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Review Article

Comparing Vildagliptin SR 100mg and Teneligliptin 20mg in Type 2 Diabetes Study

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Abstract

Diabetes Mellitus is an entity of considerable morbidity comprising a spectrum of multisystem dysfunctions stemming from the combination of insulin resistance and inadequate insulinsecretion. Management of diabetes, akin to a tightrope walk, requires a comprehensive understanding of various factors such as over-all clinical picture, adverse effect profile, the complex of inter-play of drugs, etc. More than two-thirds of people with type 2 diabetes will eventually require more than one oral agent, with or without insulin. Diabetes is emerging as a global epidemic, imposing enormous humanitarian and economic burdens on society. According to a WHO projection, by 2030, approximately 190 million people will be affected in the Asia-Pacific region alone. Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. Evidence suggests that patients with type 2 diabetes mellitus (T2DM) increasingly require multiple pharmacological combinations to reach treatment goals. Clinical inertia, with failure to advance therapy despite persistently elevated HbA1c levels above target, has become a major problem for the stepwise approach to treatment. Initial combination therapy using two oral anti-diabetic drugs (OAD) with complementary mechanisms of action is an alternative approach that may provide better or more sustained glycemic control. It may also allow the useof lower doses of the component OADs and thus minimize any dose-related adverse events (AEs). Vildagliptin is a selective and reversible inhibitor of Dipeptidyl peptidase 4 (DPP-4), the enzyme which inactivates the incretin hormones, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP), hormones which significantly contribute to the maintenance of glucose homeostasis. Vildagliptin improved glycaemic control when given as monotherapy or when used in combination with Metformin, a sulphonylurea, and a thiazolidinedione, as measured by clinically relevant reductions in HbA1c from baseline at study endpoint. In clinical trials, the magnitude of HbA1c reductions with Vildagliptin was greater in patients with higher baseline HbA1c.

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycaemia. It may be due to impaired insulin secretion, resistance to peripheral actions of insulin, or both. Chronic hyperglycaemia in synergy with the other metabolic aberrations in diabetic patients can cause damage to various organ systems, leading to the development of disabling and life-threatening health complications, most prominent of which are microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications leading to a 2-fold to a 4-fold increased risk of cardiovascular diseases. [1] DM is broadly classified into 3 types by etiology and clinical presentation, type 1 diabetes, type 2 diabetes, and gestational diabetes (GDM). Some other less common types of diabetes include monogenic diabetes and secondary diabetes.

Type 1 Diabetes Mellitus (T1DM)

Type 1 diabetes mellitus (T1DM) accounts for 5% to 10% of DM and is characterized by autoimmune destruction of insulin-producing beta cells in the islets of the pancreas. As aresult, there is an absolute deficiency of insulin. A combination of genetic susceptivity and environmental factors such as viral infection, toxins, or some dietary factors has been implicated as triggers for autoimmunity. T1DM is most commonly seen in children and adolescents though it can develop at any age.

Type 2 Diabetes Mellitus (T2DM)

Type 2 diabetes mellitus (T2DM) accounts for around 90% of all cases of diabetes. In T2DM, the response to insulin is diminished, and this is defined as insulin resistance. During this state, insulin is ineffective and is initially countered by an increase in insulin production to maintain glucose homeostasis, but over time, insulin production decreases resulting in T2DM. T2DM is most commonly seen in persons older than 45 years, but it is increasingly seen in children, adolescents, and younger adults due to rising levels of obesity, physical inactivity, and energy- dense diets.

Gestational Diabetes Mellitus

Hyperglycaemia which is first detected during pregnancy is classified as gestational diabetes mellitus (GDM), also known as hyperglycaemia in pregnancy. Although it can occur anytime during pregnancy, GDM generally affects pregnant women during the second and third trimesters. According to American Diabetes Association (ADA), GDM complicates 7% of all pregnancies. Women with GDM and their offspring have an increased risk of developing type 2 diabetes mellitus in the future.

GDM can be complicated by hypertension, preeclampsia, and hydramnios and may also lead to increased operative interventions. The foetus can have increased weight and size (macrosomia) or congenital anomalies. Even after birth, such infants may have respiratory distress syndrome, and subsequent childhood and adolescent obesity. Older age, obesity, excessive gestational weight gain, history of congenital anomalies in previous children, or stillbirth, or a family history of diabetes are risk factors for GDM.

Monogenic Diabetes

A single genetic mutation in an autosomal dominant gene causes this type of diabetes. Examples of monogenic diabetes include conditions like neonatal diabetes mellitus and maturity-onset diabetes of the young (MODY). Around 1% to 5% of all diabetes cases are due to monogenic diabetes. MODY is familial disorder and usually presents under age of 25 years.

Secondary Diabetes

Secondary diabetes is caused due to the complication of other diseases affecting pancreas (for example, pancreatitis), hormone disturbances (for example, Cushing's disease), or due to drugs (for example, corticosteroids). [1]

Epidemiology

Diabetes is a worldwide epidemic. With changing lifestyle and increasing obesity, the prevalence of DM has increased worldwide. The worldwide prevalence of DM was 425 million in 2017. According to International Diabetes Federation (IDF), in 2015, about 10% of the American population had diabetes. Of these, 7 million were undiagnosed. With an increase in age, the prevalence of DM also increases. About 25% of the population above 65 years of age has diabetes. [1]

Diabetes is a growing challenge in India with estimated 8.7% diabetic population in the age group of 20 and 70 years. The rising prevalence of diabetes and other noncommunicable diseases is driven by a combination of factors - rapid urbanization, sedentary lifestyles, unhealthy diets, tobacco use, and increasing life expectancy. [3]

Over 30 million have now been diagnosed with diabetes in India. The CPR (Crude prevalence rate) in the urban areas of India is thought to be 9 per cent. In rural areas, the prevalence is approximately 3 per cent of the total population. The population of India is now more than 1000 million: this helps to give an idea of the scale of the problem. The estimate of the actual number of diabetics in India is around 40 million. This means that India actually has the highest number of diabetics of any one country in the entire world. IGT (Impaired Glucose Tolerance) is also a mounting problem in India. The prevalence of IGT is thought to be around

8.7 per cent in urban areas and 7.9 per cent in rural areas, although this estimate may be too high. It is thought that around 35 per cent of IGT sufferers go on to develop type 2 diabetes, so India is genuinely facing a healthcare crisis. In India, the type of diabetes differs considerably from that in the Western world. [4]

Pathophysiology

T2DM is an insulin-resistance condition with associated beta cell dysfunction. Initially, there is a compensatory increase in insulin secretion which maintains glucose levels in normal range. As the condition progresses, beta cells change, and the insulin secretion is unable to maintain glucose homeostasis, producing hyperglycaemia. Most of the patients with T2DM are obese or have higher body fat percentage, distributed predominantly in the abdominal region.

This adipose tissue itself promotes insulin resistance through various inflammatory mechanisms including increased FFA (free fatty acids) release and adipokine dysregulation. Lack of physical activity, prior GDM in those with hypertension, or dyslipidaemia also increase the risk of developing T2DM. Evolving data suggest a role for adipokine dysregulation, inflammation, abnormal incretin biology with decreased incretins such as glucagon-like peptide-1 (GLP-I) or incretin resistance, hyperglucagonemia, increased renal

glucose reabsorption and abnormalities in gut microbiota. [1]

Diagnosis: The clinical diagnosis of diabetics is often prompted by symptoms such as increased thirst andurination and recurrent infections.

Blood Tests - Fasting plasma glucose, two-hour postprandial test and oral glucose tolerance test are done to know blood glucose levels.

Management

Through lifestyle and diet modification. Studies have shown that there was significant reduction in the incidence of type 2 DM with a combination of maintenance of body massindex of 25 kg/m2, eating high fibre and unsaturated fat and diet low in saturated and trans-fats and glycaemic index, regular exercise, abstinence from smoking and moderate consumption of alcohol.

Suggesting that majority of type 2 DM can be prevented by lifestyle modification. Patients with type 2 DM should receive a medical nutrition evaluation; lifestyle recommendations should be tailored according to physical and functional ability. [6]

Treatment

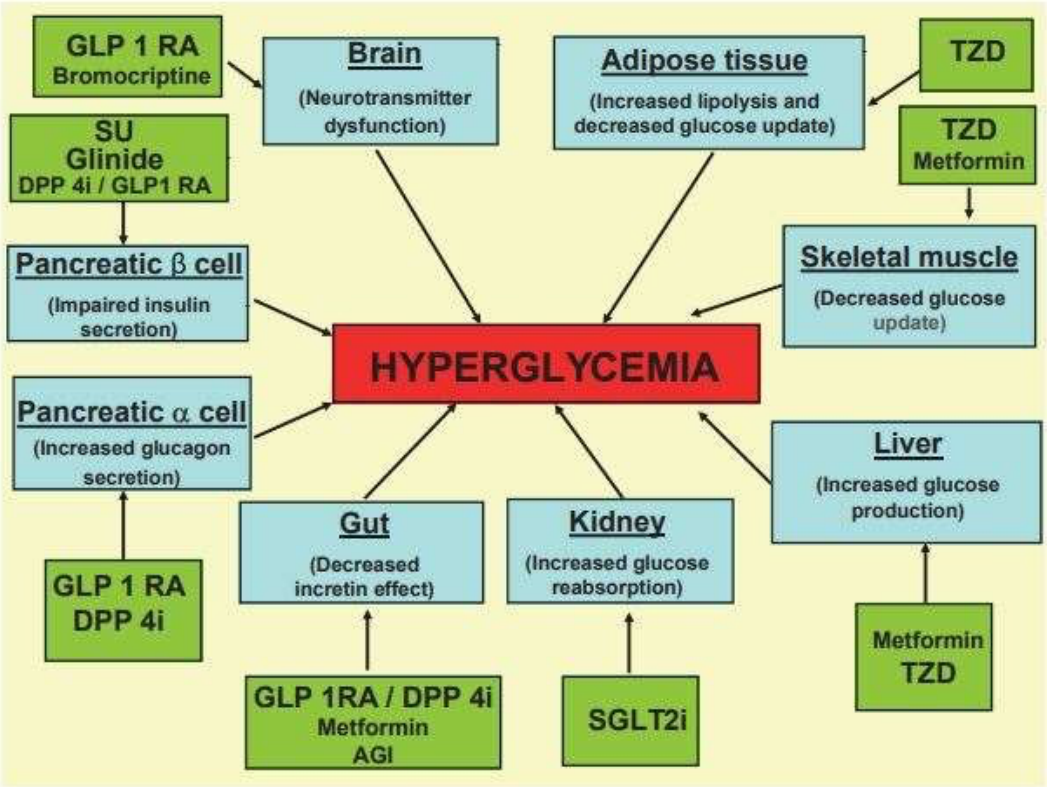

Diagram 1: Mechanism of action of Anti-Hyperglycaemic drugs

SU- Sulfonylureas; DPP4i- Dipeptidyl peptidase-4 inhibitors (Gliptins); GLP-1RA- Glucagon-like peptide-1 receptor agonists; TZD- Thiazolidinediones (Glitazones); AGI- Alpha-glucosidase inhibitor; Glinide- Non- sulphonyl urea insulin secretagogue (Repaglinide and Nateglinide); SGLT2i- Sodium-glucose cotransporter-2 inhibitor [5]

Biguanides

Biguanides, of which Metformin is the most commonly used in overweight and obese patients, suppresses hepatic glucose production, increases insulin sensitivity, enhances glucose uptake by phosphorylating GLUT-enhancer factor, increases fatty acid oxidation, and decreases the absorption of glucose from the gastrointestinal tract. Research published in 2008 shows further mechanism of action of Metformin as activation of AMP-activated protein kinase, an enzyme that plays a role in the expression of hepatic gluconeogenic genes. Due to the concern of development of lactic acidosis, Metformin should be used with caution in elderly diabetic individuals with renal impairment. [9] It has a low incidence of hypoglycaemia compared to sulfonylureas.

Sulfonylureas

These generally well tolerated but because they stimulate endogenous insulin secretion, they carry a risk of hypoglycaemia. Elderly patients, with DM who are treated with sulfonylureas have a 36%

increased risk of hypoglycaemia compared to younger patients. Glyburide is associated with higher rates of hypoglycaemia compared to glipizide. [10] Some of the risk factors for hypoglycaemia are age-related impaired renal function, simultaneous use of insulin or insulin sensitizers, age greater than 60 years, recent hospital discharge, alcohol abuse, caloric restriction, multiple medications or medications that potentiate sulfonylurea actions. Use of long acting sulfonylurea such as glyburide should be avoided in elderly patients with DM and use of short-acting glipizide should be preferred.

Meglitinides

Repaglinide and Nateglinide are non-sulfonylurea secretagogues which act on the ATP- dependent K-channel in the pancreatic beta cells thereby stimulating the release of insulin fromthe beta cells, similar to sulfonylurea, though the binding site is different. Meglitinides have a rapid onset and a short duration of action (4-6 hrs) and thus lower risk of hypoglycaemia. Meglitinides are given before meals for postprandial blood glucose control. Pre-prandial administration allows flexibility in case a meal is missed without increased risk of hypoglycaemia. Repaglinide is mainly metabolized in the liver with very minimal amounts excreted via the kidneys and thus dose adjustment is not necessary in patients with renal insufficiency except those with end-stage renal disease. [11]

Thiazolidinediones

Thiazolidinedione is an insulin sensitizer, selective ligands transcription factor peroxisomes proliferator-activated gamma. They are the first drugs to address the basic problem of insulin resistance in type 2 DM patients, whose class now includes mainly Pioglitazone after the restricted use of Rosiglitazone recommended by Food and Drug Administration (FDA) recently due to increased cardiovascular events reported with rosiglitazone. Pioglitazone use is not associated with hypoglycaemia and can be used in cases of renal impairment and thus well tolerated in older adults. On the other hand, due to concerns regarding peripheral oedema, fluid retention and fracture risk in women, its use can be limited in older adults with DM. Pioglitazone should be avoided in elderly patients with congestive heart failure and is contraindicated in patients with class III-IV heart failure. [12]

Alpha-Glucosidase Inhibitors

Acarbose, Voglibose and Miglitol have not widely been used to treat type 2 DM individuals but are likely to be safe and effective. These agents are most effective for postprandial hyperglycaemia and should be avoided in patients with significant renal impairment. Their use is usually limited due to high rates of side-effects such as diarrhoea and flatulence. Voglibose, which is the newest of the drugs, has been shown in a study to significantly improve glucose tolerance, in terms of delayed disease progression and in the number of patients who achieved normoglycemia. [13]

Incretin-Based Therapies

Glucagon-like peptide 1 (GLP-1) analogues are the foundation of incretin-based therapies which are to target this previously unrecognized feature of DM pathophysiology resulting in sustained improvements in glycaemic control and improved body weight control. They are available for use as monotherapy, as an adjunct to diet and exercise or in combination with oral hypoglycaemic agents in adults with type 2 DM. Examples are Exenatide, an incretin mimetic, and Liraglutide. [14]

There is no risk of hypoglycaemia with the use of GLP-1 therapies (unless combined with insulin secretagogues). In addition, emerging evidence suggests incretin-based therapies may have a positive impact on inflammation, cardiovascular and hepatic health, sleep, and the central nervous system.

Dipeptidyl-Peptidase IV Inhibitors

Dipeptidyl-peptidase (DPP) IV inhibitors inhibit dipeptidyl peptidase-4 (DPP-4), a ubiquitous enzyme that rapidly inactivates both GLP-1 and GIP, increase active levels of these hormones and, in doing so, improves islet function and glycaemic control in type 2 DM. DPP-4 inhibitors are a new class of anti-diabetogenic drugs that provide comparable efficacy to current treatments.

They are effective as monotherapy in patients inadequately controlled with diet and exercise and as add-on therapy in combination with Metformin, Thiazolidinediones, and Insulin. The DPP-4 inhibitors are well tolerated, carry a low risk of producing hypoglycaemia and are weight neutral. However, they are relatively expensive. [15] The long-term durability of effect on glycaemic control and beta-cell morphology and function remain to be established.

Complications

The complications of diabetes mellitus are less common and less severe in people who havewell-controlled blood sugar levels. Its complications are:

Acute:

Diabetic ketoacidosis (DKA): It is an intense and dangerous complication that can always result in a medical emergency. It is generally seen due to low insulin levels which may cause the liver to turn fatty acid to ketone for fuel as ketone bodies are intermediate substrates in that metabolic sequence.

This is a normal condition if occurs periodically, but can become a serious problem if sustained. Elevated levels of ketone bodies in the blood decrease the blood's pH leading to DKA. [16] The patient with DKA is typically dehydrated and breathing rapidly and deeply. Abdominal pain is common and may be severe.

Hyperglycaemia: Hyperglycaemia is another acute complication. If a person has very high (usually considered to be above 300 mg/dl (16 mmol/L)) blood glucose levels, water is osmotically drawn out of cells into the blood and the kidneys eventually begin to dump glucose into the urine. This results in loss of water and an increase in blood osmolarity. [17] If fluid is not replaced (by mouth or intravenously) the osmotic effect of high glucose levels combined with the loss of water will eventually lead to dehydration. The body's cells become progressively dehydrated as water is taken from them and excreted. Electrolyte imbalances are also common and can be very dangerous.

Hypoglycaemia: Hypoglycaemia or abnormally low blood glucose is an acute complication of several diabetes treatments. It is rare otherwise, either in diabetic or non-diabetic patients. The patient may become agitated, sweaty, weak, and have many symptoms of sympathetic activation of the autonomic nervous system resulting in feelings akin to dread and immobilizedpanic.

Drug Name: Vildagliptin

Mechanism of Action

Vildagliptin inhibits dipeptidyl peptidase-4 (DPP-4). This in turn inhibits the inactivation of GLP-1 by DPP-4, allowing GLP-1 to potentiate the secretion of insulin in the beta cells. Dipeptidyl peptidase-4's role in blood glucose regulation is thought to be through degradation of GIP and the degradation of GLP-1. [8]

Preclinical Pharmacology

In vivo primary pharmacodynamics studies were conducted in mice, rats, and monkeys by the oral route. Vildagliptin inhibited plasma DPP-4 activity resulting in increased GLP-1 and insulin levels and corresponding decreases in plasma glucose following glucose challenge. Vildagliptin reduced glycated haemoglobin A1c (HbA1c) levels in diabetic monkeys, which indicated the potential for sustained glucose-lowering efficacy. Dose levels in rats resulting in maximal pharmacological activity corresponded to exposures similar to those expected in humans receiving the maximum proposed dose.

Preclinical Toxicology

Intra-cardiac impulse conduction delays were observed in dogs with a no-effect dose of 15 mg/kg (7-fold human exposure based on C_{max}).

Accumulation of foamy alveolar macrophages in the lung was observed in rats and mice. The no-effect dose in rats was 25 mg/kg (5-fold human exposure based on AUC) and in mice 750 mg/kg (142-fold human exposure). [18]

Gastrointestinal symptoms, particularly soft faeces, mucoid faeces, diarrhoea and, at higher doses, faecal blood were observed in dogs. A no-effect level was not established.

Vildagliptin was not mutagenic in conventional in vitro and in vivo tests for genotoxicity.

Drug Name: Teneligliptin

Mechanism of Action

Teneligliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by Teneligliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose- dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. [19] These hormones are rapidly inactivated by the enzyme, DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, Teneligliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. [20]

Preclinical Pharmacology

Compound 8g (HBr salt) was administered orally to Wistar rats at a dose of 0.03, 0.1, 0.3 or 1 mg/kg and the plasma DPP-4 activity was evaluated ex vivo. 8g indicated dose-dependent, fast-onset and long-lasting DPP-4 inhibitory activity. It is most noteworthy that more than 50%inhibition of plasma DPP-4 level was sustained at a single oral dose of 1 mg/kg until 24 h. Compound 8g was assessed for its ability to improve glucose tolerance in Zucker fatty rats. Pretreatment with compound 8g at the doses from 0.03 mg/kg to 1 mg/kg 30 min before glucose challenge (1 g/kg) inhibited the increase in glucose levels in an oral glucose tolerance test. The treatment with compound 8g significantly lowered the delta AUC(0–60min) and the maximum increase in glucose levels in Zucker fatty rats. Near

normalization of the glucose excursion relative to lean controls was seen following a 0.03 mg/kg oral dose of compound 8g and the significant improvements were observed at more than 35% of DPP-4 inhibition in compared to pre-dosing. These ex vivo and in vivo studies in rats suggest that once-daily and lower dosing of compound 8g is expected to keep proper blood glucose without causing hypoglycemia in humans. [21]

Preclinical Toxicology

In the single-dose study in which Teneligliptin (0 [vehicle], 1000, 2000 mg/kg) was administered orally to Wistar rats (5 each of males and females per group), 1 male in the 2000 mg/kg group showed a hunched position, decreased response, slowing of respiration, etc., and was sacrificed moribund and necropsied on Day 6 of administration. [22] Therefore, the approximate lethal dose in rats was determined to be 2000 mg/kg. In the oral dose titration study in cynomolgus monkeys (1 each of male and female), vomiting, salivation, and eyelid closure (female only) were observed after 1000 mg/kg administration, and severe convulsion occurred in the male from 22 minutes after 2000 mg/kg administration, and the animal was sacrificed moribund at 30 minutes after administration and necropsied. From these results, the approximate lethal dose of Teneligliptin in cynomolgus monkeys was determined to be 2000 mg/kg, and administration of Teneligliptin 2000 mg/kg in the female was therefore cancelled.

Literature Review:

Clinical Studies: Vildagliptin

More than 15,000 patients with type 2 diabetes participated in double-blind placebo- or active controlled clinical trials of up to more than 2 years' treatment duration. In these studies,

Vildagliptin was administered to more than 9,000 patients at daily doses of 50 mg once daily, 50 mg twice daily or 100 mg once daily. More than 5,000 male and more than 4,000 female patients received Vildagliptin 50 mg once daily or 100 mg daily. [23] More than 1,900 patients receiving Vildagliptin 50 mg once daily or 100 mg daily were ≥ 65 years. In these trials, Vildagliptin was administered as monotherapy in drug naïve patients with type 2 diabetes or in combination in patients not adequately controlled by other antidiabetic medicinal products.

Overall, Vildagliptin improved glycaemic control when given as monotherapy or when used in combination with metformin, a sulphonylurea, and a thiazolidinedione, as measured by clinically relevant reductions in HbA1c from baseline at study endpoint.

In clinical trials, the magnitude of HbA1c reductions with Vildagliptin was greater in patients with higher baseline HbA1c.

In a 52-week double-blind controlled trial, Vildagliptin (50 mg twice daily) reduced baseline HbA1c by -1% compared to -1.6% for Metformin (titrated to 2 g/day) statistical non-inferiority was not achieved. Patients treated with Vildagliptin reported significantly lower incidences of gastrointestinal adverse reactions versus those treated with Metformin.

In a 24-week double-blind controlled trial, Vildagliptin (50 mg twice daily) was compared to Rosiglitazone (8 mg once daily). Mean reductions were -1.20% with Vildagliptin and -1.48% with Rosiglitazone in patients with mean baseline HbA1c of 8.7%. Patients receiving Rosiglitazone experienced a mean increase in weight (+1.6 kg) while those receiving Vildagliptin experienced no weight gain (-0.3 kg). The incidence of peripheral oedema was lower in the Vildagliptin group than in the Rosiglitazone group (2.1% vs. 4.1% respectively).

In a clinical trial of 2 years' duration, Vildagliptin (50 mg twice daily) was compared to Gliclazide (up to 320 mg/day). After two years, mean reduction in HbA1c was -0.5% for Vildagliptin and -0.6% for Gliclazide, from a mean baseline HbA1c of 8.6%. Statistical non- inferiority was not achieved. Vildagliptin was associated with fewer hypoglycaemic events (0.7%) than Gliclazide (1.7%).

In a 24-week trial, Vildagliptin (50 mg twice daily) was compared to Pioglitazone (30 mg once daily) in patients inadequately controlled with Metformin (mean daily dose: 2020 mg). Mean reductions from baseline HbA1c of 8.4% were -0.9% with Vildagliptin added to Metformin and -1.0% with Pioglitazone added to Metformin. A mean weight gain of +1.9 kg was observed in patients receiving Pioglitazone added to Metformin compared to +0.3 kg in those receiving Vildagliptin added to Metformin.

Clinical Studies: Teneligliptin:

Efficacy and Safety of Teneligliptin in Indian Patients with Inadequately Controlled Type 2 Diabetes Mellitus: A Randomized, Double-blind Study

Aims: This study evaluated the efficacy and safety of Teneligliptin in patients with inadequately controlled type 2 diabetes mellitus (T2DM).

Settings and Design: This was a randomized, doubleblind, placebocontrolled, parallelgroup, multicenter, Phase III study.

Subjects and Methods: Patients with T2DM and

inadequate glycemic control (glycosylated hemoglobin [HbA1c]: >7.0-≤8.5%) were enrolled. Patients were randomly assigned (ratio: 2:1) to receive Teneligliptin 20 mg (Glenmark) or placebo. The primary efficacy variable was change from baseline in HbA1c at week 16. Additional analyses included the proportion of patients who achieved target of HbA1c ≤7.0%, changes in fasting plasma glucose (FPG), and postprandial glucose (PPG).

Statistical Analysis: Mean change in HbA1c was analyzed using an analysis of covariance model, least square (LS) means, 95% confidence intervals (CIs), and P values were calculated.

Results: Overall, 237 patients were included. Patients of the Teneligliptin group showed reduced HbA1c levels (LS mean difference = -0.304% for intent-to-treat [ITT]; -0.291% for per-protocol (PP) populations) after 16 weeks of treatment, and a statistically significant difference was observed between the ITT (LS mean difference = 0.555; 95% CI: 0.176-0.934; P = 0.0043) and PP populations (LS mean difference = 0.642; 95% CI: 0.233-1.052; P = 0.0023). Target HbA1c level was achieved by a greater proportion of Teneligliptin group patients (ITT, 43.4%; PP, 43.6%) than placebo group patients (ITT, 27.3%; PP, 26.6%). Reduction in FPG levels was observed in ITT (LS mean difference: 8.829; 95% CI: -4.357- 22.016; P = 0.1883) and PP populations (LS mean difference: 11.710 mg/dL; 95% CI: -2.893- 26.312; P = 0.1154). Reduction in PPG levels was higher in Teneligliptin group than placebo group in both ITT (LS mean difference = 25.849 mg/dL; 95% CI: 7.143-44.556; P = 0.0070) and PP populations (LS mean difference = 25.683 mg/dL; 95% CI: 5.830-45.536; P = 0.0115). Overall, 44 patients (18.6%) experienced at least one adverse event. Three or more hypoglycemic events were experienced by 2.5% patients of Teneligliptin group and none in placebo group.

Conclusion: Treatment with once-daily Teneligliptin led to statistically significant and clinically meaningful reductions in HbA1c and PPG, and was well tolerated in Indian patients with T2DM.[22]

Efficacy and Safety of Teneligliptin in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Background: Teneligliptin is a 3rd-generation dipeptidyl peptidase-4 (DPP-4) inhibitor. Thereis a limited evidence regarding the effect of Teneligliptin. Therefore, this study is to assess the efficacy and safety of Teneligliptin in type 2 diabetes mellitus (T2DM) patients with inadequately glycemic controlled.

Methods: A search of PubMed, Medline, Embase, and The Cochrane Library during 2000.01–2018.03 was performed for randomized controlled trials of Teneligliptin compared to placebo in patients with T2DM with monotherapy or add-on treatment.

Results: Ten trials with 2119 patients were analyzed. Teneligliptin produced absolute reductions in glycated hemoglobin A1c (HbA1c) levels (weighted mean difference (WMD) 0.82%, 95% confidence interval (CI) [−0.91 to −0.72], p < 0.00001) compared with placebo. However, after 36–42 weeks of follow-up (open-label), HbA1c level rise higher than duration (double-blind) in Teneligliptin group. Teneligliptin led to greater decrease of fasting plasma glucose (FPG) level (vs. placebo, WMD −18.32%, 95% CI [−21.05 to −15.60], p < 0.00001). Teneligliptin also significantly decreased the 2 h post-prandial plasma glucose (2 h PPG) (WMD −46.94%, 95% CI [−51.58 to −42.30], p < 0.00001) and area under the glucose plasma

concentration-time curve from 0 to 2 h (AUC0−2h) for PPG (WMD −71.50%, 95% CI [−78.09 to −64.91], p < 0.00001) compared with placebo. Patients treated with Teneligliptin achieved increased homeostasis model assessment of β cell function (HOMA-β) with 9.31 (WMD, 95% CI [7.78–10.85], p < 0.00001). However, there was no significant difference between Teneligliptin and placebo in overall adverse effects (0.96 risk ratio (RR), 95% CI [0.87, 1.06],p = 0.06). The risks of hypoglycemia were not significantly different between Teneligliptin and placebo (1.16 RR, 95% CI [0.59, 2.26], p = 0.66).

Conclusions: Teneligliptin improved blood glucose levels and β-cells function with low risk of hypoglycemia in patients with T2DM. Common adverse effects of Teneligliptin including hypoglycemia were identified and reviewed. Risks of cardiovascular events are less certain, and more data for long-term effects are needed.[23]

Teneligliptin real-world efficacy assessment of type 2 diabetes mellitus patients in India (TREAT-INDIA study)

Background and aims: Teneligliptin was introduced in India in May 2015. It has gained popularity and is already widely prescribed in type 2 diabetes mellitus (T2DM). This “real life” data collection was conducted to assess the efficacy of Teneligliptin in Indian T2DM patients.

Methods: Predesigned structured proforma was used to collect information from the prescribing physicians regarding the efficacy of Teneligliptin when prescribed as monotherapy as well as combination therapy with other antidiabetic drugs in T2DM patients. Information on the glycemic parameters at baseline prior to starting Teneligliptin

and at the end of 3 months therapy was collected. The efficacy was assessed by analyzing the mean change in 3-month values of glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG), and postprandial plasma glucose (PPG).

Results: Data of 4305 patients was available for analysis. There was statistically significant improvement in mean HbA1c, FPG, and PPG with Teneligliptin therapy. Means changes in HbA1c, FPG, and PPG were −1.37%±1.15%, 51.29±35.41 mg/dL, and 80.89±54.27 mg/dL, Respectively. Subgroup analysis revealed that HbA1c (%) reduction with Teneligliptin when used as monotherapy, add-on to metformin or add-on to metformin plus sulfonylureas combination, add-on to metformin plus alpha glucosidase inhibitor combination or add-on to insulin was 0.98±0.53, 1.07±0.83, 1.46±1.33, 1.43±0.80, and 1.55±1.05, respectively.

Conclusion: Real-world data suggests that Teneligliptin significantly improves glycemic control in Indian patients with T2DM when prescribed either as monotherapy or as an add-on to one or more other commonly prescribed antidiabetic drugs. [24]

Study Rationale

Diabetes Mellitus is an entity of considerable morbidity comprising a spectrum of multisystem dysfunctions stemming from the combination of insulin resistance and inadequate insulin secretion. Management of diabetes, akin to a tightrope walk, requires a comprehensive understanding of various factors such as over-all clinical picture, adverse effect profile, the complex of inter-play of drugs, etc. More than two-thirds of people with type 2 diabetes will eventually require more than one oral agent, with or without insulin.

Diabetes is emerging as a global epidemic, imposing enormous humanitarian and economic burdens on society. According to a WHO projection, by 2030, approximately 190 million people will be affected in the Asia-Pacific region alone. Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease.

Evidence suggests that patients with type 2 diabetes mellitus (T2DM) increasingly require multiple pharmacological combinations to reach treatment goals. Clinical inertia, with failure to advance therapy despite persistently elevated HbA1c levels above target, has become a major problem for the stepwise approach to treatment. Initial combination therapy using two oral anti-diabetic drugs (OAD) with complementary mechanisms of action is an alternative approach that may provide better or more sustained glycemic control. It may also allow the useof lower doses of the component OADs and thus minimize any dose-related adverse events (AEs).

Vildagliptin is a selective and reversible inhibitor of Dipeptidyl peptidase 4 (DPP-4), the enzyme which inactivates the incretin hormones, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP), hormones which significantly contribute to the maintenance of glucose homeostasis. [25] Vildagliptin improved glycaemic control when given as monotherapy or when used in combination with Metformin, a sulphonylurea, and a thiazolidinedione, as measured by clinically relevant reductions in HbA1c from baseline at study endpoint. In clinical trials, the magnitude of HbA1c reductions with Vildagliptin was greater in patients with higher baseline HbA1c.

Methodology

Study Design

This trial is a Phase IV, Prospective, Randomized, Comparative, Parallel Group, Clinical Study to Evaluate the Efficacy, Safety and Tolerability of Vildagliptin SR 100 mg Versus Teneligliptin 20 mg in Patients with Type 2 Diabetes Mellitus.

After confirming the inclusion/exclusion criteria the subject will be randomized and provided with study medication at randomization visit. Subjects will be provided with diary at randomization visit, which need to be brought along with in each subsequent visit till the last visit. Follow up visits will be done on week 2/day 14(±3), week 6/day 42(±3), week 12/day 84(±3) and week 16/day 112(±3) (Final Visit) of treatment to assess efficacy, safety and tolerability.

Subject Eligibility

Inclusion Criteria

Patients will be entered into this study only if they meet all the following criteria:

1. Male or Female Patients aged between 18 to 65 (both inclusive) years with diagnosis of Type 2 diabetes mellitus.
2. Patients who have received stable dose of Metformin ≥ 1500 mg/day as monotherapy for at least 3 months prior to screening and having inadequate glycemic control at screening defined as HbA1c levels of ≥ 8.0% to ≤ 9.5%.
3. Women of childbearing potential (WOCBP) must be using an acceptable method of contraception to avoid pregnancy throughout the study. WOCBP must have a negative urine pregnancy test at screening / baseline visit.
4. Patient with ability to understand and provide written informed consent form, which must

have been obtained prior to screening.
5. Patients willing to comply with the protocol requirements.

Exclusion Criteria

Patients that meet any of the following criteria must not be enrolled in the study:

1. Patients with a history of Type 1 diabetes mellitus or secondary diabetes mellitus or diabetes insipidus.
2. Patients with a history of metabolic acidosis or diabetic ketoacidosis.
3. Patients with a history of bariatric surgery or lap-band procedure within 12 months prior to screening.
4. Patients with Fasting Plasma Glucose (FPG) > 270 mg/dL at screening (If FPG is > 270 mg/dL at screening, FPG will be repeated within 1 week. If repeat FPG is > 270 mg/dL, patient will be excluded from the study).
5. Patients with the Body Mass Index (BMI) ≥ 45.0 kg/m^2 at screening.
6. Patients with Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 [using the Modification of Diet in Renal Disease (MDRD) equation] at screening.
7. Patients with clinically significant impaired hepatic function (SGOT & SGPT more than 3X the UNL and/or Total bilirubin more than 1.5X the UNL) at screening.
8. Patients with a history of congestive heart failure defined as New York Heart Association (NYHA) class III/IV, unstable or acute congestive heart failure.
9. Patients with significant cardiovascular history defined as: myocardial infarction, unstable angina pectoris, transient ischemic attack, unstable or previously undiagnosed arrhythmia,cardiac surgery or revascularization (coronary angioplasty or bypass grafts), or cerebrovascular accident.
10. Patients with uncontrolled hypertension with sitting systolic BP ≥ 160 mmHg and/or diastolic BP ≥ 100 mmHg at screening.
11. Any abnormality on 12-lead ECG at screening that in the opinion of the investigator is clinically significant and is judged as potential risk for patient's participation in the study.
12. Patients with history of hereditary QT prolongation syndrome or patients having history of Torsades de pointes.
13. Patients who are accepting treatments of arrhythmias.
14. Patients with a history of anaemia or haemoglobinopathy and/or haemoglobin < 10 g/dL for men; haemoglobin < 9 g/dL for women at screening.

Discontinuation/Withdrawal Criteria:

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw consent for participating in the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

Patients may be withdrawn entirely from the study for the following reasons:

Patients will be allowed to withdraw from the study anytime without stating the reason.However, every attempt will be made by the investigator to find out and record the reason. Also, patients will be explained the risks of sudden cessation of therapy. Conversely, if the investigator feels appropriate, he/she may withdraw the patient from the study and reasons for the same should be documented properly.

It will be documented whether each patient completed each study phase or not. If the study treatment or observations were discontinued for any patients, the reason will be recorded. Reason for the discontinuation of study treatment by patient may be one of the following:

1. Patients at their own request voluntarily or at the request of their legally acceptable representative can be withdrawn from the study.
2. Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the patient.
3. If a concomitant therapy is reported or required which is liable to interfere with the result of the study.

If at any point of the study patient is found to be non-compliant with the study protocol.

Study Population

A total of 86 evaluable patients in each treatment group is estimated to provide a power of 90%at one sided significance level of 2.5% (2 sided 5%), with assumed standard deviation of 1.0% of HbA1c, to demonstrate non-inferiority of Vildagliptin SR 100 mg Tablets in comparison with Teneligliptin 20 mg in HbA1c change from baseline to week 16, with a non-inferiority margin (Δ) of 0.40. Assuming a mean difference of 0.1% in HbA1c between Vildagliptin SR 100 mg and Teneligliptin 20 mg Tablets. Total 172 evaluable patients will be considered for this study.

86 Patients in Vildagliptin SR 100 mg, 86 Patients in Teneligliptin 20 mg.

Sufficient number of patients will be enrolled to get 172 evaluable patients for completing 16weeks of treatment.

Study Assessment

Primary Efficacy End Point:

Mean change in glycosylated hemoglobin (HbA1c) from baseline to end of the study visit (16 weeks).

Secondary Efficacy End Points:

Mean change in fasting plasma glucose (FPG) from baseline to end of the study visit (16weeks).

Proportion of patients achieving a therapeutic glycemic response, defined as HbA1c < 7% at the end of the study visit (16 weeks).

Mean change in body weight from baseline to end of the study visit (16 weeks).

Safety End Points:

- Hypoglycemic episodes during the study.
- Adverse events reported during the study.
- Serious adverse events reported during the study.

Changes in clinical laboratory parameters from baseline to end of the study visit (16 weeks).

Study Procedures
Study Schedule

Study Procedures	**Visit 1 (Screening/ Baseline) Day -7**	**Visit 2 (Randomization) Day 1**	**Visit 3 (Follow up visit) Week 2/ Day 14 (±3)**	**Visit 4 (Follow up visit) Week 6/ Day 42(±3)**	**Visit 5 (Follow up visit) Week 12/ Day 84 (±3)**	**Visit 6 (End of the study visit) Week 16 /Day 112 (±3)**
Written Informed consent form	X	-	-	-	-	-
Demography	X	-	-	-	-	-
Medical & Surgical history	X	-	-	-	-	-
Vital Signs measurement	X	X	X	X	X	X
Body weight & BMI	X	-	X	X	X	X
Physical Examination	X	X	X	X	X	X
COVID-19 signs & symptoms	X	X	X	X	X	X
Verification of Concomitant medications	X	X	X	X	X	X
Urine pregnancy test	X	-	-	X	X	X
HbA1c measurement	X	-	-	-	X	X
FPG measurement	X	-	X	X	X	X
Inclusion / Exclusion criteria	X	-	-	-	-	-
Inclusion / Exclusion criteria verification	-	X	-	-	-	-
Patient randomization	-	X	-	-	-	-
Study medication dispensing	-	X	X	X	X	-
Study medication return	-	-	X	X	X	X
Study medication compliance check	-	-	X	X	X	X
AE and SAE assessment	-	-	X	X	X	X
Hypoglycemic episodes assessment	-	-	X	X	X	X

Note:

Vital signs include resting blood pressure, pulse rate, respiratory rate and oral temperature.

Subjects should be instructed to self-monitor their blood glucose at least once weekly and at the occurrence of hypoglycaemia symptoms. Subjects should record blood glucose readings in the diary and report to the investigator in the event of usually high or low blood glucose.

Conclusion

Vildagliptin improved glycaemic control when given as monotherapy or when used in combination with Metformin, a sulphonylurea, and a thiazolidinedione, might increase reductions in HbA1c from baseline at study endpoint.

In clinical trials, the magnitude of HbA1c reductions with Vildagliptin might be greater in patients with higher baseline HbA1c.

We are expecting Teneligliptin and vildagliptin appear to effective and safe as add-on treatment for T2DM patients inadequately controlled on stable dose of metformin. Teneligliptin will be non-inferior to vildagliptin in controlling glycemic

parameters (HbA1c) and Vildagliptin will show higher reduction in Post prandial glucose level.

When treating type 2 diabetes mellitus, and especially patients who cannot achieve adequate glycemic control by monotherapy, it is helpful to consider combination therapies. Indeed, the majority of patients with type 2 diabetes mellitus will require combination therapy in their long-term treatment history. When considering the most appropriate drug combination, selecting drugs with different mechanisms of actions is recommended.

We are expecting both drugs will be well tolerated and safe. We also expecting that vildagliptin as the add-on therapy with metformin may have a lower incidence of hypoglycemia.

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