Authors and Disclosures

Journalist

Jennifer Garcia

Jennifer Garcia is a freelance writer for Medscape.

Disclosure: Jennifer Garcia has disclosed no relevant financial relationships.

From Medscape Medical News

Dapagliflozin Effective Addition in Type 2 Diabetes

Jennifer Garcia

March 21, 2012 — Dapagliflozin, a selective inhibitor of sodium–glucose cotransporter 2 (SGLT2), improves glycemic control, stabilizes insulin requirements, and reduces weight without increasing major hypoglycemic episodes when added to insulin therapy in patients with inadequately controlled type 2 diabetes mellitus. These are the findings of a 48-week, randomized, placebo-controlled, multicenter study by John Wilding, MD, from the Diabetes and Endocrinology Research Group, Department of Obesity and Endocrinology, Clinical Sciences Center, University Hospital Aintree, Liverpool, United Kingdom, and colleagues, published in the March 20 issue of the *Annals of Internal Medicine*.

From April 2008 to November 2009, the researchers evaluated 808 patients with inadequately controlled type 2 diabetes (defined as a hemoglobin A1C [HbA1c] level ≥7.5% and ≤10.5%) who were receiving at least 30 U of insulin daily, with or without an oral antidiabetic drug (OAD). Patients were randomly assigned to receive placebo or 2.5, 5, or 10 mg of dapagliflozin daily, in addition to their insulin and existing OAD, for 24 weeks, with a 24-week extension period. An additional 56-week extension period is ongoing.

The primary outcome of the trial was a change in HbA1c from baseline to 24 weeks. Secondary outcomes included changes in insulin dose, body weight, and fasting plasma glucose level at 24 weeks and during the 24-week extension period. The investigators also evaluated adverse events throughout the 48-week period.

The researchers found that after 24 weeks, the mean HbA1c decreased by from 0.79% to 0.96% with dapagliflozin compared with 0.39% with placebo (mean difference, −0.40% [95% confidence internal [CI], −0.54% to −0.25%] in the 2.5-mg dapagliflozin group, −0.49% [95% CI, −0.65% to −0.34%] in the 5-mg group, and −0.57% [95% CI, −0.72% to −0.42%] in the 10-mg group).This effect was sustained at the 48-week follow-up.

In addition, patients in the intervention group lost more weight than those receiving placebo (mean difference, −1.35 kg [95% CI, −1.90 to −0.80 kg] in the 2.5-mg group, −1.42 kg [95% CI, −1.97 to −0.88 kg] in the 5-mg group, and −2.04 kg [95% CI, −2.59 to −1.48 kg] in the 10-mg group).

Less Insulin Required

Patients in the dapagliflozin group also required less insulin compared with those treated with placebo (mean difference, −7.60 U [95% CI, −10.32 to −4.87 U] in the 2.5-mg group vs placebo, −6.28 U [95% CI, −8.99 to −3.58 U] in the 5-mg group, and −6.82 U [95% CI, −9.56 to −4.09 U] in the 10-mg group).

"Dapagliflozin, a competitive and highly selective inhibitor of [SGLT2], reduces renal glucose reabsorption, increases renal glucose excretion, and reduces hyperglycemia in a dose-dependent manner. Because dapagliflozin acts independently of insulin, it may provide additional glycemic control when used with insulin. Moreover, the caloric loss and osmotic diuresis secondary to increased urinary glucose excretion may counter insulin-related weight gain and fluid retention, respectively," the authors write.

They note, however, that adverse effects were more likely among patients in the dapagliflozin group. These patients were more likely to have at least 1 hypoglycemic event compared with those patients in the placebo group: "60.4%, 55.7%, and 53.6% in the 2.5-mg, 5-mg, and 10-mg dapagliflozin groups, respectively, vs. 51.8%" in the placebo group. However, none of these events led to discontinuation of therapy.

Signs and symptoms of genitourinary infections were also noted more often among patients receiving dapagliflozin, mostly during the first 24 weeks of treatment. These events were noted primarily among women and most responded to routine therapy. Two patients in the 10-mg dapagliflozin group, 2 patients in the 5-mg dapagliflozin group, and 1 patient in the 2.5-mg dapagliflozin group discontinued treatment as a result of a genitourinary infection.

The researchers note that adjustments to the OAD or insulin doses were only made if they were needed to ensure patients' well-being. If fasting blood glucose concentration were higher than 13.3 mmol/L (>240 mg/dL) between weeks 0 and 12, higher than 12.2 mmol/L (>220 mg/dL) between weeks 12 and 24, or higher than 9.9 mmol/L (>180 mg/dL) between weeks 25 and 48, an increase in the insulin dose of less than 5 U or less than 10% from baseline was permitted. Changes were based on a site-measured reading at the study visit or on at least 3 self-monitored readings in the 7 days before the study visit. An increase was also permitted if HbA1c was greater than 8% between weeks 25 and 48. The insulin dose was reduced if 2 or more self-monitored blood glucose readings were 4.4 mmol/L or lower (≤80 mg/dL) in the first 7 days of active treatment or ≤3.8 mmol/L (≤70 mg/dL) after the first 7 days.

Patients with type 1 diabetes, calculated creatinine clearance of less than 50 mL/minute/1.73 m^2, or a measured serum creatinine level higher than 177 µmol/L (>2 mg/dL) were excluded from the study. Those patients with symptoms of poorly controlled diabetes or those receiving more than 133 µmol/L (men) or at least 124 µmol/L (women) of metformin were also excluded. Patient demographic characteristics were similar for all groups, with a mean insulin dose of 77.1 U, a mean baseline HbA1c level of 8.53%, and a mean baseline fasting plasma glucose level of 9.9 mmol/L (177.6 mg/dL).

Study Limitations

The authors acknowledge the limitations of the study, which include the predominately white patient population, the post hoc statistical analysis used to account for missing data, the fact that insulin doses were not titrated to target, and that the sample size and duration did not allow for evaluation of the risk for cancer with long-term dapagliflozin use.

Despite the study limitations and increased rates of hypoglycemia, Dr. Wilding and colleagues found that the addition of dapagliflozin to the treatment regime of patients with inadequately controlled type 2 diabetes successfully reduced HbA1c levels and weight over 48 weeks. "These data suggest that dapagliflozin may offer a new treatment option for patients receiving insulin therapy whose type 2 diabetes remains inadequately controlled," the study authors conclude.

In an accompanying editorial, Steven A. Smith, MD, from the Mayo College of Medicine, Rochester, Minnesota, notes that, "Although SGLT inhibitors may represent a new class of drugs for managing hyperglycemia and

possibly obesity, the understanding of the SGLT system, cellular glucose transport, and the ability to induce glycosuria as a potential management option for type 2 diabetes has been evolving over the past 2 centuries."

Dr. Smith notes that the study did not clearly evaluate the hypothesis that dapagliflozin may be beneficial to patients at risk for fluid retention, and lacked the statistical power needed to evaluate the possible association between dapagliflozin and breast and bladder cancer. This concern regarding the risk for cancer was also raised by the US Food and Drug Administration (FDA) advisory committee, in response to a new drug application for dapagliflozin. The FDA voted against approval in July 2011, and Dr. Smith comments that they will likely not approve dapagliflozin without more data.

Another limitation not discussed by the study authors, notes Dr. Smith, is the absence of information regarding patient experience with the use of dapagliflozin. The effect of gastrointestinal adverse effects, polyuria, and genitourinary infections on patient well-being remains unknown, as does the long-term effect of the drug on renal function.

Despite what appear to be promising results, "[i]n truth, after 2 centuries of study, we remain uncertain of the appropriate use and long-term safety of SGLT2 inhibition in persons with diabetes," concludes Dr. Smith.

Funding for this study was provided by AstraZeneca and Bristol-Myers Squibb. Dr. Wilding and one coauthor are consultants for AstraZeneca and Bristol-Myers Squibb, and 4 coauthors are employees of AstraZeneca. The other authors and the editorialist have disclosed no relevant financial relationships.

Ann Intern Med. 2012;156:405-415, 466-467. Article abstract, Editorial extract