Section A -Research paper

A review on glimepiride vs teneligliptin as a second line drug for the treatment of type 2 diabetes mellitus

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Abstract:

Type 2 diabetes mellitus (T2DM) is a condition caused by reduced insulin sensitivity. Those above the age of 45 have an increased risk of developing type 2 diabetes. Oral hypo-glycaemic agents are used to treat type 2 diabetes. Metformin is usually the initial therapy and if it is still insufficient, a second oral medication of a different class will be added. Whereas sulfonylureas and dipeptidyl peptidase-4 inhibitors are the most commonly used second-line drug categories for type 2 diabetes mellitus. Sulfonylureas are used to control hyperglycemia and the glycated haemoglobin A1C (HbA1c) levels can be lowered by 1% to 1.25% when using a sulfonylurea, making them just as effective as other options. Mainly glimepiride remains the most widely used sulfonylurea in type 2 diabetes mellitus. Glimepiride enhance glycemic control although glimepiride stimulates endogenous insulin secretion, causing hypoglycemia also causes weight gain, which might complicate diabetes therapy. DPP-4 is a widely distributed enzyme that regulates incretin hormones, which regulate glucose homeostasis by boosting insulin production and lowering glucagon secretion. When compared to other DPP-4 inhibitors, teneligliptin has a unique J-shaped or anchor-locked domain structure because of which it has a potent inhibitory effect on the DPP-4 enzyme and also has a low IC50, high potency, and fewer side effects. It is the only DPP-4 inhibitor with a prolonged half-life. Teneligliptin was found to improve blood glucose levels over a period of 24 hours such as reducing the postprandial insulin requirement, and reducing glucagon secretion. Thus, compared to glimepiride, teneligliptin is a better choice as a second-line drug for type 2 diabetes mellitus after metformin usage, irrespective of the patient's age and gender.

Keywords: Type 2 diabetes mellitus, sulfonylurea, dipeptidyl peptidase-4 inhibitors, glimepiride, teneligliptin

Introduction:

Around 90% of all instances of diabetes are due to type 2 diabetes mellitus (T2DM). Reduced insulin sensitivity characterises type 2 diabetes, a condition known as insulin resistance. Initially, an increase in insulin production is mounted to compensate for insulin resistance and keep glucose homeostasis stable, but this response eventually wears off, leaving the body vulnerable to the development of type 2 diabetes. Those above the age of 45 have an increased risk of developing type 2 diabetes. Yet, owing to increased rates of obesity, inactivity, and energy-dense meals, its prevalence among children, adolescents, and young adults is on the rise[1]. Common symptoms of diabetes mellitus include excessive thirst and urination, extreme weariness and weakness, susceptibility to infections from bacteria and fungi, and impaired wound healing. Patients may also experience blurred vision, numbness,

or tingling. Haemoglobin A1C or plasma glucose will be used to diagnose diabetes. Oral hypo-glycaemic agents are used to treat type 2 diabetes. Metformin is usually the initial therapy since it may reduce mortality[2,3,4]. If, after three months, metformin is still insufficient, a second oral medication of a different class will be added. Sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and glucagon-like peptide-1 (GLP-1) analogues are further groups of drugs used to treat diabetes[5]. Whereas sulfonylureas and dipeptidyl peptidase-4 inhibitors are the most commonly used second-line drug categories for type 2 diabetes mellitus. Thus, this review gets further narrowed down to a particular drug from each drug class, such as glimepiride (sulfonylurea) versus teneligliptin (dipeptidyl peptidase-4 inhibitors) as the best second-line drug for the treatment of type 2 diabetes mellitus.

Sulfonylurea

The first and foremost discovered sulfonylurea is carbutamide in 1942, as it has high side effects it has been failed to use. During 1960s several sulfonylureas were discovered as first generation and later with second generation. On consideration second generations are widely used now. Both the generations has same efficacy and safety[6].

Sulfonylureas stimulates pancreatic beta cells to secrete insulin and also reduces its hepatic clearance by blocking the inflow of potassium (K+) through the ATP-dependent channel: the flow of K+ within the β-cell goes to zero, the cell membrane becomes depolarized, thus removing the electric screen which prevents the diffusion of calcium into the cytosol. The increased flow of calcium into β-cells causes the contraction of the filaments of actomyosin responsible for the exocytosis of insulin, which is therefore promptly secreted in large amounts[6].

Sulfonylureas have a high rate of absorption. The absorption of glipizide is slowed down by meals. Ninety to ninety-nine percent of sulfonylureas are linked to proteins in the plasma. Chlorpropamide has the lowest affinity for plasma proteins, whereas glyburide has the highest affinity. The liver is responsible for metabolising sulfonylureas, and the metabolites are then eliminated in the urine. There is a significant amount of variety among first-generation sulfonylureas with regard to both their half-lives and the degree of their metabolism. Chlorpropamide has an inefficient metabolic pathway, which results in roughly 20% of the medication being excreted intact. This presents a challenge for individuals whose renal function is already compromised[7].

Based on their effectiveness in controlling diabetes, sulfonylureas are categorised into three groups: Acetohexamide, carbutamide, chlorpropamide, glycyclamide (tolcyclamide), metahexamide, tolazamide, and tolbutamide are a few examples of first-generation medications. A few of these are glibenclamide, glyburide, glibornuride, gliclazide[8], glipizide, gliquidone, glisoxepide, and glyclopyramide. Glimepiride is a third-generation medication, although occasionally being categorised as a second-generation drug[9,10].

Table 1- types of sulfonylurea

Sulfonylureas	Dose	Half life	Comments
Chlorpropamide	250mg	36 hours	It's a long acting first generation sulfonylurea derivative. It acts by increasing the secretion of insulin.
Glimepiride	0.5mg	5 - 9 hours	Its more rapid onset and longer acting second generation sulfonylurea derivative. It acts by stimulating less insulin secretion.

Glipizide	5mg	2 - 5 hours	It's an oral, rapid and short acting second generation sulfonylurea derivative. It acts by blocking potassium channel in the beta cells and remains depolarized which results in calcium influx. The increase in calcium will initiate more insulin release from beta cells.

Sulfonylureas are used to control hyperglycemia in type 2 diabetics who cannot achieve appropriate control with changes in diet and exercise alone[7]. The glycated haemoglobin A1C (HbA1c) levels can be lowered by 1% to 1.25% when using a sulfonylurea, making them just as effective as other options[11]. Despite better glycemic control in the short term, diabetes could worsen in the long term as sulfonylureas act directly on beta cells which may lead to destruction of beta cells of pancreas. The clinical result of this phenomenon is known as "secondary failure"[12].

Despite the large number of anti-diabetic agents available, however, sulfonylureas mainly glimepiride remains the most widely used drugs for treating patients with type 2 diabetes[13].

Glimepiride:

Glimepiride is a part of the pharmacological family known as second-generation sulfonylurea (SU), which was first made available in 1995. It is prescribed for the treatment of type 2 diabetes mellitus (T2DM), which aims to enhance glycemic control[6] and is also used as a second-line medication in combination therapy with metformin.

Like other sulfonylureas, glimepiride is an insulin secretagogue that works best in those who still have some functioning beta cells in their pancreas. Iatrogenic depolarization is induced by their blocking of potassium efflux via ATP-dependent potassium channels on the cell membrane of pancreatic beta cells. Increased intracellular calcium triggers insulin exocytosis into the circulation, and membrane voltage-dependent calcium channels are activated by the depolarization[14]. The action of insulin on cell membrane receptors results in the production of GLUT-4 and the uptake of glucose into the cell, hence reducing glucose levels in the blood. In addition, studies have demonstrated that glimepiride interacts with Epac3, a nucleotide exchanger that plays a role in mediating the exocytosis of insulin granules[15,16,17].

Glimepiride has a pharmacokinetics profile that is linear, which means that it is entirely absorbed after oral administration within one hour of administration[18]. The amount of glimepiride that is bound to proteins in plasma is more than 99.5%[19]. It has been stated that glimepiride is subject to hepatic metabolism. Whether glimepiride is administered intravenously or orally, the drug goes through an oxidative biotransformation that is mediated by the CYP2C9 enzyme. This biotransformation results in the formation of a major metabolite called cyclohexyl hydroxymethyl derivative (M1), which is pharmacologically active. One or more of the cytosolic enzymes may convert M1 into the inactive metabolite carboxyl derivative (M2) as a next step in the metabolic pathway. In an animal model, M1 maintained roughly one third of the pharmacologic activity of its parent, and its half-life ranged from three to six hours[6]. It is not quite obvious, however, whether or not the glucose-lowering impact of M1 is important on a clinical level. Around 65% of it is eliminated in the urine, while the remaining 35% is eliminated in the faeces[19].

Glimepiride's effect lasts far longer than that of glipizide, which is also a second-generation sulfonylurea medication. Due to the fact that it has a greater number of substitutions than other SUs of the second generation, it is frequently referred to as a third-generation

sulfonylurea. It has been shown to be successful in lowering levels of glycosylated haemoglobin, fasting plasma glucose, and postprandial glucose and is regarded as a beneficial and cost-effective therapy choice for the management of type 2 diabetes mellitus[18].

Although glimepiride stimulates endogenous insulin secretion, causing hypoglycemia. Hypoglycemic unawareness may cause neuroglycopenia and hypoglycemic coma in long-term diabetics. If additional hypoglycemic agents are used, drivers and skilled workers are at risk. Sulfonylureas like glimepiride can cause weight gain, which might complicate diabetes therapy as weight reduction is a goal. Additional potentially dangerous side effects include nausea, vomiting, stomach discomfort, diarrhoea, Stevens-Johnson syndrome, and erythroderma[6,18]. Nevertheless, in comparison to the incidences of adverse effects related with other sulfonylureas, those connected with glimepiride are typically lower[18].

Dipeptidyl peptidase-4 inhibitor (Dpp- 4 inhibitor):

DPP-4 inhibitors are generally effective at inhibiting DPP-4, and under clinical circumstances, DPP-4 is inhibited by >80-90%. This inhibition causes a 2-3-fold increase in post-prandial GLP-1 plasma concentrations, which mediates the glucose-dependent stimulation of insulin secretion and suppression of glucagon secretion[20,21]. Apart from this "endocrine" impact, DPP-4 inhibitors' local inhibitory effect on GLP-1 breakdown in the intestinal mucosa may help to beneficial metabolic control by activating the autonomic afferent neural system[20,21]. DPP-4 inhibitors can reduce the HbA1c percentage by 0.5-1 unit. The decrease in HbA1c, like with other antihyperglycemic medicines, is mostly determined by the patient group observed, the baseline glycemic status at the start of the observation, and the concomitant therapy, including lifestyle modification[21,22,23,24].

DPP-4 is a widely distributed enzyme that regulates incretin hormones, primarily GIP (gastric inhibitory peptide and GLP-1 (glucagon-like peptide-1), which regulate glucose homeostasis by boosting insulin production and lowering glucagon secretion[25]. GLP-1 is a hormone released by enteroendocrine L cells which is present in the small intestine that decreases blood glucose by boosting insulin production, decreasing glucagon concentrations, and prolonging stomach emptying[26].

A study of sitagliptin oral and IV delivery in healthy volunteers found that the oral dosage was approximately 87% bioavailable. When compared to fasting levels, eating a high-fat meal had no effect on the agent's bioavailability, maximum plasma concentration (Cmax), or half-life[27]. Studies comparing fed and fasted states in plasma area-under-the-curve (AUC) concentrations of sitagliptin and saxagliptin found a 20% and 27% elevation when the medications were taken with a meal, respectively[28,29]. The distribution of sitagliptin and saxagliptin is usually influenced by a number of variables, including plasma protein binding. These medicines have a modest affinity for serum proteins. Illness conditions that modify protein levels are therefore unlikely to cause large differences in the disposition of these drugs[28,30]. Metabolism is predominantly handled by the cytochrome P450 (CYP 450) 3A4/5 pathway, as a result, inhibitors and inducers of this pathway are predicted to alter the drug concentrations[28]. Oral dosages of DPP4 inhibitors are eliminated via renal and hepatic routes. Sitagliptin has a terminal half-life of roughly 12.4 hours, compared to saxagliptin with a half-life life of 2.5 hours and metabolite has 3.1 hours[28,30].

Table 2 – Types of dipeptidyl peptidase-4 inhibitor

DPP IV inhibitors	Dose	Half life	Comments
Sitagliptin	50mg	8 - 14 hours	It increases glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP) concentration and prolonged action of these hormones. 76-87% is excreted in urine whereas 13-15% is excreted in feces
Vidagliptin	50mg	1.32 - 2.43 hours	It acts by degrading two major incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP) in small intestine. As a result glucagon-like peptide-1 (GLP-1) levels are increased in the blood stream and its actions prolonged. 76-87% is excreted in urine whereas 13-15% is excreted in feces
Saxagliptin	2.5mg	13 hours	It increases the concentration of incretin hormones. These hormones are inactivated by dipeptidyl peptidase -4 inhibitors within minutes. Saxagliptin slows the inactivation of the incretin hormones. 76-87% is excreted in urine whereas 13-15% is excreted in feces
Teneligliptin	20mg	24.4 hours	Anchor lock domain which binds to the S2 extensive subset gives higher potency and selectivity. 45.4% is excreted in urine and 46.5% is excreted in feces

When compared to other DPP-4 inhibitors, teneligliptin has a unique J-shaped or anchor-locked domain structure because of which it has a potent inhibitory effect on the DPP-4 enzyme[31] and also has a low IC50, high potency, and fewer side effects. It is the only DPP-4 inhibitor with a prolonged half-life[32].

Teneligliptin:

Teneligliptin is an inhibitor of dipeptidyl peptidase-4 that belongs to the third generation and was first created by Mitsubishi Tanabe Pharma Company [33], which was authorised for the treatment of T2DM in Japan in September 2012[34]. It is presently accessible in Japan, India, Argentina and South Korea[35].

Teneligliptin has a very rigid "J-shaped" structure, which is formed by five rings. Four of these rings are directly attached to DPP-4, which results in the highest binding to DPP-4 enzymes when compared to other gliptins[35]. Since plasma DPP-4 activity dropped by a large amount after switching to teneligliptin, it is possible that teneligliptin is a stronger DPP-4 inhibitor than other drugs. Teneligliptin binds to the DPP-4 enzyme's S1, S2, and S2 extensive subsites. This makes the drug more effective and selective. In addition, when teneligliptin is bound to the S2 extensive site in addition to the S1 and S2 sites, a more potent inhibitory effect is bestowed upon the DPP-4 enzyme. Furthermore, teneligliptin was shown to have the J-shaped anchor-lock domain, strong covalent connections with DPP-4, and more widespread S2 extensive binding, all of which demonstrated that it has a stronger inhibitory action[34,36,37].

A meal triggers the release of glucagon-like peptide-1 (GLP-1) from the alimentary canal, which encourages pancreatic insulin production and controls glucagon secretion to manage blood sugar levels after meals. By decreasing the activity of dipeptidyl peptidase-4 (DPP-4) and thus raising the blood levels of active GLP-1, teneligliptin has a hypoglycemic effect by preventing GLP-1 from being degraded[38].

Teneligliptin has a quick absorption rate in healthy volunteers following a single 20 mg dosage, with maximal plasma concentrations being reached in 1.33 hours. Between 78% and 80% of the medication is bound to the proteins in the plasma[35]. Teneligliptin is largely metabolised in humans by cytochrome P450 (CYP) 3A4 and flavin monooxygenases (FMO) 1 and 3, which results in the production of a number of metabolites with unclear biological activity[35,39]. After a single dosage of 20 mg radiolabelled teneligliptin, the most abundant metabolite is a thiazolidine-1-oxide derivative that has been classified as M1. This thiazolidine-1-oxide derivative accounts for 14.7% of the AUC total radioactivity[40]. At least 90 percent of the dosage was eliminated from the body after 216 hours, with 45.4% of it being eliminated via the urine and 46.6% through the faeces[41].

Teneligliptin indicated for the managing type 2 diabetes mellitus along with diet and exercise[37]. Teneligliptin was found to improve blood glucose levels over a period of 24 hours by increasing active incretin levels and early-phase insulin secretion, reducing the postprandial insulin requirement, and reducing glucagon secretion. The researchers who conducted the study came to the conclusion that even short-term treatment with teneligliptin may offer benefits to patients who suffer from type 2 diabetes. Most notably, there is no need to change the dosage of teneligliptin for patients with type 2 diabetes (T2D) who have renal impairment or even end-stage renal disease since it is efficacious and well tolerated by these people[42]. Thus, Teneligliptin was regarded as well tolerated and manageable in Type 2 diabetes mellitus[37].

Another study has reported that the postprandial blood glucose-lowering effects of teneligliptin administered prior to breakfast were sustained throughout the day, and the effects observed after dinner were similar to those observed after breakfast or lunch. Thus, although clinical data for this new drug are limited, this drug shows promise in stabilizing glycaemic fluctuations throughout the day and consequently suppressing the progression of diabetic complications[34].

The usage of teneligliptin was not linked to an elevated risk of cardiovascular events, including all-cause mortality, heart failure, or atherothrombotic events. In addition, when compared to sulfonylureas, teneligliptin was shown to be related with a reduced likelihood of hypoglycemia[43].

Conclusion:

The most prevalent endocrine illness and a major contributor to death and morbidity is type 2 diabetes mellitus. In order to effectively treat patients with type 2 diabetes mellitus, it is crucial to choose the right second-line medications. Generally, metformin is the first-line treatment, and the second-line medicine is selected from different anti-diabetic drug groups. This review has discussed glimepiride against teneligliptin as a second-line therapy for type 2 diabetes mellitus. It has been shown that both drugs have an effective role in improving glycaemic levels. Whereas teneligliptin has shown to have more benefits, such as it significantly controls glycaemic parameters in a shorter period with safety, enhances weight loss, and no dose adjustment is required in renally impaired diabetes patients. Thus, compared to glimepiride, teneligliptin is a better choice as a second-line drug for type 2 diabetes mellitus after metformin usage, irrespective of the patient's age and gender.

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