Review Article

Sodium Glucose Co-transporters-2 (SGLT2) Inhibitors in the Treatment of Type 2 Diabetes Mellitus: Updates on Bexagliflozin

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ABSTRACT

Treatment of Diabetes mellitus continues to be a challenge for the Health Care Professionals as it is estimated that 537 million adults are living with diabetes with the number expected to rise to 643 million by 2030. Uncontrolled diabetes is causing several complications due to macrovascular and macrovascular changes contributing to morbidity and mortality. Therefore, it is considered as 9th leading cause of death. Despite several medications being available, control of diabetes has been difficult because of several issues such as the comorbid state of the individual, age related physiological changes along with the safety and efficacy of the medications used. SGLT2 inhibitors are currently the preferred class of medications in Type 2 diabetes mellitus to achieve good glycaemic control, and manage the other related health problems. Bexagliflozin (Brenzavvy) is, a new member added to the class has several health benefits overweighing the risks associated. It helps in achieving good glycaemic control, reduce, blood pressure, reduce bodyweight, reduce the heart failure and risk of cardiovascular accidents, making it a better SGLT2 for adjunct therapy for type 2 diabetes mellitus.

Keywords: Bexagliflozin, Diabetes Mellitus, SGLT2 inhibitors.

INTRODUCTION

Diabetes mellitus is considered a significant health challenge affecting millions of people worldwide. Prevalence of diabetes continues to rise, largely driven by factors such as population growth, aging, urbanization, unhealthy diet, and lifestyles. As of 2023, it is estimated that 537 million adults are living with diabetes with the number expected to increase to 643 million by 2030 and 783 by 2045. This means that 1 in every 10 adults globally could be diabetic [1]. Type II diabetes mellitus accounts for approximately 90-95% of all cases, affecting individuals irrespective of economic status. Furthermore, India ranks 2nd in the global pandemic scenario, also diabetes mellitus is considered one of the largest global health problems as it is the 9th leading cause of death [2].

Thus, type II diabetes is a major public health concern. India has the second highest number of people with diabetes worldwide after China, therefore, India is considered as the "Diabetes capital of the world". India is further witnessing a sharp rise in the prevalence affecting 77 million people as of 2023, and the number is expected to grow to 134 million by 2045. Thus, the economic cost of this disease is enormous. The global expenditure on diabetes in 2021 was estimated to be over $966 billion which has increased by 316% over the last 15 years. Similarly, in India, the economic burden is substantial for both the individuals and the country as a whole, as diabetes is one of the leading causes of work absenteeism and reduced productivity. The treatment of diabetes and its complications have significantly increased thus causing an impact on the economic burden in health care management [1].

The chronic disease occurs when the pancreas fails to produce the required amount of insulin or when the body cannot effectively utilize the secreted insulin. Thus, good glycemic control is essential. The uncontrolled diabetes or untreated hyperglycemic status leads to tissue damage resulting in micro and macrovascular pathologies leading to high incidence of complications such as; cardiovascular disease, renal failure, neuropathies, diabetic retinopathy (leading to blindness), and gangrene [3]. Most individuals are unaware of their clinical condition until they develop these complications which indirectly add to economic constraints.

Currently, the treatment of type II diabetes primarily involves the use of oral antidiabetic drugs such as; metformin, sulfonylureas, thiozolidinediones, α glucosidase inhibitors, glucagon-like peptide -1 (GLP-1) agonists and dipeptidyl peptidase 4 inhibitor (DPP4) inhibitors [4]. These antidiabetic agents have benefited from increasing insulin release, increasing insulin sensitivity, controlling the hepatic release of glucose, or interfering with the interstitial absorption of glucose. However, metformin remains the first-line therapy due to its effectiveness and affordability. Despite the availability of medications, it is difficult to achieve the glycemic target. Furthermore, all of these medications are associated with several side effects such as weight gain, hypoglycemia, fluid retention, nausea, abdominal discomfort and diarrhea [5, 6, 7] .Therefore, there has been an increasing demand for the development of new molecules/ drugs that can benefit diabetic individuals to achieve good glycemic control independent of insulin with better tolerability and fewer side effects than the available traditional preparations do.

In this review an effort has been made to review the evolution of the sodium glucose co transporter -2 (SGLT-2) inhibitors and highlight the newly introduced preparation for this family, bexagliflozin (Brenzavvy).

EVOLUTION OF SGLT2 INHIBITORS:

The kidneys play a major role in glucose homeostasis. This is achieved mainly through the transport protein sodium glucose transport 2 (SGLT2) isoforms present in the epithelial cells of proximal tubules. The discovery of the familial renal glucosuria (FRG) which occurs due to the defects in SGLT2 expression in the kidney can guide the use of SGLT2 inhibitors as potential targets for the control of diabetes [8]. This led to the introduction of SGLT2 inhibitors in the treatment of diabetes mellitus which increased the urinary excretion of glucose by inhibiting tubular reabsorption without affecting insulin secretion but ultimately resulted in decreased plasma glucose levels. The advantage of this class of drugs is that they reduce the plasma glucose level by selectively inhibiting SGLT2 isoforms, without affecting the glucose transport in other major organs such as the brain, liver, and muscles [9].

The sodium glucose co transporters play a major role in decreasing the glucose reabsorption (50%) thus increasing glucosuria and resulting in reduced plasma glucose levels [10, 11]. SGLT2 has been identified as a target and its inhibition has therapeutic potential in the management of diabetes [9, 12, 13, 14].

The nonselective SGLT2 phlorezine was first introduced and was obtained from the bark of the apple tree; it inhibits both SGLT-1 & SGLT-2 thus lowering the blood glucose levels. It produced an active metabolite aglycone phloretin that inhibited the glucose transporter. However, phlorezine was soon withdrawn because of its unacceptable intestinal toxicity which was caused by its SGLT 1 blockade action because of its low bioavailability due to rapid intestinal degradation [15, 16].

Similarly, sergliflozin and remigliflozine were introduced to the family of SGLT2 inhibitors. Compared to phlorezine, sergliflozin has no side effects on the gastrointestinal tract[17, 18]. However, both preparations are not preferred because of the unfavorable pharmacokinetic profiles, as they contain O-glucoside linkages which make them susceptible to hydrolysis by intestinal β glucosidase which reduces their plasma half-life, whereas dapagliflozin, a competitive reversible SGLT2 inhibitor has 1200 fold greater selectivity for SGLT-2 than SGLT-1 as compared with phlorezine and has a favorable pharmacokinetic profile compared to sergliflozin and remigliflozine [19, 20, 21].

Dapagliflozin which is orally effective, and long acting, suppressed both postprandial and fasting blood glucose for 24 hours, thus it is preferable for once-daily dosing [19, 22]. It also reduces the mean diastolic and systolic blood pressure due to its diuretic action without increasing the incidence of orthostatic hypotension [23]. Furthermore, it has also been shown to decrease plasma triglyceride levels and increase plasma high-density lipoprotein (HDL) levels [24]. These observations with dapagliflozin restrict its use in patients with normal renal function and patients with mild renal impairment. However, they are preferred for use after the risks and benefits are weighed. Dapagliflozin used as monotherapy or in combination has improved glycemic control along with a reduction in blood pressure due to the diuretic action. However, the limitations of dapagliflozin include genitourinary tract infections and severe mycotic vulvovaginal infections in women [25, 26, 27]. It is also known for its hepatotoxic effects and increases the risk of breast and bladder carcinomas [28, 29]. Hence, newer preparations have gained importance although dapagliflozin continues to be preferred in the treatment of type 2 diabetes mellitus.

Bexagliflozin was approved for its use in type 2 diabetes by the U.S. Food and Drug Administration (FDA) with the brand name Brenzavvy in January 2023[30]. As a new addition to the class, it is considered an alternative option in the treatment of type 2 diabetes for better glycemic control either as monotherapy or in combination with other antidiabetic medications. Like other SGLT-2 inhibitors, bexagliflozin targets the sodium glucose co transporter 2 proteins in the kidneys. These proteins are responsible for reabsorbing glucose back into the stream during the filtration process by inhibiting SGLT2, Bexagliflozin, prevents glucose reabsorption causing excessive glucose to be excreted through the urine and thus lowering blood glucose levels without inducing excessive insulin secretion [31].

BENEFITS OF BEXAGLIFLOZIN:

1. It reduces fasting as well as postprandial blood sugar spikes and is effective in lowering the HbA1c level, hence it can be considered for long-term glucose control in individuals with type 2 diabetes.
2. It also benefits from its use in patients with mild to moderate renal impairment without dose reduction. However, it is not recommended for patients with advanced kidney disease with a GFR < 30 ml/min [32].
3. The Natriuretic effect explains its benefit in reducing blood pressure without increasing heart rate indicating a lack of sympathetic activation. Thus it protects against arrhythmias [33, 34, 35].
4. Natriuretic effects result in a reduction in plasma volume and cardiac preload without the activation of the renin angiotensin aldosterone system (RAAS) [36].
5. It has an added renoprotective action associated with the preservation of renal function which is attributed to changes in tubule-glomerular feedback that result in neurohumoral stimulation resulting in fluid and electrolyte homeostasis [37].
6. Furthermore, bexagliflozin as a class of SGLT-2 inhibitors has demonstrated cardiovascular benefits by decreasing cardiovascular risk, reducing heart failure, and decreasing hospitalization due to either heart failure or cardiovascular events and it has also reduced the mortality rate due to cardiovascular events [33,38, 39].

7. Like other SGLT-2 inhibitors, bexagliflozin is associated with modest weight loss in patients which primarily occurs through the loss of caloric glucose and a reduction in hepatic fat and fibrosis. It has also been shown to reduce in epicardial fat accumulation.

Adverse effects of bexagliflozin:

The adverse drug reaction risk is lower among patients with type 2 diabetes in their early stage than among those with a long duration of diabetes. Bexagliflozin is considered a well-tolerated SGLT- 2 inhibitor without increasing the risk of hypoglycemia, even when it is used along with metformin, and DPP - 4 inhibitors. Thiozolidinediones are known to cause genital mycotic infection affecting approximately 10% of individuals who range from mild to moderate infection which can be alleviated by maintaining hygiene and the use of antifungal agents [40].

It causes volume depletion mostly in elderly individuals with a long duration of type 2 diabetes with a GFR less than 60 ml /min /173m2 who are concomitantly treated with ACE inhibitors, diuretics, or ARBs resulting in prominent hypotension and dizziness. These adverse effects can be managed with excessive fluid intake or discontinuation of diuretics. It also causes rare adverse effects such as Fournier's gangrene – which is a potentially life-threatening complication that can be managed with broad-spectrum antibiotics, surgical debridement, and discontinuation of SGLT-2 inhibitors. Furthermore, it has the potential to cause diabetic ketoacidosis, amputations, and fractures. They should be discontinued or avoided in patients at risk of amputation or individuals who develop ulcers or infections of the lower limbs. Overall, the adverse drug reactions caused by bexagliflozin can be weighed against the greatest potential benefits caused by it[41, 42, 43, 44].

CONCLUSION

Bexagliflozin has been shown to reduce the progression of atherosclerotic changes, reduce macrovascular complications, and reduce long-term cardiovascular and renal complications. Its outcome in high-risk cardiovascular patients is visible with the Bexagliflozin Efficacy & Safety Trial (BEST). Initiating the management of diabetes with SGLT-2 inhibitors such as bexagliflozin is likely to reduce complications and help achieve targeted glycemic control. In comparison with add-on therapy medications such as DPP-4 inhibitors, sitagliptin, bexagliflozin reduces body weight and blood pressure thus contributing to the prevention of diabetic complications.

SGLT2 inhibitors as a new class of oral hypoglycemic agents for the treatment of type 2 diabetes mellitus, help reduce blood sugars and achieve good glycemic control. Hence, it is preferred as monotherapy and combined therapy. However, the limitations associated with various classes of medications such as urinary tract infections, increased risk of breast and bladder cancer, and hepatotoxicity all pose potential safety concerns for long-term use. Thus, it is important to outweigh their potential benefits given to the introduction of newer preparations with added advantages and fewer adverse effects.

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REFERENCES

1. https://www.WHO.int/ accessed on 29/8/2024
2. World Health Organization. The top 10 causes of death. Available from : http://www.who Int/en news room/fact sheets/detail//the top 10 causes of death [Accessed on 29/8/2024]
3. L' Abbate. "A large and micro coronary vascular involvement in diabetes" Pharmacol Rep, 2005; 57 (Suppl): 3-9.
4. Inzucchi SE, "Oral antihyperglycemic therapy for type 2 diabetes: scientific review". JAMA 2002; 287: 360-372.
5. Holman R R, Paul S K, Bethel M A et.al.,"10 year follow up of intestine glucose control in type 2 diabetes. N Engl J Med. 2008;35 (15):1577-1589.
6. Patel A Mac Mohan S, Chalmer J et al, " Intestinal blood glucose control and vascular outcomes in patients with type 2 diabetes ".N Engl Med, 2008;358(24): 2560-2572.
7. Palmar SC, Mavridis D, Nico Lucci A et.al., "Comparison of clinical outcomes and adverse events associated with glucose lowering drugs in patients with type 2 diabetes a meta analysis. JAMA, 2016; 316 (3):313-324.
8. Santer R, Kinner M, Lassen CL et. al., "Molecular analysis of SGLT2 gene in patients with renal glucosuria". J Am Soc Nephrol, 2003:14:2873-2882.
9. Jabbour SA, Goldstein BJ." Sodium glucose co-transporter 2 inhibitors; blocking renal tubular reabsorption of glucose to improve glycaemic control in patients with diabetes." Int J Clin Pract. 2008; 62: 1279-1284.
10. Defronzo R A, Davidson J A, Del PS. "The role of the Kidneys in glucose homeostasis; a new path towards normalizing glycemia". Diabetes obes metab.2012; 14(1):5-14.
11. Abdul Ghani MA, Defronzo RA, Norton L. "Novel hypothesis to explain why SGLT2 Inhibitors inhibit only 30-50% of filtered glucose load in human". Diabetes, 2013; 62 (10): 3324-3328.
12. Patel AK, Fonseca V. "Turning glucosuria into a therapy; efficacy and safety with SGLT2 inhibitors". Curr Diabetes Rep. 2010; 10:101-107.
13. Defronzo RA, Davidson JA, Del PS. "The role of kidneys in glucose homeostasis; a new path towards normalizing glycemia." Diabetes Obes Metab.2012; 14(1): 5-14.
14. Vallon V. "The mechanisms and therapeutic potential of SGLT2 inhibitors in diabetes mellitus. Annu Rev Med. 2015; 66(1): 255-270.
15. Rossetti L , Smith D, Shulman GI, Papa Christon D, Defronzo RA." Correction of hyperglycemia with Phlorizin normalizes tissue sensitivity to insulin in diabetic rat." J Clin Invest.1987; 79: 1510-1515.
16. Ehrenkranz J R, Lewis NG, Khan CR, Roth J. "Phlorizin; a review". Diabetes Metab Res Rev. 2005; 21: 31-38.
17. Fujimou Y, Kalsuno k, Ojima K, et.al,. "Sergliflozine SGLT2 Inhibitor, improves glycaemic control in Streptozotocin induced diabetic rats and Zucker fatty rats. Eur J Pharmacol.2009; 609:148-154.
18. Minoura H, Takeshila S, Yamomoto T et.al., "Ameliorating effects of FK614, a novel non thiazolidinedione peroxisome proliferator

activated receptor gamma agonist on insulin resistance in Zucker fatty rat. Eur J Pharmacol.2005; 519: 182-190.

19. Isaji M. SGLT2 inhibitors: molecular design and potential differences in effect. Kidney Int Suppl 2011; 79 (Suppl 120) : S14 – S19.
20. Zhang L, Feng Y, list J, Kasichayanula S, P Fiser M. "Dapagliflozin treatment in patients with different stages of type 2 diabetes mellitus; effects on glycaemic control and body weight. Diabetes Obes Metab.2010; 12: 510-516.
21. Hans et al. Dapagliflozin, a selective SGLT2 inhibitor, improves glucose homeostasis normal and diabetic rats. Diabetes 2008; 57: 1723 – 1729.
22. Meng W et al. Discovery of Dapagliflozin; a potent selective renal sodium –dependent glucose transporter 2(SGLT-2) inhibitors for the treatment of type 2 diabetes. J Med Chem. 2008; 51: p1145-1149.
23. Ferrannini E et al. Dapagliflozin Monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise; a randomized, double – blind, placebo controlled phase 3 trial. Diabetes Care 2010; 33: 2217-2224.
24. Bailey CJ et al. "Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomized double blind, placebo control trial". Lancet 2010; 375: 2223-2233.
25. Kipnes MS. Sodium – Glucose Co transporter 2 inhibitors in the treatment of type 2 diabetes; A review of Phase II & III trials. Clin Invest 2010; 1:145-156.
26. Strojek K et al. Effect of Dapagliflozin in patients with type 2 diabetes who have inadequate glycemic control with glimepiride: A randomized, 24 week double blind, placebo – controlled trial. Diabetes obes- Metab 2011; 13: 928 – 938.
27. List IF et al. Sodium–glucose cotransport inhibition with dapagliflozin in type 2 diabetes. *Diabetes Care* 2009; 32: 650-657.
28. Catarina Borges, Fernandes Paulo, Torres Ramalho. "A Rare Case of Dapagliflozin-Induced Hepatic Toxicity". September 2024 , Medicina Interna 31(3):39-42.
29. Zhou J, Zhu J, Yu SJ, Ma HL, Chen J, Ding XF, et al. Sodium glucose co-transporter-2 (SGLT-2) inhibition reduces glucose uptake to induce breast cancer cell growth arrest through AMPK/mTOR pathway. Biomed Pharmacother Biomed Pharmacother. (2020) 132:110821.doi: 10.1016/j.biopha.2020.110821
30. Dindere ME. New FDA-approved SGLT2 Inhibitor Bexagliflozin for Type 2 Diabetes Therapy. Discoveries Reports 2023; 1-5.
31. Bexagliflozin (Brenzavvy): Advancing Diabetes Management with SGLT-2 Inhibition. PharmacyTimes.com. [cited 2023 Dec 30]. Available from: https://www.pharmacytimes.com/view/bexagliflozi n-brenzavvy-advancing-diabetes-managementwith-sglt-2-inhibition
32. Allegretti AS, Zhang W, Zhou W, Thurber TK, Rigby SP, Bowman-Stroud C, et al. Safety and Effectiveness of Bexagliflozin in Patients With Type 2 Diabetes Mellitus and Stage 3a/3b CKD. Am J Kidney Dis. 2019;74 (3):328–37.
33. Zelniker TA, Braunwald E. Cardiac and renal effects of sodium glucose co transporter and inhibitors in diabetes: JACC state of the art review. Jam coll Cardiol. 2018; 72:1845 – 55.
34. Halvorsen Y-DC, Lock JP, Freeman MW. 1117-P: Cardiovascular and Glycemic Benefits of Bexagliflozin as an Adjunct to Metformin for the Treatment of Type 2 Diabetes in Adults: A 24-Week, Randomized, Double-Blind, Placebo-Controlled Trial.Diabetes.2020; 69: P-1117.
35. Halvorsen YD, Walford G, Thurber T, et al. " A 12-week,randomized double blind, placebo Controlled, four arm dose finding phase 2 study evaluating Bexagliflozin as monotherapy for adults with type 2 diabetes ". Diabetes Obes Metab. 2020; 22(4):566-573.
36. Weber MA, Mansfield TA, Alessi F, et al. "Effects of dapagliflozin on blood pressure in Hypertensive diabetic patients on Renin Angiotensin system blockade". Blood Press.2016; 25 (2):93-103.
37. Garofalo C, Borrelli S, Liberti ME, et al.: SGLT2 inhibitors: nephroprotective efficacy and side effects. Medicina (Kaunas). 2019, 55:268.
38. Mc Murray JJV, Freeman MW, Massaro J, et al. 32-OR: the Bexagliflozin Efficacy and Safety Trial BEST): a randomized, double blind, placebo controlled, Phase III. Diabetes 2020; 69(1):32-OR.Clinical Trial.
39. Vadugantha M, Claggett BL, Jhund PS, et al. Estimating lifetime benefits of comprehensive disease modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomized controlled trials. Lancet . 2020; 396(10244):121-128.
40. Halvorsen YC, Lock JP, Jhou W et al, " A 96 week , multinational randomized , double – Blind, parallel- group, clinical trial evaluating the safety and effectiveness of Bexagliflozin as a monotherapy for adults with type 2 diabetes". Diabetes Obes Metab. 2019; 21 (11): 2496-2504.
41. US Food and Drug Administration. Invokana (canagliflozin) tablets for oral use: prescribing information.2018. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204042s001bl.pdf.
42. Handelsman Y, Henry RR, Bloomgarden ZT, et. al. American Association of clinical Endocrinologists and American College of endocrinology position statement on the association of SGLT2 inhibitors and Diabetic ketoacidosis. Endocr pract.2016; 22:753-62.
43. Veda P, Svanstorm H, Melbye M, et al. Sodium glucose co-transporter 2 inhibitors and risk of serious adverse events nationwide register based cohort study. BMJ. 2018; 363:K 4365.
44. Zhang XL, Zhu Q, Chen YH, et al. Cardiovascular safety long term non cardiovascular safety and efficacy of sodium glucose co- transporter 2 inhibitors in patients with type 2 diabetes mellitus: a systemic review and meta-analysis with trial sequential analysis. J Am heart Assoc. 2018;7(2):33-36.