Original Article

Efficacy and Safety of Canagliflozin 300 mg in Overweight and Obese Type 2 Diabetes Mellitus Patients in a Real-world Setting: COLOR Study

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Abstract

Background and Aims: To assess the efficacy and safety of canagliflozin (CANA, 300 mg/d) in overweight and obese patients with type 2 diabetes mellitus (T2DM). **Methods:** In a single centre, retrospective, observational study, we included overweight or obese patients with T2DM who had HbA1c >7% and received CANA as addition to existing therapy for at least 24 weeks. Primary endpoint assessed was changes in HbA1c, fasting and post-prandial plasma glucose (FPG and PPG), and secondary endpoints included changes in weight, waist circumference (WC), systolic blood pressure (SBP) and diastolic BP (DBP) over 12 and 24 weeks. **Results:** Among 90 patients, mean age was 53.5 ± 10.8 years and 42.2% were females. Majority of the patients (46.7%) were receiving two antidiabetic drugs. Significant reduction in HbA1c from baseline to week 24 (9.1 ± 1.8% vs. 7.5 ± 1.1% respectively, mean difference: -1.6 ± 0.9%, $P < 0.0001$) was seen. Reduction in FPG (mean difference: -63.0 ± 45.2 mg/dL, $P < 0.0001$) and PPG (mean difference: -97.7 ± 54.3 mg/dL, $P < 0.0001$) was also significant. Mean reduction in weight was -4.3 ± 2.2 kg ($P < 0.0001$) at 24 weeks. Reductions in WC, SBP and DBP were also significant at week 24 ($P < 0.0001$ for all). Changes in all these parameters were also significant at week 12. Proportion of patients achieving the target HbA1c of <7% was 28.9% and 52.2% at week 12 and week 24, respectively. Genital mycotic infections were seen in 20% patients and was present in higher proportion of females than males (28.9% vs. 13.5%, $P = 0.070$). No episodes of hypoglycaemia were found. **Conclusion**: Canagliflozin should be considered from among the various antidiabetic drugs in overweight and obese patients with T2D in India.

Keywords: Canagliflozin, HbA1c, India, obese, type 2 diabetes mellitus

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is rapidly increasing in India which harbours the increased risk of cardiovascular (CV) morbidity and mortality. Glycemic control is the key to reduce the risk of complications in T2DM.[1] In a quest to achieve better control, the research and developments in T2DM therapeutics in the last few decades has added various newer treatments to the armamentarium of T2DM management. In recent years, agents targeting renal glucose homeostasis, the sodium-glucose cotransporter 2 inhibitors (SGLT2i), have shown significant therapeutic efficacy with acceptable safety profile.[2]

Beside glycemic lowering, additional pleotropic effects of SGLT2 inhibitors (SGLT2i) are beneficial in reducing the CV outcomes and proving it to be a class effect.[3] In Indian patients with T2DM, the phenotype is different and is associated with increased levels of insulin resistance.[4] This necessitates adequate control of glycemia to reduce the development of complications.

Among different SGLT2I, canagliflozin (CANA) is one of the widely used SGLT2i globally as well as in Indian setting.[5] It has been shown to provide effective glycemic control as add-on to metformin, metformin and sitagliptin or to other antidiabetic agents.[6-8] Though global clinical data is available, there is a relative lack of studies assessing benefits of CANA

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in the Indian setting. To understand the glycemic lowering and other benefits of CANA, we performed this retrospective study.

Methods

Study setting

The study was conducted at an endocrine centre in a metro city in North India. This centre caters to the urban and semi-urban population. The centre delivers both primary and a secondary care with comprehensive approach to endocrine disease management.

Study design

This study was a single-centre, retrospective, observational study.

Study population

We screened medical records of patients who had type 2 diabetes mellitus (T2DM), either overweight or obese (Body mass index (BMI) >25.0 kg/m^2), had glycated haemoglobin (HbA1c) level >7%, with or without hypertension, and were initiated canagliflozin 300 mg/0064ay for treatment of T2DM to the existing antidiabetic treatment. Only those patients who were initiated with canagliflozin at least 24 weeks prior were eligible for inclusion in to the study. This was done to understand the effectiveness of canagliflozin over a 24 week period. A total of 90 patients who met the above criteria were included in the study.

Study conduct

Being a retrospective study, there was no formal sample size calculation in this study. All the patients who fulfilled above criteria were included for analysis. Their data on demographics, glycemic parameters, clinical parameters and anthropometric parameters was entered into Microsoft Excel (2010 version). Data on adverse events available from the medical records was also captured.

Outcome assessments

We considered the following parameters for primary and secondary endpoint evaluation: change from baseline in HbA1c, fasting plasma glucose (FPG) and post-prandial plasma glucose (PPG) over 24 weeks were considered as primary endpoints; change from baseline in weight, BMI, waist circumference (WC), systolic blood pressure (SBP) and diastolic blood pressure (SBP) were considered as secondary endpoints. Incidence of adverse effects in the study population over 24 weeks was considered as exploratory endpoint. Genital mycotic infections (GMIs) were identified on detailed clinical history and were considered present if the symptoms responded to anti-fungal treatment.

Results

Baseline characteristics

In total, we included 90 patients in the final analysis. Baseline characteristics of the study population are shows in Table 1. Mean age was 53.5 ± 10.8 years and 42.2% were females. Hypertension with coexisting dyslipidemia (31.1%) was the most common comorbid condition in study patients. Among anthropometric parameters, mean weight was 80.7 ± 8.6 kgs, mean body mass index (BMI) was 28.9 ± 2.6 kg/m^2 and waist circumference (WC) was 84.6 ± 7.3 cm. Mean systolic BP (SBP) and diastolic BP (DBP) were 136.3 ± 17.2 mmHg and 82.1 ± 10.3 mmHg, respectively. Baseline HbA1c was 9.1 ± 1.8% whereas FPG and PPG were 185.3 ± 56.2 mg/dl and 256.7 ± 67.8 mg/dl. Mean duration of T2DM was 8.0 ± 3.1 years. Among existing antidiabetic drugs, most patients were receiving two drugs (46.7%) followed by a single drug (28.9%) or three or more drugs (24.4%). Metformin (95.6%) and sulphonylureas (66.7%) were the most commonly prescribed anti-diabetic medications.

Table 1: Baseline characteristics

Characteristics	Observation (n=90)
Age (years)	53.5±10.8
Age groups	
≤50	34 (37.8)
51-60	34 (37.8)
61-70	14 (15.6)
>70	8 (8.9)
Sex (%)	
Males	52 (57.8)
Females	38 (42.2)
Comorbidities (%)	
Dyslipidemia alone	9 (10.0)
Hypertension alone	21 (23.3)
Hypertension + Dyslipidemia	28 (31.1)
Hyperthyroidism	1 (1.1)
Anthropometric	
Weight (kg)	80.7±8.6
BMI (kg/m^2)	28.9±2.6
Waist circumference (cm)	84.6±7.3
Blood pressure	
Systolic (mmHg)	136.3±17.2
Diastolic (mmHg)	82.1±10.3
Glycemic	
HbA1c (%)	9.1±1.8
FPG (mg/dL)	185.3±56.2
PPG (mg/dL)	256.7±67.8
Duration of T2DM (years)	8.0±3.1
Number of antidiabetic medications	
One	26 (28.9)
Two	42 (46.7)
Three	19 (21.1)
Four	3 (3.3)
Antidiabetic drugs	
Metformin	86 (95.6)
Sulphonylureas	60 (66.7)
DPP4 inhibitors	17 (18.9)
Voglibose	11 (12.2)
Pioglitazone	2 (2.2)
Prandial Insulin	2 (2.2)
Basal insulin	1 (1.1)

Changes in glycemic parameters

Mean changes in primary endpoint parameters are shown in Table 2. At 12 and 24 weeks, HbA1c reduced from baseline levels to 8.08 ± 1.5 and 7.5 ± 1.1 (mean difference from baseline: -1.07 ± 0.7% and -1.6 ± 0.9%, respectively, $P < 0.0001$ for both comparisons). Similarly, reductions were noted in FPG and PPG as well. Mean change from baseline in FPG was -40.8 ± 37.0 mg/dl ($P < 0.0001$) at 12 weeks and -63.0 ± 45.2 mg/dL ($P < 0.0001$) at 24 weeks. Mean changes in PPG were -57.7 ± 49.2 mg/dL ($P < 0.0001$) and -97.7 ± 54.3 mg/dL ($P < 0.0001$) at 12 and 24 weeks, respectively. With continued canagliflozin treatment, percentage of patients who achieved target HbA1c <7% were 28.9% at 12 weeks and 52.2% at 24 weeks [Figure 1].

Changes in other parameters

Changes in secondary endpoint parameters are summarized in Table 3. Reduction in weight was -2.0 ± 1.5 kg and -4.3 ± 2.2 kg at 12 and 24 weeks ($P < 0.0001$ for both comparisons). This was accompanied by reductions in WC (-0.3 ± 0.6 cm [$P < 0.0001$] and -1.1 ± 0.9 cm [$P < 0.0001$] respectively). Change in SBP and DBP was -3.2 ± 6.5 mmHg ($P < 0.0001$) and -2.3 ± 10.6 mmHg ($P = 0.044$) respectively at 12 weeks and was -6.6 ± 8.9 mmHg ($P < 0.0001$) and -3.7 ± 8.4 mmHg ($P < 0.0001$) at 24 weeks, respectively.

Table 2: Change in primary endpoints at 12 and 24 weeks

Endpoint	Observations ($n=90$)		
	Baseline	12 weeks	24 weeks
HbA1c (%)			
Mean±SD	9.1±1.8	8.08±1.5	7.5±1.1
Change from baseline		1.07±0.7*	1.6±0.9*
FPG (mg/dL)			
Mean±SD	185.3±56.2	144.5±37.4	122.3±22.6
Change from baseline		40.8±37.0*	63.0±45.2*
PPG (mg/dL)			
Mean±SD	256.7±67.8	199.0±49.6	159.0±28.5
Change from baseline		57.7±49.2*	97.7±54.3*

*P<0.0001 in comparison to baseline levels

Table 3: Changes in secondary endpoints at 12 and 24 weeks

Parameters	Observations		
	Baseline	12 weeks	24 weeks
Weight (Kg)			
Mean±SD	80.7±8.6	78.7±8.1	76.4±7.7
Change from baseline		-2.0±1.5*	-4.3±2.2*
Waist circumference (cm)			
Mean±SD	84.6±7.3	84.3±7.2	83.5±7.0
Change from baseline		-0.3±0.6*	-1.1±0.9*
SBP (mmHg)			
Mean±SD	136.3±17.2	133.1±16.2	129.7±13.5
Change from baseline		-3.2±6.5*	6.6±8.9*
DBP (mmHg)			
Mean±SD	82.1±10.3	79.8±10.2	78.4±7.5
Change from baseline		2.3±10.6**	3.7±8.4*

*P<0.0001, **P=0.044 in comparison to baseline levels

Safety assessment

Overall, 20% developed genital mycotic infections (GMIs) as shown in Table 4. Among two genders, prevalence of GMIs was non-significantly higher in females than males (28.9% vs. 13.5%, $P = 0.070$). One patient had a urinary tract infection. There were no episodes of glycemia observed. No other adverse effects peculiar to SGLT2i like volume depletion were not seen in any of the patients. Moreover, none of the patients required hospitalization during the 24 weeks period.

Discussion

Canagliflozin is one of the most effective SGLT2i that is currently being used in India at present. The glycemia-lowering benefits were observed over the 24 weeks period. It provided reduction in all three glycemic parameters with mean reduction in HbA1c of -1.6 ± 0.9% corroborating with reduction FPG (-63.0 ± 45.2 mg/dl) and PPG (-97.7 ± 54.3 mg/dl). In a 26 week study from Wilding *et al.*, CANA 300 mg/d provided HbA1c reduction of -1.04%, suggesting significant lowering of HbA1c when it was added to the metformin or combination of metformin with pioglitazone or sulfonylurea. When analysed by baseline HbA1c levels, maximum reduction was observed in patients with baseline HbA1c of 9% or more (-1.80%).[9] This correlates to our finding of baseline HbA1c being 9.1% wherein reduction by -1.6% was observed. A meta-analysis of 9 studies (n = 1568) with CANA 300 mg/d compared to placebo reported significant reduction in HbA1c (mean difference (MD) -0.77% [95% confidence interval (CI) -0.90, -0.64, $P < 0.001$]) and FPG (MD -2.17 mmol/l [CI 95% -2.44, 1.91, $P < 0.001$]) after 26 weeks therapy.[10] This establishes that our findings are consistent with global observations for glycemia lowering, and that an Indian patient can benefit from CANA treatment. This was reflected in the fact that more than half of the study

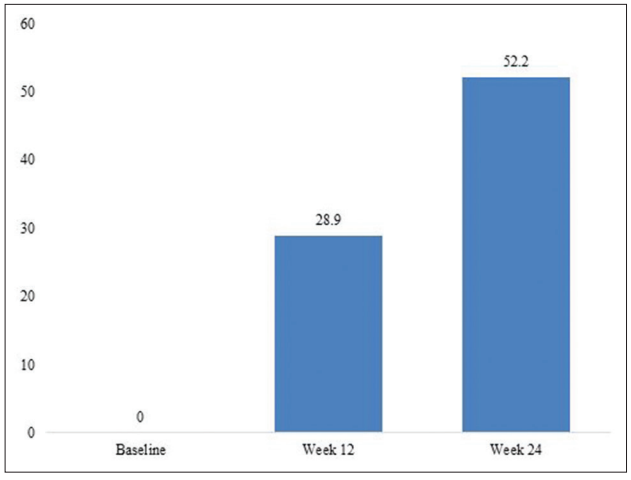

Figure 1: Proportion of patients achieving target HbA1c <7%

Table 4: Adverse effects

Adverse effects	Observation (%)
Genital mycotic infection	18 (20.0)
Males	7 (13.5)*
Females	11 (28.9)
Urinary tract infection	1 (1.2)

*P=0.070

patients achieved target HbA1c of < 7% from baseline to 24 weeks.

Among the obese/overweight patient included in our study, we observed weight reduction of 4.4 kg, translating to BMI reduction of -1.57 kg/m^2 over a 24 week period. CANA does not promote weight gain, but instead leads to weight loss amounting to nearly 300-400 kcal/d. The weight loss with CANA in different studies ranged from -2.5 to -4.7 kg.[5] A meta-analysis to study efficacy and safety of CANA in T2DM reported mean change in body weight of -2.91 kg [95% CI -3.50, -2.32] over 26 weeks.[10] This suggests that reduction in weight in obese patients can be successfully achieved after treatment with CANA which can be beneficial in improving overall insulin sensitivity. In support to the weight reduction, we also observed reduction in waist circumference (-1.2 cm). A study from Blonde *et al*. reported the reduction in weight, BMI and WC with CANA 100 and 300 mg/d compared to glimepiride or placebo were sustained over a long-term period (104 weeks). The body composition analysis revealed that most of weight loss was attributable to loss of body fat.[11]

This is important in the Indian context where there exists substantial presence of central obesity in general population as well as in patients with T2DM. This can reduce the overall insulin resistance and improve the efficacy of other insulin sensitizing agents assisting in achievement of glycemic control.

Additionally, there was significant reduction in both systolic and diastolic BP at 12 and 24 weeks. This is the inherent property of all SGLT2 inhibitors. By virtue of their glucosuric effects, there is simultaneous excretion of sodium and water which leads to fall in BP. The reduction in mean BP -2.4/1.8 mmHg and -5.7/-3.1 mmHg placebo-corrected at week 18 has been reported with CANA 300 mg per day dosing.[6] Though we did not evaluate the effects on lipid parameters, CANA has been shown to improve the risk parameters associated with metabolic syndrome (MetS) in patients of T2DM with MetS.[12]

SGLT2i, including CANA, are associated with side effects such as genital mycotic infections (GMIs), urinary tract infections (UTIs), and events related to volume-depletion.[5] It has been reported that generally CANA is well tolerated.[2] We observed genital mycotic infections in 20% patients with higher incidence in females (28.9%). Overall, the incidence of GMIs reported with CANA 300 mg/d in females is 11.4% and in males it is 3.7%. These tend to decline over continued treatment.[13]

A relatively higher incidence of GMIs with SGLT2i can been attributed to many factors. A study from Thong *et al*. reported that female gender and history previous genital fungal infections are associated with increased risk of GMIs.[14] Identification of GMIs in the Indian setting may be problematic as women find it difficult to reveal their information, due to cultural differences from western population.[15] Recently, two studies from India identified that the prevalence of GMIs with SGLT2i vary from 20.6% to 25.9%.[16,17] Gill *et al*. reported that the prevalence of GMIs was much higher in females than males (27.5% vs. 17.5% respectively).[16] Thus, when initiating SGLT2i treatment, educational information related to such adverse effects need to be conveyed for their prompt and early identification in Indian setting. There was one case of UTI in our study. UTIs with CANA are reported to be mild, more frequent in women and have been reported to be comparable in incidence to therapy with sitagliptin.[5] There were no hypoglycemia events or events related to volume-depletion identified in any patient. This suggests that CANA is well tolerated and is safe in most Indian patients with T2DM.

Conclusion

The novelty of this study is that we provided one of the first evidences with canagliflozin in a real-world setting in India. Canagliflozin provides effective reduction in glycemia in overweight/obese patients with T2DM in India. The benefits are extended to reduction in body weight and WC which is beneficial in obese and overweight patients. Improvement in these parameters suggest that canagliflozin can be effectively used in patients of T2DM with metabolic syndrome. A relatively higher incidence of genital mycotic infections needs to be looked upon. Patient education can help address early identification such events. With no hypoglycemic events, canagliflozin can be considered as well tolerated and effective agent for control of glycemia in Indian patients with T2DM.

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Conflicts of interest

There are no conflicts of interest.

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