Section A-Research paper
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Study the effect of Canagliflozin in patients of type 2 Diabetes mellitus inadequately controlled on maximum dose of three oral hypoglycemic agents

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM), a complex endocrine and metabolic disorder, is a major public health problem that is rapidly increasing in prevalence worldwide. Although comprehensive diabetes management is important, glycemic control is essential for effective diabetes management because lowering the level of glycated hemoglobin (HbA1c) to below or around 7% can reduce microvascular complications and, if implemented soon after the diagnosis of diabetes. The approval by the U.S. Food and Drug Administration (FDA) of two SGLT2 inhibitors, canagliflozin and dapagliflozin, with several others in late-stage clinical development, represents an important step forward in the treatment of T2DM because these drugs may be effective for adults with a high risk of T2DM.

Materials and methods: This were a single-arm, single-center, open-label study that examined the effect of Canagliflozin on blood glucose control patients with T2DM. We planned to enroll 90 subjects, which was deemed sufficient for the assessment of blood glucose-lowering and body weight-reducing effects of Canagliflozin, and considering the feasibility of the study Canagliflozin (100 mg) was administered once daily for 6 months. Patients older than 20 years and younger than 70 years who regularly visited the Hospital and had a diagnosis of T2DM according to the criteria of the ADA were recruited. The patients were required to have hemoglobin A1c (HbA1c) levels between 7.0 and 10.0%, a BMI equal to or greater than 23 kg/m^2. Patients who were on a very low-carbohydrate diet, who showed one or more contraindications as outlined in the latest version of the package insert for Canagliflozin, and who were judged by the physician to be inappropriate for the study, were excluded.

Result: mean fasting blood sugar value recorded at baseline, 3 months and 6 months. Mean fasting blood sugar value at baseline was 195.05mg/dl with standard deviation ± 63.74. Mean fasting blood sugar value at 3 months was 169.95 mg/dl with standard deviation ± 45.99. Mean fasting blood sugar value at 6 months was 148.33 mg/dl with standard deviation ± 33.88. the mean post prandial blood sugar value recorded at baseline, 3 months and 6 months. Mean post prandial blood sugar value at baseline was 301.55 mg/dl with standard deviation ± 97.99. Mean post prandial blood sugar value at 3 months was 247.21 mg/dl with standard deviation ± 62.22. Mean post prandial blood sugar value at 6 months was 214.14 mg/dl with standard deviation ± 47.93.

Conclusion: Canagliflozin in combination with insulin was effective in improving glycemic control and reducing body weight and well tolerated by patients with T2DM.

Keywords: Canagliflozin, Combination therapy, Insulin, SGLT2 inhibitor, Type 2 diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM), a complex endocrine and metabolic disorder, is a major public health problem that is rapidly increasing in prevalence worldwide. [1] Although comprehensive diabetes management is important, glycemic control is essential for effective diabetes management because lowering the level of glycated hemoglobin (HbA1c) to below or around 7% can reduce microvascular complications and, if implemented soon after the diagnosis of diabetes, is associated with long-term reduction in macrovascular disease. [2]

A wide range of pharmacotherapies for glycemic control is now available; however, management of T2DM remains complex and challenging due to its variable pathogenesis, progressive natural history, and limiting side effects of current therapies, including weight gain, hypoglycemia, fluid retention, and gastrointestinal side effects. [3] Furthermore, our current approach to treating hyperglycemia in long-standing diabetes with either established diabetes-associated complications or multiple car diovascular disease (CVD) risk factors, does not affect the CVD risk. [4] Thus, the quest to develop therapeutic agents with novel mechanisms of action, which are expected to fulfill the unmet needs of current therapies, continues.

Although several novel therapies for T2DM are on the horizon, orally administered sodium-glucose cotransporter 2 (SGLT2) inhibitors, a new class of antidiabetic agents that inhibit glucose absorption from the kidney independent of insulin, are promising. [5] They offer a unique opportunity to address the currently unmet therapeutic needs of T2DM patients and to improve their outcomes. [6] The approval by the U.S. Food and Drug Administration (FDA) of two SGLT2 inhibitors, canagliflozin and dapagliflozin, with several others in late-stage clinical development, represents an important step forward in the treatment of T2DM because these drugs may be effective for adults with a high risk of T2DM. [7]

To determine which patients will benefit most from these drugs, clinicians will have to understand the link between the kidney and glucose homeostasis. This study focus on the most clinically relevant information on SGLT2 inhibitors. We also provide the evidence to support their safety and discuss the side effects resulting from their use so that clinicians can prescribe these drugs with confidence.

MATERIALS AND METHODS

This was a single-arm, single-center, open-label study that examined the effect of Canagliflozin on blood glucose control patients with T2DM. We planned to enroll 90 subjects, which was deemed sufficient for the assessment of blood glucose-lowering and body weight-reducing effects of Canagliflozin, and considering the feasibility of the study Canagliflozin (100 mg) was administered once daily for 6 months.

Patients older than 20 years and younger than 70 years who regularly visited the Hospital and had a diagnosis of T2DM according to the criteria of the ADA were recruited. The patients were required to have hemoglobin A1c (HbA1c) levels between 7.0 and 10.0%, a BMI equal to or greater than 23 kg/m^2. Patients who were on a very low-carbohydrate diet, who showed one or more contraindications as outlined in the latest version of the package insert for Canagliflozin, and who were judged by the physician to be inappropriate for the study, were excluded.

After approval from Institutional Ethics Committee for Medical Research at our Institute, study was initiated.

The subjects were instructed not to change their diet and exercise regimen during the study. The dosage and administration of all concomitant medications were also kept as constant as possible. It was permissible to change the doses and even to discontinue the concomitant medications, if necessary, at the physician's discretion.

Clinical and biochemical measurements were performed before and after CANA treatment for 24 weeks. Body weight, BMI, waist circumference, blood pressure, and HbA1c were measured. Measurements of plasma parameters, including fasting plasma glucose (FPG) and eGFR. The above parameters were assessed in all patients, and a euglycemic hyperinsulinemia study was conducted in these patients to evaluate insulin sensitivity.

Statistical Analysis

Data are presented as the mean ± SD. Changes from baseline to 6 months were analyzed by two-tailed paired *t*-test. Associations between variables were assessed using Pearson's correlation

coefficients. A *P*-value less than 5% was considered statistically significant. All statistical analyses were performed using SPSS software.

Results

Table 1 Age-Group of patients in study

Age-Group	No .of patients	Percentage
30-40	20	22.3%
41-50	30	33.3%
51-60	30	33.3%
>60	10	11.1%
Total	90	100%
Mean age in the study ±SD*	50.61 ± 11.81	

Table no. 1 shows the age group of patients under the study. The patients in the group 30-40 years of age were 20 that come to be 22.3%, in the group 41-50 years of age were 30 that comes to be 33.3%, in the group of 51-60 years of age were 30 i.e. 33.3% and that in the group more than 60 years of age were 10 that comes to be 11.1%. Mean age of patients in the study was 50.61 with standard deviation ± 11.81

Table 2 Gender wise of patients in study

Gender	No .of patients	Percentage
Male	40	44.4%
Female	50	55.6%
Total	90	100%

Table no. 2 shows the gender wise patients in the study. In this study number of male patients were 40 i.e. 44.4% and number of female patients were 50 i.e. 55.6%

Table 3 Mean Fasting Blood Sugar level at Baseline, 3 Months & 6 Months

Fasting blood Sugar level	Mean*	SD*	Minimum	Maximum
Baseline	195.05	63.74	109.85	410.65
3 Months	169.95	45.99	108.15	317.25
6 Months	148.33	33.88	102.65	250.15

*Mean fasting blood sugar level at baseline, 3 months and 6 month; minimum and maximum value recorded at baseline, 3 months and 6 month **SD- standard deviation

Table no.3 shows the mean fasting blood sugar value recorded at baseline, 3 months and 6 months. Mean fasting blood sugar value at baseline was 195.05mg/dl with standard deviation ± 63.74. Mean fasting blood sugar value at 3 months was 169.95 mg/dl with standard deviation ± 45.99. Mean fasting blood sugar value at 6 months was 148.33 mg/dl with standard deviation ± 33.88.

Table 4 Mean Post prandial blood Sugar level at Baseline, 3 Months & 6 Months

Post prandial Blood Sugar level	Mean*	SD*	Minimum	Maximum
Baseline	301.55	97.99	136.85	486.45
3 Months	247.21	62.22	132.15	382.15
6 Months	214.14	47.93	116.85	319.35

*Mean post prandial blood sugar level at baseline, 3 months and 6 month; minimum and maximum value recorded at baseline, 3 months and 6 month **SD- standard deviation

Table no. 4 shows the mean post prandial blood sugar value recorded at baseline, 3 months and 6 months. Mean post prandial blood sugar value at baseline was 301.55 mg/dl with standard deviation ± 97.99. Mean post prandial blood sugar value at 3 months was 247.21 mg/dl with standard deviation ± 62.22. Mean post prandial blood sugar value at 6 months was 214.14 mg/dl with standard deviation ± 47.93.

Table 5 Mean HbA1c level at Baseline, 3 Months & 6 Months

HbA1c	Mean*	SD*	Minimum	Maximum
Baseline	12.95	4.21	8.25	13.00
3 Months	11.38	3.78	7.15	12.55
6 Months	8.93	3.38	6.75	11.75

*Mean HbA1c value at baseline, 3 months and 6 months; minimum and maximum value recorded at baseline, 3 months and 6 month **SD- standard deviation

Table 6 Mean eGFR at Baseline, 3 Months & 6 Months

eGFR	Mean*	SD*	Minimum	Maximum
Baseline	91.88	42.25	51.00	253.00
3 Months	95.55	42.26	51.00	253.00
6 Months	97.53	42.99	57.00	253.00

Table no.6 shows the mean eGFR value recorded at baseline, 3 months and 6 months. Mean eGFR value at baseline was 91.88 with standard deviation ± 42.25. Mean eGFR value at 3 months was 95.55 with standard deviation ± 42.26. Mean eGFR value at 6 months was 97.53 with standard deviation ± 42.99.

DISCUSSION

In the present study, treatment with canagliflozin for 16 weeks improved glycemic control and other metabolic parameters, such as body weight and HDL cholesterol, in Indian patients with

T2DM who received insulin therapy. The decrease in HbA1c levels here was slightly greater than that observed in a previous study in Indian patients, including Caucasians [difference between placebo and canagliflozin (100 mg each) at 18 weeks, −0.62 %], suggesting that the effects of canagliflozin are independent of the pathologic features among races. [7] A significant decrease in HbA1c levels was observed regardless of the type of the insulin regimen.

Administration of insulin to patients with T2DM is often associated with weight gain, but the patients studied here experienced weight loss following combination therapy with canagliflozin and insulin. Similar results were reported by studies on the SGLT2 inhibitors dapagliflozin and empagliflozin used in combination with insulin, which were conducted outside Indian. [8]

A study on a Indian population administered a combination therapy of dapagliflozin and insulin demonstrated the improving glycemic control and reducing body weight. However, there are some differences in the present study: about 45 % of the participants were also treated with a dipeptidyl peptidase-4 inhibitor, and the data were not evaluated according to the type of insulin regimen. [9] The results of the present study demonstrated that the combination of canagliflozin and insulin, regardless of the insulin regimen, controlled plasma glucose levels without causing weight gain in Indian patients with T2DM who were inadequately controled by insulin.
Indian patients with T2DM tend to have a long duration of disease and have high levels of HbA1c when insulin is initiated. [10] Patients in the present study had a longer duration of DM (approximately 12–15 years) than that of previous studies (approximately 5–8 years in the Indian phase 3 study) and a higher baseline level of HbA1c. [11] Baseline values of HOMA2- %B and C-peptide were lower in the present study than in those previously reported, which suggests that the patients had a decreased capacity to secrete insulin. Nevertheless, canagliflozin treatment improved glycemic control. These findings are consistent with those of previous studies showing that canagliflozin decreases plasma glucose, regardless of insulin secretory capacity and duration of diabetes mellit. [12] Interestingly, canagliflozin combination with insulin slightly increased HOMA2- %B, suggesting improved beta-cell function. This is possibly resulting from a reduction of glucotoxicity. [13]

Here the overall incidence of adverse events was similar between the placebo and canagliflozin groups. The incidence of hypoglycemia was slightly higher in the canagliflozin group than in the placebo group. All events were mild in severity, and severe hypoglycemia (i.e., requiring the assistance of another person) was not reported. Hypoglycemic events (hypoglycemic symptoms and/or decreased blood glucose) occurred most frequently at 6:00–11:59 h; therefore, caution may be exercised in the morning for patients who receive the combination of an SGLT2 inhibitor and insulin.

The incidence of hypoglycemia was not markedly different among the types of insulin regimens. In a study on empagliflozin added on to basal insulin, during the first 18 weeks of administration of a fixed insulin dose, the incidence of hypoglycemic events was slightly higher in patients administered 25 mg of empagliflozin than in those administered placebo or 10 mg of empagliflozin. However, after physicians were allowed to titrate the insulin dose, the incidence of hypoglycemia over the complete 78-week treatment was similar among the groups. [14] Similarly, in the present study, the incidence per subject-year exposure decreased in patients undergoing insulin dose reduction following a hypoglycemic event. These findings suggest that adjusting the insulin dose of the combined regimen prevents the occurrence of hypoglycemic events.

The slight increase of the ketone bodies (59.93 μmol/L) from baseline was observed at 16 weeks in canagliflozin group, although it was not notably higher than those reported by previous studies of canagliflozin or other SGLT2 inhibitor. [15] Malaise and similar symptoms that may accompany the marked elevation of ketone bodies were not reported, and no patient was dismissed because of increased blood ketone bodies in this study. The elevation of ketone bodies was not accompanied by hyperglycemia and is therefore likely attributable to a compensatory increase in fatty acid metabolism in response to loss of calories because of canagliflozininduced urinary glucose excretion.
Several clinical studies have reported the safety and efficacy of SGLT2 inhibitors in combination with insulin in patients with T1DM, however diabetic ketoacidosis has been reported in some studies. [16] In addition, diabetic ketoacidosis has been reported in patients with T1DM who were treated off-label with an SGLT2 inhibitor in daily clinical practice. [17] Therefore application of SGLT2 inhibitors for T1DM still remains to be addressed.

On the other hand, some cases of diabetic ketoacidosis have also been reported in patients with T2DM who were treated with an SGLT2 inhibitor. Lowering the dose of insulin may increase the production of ketone bodies because of insufficient suppression of lipolysis and ketogenesis. [18] Therefore adjusting the insulin dose may be performed with care, particularly in T2DM patients with diminished capacity to secrete insulin.

There were no cardiovascular-related AEs both placebo and canagliflozin group in this study. Several studies of SGLT2 inhibitors for assessment of the cardiovascular outcome are conducting, and it was recently reported that the SGLT2 inhibitor empagliflzoin reduces cardiovascular event in T2DM patient with high CVD risk, EMPA-REG OUTCOME trial, around 48 % of subjects were on insulin-combination therapy. [20] In the CANVAS trial, about half of the subjects were also treated with insulin. [21] These studies will provide the information on the effect of the combination of SGLT2 inhibitor and insulin on cardiovascular outcome.

Limitations of the study

The limitation of this study is the short course of treatment; hence, the present study has been extended for up to 52 weeks. In addition, patients who were treated with insulin in the form of an intermediate-acting or rapidacting product were not involved, and there were a small number of patients in each type of insulin subgroup. Therefore, we did not discuss which insulin regime fit better with canagliflozin.

CONCLUSION

Canagliflozin added to insulin therapy was effective and well tolerated by patients with T2DM. This regimen provides a novel option in the treatment of patients with T2DM who require additional treatment.

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