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Mini-Review

Teneligliptin- An Effective Dipeptidyl Peptidase – 4 Inhibitor In The Management Of Type 2 Diabetes Mellitus : An Overview

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ABSTRACT

Teneligliptin, a medication classified as a dipeptidyl peptidase-4 (DPP-4) inhibitor, has proven to be an efficient therapeutic choice in the management of type 2 diabetes mellitus. This overview discusses the pharmacological properties, efficacy, safety profile, and clinical use of teneligliptin in the management of T2DM.Teneligliptin functions by suppressing the degradation of incretin hormones, resulting in increased insulin secretion and reduced release of glucagon, thereby improving glycaemic control. Clinical studies have demonstrated its ability to lower HbA1c levels and enhance beta-cell function. Teneligliptin exhibits a favourable safety profile, with minimal risk of hypoglycaemia and well-tolerated adverse effects. Additionally, its once-daily dosing regimen and tolerability make it a valuable option for treating T2DM, potentially reducing the risk of complications associated with uncontrolled diabetes. Further research and trials in clinical settings are necessary to investigate its efficacy and safety over extended periods in various patient groups.

INTRODUCTION

Diabetes mellitus encompasses a group of metabolic disorders characterized by consistently elevated blood sugar levels due to deficiencies in insulin secretion, its effectiveness, or both. As insulin plays a crucial role as an anabolic hormone, abnormalities in the metabolism of proteins, lipids, and carbohydrates occur.[1]

Diabetes mellitus exists in three distinct types:

“Type 1 Diabetes”:

The immune system erroneously targets and eliminates the insulin-producing beta cells in the pancreas. Individuals with this condition need insulin injections to control blood sugar levels effectively.[2]

“Type 2 Diabetes”:

Diabetes type 2 is a common metabolic disease characterized by persistent high blood sugar levels. It is linked to a shortened lifespan due to an increased likelihood of heart disease, stroke,

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peripheral neuropathy, kidney issues, loss of vision, and limb amputation.[3]

"Gestational Diabetes":

Gestational diabetes mellitus (GDM) is the term used for any elevated blood sugar levels detected for the first-time during pregnancy. Additionally, GDM is linked to lipid irregularities, hypertension issues, and elevated insulin levels, serving as cardiometabolic risk factors that may contribute to the emergence of metabolic syndrome and cardiovascular disease.[4] Good results in individuals with diabetes are predicted by seven critical self-care activities. These include controlling blood sugar, monitoring blood pressure, adhering to drug regimens, maintaining a balanced diet, and engaging in risk reduction [5]. Raising public awareness, providing education, and offering support are vital in preventing and handling diabetes. Making lifestyle changes, like adopting a nutritious diet, staying physically active, and managing a healthy weight, are essential elements in both preventing and managing diabetes.[6]

PATHOPHYSIOLOGY OF TYPE 2 DIABETES MELITUS AN OVERVIEW

Peripheral insulin resistance, poor control over the synthesis of glucose in the liver, and a decline in β - cell function that ultimately results in β - cell failure are the hallmarks of the pathophysiology of type 2 diabetes mellitus.[7]

Damage to the kidneys, heart, nerves, eyes, and peripheral vascular system are just a few of the major, sometimes fatal consequences that can arise from uncontrolled hyperglycaemia.[8]

1. **Insulin Resistance:**

The desensitization of muscle to the insulin secreted by the pancreas to stimulate glucose uptake results in insulin resistance and high blood glucose levels.[9]

2. **Beta-Cell Dysfunction:**

Impaired Insulin Secretion: Over time, the beta cells in the pancreas that produce insulin may become dysfunctional. They are unable to secrete an adequate amount of insulin in response to elevated blood glucose levels.[10]

3. **Glucose Overproduction by the Liver:**

Unregulated Gluconeogenesis: The liver normally produces glucose through a process called gluconeogenesis. In T2DM, there is often excessive production of glucose by the liver, contributing to elevated blood sugar levels even in the fasting state.[11]

4. **Adipose Tissue Dysfunction:**

When adipose tissue doesn't function well due to obesity, it creates condition that promote inflammation, high lipid levels, and resistance to insulin. These factors play a role in causing type 2 diabetes mellitus (T2DM) [12]

5. **Genetic Predisposition:**

It is well known that type 2 diabetes runs in families and that a person's chance of getting the disease is influenced by both genetic and environmental factors. Nevertheless, heritability estimates have varied from 25% to 80% in various research;.[13]

6. **Environmental and Lifestyle Factors:**

Obesity and Sedentary Lifestyle: Excess adiposity, particularly abdominal obesity, and a lack of physical activity contribute significantly to the development and exacerbation of insulin resistance and T2DM. [14]

MANAGEMENT OF TYPE 2 DIABETES MELITUS:

Significant advancements have been made in the pharmacotherapy of diabetes, especially in type 2, diabetes mellitus in the last five years. A number of novel agents have made their way into clinical practice,[15]

Novel medication classes utilized in advanced therapy. More recent medication classes used to treat type 2 diabetes are:

a Alpha glucosidase inhibitors

b Amylin agonists

c Incretin mimetics (DPP-IV inhibitors and GLP-1agonists)

d Antagonists and inhibitors of SGLT2 [16]

ROLE OF DPP-4 IN TYPE – 2 DIABETES MELLITUS

In type 2 diabetes (DM 2), there's a decrease in GLP-1 secretion, contributing to the diminished "incretin effect" where the insulin response to oral glucose is more pronounced than intravenous delivery. DPP-4 inhibitors counteract this effect by hindering the enzyme responsible for breaking down incretin hormones, such as GLP-1 and GIP. Consequently, DPP-4 inhibitors prevent the proteolytic degradation and inactivation of GLP-1 and GIP [17]. DPP-4 inhibitors reduce the risk of hypoglycaemia and weight gain while effectively lowering fasting and post-meal plasma glucose levels, leading to a decreased HbA1c. [18]

TENELIGLIPTIN IN THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS:

Mitsubishi Tanabe Pharma Co developed the unique oral DPP-4 inhibitor teneligliptin, which was approved in September 2012 for the treatment of type 2 diabetes in Japan. Class 3 inhibitor teneligliptin demonstrated five times the activity of sitagliptin. Teneligliptin is a peptidomimetic drug with a distinct structure consisting of five successive rings. Teneligliptin works on the S2 extended subsite of DPP-4 as a result of its distinct structure, which increases its potency and selectivity.[19] As a competitive antagonist of DPP-4, teneligliptin, a third-generation DPP-4 inhibitor, reduces the breakdown of incretins, particularly GLP-1, which in turn stimulates insulin secretion and suppresses glucagon release in a glucose-dependent way.[20] Teneligliptin exhibits an ideal pharmacokinetic profile, rendering it a plausible medication for alternating-day administration. Teneligliptin has demonstrated anti-diabetic efficacy at a dosage as low as 10 mg. These methods can decrease costs and increase patient compliance and treatment satisfaction [21]

IMPACT OF TENELIGLIPTIN ON BLOOD GLUCOSE LEVELS

Dipeptidyl peptidase 4 (DPP-4) inhibitors work by boosting the body's natural ability to regulate blood glucose. They achieve this by elevating the active levels of incretin hormones, presenting a unique mechanism not found in other oral-glucose lowering medications. DPP-4 inhibitors primarily impact after-meal blood sugar levels, pose minimal risk of inducing hypoglycaemia, and are generally well-received, making them commonly prescribed for managing diabetes in older individuals.[22] Teneligliptin shows a good potential for achieving specific glycemic control in individuals with type 2 diabetes without extending the QT/QC interval.[23]

CLINICAL USE

Individuals with type 2 diabetes who are adults and have not improved with diet, exercise, or other drugs like sulfonylureas or thiazolidine to adequately control their condition are clinically treated with teneligliptin. The recommended oral dosage of teneligliptin is 20 mg once daily; if this dose is insufficient, it is increased to 40 mg once daily.[24]

UNIQUENESS OF TENELIGLIPTIN

The DPP-4 enzyme possesses multiple binding sites, including those found in the extended subunits of S1, S2, S1', S2'and S2. Teneligliptin exhibits superior DPP-4 enzyme binding among gliptins due to its notably rigid "J- shaped" structure composed of five rings, with four directly linked to DPP-44. The addition of the "anchor lock domain" to teneligliptin, binding specifically to the S2 extensive subsite, resulted in a 1500 – fold increase in its activity compared to a fragment that binds exclusively to both S1 and S2. While both sitagliptin and Teneligliptin, belonging to class 3, target the S2 extensive subunit, Teneligliptin demonstrates five times the efficacy of

sitagliptin.[25] Teneligliptin has a high tissue distribution and a decent oral bioavailability. The binding of plasma proteins ranged from 78-80% [26] Teneligliptin emerges as a favourable choice for treating type 2 diabetes, demonstrating sustained effectiveness and safety over an extended period. Its ability to enhance β-cell function and proficiently regulate blood glucose levels contribute to its appeal in managing the condition.[27]

DOSING AND ADMINISTATION

Teneligliptin belongs to the class of antihyperglycemic medications known as dipeptidyl peptidase-4 inhibitors, typically prescribed at a daily dose of 20 mg, the dosage can be increased to 40 mg per daily if required.[28] On escalating the dosage of teneligliptin in individuals with type 2 diabetes mellitus from 20 mg to 40 mg, the findings indicate that, after 3 months, there was no statically significant enhancement in glycaemic parameters. However, by the 6- month mark, there was a modest reduction in FBS and PPB, respectively, while HbA1c exhibited no change.[29]

COMBINATION THERAPY

DPP-4 inhibitors have become popular in treating type 2 diabetes mellitus patients, from young adults to the elderly, because of their ability to effectively lower glucose levels while posing minimal risk of hypoglycaemia.[30] The advantages of pairing the dipeptidyl peptidase-4 inhibitor teneligliptin with sodium-glucose co-transporter-2 inhibitor canagliflozin in diabetes management offers a synergistic approach. When used as a standalone treatment, SGLT-2 inhibitors were associated with an increased risk of hypoglycaemia. However, when combined with DPP-4 inhibitor, glucose variations in people with type 2 diabetes were reduced by combining the two medications, and there was no added risk of hypoglycaemia [31] Adding teneligliptin to the treatment of patients with type 2 diabetes, who have not achieved sufficient control with a combination of three oral medications, have shown positive outcomes in both effectiveness and safety.[32]

PHARMACOLOGICAL PROPERTIES OF TENELIGLIPTIN

The chemical structure of teneligliptin consist of five successive rings, a phenyl ring on the pyrazole, and an S2 extended subsite that increases its potency and sensitivity.[33] Teneligliptin demonstrated competitive, high selective, powerful, and long-lasting suppression of human and recombinant DPP-4 in both in vitro and in vivo experiments.[34]Teneligliptin enhances 24-hour blood glucose control by elevating active incretin levels, boosting early-phase insulin release, minimizing postprandial insulin needs, and decreasing glucagon secretion.[35]

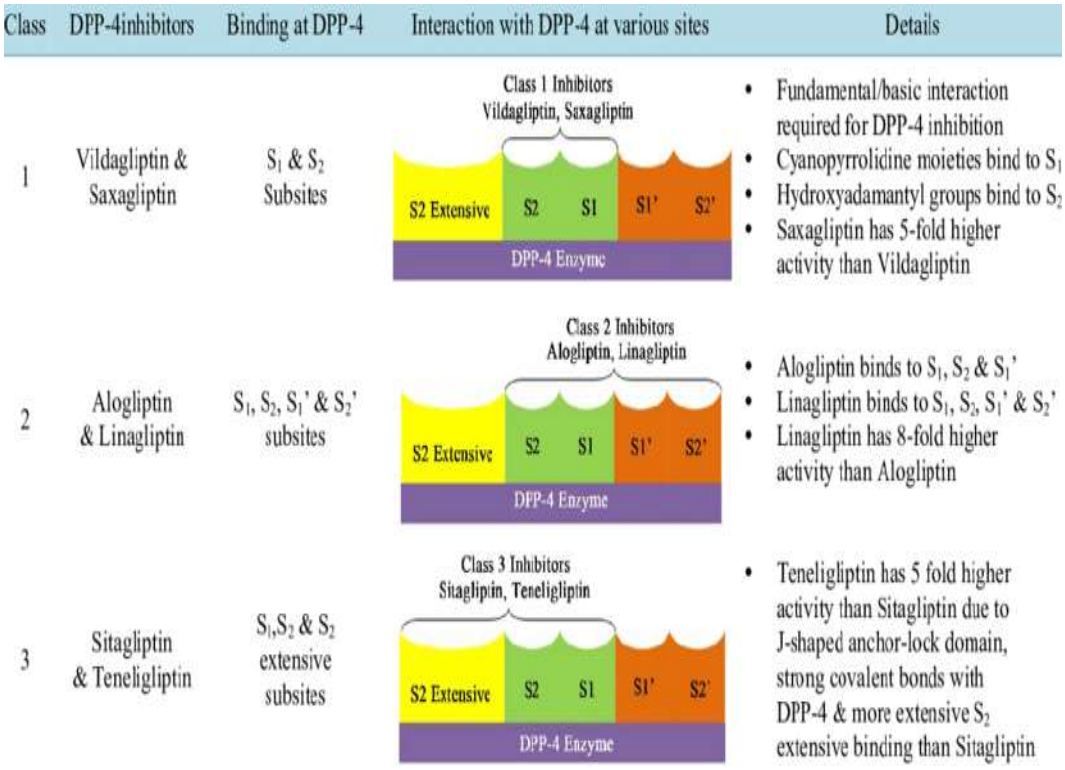

FIGURE 1: INTERACTION OF DPP-4 AT VARIOUS SITES [36]

According to an x-ray co-crystallography study, teneligliptin's potency, duration of action in vivo, and selectivity are all increased by the critical interaction between the phenyl ring the pyrazole and binding to the S2 extensive subsites anchor lock domain.[37]

IMPACT OF TENELIGLIPTIN IN LIPID PROFILE

A significant factor contributing to cardiovascular events is diabetes mellitus (DM). Diabetes and dyslipidaemia together increase the risk of cardiovascular events. Patients with diabetes suffer from postprandial hyperlipidaemia may benefit from teneligliptin medication. [38] On examining the impact of teneligliptin and atorvastatin impact in type 2 diabetes patients it was found that teneligliptin 20 mg and atorvastatin 20 mg have demonstrated comparable effectiveness in influencing lipid profiles.[39]

TENELIGLIPTIN IN RENAL SAFETY

The most frequent microvascular consequence linked to type 2 diabetes mellitus (T2DM)is diabetic nephropathy. It has been shown that over 45% of individuals receiving dialysis for renal failure have T2DM as a primary etiological cause.[40] pharmacokinetics of teneligliptin was compared in renally impaired and healthy subjects. In individuals with renal impairment or end-stage renal disease (ESRD), teneligliptin was generally well-tolerated.[41] In patients with any level of renal impairment, from normal to end-stage renal disease, including those on dialysis, teneligliptin was typically well tolerated over long-term treatment and improved glycaemic management.[42]

CONCLUSION

Teneligliptin, a dipeptidyl peptidase 4 inhibitor (DPP-4 inhibitor), has shown efficacy in managing type 2 diabetes mellitus (T2DM). It works by increasing insulin secretion and suppressing glucagon release, leading to improved glycaemic control. Clinical studies have demonstrated its ability to lower HbA1c levels and enhance beta-cell function. Additionally teneligliptin has a favourable safety profile with minimal side effects. Its once-daily dosing and tolerability make it a valuable option in the treatment of T2DM, contributing to better glucose regulation and potentially reducing the risk of complications associated with uncontrolled diabetes.

CONFLICT OF INTEREST:

I declare that there are no financial or non-financial competing interests during the conduct of review

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