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Review Article

SODIUM-GLUCOSE LINKED COTRANSPORTER 2 INHIBITOR: A NEW HORIZON IN THE TREATMENT OF TYPE-2 DIABETES

REKHA BISHT*

Department of Pharmacology, Indore Institute of Pharmacy, Indore, Madhya Pradesh, India. Email: rekha.bisht@indoreinstitute.com

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ABSTRACT

Hyperglycemia is a key therapeutic focus in the management of patients with type 2 diabetes (T2D) mellitus. The various therapeutic classes of antidiabetic drugs presently existing in the market are not sufficiently effective in maintaining long-term glycemic control in most of the diabetic patients, even when used in combination. The undesirable adverse effects of these drugs, such as hypoglycemia, weight gain, and hepatic and renal toxicity, have escalated the demand for the discovery of new and safer antidiabetic drugs. The progressive nature of T2D requires practitioners to periodically evaluate patients and intensify glucose-lowering treatment once glycemic targets are not attained. Sodium-glucose cotransporter 2 inhibitors (SGLT2-is) are the new class of antidiabetic medications that are approved (2013) by the Food and Drug Administration recently for treating diabetes. These inhibitors block the SGLT2 protein involved in glucose reabsorption from the proximal renal tubule resulting in escalated glucose excretion and lower blood glucose levels. These inhibitors exhibit favorable effects beyond glucose control, such as consistent body weight, blood pressure, and serum uric acid reductions. This review highlighted the brief updates of SGLT2-i, their benefits, and adverse effects.

Keywords: Type-2 diabetes mellitus, Sodium-glucose linked cotransporter 2, Sodium-glucose linked cotransporter 2 inhibitors, Gliflozins, Antidiabetic drugs.

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INTRODUCTION

Diabetes is a complex and chronic disease that affected an estimated 29.1 million Americans in 2012 [1]. As per the statistical data of the International Diabetes Federation, diabetes mellitus (DM) patients were 415 million. By 2040, the projected number of patients will be about 642 million [2]. Billions of dollars are spent each year around the world in health disbursement related to diabetes [3]. Increasing insulin resistance, escalating the deterioration of β-cell function, dysfunctional adipocytes, gastrointestinal incretin defects, and increased glucose reabsorption from the kidneys, hyperglucagonemia, and neurotransmitter dysfunction may give rise to the progression of diabetes [4,5]. Progressive nature of type 2 diabetes (T2D) typically requiring multiple medications to control blood glucose levels and periodical evaluation of patients and intensify glucose-lowering treatment once the glycemic target is not attained [6]. Although hyperglycemia is a lead therapeutic focus in the management of T2DM, many patients experience suboptimal glycemic control [7].

Due to the intricacies of diabetes and the maintenance of the compliance of patients with diabetes [8], various oral antidiabetic drugs (OADs) approved in DM combined with insulin such as metformin, sulfonylureas, a-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitors (DDP-4 inhibitors), glucagon-like peptide-1 receptor agonist, and thiazolidinedione [9], Nevertheless, some undesirable adverse effects caused by administrating these medications, including hypoglycemia, weight gain, gastrointestinal symptoms, and hepatic and renal toxicity, have escalated demand for the discovery of safer antidiabetic agents with new therapeutic mechanisms [8].

In normoglycemic people, approximately 180 g of glucose is filtered daily by renal glomeruli and is then reabsorbed in the proximal convoluted tubule (PCT). This is attained by passive transporters, namely, facilitated glucose transporters (GLUTs) and active cotransporters, namely, sodium-glucose cotransporters (SGLTs) [10]. Increased blood glucose level stimulates proximal tubular growth and SGLT2 expression, thus increases renal glucose reabsorption and an unsatisfactory control of diabetes. Inhibition of SGLT2 stimulates glucosuria and reduces blood glucose levels [8].

Recently, the US Food and Drug Administration (FDA) has introduced SGLT-2 inhibitors (SGLT2-is), a novel class of glucose-lowering compounds known as the gliflozins for treating T2DM. SGLT2-is including dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, and tofogliflozin have only been applied in T2DM [9,11-14].

Phlorizin (non-specific SGLT2-i) [15] was the first SGLT2-i discovered over 100 years ago. It is a flavonoid found in the root bark, leaves, shoots, and fruit of the apple tree [11,16]. In the proximal tubule, the two main active GLUT systems were characterized as the SGLT1 (high affinity, low capacity) and SGLT2 (low affinity, high capacity) [8]. SGLT1 is expressed mainly in the small intestine, proximal tubule of nephrons, and the myocardium and is responsible for glucose reabsorption [16,17]. SGLT1-i by phlorizin can lead to extrarenal side effects such as diarrhea and nausea [18]. Besides poor solubility of phlorizin in water and its poor oral bioavailability [19], it was not an ideal therapeutic candidate to treat diabetes [11]. To avoid SGLT1-dependent side effects, phlorizin derivatives have been developed that are more specific inhibitors of SGLT2 [16].

SGLT2, the most prevalent and important SGLT subtype, accounts for more than 90% of glucose reabsorption in the early proximal tubule and optimally maintains blood glucose levels [8,20,21]. As a key mechanism for glucose homeostasis in a kidney, therefore, SGLT2-is are considered promising agents for treating T2D as SGLT2-is that target the kidney, reduce renal glucose reabsorption, and increase urinary glucose elimination, thus lowering glucose blood levels [7,22-24]. SGLT2-is achieve a reduction in glycated hemoglobin (HbA1c) of 4.4–12.1 mmol/mol (0.4–1.1%), depending on the baseline HbA1c and the specific drug and dose used [22].

Two SGLT2-is have been evaluated in major clinical trials in individuals with T2D: Empagliflozin in the EMPA-REG OUTCOME trial and canagliflozin in the Canagliflozin Cardiovascular Assessment Study

program and reported a significant reduction in the incidence of cardiovascular events in individuals with underlying cardiovascular disease (CVD) [11,22,25] and also revealed a renoprotective effect exerted by SGLT2-is on kidney function [26]. The FDA has approved three SGLT2-is as monotherapy for patients with T2DM: Canagliflozin (Invokana, Janssen), dapagliflozin (Farxiga, AstraZeneca), and empagliflozin (Jardiance, Boehringer Ingelheim) in March 2013, January 2014, and August 2014, respectively [1]. Of the three FDA approved drugs, empagliflozin has the greatest selectivity for SGLT2 compared to SGLT1, while canagliflozin is the least selective. FDA has approved four combination drugs: Canagliflozin/metformin (Invokamet®), dapagliflozin/metformin (Xigduo XR®), empagliflozin/metformin (Synjardy®), and empagliflozin/linagliptin (Glyxambi®) [5] (Table 1).

MECHANISM OF ACTION

SGLT2-is act by inhibiting SGLT2 in the PCT to prevent reabsorption of glucose and facilitate its excretion in urine [27,28]. As glucose is excreted, its plasma levels reduce leading to amelioration in all glycemic parameters [1,10,29].

BENEFITS OF SGLT2-I

SGLT2-is provide various clinical benefits in patients with T2DM. For example, they can reduce body weight by augmenting the excretion of glucose and decreasing plasma glucose concentrations [1,10,30]. SGLT2-is lower blood pressure (BP) [31] by promoting osmotic diuresis and intravascular volume contraction [22,32]. The risk of major hypoglycemic events is also low with these agents because they do not interfere with normal endogenous glucose production in response to hypoglycemia or stimulate insulin release, suggesting that they may preserve the hypoglycemia counter-regulatory response of glucagon-mediated glucose production [1]. Based on these benefits and their ability to ameliorate cardiovascular outcomes [33] in high-risk individuals and slow the advancement of diabetic kidney disease, the SGLT2-is can be considered appropriate second-line treatment options for patients at risk of cardiovascular events or those with underlying nephropathy [30].

ADVERSE EFFECTS OF SGLT2-IS

Genital mycotic infections, rare episodes of diabetic ketoacidosis, particularly in patients with long-standing T2D [6,34,35], are some commonly associated adverse events with SGLT2-is. Canagliflozin has been associated with a higher risk of bone fractures and lower limb amputations [6,30]. Dapagliflozin is associated with increased risk of bladder and breast cancer. SGLT2-is reduce BP by inducing osmotic diuresis. This effect is beneficial in patients with uncontrolled hypertension but can cause postural dizziness, orthostatic hypotension, and dehydration, especially in elderly patients with kidney disease or those administering loop diuretics [22]. Osmotic diuresis with subsequent intravascular volume contraction induced by SGLT2-is could pose a risk of volume depletion [34]. Urosepsis and pyelonephritis have been reported in the post-marketing report. Urinary frequency and dehydration are also reported with the use of these drugs [34].

FEW SGLT2-IS

Dapagliflozin

Dapagliflozin, the first in a novel class of glucose-lowering agents, is a selective SGLT2-i approved as an adjunct to diet and exercise to improve glycemic control in individuals with T2D [36,37]. Dapagliflozin was approved by the FDA on January 8, 2014 [38]. By inhibiting the transporter protein SGLT2 in the kidneys, dapagliflozin diminishes blood glucose independent of insulin secretion, leading to urinary glucose excretion and a reduction in blood glucose levels [39-42]. Dapagliflozin escalates glucose control without causing any adverse effects on body weight, BP, and lipids like other conventional OADs. These asserted advantages of dapagliflozin would be favorable for combining conventional OADs with dapagliflozin in treating T2D [43].

In the European Union (EU), oral dapagliflozin once daily is approved for use as monotherapy (in patients who are intolerant of metformin) and as add-on combination therapy (with other glucose-lowering agents, including insulin) for T2D when diet and exercise alone do not provide adequate glycemic control [44].

Canagliflozin

Canagliflozin is a new SGLT2-i that has been approved as an adjunct to diet and exercise for treating of adults with T2DM in more than 30 countries [45,46]. Canagliflozin became the first SGLT2-i approved by FDA on March 29, 2013 [47,48]. Canagliflozin lowered the renal threshold for glucose, enhanced urinary glucose excretion, improved glycemic control and functions of beta-cell in rodent models of T2DM, and lowered body weight gain in rodent models of obesity [17]. Canagliflozin diminishes the risk of myocardial infarction, stroke, and cardiovascular mortality with additional benefits include a reduction in hospital admission rate for heart failure and renal failure, and lowering systolic BP, weight, and proteinuria [49].

On April 14, 2019, investigators for Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) reported that canagliflozin reduces the risk of renal failure or death by 30% in patients with T2D and chronic kidney disease. Canagliflozin is sold under the brand name as Invokana by Janssen Pharmaceutical Companies of Johnson and Johnson [50].

Empagliflozin

Empagliflozin is a potent and highly selective SGLT2-i. It is an effective and generally well-tolerated anti-hyperglycemic agent approved for the

Table 1: List of current SGLT2-I [5,55]

Generic name	Brand name	Available doses (mg)	Administration
Canagliflozin[a]	Invokana®	5, 10	qam before 1st meal
Dapagliflozin[a]	Farxiga™	10, 25	qam
Empagliflozin[a]	Jardiance®	50/500, 50/1000, 150/500, 150/1000	qam
Canagliflozin/metformin[a]	Invokamet®	5/500, 5/1000, 10/500, 10/1000	BID with meals, max. dose 300 mg/2000 mg
Dapagliflozin/metformin	Xigduo™ XR	5/500, 5/1000, 12.5/500, 12.5/1000	qam with food, max. dose 10 mg/2000 mg
Empagliflozin/metformin	Synjardy®	10/5, 25/5	BID with meals, max. dose 25 mg/2000 mg
Empagliflozin/linagliptin	Glyxambi®	25, 50	qam
Ipragliflozin[b]	Suglat®	20	qam, max. dose 100 mg
Tofogliflozin[bc]	Apleway®, Deberza®		qam
Ertugliflozin	Steglatro	5, 15	qam
Luseogliflozin[c]			
Remogliflozin etabonate			
Sotagliflozin[c]			

[a]Food and Drug Administration and European Medicines Agency approved; [b]Ministry of Health, Labor, and Welfare approved in Japan, [c]Currently in clinical trials or seeking a market approval; qam taken once daily in the morning, BID twice daily; SGLT2-I: Sodium-glucose cotransporter 2 inhibitor

treatment of adults with T2DM in the EU, the USA, and Japan and among other parts of the world. Once-daily oral administration of empagliflozin is recommended and due to its insulin-independent mechanism of action; it carries a low inherent risk of hypoglycemia [51]. Absence of weight gain, low risk of hypoglycemia, and lower cardiovascular risk reinforce its consideration as a first-line medication in addition to metformin for patients with T2DM and CVD [12].

NEW SGLT2-I

Ertugliflozin developed to improve glycemic control in adults with T2D, met the primary outcomes in 2 years long Phase 3 trials, VERTIS SU (eValuation of ERTugliflozin efflcacy and Safety) and VERTIS SITA2 [21]. Ertugliflozin is the fourth SGLT2-is to be approved in the US and newest agent among SGLT2-i, having received FDA approval in December 2017 [50-54]. Ertugliflozin is recommended as an adjunct to diet and exercise for glycemic control in adults (≥18 years of age) with T2D. It can also be used in combination with other antidiabetic agents such as metformin or a DDP-4 inhibitor to help reduce HbA1C. At present, ertugliflozin is available in the market as an oral tablet (brand name Steglatro) or oral tablet combinations with the DPP-4 sitagliptin (brand name Steglujan) or with metformin (brand name Segluromet). Ertugliflozin is not approved for treating T1D, renal impairment, or ketoacidosis [54]. This drug was developed under the collaboration of Merck and Pfizer and it was approved by FDA on December 22, 2017 [55].

CONCLUSION

SGLT2-is, the newest class of oral antidiabetic agents, represent a therapeutic approach for treating T2DM that is independent of insulin secretion and activity. Since this mechanism is not restrained by the extent of insulin resistance or beta-cell dysfunction, these drugs are quintessential candidates to be used at any stage in the natural history of diabetes – from newly diagnosed to chronic disease, including extremes of insulin resistance and β-cell dysfunction, as well as in T1D (not approved but studied). Their distinctive mechanism of action, coupled with pleiotropic benefits on weight and BP, should make them attractive choices for add-on therapy to individuals with diabetes not controlled on other medications. This class of drugs is currently under investigation in diabetic and non-diabetic patients with heart failure, chronic kidney disease, and non-alcoholic fatty liver disease. Furthermore, larger, multicenter trials need to be performed to discuss the safety of SGLT2-is combined with insulin in subjects with diabetes. Their prospective use is further enhanced by the fact that these drugs can be used as monotherapy for patients seeking different treatment options and in complementary manner with other antidiabetic agents or insulin.

AUTHOR'S CONTRIBUTIONS

The author has contributed to the conception and design of the article and interpreting the relevant literature and drafted the article and revised it critically for important intellectual content.

CONFLICTS OF INTEREST STATEMENT

The author declared no conflicts of interest.

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