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Canagliflozin – A Novel Oral Hyperglycemic Agent in The Fight Against Diabetic Mellitus

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Abstract: *Canagliflozin, is a first-in-class,oral hypoglycemic drug to be approved by US FDA, that acts through inhibition of sodium glucose co- transporters in the renal tubules, resulting in glucosuria. Clinical trials with canagliflozin have shown that it causes consistent dose-dependent reduction in HbA1c. The drug has a risk of causing genito-urinary infections& amputations in patients with diabetic foot ulcers. This article summarizes the current knowledge regardingcanagliflozin and its future perspectives in the treatment of type 2 diabetes mellitus.*

Keywords: *canagliflozin, SGLT-2 inhibitors, type 2 diabetes mellitus, amputations, infections.*

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I. Introduction

Diabetes is a global health concern, affecting 425 million people worldwide. The global prevalence of diabetes is expected to reach 629 million by 2045[1] and as many as 69.2 million were afflicted with the disease in India as of 2015 [2].Diabetes is a common non-communicable disease characterized by an elevation of blood glucose level due to either insulin resistance or insulin deficiency[3]. A variety of anti-diabetic drugs are available in market for T2DM patients [4], among them metformin is often the first drug prescribed to patients who have inadequate glycemic control in addition to diet and exercise [5]. While recent additions such as GLP analogues and DPP-4 inhibitors have propped up the scenario in the pharmacological management of diabetes, there is still room for additional drugs which offer better control of blood glucose and also reduce the long term complication of the disease [6]. Several years of intense research in diabetes has led to the successful identification of a new class of drugs for treating diabetes [7,8] Canagliflozin (Invokana®)is the first oral SGLT2 (sodium glucose transporter) inhibitor to be approved by FDA for T2DM[9]. This article aims to discuss the mechanism of canagliflozin, its efficacy, safety and its current status in the treatment of T2DM.

II. Mechanism Of Action

Kidney's contribution in maintainingblood sugar is significant through glomerular filtration and most of the glucose is re-absorbed in the proximal tubule[1]. In a normal healthy adult the glomeruli filtersroughlyabout 180g of glucose per day with 1% being excreted in the urine. When the tubular glucose load exceed 220mg/min with no glucose excretion glucosuria begins to occur leading to plasma glucose concentration an important modulator of SGLT2 activity [2].Canagliflozin reduces plasma glucose levels by inhibiting the effects of SGLT2. It reduces re-absorption of glucose being filtered and thereby increases urinary glucose excretion. Canagliflozin's urinary glucose excretion mechanism also leads to reduction of body weight and blood pressure due to loss of caloriesand diuretic effect. Canagliflozin results in a loss of 100mg of glucose/day in diabetic patients [3].

2.1 Pharmacoki etics

Pharmacokinetic profile of Canagliflozin is similar with T2DM patients and healthy individuals. Canagliflozin is absorbed rapidly when administered orally and reaches its peak plasma concentration within 1-2 hrs and its half live is between 10.6 and 13.1 hrs. The drug reaches steady state concentration within 4 to 5 days of dosing [9]. The plasma protein binding of canagliflozin is 99% and metabolized by *O*-glucuronidation pathway into three metabolites M5,M7 and M9 inactive conjugates with minimum oxidative metabolism. Canagliflozin is primarily excreted via feces (60%)and most of the remaining (33%) is excreted in urine and 1% as unchanged drug into urine[13].

2.2 Efficacy

Across several clinical studies,canagliflozin has been found to consistently reduce HbA1c and fasting plasma glucose from baseline [9]. Canagliflozin provided dose dependent reduction in HbA1c when studied as a

monotherapy against placebo. In these studies, the mean HbA1c reduction rate was between -0.32 to -1.03% from baseline and greater number of patients achieved HbA1c <7.0% relative to placebo [14-18]. Reduction in fasting glucose was also seen. Canagliflozin showed greatest reduction in HbA1c by 12thweek and the reduction was sustained up to 104 weeks. Canagliflozin when studied in combination with other agents such as metformin, sulphonylureas, DPP-4 inhibitors and GLP-1 receptor analogues. Canagliflozin 300 mg showed prominent efficacy in lowering HbA1c when compared to Sitagliptin and Glimepiride over 52 weeks [19,24] and also provided dose dependent reduction in HbA1c and fasting glucose with other active comparator [20-23].Studies to date reveal that the combination of canagliflozin and insulin always provided apparent reduction on HbA1c (-0.4 to -1.09%) and also reduction in the daily dose of insulin from baseline relative to placebo over 18 weeks and sustained upto 52 weeks[25-27]. Canagliflozin at a dose of 300mg in patients with Type 1 diabetes showed greater reduction in HbA1c when combined with insulin. [25].However, the drug is yet to receive marketing approval in this population.

2.3Additional Benefits Of Canagliflozin

Body weight reduction is an added benefit with canagliflozin.In several studies, both doses of canagliflozin provided consistent, dose-dependent reductions in bodyweight relative to placebo and other anti hyperglycemic agents.Canagliflozin at a dose of 100 mg and 300 mg had a greater proportion of subjects achieving ≥5% body weight reduction (27.8%, 33.1% and 10.5%, respectively) relative to placebo after 104 weeks of treatment**[**19**].**Canagliflozin also provided significant reduction in bodyweight compared with sitagliptin (approximately up to 3%) over 26 weeks **[**24]. In addition to weight loss,canagliflozin is also associated with lowering of blood pressure due toits diuretic effect. [15] Both doses of canagliflozin showed a reduction in systolic anddiastolic BP across all phase 3 studies compared with placebo or active comparator [20,22,27]. From two major clinical trials, namely CANVAS and CANVAS-R involving T2DM patients with an elevated risk of cardiovascular disease, it has become known that canagliflozin reduces the risk of death caused by myocardial infraction or stroke compared with placebo [28, 29]. This pharmacological effect is something that can catapult canagliflozin towards becoming one of the front-line contenders in the fight against diabetes.

III. Adverse Events

Canagliflozin is generally well tolerated as monotherapy and as part of combination therapy for T2DM. The overall frequency of adverse events was modestly higher in patients receiving canagliflozin relative to placebo. [30]. Some of the adverse events seen with canagliflozin were genital mycotic infections, urinary tract infection, hypoglycemia and polyuria or pollakiuria. The less commonly observed adverse events were hypotension, ketoacidosis, hyperkalemia, urosepsis and lower limb amputation, bone fracture, impairment in renal function.One of the recent concerns with canagliflozin is its association with an increased frequency of amputations as witnessed in the CANVAS trials. This has resulted in FDA placing a black box warning in the package insert of canagliflozin. Hence the drug is to be avoided among patients who are having diabetic foot ulcers.

3.1 Current Status

Canagliflozin has been approved in the USA, Europe and India for treating T2DM as an adjunct to diet and exercise. One of the limiting factors in the molecule to gain substantial popularity among diabetologists is its prohibitive cost. For instance, one monthcourse of canagliflozin would cost Rs.1530 (30 tablets)[31]while a course of sitagliptin would cost around Rs.1281[32].Several studies have already evaluated canagliflozin's efficacy in adult patients, therefore currently a study NCT03170518is investigating canagliflozin's safety and efficacy in children and adolescents (≥10 to <18 Years) With Type 2 Diabetes Mellitus[33].Another ongoing study is evaluating the effect of canagliflozin on bone metabolism in healthy volunteers, since canagliflozin increases the bone fracture risk in people with diabetes[34].However certain questions do remain unanswered such as the lack of head to head trials with other SGLT-2 inhibitors and itslong-term effects in diabetes patients.

IV. Conclusion

Canagliflozin has shown considerable promise as an anti-diabetic agent both as monotherapy and as combination therapy with other OHA and insulin. The drug also has a reasonable safety margin but one should be wary of the higher risk of genito-urinary infections and the risk of amputations especially in those with pre-existing diabetic foot ulcers. Hypoglycemia could be a cause for concern if the drug is taken along with insulin.The most gratifying fact about the drug is the robust evidence for its cardiovascular benefit in clinical trials, and this could turn out to be a game changer as far as its place is concerned among anti-diabetic agents in the market.

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TABLE 1: Major studies which evaluated the anti-diabetic efficacy of canagliflozin**.**

Authors	**Population**	**Ethnicity**	**Subjects**	**Dosage& Frequency**	**Comparator**	**Background**	**Results**
Inagaki.N et al., (2017)	T2DM Japanese patients	Japanese	143	Cana 100 mg QD	Placebo	Insulin	Canagliflozin 100 mg showed reduction in HbA1c in relative to placebo at 16th weeks of treatment and remained stable upto 36 weeks.
Yale.J.F. *et al.*, (2017)	Patients were required to have a stable background of SU for 8 weeks	Mixed	215	Cana 100/300 mg QD	Placebo	Sulphonyl urea	Both doses of canagliflozin achieved sustained reduction in HbA1c relative to placebo after 52 weeks of treatment.
Fulcher. G.et al., (2016)	T2DM patients enrolled in CANVAS study	Mixed	411	Cana 100/300 mg QD	Placebo	DPP-4 inhibitors or GLP-1 receptor	Canagliflozin 100 & 300 mg showed change in HbA1c (from baseline) relative to placebo after 18 weeks of treatment.
Davidson .J*et al.*, (2016)	Diabetic patients Of Different Ethnicity	Hispanic/Latino Vs NonHispanic/ Latino	2313	Cana100/300 mg QD	Placebo Or Sitagliptin 100 mg	Metformin	Reduction in HbA1c was seen in a dose related manner with canagliflozin compared with placebo in both cohorts after 26 weeks of treatment.
Wilding.J *et al.*, (2015)	Adult patients with known duration of T2DM.	Mixed	2313	Cana100/300 mg QD	Placebo	Metformin	Reduction in HbA1c (from baseline) relative to placebo after 26 weeks of treatment.
Bode.B*et al.*, (2015)	Adult patients between 55 and 85 years with T2DM.	Mixed	714	Cana100/300 mg QD	Placebo	NIL	Both doses of Canagliflozin showed reduction in HbA1c at 12 weeks followed by progressive increase at 104 weeks in relative to placebo.
Henry.R*e t al.*, (2015)	Patients with Type 1 Diabetes	Mixed	352	Cana100 / 300 mg	Placebo	Insulin	Reduction in HbA1c and daily insulin dosage (from baseline) was seen in canagliflozin 100&300mg relative to placebo after 18 weeks of treatment.
Neal.B et al., (2015)	Patients with inadequate glycaemic control	Mixed	2072	Cana 100/300 mg QD	Placebo	Insulin	Both doses of Canaglilozin showed reduction in HbA1c relative to placebo at 18th week with comparable reduction also seen after 52 weeks.
Leiter.L*et al.*, (2015)	T2DM patients inadequately controlled with metformin	Mixed	1450	Cana 100 /300 mg QD	Glimepiride	Metformin	Both doses of Canagliflozin showed reduction in HbA1c compared with Glimepiride by the end of 52 weeks. Later Cana 300 mg confirmed superiority to glimepiride in lowering of A1C after 104 weeks of treatment.
Inagaki .N *et al.*, (2014)	Patients with T2DM inadequately controlled with diet and exercise.	Japanese	352	Cana100/200 mg QD	Placebo	Diet/exercise	Canagliflozin improved HbA1c reduction in relative to placebo after 24 weeks of treatment.
Qui.R*et al.*, (2014)	T2DM patients aged between 18 &80 years	Mixed	279	Cana 50/150 mg BID	Placebo	Metformin	Both doses of Canagliflozin showed significant reduction in HbA1c relative to placebo after 18 weeks of treatment.
Wilding.J *et al.*, (2013)	T2DM patients with inadequate glcaemic control on Metformin plus Sulhonylurea	Mixed	469	Cana 100/300 mg QD	Placebo	Metformin plus Sulphonyl urea	Canagliflozin 100 and 300mg showed reduction in HbA1c relative to placebo at 26weeks and were maintained up to 52 weeks.

Gonzalez .L.*et al.*, (2013)	Patients with inadequate glycaemic control on metformin.	Mixed	1284	Cana 100/300mg QD	Placebo Or Sitagliptin 100mg	Metformin	Canagliflozin 100 mg showed reduction in HbA1c (from baseline) relative to Sitagliptin and Placebo. Canagliflozin 300mg showed superiority to sitagliptin in glucose lowering effect after 26 weeks of treatment.
Stenlo.K*e t al.*, (2013)	Diabetic patients inadequately controlled with diet and exercise	Mixed	584	Cana100/300 mg QD	Placebo	Metformin plus sulfonylurea	Reduction in HbA1c from baseline with canagliflozin 100 and 300 mg compared with placebo after 26 weeks of treatment.

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