Risk and Benefits of Canagliflozin, a New Sodium-Glucose Co-Transporter Type 2 Inhibitor, in the Treatment of type-2 Diabetes Mellitus

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Abstract: *Anti-diabetic medications are used to control blood sugar levels if diet and exercise fail to do so. On March 29, 2013, canagliflozin became the first SGLT2 inhibitor to be approved in the United States for the treatment of type-2 diabetes. This drug blocks reabsorption of glucose in the proximal tubule, lowering the renal threshold for glucose and thereby increasing glucose excretion. Its novel mechanism of action is insulin-independent. In clinical trials, canagliflozin significantly decreased fasting glucose and HbA1c level when administered either as monotherapy or as combined therapy with other anti-diabetic drugs, with added benefit of weight loss and lowering of blood pressure. It possesses favourable pharmacokinetic and pharmacodynamic profiles. It is administered orally and may be a viable option for adults with Type-2 DM who cannot achieve glycemic control with multiple agents but refuse injectable medications. However, it is not devoid of unfavourable adverse effects like urinary tract infections, genital yeast infections, postural hypotension, hyperkalemia, dose-dependent increases in low-density lipoprotein cholesterol etc. Canagliflozine should not be used in chronic kidney disease due to decreased or lack of efficacy and nephrotoxicity.*

Keywords: Type 2 diabetes, Canagliflozin, SGLT2 inhibitor, HbA1c, Weight loss, Hypoglycemia, urinary tract infections, Genital Infection, Chronic kidney disease.

1. Introduction

There is an emerging global epidemic of diabetes that can be traced back to physical inactivity, rapid increase in weight and obesity. According to WHO about 347 million people worldwide have diabetes, and is predicted to become the seventh leading cause of death in the world by the year 2030 [1], [2]. According to Diabetes Atlas 2014, released by *'International Diabetes Federation'* India has 65 million people living with diabetes and is only second to China [3].

By 2030, India's diabetes burden is expected to cross the 100 million mark as against 87 million earlier estimated. India is also the largest contributor to regional mortality with 983, 000 deaths caused due to diabetes this year [4]. Worldwide, Diabetes caused 4.9 million deaths in 2014; every seven seconds, a person dies from diabetes.

Type 2 diabetes mellitus, which constitutes more than 95% of all the diabetic populations, has an insidious onset with a long, latent, asymptomatic phase and is characterized by chronic hyperglycemia with disturbance of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both [5]. Several distinct types of Diabetes mellitus are caused by a complex interaction of genetics and environmental factors. Depending on the aetiology of the Diabetes mellitus, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production [6], [7]. The metabolic dysregulation associated with Diabetes mellitus causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system.

DM is the leading cause of end-stage renal disease (ESRD), nontraumatic lower-limb amputation, retinopathy, and neuropathy, as well as cardiovascular disease. Type 2 diabetes accounts for more than 90% of cases of diabetes in the United States, Europe, and Canada [8]. It is characterized by insulin resistance, decreased beta-cell function, and progressive beta-cell decline [9]. This concludes that the available drugs for DM are not able to maintain or achieve good glycemic control. Potential adverse effects like gastrointestinal disturbances (with biguanides like metformin, α-glucosidase inhibitors like acarbose, glucagon-like peptide-1 agonists like exenatide, amylin agonists like pramlintide), hypoglycemia (with insulin, secretagogues like sulfonylureas and meglitinides), weight gain (with insulin, secretagogues like sulfonylureas and meglitinides, thiazolidinediones like pioglitazone) and risk of cardiovascular disease (with thiazolidinediones like pioglitazone) limit their dosage; and ensuing β-cell failure limits their effectiveness. Current guidelines recommend a target HbA1c value of $< 7.0\%$, and treatment with lifestyle changes and drugs for better glycemic control in diabetics. But the target HbA1c is rarely achieved with a single anti-diabetic drug; rather it is achieved by combination therapy [10], [11]. Hence, there is ongoing research for newer efficacious and safer treatment strategies.

On March 29, 2013, canagliflozin became the first SGLT2 inhibitor to be approved in the United States for the treatment of type 2 diabetes mellitus [12]. However, it is not the first of its class to be introduced. Dapagliflozin was the first SGLT2 inhibitor approved in Europe and has been available there since November 2012. However, the US Food and Drug Administration withheld its approval in the United

States in January 2012 because of risk of a possible association with cancer, specifically breast and bladder cancers, as well as possible hepatic injury. But, these risks are not associated with Canagliflozin.

2. Mechanism of action

There is crucial role of kidney in glucose homeostasis through glomerular filtration and reabsorption in the proximal convoluted tubule (PCT) [13]. In a normal healthy adult, approximately 180 g of glucose is filtered daily [14]. The kidneys reabsorb most of the glucose, with less than 1% being excreted into the urine. The normal tubular glucose load is approximately 120 mg/min, with no glucose excreted into the urine [15]. Glucosuria begins to occur when the tubular glucose load exceeds 220 mg/min; which corresponds to a plasma glucose concentration of approximately 200 mg/dl [16]. The plasma glucose concentration is an important modulator of SGLT expression and activity. The fundamental concept underlying current research on SGLT2 inhibitors is that by blocking the effects of SGLT, increased urinary glucose excretion (UGE) and reduced plasma glucose levels can be achieved.

Glucose reabsorption is accomplished with the active transport of glucose by sodium-coupled glucose co-transporters (SGLT1 and SGLT2) found in the kidneys [17]. SGLT1 is located in the heart, intestine, trachea, and kidney, whereas SGLT2 is located only in the kidney [18]. SGLT1 is shown to reabsorb 10% of filtered glucose reabsorption in the S3 segment of the PCT, whereas, the SGLT2 has been identified to conduct 90% of reabsorption in the S1 segment of the PCT [19]. The underlying mechanism through which this novel class of drug (SLGT2 inhibitor) acts is through inhibition of these SGLT2 co-transporters, ultimately resulting in decreased renal reabsorption of the filtered glucose [20]. This inhibition of glucose reabsorption results in increased renal glucose excretion in the urine. There is loss of almost 80-100 gm of glucose per day which is responsible for loss of about 300-400 kcal of energy. This increased excretion of glucose may have beneficial effects of weight loss [21].

3. Pharmacokinetics and Therapeutic Efficacy

Canagliflozin is well tolerated orally and achieves its peak plasma concentration within 1 to 2 hours of oral administration [22]. Its half-life is 10.6 hours with a 100- mg dose and 13.1 hours with a 300-mg dose. Steady state concentration is achieved in about 4 to 5 days. Canagliflozin can be administered without regards to meals, but improved glycemic control may occur when it is administered before the first meal of the day due to delayed gastrointestinal absorption of glucose. The oral bioavailability of canagliflozin is nearly 65%. It is 99% plasma protein bound, mainly to albumin. The mean apparent volume of distribution is 119 L after single intravenous (IV) administration. It is metabolised mainly through O-glucuronidation by UGT1A9 and UGT2B4, producing two inactive metabolites. In humans, small amounts (7%) are metabolized through CYP3A4. The average clearance of canagliflozin is 192 ml/min when administered by IV route

to healthy individuals. Approximately 33% and 41.5% of the administered dose is excreted in the urine and faeces, respectively. The renal clearance of canagliflozin ranges from 1.30 to 1.55 mL/min.

Canagliflozin lowers fasting plasma glucose and hemoglobin A1c levels in a dose dependent manner. These effects are independent of age, sex, body mass index, and race [23]. It also lowers postprandial glucose levels. Other potential benefits of canagliflozin include lowering of the systolic blood pressure and, especially important in obese person with type 2 diabetes mellitus, causing weight loss. Aside from metformin, which occasionally results in modest reduction in weight, other oral hypoglycaemic drugs used in treating type 2 diabetes mellitus are either causing weight-neutral or can cause weight gain.

So, Canagliflozin is approved for use as monotherapy in addition to lifestyle modifications. It is also approved for use as add on therapy with other antihyperglycemic drugs, including metformin. Obese patients with type 2 diabetes and normal renal function may have the greatest benefit. Because of canagliflozin's insulin independent mechanism of action, patients with both early and late type 2 diabetes may benefit from its ability to lower haemoglobin A1c and blood glucose [24]. Canagliflozin is also used as an additional oral antihyperglycemic option which may prove helpful in managing patients with type-2 diabetes mellitus who experience adverse effects with other antihyperglycemic drugs.

Adverse Effects

Overall, canagliflozin seems to be well tolerated. But, it has also some adverse effects. The most common adverse effects reported are urinary tract infections, increased urination, Genital yeast infections, Postural hypotension, hyperkalemia, dose-dependent increases in LDL-cholesterol, Thirst etc. Less commonly it also causes constipation, nausea, abdominal pain, fatigue, asthenia, acute or chronic pancreatitis, bone fracture, hypersensitivity reactions and photosensitivity.

Contraindications

- Canagliflozin is contraindicated in patients with a history of serious hypersensitivity reactions.
- It is contraindicated in patients with severe renal impairment [estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m2], end stage renal disease (ESRD), and in patients on dialysis.
- elderly patients,
- patients with low systolic blood pressure,
- Patients on diuretics or drugs which interfere with the renin-angiotensin aldosterone system.
- Patients with increased serum creatinine

4. Precaution in Special Populations:

Pediatrics: The safety and efficacy of canagliflozin have not been determined in patients under 18 years old.

Pregnancy: Pregnancy Category C.

Geriatrics: From clinical trials, it is concluded that Patients of 65 years and older age experienced a higher incidence of adverse reactions pertaining to reduced intravascular volume by using canagliflozin as compared to younger patients, especially with the canagliflozin 300 mg dose. There are smaller reductions in HbA1C relative to placebo in patients of older age.

Renal Impairment: Clinical trials reveals that Patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m2) had less glycemic efficacy and higher occurrence of intravascular volume adverse reactions, renal-related adverse reactions, and decreases in eGFR as compared to patients with mild renal impairment or normal renal function. There is also increase in serum potassium level in patients taking 300 mg of canagliflozin. Efficacy and safety has not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m2) or those patients with ESRD or on dialysis. So, it is not effective in such patients.

Drug Interactions: The efficacy of canagliflozin is reduced when it is administered with UDP-Glucuronosyl Transferase (UGT) enzyme inducers such as rifampicin, phenytoin, ritonavir, Phenobarbital etc. Other antihyperglycemic therapy should be considered in patients with an eGFR of 45 to 59 mL/min/1.73 m2 who are also taking an UGT inducer and require additional glycemic control. Co-administration of digoxin and canagliflozin may increases the exposure to digoxin and, therefore, close monitoring is warranted.

5. Conclusion

Canagliflozin is a novel medication, acts by a novel mechanism in the treatment of Type-2 diabetes mellitus, inhibits the SGLT2 receptor in the PCT of kidney and increases glycosuria, thereby improving glycemic control and increasing caloric loss with an insulin-independent mechanism. Although, Canagliflozin has beneficial role in the treatment of type-2 D.M in obese, hypertensive and in those patients who cannot achieve proper glycemic control with multiple agents, and refuse injectable medications. But, however, because of its certain adverse effects, canagliflozin should not be used in those patients who are of older age, use sulfonylurea or insulin medications, or have risk factors for genitourinary infections, renal impairment, postural hypotension, uncontrolled hyperlipidemia, or urinary frequency.

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