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RESEARCH ARTICLE

DAPAGLIFLOZIN– A SGLT2 INHIBITOR: A NEW ROAD TO ANTIDIABETIC TREATMENT

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Abstract

INTRODUCTION

Diabetes, earlier considered primarily as a high risk factor for cardiovascular disease, diabetes now has become a far above the ground public health concern, due to the increasing epidemic of diabetes in older people, and also the emergence of type 2 diabetes in children. As estimated the number of people with diabetes worldwide is set to double in the next 20 years, as a consequence of increasing obesity and longevity. Some of this increase in the number will be observed in Europe and North America, bulk of the epidemic will be observed in non-European origin populations, the countries undergoing rapid westernization. [1]. The prevalence of diabetes for all age-groups worldwide has been estimated to be 4.4% in 2030. The estimated number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. Also the occurrence of diabetes is higher in men as compared women. The urban population in developing countries is projected to the risk of diabetes double between 2000 and 2030. One of major demographic change to diabetes prevalence across the world appears to be the rise in the proportion of people >65 years of age.[2,3,4]

Type2 diabetes mellitus(T2DM) is referred to as a progressive disorder characterized by hyperglycemia, peripheral insulin resistance, and a decrease in insulin secretion. Development of T2DM is a multistage process and changes in insulin resistance, insulin secretion, and plasma glucose can be present many years before a diagnosis of T2DM is done. Increasing insulin resistance usually occurs as the first in this sequence of events and is followed by a compensatory raise in insulin secretion by the pancreatic beta-cells, therefore maintaining close to normal plasma glucose levels.[5,6]. In the individuals who eventually develop T2DM a combination of beta-cell dysfunction and also reduction in beta-cell mass culminates in diminishing insulin secretion and associated hyperglycemia.[7.8,9]
The symptoms of diabetes may include Blurred vision , Unusual thirst ,Frequent urination , Slow-healing cuts , unexplained tiredness , Rapid weight loss (Type 1 diabetes) ,Erectile dysfunction ,Numbness or tingling in hands or feet[10]. There are many drugs that have been used to treat diabetes and apart from multiple pathophysiological defects, there are other factors that hamper efforts to attain glycemic goals including various adverse effects of the currently available agents for Type 2 diabetes mellitus[11]. Metformin being a biguanide can cause gastrointestinal effects, such as diarrhea and nausea, and, also lactic acidosis in some cases; at the same time insulin or sulfonylureas may produce hypoglycemia, as well as a major weight gain; and the thiazolidinedione use is also associated with weight gain and edema. The well known incretin mimetics may cause nausea, vomiting, and diarrhea. As most of the current diabetes agents

address insulin secretion or insulin action, with time, and as the disease progresses, endogenous insulin production becomes insufficient. Therefore, the quest to develop novel therapeutic agents, without the above mentioned side effects, continues.The investigations so far on sodium-glucose co-transporter-2 (SGLT2) inhibitors have elucidated new perspectives on potential therapeutic applications of this knowledge. Historically, glucosuria known as the glucose excretion in the urine, has been viewed as a marker of metabolic decompensation and an adverse clinical consequence in the natural process of diabetes. The kidney plays a major role in glucose homeostasis by regulating the reabsorption of glucose back again into the plasma after filtration of the blood. In individuals with diabetes, glucose reabsorption may increase up to 20% and perpetuate continued elevation in serum glucose levels. Therefore, blocking this process and, thus, facilitating glucose to be excreted in the urine, is being examined as a potential new therapeutic target to treat diabetes.[12.13]

So, this has led to the development of a new drug Dapagliflozin, the very first in a class of compounds referred to as sodium- glucose cotransporter 2 (SGLT2) inhibitors. SGLT2 are located almost in the kidney proximal tubules where it reabsorbs most of the 180 g of glucose that is filtered through the glomeruli per day. Dapagliflozin is a highly selective and reversible inhibitor of SGLT2. The properties of the drug such as the prolonged pharmacokinetic half-life due to the C-aryl glucoside derived chemical structure, also a nearly 3,000-fold selectivity for SGLT2 as compared to SGLT1, make it possible for dapagliflozin to be administered in an unmodified oral form without affecting SGLT1- mediated glucose transport in other tissues. Dapagliflozin is capable of inhibiting up to one-half of the filtered glucose from being reabsorbed by the kidney, resulting in a dose-dependent raise in urinary glucose excretion and, ultimately, improvement in glycemic parameters.[14,15]

DAPAGLIFLOZIN CLINICAL DATA[5]

PRECLINICAL STUDIES

During the preclinical studies, dapagliflozin exhibited potent inhibition of human SGLT2 with an EC50 of 1.1 nM and a 1200-fold selectivity for human SGLT2 compared to human SGLT1, and structurally contained a beta-glucosidase-resistant C-glucoside in place of the O-glucoside linkage, permitting oral administration. It was reported that in both normal and experimentally diabetic rats dapagliflozin induced significant renal glucose excretion. The normal rats exhibited an improved glucose tolerance profile with a single dose of dapagliflozin and this was related with reductions in glucose excursions following oral glucose tolerance testing (OGTT). In the other two different rat models of diabetes (streptozotocin and Zucker diabetic fatty [ZDF] rats) hyperglycemia was reduced after administration of a single oral dose of dapagliflozin and was this was observed within 6 hours of dosing. In both fasting and postprandial glucose levels reductions were maintained in ZDF rats over 2 weeks with once-daily dosing with dapagliflozin. The promising results exhibiting efficacy, tolerability, and overall favorable absorption, distribution, metabolism, and also the excretion profile of dapagliflozin led to its clinical evaluation in healthy and T2DM subjects.

DAPAGLIFLOZIN METHODS

Many observations have been made on the basis of the various research parameters. A study conduted on Type 2 Diabetic Patients With Inadequate Glycemic Control by Diet and Exercise with a 24-week parallel-group, double- blind, placebo-controlled phase 3 trial. Patients with A1C 7.0–10% where n _485 were randomly assigned to one of seven groups to receive once-daily placebo or on the other side 2.5, 5, or 10 mg dapagliflozin once daily in the morning (said as the main cohort) or evening (as the exploratory cohort). Whereas the patients with A1C 10.1–12% (n as 73) were again randomly assigned 1:1 to receive a blinded treatment with a morning dose of 5 or 10 mg/day dapagliflozin.the results showed that in the main cohort, mean A1C changes from baseline at week 24 were _0.23% with placebo and _0.58, _0.77 , and _0.89% with 2.5, 5, and 10 mg dapagliflozin, respectively. It was also marked that Dapagliflozin lowered hyperglycemia in treatment of naive patients with newly diagnosed type 2 diabetes. The near to absence of hypoglycemia and an insulin-independent mechanism of action makes dapagliflozin a very unique addition to existing treatment options for type 2 diabetes.[14]

With a objective to determine whether dapagliflozin, which has the ability to selectively inhibit renal glucose reabsorption, lowers hyperglycemia in patients with type 2 diabetes which is poorly controlled with high insulin doses plus oral antidiabetic agents (OADs), another study which was a randomized, double-blind, three arm parallel-group, placebo-controlled, 26-center trial (U.S. and Canada)[16,17]. Based on the data gathered from an insulin dose-adjustment setting cohort (n as 4),and the patients in the treatment cohort (n _ 71) were randomly assigned 1:1:1 to placebo, with 10 mg dapagliflozin, or 20 mg dapagliflozin,

plus OAD(s) and 50% of their regular daily insulin dose[18]. The primary outcome observed was change from baseline in A1C at week 12. At week 12 , the 10- and 20-mg dapagliflozin groups demonstrated _0.70 and _0.78% mean differences in A1C change from baseline versus placebo[19,20]. The mean changes from baseline in fasting plasma glucose (FPG) were _17.8, _2.4, and _9.6 mg/dl (placebo, 10 mg dapagliflozin, and 20 mg dapagliflozin, respectively). The Postprandial glucose (PPG) reductions with dapagliflozin also showed dose dependence reduction. Also the Mean changes in total body weight were reporetd to be _1.9, _4.5, and _4.3 kg (placebo, 10 mg dapagliflozin, and 20 mg dapagliflozin). Overall, adverse events were balanced across all groups, although the only point to be noticed in this research was that there were more genital infections occurring in the 20-mg dapagliflozin group than in the placebo group.[21,22]

SGLT2 Inhibitors[24]

Dapagliflozin

Dapagliflozin (Forxiga®; Bristol-Myers Squibb, New York, NY, USA; AstraZeneca, London, UK) was the very first SGLT2 inhibitor to have its NDA submitted to the FDA i.e on December 2010. But , on January 19, 2012 the FDA declined its approval of dapagliflozin and thereby issued a complete response letter requesting "additional clinical data to permit a better assessment of the benefit–risk profile" for dapagliflozin. Also on November 12, 2012 the European Commission approved the use of dapagliflozin in a dose of 10 mg once daily in type 2 diabetics to improve the glycemic control serving as a monotherapy when diet and exercise alone are unable to provide adequate glycemic control in patients for whom the use of metformin is considered inappropriate due to its intolerance.

The clinical studies from the Phase III results demonstrated that dapagliflozin was effective in lowering hemoglobin HbA1c as a monotherapy, dual therapy, and triple therapy along with the oral agents, as well as with combination therapy with insulin with or without oral AHAs. Throughout all the Phase III studies, dapagliflozin doses of 5 mg and 10 mg once daily both resulted in significant HbA1c reductions when compared to a placebo or any active comparator.

Canagliflozin

Canagliflozin (Invokana®; Janssen Research and Development, LLC, Raritan, NJ, USA; Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) was approved by FDA on March 29, 2013 prescribed to be used with diet and exercise, to improve the glycemic control in adults with type 2 diabetes.

The Phase III studies results demonstrated that canagliflozin was effective in reducing HbA1c served as monotherapy, dual therapy, and triple therapy with oral agents, also with combination therapy with insulin with or without oral AHAs. Throughout the Phase III studies, canagliflozin on doses 100 mg and 300 mg once daily both of which resulted in significant HbA1c reductions compared to a placebo or any active comparator, with slightly better reductions with canagliflozin 300 mg once daily.

Empagliflozin

Empagliflozin (Boehringer Ingelheim Pharmaceuticals, Inc, Ingelheim, Germany; Eli Lilly and Company, Indianapolis, IN, USA) was on its plan to file for NDA submission to the FDA in 2013. Boehringer Ingelheim and Eli Lilly and Company announced on January 7, 2013 the results from four of empagliflozin's Phase III studies, all of which met their primary endpoints.

The Phase III program assessed the efficacy and safety of the drug amongst a wide range of type 2 diabetics as monotherapy, add-on therapy with metformin, pioglitazone, metformin and Sulfonyl ureas, metformin and pioglitazone, metformin and linagliptin,as an add on therapy. The Phase III results revealed that empagliflozin was effective in reducing HbA1c as monotherapy, dual therapy, and triple therapy along with OADs.

CLINICAL SUMMARY FOR DAPAGLIFLOZIN IN TREATMENT OF TYPE-2 DIABETES:[11]

Improved plasma glucose and HbA_{1c}

Dapagliflozin has been shown,to reduce both HbA1c and fasting plasma glucose. The subjects with T2DM exhibited blockade of glucose reabsorption that was again dose-dependent for 5, 25, and 100 mg of dapagliflozin, which ranged from 20% to 44% over 14 days; the glucosuria was observed to be up to 70 g/day. Dapagliflozin administration to the subjects led to significant placebo-adjusted reductions in HbA1c of −0.58%, −0.77%, and −0.89% in 485 newly diagnosed, treatment-naïve T2DM patients controlled by diet and exercise also administered 2.5, 5, and 10 mg of dapagliflozin, respectively. The HbA1c change observed in the placebo group was −0.23%.21 Dapagliflozin 5 and 10 mg daily administered to a subgroup

of about 74 subjects with HbA1c between 10.1% and 12.0% lowered this count by 2.88% and 2.66%, respectively.

Reduced total body weight

Dapagliflozin, whether given as monotherapy or when added to other anti diabetic agents, has resulted in statistically significant weight loss. As a monotherapy, dapagliflozin caused weight loss from −2.7 to −3.2 kg at 24 weeks. Statistically significant, and dose-dependent reductions were observed on day 13 of a two-week study of 47 patients with T2DM i.e 18.8, −28.8, and −38.7 mg/dL for the 5 mg (−11.7%), 25 mg (−13.3%), and 100 mg (−21.8%) doses, respectively, when compared with the placebo group.

Reduced fasting glucose

Dose-dependent decreases in fasting plasma glucose (FPG) have been readily observed. Mean changes in FPG from the baseline FPG as reported were −18.8, −28.8, and −38.7 mg/dL in the 5 mg, 25 mg, and 100 mg dose groups, respectively. In another study, as reported they were +17.8, +2.4, and −9.6 mg/dL (placebo, 10 mg dapagliflozin, and 20 mg dapagliflozin, respectively). Ferrannini et al found FPG reductions of −15.2, −24.1, −28.8, and −4.1 mg/dL for the doses of 2.5 mg, 5 mg, 10 mg, and placebo, respectively. In the study by Strojek et al, FPG was decreased by −2.0, −16.8, −21.3, and −28.5 mg/dL in the placebo and dapagliflozin 2.5 mg, 5 mg, and 10 mg dose groups, respectively.

Effect on fat mass and regional adipose tissue distribution

Bolinder et al also tried examining the secondary endpoints of waist circumference, and reported a decrease of −1.52 cm. The fat mass declined −1.48 kg; the visceral adipose tissue (VAT) decreased −258.4 cm3, and also the subcutaneous adipose tissue (SAT) reduced by 184.9 cm3.

Outcome measure	Evidence	Implications
Disease-oriented evidence	Lowers measures such as HbA_{1c}, fasting glucose, and postprandial glucose, via a novel mechanism – inhibition of renal glucose reabsorption	Weight loss without the potential for hypoglycemia, which could result in improved glycemic control without limiting adverse effects. Possible greater patient acceptance due to being a PO agent
Patient-oriented evidence	Awaiting long-term studies. Citing increased numbers of cases of bladder and breast cancer in patients administered dapagliflozin compared with control subjects, the US Food and Drug Administration (FDA) recently decided against approving this agent	Unclear at present; potential adverse effects, such as fungal genital infections and UTI, may affect patient and provider acceptance. Whether dapagliflozin is associated with the cancers that have raised concern is uncertain

Summary Of Dapagliflozin Versus Glipizide As Add On Therapy In Patients With Type 2 Diabetes, Who Have Inadequate Glycemic Control With Metformin[23]

As the , sulfonylureas are associated with poor glycemic efficay, weight gain, and hypoglycemia. So Dapagliflozin, which is selective inhibitor of sodium-glucose cotransporter was observed to reduce hyperglycemia by increasing urinary glucose excretion that too independent of insulin and caused fewer adverse effects. In this study the efficacy, safety, and tolerability of dapagliflozin with the sulfonylurea glipizide was compared in patients with type 2 diabetes which was inadequately controlled with metformin monotherapy.

PARAMETERS	EFFECT OF DAPAGLIFLOZIN	EFFECT OF GLIPIZIDE
HbA	Initially smaller response followed by sustained effect.	Rapid Initial response followed by gradual increase.

Weight Loss	Significant weight loss	Led to Weight Gain
Hypoglycemia	Lesser episodes of hypoglycaemia.	Frequent episodes of Hypoglycemia.
Blood Pressure	_	Reduced Blood Pressure

Other SGLT2 inhibitors in their development[24]

There are various other SGLT2 inhibitors in clinical trials.

Ipragliflozin

ASP1941; Astellas Pharma US, Inc., Northbrook, IL, USA is currently ongoing Phase III studies in Japan. The results uptill now from two Japanese Phase III studies demonstrated significant decreases in HbA1c compared to placebo.

LX4211

Lexicon Pharmaceuticals, Inc., The Woodlands, TX, USA, differs from the other agents as it is a dual SGLT1/SGLT2 inhibitor. As known, inhibition of SGLT1 is purposely avoided due to the GI symptoms (eg, nausea, vomiting, abdominal pain, constipation, and diarrhea) linked with inhibition of SGLT1 in the small intestine.

The Phase I and Phase II studies with LX4211 in healthy and type 2 diabetic patients have revealed that the partial inhibition of SGLT1 does not result in any additional GI symptoms compared to placebo and also has less GI symptoms as compared to metformin. LX4211 has completed its Phase IIb trial in type 2 diabetics and is presently undergoing a proof-of-concept study in type 2 diabetes with renal impairment and the other one in type 1 diabetes.

Tofogliflozin

CSG452; Kowa Company, Ltd., Nagoya, Japan; Sanofi SA, Paris, France; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan is at present undergoing Phase III clinical trials in Japan and has completed a Phase II study in the US to evaluate its efficacy and safety for the target indication of type 2 diabetes. The results from the Phase II study in the US indicated that tofolgiflozin in a dose of 5, 10, 20, and 40 mg daily resulted in significant dose-dependent reductions in HbA1c compared to placebo as well as with an increase in urinary glucose excretion as expected.

Luseogliflozin

TS-071; Taisho Pharmaceutical Co., Ltd., Tokyo, Japan; Novartis Pharmaceuticals, Basel, Switzerland has successfully completed Phase II clinical trials in Japan, which confirmed sufficient blood glucose lowering and is now implementing Phase III clinical trials in Japan with a designed application for type 2 DM.

Ertugliflozin

PF04971729; Pfizer, Inc., New York, NY, USA also has completed Phase I and Phase II studies and currently does not have any active studies enrolling.

CONCLUSION

SGLT2 inhibition is budding as an elegant mechanism for slowing the attack of diabetes on patients who have been treated with the other conventional agents. There are several agents with such profiles which are racing to market. These drugs come into view having similar benefits and risk within their respective class, which includes meaningful reductions on HbA1c and FPG and also an increase in the risk for certain infections. Most captivating perhaps is their strong ability to positively influence other important metrics, such as body weight, blood pressure, lipids, and uric acid. The older agents have been riddled with unfavorable effects on body weight such as SU, TZDs, insulin, and the CV system including SU and TZDs, and lipids TZDs.[24]

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