Novel Drug Aids Type 2 Diabetics on Metformin

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Dapagliflozin significantly reduced hemoglobin A_{1c} levels compared with placebo in a phase III, multicenter, randomized, double-blind, placebo-controlled trial involving 534 patients with type 2 diabetes inadequately controlled with metformin alone.

The study was funded by dapagliflozin codevelopers Bristol-Myers Squibb (BMS) and AstraZeneca (AZ). The drug is a selective inhibitor of the sodium-glucose cotransporter 2 (SGLT2), which is located in the proximal tubule of the kidney nephron and functions to reabsorb most of the glucose filtered by the glomerulus. By binding to SGLT2 and inhibiting renal glucose reabsorption, dapagliflozin promotes urinary glucose excretion and reduces blood glucose levels independently of beta-cell function or insulin sensitivity, Dr. Clifford J. Bailey reported at the meeting. The findings were published simultaneously (Lancet 2010;375:2223-33).

In all, 546 patients were randomized to 2.5-mg, 5.0-mg, or 10.0-mg once-daily doses of dapagliflozin or placebo for 24 weeks, in addition to their usual metformin doses. Among the 534 who completed the trial, reductions in HbA_{1c} were significantly greater in the dapagliflozin groups, with mean reductions from baseline of 0.67, 0.70, and 0.84 percentage points with the 2.5-, 5.0-, and 10.0-mg doses, respectively, compared with 0.30 for placebo.

More patients in the dapagliflozin groups achieved an HbA_{1c} value of less than 7.0% at week 24 than did those in the placebo group, with the difference reaching statistical significance for the 5.0- and 10.0-mg doses (37.5% and 40.6%, respectively, vs. 25.9% for placebo). Differences in plasma fasting glucose concentrations were notable by week 1 in the dapagliflozin groups, and by week 24 were significant for all three doses (reductions of 18-23 mg/dL compared with 6 mg/dL with placebo).

Weight loss was also greater with dapagliflozin, compared with those assigned to placebo. At week 24, the 2.5-, 5.0-, and 10.0-mg groups had lost 2.2, 3.0, and 2.9 kg, respectively, compared with 0.9 kg for placebo patients. This reduction is potentially attributable to the loss of excess energy through glucose excretion in the urine, said Dr. Bailey, of Aston University, Birmingham, England.

Urinary glucose excretion increased in all of the dapagliflozin groups, whereas creatinine remained constant, Dr. Bailey noted.

There were no deaths during the study, and overall adverse events leading to discontinuation were less frequent with dapagliflozin than placebo. There were no major hypoglycemic events.

Signs, symptoms, and other reports suggestive of urinary tract infections were not increased with dapagliflozin, but reports of those suggesting genital infections were: These were reported by 8%-13% in the dapagliflozin groups, compared with 5% in the placebo group. The increased rate occurred in both men and women. All were of mild or moderate intensity and resolved with treatment, and none led to study discontinuation.

Genital infections are not uncommon in patients with diabetes and can be appropriately managed with better appreciation of those at higher risk, Dr. Bailey pointed out.

Serious adverse events were not associated with any particular group. No clinically meaningful changes in serum electrolytes occurred in any of the groups, and abnormalities in serum sodium and serum potassium were rare and transient. No alterations were seen in measures of renal function, including serum creatinine. No apparent changes occurred in fasting lipid profiles with dapagliflozin other than greater mean HDL cholesterol and lower triglycerides compared with placebo, he noted.

Aside from BMS and AZ, Dr. Bailey also has consulted for Merck Sharp & Dohme, Novo Nordisk, GlaxoSmithKline, and Takeda and has received research grants from Sanofi-Aventis. Three other study authors are employees of BMS, while BMS was the only disclosure for the fifth investigator. ■