Long-term Canagliflozin Is Efficacious and Generally Well Tolerated in Older Patients

Written by Kate Mann

Kaj Stenlöf, MD, PhD, Sahlgrenska University Hospital, Gothenburg, Sweden, presented the results of a double-blind phase 3 study of the sodium-glucose cotransporter 2 inhibitor canagliflozin in patients aged 55 to 80 years. The investigators found that the 100-mg and 300-mg doses of canagliflozin each improved glycemic control, reduced body weight, lowered blood pressure (BP), and were generally well tolerated in older patients with type 2 diabetes mellitus (T2DM) over 104 weeks. The adverse event (AE) profile was similar with that observed in a broad range of canagliflozin-treated patients.

Treatment of the older patients with T2DM can be complex given that these patients often have advanced T2DM, multiple comorbidities, and need combination therapy [Inzucchi SE et al. *Diabetes Care*. 2012]. In short-term trials, canagliflozin has demonstrated improvement in glycemic control and bodyweight [Lavalle-González FJ et al. *Diabetologia*. 2013; Schernthaner G et al. *Diabetes Care*. 2013; Stenlöf K et al. *Diabetes Obes Metab*. 2013; Wilding JP et al. *Int J Clin Pract*. 2013; Yale JF et al. *Diabetes Obes Metab*. 2013; Rosenstock J et al. *Diabetes Care*. 2012], as well as reductions in BP across a broad population of patients with T2DM, including older patients [Forst T et al. *Diabetes Obes Metab*. 2014; Bode B et al. *Hosp Pract (1995)*. 2013].

According to Prof Stenlöf, the objectives of this trial were to evaluate the long-term efficacy and safety of canagliflozin, 100 mg and 300 mg, in older patients with T2DM whose HbA_{1c} values were inadequately controlled (7% to 10%) on their current treatment regimens. Among the 714 patients in the study, 74% were currently taking an antihyperglycemic agent (AHA) associated with hyperglycemia; 23% were on an AHA not associated with hyperglycemia; and 3% were taking no AHA. Patients were randomized to canagliflozin–100 mg, canagliflozin–300 mg, or placebo and followed for 104 weeks. During the trial, patients were continued on a stable AHA regimen, and progressively stricter glycemic rescue criteria were employed as the study progressed.

The mean age of the sample was 64 years; the mean HbA_{1c} level was 7.7%; and the mean body mass index was 32 kg/m^2. End points included the change from baseline in HbA_{1c}, fasting plasma glucose, percentage change in bodyweight, systolic BP, percentage change in low-density lipoprotein cholesterol (LDL-C), and percentage change in high-density lipoprotein cholesterol (HDL-C) at week 104. The overall safety and tolerability of the drug, including selective AEs, were also assessed. Statistical testing of canagliflozin compared with placebo was not prespecified and thus not conducted for the analyses of efficacy parameters; therefore, no *P* values were reported.

Over 104 weeks, changes in baseline for HbA_{1c} were +0.17% (placebo), –0.49% (canagliflozin, 100 mg), and –0.60% for (canagliflozin, 300 mg). Positive changes were also seen in HbA_{1c}, fasting plasma glucose, bodyweight, and systolic BP (–1.2 mm Hg and –3.0 mm Hg from baseline in the 100-mg and 300-mg treatment groups, respectively). The proportions of patients who achieved $HbA_{1c} < 7.0\%$ at week 104 were 20.3% (placebo), 35.8% (canagliflozin, 100 mg), and 41.9% (canagliflozin, 300 mg). Compared with that of placebo, body weight decreased in both the 100-mg group (–2.3%) and the 300-mg group (–3.2%). Small increases in LDL-C and HDL-C were observed in the 2 canagliflozin groups as compared with patients receiving placebo, although these increases plateaued after 26 weeks.

Canagliflozin was generally well tolerated over 104 weeks, but it was associated with an increased incidence of fungal infections of the genitourinary system and AEs related to osmotic diuresis when compared with placebo (Table 1). The majority of these AEs occurred during the first 26 weeks of treatment.

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Table 1. AEs Specific to SGLT2 Inhibitor Class of Agents Observed, No. (%)

		Canagliflozin	
	Placebo, n = 237	100 mg, n = 241	300 mg, n = 236
Urinary tract infection	24 (10.1)	35 (14.5)	39 (16.5)
Genital mycotic infection			
Male	2 (1.4)	7 (5.6)	14 (10.9)
Female	4 (4.3)	28 (23.9)	20 (18.7)
Osmotic diuresis-related AEs[a]	13 (5.5)	22 (9.1)	29 (12.3)

AEs, adverse events; SGLT2, sodium-glucose cotransporter 2.

[a]Includes dry mouth, dry throat, micturition disorder, micturition urgency, nocturia, pollakuria, polydipsia, thirst, and increased urine output.

Table 2. Documented Hypoglycemia Through Week 104, No. (%)

Antihyperglycemic Agent Associated With Hypoglycemia	Placebo	Canagliflozin	
		100 mg	300 mg
Patients on agent	176	181	172
Hypoglycemia[a]	86 (48.9)	98 (54.1)	105 (61.0)
< 3.1 mmol/L (< 56 mg/dL)	43 (24.4)	42 (23.2)	51 (29.7)
Severe hypoglycemia	8 (4.5)	5 (2.8)	5 (2.9)
Patients not on agent	61	60	64
Hypoglycemia[a]	4 (6.6)	11 (18.3)	7 (10.9)
< 3.1 mmol/L (< 56 mg/dL)	1 (1.6)	0	0
Severe hypoglycemia	0	1 (1.7)	0

[a]Documented hypoglycemia included episodes that were biochemically documented (≤3.9 mmol/L [<70 mg/dL]) or severe (ie, requiring the assistance of another individual or resulting in seizure or loss of consciousness).

Volume-related AEs (eg, dehydration, dizziness, and presyncope) were more common in canagliflozin patients, occurred more frequently in the first 26 weeks, but were relatively infrequent (5.4% and 5.9% in the 100-mg and 300-mg treatment groups, respectively). The majority of fungal infections were treated with topical therapy. Incidence of documented hypoglycemia was higher with both canagliflozin doses than with placebo, but there were few severe hypoglycemia episodes in any of the treatment groups (Table 2).

In summary, canagliflozin, both 100 mg and 300 mg, improved glycemic control, reduced bodyweight, and lowered BP when compared with placebo over 104 weeks in older patients with T2DM whose HbA_{1c} values were inadequately controlled by their current regimens. The incidence of documented hypoglycemia was higher with both doses of canagliflozin than with placebo, although there were few severe episodes noted. Canagliflozin was generally well tolerated, with a safety profile in this study consistent with that seen in other phase 3 canagliflozin studies.

Combined Saxagliptin and Dapagliflozin Reduce Blood Glucose Levels in T2DM Patients

Written by Nicola Parry

Julio Rosenstock, MD, Dallas Diabetes and Endocrine Center, Dallas, Texas, USA, presented results from the Safety and Efficacy of Combination Saxagliptin & Dapagliflozin Added to Metformin to Treat Subjects With Type 2 Diabetes trial [NCT01606007]. This active-controlled, double-blind, parallel-group phase 3 study demonstrated that combined saxagliptin and dapagliflozin, when added to metformin, were more effective in reducing glucose than treatment with metformin alone in adults with type 2 diabetes mellitus (T2DM).

According to Dr Rosenstock, the sequential addition of a single glycemic control agent is the recommended approach for T2DM patients who are poorly controlled on metformin monotherapy. However, this approach may be inadequate, particularly when HbA_{1c} levels are significantly elevated.

The study aimed to investigate the efficacy and safety of early triple therapy that includes metformin and the concomitant initiation of dual oral therapy with the dipeptidyl peptidase 4 inhibitor saxagliptin and the sodium-glucose cotransporter 2 inhibitor dapagliflozin.

Patients (n = 534) were randomized to saxagliptin –5 mg + dapagliflozin–10 mg + metformin (n = 179), saxagliptin–5 mg + metformin + placebo (n = 176), or dapagliflozin–10 mg + metformin + placebo (n = 179). The study enrolled adults (> 18 years) with a body mass index ≤ 45 kg/m^2, HbA_{1c} levels ≥ 8% and ≤ 12%, and an estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2. All participants were receiving ≥ 1500 mg/d of metformin before randomization.

The primary end point was the adjusted mean change in baseline HbA_{1c} levels at week 24. At 24 weeks, the reduction in mean HbA_{1c} levels was significantly greater in patients treated with saxagliptin + dapagliflozin + metformin when compared with saxagliptin + metformin (–1.5% vs –0.9%; $P < .001$) and dapagliflozin + metformin (–1.5% vs –1.2%; $P = .02$;). Additionally, more patients