Review Article

Sodium Glucose Co-Transporter-2 (SGLT2) Inhibitors as a New Class of Anti-diabetic Drugs: Pharmacokinetics, Efficacy and Clinical significance

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ABSTRACT

SGLT2 Inhibitors are a new class of oral antidiabetic agents which reduce the plasma glucose concentration by preventing the reabsorption of glucose from the S1 segment of proximal convoluted tubule, thereby increasing urinary glucose excretion. Most recent understanding about the physiology of renal glucose transport system and increased knowledge about rare genetic syndromes of renal glucosuria has resulted in the development of drugs that selectively inhibit sodium glucose transporter-2(SGLT2). Their mechanism of action is independent of beta cell and tissue sensitivity to insulin, but they improve glycemic control while avoiding hypoglycemia and promoting weight loss. This article discusses the basic physiology of SGLT2 transporter system, mechanism of action and chemistry of various agents under this class. Dapagliflozin and Canagliflozin are the first agents of this class, approved from the European Medicine Agency and FDA, respectively.

Keywords: Anti-diabetic agents, Diabetes, Glucosuria, SGLT2 Inhibitor, Weight loss

INTRODUCTION

Diabetes Mellitus and its Epidemiology

Diabetes mellitus is a chronic disease that requires life-long pharmacological and non pharmacological management to prevent complications such as cardiovascular disease, retinopathy, nephropathy, and neuropathy.[1,2] People with diabetes are at risk of developing a number of disabling and life-threatening health problems. Consistently high blood glucose levels can lead to serious diseases affecting the heart and blood vessels, eyes, kidneys, and nerves. Diabetic patients are also at increased risk of developing infections. In almost all high income countries, diabetes is a leading cause of cardiovascular disease, blindness, kidney failure, and lower-limb amputation.

While type 2 diabetes mellitus is most common form of diabetes comprising of 90% to 95% of all diabetes cases[2]. An estimated 387 million people worldwide live with diabetes, resulting in 4.9 million deaths in 2014, with more than 77% of these deaths occurring in low- and middle income countries. It is projected that the death burden from diabetes will double by the year 2035[3]. According to the 2014 IDF report, the estimated prevalence of diabetes in 2014 was about 8% for men and women in low-income countries and 10% for both sexes in upper-middle-income countries with the highest global prevalence of diabetes in Eastern Mediterranean Region and Region of the Americas[4]. The high prevalence rate is of concern since diabetes is the leading cause of renal failure, visual impairment, blindness and increases the risk of lower limb amputation by at least 10 times[3,4]. Additionally, patients living with diabetes may need 2 to 3 three times of the health-care resources compared to people without diabetes and diabetes care may require allocation of up to 15% of national health care budgets[4].

Introduction

Sodium-dependent glucose co-transporters (SGLT) belong to the family of glucose transporter found in the intestinal mucosa of small intestine (SGLT1) and in the proximal tube of nephron (SGLT2 in PCT and SGLT1 in PST) which contribute to renal glucose reabsorption. In kidneys, 100% of the filtered glucose in the glomerulus has to be reabsorbed along the nephron via SGLT2[5,6]. In case of high plasma glucose concentration (hyperglycemia), glucose is excreted in urine (glucosuria); because SGLT are saturated with the filtered monosaccharide[7]. Diabetes mellitus is the most common metabolic disorder characterized by hyperglycaemia which is associated with long term complications affecting kidney, heart, eyes and nerves[8-10]. Insulin regulates carbohydrate metabolism by aiding the transport of glucose and amino acid from the blood stream into the storage organs such as liver and muscles. In diabetes mellitus, hindrance in glucose transport takes place of such a degree that threatens or impairs health[11].

Management of type 2 diabetes mellitus (T2DM) remains complex and challenging. A wide range of pharmacotherapy for T2DM which includes metformin, insulin secretagogues (predominantly sulfonylureas), thiazolidinediones, α-glucosidase inhibitors, insulin and more recently glucagon like peptide-1 agonists and dipeptidyl-peptidase-IV inhibitors, many patients do not achieve glycemic targets due to side effects of current therapies, including weight gain, hypoglycemia, fluid retention and gastrointestinal side effects. Hence, the

search for new treatment strategies is ongoing[12]. Among the new therapies on the horizon, sodium-glucose co-transporter 2 (SGLT2) inhibitors seem to be promising and there are a number of ongoing phase II and III clinical trials with a variety of these compounds. SGLT2 is expressed in the renal proximal tubules and accounts for 90% of the renal glucose reabsorption[13,14]. SGLT2 inhibitors work independently of insulin leading to negative energy balance by enhanced urinary glucose excretion. This makes mechanistically possible for this class of drugs to reduce glucose levels without causing hypoglycemia and weight gain. However, the side effect profile remains to be further elucidated in ongoing phase III trials and these compounds will need to be proved safe from a renal and cardiovascular perspective in order to meet current regulatory requirements for new diabetes treatment[15].

Types of SGLT

The two well known members of SGLT family are SGLT1 and SGLT2 (Tables 1, 2), which are members of the SLC5A gene family[13,14].

Including SGLT1 and SGLT2, there are total seven isoforms in the human protein family SLC5A, many of which may also be sodium-glucose transporters[15,16].

Table 1: SGLT1 and SGLT2 and their Properties

Gene	Protein	Acronym	Tissue distribution in proximal tubule	Na:Glucose cotransport ratio	Glucose reabsorption
SLC5A1	Sodium/Glucose co-transporter 1	SGLT1	S3 segment	2:1	10
SLC5A2	Sodium/Glucose co-transporter 2	SGLT2	Mainly in the S1 and S2 segments	1:1	90

Table 2: Types of Sodium Glucose Transporters

Gene	Protein	Substrate	Tissue distribution
SLC5A1	SGLT1	Glucose and galactose	Small intestine, trachea and kidney
SLC5A2	SGLT2	Glucose	Kidney
SLC5A4	SGLT3	Glucose sensor	Small intestine, lung, uterus, thyroid and testes
SLC5A9	SGLT4	Mannose, glucose, fructose and 1,5-Anhydroglucitol	Small intestine, kidney, lung and liver
SLC5A10	SGLT5	Glucose and galactose	Kidney
SLC5A11	SGLT6	Myo-inositol, xylose and chiro-inositol	Spinal cord, kidney, brain and small intestine

Table 3: SGLT2 Inhibitors in Clinical Development

Drug	Stage	Company
Dapagliflozin	Approved in US, UK and Germany	Bristol-myerssquibb in partnership with Astra Zeneca.
Canagliflozin	Approved in US	Marketed under license by Janssen, a division of Johnson & Johnson.
Ipragliflozin	Phase III clinical trials	Discovered by Astellas and Kotobuki Pharmaceutical Co. Ltd
Tofogliflozin	Phase III clinical trials	Chugai Pharma in collaboration with Kowa and Sanofi
Empagliflozin	Phase III clinical trials	Discovered by Boehringer Ingelheim and Eli lily and company
Remogliflozin	Phase IIb clinical trals	Developed by Chugai Pharma in collaboration with Kowa and Sanofi.

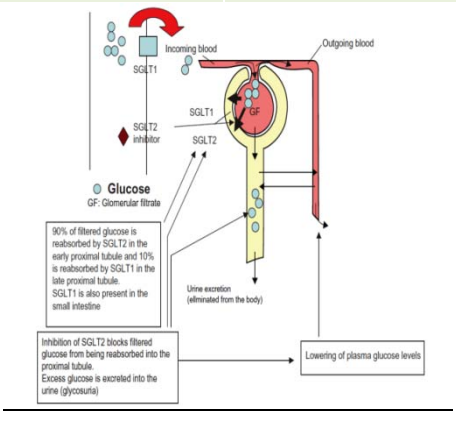


Figure 1: Schematic representation of SGLT2 co-transporter Inhibition

Mechanism of Action

Glucose reabsorption in renal tubules is largely due to two key glucose transporters: SGLT2 and SGLT1. The SGLT2 is a high-capacity and low-affinity glucose transporter expressed in the proximal renal tubules, which is responsible for majority of re-absorption into the blood stream of glucose filtered through the glomerulus[16]. SGLT1 is a high affinity low capacity transporter, which is responsible mainly for absorption of glucose in the gastrointestinal tract. It is also expressed in the liver, lungs and kidneys[15-17]. Transport of each glucose molecule is coupled to co transport of sodium (Na+) ion in the kidneys and once inside the cell, glucose diffuses into blood via facilitated transport. Reabsorption of glucose in

proximal tubule of kidney is an active process requiring energy, which comes from electrochemical gradient generated by reabsorption of Na+ across the brush border and is maintained by continuous transport of Na+ across the basolateral membrane into blood via Na+/K+ ATPase. Therefore, blocking the reabsorption of glucose in the kidneys serves as a strategy to treat hyperglycaemia[17].

Renal Glucose Transport in Normal Condition

Kidneys play a very important role in glucose homeostasis. Blood glucose is freely filtered by the glomeruli and is completely reabsorbed from the proximal tubules via sodium-coupled transporters in the brush border membrane. The glomeruli filter about 144 g of glucose per 24 hours, nearly 100% of which is reabsorbed in the renal tubules. When blood glucose level reaches the renal threshold for reabsorption, which is about 8 to 10 mmol/liter (180 mg/dl), glucosuria starts to develop. The proximal tubule has been divided into S1, S2 and S3 segments based on the cell morphologies, although more recent ultra structural analyses of computer-assisted three-dimensional reconstruction of mouse proximal tubules revealed no obvious morphological segmentation of the proximal tubule[18,19]. There is evidence for heterogeneity of sodium-dependent glucose transport along the proximal tubule. The S1 and S2 segments of the proximal convoluted tubules show low affinity and high capacity for sodium-dependent glucose absorption, whereas the distal parts show higher affinity and low capacity for the same. SGLT2 is located in the S1 and S2 segments where the majority of filtered glucose is absorbed and SGLT1 is located in S3 segments responsible for reabsorbing the remaining glucose[17,20].

Renal Glucose Transport in Diabetic Condition

Renal tubular reabsorption is known to undergo adaptations in uncontrolled diabetes; particularly relevant in this context is the up-regulation of renal glucose transporters (GLUTs). The increase in extracellular glucose concentration in diabetes lowers its outwardly directed gradient from the tubular cells into the interstitium.

Hence, up-regulation of SGLT2 is an important adaptation in diabetes to maintain renal tubular glucose reabsorption[19,20]. SGLT2 mRNA expression is up-regulated in diabetic rat kidneys and this up-regulation is reversed by lowering blood glucose levels.

Human exfoliated proximal tubular epithelial cells from fresh urine of diabetic patients express significantly more SGLT2 and GLUT2 than cells from healthy individuals[21]. There is also evidence for up-regulation of GLUT2 gene expression in renal proximal tubules in diabetic rat models. Uncontrolled diabetes leading to increased expression of SGLT2 has practical significance as the inhibitors are likely to produce greater degrees of glucosuria in the presence of higher prevailing plasma glucose levels. This has been shown in preclinical studies with the nonspecific SGLT inhibitor, T-1095[22-24].

Interestingly, this up-regulation of SGLT2 receptors is also seen in renovascular hypertensive rat models. The authors speculated that angiotensin II-induced SGLT2 over expression probably contributes to increased absorption of Na+ and thereby leading to development or maintenance of hypertension. Rats treated with either Ramipril or Losartan showed significant reduction in the intensity of immunostaining and levels of SGLT2 protein and mRNA. This may have relevance in diabetes, given the high prevalence of hypertension in diabetes[25-27].

Initial Discovery of Therapeutic Potential of SLGTs to Produce Glucosuria

Phlorizin is a glucoside consisting of a glucose moiety and two aromatic rings (a glycone moiety) joined by an alkyl spacer[28]. In the 19th century, French chemists isolated it from the bark of apple tree to be used in treatment of fever and infectious diseases, particularly malaria. Von Mering observed in 1886 that Phlorizin produces glucosuria and has been used as a tool for physiological research for more than 150 years. In 1975, a study showed that infusion of Phlorizin in dogs increased fractional excretion of glucose by 60%, whereas glomerular filtration rate and renal plasma flow remained unchanged[29].

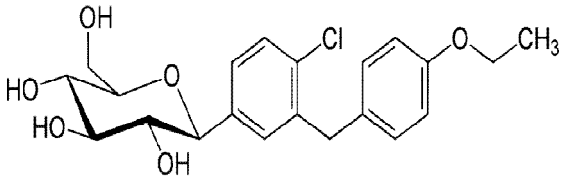
Phlorizin is a high-affinity competitive inhibitor of sodium-dependent glucose transport in renal and intestinal epithelia. Hence, it causes mal-absorption of glucose and galactose from the small intestine and of glucose from the renal tubules[30]. Phlorizin causes heavy glucosuria and marks inhibition of glucose uptake in the small intestine during enteric perfusion in normal rats. It also significantly reduces blood glucose on oral glucose tolerance test in mice and lowers blood glucose in streptozotocin-induced diabetic rats. It improves counter-regulatory responses reducing the risk of hypoglycemia in animal models[31]. In 1986, Unger's group reported that i.v. glucose failed to suppress the marked hyperglucagonemia found in insulin-deprived alloxan-induced diabetic dogs; however, when hyperglycemia was corrected by phlorizin, the hyperglucagonemia became readily suppressible. Phlorizin treatment of partially pancreatectomized rats completely normalized insulin sensitivity but had no effect on insulin action in controls, suggesting that the effect on insulin sensitivity was by reversal of glucotoxicity, rather than by a direct effect on insulin sensitivity[32]. Animal studies with Phlorizin have shown that its effect of changing the ambient glucose independent of insulin levels can up-regulate the glucose transport response to insulin in adipose cells, which may be as a result of changes in GLUT functional activity[33].

These findings provided important proof of concept data, that Phlorizin itself is unsuitable for development as a drug for the treatment of diabetes because of its non-selectivity and low oral bioavailability. T-1095 is a

synthetic Phlorizin derivative, which unlike Phlorizin is absorbed into the circulation on oral administration and is metabolized to its active form T-1095A. It suppresses the activity of SGLT1 and SGLT2 in the kidney and increases urinary glucose excretion in diabetic animals, thereby decreasing blood glucose levels. With long-term T-1095 treatment, both blood glucose and glycosylated hemoglobin (HbA1c) levels were reduced in streptozotocin-induced diabetic rats and the obese insulin resistant yellow KK rat models. Chronic administration of T-1095 lowered blood glucose and HbA1c levels, partially improved glucose intolerance and insulin resistance and prevented the development of diabetic neuropathy in the diabetic insulin-resistant GK rat models. There were no adverse side effects reported at the end of the study. This drug, however, did not proceed to clinical development, presumably because it also inhibits SGLT1.[26,34]

SGLT2 Inhibitor Drugs

Dapagliflozin



IUPAC name

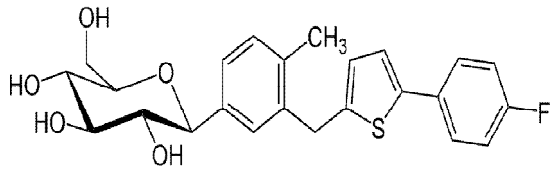
(2*S*,3*R*,4*R*,5*S*,6*R*)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6 (hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol

Dapagliflozin (Trade name **Farxiga** in the US and **Forxiga** in the EU) is a drug used to treat type 2 diabetes. It was developed by Bristol-Myers Squibb in partnership with AstraZeneca. The FDA approved dapagliflozin on January 8, 2014 for glycemic control, along with diet and exercise, in adults with type 2 diabetes. It is now marketed in a number of European countries including UK and Germany[35]. Dapagliflozin has been associated with modest reductions in body weight (2–3 kg), when used as monotherapy or dual therapy with metformin, dapagliflozin is not associated with an increased risk of hypoglycaemia. Dapagliflozin has been associated with a modest reduction in systolic blood pressure (1–2 mmHg)[35,36].

Pharmacokinetics

Dapagliflozin is a C-aryl glucoside-derived SGLT2 Inhibitor resistant to gastrointestinal glucosidase enzymes and can be administered orally in an unmodified form. Dapagliflozin is rapidly and extensively absorbed after oral administration. The oral bioavailability of a 10 mg dose is ≥75%[36]. Dapagliflozin is extensively metabolised into inactive conjugates, predominantly dapagliflozin 3-O-glucuronide, and then eliminated by the kidneys. The glucosuric efficacy of dapagliflozin is dependent on renal function, because its efficacy is reduced in patients with renal impairment[36,37].

Canagliflozin



IUPAC name

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-{3-[5-[4-Fluoro-phenyl)-thiophen-2-ylmethyl]-4-methyl-phenyl}-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol

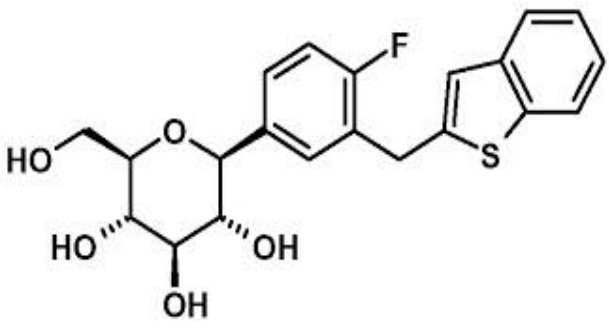
Canagliflozin (trade name **Invokana**) is a drug for the treatment of type 2 diabetes. It was developed by Mitsubishi Tanabe Pharma and is marketed under license by Janssen, a division of Johnson & Johnson. In March 2013, Canagliflozin became the first SGLT2 inhibitor to be approved in the United States.[38,39]

Canagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes and is used as a single agent (monotherapy), or in combination with other glucose-lowering agents. The Main merit of this drug is that it produces beneficial effects on HDL cholesterol and systolic blood pressure.[38-40]

Pharmacokinetics

Canagliflozin is rapidly absorbed in the gastrointestinal (GI) tract. Relative oral bioavailability of Canagliflozin is 65% and reaches peak concentrations within 1 to 2 hours. It is recommended that it has to be taken before the first meal of the day to allow for the potential to reduce postprandial plasma glucose excursions resulting from delayed intestinal glucose absorption. It is highly protein-bound, mostly to albumin at 99%. UGT enzyme inducers (e.g., rifampin, phenytoin, ritonavir) may decrease the plasma levels and efficacy of canagliflozin. No Appearance of significant interactions between canagliflozin and CYP450 enzymes 1A2, 2A6, 3A4, 2B6, 2C9, 2C19, 2D6, and 2E[41]. The drug is metabolized primarily into two inactive metabolites by uridinediphosphateglu-curonosyl transferase (UGT) enzymes: UGT 1A9 and UGT 2B4 via glucuronidation. The recommended starting dose of canagliflozin is 100 mg once daily before the first meal which can be increased to 300 mg[41,42].

Ipragliflozin



IUPAC name

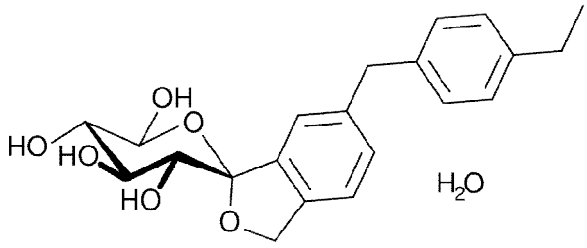
(1S)-1,5-Anhydro-1-C-[3-[(1-benzothiophen-2-yl)methyl]-4-fluorophenyl]-D-glucitol.

Ipragliflozin (trade name-Suglat) is a selective SGLT2 inhibitor discovered through research collaboration between Astellas and Kotobuki Pharmaceutical Co., Ltd. Astellas has been granted approval in Japan for this drug, in order to bring a new drug in this class to the market[43]. Astellas has conducted six Phase III studies to investigate the safety and efficacy of ipragliflozin used in combination with other hypoglycemic agents for a long term period demonstrating significant decrease of HbA1c, an index of glycemic control, in change from baseline compared to placebo. It is an SGLT-2 inhibitor in Phase III clinical development.[43,44]

Pharmacokinetics

The recommended dose is 50 mg once daily, in the morning which may be increased up to 100 mg once a day. It is absorbed rapidly, taking approximately 1 h to reach the maximum concentration[44]. It significantly reduces glycosylated hemoglobin, fasting plasma glucose, and mean amplitude of glucose excursions. Ipragliflozin is primarily eliminated via conjugation by the liver as five pharmacologically inactive metabolites (M1, M2, M3, M4 and M6). Significant dose-dependent increases in urinary glucose excretion are observed in all ipragliflozin groups[43-45].

Tofogliflozin



IUPAC name

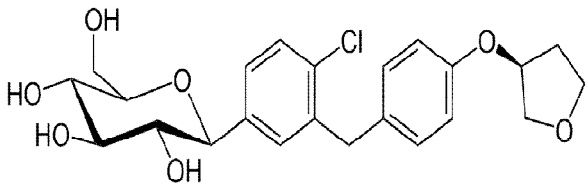
(1*S*,3'*R*,4'*S*,5'*S*,6'*R*)-6-(4-Ethylbenzyl)-6'-(hydroxymethyl)-3',4',5',6'-tetrahydro-3*H*-spiro[2-benzofuran-1,2'-pyran]-3',4',5'-triol hydrate (1:1)

Tofogliflozin (USAN, codenamed **CSG452**) is an experimental drug for the treatment of diabetes mellitus and is being developed by Chugai Pharma in collaboration with Kowa and Sanofi. As of 2013, the drug is in Phase III clinical trials. Currently, Chugai is conducting phase III clinical trial in Japan to evaluate its efficacy and safety for the target indication of type 2 diabetes.[46]

Pharmacokinetics

It is a novel C-arylglucoside with an O-spiroketal ring system[46]. The results of the Phase II study in the US indicated that tofogliflozin 5, 10, 20, and 40 mg daily resulted in significant dose-dependent reductions in HbA_{1c} compared to placebo along with an increase in urinary glucose excretion (UGE) as expected.[46,47]

Empagliflozin



IUPAC name

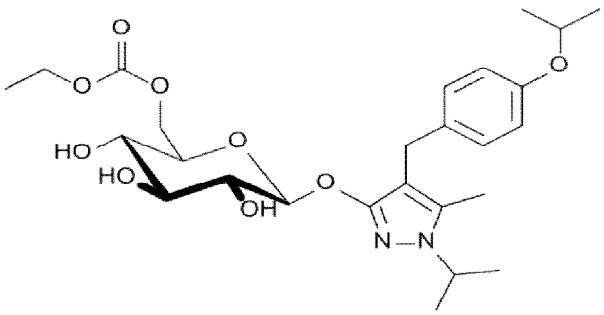
(2S,3R,4R,5S,6R)-2-[4-chloro-3-[[4-[(3S)-oxolan-3yl]oxyphenyl]methyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol.

Empagliflozin (BI-10773) is a sodium glucose co-transporter Type 2 (SGLT-2) inhibitor. It is discovered through collaboration between BoehringerIngelheim Pharmaceuticals, Inc. and Eli Lilly and Company. Currently, in the phase III clinical trial, it is administered orally at 10mg or 25mg once daily.[48]

Pharmacokinetics

It demonstrates a dose proportional increase in drug exposure and supports once daily dosing. It is rapidly absorbed, reaching peak levels in 1.5–3.0 h after dosing and shows a biphasic decline. Elevated urinary glucose excretion is observed with all the doses. Multiple once daily oral doses of empagliflozin (2.5-100 mg) reduced plasma glucose and is well tolerated in type 2 patients.[48,49]

Remogliflozin etabonate



IUPAC Name

5-methyl-4-[4-(1-methylethoxy)benzyl]-1-(1-methylethyl)-1H-pyrazol-3-yl 6-O-(ethoxycarbonyl)-β-D-glucopyranoside.

Remogliflozin etabonate (INN/USAN) is a proposed drug for the treatment of type 2 diabetes being investigated by GlaxoSmithKline[50,51]. Remogliflozin is now being developed by BHV Pharma. Remogliflozin etabonate (RE) is prodrug of remogliflozin, the active entity that inhibits SGLT2. An inhibitor of this pathway enhances urinary glucose excretion (UGE), and potentially improves plasma glucose concentrations in diabetic patients. It is currently in phase IIb trials.[50]

Pharmacokinetics

Remogliflozin ebonite salt is metabolized to remogliflozin in body. It is a benzylpyrazole glucoside. Remogliflozin is further metabolized to GSK279782, which is an equally potent inhibitor of SGLT2 but circulates at approximately 20% of the plasma concentrations of remogliflozin. Single oral doses of remogliflozin etabonate up to 1000 mg in healthy subjects and repeated dosing in subjects with T2DM (up to 1000 mg BID for 2 weeks) have been safe and well tolerated. It is intended for use in the treatment of T2DM as monotherapy orin combination with metformin and other antidiabetic therapies as well.[50,51]

Merits and De-merits of SGLT2 Inhibitors

Merits

Weight maintenance is a key target for any type 2 diabetes treatment. No hypoglycemia as SGLT2 inhibitors do not induce insulin secretion or inhibit hepatic glucose production. Improve insulin sensitivity and indirectly preserve β-cells by depletion of toxic glucose concentration in blood. SGLT2 inhibitors produce osmotic diuretic effect which may be advantageous in patients with hypertension and Cardiac Heart Failure.

Demerits

There may be a risk of negative effect of glucosuria on the kidneys, polyuria and increased thirst, but there is no strong evidence about it. Another problem in relation to the genitourinary tract is increased risk for bacterial or fungal infection, but only long term clinical trial can result in this risk.

CONCLUSION

Renal SGLT-2 inhibition is a clinically useful strategy for control of diabetes. A number of agents having glucoside moiety are being developed and are in various stages of clinical testing. SGLT2 inhibitors are referred to as a chemical inducer of familial renal glucosuria and as an energy controller acting in the negative direction, alongside lifestyle interventions. On the basis of this principle, SGLT2 inhibitors are expected to achieve long-term glycemic control, improve insulin resistance, and preserve pancreatic β-cell function without inducing bodyweight gain or increasing hypoglycemic risk. The therapeutic potency, safety, and tolerability of SGLT2 may be beneficial for the treatment of diabetes, and they may be expected to display synergistic effects when used in combination with multiple anti diabetic drugs.

REFERENCES

1. ADA, Standards of medical care in diabetes, American Diabetes Association. Diabetes Care, 35 Suppl 1, 2012, S11-63.
2. Qaseem A. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med., 156(3), 2012, 218-231.
3. WHO. WHO Diabetes Fact Sheet, October 2014; Available from: http://www.who.int/mediacentre/factsheets/fs312/en/index.html.
4. WHO, Global status report on non communicable disease 2014.
5. Tian H.L., L.S. Wei, Z.X. Xu, R.T. Zhao, D.L. Jin, J.S. Gao. Correlations between blood glucose level and diabetes signs in streptozotocin induced diabetic mice. Global Pharmacol., 4, 2010, 111-116.
6. Arora S., S.K. Ojha, D. Vohora. Characterization of streptozotocin induced Diabetes mellitus in swiss albino mice. Global J. Pharmacol., 3, 2009, 81-84.
7. Marjani A. and A. Shirafkan. The metabolic syndrome in type 2 diabetic patients in Gorgan: According to NCEP ATP III and IDF definitions. Advan. Biol. Res., 5, 2011, 200-205.
8. Ibrahim M.Y., A.M. Abdelatif. Effects of alloxan-induced diabetes mellitus on blood metabolites and serum minerals and hormones in rabbits (lepus cuniculus) in relation to starch supplementation and season. Advan. Biol. Res., 5, 2011, 45-58.
9. Hossien B.M. and A.A. Mohammad. Effect of Education on Improvement of Quality of Life by SF-20 in Type 2 Diabetic Patients. Middle-East J. Sci. Res., 3, 2008, 67-72.
10. Khushk I., M.U. Dahot, S.A. Baloach and M.A. Bhutt. The evaluation of soybean extracts in alloxan induced diabetic rabbits. World Appl. Sci. J., 8, 2010, 22-25.
11. Udoh B.E., B.C. Ezeokpo, K.K. Agwu and O.C. Okpal. Effects of Type Two Diabetes Mellitus on the Plantar Aponeurosis of Nigerians. World J. Med. Sci., 5, 2010, 81-84.
12. Kanai Y., W.S. Lee, G. You, D. Brown and M.A. Hediger. The human kidney low affinity Na+/glucose cotransporter SGLT2, Delineation of the major renal re-absorptive mechanism for D-glucose. J. Clin Invest., 93, 1994, 397-404.
13. Wright E.M., B.A. Hirayama and D.F. Loo. Active sugar transport in health and disease. J. Intern Med., 261, 2007, 32-43.
14. Wright E.M. Renal Na(+)-glucose cotransporters. Am. J. Physiol. Renal. Physiol., 280, 2001, 10-18.
15. Chen J., J. Feder, I. Neuhaus, J.M. Whaley. Tissue expression profiling of the sodium-glucose co-transporter (SGLT) family: implication for targeting SGLT2 in type 2 diabetes patients. Diabetes, 57, 2008, 2493.
16. Jabbour, S.A. and B.J. Goldstein. Sodium glucose co-transporter 2 inhibitors: blocking renal tubular reabsorption of glucose to improve glycaemic control in patients with diabetes. Int. J. Clin Pract., 62, 2008, 1279-1284.
17. Wright E.M., E. Turk. The sodium/glucose co-transport familySLC5. Pflugers Arch, 447, 2004, 510-518.
18. Ganong W.F. Formation and excretion of urine. Rev. Med. Physiol., 22, 2005, 699-734.
19. Zhai X.Y., H. Birn, K.B. Jensen, J.S. Thomsen, A. Andreasen and E.I. Christense. Digital three-dimensional

reconstruction and ultra structure of the mouse proximal tubule. J. Am. Soc. Nephrol., 14, 2003, 611-619.

20. Pajor A.M., B.A. Hirayama and E.M. Wright. Molecular evidence for two renal Na+/glucose cotransporters. Biochim Biophys Acta., 1106, 1992, 216-220.

21. Freitas H.S., G.F. Anhe, K.F. Melo, M.M. Okamoto, M. Oliveira-Souza, S. Bordin and U.F. Machado. Na+-glucose transporter-2 messenger ribonucleic acid expression in kidney of diabetic rats correlates with glycemic levels: involvement of hepatocyte nuclear factor-1 α expression and activity. Endocrinol., 149, 2008, 717-724.

22. Rahmoune H., P.W. Thompson, J.M. Ward, C.D. Smith, G. Hong and J. Brown. Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes. Diabetes, 54, 2005, 3427-3434.

23. Kamran M., R.G. Peterson and J.H. Dominguez. Over expression of GLUT2 gene in renal proximal tubules of diabetic Zucker rats. J. Am. Soc. Nephrol., 8, 1997, 943-948.

24. Dominguez J.H., K. Camp, L. Maianu, H. Feister and W.T. Garvey. Molecular adaptations of GLUT1 and GLUT2 in renal proximal tubules of diabetic rats. Am. J. Physiol., 266, 1994, F283-F290.

25. Chin E., A.M. Zamah, D. Landau, H. Gronbcek, A. Flyvbjerg, D. LeRoith and C.A. Bondy. Changes in facilitative glucose transporter messenger ribonucleic acid levels in the diabetic rat kidney. Endocrinol., 138, 1997, 1267-1275.

26. Oku A., K. Ueta, K. Arakawa, T. Ishihara. T-1095, an inhibitor of renal Na+-glucose cotransporters may provide a novel approach to treating diabetes. Diabetes, 48, 1999, 1794-1800.

27. Bautista R., R. Manning, F. Martinez, C. Avila-Casado Mdel, V. Soto, A. Medina and B. Escalante. Angiotensin II-dependent increased expression of Na+-glucose cotransporter in hypertension. Am. J. Physiol. Renal. Physiol., 286, 2004, 127-133.

28. Ehrenkranz J.R., N.G. Lewis, C.R. Kahn and J. Roth. Phlorizin: a review. Diabetes Metab Res. Rev., 21, 2005, 31-38.

29. Defronzo R.A., M. Goldberg and Z. Agus. Effects of phlorizin and insulin on tubular phosphate reabsorption. Evidence for 2 transport pathways. Kidney Int., 8, 1975, 470-472.

30. Panayotova-Heiermann M., D.D. Loo and E.M. Wright. Kinetics of steady-state currents and charge movements associated with the rat Na+/glucose cotransporter. J. Biol. Chem., 270, 1995, 27099-27105.

31. Shi Z.Q., K.S. Rastogi, M. Lekas, S. Efendic, D.J. Drucker and M. Vranic. Glucagon response to hypoglycemia is improved by insulin-independent restoration of normoglycemia in diabetic rats. Endocrinol., 137, 1996, 3193-3199.

32. Rossetti L., G.I. Shulman, W. Zawalich and R.A. DeFronzo. Effect of chronic hyperglycemia on *in vivo* insulin secretion in partially pancreatectomized rats. J. Clin Invest., 80, 1987, 1037-1044.

33. Kahn B.B., G.I. Shulman, R.A. DeFronzo, S.W. Cushman and L. Rossetti. Normalization of blood glucose in diabetic rats with phlorizin treatment reverses insulin-resistant glucose transport in adipose cells without restoring glucose transporter gene expression. J. Clin Invest., 87, 1991, 561-570.

34. Ueta K., T. Ishihara, Y. Matsumoto, A. Oku, M. Nawano, T. Fujita, A. Saito and K. Arakawa. Long-term treatment with the Na+-glucose cotransporter inhibitor T-1095 causes sustained improvement in hyperglycemia and prevents diabetic neuropathy in Goto-Kakizaki Rats. Life Sci., 76, 2005, 2655-2668.

35. Kim Y, Babu AR. Clinical potential of sodium-glucose cotransporter 2 inhibitors in the management of type 2 diabetes. Diabetes MetabSyndrObes., 5, 2012, 313–327.

36. Tahrani AA, Barnett AH. Dapagliflozin: a sodium glucose cotransporter 2 inhibitor in development for type 2 diabetes. Diabetes Ther., 1, 2012, 1–12.

37. Gerich JE, Bastien A. Development of the sodium-glucose co-transporter 2 inhibitor dapagliflozin for the treatment of patients with type 2 diabetes mellitus. Expert Rev ClinPharmacol., 4, 2011, 669–683.

38. Nomura S, Sakamaki S, Hongu M. Discovery of canagliflozin, a novel c-glucoside with thiophene ring, as sodium-dependent glucose cotransporter2 inhibitor for the treatment of type 2 diabetes mellitus. J Med Chem., 53, 2010, 6355–6360.

39. AMCP Dossier Invokana (Canagliflozin). Titusville N.J.: Janssen MedInfo; April 15, 2013.

40. Invokana (Canagliflozin), prescribing information. Titusville N.J.: Janssen; March 2013.

41. Neumiller JJ, White JR Jr, Campbell RK. Sodium-glucose co-transport inhibitors: Progress and therapeutic potential in type 2 diabetes mellitus. Drugs, 70, 2010, 377–385.

42. Stenlof K, Cefalu WT, Kim KA. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab., 15, 2013, 378–382.

43. Poole RM, Dungo RT. Ipragliflozin: first global approval. Drugs, 74(5), 2014, 611-617.

44. Kadokura T, Zhang W, Krauwinkel W, Leeflang S, Keirns J, Taniuchi Y, Nakajo I, Smulders R. Clinical pharmacokinetics and pharmacodynamics of the novel SGLT2 inhibitor ipragliflozin. Clin Pharmacokinet., 53(11), 2014, 975-988.

45. Takasu T, Hayashizaki Y, Tahara A, Kurosaki E, Takakura S. Antihyperglycemic effect of ipragliflozin, a sodium-glucose co-transporter 2 inhibitor, in combination with oral antidiabetic drugs in mice. Clin Exp Pharmacol Physiol., 42(1), 2015, 87-93.

46. Ohtake Y, Sato T, Kobayashi T, Nishimoto M, Taka N, Takano K, Yamamoto K, Ohmori M, Yamaguchi M, Takami K, Yeu S. Y, Ahn K. H, Matsuoka H, Morikawa K, Suzuki M, Hagita H, Ozawa K, Yamaguchi K, Kato M, Ikeda S. "Discovery of Tofogliflozin, a Novel C-Arylglucoside with an O-Spiroketal Ring System, as a Highly Selective Sodium Glucose Cotransporter 2 (SGLT2) Inhibitor for the Treatment of Type 2 Diabetes". Journal of Med Chem., 55(17), 2012, 7828–7840.

47. Nagata T, Fukazawa M, Honda K, Yata T, Kawai M, Yamane M, Murao N, Yamaguchi K, Kato M, Mitsui T, Suzuki Y, Ikeda S, Kawabe Y. "Selective SGLT2 inhibition by tofogliflozin reduces renal glucose reabsorption under hyperglycemic

but not under hypo- or euglycemic conditions in rats". AJP: Endocrinology and Metabolism, 304(4), 2012, E414–E423.

48. Grempler R, Thomas L, Eckhardt M, Himmelsbach F, Sauer A, Sharp DE, Bakker RA, Mark M, Klein T, Eickelmann P. "Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterization and comparison with other SGLT-2 inhibitors". Diabetes Obes Metab., 14(1), 2012, 83–90.

49. Nair S, Wilding JP. "Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus". J. Clin. Endocrinol. Metab., 95(1), 2010, 34–42.

50. Polli JW, Humphreys JE, Harmon KA, Webster LO, Reese MJ. Assessment of Remogliflozin Etabonate, a Sodium-Dependent Glucose Co-Transporter-2 Inhibitor, as a Perpetrator of Clinical Drug Interactions: A Study on Drug Transporters and Metabolic Enzymes. J Diabetes Metab. 2012, 3, 200.

51. Fujimori Y, Katsuno K, Nakashima I, Ishikawa-Takemura Y, Fujikura H, Isaji M. "Remogliflozin etabonate, in a Novel Category of Selective Low-Affinity/High-Capacity Sodium Glucose Cotransporter (SGLT2) Inhibitors, Exhibits Antidiabetic Efficacy in Rodent Models". J. Pharmacol. Exp. Ther., 327(1), Jun 2008, 268–276.

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