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An Upgrade on Sodium-Glucose Co-Transporter-2 Inhibitors for Treating Diabetes

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ABSTRACT:

Over 15% of the adult population worldwide may have diabetes mellitus (DM) by 2030, according to predictions from the World Health Organization. SGLT-2 inhibitor is also called gliflozin or flozin, a class of drugs responsible for inhibiting sodium-glucose transport in the nephron (the effective unit of the order), as opposed to an SGLT-1 inhibitor that inhibits sodium-glucose transport in the intestinal mucosa. In people with "type 2 diabetes", this threshold may rise and the expression of SGLT2 proteins may be constrained, leading to an unfavourable reaction that exacerbates hyperglycemia. For the treatment of "type 2 diabetes", "SGLT2 inhibitors" are the most recent family of oral hypoglycemic medications to receive approval.

Keywords: "sodium-glucose co-transporter-2, SGLT2-inhibitors, type-2-diabetes mellitus".

INTRODUCTION:

Over 15% of the adult population worldwide may have diabetes mellitus (DM) by 2030, according to predictions from the "World Health Organization". The most frequent reason for end-stage renal disease is this. Inhibitors of "renal sodium-glucose co-transporter-2 (SGLT2)", which prevent "glucose reabsorption into proximal tubular cells" and cause mild glycosuria, are among the new medication classes that have been developed in recent years to cure type 2 diabetes.

An SGLT-2 inhibitor is also called gliflozin or flozin, a class of drugs responsible for inhibiting "sodium-glucose transport" in the nephron (the effective unit of the order), as opposed to an SGLT-1 inhibitor that inhibits sodium-glucose transport in the intestinal mucosa. As a result of blocking the sodium-glucose transport protein 2, they lower blood sugar by inhibiting glucose reabsorption. (SGLT2). A common form of diabetes is type 2 diabetes, in which SGLT2 inhibitors are prescribed. Type II diabetes patients with diabetes have shown significant for cardiovascular benefits from gliflozins in addition to blood sugar control. In the development stages, several specifics of this class of drugs have been approved

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or are in the process of approval. Researchers studied canagliflozin to see if it could lower systolic and diastolic blood pressure and improve blood sugar control.

"Canagliflozin, the first SGLT-2 inhibitor, was approved for use in the United States in March 2013 under the brand name Invokana". [2]

Physiology of SGLT-2 inhibitors

According to the botanical expert, phlorizin glucosuria has been studied for over 150 times. Later phlorizin was linked as general Inhibitors of SGLT- 2 proteins, and numerous types of SGLT- 2 proteins were linked. These all are proteins that function sufficiently in the presence of insulin. A compelling idea for the treatment of diabetes emerged from the observation that inhibition of these proteins causes changes that noticeably enhance glucose metabolism. The kidney's proximal tubule expresses SGLT-2 proteins. In people with "type 2 diabetes", this threshold may rise and the expression of SGLT2 proteins may be constrained, leading to an unfavourable reaction that exacerbates hyperglycemia. This level might be decreased to between 40 and 120 mg/dl with the careful suppression of SGLT2 proteins. Individuals with familial renal glucosuria, an uncommon "nondisease," contrasted by this, lack functioning SGLT2 proteins.[3, 4]

Development phase

These are the members of the gliflozins class that are currently recognized. Canagliflozin was the first SGLT2 drug to obtain U.S. approval.[5] In March 2013, the EU authorized dapagliflozin, the first SGLT2 inhibitor to receive global approval.[6] In January 2014, the Food and Drug Administration granted permission for it to be used in the US under the brand name Farxiga. Empagliflozin obtained approval in the US in August 2014 under the brand name Jardiance. Steglatro, the brand name for ertugliflozin, was authorized in the US in December 2017. Ipragliflozin, sold by Astellas Pharma as Suglat in Japan, obtained clearance in January 2014, and Luseogliflozin, marketed as Lusefi, received approval in March 2014.[7] Under the trade name Lusefi, Remogliflozin etabonate was successfully launched in March 2014.[8] In May 2019, Glenmark successfully introduced Remogliflozin etabonate in India. After Phase II trials, Sergliflozin etabonate was no longer used. Under the brand name Conquista, Sotagliflozin, a double SGLT1/SGLT2 asset, is being studied in phase III studies by wordbook medicinal.[9]

Pharmacokinetics of SGLT-2 Inhibitors [12]

TABLE 1: PHARMACOKINETIC PARAMETERS OF VARIOUS SGLT-2 INHIBITORS [12]

Name of drug	Bioavailability	Protein binding	tmax (hours)	t1/2 (hours)	Cmax	SGLT2 over SGLT1
Dapagliflozin	78%	91%	1–1.5	12.9	80 ng/mL (5 mg dose); 165.0 ng/mL (10 mg dose)	1200 fold

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Tofogliflozin (10 mg)	97.50%	83%	0.75	6.8	489 ng/mL	2900 fold
Luseogliflozin	35.3% (male rats); 58.2% (female rats); 92.7% (male dogs)	96.0–96.3%	0.625±0.354	9.24±0.928	119±27.0 ng/mL	1650 fold
Canagliflozin	65% (300 mg dose)	99%	1–2	10.6 (100 mg dose); 13.1 (300 mg dose)	1096 ng/mL (100 mg dose) 3480 ng/mL (300mg dose) approx.	250 fold
Empagliflozin	90–97% (mice); 89% (dogs); 31% (rats)	86.20%	1.5	13.2 (10 mg dose); 13.3h (25 mg dose)	259nmol/L (10 mg dose); 687nmol/L (25 mg dose) approx.	2500 fold
Ipragliflozin (50 mg)	90%	96.30%	1	15–16 (50 mg dose)	975 ng/mL	360 fold
Ertugliflozin	70-90%	95%	0.5-1.5	11-17	268 ng/mL (15 mg dose)	2000 fold

1. **C_{max}:** Maximum serum concentration
2. **t_{max}:** Time required for reaching maximum plasma concentration
3. **$t_{1/2}$:** Biological half-life [(12)]

Studies on healthy people and people with type II diabetes mellitus who received the medicine in either a single ascending dose (SAD) or a multiple ascending dose corroborated the pharmacokinetic profile of dapagliflozin (MAD). Because the medication is protein-bound and has a Tmax of 1-2 hours and a half-life of 12–13 hours at dose-dependent concentrations, it is quickly absorbed and excreted in small amounts by the kidney. [28]

SGLT2 inhibitors, in contrast to all other anti-hyperglycemic diabetic drugs, stimulate rather than inhibit gluconeogenesis and ketogenesis. SGLT2 inhibitors are substantially more effective since they stimulate sirtuin 1 than Cardioprotective than that of other antidiabetic drugs (and thus PGC-1 and FGF21). [29]

Adverse event of SGLT-2 Inhibitors

Canagliflozin [(07)(14)]	**Dapagliflozin** [(03)(14)]
· Genital mycotic infections in females (10.6% - 11.6%) · Urinary tract infections (4.4% - 5.9%) · Increased urination (4.6% - 5.1%) · Genital mycotic infections in males (3.8% - 4.2%) · Thirst (2.4% - 2.8%) · Constipation (1.8% - 2.4%) · Nausea (2.1% - 2.3%) · Vulvovaginal pruritus (1.6% - 3.2%)	· Genital mycotic infections in female (6.9% - 8.4%) · Nasopharyngitis (6.3% - 6.8%) · Urinary tract infections (4.3% - 5.7%) · Back pain (3.1% - 4.2%) · Nausea (2.5 - 2.8%) · Genital mycotic infections in males (2.7% - 2.8%) · Influenza (2.3% - 2.7%) · Dyslipidemia (2.1% - 2.5%) · Constipation (1.9% - 2.2%) · Discomfort during urination (1.6% - 2.1%) · Pain in extremity (1.7% - 2%)

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Empagliflozin [13]	**Ertugliflozin** [10][13]
· Urinary tract infection (7.6% - 9.3%)	· Genital mycotic infections in female (9.1% - 12.2%)
· Genital mycotic infections in female (5.4% - 6.4%)	· Urinary tract infection (4% - 4.1%)
· Genital mycotic infections in males (1.6% - 3.1%)	· Genital mycotic infections in males (3.7% - 4.2%)
· Upper respiratory tract infection (3.1% - 4%)	· Headache (2.9% - 3.5%)
· Increased urination (3.2% - 3.4%)	· Vaginal pruritus (2.4% - 2.8%)
· Dyslipidemia (2.9% - 3.9%)	· Increased urination (2.4% - 2.7%)
· Arthralgia (2.3% - 2.4%)	· Nasopharyngitis (2% - 2.5%)
	· Back pain (1.7% - 2.5%)
	· Decrease in weight (1.2%-2.4%)

The FDA issued a warning in May 2015 that gliflozins may raise the risk of diabetic ketoacidosis (DKA) [11]. Gliflozins cause diabetic ketoacidosis by decreasing glucose blood circulation. This results in a lower dose of exogenous insulin or less stimulation of endogenous insulin production. They are only recommended when a patient is in good health, has enough fluids, and can eat a normal diet. 20 Because of decreased bone mineral density and other side effects, the FDA issued a warning about "canagliflozin (Invokana) and canagliflozin/metformin" in September 2015. (Invokamet). Canagliflozin is linked to an increased risk of lower limb amputation; however, more research is needed to confirm this risk. 24 According to a study conducted by the European Medicines Agency, people who take canagliflozin, dapagliflozin, or empagliflozin could be more likely to require lower limb amputation (mostly of the toes). The FDA issued a warning in August 2018 about a heightened incidence of Fournier gangrene in patients who are taking SGLT2 inhibitors. Changes to the prescribing information for SGLT2 inhibitor diabetes medications have been approved by the FDA, and they strongly advise that they be temporarily stopped prior to a planned surgery to lower the risk of developing ketoacidosis (a serious condition in which the body produces dangerously high blood acids called ketones) within a week of surgery.

Mechanism of action

A sodium-glucose cotransporter (SGLTs) seems to be proteins particularly abundant in feathers that play an important role in maintaining blood glucose balance. [10] Gliflozins assist feathers in retaking glucose from the tubular fluid by inhibiting SGLT2, lowering the glucose position in the blood, and helping to promote glucose excretion in the urine (glucosuria). [10-11] As a consequence, SGLT inhibitor complexes require changes in the sugar and aglycone structures. Dapagliflozin is a pretty selective and competitive SGLT-2 inhibitor. It inhibits SGLT-2 selectively and potently, and its benefits are determined by each patient involved in dealing with blood sugar management and kidney function. The glucosuria effect increases as blood glucose levels rise because of reduced kidney reabsorption of glucose. As an outcome, unlike many other types of diabetes, dapagliflozin is a medication that actually reduces blood glucose levels without relying on the secretion of insulin or sensitivity. The medication is appropriate for patients with impaired -cell function since it does not require functional pancreatic -cells to function. [18-19] The SGLT-2 protein transports sodium and glucose into tubular epithelial cells via the membrane of the proximal convoluted tubule. This is caused by

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sodium variation between the tubule and the cell, which ultimately resulted in passive diffusion of glucose transport.

FDA- Alerts on SGLT-2 Inhibitors

Patients must stop using SGLT2 inhibitors and seek medical help right once if they exhibit any symptoms of ketoacidosis, a serious illness in which the body creates excessive amounts of blood acids known as ketones. The symptoms of ketoacidosis include nausea, vomiting, discomfort in the abdomen, exhaustion, and breathing difficulties. Patients should also watch out for any new symptoms of a urinary tract infection, such as a burning sensation when peeing, the desire to urinate frequently or immediately away, lower abdominal or pelvic pain, a fever, or blood in the urine. If you see any of these symptoms, tell a health care provider. In cases when SGLT2 Inhibitors are being used and there are suggestive symptoms, healthcare practitioners should check for ketoacidosis and urinary tract infections. If the blood sugar level is not actually high, ketoacidosis related to the use of SGLT2 inhibitors can occur. However, the SGLT2 asset should be discontinued and treatment introduced instantly, if ketoacidosis is suspected.[24]

Interactions of SGLT- Inhibitors

Because most T2DM patients are on multiple medications, SGLT2 inhibitor interactions are critical. Gliflozins emerge to enhance the diuretic effect of thiazides, loop diuretics, and other diuretics, potentially putting patients at risk of dehydration and hypotension. To avoid hypoglycemia, anti-diabetic doses must be adjusted in combination therapy. Interactions with sulfonylureas, for example, have resulted in severe hypoglycemia, thought to be caused by cytochrome P450. According to one study, combining dapagliflozin with pioglitazone, metformin, glimepiride, or sitagliptin is safe, so neither medication necessitates a dose alteration. Dapagliflozin effectiveness is unlikely to be impacted by food intake; therefore, it can be administered regardless of meal timing. [25-27]

CONCLUSION:

SGLT2 inhibitors are the most recent class of oral antihyperglycemic agents approved for the treatment of type 2 diabetes. The unique treatment mechanism of these medications tends to make them an attractive alternative for patients throughout the natural history of type 2 diabetes, in addition to a potential adjunct therapy for prediabetes under strict monitoring.

One such category has earlier been linked to adverse events, including newly identified episodes of ketoacidosis linked to SGLT2 inhibitor use. However, as recently described, whenever the condition is known, euDKA is predicted, detectable, and preventable. Longer-term cardiovascular safety trials are currently underway, and indeed the reliability of this class of drugs will ultimately be tested.

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