Linagliptin: A Newly Approved Dipeptidyl Peptidase-4 Inhibitor for the Management of Type-2 Diabetes Mellitus

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Abstract
Diabetes mellitus is a metabolic disorder associated with deregulation of glucose metabolism due to lack of insulin secretion (Type-1 diabetes mellitus, T1DM) or deficient insulin secretion (Type-2 diabetes mellitus, T2DM). Studies suggest that T2DM often leads to serious complications including retinopathy, nephropathy, neuropathy and cardiomyopathy. The unsuccessful rate of diabetic control is persistently progressing in spite of effective treatment options available. It suggests the neediness of new therapeutic option to treat optimally the T2DM. Considerable number of studies demonstrated the potential of inhibitors of dipeptidyl peptidase-4 (DPP-4) in treating patients with T2DM. The first agent of this class, sitagliptin, was approved by the FDA in 2006, followed by vildagliptin (approved in 2008), saxagliptin (FDA approved in 2009) and linagliptin (FDA approved in 2011). DPP-4 inhibitors increase the levels of incretins such as glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), which subsequently stimulate the release of insulin from pancreatic beta cells after a meal, resulting in better blood glucose control. The newly approved agent of DPP-4 class, linagliptin was demonstrated to be safe and effective in double-blind, placebo-controlled clinical studies involved about 3,800 T2DM patients. The present review discussed the therapeutic potentials of linagliptin for the management of T2DM.

Keywords: Linagliptin, DPP-4 inhibition, GLP-1, Type-2 diabetes mellitus

1.0. INTRODUCTION
It remains a major task to maintain a normal sugar level in patients with type-2 diabetes mellitus (T2DM) though numerous pharmacological interventions such as sulphonylureas, biguanides, meglitinides, thiazolidinediones, aldose reductase inhibitors, α-glucosidase inhibitors etc. are employed clinically either alone or in combination. Therefore, it is obligatory to have a variety of therapeutic options to control hyperglycemia in T2DM patients. The dipeptidyl peptidase 4 (DPP-4) inhibitors are a new class of agents being developed for the management of T2DM, and linagliptin is a recently approved drug in this class [1].

Clinical studies demonstrated the efficacy of linagliptin in effectively controlling the sugar level in T2DM patients [2]. The purpose of this review is to discuss the therapeutic potential of linagliptin as antidiabetic medication.

2.0. LINAGLIPTIN: AN OVERVIEW
The U.S. Food and Drug Administration (US FDA) approved Tradjenta (linagliptin) tablets on May 02, 2011 to be used with diet and exercise for improving blood glucose control in adults with T2DM [3]. Linagliptin, a xanthine-based DPP-4 inhibitor is chemically (R)-8-(3-amino-piperidin-1-yl)-7-but-2-yn-1-yl-3-methyl-1-(4-methyl quinazolin-2-yl methyl)-3,7-dihydro-purine-2,6-dione [4].

2.1. Mechanism of Action
DPP-4 is an enzyme that rapidly degrades the incretin hormones mainly glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), the function of which are to release insulin from pancreatic beta cells in response to elevated blood glucose levels and reduce glucagon secretion from pancreatic alpha cells (Figure 1). By inhibiting DPP-
Linagliptin enhances the bioavailability of GLP-1 and GIP, resulting in stimulation of the release of insulin in a glucose-dependent manner and reduction of glucagon secretion [5]. This pharmacological event ultimately reduces the excessive circulating glucose levels, which would be beneficial to patients with T2DM.

2.2. Therapeutic Potentials

Numerous studies support therapeutic potentials of linagliptin for the management of T2DM. In this regard, Thomas et al. (2009) [4] investigated the effect of 1 to 2 months of chronic dosing of linagliptin (BI 1356) in two different animal models that include a primarily genetic model (Zucker diabetic fatty rats) and a nongenetic model (mice with diabetes induced by a combination of high-fat diet and low-dose streptozotocin). Interestingly, linagliptin enhanced the glycemic control and lowered the elevated levels of glycosylated hemoglobin (HbA1c) (a marker for average blood glucose, and HbA1c level increases in DM) after a multiple dosing in both models, suggesting that linagliptin would be efficacious in treating a broad spectrum of T2DM patients. Multiple dosing of linagliptin increased basal levels of active GLP-1 in the systemic circulation that was noted to be superior to vildagliptin, a short-acting DPP-4 inhibitor. This study suggested the potential of linagliptin as a once daily treatment for T2DM at low therapeutic doses [4]. The multiple rising doses of linagliptin were noted to be well-tolerated and resulted in significant improvements of glucose control in T2DM patients. Moreover, no serious adverse effects were reported [6].

**Figure 1:** Mechanism of action of linagliptin, a DPP-4 inhibitor, in lowering elevated glucose levels. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; GIP, gastric inhibitory polypeptide.
Linagliptin is a potent, long-acting inhibitor with high selectivity for DPP-4, and it has been suggested to be associated with minimal risk of hypoglycemia, which holds promise for treatment of T2DM [7]. It has modest oral availability in humans, and is absorbed rapidly. It is not metabolized appreciably in vivo, but binds extensively to plasma proteins, with elimination occurring primarily in the liver [7]. A short-term Phase I, randomized, double-blind, placebo-controlled trial of single and multiple escalating doses of linagliptin in healthy adult male Japanese volunteers demonstrated that multiple oral doses of linagliptin inhibited plasma DPP-4 activity and elevated active GLP-1 concentrations in a dose-dependent manner, with no episodes of hypoglycemia. In addition, the multiple dosing of linagliptin for 12 days was noted to be well tolerated [8].

Recently, Del Prato et al. (2011) [9] investigated the effect of linagliptin monotherapy on glycemic control and markers of β-cell function in patients with inadequately controlled T2DM. The authors noted that monotherapy with linagliptin produced a significant, clinically meaningful and sustained improvement in glycemic control, that are accompanied with enhanced β-cell function. Moreover, the safety profile of linagliptin was noted to be comparable with that of placebo [9]. Following this, Taskinen et al. (2011) [10] investigated the safety and efficacy of linagliptin as add-on therapy to metformin in T2DM patients in a randomized, double-blind, placebo-controlled study. This study demonstrated that the addition of linagliptin 5 mg once daily in T2DM patients, who were inadequately controlled on metformin, resulted in a significant improvement in glycemic control without any weight gain or increased risk of hypoglycemia [10]. In a recent randomized, double-blind, placebo-controlled study, Gomis et al. (2011) [11] investigated the efficacy and safety of an initial combination therapy of linagliptin with pioglitazone in patients of inadequately controlled T2DM. It was concluded in this study that the initial combination therapy with linagliptin and pioglitazone was well tolerated and produced a significant improvement in glycemic control. Moreover, this combination was suggested to offer a valuable additive initial treatment option for T2DM, particularly where metformin either is not well tolerated or is contraindicated in renal impairment [11]. Taken together, these studies support the clinical exploitations of linagliptin either alone or in combination with biguanides or glitazones for the management of T2DM. Further clinical studies are mandatory to determine the long-term potential of linagliptin in effectively controlling hyperglycemia without producing major adverse events.

3.0. CONCLUSION

Linagliptin has an ability to improve glycemic control by stimulating glucose-dependent insulin secretion from beta cells and suppressing glucagon secretion from alpha cells of islets of langerhans. Linagliptin either in monotherapy or in combination with oral hypoglycemic drugs is generally well tolerated and has minimal adverse effects with low incidence of hypoglycemia. The most common side effects of linagliptin are upper respiratory abnormality, stuffy or runny nose, sore throat, muscle pain, and headache. Long-term clinical trials are needed to further confirm the superior unique profile of linagliptin (among all oral antihyperglycemic drugs including other DPP-4 inhibitors) in the management of T2DM.

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