Dapagliflozin: A Novel Therapeutic Approach to Treat Diabetes

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ABSTRACT

Current approaches to treatment of diabetes have many drawbacks. Most of the oral hypoglycemic drugs target the insulin secretion and action. Sodium Glucose co transporters (SGLT)-2 inhibitors are a recent addition to antihyperglycemic drugs that act by reducing glucose reabsorption from the renal filtrate so that bulk of glucose is excreted in the urine. Dapagliflozin, the first in this new class of drugs, is a SGLT2 inhibitor. It causes loss in body weight and is not associated with major hypoglycemic events. Dapagliflozin is currently in advanced development for use alone or in combination with other hypoglycemic agents. Concerns regarding increased cancer risk have delayed the Food and Drug Authority (FDA) approval of this drug. SGLT2 inhibitors represent a major advancement in management of type 2 diabetes mellitus (T2DM) as they have shifted the focus onto kidney and act independent of insulin. JMS 2011;14(2):43-45

Key Words: SGLT2 inhibitors, dapagliflozin, type 2 diabetes

Diabetes is a healthcare crisis affecting 51 million Indians- the highest number of diabetics in any one country in the entire world.¹ Worldwide, the diabetic population is projected to reach 440 million by 2030. Current treatment options for diabetes target the insulin pathway and are not only unsatisfactory but also have unacceptable adverse effects. Only 7-15% of patients are able to meet their glycemic target. Moreover, most of the agents lose effectiveness as pancreatic β cell function declines.

By playing a role in gluconeogenesis and by regulating glucose excretion, kidney occupies a central role in glucose homeostasis. SGLTs are a family of membrane proteins that accomplish the task of transport of glucose from the tubules to

peritubular capillaries via tubular epithelial cells. SGLT1 is the key transporter for glucose absorption in the gastrointestinal tract (GIT) and accounts for 10% of glucose reabsorption in kidney. SGLT2, located primarily in S1 segment of proximal tubule, is responsible for 90% of glucose reabsorption by kidney, using the energy gradient of sodium reabsorption in the tubular filtrate. Diabetes patients show increased expression and activity of SGLT2 leading to increased tubular reabsorption of glucose.²

Inhibiting SGLT2 is a novel therapeutic approach to treat diabetes. It not only corrects a defective mechanism in diabetics but also promotes weight loss by causing glycosuria (1g glucose is equivalent to 4Kcal). Non selective SGLT inhibitors cause osmotic diarrhea limiting their clinical utility. Novel SGLT2 inhibitors are Dapagliflozin, Canagliflozin, Sergliflozin and Remogliflozin etabonate.

The parent compound of this new class of drugs is phlorizin- an O-glucoside. The O-glucosides have to be administered as their prodrug esters to avoid degradation by β glucosidase in the small intestine. Novel SGLT2 inhibitors are

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C- glucosides; creating a carbon- carbon bond between the glucose and aglycone moiety converts O- glucosides to C- glycosides, making them unsusceptible to β glucosidase.³

Mechanism of action

Dapagliflozin (Fig. 1) is 1200 times more selective for SGLT2 over SGLT1. SGLT2 inhibition involves competitive binding of glucose moiety binding site on the transport protein and results in reduction of plasma glucose levels by reducing the glucose T_m (transport maximum) due to increased urinary excretion. Though not a class effect, SGLT2 inhibition also causes reduction in hepatic gluconeogenesis and decreased glucotoxicity. By lowering plasma glucose, liver sensitivity is improved which leads to suppression of hepatic glucose production as a result of glucose 6 phosphatase inhibition.⁴

FIGURE 1: Molecular structure of dapagliflozin

By causing sodium excretion and possibly by a diuretic effect, these drugs can cause a mild reduction in arterial blood pressure.⁴

Clinical studies done with dapagliflozin

In a 24 week Phase III study done on more than 1200 patients, by Astrazeneca and Bristol Myers Squibb⁵, 2 distinct groups were studied using dapagliflozin 5 mg and 10 mg. Each group comprised three categories-metformin plus dapagliflozin, dapagliflozin plus placebo and metformin plus placebo.

In both these groups, combination of metformin and dapagliflozin produced maximum reduction in HbA1C [-2.05% versus (vs)-1.98% with dapagliflozin 5mg and 10 mg respectively] than either of the drugs combined with a placebo. The combination group showed significantly greater decrease in fasting plasma glucose (-61.0mg/dL and -60.4mg/dL with dapagliflozin 5mg and 10 mg respectively). Similarly, mean reduction in body weight was maximum in metformin plus dapagliflozin category (-2.66 kg vs-3.33 kg with dapagliflozin 5mg and 10 mg respectively) in both these groups. Incidence of genital infections (12.8% and 6.9% in dapagliflozin 10 and 5 mg respectively) and urinary tract infections (UTIs) (11% and 7.9% in dapagliflozin 10 and 5 mg respectively) were highest in

dapagliflozin plus placebo category in either group.

An extension of the study evaluated the drug upto 102 weeks and found that the primary endpoint – change from baseline in HbA1C in patients receiving placebo plus metformin was -0.02% compared to -0.58% for patients receiving dapagliflozin 5mg plus metformin and -0.78% for patients receiving dapagliflozin 10 mg plus metformin.⁶ These studies concluded that dapagliflozin is more efficacious than metformin alone.

A 2 year data from a randomized controlled trial (RCT) evaluated dapagliflozin (up to 10 mg/d, n=406) vs. glipizide (upto 20 mg/d, n=408) as add on therapy to metformin (up to 2g/day).⁷ A decline in HbA1C levels of 0.32% [95% confidence interval (CI), - 0.42% to -0.21%] with dapagliflozin vs. 0.14%(95% CI,-0.25% to -0.03%) with glipizide was observed. Dapagliflozin also produced a sustained reduction in body weight (-3.70 kg vs. +1.36 kg) and low risk of hypoglycemia (dapagliflozin 4.2% vs. glipizide 45.8%) over a course of 2 years.

Another phase III double blind placebo controlled trial of dapagliflozin as an add on agent examined 546 poorly controlled T2DM patients on maximum doses of metformin, randomized to receive dapagliflozin 2.5 mg 5mg, 10mg/day or placebo. At the end of 24 weeks, patients on dapagliflozin 5mg showed - 0.70 % change in HbA1C from baseline vs. -0.84 % with dapagliflozin 10 mg and -0.3 % with placebo ($p < 0.002$ for both comparisons). Moreover, dapagliflozin 5 and 10 mg showed significant fall in systolic and diastolic blood pressure.⁸

A small study examined effect of dapagliflozin in patients of T2DM who were experiencing suboptimal control on insulin and insulin sensitizers (pioglitazone >30mg/ rosiglitazone 4mg/metformin>1000mg). Change in HbA1C from baseline at week 12 was reported to decrease 0.7% with 10 mg dapagliflozin and 0.78% with 20 mg dapagliflozin.⁹

Adverse effects

Side effects observed in clinical studies done on dapagliflozin apart from diarrhea and nausea are urinary tract and genital tract infections, dizziness, headache, fatigue, backache and nasopharyngitis.¹⁰ Increased urine volume was associated with increased hematocrit and urea, suggesting slight volume depletion. Electrolyte imbalance is a consideration because physiological studies show increased sodium loss with phlorizin.³ Statistically significant increases in serum magnesium and decreased uric acid levels have been reported. An increase in parathormone concentration but no changes in 1, 25 dihydroxy vitamin D and 25- hydroxy vitamin D levels have been noted.¹³ Dapagliflozin was associated with a higher rate of genital infections as compared to metformin plus placebo group (12.8% vs. 2.4%) and UTIs (11% vs. 4.3%).⁶

There have been no reports of major hypoglycemic episodes and no patient discontinued study medication due to hypoglycemia. Drug induced liver injury is a concern because some C-glycoside SGLT2 inhibitors reported a positive

micronucleus test-indicating a potential to damage chromosomes. This observation has encouraged development of new phlorizin analogues by slight modification of chemical structure. Further evaluations are needed to clarify its effects in diabetes patients with neuropathy, hyporeninemic hypoaldosteronism, nephropathy and those vulnerable to sodium wasting and hypovolemia. Safety in pregnancy is not established.

In clinical trials, out of 5478 patients, 9 patients (0.1%) had breast cancer, 9 patients (0.35%) had bladder cancer compared with only one breast cancer (0.09%) and 1 bladder cancer (0.5%) among 3156 patients assigned to control groups. As reporting of cancer was within one year of drug initiation in all patients, it seems unlikely that dapagliflozin caused the cancer, although it might have accelerated them. Moreover, dapagliflozin has not shown genotoxic or carcinogenic potential in preclinical studies. Due to concerns over these serious adverse effects, FDA recently declined approval of this drug asking the developers to provide more data about its risk-benefit profile.

Conclusion

The clinical trials done on dapagliflozin either alone or in combination with various antidiabetic drugs have shown promising results in reducing HbA1C; this drug in future could prove to be an additional molecule in diabetes management. The studies are on to evaluate the adverse effects of the drug. Phase III trials till date have not reported any serious adverse events precluding the clinical use of this molecule. Further ongoing studies will enrich our knowledge about this drug. More RCTs are required to study the long term impact in diabetes management. Though yet to obtain FDA approval; this new class of drugs is poised to play an important role in the treatment of diabetes as they work independently of insulin and target renal glucose reabsorption.

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