Efficacy and Safety of Canagliflozin in Patients with Type II Diabetes Mellitus Inadequately Controlled on Triple Drug Therapy

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Abstract

Objective: Canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, has been associated with HbA1c reduction and weight loss in a broad range of patients with type 2 diabetes mellitus (T2DM). This analysis evaluated changes in HbA1c and body weight in patients who were inadequately responding to maximum dose of three oral hypoglycaemic agents and reluctant to take insulin therapy.

Methods: In this open label interventional single arm study, patients aged 18 to 65 years (N=118) received Canagliflozin 100 mg for in addition to an ongoing triple drug oral hypoglycemic agents (OHA) regimen for a period of 12 weeks. The said population was inadequately responding to maximum dose of three oral hypoglycemic agents and was reluctant to take insulin therapy. Percent change from baseline in HbA1c and body weight was evaluated in the study.

Results: Canagliflozin 100 mg additional dose above a triple OHA provided significant HbA1c reduction by 1.9% and weight reduction by 3.01kg over 12 weeks from baseline. Canagliflozin was generally well tolerated, with 2.54% of the patient population reporting Urinary tract infection (UTI) who were withdrawn from study and given appropriate treatment.

Conclusions: Canagliflozin 100 mg (One tablet) administered to patients in addition to the inadequately controlled triple drug OHAs who were reluctant for an insulin therapy provided a significant reduction in HbA1c and body weight over 12 weeks. Canagliflozin a SGLT 2 inhibitor is a promising new drug in patients with T2DM in patients who are inadequately controlled on triple therapy and are reluctant to insulin therapy.

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic disease that develops as a result of defective insulin secretion and is frequently associated with obesity-related insulin resistance.1 Glucose-lowering agents are regularly implemented to manage hyperglycemia when lifestyle modifications (eg, diet and exercise) are insufficient.1 The disease progression leads to treatment intensification with combination therapy, and ultimately insulin therapy is often initiated which again may be inadequate in managing hyperglycaemia in some patients.1 Some oral hypoglycaemic agents (OHAs) are associated with weight gain (e.g. sulfonylurea, insulin, thiazolidinediones, glinides), which can make it difficult for patients with T2DM to achieve and maintain weight loss.2

Canagliflozin is a novel oral antidiabetic agent belonging to the class of sodium–glucose co-transporter 2 (SGLT2) inhibitors provides glycemic control along with clinically meaningful weight loss, in a broad range of patients with T2DM who were on various background OHAs.2 This analysis evaluated changes in HbA1c and body weight in patients who were inadequately responding to maximum dose of three oral hypoglycaemic agents and reluctant to take insulin therapy.

Materials and Methods

Study Design

A 12 weeks, open label, single centre, single arm, interventional, clinical study done at Deogiri Diabetes Centre, Aurangabad, patients aged 18 to 65 years (N=118) who were inadequately controlled on triple drug therapy for Type 2 Diabetes Mellitus (T2DM). Patients fulfilling eligibility criteria were screened at first visit for fasting blood sugar, post prandial glucose, HbA1c, body weight and renal function test. Inclusion criteria was T2DM patients of either sex (male or female) on maximum dose of three OHA with inadequate response, HbA1c > 8.5% and BMI > 25 kg/m2. Newly diagnosed T2DM patients, type 1 diabetes mellitus, gestational diabetes, patients with eGFR value less than 45 ml/min/1.73 m2 calculated by MDRD formula, patients on insulin therapy, patients with recurrent UTI and patients with history of diabetic ketoacidosis or other co-morbid cardiac, hepatic and renal diseases were excluded.

Canagliflozin 100 mg (1 tablet) once daily was administered as an add-on therapy to triple drug treatment to be taken in morning with ample amount of water at the initial visit of the study. Fasting blood sugar and post prandial sugar measurements with safety assessment was performed during the intermediate visit at 6 weeks. At 12 weeks, the end of the study patients were assessed for fasting and post prandial blood glucose levels, HbA1c, body weight, and renal function test.

Primary end point was change in HbA1c (%) from baseline up to 12 weeks. Secondary end point was change in body weight from baseline up to 12 weeks. Safety assessment was performed by general and systemic examination and as per ADR reported by patients.

Statistics

The study was performed on 118 patients of which 76 were male and 42 were female. Data was collected at the
At 12 weeks

**Fig. 2: Change in Body weight (kg) at baseline and at 12 weeks**

baseline and at 12 weeks for HbA1c value and Body weight. Paired t test was applied to this data and result was derived by using SPSS v.22.

**Result**

Among 118 patients recruited, 114 patients completed the study (96.61%), 3 were withdrawn due to ADR (2.54%) and there was 1 drop out (0.8%). After 12 weeks of study, 1.9% reduction in HbA1c was observed from baseline (Figure 1) and 3.01 kg reduction in body weight was recorded (Figure 2), P value= 0.001. 3 out of 118 patients (2.54%) reported UTI and were withdrawn from study. All the three patients were female and treatment for UTI was provided as required.

**Discussion**

In healthy individuals, about 180g of glucose is filtered and reabsorbed daily through the kidneys and maximal transport rate (Tmax) is 300mg/min. This rate is about 20% higher i.e. 352 mg/min (19.5mmol/l/min) to 419mg/min (23.3mmol/l/min) in patients with poorly controlled T2DM. This pertains to the increased expression of SGLTs in persons with diabetes which represents a physiological response to increased glucose delivery to the nephrons that is ultimately maladaptive. Antagonizing these transporters with SGLT2 inhibitors is an insulin-independent mechanism that offers a considerable advantage of increasing urinary glucose excretion without inducing hypoglycaemia and promoting weight loss due to loss of 300-400 kcal/day.

Canagliflozin is the first SGLT2 inhibitor approved for reducing the risk of 3 point MACE in patients of type II diabetes with established cardiovascular diseases on basis of the CANVAS trial. The CANVAS program, was composed of 2 double-blind, randomized, placebo-controlled trials, Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS-R, analyzed jointly to address CV safety and renal outcomes. It involved 10,142 patients with T2DM and high CV risk with a median follow-up time of 126.1 weeks. Significantly fewer participants in the canagliflozin group than in the placebo group had a primary outcome event (the composite of death from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke). The results also showed that patients treated with Canagliflozin had a lower risk of hospitalization for heart failure, progression of albuminuria, and substantive loss of kidney function than patients who received placebo.

Based on the positive CV outcome of the CANVAS Program in September 2018 European Commission, granted approval to update the canagliflozin labelling to include data on the reduction in MACE events in patients with T2DM who had either a history of CV disease or at least two CV risk factors. Also, Canada health and USFDA have approved the label update and indication update respectively which includes reduction in MACE in patients with established CV event. According Canagliflozin becomes the only Oral anti-glycemic agent to receive a approval for 3 point MACE reduction and as well as in both Primary prevention and secondary prevention cohort.

In this study, at week 12, Canagliflozin 100 mg provided significant reductions in HbA1c from baseline (p<0.001). Differences in mean changes in HbA1c were −1.94 with Canagliflozin 100 mg given additionally with three drug combination therapy (Table 1). Subgroup analyses based on baseline HbA1c showed that HbA1c reductions with Canagliflozin were greater in the higher baseline HbA1c group; however, sizeable reductions were also seen in with the lowest baseline HbA1c.
patients tolerated Canagliflozin 100 mg once daily well. This is the only study done by adding Canagliflozin to triple drug therapy till now, but our results correlate with studies done on T2DM patients who were administered Canagliflozin 100 mg or 300 mg as monotherapy, or other regimens like with metformin, other two OHA and insulin.

In conclusion, Canagliflozin 100 mg (one tablet) administered to patients in addition to the inadequately controlled triple drug OHAs who were reluctant for an insulin therapy provided a significant reduction in HbA1c and body weight over 12 weeks. Canagliflozin a SGLT 2 inhibitor is a promising new drug in patients with T2DM in patients who are inadequately controlled on triple therapy and are reluctant to insulin therapy.

References