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PERSPECTIVE Article

New FDA-approved SGLT2 Inhibitor Bexagliflozin for Type 2 Diabetes Therapy

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is an escalating global challenge, standing out as a prominent public health concern with profound implications for healthcare costs.

Recent data reveals the prevalence of diabetes in adults reaching approximately 537 million in 2021, expected to rise to 643 million by 2030. Moreover, it adversely impacts functional capabilities of patients, leading to extensive morbidity and premature mortality. Between 2000 and 2019, age-standardized mortality rates for diabetes increased by 3%, attributed to alarming unhealthy lifestyles, heightened body mass indexes, and health complications due to elevated glycemia, and raising an absolute need for effective treatment approaches.

Over the last decade, Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors have gained popularity as primary medications for T2DM. A noteworthy addition to this class of drugs is TheracosBio's Brenzavvy (bexagliflozin), an FDA-approved oral SGLT2 inhibitor introduced in January 2023. Thus, phase 3 studies demonstrated bexagliflozin's efficacy in significantly reducing hemoglobin A1c and fasting blood sugar levels over 24 weeks. As a well-tolerated medication, bexagliflozin exhibits positive effects even in T2DM patients with major adverse cardiovascular events and impaired renal function.

Its potential to enhance the overall functionality and life quality of affected individuals, while mitigating the financial burden associated with diabetes care, positions bexagliflozin as a promising advancement in the management of type 2 diabetes mellitus.

SUMMARY

Keywords

Type 2 diabetes mellitus, SGLT2 inhibitors, HbA1c reduction, glucose renal reabsorption, diabetes complications

1. Introduction

Type 2 diabetes mellitus (T2DM) is a rising burden worldwide, representing one of the leading public health issues and a complex debilitating condition, exerting a substantial negative impact on healthcare costs[1]. The swift progress in economic development and urbanization has given rise to an escalating diabetes concern across various regions globally. Recent statistics indicate that the

prevalence of diabetes in adults reached approximately 537 million in 2021, with an anticipated increase to around 643 million by the end of 2030.

This ascending global pattern of diabetes mellitus has considerably faster increment observed in well-developed regions, such as Western Europe, gender distribution being equitable with an incidence peak at approximately the age of 55[2]. The ailment adversely affects the functional capabilities and overall quality of life, resulting in extensive morbidity and premature mortality.

From 2000 to 2019, age standardized mortality rates for diabetes witnessed a 3% overall gain. However, in lower-middle-income countries, the mortality rate associated with diabetes surged by 13%, accounting for over 1 million deaths annually and ranking it as the ninth leading cause of mortality[1]. Notably, concerns have emerged regarding the fact that over a third of diabetes-related deaths occur in individuals under 60 years of age. Unhealthy dietary patterns, coupled with sedentary lifestyles, leading to heightened Body Mass Index (BMI) and elevated glycemia, have been identified as major contributors to this alarming trend[3]. Specifically, those with high BMI are more prone to developing type 2 diabetes[4,5]. Additionally, the aging of the global population adds to the prevalence of diabetes, given its propensity to involve older people[2].

Moreover, the financial weight of diabetes care is a minimum of 3.2 times higher than the average per person healthcare spendings, escalating to 9.4 times when associated with complications[1]. Therefore, these concerning aspects have led the scientific community to extensively search for effective medication to complement the primary lifestyle changes a diabetes type 2 patient has to commit to: nutritional regime, regular physical activity, and tobacco abstinence[6,7].

Over the last decades, numerous classes of drugs have become of common use for type 2 diabetes treatment in addition to the standard metformin therapy, including insulin, sulfonylureas, meglitinides, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, GIP and GLP-1 receptor agonists and SGLT2 inhibitors[8]. Among these kinds of therapeutic resources, SGLT2 inhibitors have gained important popularity, and in 2022, the American Diabetes Association guidelines for treatment approaches in diabetes recommend the use of SGLT2 inhibitors as first line medication for type 2 diabetes, typically complemented with metformin. This recommendation is particularly applicable to individuals with chronic kidney disease, cardiovascular disease, or heart failure[9].

The newest and a very promising addition to this class of drugs is TheracosBio's Brenzavvy (bexagliflozin), an oral sodium-glucose cotransporter 2 (SGLT2) inhibitor, approved by the U.S. Food and Drug Administration (FDA) on 20th of January 2023, as an auxiliary to healthy regime and regular exercise to enhance the management of blood sugar levels in patients with T2DM[10].

The approval from the FDA is grounded in the outcomes of a comprehensive clinical program that assessed the safety and effectiveness of bexagliflozin through 23 clinical trials involving over 5,000 adults diagnosed with type 2 diabetes mellitus. Findings from Phase 3 studies demonstrated that bexagliflozin yielded significant reductions in hemoglobin A1c (HbA1c) and fasting blood sugar levels after a 24-week period. This effect was observed whether bexagliflozin was used as a standalone therapy, in conjunction with metformin, or as an augmentation to standard-of-care treatment, which encompassed various regimens such as insulin, metformin, DPP4 inhibitors, sulfonylureas or combinations thereof. While bexagliflozin is not specifically approved for decreasing weight or blood pressure, some clinical studies did reveal limited declines in both MBI and systolic blood pressure[11].

2. Indication and mechanism of action

Bexagliflozin stands out as a remarkably specific suppressor of SGLT2. This transporter plays a pivotal role in reclaiming a significant amount of glucose from the renal glomerular filtrate in the renal proximal tubule. By impeding the activity of SGLT2, there is a reduction in glucose reabsorption, consequently decreasing the renal threshold for glucose and enhancing its elimination through urine. This mechanism, which involves expelling surplus glucose through urine, contributes to the management of diabetes by efficiently diminishing blood sugar levels[12].

In conjunction with appropriate dietary measures and physical activity, bexagliflozin has the potential to enhance the regulation of blood sugar levels in adults diagnosed with type 2 diabetes mellitus. It is applicable either as a monotherapy or associated

with alternative medications for diabetes. It's crucial to emphasize that bexagliflozin is not recommended for individuals with type 1 diabetes due to the potential elevation of the risk of diabetic ketoacidosis (DKA) in this patient group[13].

The safety and efficiency of the trug were tested in "The Bexagliflozin Efficacy and Safety Trial (BEST)", a phase 3, randomized, double-blind, placebo-controlled study, which explored the impact of bexagliflozin on lowering HbA1c levels in individuals with type 2 diabetes mellitus who faced an elevated risk of cardiovascular adverse events (AEs). Administering bexagliflozin resulted in a statistically significant decrease in HbA1c among patients at a heightened risk of cardiovascular events, accompanied by beneficial fallout on systolic blood pressure and body weight. Furthermore, the study proved noninferiority for the composite outcome, encompassing cardiovascular death, myocardial infarction, stroke, or unstable angina[14].

Another phase 3 study, entitled "Safety and Efficacy in T2DM Patients with Moderate Renal Impairment", adopted a multi-center, randomized, double-blind, placebo-controlled, parallel-group design to assess the effectiveness and safety of bexagliflozin's once-daily oral intake in comparison to a placebo. This trial involved patients with type 2 diabetes mellitus, moderate renal dysfunction, with an estimated glomerular filtration rate (eGFR) ranging between 30 and 59 mL/min/1.73m², and insufficiently regulated glycemia (HbA1c levels between 7.0% and 10.5%). Notably, therapy with bexagliflozin produced a statistically significant decline (0.37%) in HbA1c compared to the placebo group. Moreover, patients administered bexagliflozin experienced a decrease in both body weight and systolic blood pressure (SBP), likely stemming from caloric loss and the diuretic effects on the proximal tubule associated with elevated urinary glucose excretion. The impact was more pronounced within the subgroup characterized by an eGFR between 30 and < 45 - chronic kidney disease (CKD) stage 3b, this outcome being attributed to a more substantial placebo response affecting hemoglobin A1c levels among participants with an eGFR ranging between 45 and 60 (CKD stage 3a). Comparable favorable, short-term outcomes related to body weight, systemic blood pressure, albuminuria, and eGFR have been documented for other medications within the same class. Nevertheless, no prior study has reported a statistically significant reduction in HbA1c levels in diabetic patients with stage 3b CKD[15].

3. Contraindications, warnings and adverse reactions

Bexagliflozin is not suitable for patients exhibiting hypersensitivity to bexagliflozin or any of its components. Additionally, it is contraindicated for individuals undergoing dialysis or those with advanced-stage renal dysfunction, where the eGFR is less than 30 mL/min/1.73m². This restriction is due to the diminished effectiveness of glucose reduction and a decrease in urine output observed in such patients[13]. For patients with type 1 diabetes mellitus, the use of bexagliflozin significantly elevates the risk of diabetic ketoacidosis, a critical and life-threatening condition, beyond the normal basal rate. Clinical studies with a placebo control demonstrated a notable increase in the risk of ketoacidosis among subjects receiving SGLT2 inhibitors compared to those on placebo.Thus, it is crucial to highlight that bexagliflozin is not recommended for managing blood sugar levels in patients with type 1 diabetes mellitus[16].
Moreover, considering animal data, the use of bexagliflozin is discouraged during the second and third trimesters of pregnancy. Similarly, its usage is not advisable during breastfeeding due to the potential for serious adverse events in a breastfed infant, including the impact on postnatal renal development. Furthermore, it is not recommended for individuals with severe hepatic impairment[12].

Generally, clinical trials have shown a proper tolerance to bexagliflozin. The most common adverse reactions to bexagliflozin were consistent with other SGLT2 inhibitors and included predominantly urinary tract infections, genital mycotic infections in female patients and increased urination (incidence > 5%)[17].

Additionally, the observed effects of moderate volume depletion, weight loss, and a decrease in systolic blood pressure align with the anticipated consequences of osmotic diuresis and caloric loss triggered by the suppression of SGLT2. These outcomes can sometimes occur as symptomatic hypotension or brief, acute alterations in creatinine levels. Similarly, the rise in serum creatinine concentration, as part of the manifestations of acute kidney injury, is in harmony with the pharmacological characteristics of the SGLT2

inhibitor class and the anticipated impact of natriuresis on the glomerular filtration rate. Individuals with compromised renal function (eGFR below 60 mL/min/1.73 m^2), elderly subjects, those with low systolic blood pressure, or individuals using loop diuretics might face an elevated risk of volume depletion or hypotension[15].

More severe side effects comprised an heighten prevalence of lower limb amputations (8.3 compared to 5.1 cases per 1,000 patient-years in a randomized, placebo-controlled clinical study), pyelonephritis, urosepsis, and low blood sugar levels when associated with insulin and/or insulin secretagogues, and necrotizing fasciitis of the perineum[18].

4. Conclusion

Bexagliflozin, the most recent FDA approved drug for T2DM, is an encouraging therapeutic tool and member of the SGLT2 inhibitors family, with remarkable outcomes in lowering HbA1c concentrations and providing controlled glycemic levels. As a well-tolerated medication, with beneficial fallout even on T2DM patients with major adverse cardiovascular events and impaired renal function, bexagliflozin could enhance the overall functional capabilities and quality of life in such patients, additionally decreasing the financial strain of diabetes care and other consecutive health complications.

Conflict of Interest

The authors declare no conflict of interest.

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