($P = .099$).

Recent epidemiologic studies suggest that metformin may reduce the incidence of cancer and cancer-related mortality in diabetic patients. The drug activates adenosine monophsphate-activated protein (AMP) kinase, inhibits the mammalian target of rapamycin (mTOR) pathway, and has been shown to inhibit the growth of breast cancer cell lines in pre-clinical studies, said Dr. Jiralerspong.

To explore the possibility that metformin's antiproliferative effects might increase the efficacy of neoadjuvant chemotherapy in diabetic breast cancer patients, Dr. Jiralerspong and his colleagues reviewed the charts in the M.D. Anderson Breast Medical oncology database of 2,529 patients who received neoadjuvant systemic therapy for early stage breast cancer.

Ninety-four percent of patients (2,374) did not have diabetes; 68 patients had diabetes and were treated with metformin, and 87 patients had diabetes but were not treated with metformin. The median age of the full study population was 49 years (range 21-87 years), most of the tumors were hormone receptor–positive, and 25% were HER2-positive. Baseline characteristics of patients with and without diabetes were similar, although the diabetic groups tended to be slightly older and more obese, Dr. Jiralerspong noted.

Metformin use was independently predictive of pCR (odds ratio 3.2, $P = .023$) after adjustment for diabetes, body mass index, age, stage, grade, estrogen receptor (ER)/progesterone receptor (PR) status, and neoadjuvant taxane use.

After a median follow-up of 39 months, the recurrence-free survival was similar in the three groups. Overall survival was significantly better, however, in the nondiabetic cohort (86%), compared with 81% for the diabetic patients on metformin and 78% for the diabetic patients not on metformin ($P = .02$).

"This could just be due to short follow-up, and also there may be other factors at play. Diabetics probably are going to do worse in general, and we are starting to look at the causes of death now because it might have been non-cancer causes of death that produced these results," Dr. Jiralerspong said.

He emphasized that this retrospective analysis was hypothesis generating, but said that the results warrant prospective studies to more fully evaluate the potential of metformin as an antitumor agent.

Dr. Jiralerspong said he had no conflicts of interest to declare. ■