DPP 4 INHIBITORS: A NEW ERA OF TREATING TYPE 2 DIABETES MELLITUS

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ABSTRACT

Type 2 diabetes is a complex metabolic disorder, comprising altered insulin sensitivity and impaired insulin secretion. Now-a-days various treatments are available for the treatment of type 2 diabetes mellitus. Inhibition of dipeptidyl peptidase 4 (DPP-4) is a novel treatment for type-2 diabetes. In recent years, various DPP-4 inhibitors have been released as therapeutic drugs for type 2 diabetes. These agents inhibit the degradation of the incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino tropic polypeptide (GIP) and hence potentiate glucose-dependent insulin secretion. They are well-tolerated with no weight gain and few adverse effects, and, of particular interest, no increase in hypoglycemic episodes. DPP-4 inhibition is suggested to be a first-line treatment of type-2 diabetes, particularly in its early stages in combination with metformin. Several DPP-4 inhibitors are in clinical development, and many are already available in the market like sitagliptin, vildagliptin etc. Some of them have patents for chemical entities for inhibiting DPP 4 enzyme in vitro and in vivo. However, further studies are needed to validate both longterm-cell preservation and the role of these agents in the management of diabetes. The present review gives an inside out of the DPP IV inhibitors, novel drugs in clinical trials, patents and combination therapy with other anti diabetic drugs.

KEY WORDS: DPP 4, DPP 4 inhibitors, type 2 diabetes mellitus, GLP-1.
INTRODUCTION

Inhibition of dipeptidyl peptidase 4 (DPP-4) has recently emerged as a promising new approach for the treatment of type 2 diabetes mellitus.[1] Dipeptidyl-peptidase 4 (DPP-4) is a ubiquitous enzyme that can be detected in the endothelium of different organs and that is measurable as circulating enzymatic activity in plasma. Diabetes mellitus is recognized as a major health problem affecting millions of people and predisposing to micro- and macrovascular complications including coronary heart disease. A tight glycaemic control reduces the morbidity and mortality associated to type 2 diabetes [2,3]. After food ingestion, specialized neuroendocrine cells of the gastro-intestinal tract release peptides which act to improve glucose handling and energy homeostasis. Among these gut hormones are the incretins glucagon-like peptide (GLP)-1. The incretins, namely glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), are the only substrates of DPP-4 that have been well validated in humans. DPP-4 has also been implicated in the regulation of several additional peptides, such as pituitary adenylate cyclase-activating polypeptide (PACAP) and gastrin-releasing peptide (GRP). DPP-4 preferentially cleaves peptides with the amino acid alanine or proline in position 2 of the N-terminus of the peptide chain. Active GLP-1(7–36) amide is cleaved by DPP-4 to yield a dipeptide (His-Ala) and GLP-1(9–36) amide.[4,5]

Table 1 Currently used treatment of type 2 diabetes mellitus other than Dpp 4 inhibitors:

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Molecular target</th>
<th>Site of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Insulin receptor</td>
<td>Liver muscle</td>
</tr>
<tr>
<td>Sulphonylurea</td>
<td>SU receptor</td>
<td>Pancreatic beta cell</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Unknown</td>
<td>liver</td>
</tr>
<tr>
<td>Acrabose</td>
<td>α glucosidase</td>
<td>Intestine</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>PPAR γ</td>
<td>Adipose tissue, liver, muscle</td>
</tr>
<tr>
<td>PPAR α/γ dual agonist</td>
<td>PPAR α/γ</td>
<td>Adipose tissue, liver, muscle</td>
</tr>
<tr>
<td>GLP 1 analogue</td>
<td>GLP-1 receptor</td>
<td>Pancreas</td>
</tr>
</tbody>
</table>

Incretins

The increase in plasma levels of insulin following oral administration of glucose exceed that seen after intravenous glucose administration when glucose levels during the two conditions are matched. This is defined as the incretin effect, which is attributed to the intestinal hormones which are released after oral glucose and which augment insulin secretion. The two most important incretin hormones are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). It has been estimated that the incretin hormones contribute
by more than 70% to the insulin response to an oral glucose challenge.[6]. The incretin effect is reduced in type-2 diabetes due to a combination of impaired release of GLP-1 and defective action of GIP.[7] GIP is a 42-amino-acid peptide produced mainly by the K cells, which are located predominantly in the duodenum. GIP is released into the circulation after ingestion of a meal; fat and carbohydrates seem to be predominant stimulators, whereas protein seems to be less important. GLP-1, on the other hand, is produced by the L cells, which are localized predominantly in the lower part of the small intestine. GLP-1 is released into the circulation minutes after meal ingestion; fat, carbohydrates and protein seem all to be powerful stimulators of GLP-1 secretion. Both GIP and GLP-1 are rapidly inactivated after their release. The inactivation is caused by a truncation of the peptides by removal of the N-terminal dipeptide end. This process is executed by the enzyme dipeptidyl peptidase 4 (DPP-4).[8,9]

**DPP 4**

DPP-4 (also called DPP-IV, CD26, EC 3.4.14.5) is expressed in several organs and also circulates.[10,11] A main 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.[10] This truncating effect of DPP-4 is rapid and efficient; only 40% of total GLP-1 in the circulation under fasting conditions (and 60% after meal ingestion) is active GLP-17, and the half-life of active GLP-1 is less than 2 min. Inhibition of DPP-4 substantially prolongs this half-life and increases the proportion of active GLP-1 in the total circulating GLP-1 pool.

Figure: 1 Physiological effect of GLP 1. These effects do not necessarily represent physiological actions of the native incretin hormone, but have been observed in animal models, in vitro studies or in human studies using supra physiological amount of the peptide.
Dpp-4 inhibition

Since DPP-4 truncates and thereby inactivates GLP-1, it is involved in the regulation of glucose homeostasis. This is clearly illustrated by findings that mice with a genetic deletion of DPP-4 have increased glucose tolerance following oral glucose administration in association with augmented insulin secretion.[15] The rationale for this suggestion was verified by animal studies showing that the DPP-4 inhibitor valinepyrrolide augments the active GLP-1 concentration, increases insulin secretion, and improves glucose tolerance.[16] In humans it has been shown that DPP-4 inhibition increases the prandial levels of active GLP-1 approximately three-fold, from w5–6 pmol/L to w15–20 pmol/L.[17]

Dpp 4 inhibitor

Several inhibitors are on the market or in trials (Table 1). They are all orally available and well absorbed (significant DPP-4 inhibition is observed as soon as 15 min after administration), and have high affinity for DPP-4. Sitagliptin is well absorbed (87%), and potently and selectively inhibits DPP-4. Its pharmacokinetic and pharmacodynamic properties have been determined in randomized, double-blind, placebo-controlled studies with single oral doses (1.5–600 mg) in healthy subjects. [12] Vildagliptin is also well (85%) and rapidly absorbed (within 1–2 h). Vildagliptin is quickly cleared from plasma, with a halflife of...
1.5–4.5 h, thus demanding higher dosing frequency. PD–PK relationships have been studied in a cross-over, placebo-controlled study in type 2 diabetic patients using doses ranging from 10 and 25 to 100 mg twice a day, for 28 days. More than 90% inhibition of DPP-4 activity was observed at all doses, and more than 80% 12 h postdosing. [13,14]

![Structures for different approved DPP 4 inhibitors](image)

**Figure: 3** Structures for different approved DPP 4 inhibitors

**Novel DPP 4 inhibitors**

Deyan *et al.* Synthesized several compounds and tested with biological assays. Nine compounds were found to show inhibitory effects against DPP-4. Molecular docking models give rational explanation about structure–activity relationships. Based on eight DPP-4 inhibitors, the best pharmacophore model hypo1 was obtained, consisting of one hydrogen bond donor (HBD), one hydrogen bond acceptor (HBA), and two hydrophobic (HY) features. [18] Novel deazaxanthine-based DPP-4 inhibitors have been identified that are potent (IC50 <10 nM) and highly selective versus other dipeptidyl peptidases. Their synthesis and SAR are reported, along with initial efforts to improve the PK profile through decoration of the deazaxanthine core. Optimisation of compound resulted in the identification of compound (S)-4i, which displayed an improved in vitro and ADME profile. Further enhancements to the PK profile were possible by changing from the deazahypoxanthine to the
deazaxanthine template, which displayed good ex vivo DPP-4 inhibition and a superior PK profile in rat, suggestive of once daily dosing in man.[19]

**DPP 4 inhibitors in clinical trials:[35]**

**AMG-222**

The molecule is currently in a phase 2a study in collaboration with Servier Pharmaceuticals, which owns the rights outside the United States. Although, information on *in vitro* and preclinical data of AMG-222 publicly available is less but, latest studies revealed the drug to be highly selective and to be suitable for once-daily administration [20].

**ARI-2243**

It is a potent DPP IV inhibitor that possesses an additional DPP IV independent beneficial mechanism which contributes to improved glucose control. ARI-2243 produced a 29% reduction in glucose excursion during OGTT studies in DPP IV knock-out mice. ARI-2243 showed improved insulin sensitivity following 14 days of dosing in Zucker *fa/fa* animals whereas Sitagliptin had no effect on insulin sensitivity in this diabetic animal experiment. [21]

**GRC 8200 (Melogliptin)**

Melogliptin was originally developed by Glenmark Pharmaceuticals Ltd. Preclinical data suggest that this compound is very potent with an IC50 of 1.61 nM against human recombinant DPP IV enzyme and with a selectivity of 10,000 fold over DPP2, PPCE and other proteases tested [42-43]. Melogliptin has an excellent pharmacokinetic profile with a reported oral bioavailability of 50-95% Oral administration of Melogliptin at a dose of 3 mg/kg/day in *db/db* mice resulted in 30% reduction of AUC in OGTT.[22]

**R-1579 (Carmegliptin)**

The results of a single center, double-blinded phase 1 trial suggest that both single ascending and multiple ascending doses of R-1579 were tolerated with more than 50% reduction in DPP IV activity observed even after 10 hours of dosing and data obtained in this study suggest that the drug is safe and efficacious and there was no evidence of weight loss [23]

**SYR-472**

Once-weekly SYR-472 treatment produced clinically and statistically significant improvements in glycaemic control in patients with type 2 diabetes. It was well tolerated and might be a new treatment option for patients with this disease. [25]
Table 2. Structure of Current DPP IV Inhibitors in Clinical Trial and Discovery Phases

<table>
<thead>
<tr>
<th>DPP IV Inhibitors</th>
<th>Structure</th>
<th>Reference</th>
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<tbody>
<tr>
<td>PHX-1149 (Dutogliptin tartrate)</td>
<td><img src="image1" alt="Structure" /></td>
<td>24</td>
</tr>
<tr>
<td>Denagliptin (GW823093)</td>
<td><img src="image2" alt="Structure" /></td>
<td>25</td>
</tr>
<tr>
<td>ER-319711</td>
<td><img src="image3" alt="Structure" /></td>
<td>26</td>
</tr>
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</table>

Table 3: Patents file for DPP 4 inhibitors

<table>
<thead>
<tr>
<th>Patent</th>
<th>Patent No.</th>
<th>Date of patent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of a dpp-4 inhibitor in podocytes (30) foreign application priority data related disorders and/or nephritic syndrome</td>
<td>US 2013/0303462 A1</td>
<td>Nov. 14, 2013</td>
</tr>
<tr>
<td>Aminotetrahydropyrans as dipeptidyl peptidase-iv inhibitors for the treatment or prevention of diabetes</td>
<td>US 8,455,533 B2</td>
<td>Jun. 4, 2013</td>
</tr>
<tr>
<td>Antidiabetic medications comprising a dpp-4 inhibitor (linagliptin) optionally in combination with other Antidiabetics</td>
<td>US 2012/0094894 A1</td>
<td>Apr. 19, 2012</td>
</tr>
<tr>
<td>Heterocyclic compounds as dipeptidyl peptidase-iv inhibitors for the treatment or prevention of Diabetes</td>
<td>US 2011/0224195 A1</td>
<td>Sep. 15, 2011</td>
</tr>
</tbody>
</table>
Other physiological effects of DPP 4 inhibitor

Lipid metabolism
In the clinical trials using monotherapy or combination therapy with vildagliptin or sitagliptin, only minor, if any, effects on lipids are seen. However, a recent study showed that vildagliptin (50 mg twice daily for 4 weeks) reduced the prandial 8-hour triglyceride response to a fat-rich meal intake by 85%.[28] Chylomicron triglyceride was reduced by 91%, and this was associated with a reduction in chylomicron apolipoprotein B-48 and chylomicron cholesterol. This would add another potential beneficial effect of this novel form of therapy, considering the importance of prandial lipaemia as a risk factor for cardiovascular diseases.

Blood pressure and ECG
Studies on effects of DPP-4 inhibition on blood pressure are few, and of these most report no effect. Also, no electrocardiogram abnormalities have been observed during treatment with DPP-4 inhibitors.

Gastric emptying and satiety
GLP-1 delays gastric emptying, and the reduction of prandial glucose by GLP-1 analogues such as exenatide is largely explained by this action.[29] However, DPP-4 inhibitors do not seem to exert this action. This is evident by the lack of effect of DPP-4 inhibitors on the rate of increase in circulating glucose after meal ingestion. Recently, a more direct approach also verified that vildagliptin does not affect gastric emptying by estimating the rate of gastric emptying of a tracer-enriched meal.[30]

Cardiovascular
Numerous studies have evidenced a role for GLP-1 in the cardiovascular system. On the one hand, continuous IV administration of GLP-1 in cardiac insufficiency and myocardial infarction improves cardiac function by increasing left ventricular ejection fraction [31] On the other hand, deletion of the GLP-1 receptor in mice results in increased left ventricular diastolic pressure, decreased left ventricle (LV) contractility and increased LV thickness [32] In humans, GLP-1 administration increased left ventricular ejection fraction and improved the resistance to exercise in diabetic and nondiabetic patients with cardiac insufficiency [33] suggestive of a potential cardioprotective effect of GLP-1. In the same line, GLP-1 infusion lowered arrhythmia in patients with coronary artery bypass grafting [34]
Glycaemic effects of dpp-4 inhibitors in combination therapy

Combination with metformin
A 52-week trial of vildagliptin with metformin was concluded.[36] The results showed that during the initial 12-week study period vildagliptin in combination with metformin reduced HbA1c levels by 0.7% compared to treatment with metformin alone. Sitagliptin has been evaluated in combination with metformin. In a 6-month study, sitagliptin at 100 mg daily was added to ongoing metformin in subjects with a mean baseline HbA1c of 8.0%.[37] It was found that in the group treated with sitagliptin in combination with metformin, HbA1c was reduced by 0.65% compared to patients treated with metformin alone.

Combination with thiazolidinediones
Vildagliptin was examined in combination with pioglitazone in a 6-month study. It was found that HbA1c was reduced by 0.8% by vildagliptin at 50 mg and by 1.1% by vildagliptin at 100 mg versus by 0.3% in the placebo group treated with pioglitazone alone.[38] Another study evaluated the combination of sitagliptin (100 mg daily) with pioglitazone at 30 or 45 mg daily in 6-month treatment of patients with a mean baseline HbA1c of 8.0%.[39] The results showed that sitagliptin in combination with pioglitazone reduced HbA1c by 0.7% versus pioglitazone alone; 45% of subjects reached target for control (<7%) at the end of the study compared to 23% of patients treated with pioglitazone alone.

Combination with sulfonylurea
A 24-week study examined vildagliptin (50 mg once or twice daily) versus placebo when added to glimepiride (4 mg daily) in 515 patients with a mean baseline HbA1c of mean 8.5%.[44] Placebo-adjusted HbA1c was reduced by 0.6% by vildagliptin at 50 mg once daily and 0.76% at 50 mg twice daily.

Combination with insulin
Vildagliptin has also been examined when added to insulin in subjects with more advanced type-2 diabetes in a 24-week study.[40] The results showed that HbA1c was reduced by 0.5% in the group given vildagliptin in combination with insulin versus by 0.2% in the group given insulin alone. In summary, vildagliptin and sitagliptin show good efficacy in improving glycaemic control in combination therapy with both metformin and thiazolidinediones in studies of at least 6 months duration.
Adverse effect of DPP 4 inhibitors

DPP-4 inhibitors are generally well-tolerated, and no increase in adverse events was noted compared to placebo or other comparatives, but again slight differences may exist between the different molecules of this class. DPP-4 is also present on the cell membrane of T lymphocytes known as CD26. In these cells, it acts by activating intracellular signalling pathways to simulate T-cell proliferation. In pre-clinical models, DPP-4-deficiency results in modest abnormalities in immune response, decreased CD4+ Tcell number, and reduced production of interleukin (IL)-4 while IL-10 was increased.[41]. They do not have common side effects like nausea, vomiting and diarrhea.

CONCLUSION

DPP-4 inhibitors are a novel class of orally available molecules for the treatment of type 2 diabetes. Although structurally different, they share a common mechanism of action by extending the half-life of endogenous GLP-1. It is orally active, it is safe and well tolerated, and it results in a sustained robust and clinically significant improvement in glycaemia both in monotherapy and in combination with metformin and thiazolidinediones. The pathophysiologically relevant mechanisms of action of DPP-4 inhibition, its efficacy and tolerability, and its oral availability suggest that this novel approach will be of great value in the arsenal for treatment. DPP-4 inhibition may also have advantages over existing treatment in long-term therapy of more advanced stages of the disease, provided that the beneficial effect on islet mass is also evident in humans. Moreover, DPP IV inhibitors are weight neutral and have a negligible risk of hypoglycemia. Thus DPP IV inhibitors have an advantage over other anti-diabetic agents like long-acting GLP-1 analogs, TZDs, SUs, biguanides etc. However, in addition to regulating glucose homeostasis, DPP IV has many diverse functions, such as modulating cell growth, differentiation and transformation and immune function. They show persistent, robust and clinically significant improvements in glycaemia in monotherapy and in combination with metformin, sulphonylurea and TZDs.

ABBREVIATIONS

DPP = Dipeptidyl peptidase
GLP-1 = Glucagon-like peptide-1
GIP = Gastric inhibitory peptide
T2DM = Type 2 Diabetes mellitus
HbA[1c] = Glycosylated hemoglobin A1c
OGTT = Oral glucose tolerance test  
TZDs = thiazolidinediones

REFERENCE


