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Review Article

DPP-4 inhibitors: A novel approach for management of type-2 diabetes mellitus

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ABSTRACT

Diabetes mellitus (DM) is one of the most common chronic disorders, with increasing prevalence worldwide. Type 2 diabetes (T2DM), a multifaceted disease involving multiple pathophysiological defects, accounts for nearly 85–95% of total reported cases of DM. Although being a primary objective in the management of type 2 diabetes, optimal glycemic control is difficult to achieve and usually not maintained over time. Type 2 diabetes is a complex pathology, comprising altered insulin sensitivity and impaired insulin secretion. The dipeptidyl peptidase (DPP-4) inhibitors are a new class of antihyperglycaemic agents which were developed for the treatment of type 2 diabetes. They differ in terms of their chemistry; they are all small molecules which are orally available. Several DPP-4 inhibitors (or gliptins) with different chemical structures are now available. These agents inhibit the degradation of the incretin's glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) and hence potentiate glucose-dependent insulin secretion. They improve glycemic control, reducing both fasting and postprandial glucose levels to lower HbA1c levels, without weight gain and with an apparently benign adverse event profile. Hence DPP-4 inhibitors currently available have proven similar glucose lowering efficacy.

Keywords: Dipeptidylpeptidase-4 (DPP-4) inhibitors, gliptins, glucagon-like peptide (GLP-1), glycemic control

INTRODUCTION

Now a day's diabetes becomes a very serious health issue worldwide. The prevalence is increasing at an alarming rate across the globe. It is projected that by the year 2025 36.2million people in North America will suffer from the disease which was 23million in 2003[1]. Globally it is expected that the prevalence of diabetes will become from 194 million in 2003 to 333 million in 2025 which will almost double[1]. Diabetes is associated with serious micro and macro vascular complications. If it is left untreated it may cause severe metabolic syndrome which results increase morbidity, mortality and cost of care. A critical public health challenge is represented by the looming global epidemic of this disease.

Several new oral antidiabetic agents and insulin preparations are added to the current therapeutic schedule of diabetes management. But still adequate control of hyperglycemia is remaining question mark across the world till the date. Recent US National Health and Nutrition Examination Survey (NHNES) suggested that glycated hemoglobin (HbA1c) levels were below 7% in fewer than 40% of patients with diabetes which is live evidence of inadequate management of diabetes[2]. Optimum control of hyperglycemia not achieved due to two factors among which one is progressive nature of type-2 diabetes mellitus and other one is limitation of current treatment strategies. The United Kingdom Prospective Study (UKPDS) suggested that despite the treatment with diet, sulfonylureas, biguanidines or insulin β-cell function continued to deteriorate. This was associated with a progressive loss of glycemic control so increasing the requirement of more aggressive combination regimens and ultimately insulin[3]. Thus there is a clear need for new, more effective treatment to either prevent or delay the

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onset of type-2 diabetes mellitus as well as the subsequent decline in β-cell function associated with disease progression[4,5]. During the past few years numbers of studies have demonstrated that the development of pancreatic islet α- and β-cell dysfunction is crucial to the onset and progression of hyperglycemia in type-2 diabetes mellitus[6,7,8]. This concept of diabetes pathophysiology shows a direction to maintain islet health to researcher. It has become clear that GI incretin hormones are important mediators of normal islet function and glucoregulatory hormone secretion. The most important incretin hormones involved in glucose homeostasis are glucagon-like peptide-1(GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)[9]. Due to their effects on insulin and glucagon secretion they are known as helping hand for plasma glucose modulation[7].

New therapies targeting upon incretins either incretinmimetics or inhibit dipeptidyl peptidase-4(DPP-4), the enzyme that inactivates GIP and GLP-1 are proving to be effective approaches to improving glycaemic control in type-2 diabetes mellitus[4]. This review enlighted that DPP-4 inhibitors are the rational therapeutic target for management of type-2 diabetes mellitus along with its clinical aspects for establishment of the potential for better management schedule.

Incretin hormones: Any discussion about DPP-4 and its inhibitors would be incomplete without discussing about incretin hormones. Incretin hormones released after oral glucose administration stimulate insulin secretion is called incretin effect. Two incretin hormones very essential for glucose regulation as well as insulin secretion are glucose-dependent insulinotropicpolypeptide(GIP) and glucagon-like peptide-1(GLP-1)[10]. It has been estimated that incretin hormones contributed by >70% to the insulin response to an oral glucose challenge[11]. In type-2 diabetes mellitus reduction in incretin effect resulted by both impaired release of GLP-1 and defective action of GIP[12]. GIP consists of 42 amino acid peptide produced by the K cells located in the duodenum predominantly[13]. After ingestion of food GIP used to release into the circulation. Fat and carbohydrate containing diets considered to be predominant stimulators whereas protein considered to be less important[14]. GLP-1 produced by the L cells located in the lower part of small intestine predominantly[13]. After few minutes of ingestion of food GLP-1 used to release into the circulation. Fat, carbohydrates and protein all seem to be very powerful stimulators of GLP-1 secretion[14]. After release both GIP and GLP-1 get rapidly inactivated. This inactivation is resulted by a truncation of the peptides by removal of the N-terminal dipeptide end and the whole process is executed by an enzyme named dipeptidyl peptidase-4(DPP-4)[15]. The main basis of the incretin effect is stimulation of insulin secretion is caused by both GIP and GLP-1 in a glucose dependent manner[10,12]. Along with the stimulation of insulin secretion, GLP-1 has also been shown to increase islet neogenesis and differentiation and to reduce apoptosis of β-cells in rodents[16,17,18]. GLP-1 has also had effects on increasing β-cell mass[19]. The incretin hormones also affect glucagon secretion. GLP-1 inhibits glucagon secretion[20] whereas GIP has been demonstrated to stimulate glucagon secretion[21].

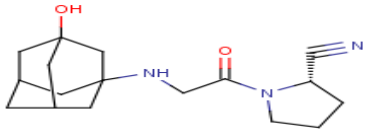
DPP-4: Dipeptidyl peptidase-4 (DPP-4) is an ubiquitous enzyme that can be detected in the endothelium of different organs and is measurable as circulating enzymatic activity in plasma and also called DPP-IV, CD26, EC 3.4.14.5 [22,23]. The prime action of DPP-4 is to cleave oligopeptides after the 2nd amino acid from the N-terminal end with preferential action if the 2nd amino acid is alanine (as in GLP-1) or proline[22]. The incretins are the only substrate of DPP-4 that have been well validated in humans.

DPP-4 inhibitors: Sitagliptin, vildagliptin, saxagliptin and alogliptin are competitive inhibitors with high affinity for DPP-4. The most abundant database is available about the pharmacokinetic and pharmacodynamic properties, efficacy and safety and tolerability assessment for sitagliptin and vildagliptin[24].

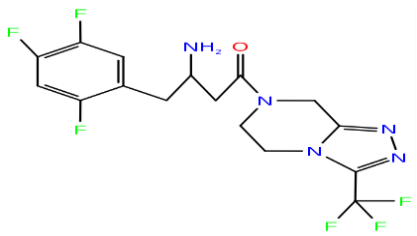
Several DPP-4 inhibitors are enlisted in the following table with their production company.

NAME	COMPANY
Sitagliptin	Merck
Vildagliptin	Novartis
Alogliptin	Takeda
Saxagliptin	Bristol-Myers-Squibs
PSN-9301	OSI Pharmaceutical
TA-6666	Tanabe
GRC-8200	Glenmark Pharmaceuticals
SYR-619	Takeda
TS-021	Taiso Pharmaceuticals
SSR-162369	Sanofi-Aventis
ALS 2-0426	Alantos Pharmaceuticals

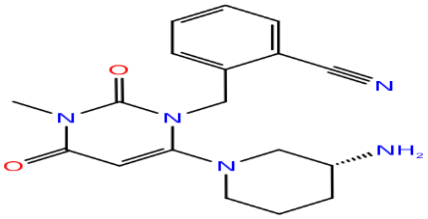
Chemical structures:
Vildagliptin



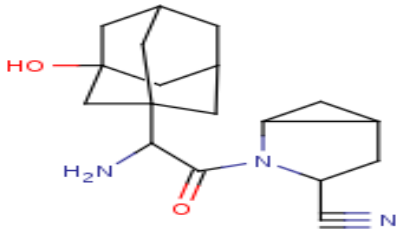
Sitagliptin



Alogliptin



Saxagliptin



Mechanisms of action of DPP-4 inhibitor: DPP-4 has a well established physiological role in the regulation of the incretin hormones. In animals that are treated with a DPP-4 inhibitor increased active GLP-1, GIP and improved glucose tolerance were observed[25,26,27,28]. Increased insulin as well as decreased glucagon levels were also observed in DPP-4 inhibitor treated rodents and humans. In addition to GLP-1 and GIP this DPP-4 enzyme has been implicated in the regulation of growth-hormone releasing hormone (GHRH), glucagon like peptide-2(GLP-2), pituitary adenylate cyclase-activating polypeptide (PACAP) and gastrin-releasing peptide (GRP) [29, 30].

Glycemic control by DPP-4 inhibitors as monotherapy: The antidiabetic action of DPP-4 inhibitors in humans was published in 2002[31]. In that study a DPP-4 inhibitor named NVP DPP728 was introduced to 93 patients of type-2 diabetes and it was found that in 4 week treatment fasting, postprandial and 24 hour glucose levels reduced. The first clinical study with vildagliptin was a 4 week study with once daily administration of 100mg tablet to 18 patients versus placebo to 19 patients with a mean baseline fasting glucose of 8.8mmol/L and HbA1c 7.2%[32]. Vildagliptin reduced mean fasting glucose by 0.7mmol/L and mean prandial glucose by 1.4mmol/L. Another study of 12 week with vildagliptin as monotherapy in different doses ranging from 25mg to 100mg with a baseline of fasting glucose of 9.3mmol/L and HbA1c of 7.7%[33]. It was found that at 50mg or 100mg once daily, vildagliptin reduced HbA1c by 0.46% and 0.40% respectively while compared with placebo. Sitaglptin was evaluated as monotherapy in 552 patients with type-2 diabetes having mean baseline of HbA1c of 7.7% for 12 weeks. A significant reduction was observed by 0.6% at 100mg daily dose[34]. Another 18 weeks study in 521 patients used sitagliptin of 100mg or 200mg once daily as monotherapy having mean baseline HbA1c of 8.1%[35]. HbA1c reduced by 0.60%and 0.48% respectively. Finally 24 weeks study with sitagliptin at 100mg or 200mg in patients having mean baseline of HbA1c of 8.0% was done[36]. Reduction of HbA1c by 0.8% and 0.9% respectively was observed. These studies on both vildagliptin and sitagliptin as monotherapy in patients with type-2 diabetes showed a fair and clinically significant effect of the DPP-4 inhibitors in improving control of glycaemia.

Glycemic control by DPP-4 inhibitors in combination Therapy

Combination with Metformin: Vildagliptin with metformin was administered to patients of type-2 diabetes for 52 weeks. During the initial 12 weeks it was observed that vildagliptin in combination with metformin reduced HbA1c levels by 0.7% while compared to metformin alone[37]. Another study for 6 month was done on sitagliptin added to ongoing metformin with the patients having mean baseline of HbA1c of 8.0%. It was found sitagliptin in combination with metformin reduced HbA1c by 0.65% while compared to metformin alone[38].

Combination with Thizolidinediones: Vildagliptin 50mg and 100mg in combination with pioglitazone reduced HbA1c by 0.8% and 1.1% respectively while 0.3% in the placebo group with pioglitazone alone[39]. Sitagliptin 100mg daily with pioglitazone 30mg or 45mg was introduced to patients having mean baseline of HbA1c 8.0% for 6 months[40].The result obtained that combination therapy of sitagliptin and pioglitazone reduced HbA1c by 0.7% versus pioglitazone alone.

Combination with Insulin: A 24 weeks study of vildagliptin added to insulin with more advanced type-2 diabetes of mean baseline HbA1c of 8.9%[41]. The result showed HbA1c reduced by 0.5% in combination therapy while insulin alone reduced 0.2%. Summarizing this we can say vildagliptin and sitagtliptin are efficacious in glycemic control in combination with metformin and thiazolidinedione for at least 6 month duration.

Impacts of DPP-4 inhibitors on patient weight: So many studies was done to know the influence of DPP-4 inhibitors on patient weight. Variable results are demonstrated hence considered to be neutral. While treated with sitagliptin for 52 weeks weight reduced by 1.5 kg and when treated with same drug for 24 weeks weight gained by 1.8 kg. Vildagliptin reduced 1.8 kg weight in 52 weeks and gained 1.3 kg in 24 weeks of therapy. Saxagliptin reduced 1.8 kg in 52 weeks and gained 0.7 kg in 24 weeks of therapy. From these studies it was concluded that the effect of DPP-4 inhibitor on weight was neutral[42,43].

Adverse effect of DPP-4 inhibitors: Both sitagliptin and vildagliptin have proved safe in monotherapy as well as combination therapy. By different studies it was proved that the numbers of adverse events were lower in combination therapy with metformin than in group treated with metformin alone[44]. Some gastrointestinal side effects includes delayed gastric emptying, nausea and vomiting are associated with GLP-1. After exogenous administration of GLP-1 the concentrations in plasma becomes high hence these side effects occurs. Compared with GLP-1 mimetics which are administered via injection lead to pharmacological GLP-1 levels can produce nausea and vomiting[45,46]. Overall the most common side effects occurring with vildagliptin were cold/flu like symptoms, headaches and dizziness[47].

Risks associated with DPP-4 inhibitors: DPP-4 effects T-cell activation and proliferation beyond its proteolytic action[48]. A large number of neuropeptides, growth factors, cytokines and chemokines have been identified as potential DPP-4 substrates[49]. Till date no evidence found for non-specific enzyme inhibition with DPP-4 inhibitors. With DPP-8 and DPP-9 inhibition toxicities are claimed[50-56]. DPP-4 inhibitors prolongs the action of hormones peptide YY and growth-hormone releasing hormone, the neuropeptides neuropeptide Y and substance P and several chemokines. Side effects resulting from the prolongation of action of these messengers include neurogenic inflammation, increases in blood pressure and enhanced general inflammation and allergic reactions. Such side effects are not observed in preclinical animal or clinical human studies till the date[51].

CONCLUSION

Large intervention trial demonstrated that anti-hyperglycemic therapy with treatment goals aiming at normoglycaemia can reduce the risk of microvascular and macrovascular disease. Normalizing HbA1c alone is not sufficient in risk reduction. The goal of antidiabetic treatment is to achieve near normoglycaemia as safely as possible regarding HbA1c, fasting plasma glucose and postprandial glucose concentration. DPP-4 inhibitors are orally active, safe and well tolerated considered to be a novel and promising therapy for improvement of glycemic condition both in monotherapy as well as combination therapy with metformin and thiazolidinediones. DPP-4 inhibitors work through preventing the inactivation of the incretin hormones that is GLP-1 and GIP through stimulation of insulin secretion and reduction in glucagon secretion with a potential to increase β-cell mass. DPP-4 inhibitors also improves prandial lipid metabolism along with the improvement in glucose metabolism. The pathophysiologically relevant mechanisms of action of DPP-4 inhibitors, its efficacy and tolerability and its oral bioavailability suggest that this novel approach of treatment will be of great value in modern therapeutics of type-2 diabetes mellitus. DPP-4 inhibitors may be established as firstline treatment as monotherapy in patients with metformin contraindication. For this long term durability trials are required for DPP-4 inhibitors. Studies required with DPP-4 inhibitors in the elderly patients and in patients with renal insufficiency to potentiate the value of the treatment. More mechanistic studies are required to make DPP-4 inhibitors as first line therapy.

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