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A Brief Review On Evogliptin-Dipeptidyl Peptidase Iv (Dpp Iv) Inhibitor Used In The Treatment Of Diabetes Mellitus

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Abstract:

Diabetes mellitus characterised by hyperglycaemia is a metabolic disorder which results due to inadequate secretion of insulin (Type-I) or increased resistance to insulin by cells (Type-II). If not control the diabetes mellitus can lead to fatal complications including cardiovascular diseases, renal disease, retinal damage, foot problems and increased susceptibility to infection. Many of the oral hypoglycaemic agents are available for the effective control of blood glucose levels. This article describes the novel Dipeptidyl-peptidase-4 (DPP-4) inhibitor- Evogliptin. Evogliptin is safe and effective in the treatment of diabetes mellitus, the pharmacokinetic, mechanism of action, adverse effect, contraindication and drug-drug interactions are well explained in this review article.

Introduction:

Over 100 million individuals worldwide, or 6% of the population, suffer from diabetes mellitus (DM), the most common endocrine disorder that is defined by hyperglycemia. It is brought on by the pancreas producing insulin insufficiently or inefficiently, which raises or lowers blood glucose levels. It has been demonstrated to damage several body systems, such as the blood vessels, eyes, kidney, heart, and nerves[1]. The main signs of diabetes mellitus include polyphagia, polyuria, and excessive thirst, all of which are signs of elevated blood glucose levels above 180 mg/dl. There are different types of diabetes mellitus comes in three varieties.

1. **Type 1 Diabetes Mellitus** - It is also known as insulin dependent diabetes mellitus. (IDDS). In this pancreas unable to produce insulin. Type I diabetes is an autoimmune disease characterized by a local inflammatory reaction in and around islets that is followed by selective destruction of pancreatic beta cells producing insulin. Approximately 10% of all diabetes cases are type 1.

2. **Type 2 Diabetes Mellitus** - It is also known as Non-insulin dependent diabetes mellitus (NIDDS). During type 2 pancreas unable to produce enough insulin for proper function means impaired secretion or the cells in the body do not react to insulin known I.e. insulin resistance. Approximately 90% of all cases of diabetes worldwide are of this type. Overweight and obese people have a much higher risk of developing type 2 diabetes compared to those with a healthy body weight.

3. **Gestational Diabetes Mellitus** - This type of diabetes mellitus affects females during pregnancy. During pregnancy the bodies of pregnant women become unable to produce enough insulin to transport all of the glucose into their cells, resulting in progressively rising levels of glucose[2].

4. **Other types of diabetes mellitus:**

Monogenic defects of β-cell function
Monogenic defects in insulin action
Diseases of exocrine pancreas (chronic pancreatitis, pancreatic tumours, post-pancreatectomy
Endocrinopathies (e.g. acromegaly, Cushing's syndrome, pheochromocytoma)
Drug- or chemical-induced (e.g. steroids, thyroid hormone, thiazides, β-blockers etc)
Infections (e.g. congenital rubella, cytomegalovirus)
Uncommon forms of immune-mediated DM (stiff man syndrome, anti-insulin receptor antibodies)

Treatment of diabetes mellitus

Following are the major approaches for the treatment of diabetes mellitus.

1. **Diet** (combined with exercise if possible)
2. **Insulin**
3. **Oral Hypoglycaemic Therapy**

3.1 Sulfonylureas (such as gliclazide, gliclazide, glimepiride, and glyburide)

Sulfonylureas stimulate insulin secretion from the pancreatic beta cells[3,4].

3.2 Biguanides (Metformin)

In addition to preventing weight gain, metformin does not result in hypoglycemia, which is commonly linked to the use of other antidiabetic medications[5]. By lowering hepatic glucose synthesis, increasing insulin sensitivity, perhaps blocking mitochondrial respiration, and lowering gluconeogenesis, biguanides reduce blood glucose. Furthermore, metformin may be used therapeutically to treat diseases including polycystic ovarian syndrome and nephropathy[6].

3.3 Thiazolidindiones (Pioglitazone, Rosiglitazone)

TZDs are insulin sensitizers that improve insulin action and raise insulin sensitivity in vital tissues by influencing intracellular metabolic pathways[7]. Additionally, TZDs raise insulin-dependent glucose absorption in muscle and fat, decrease hepatic gluconeogenesis, and raise adiponectin levels. With TZD medication, fatty acid oxidation rises and insulin sensitivity is enhanced by adiponectin, a cytokine released by fat tissue[8].

3.4 Aplha glucosidase inhibitor (Acarbose)

Alpha-glucosidase inhibitors prevent the small intestine from absorbing carbohydrates. Enzymes that convert complex nonabsorbable carbohydrates into simple absorbable carbohydrates are competitively inhibited by them. Glucoamylase, sucrase, maltase, and isomaltase are some of these enzymes. They decrease the increase in postprandial blood glucose levels by around 3 mmol/L by prolonging the absorption of carbohydrates[9].

3.5 Glucagon like peptide 1 (GLP 1) agonist (Exenatide, Liraglutide, Delaglutide, Semiglutide)

Through the incretin effect, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), two incretin hormones deactivated by dipeptidyl peptidase-4 (DPP-4), promote the release of insulin following an oral glucose load[10]. This mechanism may be inhibited or absent in type 2 diabetes; however, pharmacological level of GLP-1 doses can restore insulin excretion. Delays in stomach emptying and the inhibition of pancreatic α-cells' ability to produce glucagon in the event of elevated blood sugar levels are two advantages of this treatment for type 2 diabetes. Moreover, GLP-1 receptor agonists can increase the proliferation of pancreatic β-cells while reducing their apoptosis[11, 12].

3.6 Sodium glucose cotransporter 2 (SGLT2) inhibitor (Canagliflozin, Dapagliflozin, Ertugliflozin)

The kidneys' proximal convoluted tubules express the protein SGLT-2, which reabsorbs filtered glucose from the tubular lumen to carry out its physiological function. The renal threshold for glucose (RTG) is lowered, urine glucose excretion is increased, and the reabsorption of filtered glucose is decreased by all four SGLT-2 inhibitors. Inhibitors of SGLT2 reduce HbA1c by 0.7%[13]

3.8 **Dipeptidyl-peptidase-4 (DPP-4) inhibitor** (Linagliptine, ildagliptin, Saxagliptin, Gemigliptin, Anagliptin, Teneligliptin, Trelagliptin, Omarigliptin, Sitagliptine, Alogliptine, Evogliptine)

They function by preventing the breakdown of incretins, a class of gastrointestinal hormones, by the enzyme DPP-IV. When necessary (such as after eating), incretins help the liver produce more insulin; when not needed (such as during digestion), they help the liver produce less glucagon.

They also slow down digestion and reduce hunger. Therefore, a DPPIV inhibitor helps to regulate blood glucose levels by protecting incretins from harm[14,15].

Evogliptine:

Recently, evogliptin (DA-1229) tartrate was developed to control blood glucose levels in patients with type 2 diabetes [16]. Chemically, it is known as (3R)-4-[(3R)-3-amino-4- (2,4,5-trifluorophenyl) butanoyl]-3-[(2-methylpropan-2-yl) oxymethyl] piperazin-2-one or (2R,3R)-2,3-dihydroxybutanedioic acid[17]. Due to its strong glucose-lowering benefits and lack of major side effects, particularly on glycemic variability in patients with type 2 diabetes, evogliptin, a new dipeptidyl peptidase 4 (DPP4) inhibitor, is increasingly utilized in clinical practice [18]**.**

MECHANISM OF ACTION

The incretin hormones, namely GLP-1 (glucagon-like peptide-1) and GIP (gastric inhibitory peptide), which raise insulin secretion and reduce glucagon secretion to preserve glucose homeostasis, are impacted by the prevalent enzyme DPP-4[19].

The small intestine's enteroendocrine L cells generate the hormone GLP-1, which decreases blood glucose by promoting insulin production, lowering glucagon levels, and delaying gastric emptying. Evogliptin has been shown to reduce postprandial glucose levels by 20% to 35% and raise postprandial active glucagon-like peptide-1 (GLP-1) levels by 1.5 to 2.4 times when compared to a placebo. Its half-life is Less than two minutes[20].

Pharmacokinetics:

Evogliptin is a selective DPP-4 inhibitor that is bioavailable and used orally to treat type 2 diabetes[21]. Evogliptin was well tolerated over time after repeated once-daily administrations in healthy subjects in a first-in-human clinical trial (ClinicalTrials.gov Identifier: NCT00961025), reaching a terminal half-life (t1/2) of 33–39 hours and a maximum plasma concentration (Tmax) of 4-5 hours after administration. Evogliptin's absolute bioavailability is around 50% [22]. CYP3A4 and CYP3A523 were the primary metabolizers of evogliptin in an in vitro research, producing 4(S)-hydroxyevogliptin (M7) and 4(R)-hydroxyevogliptin (M8). At this time, the metabolites' pharmacological action is unclear[23, 24.] In healthy adult volunteers, approximately 46.1% of the dosage is removed by urine, and 42.8% is eliminated through feces, including metabolites[25]. Evogliptin did not significantly change the pharmacokinetics of glimepiride, pioglitazone and metformin [26]

Adverse effects and Side Effects

A 24-week Multicenter Randomized Placebo-Controlled Parallel-Design Phase-3 Trial with a 28-week Extension has not revealed any significant side effects[27] However, hypoglycemia, nausea, constipation, vomiting, diarrhea, headache, dizziness, and exhaustion are the most frequent adverse effects of evogliptin. When using evogliptin, allergic reactions and pancreatitis are serious adverse effects [28, 29].

Contraindication:

Heart Failure:

Before using Evogliptine in patients with heart failure, care should be exercised since observational studies and clinical trial data indicate a persistently elevated risk, particularly after starting treatment, even in people who have never had heart failure [30].

Renal Impairment: It was discovered that as human renal function declined, so did the plasma concentration of evogliptin and the level of DPP-IV inhibitor action. Therefore, individuals with renal impairment should use evogliptin with caution[31].

Hepatic impairment: When Evogliptine was given to individuals with mild to severe hepatic impairment, no negative effects were observed[32].

Acute pancreatitis: The risk for the progress of acute pancreatitis has been found to be increased with all approved DPP4 inhibitors. The exact mechanism leading to acute pancreatitis is not clear [33].

Drug-Drug Interaction

Evogliptin is primarily metabolized by CYP3A4, and in vitro studies showed that it was neither an inducer of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 enzymes nor an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2C19, and 2A4 enzymes.

Clarithromycin: The pharmacokinetic parameters of evogliptin were found to be increased in the presence of clarithromycin; specifically a nearly 2-fold increase was observed in both the C_{max} and $AUC_{0-\infty}$ values[35].

Rifampicin: Multiple administration of a potent CYP3A4 inducer, rifampicin 600 mg/day, until steady state was reached and single administration of evogliptin 5 mg showed no significant change in Cmax of evogliptin but showed a decrease in AUC by 62% [36].

Conclusion: Evogliptine a novel DPP-4 inhibitor approved by CDSCO in 2018. **(CDSCO)** Evogliptin is found to be safe and effective in controlling diabetes mellitus while produces additive effect when given in combination with glimepiride, metformin and pioglitazone. Very little adverse effect and drug-drug interactions were identified regarding the use evogliptine.

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