A novel treatment for Type2 diabetes mellitus: Canagliflozin

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ABSTRACT

Sodium glucose co-transporter type 2 (SGLT2) inhibitors, as a new class for treatment of Type 2 diabetes mellitus, offer a novel mechanism of action, and are very effective in bringing the blood sugar levels down, either alone or in combination with other oral hypoglycaemic agents, with minimal side effects. Among the several drugs in this group, which are in various stages of clinical trials, canagliflozin has been recently approved by USFDA for use in type 2 diabetes mellitus, either alone or in combination with other oral hypoglycaemic agents and insulin.

Key words: Canagliflozin, blood glucose, SGLT2 inhibitors.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) has been treated till date with the main focus on bringing the blood glucose down to normal levels using the drugs that mainly target either the insulin secretion or glucose metabolism. However, none of the drugs in vogue are able to provide efficient control on blood sugar levels or insulin secretion and functioning.[1] Another entirely different perspective for aiming stricter glycemic control is focussing on kidney which plays a central role in glucose homeostasis via gluconeogenesis and excretion of glucose in urine. Sodium glucose co transporter 2 (SGLT2) is mainly expressed in proximal convoluted tubule (PCT) and is responsible for most of the reabsorption of glucose present in the glomerular filtrate.[2] Drugs that inhibit SGLT2 will lead to increased excretion of glucose in the urine, thereby bringing down the blood sugar levels, with mechanism totally independent from pancreatic beta cell activity or gastrointestinal manipulation of glucose. Canagliflozin is the first drug in this class of SGLT2 inhibitors, which has been recently approved by United States food and drug administration (USFDA) for use in adults for treatment of T2DM.[3]

The cotransport of glucose and sodium by SGLT is an energy dependent process. SGLT1 and 2 are mainly involved in the reabsorption of glucose in kidney. SGLT2 reabsorbs approximately 90% of glucose present in the glomerular filtrate.[4] This renal glucose transport system plays a vital role in maintaining the glucose homeostasis. In patients with uncontrolled T2DM, there is an increased expression of SGLT2, as an adaptive process, compared to the normal individuals. SGLT2 inhibitors stop this reabsorption of glucose, and especially in the patients where the blood glucose levels are high, they produce higher degree of glycosuria, thereby being more effective in bringing the glucose levels down in such patients, without exposing the patients to the risk of hypoglycaemia.[5] Drugs included in this group are dapagliflozin, canagliflozin, empagliflozin, ipragliflozin, lueogliflozin, ertugliflozin, tofogliflozin etc.[6] Dapagliflozin was shown to be very effective in T2DM patients, but FDA approval was not given to this drug on the pretext that it increased the risks for development of bladder or breast cancer and caused hepatotoxicity.[7]

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All of them are mostly meant for oral administration once a day. Apart from bringing the blood glucose levels down, these drugs have several other beneficial effects as well.[6,8,9] Among the several drugs in this group, which are in various stages of clinical trials, canagliflozin has been approved by the FDA. It is first among the drugs which come under SGLT2 inhibitors, to get a FDA approval, for use in adult patients with T2DM.[3] It can be used alone or as a combination with other oral hypoglycaemic agents or insulin.

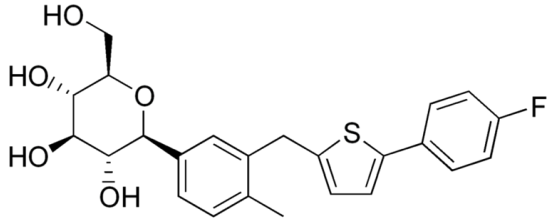
METHODS FOR DATA COLLECTION

The information was collected by thorough research of various relevant sources over a period of two months between August and September of 2013. A search was made using the key words SGLT2 inhibitors, Canagliflozin, newer antidiabetic drugs, T2DM treatment on various search engines like pubmed, pubchem, Cochrane library and relevant journals. Articles which were thereby retrieved included several abstracts, full text articles and new drug information available from websites like USFDA. Full details from all the researched articles were read and processed and suitably incorporated in this article by the authors, aiming to present a comprehensive review with complete details.

DRUG REVIEW

Chemical structure

Canagliflozin is available commercially as INVOKANA and is a C-glucoside with a thiophene ring, with a structural formula of $(C_{24}H_{25}FO_5S)2.\ H_2O$ and is a highly stable, potent and selective SGLT2 inhibitor.[10]



Mechanism of action

Canagliflozin acts by inhibiting the SGLT2 which accounts for more than 90% of renal glucose reabsorption.[4] Hence the efficacy of this drug also is dependent upon the amount of glucose which is filtered through the glomeruli and enters the tubular lumen and therefore shows maximal effect in patients with uncontrolled T2DM.[5] Apart from bringing down the blood glucose levels, it has many other beneficial actions like reduction of the glycosylated haemoglobin levels due to the better control of blood glucose levels. It additionally improved the sensitivity of liver to insulin by reducing the blood glucose levels thereby reducing the glucose production from liver.

This reduces the general glucotoxic state of the body in patients with T2DM and helps in bringing down the serum insulin levels. Since the calories are lost from the body in the form of glucose in urine of the patients taking this drug, it causes a negative energy balance and loss of weight, which is again beneficial in patients of T2DM. This drug also helps in reduction of blood pressure owing to the mild weight loss and diuretic action caused by it. It has a positive effect on blood lipids as well due to mild weight loss caused by it.[6,8,9]

Pharmacokinetics

It is given orally and reaches the peak concentration in plasma in about 1-2 hours. The steady state of plasma concentration is achieved in around 4-5 days. Oral bioavailability of canagliflozin is approximately 65%. It has a high plasma protein binding (99%) and it binds mainly to albumin.[11] Food does not interfere with its absorption. It has a half life of 11 hours with a 100 mg dose and of 13hrs with a dose of 300 mg and is mainly metabolised via glucuronidation.[12,13] A small part (~7%) of absorbed drug also undergoes oxidation through CYP3A4 enzyme.

Hence drugs which induce this enzyme e.g. rifampicin, phenytoin, ritonavir etc. will decrease the plasma level of canagliflozin. Therefore, its dose has to be increased to 300 mg/day when used in combination with these drugs. It increases the plasma concentration of digoxin, so the drug levels need to be monitored to avoid the development of digoxin toxicity. Renal function needs to be assessed whenever this drug has to be started and is contraindicated when the GFR (glomerular filteration rate) is less than 45 ml/min/1.73m^2.[11] In a study done to assess the pharmacokinetics and pharmacodynamics of canagliflozin, it was established that the profile of the drug is meant for once daily regimen.[14]

Efficacy studies

Canagliflozin has been extensively studied both in preclinical and clinical trials and its efficacy as a hypoglycaemic agent has been proved.

Preclinical studies

SGLT2 inhibitors have been studied in various preclinical studies for their efficacy and safety. Canagliflozin has been found effective in animal models for type 2 diabtese mellitus, by reducing the renal threshold for glucose excretion and increasing the excretion of glucose in urine.[15] In another preclinical study it was seen that SGLT2 inhibitors improved metabolic abnormalities and retarded the development of complications in diabetic rats.[16] Apart from these studies, SGLT2 inhibitors were tested in many different animal models with T2DM have always showed a positive result.[17,18]

Clinical studies

After the successful demonstration of efficacy and safety of SGLT2 inhibitors in animal studies, further research was done by testing certain drugs belonging to this class in clinical trials. Canagliflozin has been the first drug in this class to be proved both effective and safe in patients with T2DM. In a phase 3 trial of canagliflozin, it improved the glycemic control, reduced the level of glycosylated haemoglobin and body weight in the patients with type 2 diabtest mellitus, not controlled by diet and exercise.[19]Canagliflozin was shown to be safe and effective in older patients with T2DM, when compared with placebo, for a period of 26 weeks and there was a positive effect on blood pressure apart from the adequate control of blood glucose levels and reduction in body weight.[20]

Canagliflozin has also been studied in comparison with or in combination with other oral hypoglycaemic agents. In a phase 3, non inferiority clinical trial, canagliflozin was compared with glimepiride in patients with T2DM, not fully controlled by metformin. It was seen that canagliflozin was very well tolerated and also brought down the glycosylated haemoglobin levels better than glimepiride group.[21] It has also been compared with sitagliptin, in patients with type T2DM with inadequate glycemic control even after treatment with a combination of metformin and a sulfonylurea. Canagliflozin 300 mg had superior effects when compared to sitagliptin 100 mg in achieving proper glycemic control and bringing down the glycosylated haemoglobin levels, systolic blood pressure and body weight. However, it has been seen to be associated with increased incidence of genital infections as compared to sitagliptin.[22]

In another dose ranging study of canagliflozin, it was added to the ongoing metformin therapy in the patients with T2DM and helped in significantly achieving the glycemic control and weight loss with a slightly higher incidence of genital infections, especially in females.[23] Hence canagliflozin was tested in several clinical trials and proved to have a good safety and efficacy profile, with a slightly higher incidence of genital and urinary infections, due to the increased levels of glucose in urine.

Safety and tolerability

The most common side effects associated with canagliflozin are mycotic genital infections, more so in females, urinary tract infections, increased urination, especially at night. Though these infections are easily treatable, they do impair to certain extent, the quality of life of the person receiving treatment. Since canagliflozin is associated with polyuria, effects related to intravascular volume depletion like postural hypotension, increased thirst and a small rise in haematocrit etc. may occur. It is also said to be associated with a little increase in low density lipoprotein cholesterol (LDL-C), with no evident ill effect.[24] There is a study going on (CANVAS study) to assess the full and long term effects of canagliflozin on cardiovascular outcomes.[25] It can also cause constipation, rash and allergy in some patients.[11] It can also moderately increase the blood urea nitrogen (BUN), mildly increase serum creatinine and decrease serum urate levels.[26] There are no studies till date, which establish the use of canagliflozin in pregnant and lactating females.

Dosage regimen and precautions

It has to be given orally, once daily, before taking the first meal of the day.[20] According to the recommendations, the starting dose of canagliflozin is 100mg/day. It can be increased to 300mg/day as per the requirement. Since its mechanism of action primarily involves kidney, it is recommended to monitor the renal functioning at the beginning and during the course of treatment.[20,27]

CONCLUSION

Canagliflozin's approval by FDA has definitely cleared the mist a bit, as far as the treatment of T2DM is concerned, with no additional risk of hypoglycaemia, but rather with several beneficial effects like lowering of blood pressure, weight loss, improvement in insulin sensitivity etc. However, the increased incidence of genital mycotic infections and urinary tract infections, though easily manageable, will impair the quality of life of the patients, especially females, who are found to be more prone to mycotic vaginitis. The area of concern is that this particular side effect, can't possibly be avoided as it is intricately woven with the drug's mechanism of action.

To summarize, SGLT2 inhibitors, as a new class for treatment of T2DM, offer a novel mechanism of action, and are hugely effective in bringing the blood sugar levels down, either alone or in combination with other oral hypoglycaemic agents, with minimal side effects.

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