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Effect of canagliflozin on serum uric acid in patients with type 2 diabetes mellitus

Hyperuricaemia is associated with an increased risk of gout, kidney stones and cardiovascular disease. The present *post hoc* analysis of pooled data from four placebo-controlled phase III studies assessed the effect of canagliflozin, a sodium-glucose co-transporter 2 inhibitor, on serum uric acid levels in patients with type 2 diabetes mellitus (T2DM) and in a subset of patients with hyperuricaemia [defined as baseline serum uric acid ≥475 μmol/l (~8 mg/dl)]. At week 26, canagliflozin 100 and 300 mg were associated with a ~13% reduction in serum uric acid compared with placebo. In the subset of patients with hyperuricaemia, placebo-subtracted percent reductions in serum uric acid were similar to those in the overall cohort. More patients in the hyperuricaemic group achieved a serum uric acid level of <360 μmol/l (~6 mg/dl) with both canagliflozin 100 mg (23.5%) and 300 mg (32.4%) compared with placebo (3.1%). Incidences of gout and kidney stones were low and similar across groups. In conclusion, canagliflozin treatment decreased serum uric acid in patients with T2DM, including those with baseline hyperuricaemia.

Keywords: canagliflozin, diabetes complications, drug mechanism, SGLT2 inhibitor, type 2 diabetes

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RESEARCH LETTER

Introduction

Concerns about the side effects associated with antihyperglycaemic medications, such as weight gain and hypoglycaemia, have led to the development of diabetes treatments with novel mechanisms of action [1]. The kidney has been the focus of most recent efforts because of the significant role it plays in maintaining glucose homeostasis [2].

Sodium-glucose co-transporter 2 (SGLT2) is a high-capacity, low-affinity glucose transporter found in the proximal convoluted tubule of the kidney, and accounts for the majority of glucose reabsorption [2]. The use of SGLT2 inhibitors, such as canagliflozin, provides an insulin-independent method of increasing urinary glucose excretion and improving glycaemic control in patients with type 2 diabetes mellitus (T2DM) [1]. Probably linked to this mechanism of action, canagliflozin was associated with a higher incidence of certain adverse events (AEs) in clinical trials (e.g. genital mycotic infections, urinary tract infections, osmotic diuresis-related AEs, volume depletion-related AEs). Most of these AEs were mild or moderate in intensity and few led to discontinuations [3].

In addition to reducing blood glucose levels, SGLT2 inhibitors have been reported to lower serum uric acid levels [2]. Uric acid is a by-product of metabolism that can be influenced by diet, breakdown of cellular material and impaired renal elimination. The build-up of serum uric acid in the body can lead to an increase in uric acid crystals in various organs, which can result in gout or the formation of kidney stones [4].

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There is evidence of an association between elevated serum uric acid levels, also known as hyperuricaemia, and risk of renal and cardiovascular disease [5]. Several studies have identified hyperuricaemia as a predictor of the development of metabolic syndrome, diabetes and hypertension [6]. Patients with both T2DM and hyperuricaemia are at an increased risk of developing gout, kidney stones and vascular complications [5,7]. In addition, studies have identified an association between serum uric acid levels and mortality risk in patients with T2DM [7].

Given the various disorders associated with hyperuricaemia, lowering serum uric acid may be beneficial for patients with T2DM, who may have a higher risk of microvascular and cardiovascular disease. The aim of the present *post hoc* analysis was to further characterize the effects of canagliflozin on serum uric acid levels in both a pooled T2DM cohort and a subset of this cohort who had hyperuricaemia at baseline compared with placebo. In addition, the incidence rates of gout and kidney stones were evaluated across treatment groups in both cohorts.

Methods

Pooled Data Source

In a *post hoc* analysis, serum uric acid level changes were evaluated in pooled data from four randomized, phase III, multinational, 26-week trials, where canagliflozin (100 or 300 mg) was compared with placebo as monotherapy, or dual or triple combination therapy (add-on to metformin, metformin and sulphonylurea, or metformin and pioglitazone) [1,8–10]. A total of 2313 patients with T2DM were enrolled. Changes in serum uric acid levels were evaluated in the overall pooled cohort and in the subset of patients (n = 115) in the pooled cohort whose baseline serum uric acid levels indicated hyperuricaemia [defined as serum uric acid level ≥475 μmol/l

Table 1. Baseline demographic and disease characteristics of the overall pooled cohort and subset of patients with hyperuricaemia (baseline serum uric acid ≥8 mg/dl).

	Overall pooled cohort (N = 2313)			Subset of patients with baseline hyperuricaemia (n = 115)		
	Placebo (n = 646)	Canagliflozin 100 mg (n = 833)	Canagliflozin 300 mg (n = 834)	Placebo (n = 37)	Canagliflozin 100 mg (n = 40)	Canagliflozin 300 mg (n = 38)
Sex, n (%)						
Male	334 (51.7)	408 (49.0)	404 (48.4)	21 (56.8)	26 (65.0)	27 (71.1)
Female	312 (48.3)	425 (51.0)	430 (51.6)	16 (43.2)	14 (35.0)	11 (28.9)
Mean (s.d.) age, years	56.3 (9.8)	55.9 (10.1)	59.1 (9.6)	55.9 (9.7)	54.4 (9.4)	53.5 (10.0)
Mean (s.d.) HbA1c, %	8.0 (0.9)	8.0 (0.9)	8.0 (0.9)	8.1 (0.9)	7.7 (0.9)	7.9 (1.2)
Mean (s.d.) BMI, kg/m^2	31.9 (6.4)	32.3 (6.4)	32.0 (6.5)	35.0 (7.8)	36.4 (6.8)	36.1 (9.1)
Mean (s.d.) eGFR, ml/min/1.73 m^2	87.0 (19.8)	88.3 (19.0)	88.8 (18.9)	71.3 (18.5)	80.9 (13.6)	75.0 (14.7)

BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; s.d., standard deviation.

(~8 mg/dl)]. Furthermore, attainment of serum uric acid levels of <360 µmol/l (~6 mg/dl), a common target for uricosuric agents, was assessed in the patients with hyperuricaemia [11]. Inclusion in the *post hoc* analysis required a baseline serum uric acid measurement and ≥1 post-randomization serum uric acid measurement. Serum uric acid can be converted from mg/dl to µmol/l by multiplying by 59.48.

Statistical Analyses

The least squares mean percent change and least squares mean change from baseline in serum uric acid were calculated using an analysis of covariance model with treatment and study as factors and baseline serum uric acid as a covariate. Placebo-subtracted differences are reported with 95% confidence intervals (CIs). Statistical comparisons between groups were not performed as they were not pre-specified; therefore, no p values are reported. The safety analysis set included data regardless of rescue medication use. No missing data imputation was performed.

Results

In the overall cohort, the mean patient age was 56.0 years, glycated haemoglobin (HbA1c) 8.0%, body mass index (BMI) 32.1 kg/m^2 and estimated glomerular filtration rate (eGFR) 88.1 ml/min/1.73 m^2. In the cohort of patients with hyperuricaemia, the mean age was 54.5 years, HbA1c 7.9%, BMI 35.9 kg/m^2 and eGFR 75.9 ml/min/1.73 m^2. Baseline demographics and clinical characteristics were generally similar across treatment groups within each cohort (Table 1), but the cohort with hyperuricaemia had a greater proportion of men and tended to have a higher BMI and lower eGFR compared with the overall cohort (Table 1).

From mean baseline serum uric acid levels of 5.3–5.4 mg/dl in the canagliflozin groups, both canagliflozin 100 and 300 mg reduced serum uric acid levels by ~13% (or 0.7 mg/dl) relative to placebo at week 26 in the overall cohort (Figure 1A). In patients with hyperuricaemia (mean baseline serum uric acid ~8.5–8.6 mg/dl), the placebo-adjusted percent reductions in serum uric acid with both doses of canagliflozin were generally similar to those observed in the overall cohort (Figure 1B). Furthermore, in the cohort with hyperuricaemia, the proportion of patients achieving serum uric acid levels <6 mg/dl at week 26 was 23.5% for canagliflozin 100 mg and 32.4% for canagliflozin 300 mg compared with 3.1% for placebo [placebo-subtracted differences (95% CI) = 20.4% (1.9, 38.9) and 29.3% (9.4, 49.1) with canagliflozin 100 and 300 mg, respectively].

Incidence of Gout and Kidney Stones

The incidence rates of gout and kidney stones were similar between treatment groups in the overall pooled cohort. Gout was reported in 0.1, 0.2 and 0.5% of the patients in the canagliflozin 100 mg, canagliflozin 300 mg and placebo groups, respectively. Kidney stones were not reported in either of the canagliflozin-treated groups, and occurred in 1 (0.2%) patient in the placebo group. In the cohort with hyperuricaemia, gout was reported in 1 patient in each of the canagliflozin 100 mg, canagliflozin 300 mg and the placebo groups (2.5, 2.6 and 2.7%, respectively). No patients in the cohort with hyperuricaemia reported kidney stones.

Discussion

Canagliflozin decreased serum uric acid levels in patients with T2DM, including a subset of patients with hyperuricaemia. Furthermore, 20–30% of patients with hyperuricaemia were able to achieve normal serum uric acid levels (<6 mg/dl) with canagliflozin. Previous pharmacokinetic and pharmacodynamic studies have shown that this reduction in serum uric acid levels relates to an increased fractional excretion of uric acid during the first weeks of canagliflozin treatment [12]. By week 12, the total urinary uric acid excretion returned to near baseline levels, probably reflecting the persistent reduction in serum uric acid concentrations.

The mechanism by which SGLT2 inhibitors reduce serum uric acid has not been established; however, it may possibly involve the renal SLC2A9 (GLUT9) transporter, which is known to exchange glucose for uric acid [13]. Higher glucose concentrations in the urine attributable to canagliflozin treatment could lead to an increased exchange of uric acid in the apical membrane of tubular cells. Consequently, this would result

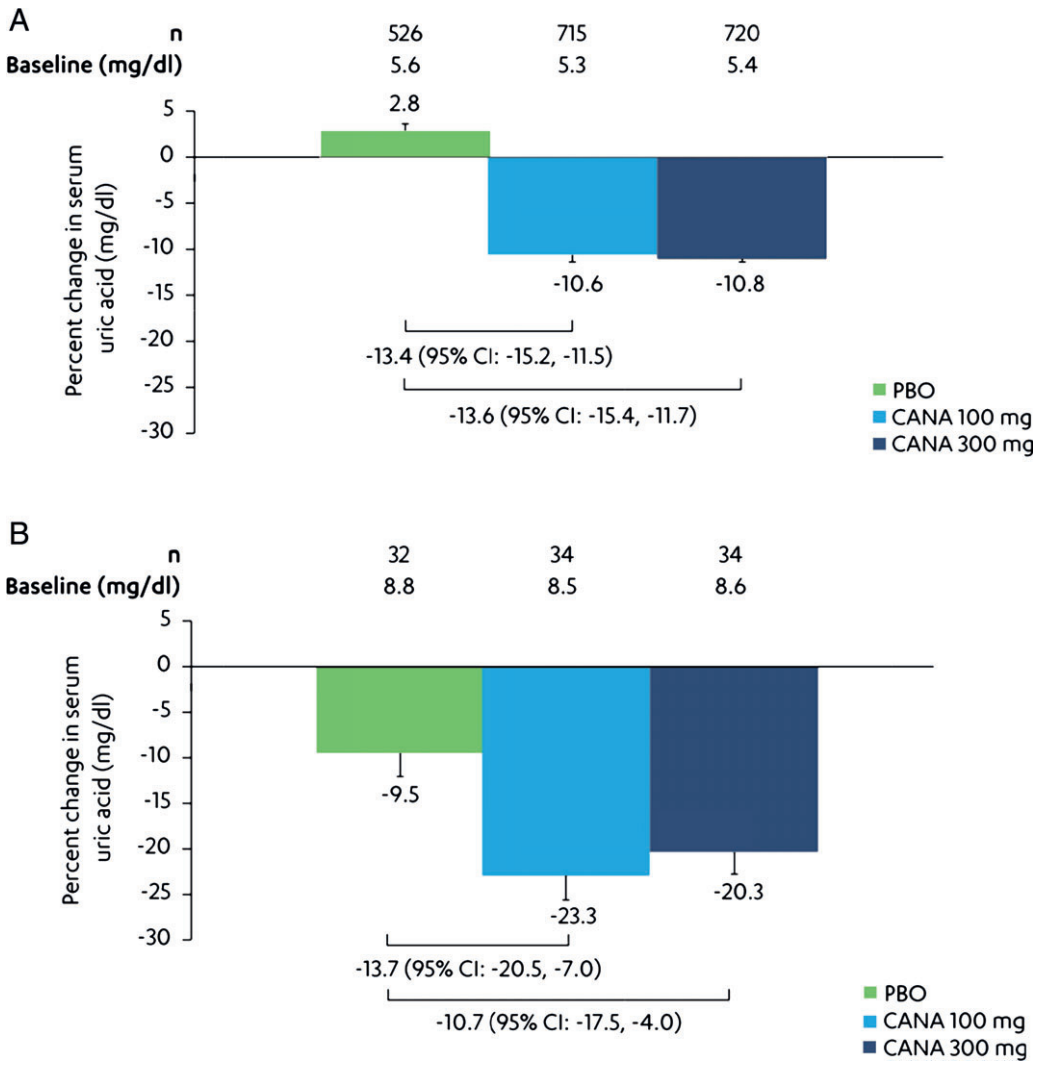

Figure 1. Percent change in serum uric acid levels in (A) the overall pooled cohort and (B) the subset of patients with hyperuricaemia (baseline serum uric acid ≥8 mg/dl). The overall pooled cohort and the subset of patients with hyperuricaemia comprised the safety analysis set, regardless of rescue medication. Patients needed baseline and ≥1 uric acid measurement at week 26 for inclusion in this analysis. Data are least squares mean percent change from baseline (± standard error). CANA, canagliflozin; CI, confidence interval; PBO, placebo.

in increased release of uric acid from blood into the urine, reducing serum uric acid levels [13]. This potential mechanism is supported by evidence of trans-stimulation of uric acid efflux with high glucose concentrations in Xenopus oocytes expressing SLC2A9b [14].

In conclusion, both doses of canagliflozin reduced serum uric acid levels in patients with T2DM. Furthermore, up to 30% of patients with baseline hyperuricaemia and T2DM achieved normal serum acid levels with canagliflozin after 26 weeks. Whether such changes have other beneficial effects on renal and/or cardiovascular complications will require evaluation in longer-term studies.

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Conflict of Interest

M. J. D. and A. T. are employees of Janssen Scientific Affairs LLC; U. V., C. V. D. and G. M. are employees of Janssen Research

and Development LLC. All authors may own stock or stock options in Johnson & Johnson. All authors participated in the analysis and interpretation of the data and the writing of the manuscript. All authors approved the final version of the manuscript.

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