Review Article

Canagliflozin: A Novel SGLT2 Inhibitor for Type 2 Diabetes Mellitus

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Abstract

Diabetes Mellitus continues to be a major non- communicable disease with global burden of 366 million at present and projected to increase to 439 to 552 million by 2030, India being the hub of diabetes. Sodium glucose transporter 2 (SGLT2) inhibitors presents a new class of anti-diabetic drugs having an insulin-independent mechanism that offers a considerable advantage of increasing urinary glucose excretion without inducing hypoglycemia and promoting weight loss due to loss of 300 to 400kcal/day, Canagliflozin being the 1st successful candidate of this group and became the first SGLT2 inhibitor to be FDA approved on March 29, 2013. In various clinical trials, it has shown promising results in controlling glycemia, causing weight loss, reducing systolic and diastolic BP and cardiovascular risk. There are some safety concerns associated with its use e.g. genital mycotic infections, increased urination, urinary tract infection and hyperkalemia, which need to be carefully addressed while using this drug.

Keywords: Canagliflozin, Diabetes Mellitus, HbA1C, Inhibitors, SGLT2

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Introduction

Diabetes Mellitus, one of the most common non-communicable diseases with the present global burden of 366 million is projected to increase to 439 to 552 million by the year 2030.[1,2] Present prevalence in India is 61.3 million and will be 101.2 million by 2030.[3]

People with Type 2 diabetes are at increased risk for microvascular (neuropathy, nephropathy, and retinopathy) and macrovascular (peripheral vascular disease, cerebrovascular disease, and cardiovascular disease) complications in addition to metabolic syndrome, which further increases risk of cardiovascular manifestations, including stroke and myocardial infarction.[4] Cardiovascular disease is attributable to ~65% of deaths in diabetic patients[5] and this is expected to rise to 75% by 2030, leading to premature deaths.[6]

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Many studies have proved the benefits of intensive glycemic control (fasting blood glucose less than 6 mmol/L [108mg/dL]) in reducing all-cause death, including microvascular and macrovascular complications from diabetes.[7-10]

Commonly used antidiabetic agents for the treatment of type 2 diabetes act by increasing insulin release, increasing insulin sensitivity, restraining glucagon secretion, controlling hepatic glucose release, or inhibiting intestinal glucose absorption.[11,12] Pertaining to the progressive dysfunction of the pancreatic β-cells and increasing insulin resistance over time, there is constant need for newer treatments with different mechanisms. Moreover, commonly used agents have multiple drawbacks e.g. thiazolidinediones and sulfonylurea contribute to weight gain during the therapeutic process,[13] due to which achievement of long-term glucose control becomes difficult.[14] Likewise, rosiglitazone was linked to increased incidence of MI and death in diabetics leading to complete withdrawal of the drug.[15] Even different sulphonylureas like tolbutamide,

glyburide, glipizide and glimepiride are associated with widely variable CVD risk and mortality outcomes.[16,17]

Among the newer FDA approved agents, GLP- 1 analogues are associated with reports of pancreatitis and gastroparesis,[18,19] and more recently there are concerns about thyroid cancer risk in rat models.[18] Also, being primarily eliminated through kidneys, these drugs are not recommended in patients with renal insufficiency (creatinine clearance, CrCl <30mL/min) or end-stage renal disease.[20] The FDA approved DPP-4 inhibitors reportedly cause nasopharyngitis (5.2 to 6.3%), upper respiratory tract infection (4.5 to 6.2%), headache (1.1 to 5.9%), and rare cases of hypoglycemia. They also carry the same pancreatitis risk as associated with GLP-1 agonists.[21] and must be dose reduced with moderate to severe renal dysfunction.[22]

Therefore, the current focus of research is an anti-diabetic agent that can improve glycemic control without increasing hypoglycemia, can promote weight loss, improve β- cell function, while reducing complications and mortality associated with the disease and which is safe enough to be used in renal or hepatic compromise.[23]

Sodium glucose transporter-2 (SGLT-2) inhibitors

Recently, kidneys have emerged as a new target for diabetes therapy. Patients with high blood glucose levels usually experience glycosuria and nocturia, which has been used as a diagnostic feature for diabetes and indicates poor glycaemic control.[23] Actually, this glucose load excreted by the body is what is left after glucose has passed through the renal nephron. Glucosuria is now recognized as a feasible insulin-independent mechanism that reduces blood glucose without causing hypoglycemia and facilitating weight loss.

SGLTs belong to a large family of sodium glucose cotransporter SLC5.[24] SGLT1 are expressed primarily in small intestines, proximal tubule of nephrons and in myocardium, whereas SGLT2 are exclusively present in the brush border of epithelial cells in S1 and S2 segments of proximal renal tubules. Their expression and activity is elevated by raised plasma glucose concentration[25] but is unrelated to renal gluconeogensis, which may be increased in diabetes.[26]

In healthy individuals, kidneys reabsorb all of the glomerullary filtered glucose[27] through high capacity SGLT2 in the early proximal tubule, which reabsorb most of the glucose load, and the low capacity SGLT1 in more distal regions of the tubule reabsorbing the remainder. These co-transporters are secondary active as they depend on Na+ to K+ATPase activity in the basolateral membrane for the active removal of sodium. GLUT2 and GLUT1 respectively facilitate glucose transport across the basolateral membrane in the early and more distal regions of the proximal tubule.[26,28] 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)[29,30] 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.[31]

Antagonizing these transporters with SGLT2 inhibitors is an insulin-independent mechanism that offers a considerable advantage of increasing urinary glucose excretion without inducing hypoglycemia[4,14] and promoting weight loss due to loss of 300-400 kcal/day.[32,33]

A look into history

A naturally occurring inhibitor of both SGLT1 and SGLT2 called phlorizin was isolated from apple tree bark by French chemists in 1835.[34] In early 1900s phlorizin administered to normal animals was noted to cause glucosuria, polydipsia and weight loss,[35] and in the 1980s it was shown to normalize glycaemia in 90% pancreatectomised animals, arousing interest in its potential to treat diabetes.[36] Since; phlorizin was a non-specific SGLT inhibitor, poorly absorbed from the gastrointestinal tract and not sufficiently stable for clinical use, it was not suited to clinical development [37] but dapagliflozin, canagliflozin (TA7264), empagliflozin, remogliflozin, sergliflozin, ipragliflozin, luseogliflozin, tofogliflozin, ertugliflozin and desoxyrhaponticin and other agents progressed in clinical development. Canagliflozin lowered renal threshold for glucose (RTG), increased urinary glucose excretion, improved glycemic control and beta-cell function in rodent models of T2DM, and reduced body weight gain in rodent models of obesity.[38,39]

Canagliflozin

It was discovered that C-glucosides bearing a heteroaromatic ring are metabolically more stable SGLT-2 inhibitors than O-glucosides. A novel thiophene derivative 4b-3 (canagliflozin) was a highly potent and selective SGLT-2 inhibitor showing pronounced anti-hyperglycemic effects in high-fat diet fed KK (HF-KK) mice.[38]

Canagliflozin lowered renal threshold for glucose (RTG), increased urinary glucose excretion, improved glycemic control and beta-cell function in rodent models of T2DM, and reduced body weight gain in rodent models of

obesity.[39] Canagliflozin became the first SGLT2 inhibitor to be FDA approved on March 29, 2013.[40]

Beneficial effects

Glycemic control

It is quite evident from multiple studies that early effective glycaemic control defers or prevents the onset and reduce the severity of microvascular complications.[8,10,41] Canagliflozin has been reported to reduce fasting glucose ranging from 0.9 to 2.1mmol/L with daily doses between 50mg and 600mg. The corresponding reduction in HbA1c was 0.9% at a dose of 300mg daily.[42-44] Canagliflozin has an additional advantage of showing moderate but sustained efficacy even in patients with moderately impaired renal function (eGFR in the range 30 to 50ml/min/1.73m2).[45]

Body weight reduction

Early weight reduction during canagliflozin use owes to its osmotic diuretic effect, whereas incremental weight loss over subsequent weeks is likely due to caloric loss.[43] With an average of 200 to 400 calories loss per day, weight loss of 2.4 to 4.7kg has been demonstrated in 12 weeks trial of canagliflozin.[33,43]

Blood pressure

Because of the chronic osmotic diuresis caused by glycosuria with increases in 24 hours urinary volumes of between 107 and 470mL [42,46] canagliflozin is associated with small but consistent reductions in systolic and diastolic blood pressure, eg. 6/2mmHg.[47] This continually controlled blood pressure provides a further advantage, considering the high prevalence of hypertension among persons with diabetes[48] and ultimately rendering a favorable effect on cardiovascular risk.

Cardiovascular effects

On the basis of meta-analyses of randomized trials, 0.8% reduction in HbA1c is anticipated to reduce coronary risk by about 8% [49] and the same level of protection is provided by a 4mmHg reduction in systolic blood pressure.[50] Jointly, these effects would be expected to reduce vascular risk by about 15%. A series of large ongoing trials will accrue a significant number of cardiovascular safety outcomes for canagliflozin for the next few years. One such phase 3 trial, (CANVAS) CANagli- flozin cardioVascular Assessment Study [51] is a major CV outcome study started in 2009 with 4411 participants and is estimated to primary completion in June 2018. It will evaluate the effects of canagliflozin compared to placebo on CV events including CV death, myocardial infarction and stroke in patients with T2DM.

Major clinical trials involving canagliflozin

Some of the major clinical trials are tabulated in Table 1

Pharmacokinetics of canagliflozin

The pharmacokinetics properties are almost similar in healthy subjects and patients with diabetes.

Following single-dose oral administration of 100 mg and300 mg, peak plasma concentrations (median Tmax) of canagliflozin occurs within 1 to 2 hours post-dose. Plasma Cmax and AUC of canagliflozin increases in a dose-proportional manners from 50mg to 300mg. The half-life (t1/2): 10.6 h and 13.1 h for the 100mg and 300mg doses, respectively and time to reach Steady-state concentration: 4 to 5 days of once-daily dosing with canagliflozin 100mg to 300mg.[55,56]

Absorption

The mean absolute oral bioavailability: 65% (may be taken with or without food). However, based on the potential to cause hypoglycemia, it is recommended it should be taken before the first meal.[55,56]

Distribution

The volume of distribution of canagliflozin following a single intravenous infusion in healthy subjects was found to be around 119 L, suggesting extensive tissue distribution. It is extensively bound (nearly 99%) to plasma proteins, mainly albumin.[55,57]

Metabolism and excretion

O- glucuronidation is the major metabolic elimination pathway for canagliflozin,. It is glucuronidated by UGT1A9 and UGT2B4 to two inactive *O*-glucuronide metabolites.

CYP3A4-mediated metabolism of canagliflozin is minimal in humans, so it is least likely to result in significant drug interactions. The two major metabolites are the inactive M5 and M7 O — glucuronide conjugates of unchanged drug Canagliflozin, M5, and M7 concentrations rose in a dose — dependent fashion over the canagliflozin dose range. Less than 1% of the administered canagliflozin dose was excreted unchanged in urine; approximately 7 to 10% was excreted in urine as M5 and approximately 21 to 32% was excreted as M7. Renal clearance of canagliflozin ranges from 1.30 to 1.55mL/min.[55-57]

Prescribing information

The initial dose of canagliflozin is 100mg daily taken before breakfast. Patients requiring additional glycemic control may be incremented to 300mg, but those with an eGFR 45 to <60mL/min/1.73 m^2 be restricted to maximum of 100mg/day. Dose

Table 1: Major trials involving canagliflozin

Trial	Study design	Comparative drugs	HbA1C reduction	FBS reduction	PPBS reduction	Weight loss	BP reduction	Incidence of Side effects
Efficacy and safety of canagliflozin monotherapy[52]	26 week, randomized, double blind, placebo controlled, phase 3 trial n = 584	Canagliflozin −100mg/300 mg daily vs placebo	Both 100 and 300 mg doses showed significant (−0.77, −1.03 respectively) reduction $P < 0.001$ for both doses	100 and 300mg doses showed a significant reduction $P < 0.001$ for both doses	100 and 300 mg doses showed a difference −2.7, −3.6 mmol/L respectively	In 100mg and 300mg doses reduction of -2.2% (−1.9kg) and −3.3% (−2.9kg) resp	Systolic:− −3.7, −5.4 mmHg in100 and 300mg respectively Diastolic:- −1.6 and −2 mmHg respectively	Incidence higher in canagliflozin group
Canagliflozin in moderate renal impairment [45]	26week, randomized, double blind, placebo controlled, phase 3 trial n= 269	Canagliflozin −100 mg/ 300 mg daily and placebo	Compared to placebo, 100mg Put a1c reduction dose− $P < 0.05$; 300mg dose− $P < 0.001$	–	–	–	-	Slightly higher hypoglycemia, genital mycotic infections, osmotic diuresis
Efficacy and safety of canagliflozin in Japanese patients[42]	12 wk, randomized, double blind, placebo controlled n= 383	Canagliflozin −50/100/200/ 300 mg/day and placebo	50/100/200/300 mg doses showed reduction of −0.61, −0.81, −0.79, −0.88 respectively $P < 0.01$	Significantly greater in all 4 doses; $P < 0.01$	Significantly greater in all 4 doses; $P < 0.01$	Significantly greater in all 4 doses; $P < 0.01$	Significantly greater in all 4 doses; $P< 0.01$	45%, 45.9%, 49.4%, 45.3% and 35% respectively in 50/100 /200/ 300mg and placebo groups
Canagliflozin compared with sitagliptin[53]	52 wk, randomized, double blind, active controlled, phase 3 trial n=755	Canagliflozin −300mg/ day Sitagliptin 100mg/ day	Canagliflozin – 1.03% (21.03%); Sitagliptin – 0.66% (20.37%)	Significant reduction in canagliflozin group $P < 0.001$	Greater reduction in canagliflozin group with LS mean difference of −1.0 mmol/L	Significant reduction in canagliflozin group $P< 0.001$	Systolic:- −5.1, −0.9 mmHg in canagliflozin and sitagliptin groups respectively Diastolic:− −3.0 and −0.3mmHg resp	Canagliflozin had higher incidence of genital mycotic infections
Canagliflozin compared with glimepiride [54]	52 week, randomized, double blind, active controlled, phase 3, multicentric trial n = 1452	Canagliflozin −100 mg/ 300mg and glimepiride 8mg daily	Canagliflozin 100 mg was non−inferior to glimepiride (least−squares mean difference −0·01% [95% CI −0·11 to 0·09]) and canagliflozin 300 mg was superior to glimepiride (−0·12% [−0·22 to −0·02])	Canagliflozin 100 mg and 300 mg lead to greater reductions than did by glimepiride	–	Both canagliflozin doses significantly reduced bodyweightat week 52,whereas a slight increase with glimepiride was noted	Systolic:− −3.3, −4.8 mmHg in 100 and 300mg doses respectively Diastolic:- −1.7, −2.4 mm Hg in 100 and 300 mg doses respectively	Serious AE in 100 mg/300 mg/ glimepiride gps: 5, 5, 8%, respectively. Canagliflozin group has greater genital mycotic infections, UTIs, but sig lower hypoglycaemia

BP = Blood Pressure, FBS = Fasting Blood Sugar, PPBS = Post Prandial Blood Sugar, HbA1C = Glycosylated Haemoglobin

adjustment may also be recommended in elderly and those on loop diuretics, and the use is contraindicated with eGFR <30mL/min/1.73m^2. Since canagliflozin is metabolized by O-glucuronidation primarily through uridine diphosphate-glucuronosyl transferase (UPD-GT), its use is not recommended with UPD-GT inducers, such as rifampin and phenytoin.[55] Canagliflozin is effective as monotherapy as well as in combination with other anti-hyperglycaemic drugs including insulin.[55,56, 58,59]

Individuals with a history of dehydration or recurrent urinary and genital infections would not be recommended. The need for adequate renal function is recognized, noting that the mode of action on the proximal tubule SGLT2 transporters should not aggravate existing damage at the glomerulus, and may offer benefit through reduced glucotoxicity, lower systolic blood pressure and reduced proteinuruia.[55,58]

Adverse effects

Generally, it is a well tolerated drug. Common side effects are genital mycotic infections in both females and uncircumcised males, increased urination, urinary tract infection and hyperkalemia.[57,60] Mycotic infections secondary to canagliflozin use are mild to moderate in nature and respond to treatment with antifungals.[56] Consequent to osmotic diuresis effect, orthostatic hypotension, increased thirst, and hypotension may also occur.[55,61]

A small increase of 4% in LDL cholesterol can also occur but this is associated with also a similar increase in HDL-Cholesterol and significant drop in triglycerides.

Future of SGLT2 inhibitors

Non-phlorizin-based molecules targeting SGLT2 are also being developed, such as ISIS-SGLT2Rx, an antisense inhibitory microRNA molecule, to reduce the expression of SGLT2.[62] SGLT1 and 2 inhibitors are also being developed (Lexicon Pharmaceuticals).

CONCLUSION

SGLT2 inhibitors offer an entirely novel, insulin-independent approach for treatment of diabetes by blocking the reabsorption of glucose in the renal nephron resulting in markedly increased glycosuria and reduced blood glucose concentrations. Since this mechanism is not constrained by the extent of insulin resistance or beta-cell dysfunction, these drugs are ideal candidates to be used at any stage in the natural history of diabetes- from newly diagnosed to long-standing disease, including extremes of insulin resistance and β-cell dysfunction, as well as in type 1 diabetes (not approved but studied). Their prospective use is further enhanced by the fact that these can be used as monotherapy for patients seeking different treatment options and in complementary manner with other antidiabetic agents or insulin. Furthermore, at low plasma glucose concentrations, SGLT1 is free to reabsorb the filtered glucose load providing for an automatic cushion against additional risk of severe hypoglycaemia.[12] Since canagliflozin significantly improves blood pressure and weight in addition to glycaemic indicators (HbA1C, fasting and postprandial plasma glucose), there is a strong rationale for expecting that it will protect against microvascular and macrovascular complications of the disease.[46] However, concrete evidences regarding this are still to be determined from the ongoing CV trials.[51] It is generally well tolerated in subjects with T2DM and Stage 3 chronic kidney disease (CKD). Possible side effects include increased risk of urinary or genital infection, headache, hypotension, and increased thirst. However, severe side effects such as hypoglycemia are rare.

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