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Original article

Effect of canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, on bacteriuria and urinary tract infection in subjects with type 2 diabetes enrolled in a 12-week, phase 2 study

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Abstract

Objective:
To examine the effects of canagliflozin, a sodium glucose co-transporter 2 inhibitor that lowers blood glucose by increasing urinary glucose excretion (UGE), on asymptomatic bacteriuria and urinary tract infections (UTIs).

Research design and methods:
In a randomized, double-blind, placebo-controlled, multicenter, dose-ranging phase 2 study, subjects with type 2 diabetes with inadequate glycemic control while receiving metformin were enrolled and randomized to one of seven arms – placebo; canagliflozin doses 50 mg, 100 mg, 200 mg, 300 mg daily, or 300 mg twice daily; and sitagliptin 100 mg daily – for 12 weeks.

Clinical trial registration:
This study is registered under Clinicaltrials.gov identification number NCT00642278.

Results:
Canagliflozin increased renal glucose excretion by 35.4–61.6 mg/mg creatinine in the five dose groups. In the placebo group renal glucose excretion was increased by 1.9 mg/mg creatinine, and in the sitagliptin group it decreased by 1.9 mg/mg creatinine. Asymptomatic bacteriuria (ASB) were present in 6.4% of canagliflozin and 6.5% of placebo/sitagliptin (control) subjects at randomization and, at 12 weeks, in 7.7% and 6.3% of subjects, respectively (odds ratio [OR] 1.23; 95% confidence interval [CI], 0.45–3.89). For subjects with initially negative urine cultures at baseline, 3 out of 82 (3.7%) who received controls and 10 out of 207 (4.8%) who received canagliflozin developed bacteriuria ($p = 0.76$) at week 12. There were 21 adverse event (AE) reports of UTI; 16 (5.0%) in canagliflozin subjects and 5 (3.8%) in control subjects (OR 1.31; 95% CI, 0.45–4.68).

Conclusions:
In this trial, when compared with control subjects, canagliflozin increased UGE but was not associated with increased bacteriuria or AE reports of UTI. However, further studies enrolling larger numbers of subjects with longer term exposure to canagliflozin will be necessary to more fully understand the impact of this agent on the risk of developing UTI.

Introduction

Sodium glucose co-transporter 2 (SGLT2) inhibitors that act to lower blood glucose by increasing urinary glucose excretion (UGE) are being developed for

the treatment of type 2 diabetes[1]. An important clinical question is whether the increased glucosuria promotes bacteriuria or genitourinary infections, including urinary tract infection (UTI). This paper reports observations from a phase 2 trial assessing the safety and efficacy of canagliflozin, an SGLT2 inhibitor in development for treatment of type 2 diabetes[2], with regards to the prevalence of bacteriuria and the frequency of adverse events (AEs) of urinary infection for women and men.

Methods

This was a 12-week, randomized, double-blind, placebo-controlled, multicenter, dose-ranging study with seven arms: placebo; canagliflozin doses 50 mg, 100 mg, 200 mg, 300 mg daily, or 300 mg twice daily; and sitagliptin 100 mg daily[3–5]. Women or men with type 2 diabetes and inadequate glycemic control while receiving a stable dose of metformin (≥1500 mg/day for at least 3 months) who were 18 to 65 years of age with A1C levels ≥7% and ≤10.5% were eligible to participate in the study. Subjects were to continue their baseline metformin doses throughout the study. Subjects with a history of UTI within 3 months prior to screening were excluded. The study was reviewed and approved by local Institutional Review Boards and Independent Ethics Committees, and is registered on ClinicalTrials.gov under the ID NCT00642278.

Study endpoints included change from baseline to week 12 in A1C (primary endpoint), fasting plasma glucose (FPG), UGE, and body weight. Safety and tolerability were also assessed. The study has been reported elsewhere in abstract form[3,4] and is currently in press[5].

At randomization and at the end of study therapy (week 12), a mid-stream clean-catch urine specimen was requested for dipstick analysis and culture. In addition, self-administered vaginal swabs were obtained at baseline and week 12 and were also to be obtained at the time of a vulvovaginal AE. The swabs were cultured for *Candida* spp. at a central laboratory. Urine specimens were processed at a central laboratory using standard clinical microbiology methods. Bacteriuria were any bacteria $\geq 10^5$ colony-forming units (cfu)/ml isolated from the urine culture. Candiduria was identified when $\geq 10^3$ cfu/ml of a *Candida* spp. was isolated. During the study, subjects were asked an open-ended question about adverse experiences. An AE of UTI was recorded based on the assessment of the site investigator. This included subjects with symptoms consistent with UTI, whether or not a urine culture was reported, and also subjects with a positive urine culture identified, irrespective of symptoms.

Summary statistics were provided for the baseline demographics and the incidence of UTI AEs for all subjects randomized and treated with canagliflozin, placebo, or sitagliptin. Since similar results across the canagliflozin treatment groups were observed, and similar results across the placebo and sitagliptin groups were observed, in order to enhance precision of the assessments, the five canagliflozin treatment groups were pooled for analysis and compared with the pooled placebo and sitagliptin groups as a control. The prevalence of bacteriuria, *Escherichia coli* bacteriuria, and candiduria was analyzed for all subjects with available urine culture data at either baseline or week 12, and stratified by gender. Odds ratios (ORs) and exact 95% confidence intervals (CI) as well as *p*-values based on Fisher's exact test have been presented to compare the prevalence of bacteriuria and candiduria for canagliflozin compared with placebo/sitagliptin subjects at week 12. For subjects with urine culture data available at both baseline and week 12, changes in the proportion with bacteriuria between treatments was assessed using an exact Mantel–Haenszel test stratified by baseline urine culture status (bacteriuric or not). The unadjusted OR and 95% exact CI for canagliflozin compared with placebo/sitagliptin were presented for the incidence of UTIs. This was further explored through logistic regression, adjusting for factors such as age (mean age ≤52.9 years vs. >52.9 years), sex (female vs. male), region (rest of world vs. North America), body mass index (BMI) (≤35 kg/m^2 vs. >35 kg/m^2), baseline A1C (≤8% vs. >8%), baseline FPG (≤160 mg/dL vs. >160 mg/dL), baseline bacteriuria growth (yes/no), and presence of leukocyte esterase (yes/no). As these analyses were post-hoc assessments, significance was assessed at the $p < 0.05$ level for descriptive purposes and should be considered exploratory.

Results

There were 215 women and 236 men enrolled in this study. The mean age was 52.9 years; the mean A1C at randomization, 7.7%; mean FPG, 162 mg/dL; and BMI, 31.5 kg/m^2 (Table 1). The study groups were well balanced with respect to baseline characteristics of age, sex, race, baseline BMI, A1C, FPG and UGE/creatinine[3–5].

A1C reductions from baseline in canagliflozin groups ranged from 0.70% to 0.95% with the greatest reductions observed in the 300 mg once-daily and twice-daily treatment groups (LOCF ITT analysis). A1C was reduced by 0.22% and 0.74% in placebo and sitagliptin groups, respectively. Increases in $U_{Glucose}/U_{Creatinine}$ from baseline in canagliflozin groups ranged from 35.4 to 61.6 mg/mg, with greatest increases observed at doses of 100 mg once daily and greater. $U_{Glucose}/U_{Creatinine}$ increased by 1.9 mg/mg and decreased by 1.9 mg/mg in the placebo and sitagliptin groups, respectively. In this study, canagliflozin was safe and well tolerated. AEs were generally similar across groups with the exception of an increase in symptomatic vulvovaginal AEs in the canagliflozin-treated women.

Table 1. Baseline demographics.

	Treatment groups						
	PBO ($n=65$)	SITA ($n=65$)	CANA 50 mg q.d. ($n=64$)	CANA 100 mg q.d. ($n=64$)	CANA 200 mg q.d. ($n=65$)	CANA 300 mg q.d. ($n=64$)	CANA 300 mg b.i.d. ($n=64$)
Male, *n* (%)	31 (47.7)	38 (58.5)	34 (53.1)	36 (56.3)	33 (50.8)	36 (56.3)	28 (43.8)
Age, y	53.3 ± 7.8	51.7 ± 8.1	53.3 ± 8.5	51.7 ± 8.0	52.9 ± 9.6	52.3 ± 6.9	55.2 ± 7.1
Weight, kg	85.9 ± 19.5	87.2 ± 18.0	87.6 ± 16.3	87.7 ± 15.5	87.7 ± 17.0	87.3 ± 15.9	86.0 ± 19.7
BMI, kg/m^2	30.6 ± 4.6	31.6 ± 5.0	31.7 ± 4.6	31.7 ± 5.0	31.4 ± 5.2	31.6 ± 4.9	31.8 ± 5.2
Region, *n* (%)							
North America*	32 (49)	28 (43)	27 (42)	25 (39)	26 (40)	26 (41)	24 (38)
Latin America*	5 (8)	4 (6)	7 (11)	12 (19)	10 (15)	8 (13)	14 (22)
Europe*	21 (32)	26 (40)	24 (38)	18 (28)	22 (34)	24 (38)	19 (30)
Asia Pacific*	7 (11)	7 (11)	6 (9)	9 (14)	7 (11)	6 (9)	7 (11)
A1C, %	7.7 ± 0.83	7.6 ± 0.95	8.0 ± 0.99	7.8 ± 0.96	7.6 ± 0.80	7.7 ± 1.02	7.7 ± 0.89
FPG, mg/dL	163.8 ± 37.98	158.4 ± 41.76	169.2 ± 44.46	167.4 ± 41.40	160.2 ± 37.44	158.4 ± 45.00	156.6 ± 34.02
UGE, g/g†	7.9 ± 17.21	6.0 ± 14.62	10.1 ± 17.99	4.7 ± 8.87	4.8 ± 9.37	7.8 ± 26.02	6.0 ± 11.64

Data are mean ± standard deviation unless otherwise indicated.
b.i.d.: twice daily; BMI: body mass index; CANA: canagliflozin; FPG: fasting plasma glucose; PBO: placebo; SITA: sitagliptin; UGE: urinary glucose excretion; q.d.: daily.
*North America includes the United States and Canada; Latin America includes Mexico and Argentina; Europe includes Bulgaria, Czech Republic, Great Britain, Poland, Romania, and Russia; Asia Pacific includes India and Malaysia.
†Expressed as a ratio of urinary glucose to urinary creatinine.

At randomization, urine cultures were obtained for 264 (82.2%) of 321 subjects randomized to the canagliflozin arms, and 107 (82.3%) of 130 placebo or sitagliptin subjects. The initial prevalence of bacteriuria was 6.4% for the pooled canagliflozin and 6.5% for the pooled placebo/sitagliptin (control), and was higher for women (Table 2). *Escherichia coli*, the most common organism, was isolated only from women. At 12 weeks, urine cultures were obtained from 248 (77.2%) canagliflozin and 95 (73.1%) pooled control subjects. The 12-week prevalence of bacteriuria was not numerically different from the baseline prevalence for either of the two groups or between groups. There was no evidence for dose dependency in the canagliflozin arms. There were 312 subjects with cultures obtained at both randomization and 12 weeks. After stratifying by baseline urine culture, the proportion of patients with bacteriuria at week 12 was not different between the two groups. For patients with initially negative urine cultures at baseline, 3 out of 82 (3.7%) control subjects and 10 out of 207 (4.8%) canagliflozin subjects became bacteriuric ($p=0.76$); corresponding with this, 1 out of 7 (14%) initially bacteriuric control subjects and 4 of 16 (25%) canagliflozin subjects remained bacteriuric ($p=0.65$).

No baseline urine cultures grew *Candida* spp. (Table 2). At 12 weeks, *Candida* spp. was cultured from the urine specimens of 4.4% of the study drug subjects compared with 1.1% of control subjects ($p=0.19$). The 12-week prevalence of *Candida* spp. was similar for men and women in the canagliflozin arms. Seven out of seven women with candiduria in the canagliflozin groups had a positive vaginal culture for *Candida* spp. The 12 subjects in all groups with candiduria at week 12 all had low quantitative counts; 9 subjects had 10^3–10^4 cfu/ml isolated, and 3 had 10^4–10^5 cfu/ml.

UTI was reported as an AE for 21 subjects; 15 of these events occurred in women. There were 16 (5.0%) reports in canagliflozin subjects (13 in women and 3 in men) and 5 (3.8%) in controls (2 in women and 3 in men) (unadjusted OR 1.31; 95% CI 0.45–4.68). The post-hoc logistic regression adjusting for selected prognostic factors suggested that treatment with canagliflozin compared with placebo or sitagliptin was not a significant predictor of UTI (adjusted OR 2.39; CI 0.58–9.94; $p=0.23$); significant predictors were younger age (adjusted OR 4.48; 95% CI 1.27–15.73; $p=0.02$), female sex (adjusted OR 4.50; 95% CI 1.13–18.03; $p=0.03$), baseline bacteriuria (adjusted OR 4.51; 95% CI 1.00–20.33; $p=0.05$), and living outside of North America (adjusted OR 8.33; 95% CI 1.03–66.67; $p=0.05$). UTI AEs were reported for 3% to 9% of subjects receiving the different canagliflozin doses with no evidence of dose dependence. All UTIs reported were of mild or moderate intensity, and none resulted in study discontinuation.

Discussion

In this clinical trial, the anticipated increase in urine glucose excretion was observed for all doses of canagliflozin. Despite increased glucosuria accompanying treatment with canagliflozin, the prevalence of all bacteriuria and *E. coli* bacteriuria was similar across subjects with urine cultures after 12 weeks of therapy and at randomization. There was no statistically significant difference, and only a small numerical difference, in bacteriuria prevalence at

Table 2. Prevalence of asymptomatic bacteriuria, *E. coli,* and candiduria in study cohorts at baseline and 12 weeks.

	Positive culture/total subjects with culture (% positive)				OR (95% CI)*	*p*-value†
	Canagliflozin		Placebo/Sitagliptin			
	Baseline	12 weeks	Baseline	12 weeks		
Bacteriuria	17/264 (6.4)	19/248 (7.7)	7/107 (6.5)	6/95 (6.3)	1.23 (0.45, 3.89)	0.82
Women	13/137 (9.5)	15/132 (11.4)	5/57 (8.8)	3/53 (5.7)	2.14 (0.57, 11.98)	0.29
Men	4/127 (3.1)	4/116 (3.4)	2/50 (4.0)	3/42 (7.1)	0.46 (0.08, 3.33)	0.38
E. coli	8/264 (3.0)	10248 (4.0)	2/107 (1.9)	3/95 (3.1)	1.29 (0.32, 7.44)	1.00
Women	8/137 (5.8)	8/132 (6.1)	2/57 (3.5)	2/53 (3.8)	1.65 (0.31, 16.39)	0.73
Men	0	2/116 (1.7)	0	1/42 (2.4)	0.72 (0.04, 43.46)	1.00
Candida spp.	0/264	11/248 (4.4)	0/107	1/95 (1.1)	4.36 (0.62, 189.76)	0.19
Women	0	6/132 (4.5)	0	1/53 (1.9)		
Men	0	5/116 (4.3)	0	0		

*Odds ratio (OR) for canagliflozin versus placebo/sitagliptin at 12 weeks.
†*P*-value based on Fisher's exact test for canagliflozin versus placebo/sitagliptin at 12 weeks.
CI: confidence interval.

12 weeks for subjects who received canagliflozin compared with those in the pooled control group, where increased glucose excretion was not observed. Conversion of bacteriuria from positive to negative or negative to positive was similar for canagliflozin and control groups. In addition, there was no statistically significant increase, and only a small numerical difference, in AE reports of UTI for the canagliflozin group compared with the control group. Since the study size was small and the duration, short, the sensitivity to detect an increase in UTIs is limited.

There was a trend, however, towards an increased prevalence of *Candida* spp. isolated from urine cultures at 12 weeks, compared with baseline, for subjects who received canagliflozin. The increased prevalence was similar for men and women. The quantitative count of $\geq 10^3$ cfu/ml for candiduria would have identified some individuals with contamination from vaginal or periurethral *Candida* colonization, rather than true candiduria. Consistent with this is the observation that quantitative counts of yeast were $<10^5$ cfu/ml for all subjects with candiduria, and that 7 out of 7 women with candiduria had positive vaginal swabs for *Candida* spp. The effects of canagliflozin on Candida colonization and symptomatic vulvovaginal adverse events in women in this study are reported elsewhere[6].

In vitro studies have reported that glucosuria provides a substrate for bacteria in the urine, and increasing urine glucose levels in turn increase the growth rate of potential uropathogens[7]. Despite this, glucose control is not correlated with bacteriuria[8] or symptomatic UTIs[9] in women with diabetes. The lack of association of bacteriuria or symptomatic UTIs with canagliflozin therapy supports these findings, indicating that glucosuria is not a risk factor for the development of asymptomatic bacteriuria or UTIs in patients with type 2 diabetes[10,11].

A limitation of this study is the non-uniform criteria for reporting the AE of urinary infection across the investigative sites. Urine cultures were not consistently obtained from symptomatic subjects and a positive urine culture could be reported as an UTI irrespective of symptoms. However, the identification of a potential UTI as an AE was inclusive and, if anything, likely to overestimate symptomatic infection. The study also excluded persons with a recent history of urinary infection and the impact of canagliflozin therapy on these high risk patients has not been studied. The observations for candiduria likely reflect contamination from vaginal or periurethral colonization, rather than true candiduria. Finally, the study period of 12 weeks is relatively short, and UTI outcomes with more prolonged therapy require further assessment.

Conclusions

In summary, this study provides evidence that the increased UGE observed with canagliflozin is not associated with an increased prevalence of bacteriuria after 12 weeks of therapy. There was also no significant increase in AEs attributed to UTI in subjects who received canagliflozin. However, longer-term studies in larger numbers of patients, including those with a prior history of UTI, and the application of more precise definitions for incident UTI, are necessary to fully characterize the association of SGLT2 inhibitors and UTIs.

Transparency

Declaration of funding
The study DIA 2001 was funded by Johnson & Johnson Pharmaceutical Research & Development, LLC.

Declaration of financial/other interests
G.C., K.U., and K.W. are employees of Johnson & Johnson Pharmaceutical Research & Development, LLC. L.E.N. serves

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Previous presentation: a portion of this work has been previously presented as a poster entitled 'No increase in bacteriuria or urinary tract infections in patients with type 2 diabetes mellitus, treated with canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor' at the American Diabetes Association 71st Scientific Sessions, San Diego, CA, USA, 24–27 June 2011.

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