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Review Article

DPP-4 INHIBITOR LINAGLIPTIN: A NEW ANTI-DIABETIC DRUG IN THE TREATMENT OF TYPE-2 DIABETES

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ABSTRACT

Rates of type-2 diabetes have increased markedly over the last 50 years. Type-2 diabetic patients require multiple therapies to effectively control hyperglycemia. Linagliptin is a new approved oral antidiabetic drug and it acts by inhibiting the enzyme dipeptidyl peptidase-4 (DPP-4). Linagliptin was approved by the US Food and Drug Administration on 2 May 2011 based on a large development program, including four pivotal trials in patients with type-2 diabetes (T2DM). The efficacy and safety of linagliptin has seen when used as monotherapy or in combination with other oral antidiabetic drugs. Linagliptin was associated with significant improvements in glycosylated hemoglobin, fasting plasma glucose and postprandial glucose, and more patients receiving linagliptin showed meaningful improvements and achieved targets for glycosylated hemoglobin. Linagliptin was well tolerated, with an adverse event profile similar to that of placebo, and low rates of hypoglycemic events. Taken together, the pivotal trials confirm linagliptin is effective and safe in patients with T2DM: the convenience of oral dosing with no requirement for dose adjustment in patients with renal or hepatic impairment make linagliptin a valuable option when considering therapies for patients with T2DM.

Keywords: Type-2 diabetes, DPP-4 inhibitor, Linagliptin, Incretins, GLP-1

INTRODUCTION

Type-2 diabetes is a metabolic disorder and it is characterized by high blood glucose level due to insulin resistance and relative insulin deficiency. The classic symptoms of type-2 diabetes are frequent urination (polyurea), increased thrist (polydipsia), increased hunger (Polyphagia) and weight loss. Rates of type-2 diabetes have increased markedly over the last 50 years. Recent estimates revealed that in the year 2007, 246 million people suffered from diabetes worldwide. In 2010, approximately 285 million people suffered from diabetes. This number is projected to rise to 366 million people affected in the year 2030 [1, 2, 3, 4, 5]. Type-2 diabetes caused various diseases such as heart disease, strokes, diabetic retinopathy where eyesight is affected, kidney failure.

DPP-4 inhibitors increased and prolong the effects of endogenous glucagon-like peptide-1(GLP-1) and glucose-dependent insulinotropic (GIP) by inhibiting the DPP-4 enzyme that rapidly degrades this incretin hormone. DPP-4 inhibitors prolonging GLP-1 half life and significantly reduce hemoglobin A1c (HBA1c), fasting plasma glucose (FPG) and postprandial blood glucose (PPG). GLP-1 is a gut-derived peptide and it is secreted from intestinal L-cells after meal. GLP-1 has various physiological functions such as

a) Inhibiton of glucagon release, gastric emptying and food intake
b) Enhancement of β-cell growth and survival
c) Potential of glucose simulated insulin secretion

GLP-1 and GIP-1 exert their effects by binding to their specific receptor, the GIP receptor (GIPR) and the GLP-1 receptor (GLP-1R) which belongs to the G-protein coupled receptor family. DPP-4 inhibitor treatment is associated with a low incidence of hypoglycaemia [6] due to their glucose-dependent mode of action. DPP-4 inhibitors are body-weight neutral.

Linagliptin (BI-1356) was approved on 2 May 2011 by US FDA for treatment of Type-2 diabetes. Its trade names are Tradjenta and Trajenta. It is a DPP-4 inhibitor. It is being marketted by Boehringer Ingelheim and Lilly. Tradjenta is specifically indicated as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes mellitus. Linagliptin has been approved for monotherapy or in combination with other medications, in conjunction with exercise and dietary modification. It is administered orally in tablet form. The recommended dose is 5 mg once daily with or without food. High-throughput screening is a method for scientific experimentation is used in linagliptin drug discovery to detect inhibition of DPP-4 enzyme in type-2 diabetes [7].

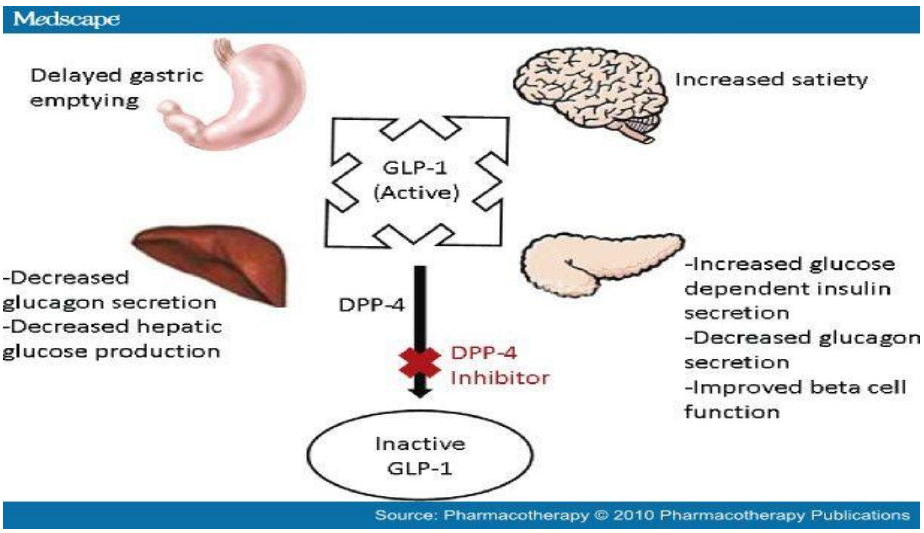

Fig. 1: Mechanism of linagliptin which inhibit DPP-4 enzyme

MECHANISM OF ACTION: LINAGLIPTIN

Linagliptin works by blocking the action of DPP-4, an enzyme that destroys the hormone GLP-1, which helps the body to produce more insulin when it is needed. GLP-1 and GLP-2 hormones are released from intestine. They act by reduced blood glucose by increasing the production and release of insulin from the pancreas. GLP-1 has other mechanism to reduce blood glucose level by reducing the secretion of glucagon by the pancreas. Glucose-dependent incretin concentration is increased, when food is consumed. It stimulates the release of insulin and inhibits the release of glucagon, resulting decrease levels of circulating glucose [8, 9]. Linagliptin binds tightly, but not irreversible, to the DPP4 enzyme.

CHEMICAL STRUCTURE

Fig. 2: Chemical structure of linagliptin [9]

Linagliptin has xanthin-based [9] structure. The chemical name of Linagliptin is 8-(3-aminopiperidin-1-yl)-(but-2-yn-1-yl)-methyl-1-((4-methylquinazolin-2-yl) methyl)-1H-purine-2,6(3H,7H)-dione. Its molecular weight is 472.54. Its chemical formula is $C_{25}H_{28}N_8O_2$. Linagliptin is a white to yellowish, not or only slightly hygroscopic solid substance. It is very slightly soluble in water (0.9 mg/mL). Linagliptin is soluble in methanol, sparingly soluble in ethanol, very slightly soluble in isopropanol, and very slightly soluble in acetone and insoluble in ether, chloroform etc.

PHARMACOKINETIC STUDY

Linagliptin has non-linear pharmacokinetics. Cmax is reduced up to 15% after taking a high fat meal. The absolute bioavailability of linagliptin is approximately 30%. Linagliptin binds to the plasma-protein in a concentration dependent manner. It has a large volume of distribution. The cytochrome P450 enzyme is responsible for metabolism of linagliptin. Linagliptin is excreted through both the feces (90%) and urine (5%) in unchanged condition, indicating that metabolism plays a minor role in linagliptin elimination. A very small quantity of linagliptin is absorbed and converted into an inactive metabolite. For pharmacokinetic study, a single 5-mg dose of linagliptin is administered orally to healthy subjects and patients with type 2 diabetes. According to FDA, [10] pharmacokinetic information for linagliptin are following below-

Property	Linagliptin
Cmax	8.9 n mol/L
AUC	139 n mol*h/L
Tmax	1.5 hours
Terminal$^{1}/_{2}$ life	>100 hours
Bioavailability	30%
Volume of distribution	1110L
Elimination	5% urine

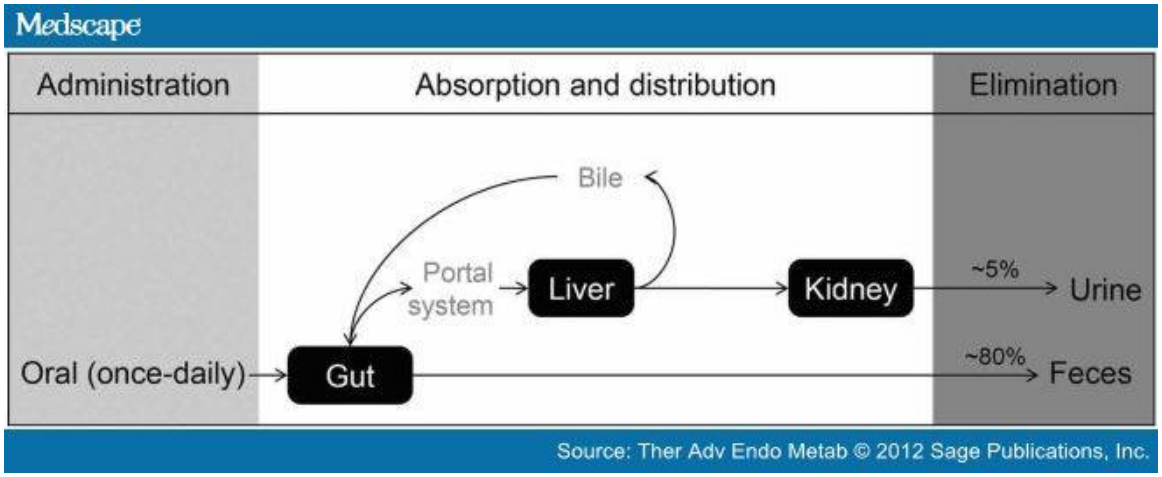

Fig. 3: Excretion of linagliptin. Approximately 90% of linagliptin is excreted unchanged, indicating that metabolism is a minor elimination pathway.

Renal impairment

The evaluation of the pharmacokinetic activity of linagliptin was conducted with the help of a multi dose open label study, where 5 mg of linagliptin were given to patients with varying degrees of chronic renal insufficiency as compared to normal healthy control subjects. The study included patients with renal insufficiency defined on the basis of creatinine clearance as mild, moderate and severe, as well as in patients having ESRD on hemodialysis. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula, CrCl = (140 – age) x weight/72 x serum creatinine [x 0.85 for females], where age is in years, weight in kg, and serum creatinine is in mg/dl.

Under favorable conditions, linagliptin exposure in patients with mild renal impairment was compared to healthy subjects, it was found that in moderate renal impairment, a moderate increase of about 1.7 fold was observed compared to control. Exposure in T2DM patients with severe RI an increase of about 1.4 fold was observed as compared to T2DM patients with normal renal function. Linagliptin is not expected to be eliminated to a therapeutically significant degree by hemodialysis or by peritoneal dialysis. Therefore no dosage adjustment of linagliptin is necessary in patients with any degree of renal insufficiency [11].

Hepatic impairment

In non-diabetic patients with mild moderate and severe hepatic insufficiency, the mean AUC and Cmax of linagliptin were found to be similar when compared to healthy controls patients when administered with multiple 5 mg doses of linagliptin. Therefore no dosage adjustment for linagliptin was made for diabetic patients having mild, moderate or severe hepatic impairment [12].

PHARMACODYNAMICS

The treatment process of type-2 diabetes by linagliptin resulted in rapid, potent and long-lasting inhibition of plasma DPP-4 in clinical studies. Linagliptin does not bind to DPP-8 or DPP-9 activity in vitro at concentrations approximately therapeutic exposures. Linagliptin

has the tendency to increase the concentration of incretin hormones and increases insulin secretion and lowers glucagon secretion [13]. As a result, glucose level is regulated in a controlled manner. Glucose excursion was measured by an OGTT, as the increment of the area under the plasma concentration-time curve (AUC) of glucose.

MONOTHERAPY

In the placebo-controlled study, patients were allocated in a 3:1 ratio to linagliptin or placebo respectively. 503 patients were randomly subjected to linagliptin (n=336) and placebo (n=167) for once daily. The rescue medication was done during 24-week where the primary outcome was a change in HbA1c from its base line. It is observed that linagliptin reduces HbA1c level by 0.49% from its base line of 8.09% where as in case of placebo it is seen that the changed in HbA1c level was 0.15% from its mean base line of 8.025, therefore linagliptin was found to be superior to placebo.

Few adverse events were also encountered during the trial of linagliptin and placebo were hyperglycemia, [14] headache, hypertension and backpain.

COMBINATION THERAPY

Add-on combination therapy with metformin

A double blind randomized study was performed to evaluate the efficacy and safety of add-on therapy with linagliptin in patients having type-2 diabetes which were not properly controlled with metformin [15]. 701 patients were controlled to receive linagliptin 5 mg daily (n=524) or placebo (n=177) with metformin for 24 weeks. Two parameters were observed between the test group decrease in HbA_{1c} level and fasting plasma glucose level, as because the adverse event profile of both the treatment groups were similar and no increase in liver transaminose or creatine level or hypoglycemic were seen.

In another study, linagliptin was administered to ongoing metformin [16, 17] therapy with patients having type-2 diabetes that was not properly controlled by metformin alone. 333 patients were assigned to receive double-blind linagliptin (1 mg, 5 mg or 10 mg once daily) or placebo, or open-lable glimepride. Linagliptin with dose of 1 mg, 5 mg or 10mg and in placebo a reduction in HbA_{1c} was observed (0.04%, 0.73% and 0.67%).

Add-on combination therapy with pioglitazone

A double blind placebo-controlled study was performed to evaluate the efficacy and safety of a combination therapy of linagliptin and pioglitazone [18] in patients having in sufficient controlled type-2 diabetes. 707 patients were allocated to receive 5mg linagliptin plus 30 mg pioglitazone once daily or given placebo plus 50 mg pioglitazone once daily (n=130) and the end point was measured in respect to the change in base line in HbA_{1c} after a time span of 24 weeks.

After comparing the results of the two groups it is observed that the drug from base line in HbA_{1c} was 1.06% in case of combined drug therapy of linagliptin/pioglitazone where as in case of placebo/pioglitazone a change of 0.56% was seen.

In the combination therapy of linagliptin and pioglitazone, a marked decrease in fasting plasma glucose level was observed as compared to placebo and pioglitazone.

Add-on combination therapy with sulfonylureas

A double blind, placebo-controlled study was performed to evaluate the efficacy of linagliptin in combination with sulfonylurea (SU). In this study, 245 patients with type-2 diabetes were subjected in 18 week. Sulfonylurea monotherapy on patients (n=142) were randomized after completing a 2-week single-blind placebo run-in period. Sulfonylurea plus one additional oral antihyperglycemic agent (n=103) were randomized after a washout period of 4 weeks and a 2 weeks single-blind placebo run in period. Patients were allocated to receive linagliptin 5 mg or to placebo, each administered once daily. Linagliptin/sulfonylurea [19] combination lowered fasting plasma glucose (FPG) level by 8.2 mg/dL from base line, compared with a decrease of 1.8 mg/dL with placebo/sulfonylurea.

Add-on combination therapy with sulfonylureas and metformin

A double blind, placebo-controlled study was performed to evaluate the efficacy of linagliptin in combination with sulfonylurea (SU) and metformin. In this study, 1058 patients with type-2 diabetes were subjected in 24 week. Glimepiride (31%), glibenclamide (26%), and gliclazide (26%) are most common sulfonylureas used by patients. Patients were allocated to receive combination of sulfonylurea and metformin with linagliptin or placebo. This combination reduced HbA_{1c} from base line compared with a sulfonylurea, metformin, and placebo at 24 weeks [19].

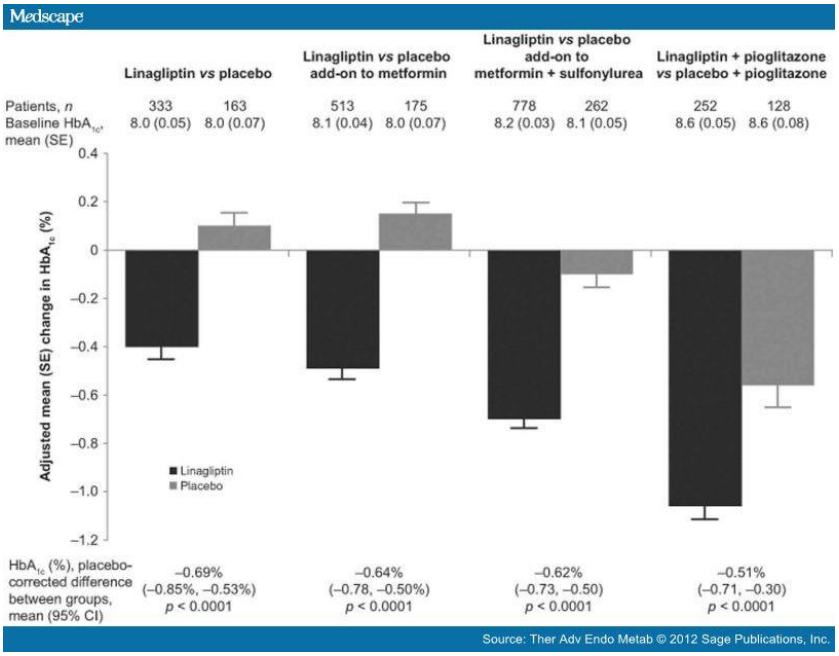

Fig. 4: Glycosylated hemoglobin (HbA_{1c}): change from baseline with linagliptin or placebo.

Number of patients is the full analysis set (all patients with a baseline and at least one on-treatment HbA_{1c} value). All studies were of 24 weeks' duration. Mean change in HbA_{1c} from baseline to week 24 was adjusted for baseline HbA_{1c} and previous oral antidiabetic drug treatment. The treatment difference (linagliptin minus placebo) was highly significant for all studies ($p < 0.0001$). SE, standard error; CI, confidence interval.

SAFETY

Linagliptin is a well tolerated drug and it has no specific side effects in dose up to 100-fold of the therapeutic dose of 5 mg. Nasopharyngitis is the most common adverse reaction (reported in ≥ 5% of patients treated with linagliptin and more commonly than in patients treated with placebo).

Another common adverse reaction is hypoglycemia. Hypoglycemia was reported more in patients treated with the combination of linagliptin and sulfonylurea than in patients treated with the combination of placebo and sulfonylurea.

Pancreatitis was reported more often in patients randomized to linagliptin (1 per 538 person years versus zero in 433 person years for comparator) [19].

Less serious side effects of linagliptin may include runny or stuffy nose, sore throat; cough; weight gain; muscle or joint pain; headache; or back pain.

NON-CLINICAL TOXICOLOGY

Mutagenesis, Impairment of Fertility, Carcinogenesis

Linagliptin was not mutagenic or clastogenic [10] with or without metabolic activation in the Ames bacterial mutagenicity assay, a chromosomal aberration test in human lymphocytes, and an *in vivo* micronucleus assay.

In fertility studies in rats, linagliptin had no adverse effects on early embryonic development, mating, fertility, or bearing live young up to the highest dose of 240 mg/kg (approximately 943 times the clinical dose based on AUC exposure).

Linagliptin did not increase the incidence of tumors in male and female rats in a 2-year study at doses of 6, 18, and 60 mg/kg. The highest dose of 60 mg/kg is approximately 418 times the clinical dose of 5 mg/day based on AUC exposure. Linagliptin did not increase the incidence of tumors [10] in mice in a 2-year study at doses up to 80 mg/kg (males) and 25 mg/kg (females), or approximately 35- and 270-times the clinical dose based on AUC exposure. Higher doses of linagliptin in female mice (80 mg/kg) increased the incidence of lymphoma at approximately 215-times the clinical dose based on AUC exposure.

DRUG INTERACTIONS

Inducers of P-glycoprotein and CYP3A4 Enzymes

Rifampin is strong CYP_3A_4 or p-glycoprotein inducer. The efficacy of linagliptin may be reduced when the drug is co administered with a strong P-gp inducer or CYP 3A4 inducer such as rifampin. As JENTADUETO is a fixed-dose combination of linagliptin and metformin, [20] use of alternative treatments (not containing linagliptin) is strongly recommended when concomitant treatment with a strong P-gp or CYP 3A4 inducer is necessary.

DOSAGE AND CONTRAINDICATION

Linagliptin may be taken with or without food. The recommended dose is 5 mg once daily. Patients having various hypersensitivity reactions such urticaria, angioedema,or bronchial etc, in that case linagliptin should not be prescribed [21].

SPECIAL POPULATIONS

Patients who have hepatic or renal insufficiencies do not require dose adjustments because renal elimination is not a primary excretion pathway and plasma protein binding is not affected in these patients. Linagliptin has not been studied in patients younger than 18 years of age and should be used with caution in this population. Currently, there are ongoing studies investigating the safe and effective use of linagliptin in patients with moderate to end stage renal disease [22].

CONCLUSIONS

Linagliptin provided clinically meaningful reductions in FPG and HbA_{1c}, significantly increasing the odds of achieving HbA_{1c} targets. In addition, linagliptin was well tolerated, with a similar safety profile to placebo and low rates of hypoglycemic events. Other than when used in combination with pioglitazone, patients receiving linagliptin did not gain weight or have adverse changes in cardiovascular biomarkers. This article highlights the type 2 diabetes treatment by a new oral antidiabetic drug linagliptin and it combination therapy with other anti-diabetic drug.

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