Linagliptin: The Game Changer in Type 2 Diabetes Mellitus

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Abstract: The rate of occurring of Type 2 diabetes mellitus have been proportionally increased with respect to time in the last 50 years. Multiple therapies are required by the type 2 diabetes patients for proper treatment of hyperglycaemic condition. Linagliptin is the latest approved oral hypoglycaemic agent which act by inhibition of DPP-4 (Dipeptidyl peptidase-4) enzyme. On 2 May 2011, USFDA approved Linagliptin based on a large development program, including 4 trials on type 2 diabetes patients. In type 2 diabetes patients there is dysfunctioning of incretin hormones (Glucagon-like peptide-1 or GLP-1 and glucose-dependent insulinotropic polypeptide or GIP). Inhibition of DPP-4 enzyme causes the slow down of inactivation of GLP-1 and GIP, which promotes the secretion of insulin. In present era, Linagliptin is the most potent oral hypoglycaemic agent which is indicated for the treatment of type 2 diabetes.

Key words: Type 2 Diabetes Mellitus • GIP • GLP-1 • DPP-4

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is now reached almost every corner of the world, with increase in its incidence rates parallel to the obesity condition. Chronic hyperglycemia causes micro and macrovascular complications representing major problem in public health. Frequent hospitalizations are caused by the renal failure, cardiovascular diseases, blindness and limb amputations. If people control over the glucose level from the early stage of life then these complications can be omitted.

Role of DPP-4 in Diabetes Mellitus

Glucagon-like peptide-1 (GLP-1) and Glucose dependent insulinotropic polypeptide (GIP) are hormones, which are released after meals and pancreas are stimulated to release insulin. They are broken down by an enzyme serine protease dipeptidyl peptidase-4 (DPP-4), due to this pancreas stops insulin secretion. Therere, inhibition of DPP-4 increases GLP-1 levels in the blood and, hence, insulin is secreted when required, i.e. after eating od but not during starvation. The principle of using DPP-4 inhibitors as therapy of T2DM is now firmly established and numerous inhibitors are already approved: sitagliptin in 2006, vildagliptin in 2007 and recently, saxagliptin in 2009 and alogliptin in 2010 and Linagliptin in 2011.

Chemistry of Linagliptin: Linagliptin has xanthine-based structure. The chemical name of Linagliptin is 8-(3-amino-piperidin-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 [2]. Its chemical rmula is C_{25}H_{22}N_{3}O_{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) [2]. Linagliptin is soluble in methanol, sparingly soluble in ethanol, very slightly soluble in isopropanol and very slightly soluble in acetonede insoluble in ether, chlororm etc.

Linagliptin: On 2 May 2011, US FDA approved Linagliptin (BI-1356) for the treatment of Type 2 Diabetes Mellitus. Its brand names are Tradjenta and Trajenta, marketed by Boehringer Ingelheim and Lilly. Tradjenta is also specified as a supplement in diet and exercise for the control of glucose levels in diabetic adults. Linagliptin is approved for monotherapy as well as for combination with other drugs. It has its combination with metformin which is available in market. Its route of administration is oral in the tablet rm. The dose recommended for linagliptin is 5 mg once in a day with or without od. Its scientific experimentation is done by high throughout screening which proves that it actually inhibit the DPP-4 enzyme.
Mechanism of Action of Linagliptin: The hormones, which are also known as incretins (Glucagon Like Peptide-1 and Glucose dependent Insulino trope Polypeptide) are released from intestine which increase the insulin secretion to combat the increased glucose level after meals. GLP-1 (Glucagon Like Peptide-1) also act indirectly by reducing the glucagon secretion from pancreas. There is an enzyme, Dipeptidyl peptidase-4 (DPP-4) which breakdown the GLP-1 and GIP (Glucose dependent Insulino tropic Polypeptide) after their work is over. Linagliptin inhibit DPP-4 enzyme, which results in longer duration working of GLP-1 and GIP which causes increased secretion of insulin and reduction in the levels of glucagon [2].

Pharmacokinetics
Absorption: All DPP-4 inhibitors are orally available and are rapidly absorbed and inhibition of plasma DPP-4 can be seen within 5 minutes but oral bioavailability is lower r linagliptin (30%) [3].

Distribution: Linagliptin binds the plasma proteins in a concentration dependent manner. With a therapeutic dose of 5 mg, most of it remains protein bound mainly to DPP-4. High concentration of drug is und in intestines, kidney and liver and low levels are und in brain [4].

Metabolism: It does not undergo appreciable metabolism. Around 80% of linagliptin mis eliminated unchanged. 70% of the drug related material in plasma is made up of parent drug, major metabolite is CD1790 (S-3-hydroxy piperidinyl derivative of linagliptin) which is 17% of parent compound [5].

Excretion: Linagliptin is an exception in gliptins, because less than 6% of the dose is excreted through renal route. This is due to high protein binding of the drug. Excretion through bile is about 78%. Major metabolite CD1790 is negligibly excreted in urine and primarily eliminated in faeces [6].

Interactions: Linagliptin is weak competitive and poor mechanism based inhibitor of DPP-4 and it decreases the clearance of those agents which llow this pathway. It does not have any significant interactions with other drugs [7].

Safety: Linagliptin is well tolerated upto 600 mg (120 times the effective dose of 5 mg), it is more selective r DPP-4 than DPP-8/9 (Less off target inhibition, reduces toxicity-rash, alopecia, immunological reaction seen in animals).

How Linagliptin Is Better than Other Gliptins?
- Linagliptin provide A1c reduction of 0.7% similar to other gliptins ranging from 0.5% to 0.8% [8].
- Linagliptin can control the disease at any duration (<1 year to >5 years) [9].
- True 24 hour control (As seen from DPP-4 inhibition) [10].
- Greater than 80% inhibition at > 24 hours [11].
- High enzyme affinity at low concentration to DPP-4 enzyme [12].
- Non-covalent tight binding and slow dissociation [13].
- It shows less than 66% cardiovascular events than other gliptins in phase III clinical trials [13].
- Linagliptin is first DPP-4 inhibitor approved by USFDA with pre-specified prospective independently adjudicated CV safety data [13].
- Linagliptin has less than 5% renal excretion so there is no requirement of dose adjustment at any stage of renal function [13].
- Linagliptin is first DPP-4 inhibitor which has established safety and efficacy in all three stages of renal excretion at same dose of 5 mg [13].
- 80% mainly excreted unchanged (Not metabolized by CYP450) [13].
- No dose adjustment at any stage.
- Linagliptin increases post prandial active GLP-1 levels in T2DM patients to 3.2 ld. Sitagliptin in doses of 50 and 200 mg increased active GLP-1 levels by approximately 2 ld [13].

CONCLUSION
At present, gliptins are the best DPP-4 inhibitors in the therapy of T2DM and they have suddenly enhanced the competition to develop the new lead compounds in order to achieve an ideal antidiabetic agent. Linagliptin is
somewhat meeting the requirements of being an ideal drug for the treatment of T2DM because it have lower dose frequency and less dose adjustments according to renal and hepatic impairments. Due to its unique pharmacokinetic and pharmacodynamic profile, it is the best oral hypoglycaemic agent in present era.

REFERENCES