INTRODUCTION

Diabetes mellitus (DM) is one of the most common non-communicable diseases (NCDs) globally. In India, 61.3 million persons affected with diabetes in 2011 and it will be 101.2 million by 2030. The number of people with type 2 diabetes is increasing in every country and is associated with significant morbidity and mortality due to cardiovascular complications.1

There is a recognized need for new treatment options for type 2 diabetes mellitus (T2DM). There is a move towards introducing different classes of anti-diabetic drugs as additional therapeutic options with complementary mechanisms of existing therapies to achieve and maintain better glycemic control.

Only two organs in the human body—the liver and the kidney—possess sufficient gluconeogenic enzyme activity and glucose-6-phosphatase activity to enable them to release glucose into the circulation as a result of gluconeogenesis.2 Normally, the kidneys account for ~40% of total gluconeogenesis and ~20% of all glucose released into the circulation in humans.3 In contrast to the liver, the kidney increases its release of glucose after glucose ingestion, potentially contributing to postprandial hyperglycemia in diabetic patients. Hypoglycemia promotes renal gluconeogenesis by increasing the renal uptake of circulating gluconeogenic substrates.4

Patients with type-2 diabetes mellitus have an increase in glucose production by as much as 300%, which is equally contributed to by hepatic and renal sources.5 Plasma glucose is neither protein-bound nor complexed with macromolecules and is therefore freely filtered at the glomerulus and in normal situations almost all of it is reabsorbed in the proximal tubule by an insulin-independent process. Patients with diabetes mellitus have been shown to experience hyperglycemia without resultant glycosuria, and the maximal glucose reabsorptive capacity in these patients has been shown to increase from a normal level of 352 mg/min (19.5 mmol/l/min) to 419 mg/min (23.3 mmol/l/min).6 This may be due to increased expression of glucose transporters at proximal tubule in diabetic conditions and probably represents a physiological response to increased glucose delivery to the proximal tubule that is ultimately maladaptive.7 The transfer of glucose from the tubular lumen to the interstitial space is executed by the active process of Na-dependent glucose transport on the apical membrane to take glucose from the lumen to the cell, and facilitated diffusion glucose transport on the basolateral membrane to release glucose into the interstitium.7,8

Medical researchers were working on anti-diabetic agents that can improve glycemic control without increasing hypoglycemia while promoting weight loss and improving β-cell function.

The US Food and Drug Administration have approved (on March 29, 2013) a novel glucose-lowering agent, canagliflozin (Invokana, Janssen Pharmaceuticals) for the treatment of adults with type 2 diabetes.9 Canagliflozin is the first in a new class of drug, an oral inhibitor of sodium glucose cotransporter 2 (SGLT2). SGLT2, a 672 amino-acid, high capacity, low affinity transmembrane protein, is expressed primarily in the early proximal renal tubule and is responsible for most of the glucose reabsorption in the kidneys. Inhibition of SGLT2 decreases glucose reabsorption in the renal tubule and increases urinary glucose excretion (UGE), with a consequent lowering of plasma glucose levels as well as weight loss due to 300–400 kcal/day loss.10 11 Longer-term treatment studies are necessary to determine whether the weight loss observed in this study will persist beyond the short treatment period examined here.

Pharmacokinetic characteristics of canagliflozin:

- Half-life of 11-13 hrs supports once-daily dosing
- Balanced renal and biliary excretion
- Glucuronidation is major metabolic pathway
- No active metabolites
- No clinically meaningful drug-drug interactions observed

Dose-ranging trial demonstrates that canagliflozin, a novel oral antihyperglycemic agent, at all doses studied, significantly improved glycemic control without an increased occurrence of hypoglycemia in subjects with type 2 diabetes who had inadequate glycemic control with metformin. Studies have shown that canagliflozin was associated with significant reductions in A1C from baseline (7.6–8.0%) to week 12: -0.76, -0.74, and -0.74% for canagliflozin 50, 100, 200, 300 mg QD and 300 mg BID, respectively, versus -0.22% for placebo (all P < 0.001) and -0.74% for sitagliptin. FPG was reduced by -16 to -27 mg/dL, and body weight was reduced by 2.3 to-3.4%, with significant increases in urinary glucose-to-creatinine ratio.12

Despite the modest effect on HbA1c predicted for SGLT2 inhibitors, the introduction of a novel means of reducing hyperglycemia increases the treatment options available to physicians for a disease that frequently requires the use of multiple agents to achieve control targets.

Studies have shown that canagliflozin improved a fasting indirect measure of β-cell function (HOMA2-%B).12 13

CV risk factor changes with canagliflozin14:

- Changes in fasting lipids

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Canagliflozin: Dosing recommendations in patients with Type 2 diabetes who need improved glycemic control—

Starting dose of 100 mg in patients with eGFR < 60 mL/min/1.73m2, loop diuretics, or age ≥ 75 years

– If inadequate response in patients started on 100 mg, increase to 300 mg dose

Canagliflozin is a well tolerated drug. The most common side effects of canagliflozin are vaginal yeast infection (vulvovaginal candidiasis) and urinary tract infection. Genital infections were reported in 3–25% of female subjects across canagliflozin treatment groups (3–8% of all subjects) and in 3% of female placebo subjects (2% of all placebo subjects).12, 14

Because canagliflozin is associated with a diuretic effect, it can cause a reduction in intravascular volume leading to orthostatic or postural hypotension (a sudden fall in blood pressure when standing up). This may result in symptoms such as dizziness or fainting, and is most common in the first three months of therapy. Other side effects are balanitis or balanoposthitis, constipation, thirst, polyuria or polydipsia and less common rash/urticaria (< 2%). In Phase 3 studies have shown that hypoglycemia in patients on insulin or sulphonylurea agent whereas low rate of hypoglycemia in studies of subjects not on agents associated with hypoglycemia.

Clinical trials are underway to assess the efficacy and safety of other investigational SGLT2 inhibitors like ipragliflozin, empagliflozin, Dapagliflozin (Forxiga, Bristol-Myers Squibb/AstraZeneca), is already available in Europe since November 2012. The FDA denied approval of dapagliflozin in January 2012 because of concerns about a cancer signal.15 A third SGLT2 inhibitor, ipragliflozin (Astellas Pharma), has been filed for marketing approval in Japan, and a fourth, empagliflozin (Eli Lilly/Boehringer Ingelheim), is in phase 3 trials and has just been filed for approval in the US.16

Recovery of glucose from the glomerular filtrate represents an important mechanism in maintaining glucose homeostasis and represents a novel target for the management of Type 2 diabetes. By promoting an ‘escape’ mechanism for glucose, SGLT2 inhibitors introduce a new mode to the control of T2DM. The expected favorable safety profile and insulin-independent mechanism of action appear to support the use of SGLT2 inhibitors in combination with other antidiabetic drugs. Canagliflozin added onto metformin monotherapy provides clinically valuable improvements in glycemic control associated with weight loss and low hypoglycemia risk.12 The profile of effective glucose lowering, weight loss, improved b-cell function, and low risk of hypoglycemia suggest that canagliflozin may be a clinically useful new antihyperglycemic agent.

CANVAS- CANagliflozin Cardiovascular Assessment Study which is estimated to primary completion on June 2018 will assess canagliflozin (JNJ-28431754) in the treatment of patients with type 2 diabetes with regard to cardiovascular (CV) risk for major adverse cardiac events including CV death, heart attack, and stroke in patients with type 2 diabetes, whose diabetes is not well controlled at the beginning of the study and who have a history of CV events or have a high risk for CV events.17

REFERENCES