

Dipeptidyl Peptidase-4 as a New Target of Action for Type 2 Diabetes Mellitus: A Systematic Review

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KEYWORDS

- Dipeptidyl peptidase-4 inhibitor • DPP-4 inhibitors
- Sitagliptin • Vildagliptin • Diabetes type 2
- Glycohemoglobin A1c • Incretins

Diabetes mellitus type 2 is a consequence of decreased glucose uptake by cells either because of lack of insulin or defective insulin action or both, leading to hyperglycemia. The underlying mechanisms of reduced insulin secretion include the loss of β -cell function and mass, and apoptotic β -cell death in the pancreas.^{1,2} Insulin resistance, usually associated with obesity, is an impaired biological response to insulin, either endogenous or exogenous, leading to unregulated hepatic production of glucose and decreased insulin-stimulated peripheral insulin uptake and utilization.³ Chronic hyperglycemia leads to microvascular and macrovascular damage, causing multiple diseases including retinopathy, neuropathy, nephropathy, gastroparesis, coronary artery disease, and stroke. These diseases are responsible for a significant increase in morbidity and mortality in the general population, particularly in people who have other comorbid conditions. There is a direct relationship between the level of glycemic control and the risk of these complications. Therefore, glycemic control is important for managing diabetes.

In addition to insulin, glucagon plays a role in the pathophysiology of diabetes. In starvation, glucagon, which is produced by the α -cells of the

pancreas, helps to maintain glucose levels by stimulating hepatic glycogenolysis or gluconeogenesis. Normally, meals stimulate insulin for glucose uptake and suppress glucagon secretion to decrease endogenous production of glucose. In diabetes, this regulation is disturbed, resulting in a diminished and delayed insulin response to a meal. Furthermore, glucagon is not suppressed appropriately and even may be elevated, resulting in postprandial hyperglycemia. Disturbance in the regulation of insulin and glucagon, coupled with insulin resistance, leads to alterations in the metabolism of carbohydrates, proteins, and fats.

Treatment of diabetes is intended to control blood glucose and minimize the secondary complications of hyperglycemia.¹ Treatment modalities for type 2 diabetes include lifestyle modifications (eg, weight reduction, exercise, or dietary changes), oral medications, and subcutaneous medications, including insulin. Oral medications include biguanides, sulfonylurea and nonsulphonylurea secretagogues, thiazolidinediones, and α -glucosidase inhibitors. The management of type 2 diabetes continues to be a challenge, as less than half of United States adults who have diabetes achieve HgA1c of less

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than 7%. Progressive decline in β -cell function contributes to poor diabetes control.

In recent years, new classes of oral and subcutaneous medications have been introduced including incretin mimetic exenatide. The new oral diabetes medications are the inhibitors of the enzyme dipeptidyl peptidase isozyme 4 (DPP-4), and the subcutaneous medications include the incretin-based therapy (pramlintide and exenatide). In the United States, one DPP-4 inhibitor, namely sitagliptin (MK-04310), has been approved by the US Food and Drug Administration (FDA) for managing type 2 diabetes mellitus as monotherapy and combination therapy with other oral agents. Other DPP-4 inhibitors, namely vildagliptin (LAF237) and saxagliptin (BMS-477118) are available in other countries.

This article provides an overview of the effectiveness of DPP-4 inhibitors in glycemic control in type 2 diabetes mellitus. To have a comprehensive understanding of DPP-4 inhibitors, one must understand the role of incretins.

THE INCRETIN SYSTEM

It was observed that oral administration of glucose caused 50% to 70% higher insulin secretion as compared with an equivalent dose of intravenous glucose. This augmentation in response, called incretin effect, is caused by the gut-derived hormones, gastric inhibitory peptide (GIP) and glucagon-like peptide-1 (GLP-1).^{4,5} These hormones, called incretins, are stimulated by oral feeding and are secreted by the K-cells and L-cells of the intestinal mucosa, respectively. GLP-1 is more potent than GIP in stimulating insulin secretion. GLP-1 and GIP control glucose metabolism by their effects on the pancreas, gastrointestinal (GI) tract, and central nervous system (CNS). In the pancreas, GLP-1 causes a glucose-dependent increase in insulin and inhibits glucagon secretion. In the GI tract, it inhibits gastric emptying and increases gastric acid production, and in the central nervous system, it inhibits food intake and promotes postprandial satiety and weight loss.^{6,7}

Glucose-Dependent Insulinotropic Peptide

This incretin is produced by neuroendocrine K-cells, which exist in duodenum and jejunum. It is released in response to fats and, to a lesser extent, carbohydrate. It causes glucose-dependent release of insulin by binding to the highly specific GIP receptors on pancreatic β -cells. In diabetic patients, the levels of GIP are found to be normal, but the incretin response is decreased. The cause of this resistance is not known, but various

mechanisms have been suggested, including a defect in the GIP receptor, rapid desensitization, and decreased expression of the receptor.⁸⁻¹¹

Glucagon-Like Peptide-1

GLP-1 and GLP-2 are intestinal peptide hormones derived from proglucagon, and they bear significant amino acid homology with glucagon (thus the name). GLP-1 is the most potent of all the incretins. Its level begins to rise immediately after food ingestion. Although the mechanism of release is not known, a neural stimulus and close contact of nutrients with L-cells have been proposed as the mechanisms. GLP-1 interacts with its receptors in the pancreas, resulting in release of insulin. GLP-1 also decreases glucagon from the α -cells of the pancreas and promotes satiety in the CNS. GLP-1 has been found to stimulate growth and increase survival of β -cells and also to stimulate the proliferation and differentiation of new β -cells. The degradation product of GLP-1, GLP-1(9-36)-amide, from DPP-4 enzymatic activity, does not possess glucose-lowering activity.¹²

In diabetic patients, the postprandial release of GLP-1 is impaired, and the later (60 to 120 minutes postprandial) response is reduced also, which results in a late-phase hypoinsulinemia. The glucagon-reducing action also is impaired in diabetes mellitus, causing glycogenolysis, which results in postprandial hyperglycemia.

DIPEPTIDYL PEPTIDASE-4 AS A THERAPEUTIC TARGET

Once in circulation, incretins have a very short half-life, because they are degraded rapidly by DPP-4, also known as CD 26. The enzyme DPP-4 is extremely diverse in terms of its distribution and function. It is located in the kidneys, intestines, liver, placenta, uterus, prostate, skin, capillary endothelium, plasma, and body fluids. It cleaves incretins and many other proteins that have proline or alanine in the second position by cleaving two N-terminal amino acids.¹³ These two amino acids are important for the biological activity of the incretins GIP and GLP-1, which are rendered inactive by the proteolytic activity of DPP-4. DPP-4 is present in gut mucosa adjacent to L-cells, and 50% of GLP-1 is degraded even before it is released from gut mucosa. Both GIP and GLP-1 are inactivated in circulation, and the degradation products are cleared renally. In addition to DPP-4, another enzyme neutral endopeptidase 24.11 (NEP 24.11) cleaves GLP-1; however, its physiologic significance is unknown.

In addition to incretins, DPP-4 cleaves various neuropeptides. These include pituitary adenylate

cyclase activation polypeptide (PACAP), vasoactive intestinal polypeptide (VIP), gastrin-releasing peptide (GRP), neuropeptide Y (NPY), growth hormone-releasing hormone (GHRH), GLP-2, and peptide YY. Furthermore, DPP-4 has been found to play a role in the cellular uptake of HIV-1, malignant transformation, and tumor invasion. Additionally, it may be a tumor marker for certain malignancies.^{14,15} The clinical significance of these roles of the DPP family of enzymes and DPP-4 in particular is unknown.

Inhibition of DPP-4 enzyme results in prolonging the physiologic effect of endogenously produced incretins. The DPP-4 inhibitors are α -amino acid derivatives that can be modified to increase their affinity, potency, selectivity, oral bioavailability, and duration of action. DPP-4 inhibition caused a sixfold increase in GLP-1 given exogenously by infusion, but a similar response was not observed in endogenous GLP-1 secretion.¹⁶ In most animal studies, DPP-4 inhibition was associated with mild increase in GLP-1 level, and it is uncertain if this modest increase in GLP-1 alone could be responsible for insulinotropic and antihyperglycemic effect of DPP-4 inhibitors. Increasing the half-life of other substrates, other than GIP and GLP-1, also may contribute to the therapeutic potential of DPP-4 inhibitors. The major mechanism by which DPP-4 inhibitors exert their antidiabetic effect is by inhibition of glucagon secretion. In addition, DPP-4 inhibition improves β -cell function. Although the insulin level is not increased, the threshold of glucose level to secrete insulin is lowered by DPP-4 inhibitors, thereby increasing the insulinogenic index. This improvement in β -cell function has been demonstrated by multiple indices, including improvement in the homeostasis model assessment (HOMA) β -cell, fasting proinsulin:insulin ratios, and 3-hour postmeal insulin:glucose area-under-the-curve (AUC) ratios.¹⁷

A comparison between use of DPP-4 inhibitors and GLP-1 mimetics indicates that an increase in GLP-1 is not the sole mechanism of action of DPP-4 inhibitors. Various DPP-4 inhibitors are either in preclinical or clinical use. These include sitagliptin, vildagliptin, and saxagliptin. The data on the efficacy of DPP-4 inhibitors suggest that not only are they effective as antihyperglycemic agents in the treatment of diabetes, but they also have disease-modifying abilities by attenuating or reversing the loss of β -cell mass and function. Treatment of streptozotocin-treated animal models with DPP-4 inhibitors resulted in restoration of β -cell function.¹⁸ DPP-4 inhibitor use also resulted in dose-dependent increases in the number of β -cells in islets and increased glucose-stimulated insulin secretion in isolated islets. There are

various other DPP-4 inhibitors that are at various stages of clinical trials.

DATA SOURCES AND SEARCHES

The authors conducted a search of MEDLINE (1966 to April 2008) and the Cochran Central Register of Controlled trials (first quarter of 2008) for English language randomized-controlled trials of DPP-4 inhibitor therapy in adults who had type 2 diabetes. They used the following search terms: diabetes, blood glucose, hemoglobin A1c, glycohemoglobin, GLP-1, dipeptidyl peptidase, DPP, LAF237, MK-0431, sitagliptin, vildagliptin, saxagliptin, human, and clinical trial. The authors also searched the clinical trials Web site (www.clinicaltrials.gov) and the references from the previously mentioned searches. Here the focus is on sitagliptin and vildagliptin as these are the most commonly used DPP-4 inhibitors.

EFFICACY OF DIPEPTIDYL PEPTIDASE-4 INHIBITORS

Sitagliptin

Sitagliptin causes an effective dose-dependent inhibition of DPP-4 enzyme, resulting in an increase in incretin levels without causing hypoglycemia. It is highly selective for the DPP-4 enzyme, well-tolerated at high doses (up to 600 mg daily) with no GI adverse effects.^{19,20} A single dose of sitagliptin (50 to 200 mg) caused greater than 80% reduction in DPP-4 activity, producing two- to threefold increase in GLP-1 and GIP levels, increasing insulin and C-peptide levels, reducing plasma glucagon levels, and reducing hyperglycemia after oral glucose tolerance test (OGTT).^{19,21}

Sitagliptin does not inhibit CYP enzymes in vitro,²² and its half-life is 8 to 14 hours, achieving a steady-state concentration in 3 days.^{19,20,23} The renal clearance is independent of the dose, and over 80% of the dose is excreted in urine unchanged. The pharmacokinetic and pharmacodynamic profile on multiple doses of sitagliptin in healthy, normoglycemic male subjects was similar to the daily doses, indicating once daily is a suitable dosing schedule.²⁰ Food intake does not affect the pharmacokinetics of sitagliptin, indicating that the medication can be taken with or without food.²⁴

In animal studies done on a high fat diet (HFD) streptozotocin (STZ)-induced diabetic mice, it has been demonstrated that chronic treatment with des-fluoro-sitagliptin, an analog of sitagliptin, not only improved postprandial and fasting hyperglycemia and HgA1c, but also caused a dose-dependent increase in insulin-producing

β -cells in islets, resulting in normalization of β -cell mass and β -cell to α -cell ratio.¹⁸

The efficacy of sitagliptin in controlling hyperglycemia has been demonstrated in several studies (Table 1).^{21,25-28} Patients who had diabetes for less than 3 years had greater benefit than those who had longer duration of disease. Also, the patients with higher HgA1c (greater than 9%) had a greater decrease in HgA1c than those who had lower (less than 8%) HgA1c. In addition, fasting blood sugar, postmeal glucose, proinsulin:insulin ratio, and β -cell function also improved. Patients on sitagliptin experienced higher incidence of nasopharyngitis, back pain, osteoarthritis, and pain in extremities compared with the placebo groups. Apart from very small increases in white blood cells (WBCs) and absolute neutrophil counts (ANCs), there were no meaningful changes in routine laboratory tests. Various trials have looked at the effect of sitagliptin on lipid parameters; however, the results have been inconsistent. It is likely the lipid profile is unchanged.

Sitagliptin is approved as initial monotherapy, as well as combination therapy, and also is marketed as a combination product with metformin. Metformin has been demonstrated to increase GLP-1 levels;²⁹ therefore a combination of metformin with a DPP-4 inhibitor is theoretically appealing. Initial therapy with sitagliptin (50 mg twice daily and 100 mg daily) and metformin (500 mg and 1000 mg twice daily) as monotherapy and combination therapy in 1,091 patients who had type 2 diabetes (ages 18 to 78 years) over a 24-week period showed that the two medications were effective individually in improving β -cell function, insulin resistance, and glycemic control. Additionally, metformin exhibited additive effect in the combination therapy.^{17,30-33} Metformin treatment resulted in a small but significant weight reduction, while sitagliptin was weight neutral.

Sitagliptin has been studied in type 2 diabetic patients who were controlled poorly on glimepiride alone or glimepiride and metformin combination.

Table 1
Efficacy studies

Drug	Add on to	Decrease in A1c	Study
Sitagliptin	Monotherapy	0.38% to 0.77%	Scott et al (2007) ²⁸
Sitagliptin	Monotherapy	0.48% to 0.6%	Raz et al (2006) ²⁶
Sitagliptin	Monotherapy	0.79% to 0.94%	Aschner et al (2006) ²⁷
Sitagliptin	Monotherapy	0.4% to 0.6%	Hanefeld et al (2005) ²⁵
Sitagliptin	Monotherapy	1.05%	Nonaka et al (2008) ⁶¹
Sitagliptin	Metformin	0.77%	Goldstein et al (2007) ³⁰
Sitagliptin	Metformin	1.00%	Raz et al (2008) ¹⁷
Sitagliptin	Metformin	0.67%	Nauck et al (2007) ³⁵
Sitagliptin	Metformin	0.65%	Charbonnel et al (2006) ³³
Sitagliptin	Pioglitazone	0.70%	Rosenstock et al (2006) ³⁶
Sitagliptin	Glimepiride	0.74%	Hermansen et al (2007) ³⁴
Sitagliptin	Glimepiride + Metformin	0.89%	Hermansen et al (2007) ³⁴
Vildagliptin	Monotherapy	0.53% to 0.56%	Ristic et al (2005) ⁴²
Vildagliptin	Monotherapy	0.6% to 1.2%	Pratley et al (2006) ⁴⁴
Vildagliptin	Monotherapy	0.5% to 0.9%	Pi-Sunyer et al (2007) ⁴⁵
Vildagliptin	Monotherapy	0.7% to 0.9%	Dejager et al (2007) ⁴⁶
Vildagliptin	Monotherapy	0.30%	Mari et al (2008) ⁵¹
Vildagliptin	Monotherapy	1.0% to 1.2%	Pratley et al (2007) ⁵³
Vildagliptin	Monotherapy	0.15%	Rosenstock et al (2008) ⁵²
Vildagliptin	Metformin	0.70%	Ahren et al (2004) ⁵⁶
Vildagliptin	Metformin	0.7% to 1.1	Bosi et al (2007) ⁵⁷
Vildagliptin	Pioglitazone	0.8% to 1.0%	Garber et al (2007) ⁵⁷
Vildagliptin	Pioglitazone	1.7% to 1.9%	Rosenstock et al (2007) ⁵⁹
Vildagliptin	Insulin	0.60%	Fonseca et al (2007) ⁶⁰

In this 24-week study of 441 patients 18 to 75 years of age, sitagliptin 100 mg daily improved glycemic control and β -cell function in both groups.³⁴ Sitagliptin caused a small increase in hypoglycemia and weight gain, possibly because of the sulfonylurea. Similar results were obtained when sitagliptin was compared with another sulfonylurea glipizide in a 52-week study involving 1,172 type 2 diabetic patients who were controlled inadequately on metformin alone.³⁵ At the end of the study, proinsulin:insulin ratio, which is a function of β -cell dysfunction was higher in glipizide treated diabetic patients compared with sitagliptin-treated patients. This deterioration in β -cell function is most likely because of chronic β -cell stimulation by glipizide.

The efficacy of sitagliptin added to on going pioglitazone therapy was studied in a 24-week study of 175 patients who had type 2 diabetes.³⁶ The addition of sitagliptin 100 mg daily to pioglitazone (30 or 40 mg daily) therapy resulted in a drop of HgA1c from 7.82% to 7.17%, a reduction of 0.70%. In the combination therapy group alone, 45.4% of patients achieved HgA1c of less than 7.0%, compared with only 23.0% in the pioglitazone treatment group. Fasting serum proinsulin and the proinsulin:insulin ratio also were reduced by the addition of sitagliptin. Sitagliptin and rosiglitazone have not been studied in combination therapy, but in a two-period crossover study of 5 days on 18 adult healthy patients, where sitagliptin was not found to change the pharmacokinetics of rosiglitazone.³⁷

Incretins have been reported to have some relationship, not yet fully understood, with hypertension. Although GLP-1 and GLP-1 receptor agonists have been reported to increase blood pressure and heart rate in animal models, continuous intravenous administration of GLP-1 resulted in a mild decrease in blood pressure in patients who had type 2 diabetes.³⁸⁻⁴⁰ Because sitagliptin increases GLP-1, its effect on hypertension was studied by Mistry and colleagues,⁴¹ who found no significant effect on blood pressure.

Vildagliptin

Vildagliptin is a selective DPP-4 inhibitor that enhances islet cell function by increasing α - and β -cell responsiveness to glucose, resulting in meal-stimulated increase in biologically active GLP-1. Additionally, it improves glucose tolerance. Vildagliptin was studied in 279 patients who had type 2 diabetes over 12 weeks, in which vildagliptin was used from 25 to 100 mg daily doses; 50 mg and 100 mg daily doses resulted in a reduction in HgA1c by 0.56% and 0.53%, respectively.⁴² The

number of patients who achieved HgA1c less than 7% was higher among patients who received doses of 100 mg daily, 50 mg daily, or 25 mg twice daily, compared with 25 mg daily or placebo groups. As seen with sitagliptin, patients who had higher HgA1c and those who had body mass index (BMI) of greater than 30 kg/m² had increased reduction in HgA1c. In this study, an improvement in β -cell function was observed. Other studies have demonstrated similar effects of vildagliptin increasing β -cell mass.⁴³⁻⁴⁷ Vildagliptin treatment resulted in a decrease in glucagon levels, with no effect on insulin levels over the study period. Baseline GLP-1 levels were increased with increased GLP-1 response to breakfast, with a reduced glucose and glucagon response. Balas and colleagues also found a sustained elevation in the incretins for a period beyond the duration of DPP-4 inhibition.⁴⁷

The potential effect of vildagliptin on pancreatic mass was studied, which showed that 2 to 3 months of treatment results in a dose-dependent increase in pancreatic β -cell mass and improved islet function in high-fat fed streptozotocin-injected diabetic mice.¹⁸ Studies done on animals have shown that GLP-1 may increase β -cell mass by reducing apoptosis and also by helping endocrine precursor cells to differentiate into β -cells, stimulating replication of β -cells, and forming new islets. A long-duration study was conducted by Ahren and colleagues,⁴⁸ however, in which 55 type 2 diabetic patients on metformin were randomized to receive either vildagliptin or placebo. The patients had an average age of 56 \pm 1.5 years with BMI of 29.6 \pm 0.5 kg/m² and HgA1c of 7.7 \pm 0.1%. At baseline and after 52 weeks of treatment, proinsulin related to insulin secretion was measured with C-peptide in the fasting and postprandial (4 hours after meal) states to assess β -cell function. It was observed that the dynamic proinsulin to C-peptide ratio (DyP/C) relative to glucose was reduced significantly with vildagliptin compared with placebo, both in the fasting state ($p = 0.023$) and postprandially ($p = 0.004$). This indicates that vildagliptin treatment improves β -cell function as evident by a more efficient β -cell insulin processing capacity.

Because GLP-1 is an inhibitor of gastric emptying, a study was conducted to see the effect of vildagliptin, which increases GLP-1, on gastric emptying.^{49,50} It was concluded that although DPP-4 inhibition results in doubling of the postprandial concentration of GLP-1, it does not alter the gastric emptying.

To evaluate the effect of vildagliptin on patients with mild hyperglycemia, 306 patients with HgA1c of 6.2 to 7.5% were studied over 2 weeks using

vildagliptin at 50 mg daily dose.⁵¹ Vildagliptin showed statistically significant increase in fasting insulin, glucose sensitivity, and rate sensitivity, but the total insulin secretion excursion during meals were unchanged. These changes caused reduction in glucose and an improvement in HgA1c by $-0.3 \pm 0.1\%$ ($p = <0.001$). Vildagliptin also has been studied in a 12-week, double blind and randomized study on 179 patients with impaired glucose tolerance (IGT) with average HgA1c 5.9%.⁵² This unique study on pre-diabetic patients showed that vildagliptin 50 mg twice daily decreased HgA1c by 0.15% and glucagon by 3.3 pmol/L/h, and increased insulin by 37 pmol/L/h, GLP-1 by 8.8 pmol/L/h, and GIP by 51.3 pmol/L/h. Postprandial hyperglycemia was decreased. The decrease in HgA1c occurred despite normal baseline HgA1c, and contrary to previous studies on patients who had type 2 diabetes, there was no change in FPG. It is evident that vildagliptin is effective in improving glycemic control and the β -cell function in patients who have mild hyperglycemia, as in patients who have severe hyperglycemia.

A study was conducted to evaluate the efficacy and risks of vildagliptin as monotherapy in elderly patients.⁵³ Vildagliptin as monotherapy in 100 mg daily doses (50 mg twice daily or 100 mg once a day) were studied over 24 weeks in younger (less than 65 years; $n = 1,231$) and older (≥ 65 years; $n = 338$) patients and the data from five double-blind, randomized, placebo-controlled trials were pooled. The study also included active groups who were treated with either metformin (1,000 mg twice daily) or one of the TZDs (pioglitazone 30 mg daily or rosiglitazone 8 mg daily). The baseline HgA1c in older patients was $8.3 \pm 0.1\%$, which dropped by $1.2 \pm 0.1\%$ whereas the baseline HgA1c in younger patients was $8.7 \pm 0.0\%$, which dropped by $1.0 \pm 0.0\%$. Vildagliptin did not increase the adverse side effects in 62% of the older patient population with mild renal impairment and hypoglycemia was rare (0.8%). These results showed that vildagliptin is effective and tolerated well in elderly patients.

Vildagliptin (50 mg twice daily) was compared with metformin (1000 mg twice daily) on 780 type 2 drug-naïve patients with baseline HgA1c between 7.5% and 11.0%.⁵⁴ In this 52-week double-blind, randomized, multicenter, parallel group study HgA1c was measured over the study period. At the end of the study, both vildagliptin and metformin reduced HgA1c by $1.0\% \pm 0.1\%$ ($p = <0.001$) and $1.4\% \pm 0.1\%$ ($p \leq 0.001$), respectively. The number of patients who experienced adverse effects was almost similar in the vildagliptin (70.1%) and metformin (75.4%)

groups. However, metformin was associated with three- to fourfold greater incidence of diarrhea, nausea and abdominal pain. The incidence of hypoglycemia was equally low with both drugs.

Vildagliptin (50 mg twice daily) also has been compared with rosiglitazone (8 mg once a day) as monotherapy in a 24-week study on 786 patients who had type 2 diabetes.⁵⁵ In this double-blind, randomized study, monotherapy with vildagliptin and rosiglitazone decreased HgA1c to a similar extent during the 24-week period. At the end of the study, vildagliptin caused a reduction in HgA1c by $1.1 \pm 0.1\%$ ($p = <0.001$), whereas rosiglitazone decreased HgA1c by $1.3 \pm 0.1\%$ ($p = <0.001$). FPG decreased more with rosiglitazone (-2.3 mmol/L) compared with vildagliptin (-1.3 mmol/L). Rosiglitazone, but not vildagliptin, caused an increase in body weight ($+1.6 \pm 0.3$ kg; $p \leq 0.001$). Incidence of edema was greater with rosiglitazone (4.1%) compared with vildagliptin (2.1%), but the incidence of other adverse effects was similar between the two drugs.

Vildagliptin has been shown to be efficacious in treating type 2 diabetes as an add-on therapy with metformin.^{56,57} Vildagliptin in 50 and 100 mg daily doses was evaluated for its antihyperglycemic effect on 544 type 2 diabetic patients who were controlled inadequately (HgA1c 7.5% to 11.0%) on metformin (≥ 1500 mg daily) therapy.⁵⁷ At the end of 24-week study period, the between-treatment difference (vildagliptin – placebo) was $-0.7\% \pm 0.1\%$ ($p < 0.001$) and $-1.1\% \pm 0.1\%$ ($p < 0.001$) with 50 and 100 mg daily doses of vildagliptin, respectively. The between-treatment difference in FPG was -1.8 ± 0.3 mmol/L ($P = 0.003$) and -1.7 ± 0.3 mmol/L ($p < 0.001$) in patients receiving 50 or 100 mg vildagliptin daily, respectively. Two doses of vildagliptin and placebo had similar incidence of adverse effect; however, GI adverse effects were higher in the placebo group than groups receiving either of the two doses. This study shows that vildagliptin at both doses is effective in improving glycemic control in patients who are not optimally controlled with metformin monotherapy. Hypoglycemia was rare and weight gain was insignificant. Similar results were observed in another study by Ahren and colleagues.⁵⁶

Vildagliptin also has been demonstrated to be effective in improving glycemic control when added to the on-going treatment with pioglitazone.⁵⁸ In this 24-week multicenter, double-blind, randomized, parallel group study, vildagliptin at 50 and 100 mg daily doses was compared with placebo as an add-on therapy to maximum-dose pioglitazone (45 mg daily) treatment in 463 type 2 diabetic patients who were controlled

inadequately with prior TZD monotherapy. Vildagliptin showed a dose-dependent decrease in HgA1c; 50 and 100 mg daily doses reduced HgA1c by $0.8\% \pm 0.1\%$ ($p = 0.001$ versus placebo) and $1.0\% \pm 0.1\%$ ($p < 0.001$ versus placebo), respectively. With a similar aim as in the previous study but a different study design, vildagliptin was compared with pioglitazone as monotherapy, and the two drugs were tested as a combination therapy.⁵⁹ In this 24-week randomized, double-blind, multicenter study 607 type 2 diabetic patients had baseline HgA1c of approximately 8.7%. Pioglitazone (30 mg daily), vildagliptin:pioglitazone (50/15 mg daily) combination, vildagliptin:pioglitazone (100/30 mg daily) combination, and vildagliptin (100 mg daily) showed an adjusted mean change in HgA1c of $-1.4\% \pm 0.1\%$, $-1.7\% \pm 0.1\%$, $-1.9 \pm 0.1\%$, and $-1.1\% \pm 0.1\%$ from baseline, respectively. These results indicate that both combinations were more potent in reducing HgA1c compared with pioglitazone alone ($p = 0.039$ and $p < 0.001$, respectively). In the high-dose combination therapy, 65% patients achieved HgA1c of 7%, with a tolerability profile similar to pioglitazone 30 mg daily monotherapy. Furthermore, the low-dose combination (50/15 mg daily) had better efficacy and tolerability benefit over pioglitazone 30 mg daily monotherapy. The adverse events ranged from 45.8% in the low-dose combination group to 51.6% in the pioglitazone monotherapy group. Pioglitazone monotherapy was associated with dose-dependent peripheral edema (up to 9.3%). Hypoglycemic events were minimal. These results indicate that vildagliptin/pioglitazone combination may be a more effective initial oral pharmacotherapy than either drug alone for managing type 2 diabetes.

Often type 2 diabetes remains uncontrolled on both oral medications and insulin. Vildagliptin was studied as an add-on therapy to insulin in a 24-week multicenter, double-blind, randomized, placebo-controlled, parallel-group study on 296 type 2 diabetic patients who were controlled inadequately (HgA1c = 7.5% to 11%) on insulin.⁶⁰ While on insulin therapy, 144 patients received vildagliptin (50 mg twice daily), and 152 patients received placebo. Patients had a baseline HgA1c of $8.4\% \pm 0.1\%$. The adjusted mean change in HgA1c from baseline (AM Δ) was $-0.5\% \pm 0.1\%$ for vildagliptin group and $-0.2\% \pm 0.1\%$ for the placebo group, with a significant difference between the interventions ($p = 0.01$). In patients older than 65 years, the AM Δ HgA1c was $-0.7\% \pm 0.1\%$ in the vildagliptin group versus $-0.1\% \pm 0.1\%$ in the placebo group ($p \leq 0.001$). Vildagliptin treatment and placebo were associated with equal

number of adverse events (81.3% and 82.9%, respectively). Hypoglycemic events with vildagliptin, however, were less common ($p < 0.001$) and less severe ($p < 0.05$) compared with the placebo group. This study demonstrated that vildagliptin improves glycemic control in patients who are not at goal with insulin. Furthermore, the drug is associated with fewer incidents of hypoglycemia.

SUMMARY

Type 2 diabetes mellitus is a major risk factor for coronary artery disease (CAD) and is considered as a CAD-equivalent. The optimal control of diabetes is often daunting, requiring multiple medications. New medications also are needed when the adverse effects (eg, fluid retention, heart failure, hypoglycemia, weight gain) of the currently available medications limit their use. DPP-4 inhibitors such as sitagliptin and vildagliptin are effective in controlling diabetes as monotherapy and combination therapy, including their use with insulin.

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