Advances in pharmacotherapy of Type 2 diabetes (Part-3: The gliptins)

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Summary
Type 2 diabetes is witnessing major advances in pharmacotherapy. After a rather dormant period spanning the period from 1960s to the 1990’s following the discovery of the sulphonylurea and biguanide groups of drugs in the 1950’s, significant advances have been achieved in discovering new drugs. This has been possible because of the advances in biotechnology. In this part of the series of reviews we will be looking at the second group of the incretin-based therapies. These gliptins which include several agents, namely sitagliptin, vildagliptin and saxagliptin, with others still in development. The other group of the incretin-based agents, the incretin mimetics have been discussed in more details in the previous issue of this journal.

Keywords: Diabetes mellitus, incretin mimetics, gliptins, type 2 diabetes Dipeptidylpeptidase-4

Introduction
In the previous articles, we have presented an overview of the conventional oral anti-hyperglycaemic agents, metformin, sulphonylurea, metiglinides, and thiazolidinediones, and their role in management of patients with type 2 diabetes(1). In the preceding issue of this journal we have discussed the role of the incretin-mimetics(2). In this article, we shall continue to discuss the mechanism of action, potential impact and the role of the other group of the incretin-based anti-hyperglycaemic therapies in management of patients with type 2 diabetes. This second...
group, the dipeptidyle peptidase-4 (DPP4) antagonists have been in clinical use for the last few years. They are known also as the gliptins. We will also review the latest clinical data in this field. In subsequent issues, we shall cover other therapies for type 2 diabetes including insulin and other non-oral agents. We are also striving to present an overview of the advances in our understanding of the pathophysiology and genetics of type 2 diabetes as well as emerging new therapies which are still in research pipelines.

**Dipeptidyl Peptidase-4 (DPP-4) Inhibitor (Gliptins)**

DPP-4 inhibitors (gliptins) have been shown to modulate glucose homeostasis mainly via preserving the action of incretin hormones through suppression of DPP-4. DPP-4 is the enzyme that inactivates GLP-1 and GIP. Inhibition of the DPP-4 prolongs the half-life and increases the circulating concentration of GLP-1 and GIP. Increase levels of GLP-1 and GIP levels in turn lead to higher incretin levels and activity in both the fasting and post-prandial states, and consequently higher insulin release and greater suppression of glucagon. Thus, DPP-4 inhibitors improve fasting and post-prandial blood glucose concentrations by increasing glucose-stimulated insulin secretion and suppressing fasting and post-prandial glucagon concentrations. It is clear that the DPP-4 inhibitors are entirely dependent on secretion of endogenous incretin; thus, they may best used early in type 2 diabetes before substantial impairments in incretin secretion and beta-cell function become apparent. DPP-4 inhibitors represent the first oral agents targeted at increasing endogenous incretin activities and levels. Several agents have been developed, including sitagliptin, vildagliptin, saxagliptin, and allogliptin. Sitagliptin, vildagliptin and saxagliptin are already licensed for clinical use in Europe and USA. All DPP-4 inhibitors are orally active, their bioavailability exceed 80%. However, the metabolism and excretion of these agents vary considerably.

**Vildagliptin**

Vildagliptin is an effective DDP-inhibitor, in a reversible, competitive and selective manner, and thus it results in an increase in GLP-1, which in turn aids in glucose homeostasis and insulin secretion. Vildagliptin is an oral medication with a half-life of about 90 minutes, however, more than 50% of its DPP-4 inhibition continues for more than 10 hours, allowing for once or twice daily dosing. Vildagliptin is extensively metabolized, primarily in the liver, and its major metabolites are pharmacologically inactive. It is largely excreted in urine, 18-22% of the amount excreted is unmetabolised drug. It is therefore contra-indicated in severe liver disease.

The efficacy and safety of vildagliptin in patients with type 2 diabetes have been assessed in many clinical studies. Vildagliptin monotherapy for 24 weeks has been shown to significantly lower blood glucose levels in drug naive patients with type 2 diabetes in 2 studies. In the first study, patients were randomized to vildagliptin 50 mg once daily, 50 mg twice daily, 100 mg once daily or placebo. HbA1c and fasting blood glucose level were both decrease with vildagliptin treatment, but were only significant with vildagliptin 50 mg twice daily and 100 mg once daily, but not with vildagliptin 50 mg once daily. Combination of vildagliptin and metformin was assessed in patients with type 2 diabetes who were treated with metformin monotherapy in a randomized, placebo controlled study for 12 weeks. This was followed by a 40-week extension in those patients agreeing to continue with the study. The vildagliptin and metformin combination showed significant A1c reduction in the 12 and 52 weeks time period, with a reduction of A1c of -0.7% and -1.1% respectively. More patients achieved the target A1c of ≤7.0% in
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vildagliptin plus metformin group compared to metformin plus placebo group, and there were significant decrease on both fasting as well as postprandial blood glucose level in the vildagliptin plus metformin group compared to placebo. Another 24-week non-inferiority study assessed the efficacy of vildagliptin 50 mg twice daily compared with rosiglitazone 8 mg daily in patients with type 2 diabetes\(^{(7)}\). From a baseline of 8.7%, A1c decreased to 7.6% in vildagliptin compared to 7.4% in the rosiglitazone group. There was a significant increase in body weight (1.6 kg) in the rosiglitazone group, with no weight change seen in vildagliptin group. The effect of vildagliptin on beta-cell function and insulin sensitivity were evaluated over the 52 weeks\(^{(8)}\). The investigators observed that a sustained increased in meal-related insulin secretion in patients receiving vildagliptin plus metformin throughout the study period and concluded that vildagliptin in combination with metformin improves beta-cell function in patients with type 2 diabetes. In a systematic review of studies involving the use of vildagliptin; Kleppinger and Helms (2007)\(^{(9)}\) concluded that, vildagliptin use in patients with type 2 diabetes either as monotherapy or in combination with metformin is associated with significant reduction in A1c and increased GLP-1 activity 45 minutes after dosing. There was reduction in the level of glucagon, but little or no change in insulin levels. Reduction in the level of fasting plasma glucose was observed, with some reduction in postprandial plasma glucose and net decrease in HbA1c. There was a slight increase in the incidence of hypoglycaemia with longer treatment duration. Another review of pooled data of vildagliptin use as monotherapy was conducted by Rosenstock & Fitchet (2008)\(^{(10)}\). Vildagliptin use showed comparable efficacy to that of pioglitazone in reducing HbA1c, with neutral effect on body weight, oedema and lipid profile maintained over a period of two years. In the same data, vildagliptin as an add-on therapy to metformin, sulphonylurea, TZD or insulin produced improvement in glycaemia and was associated with less risk of hypoglycaemia. In addition, the use of vildagliptin in subjects with impaired glucose tolerance has been reported to result in improved beta cell function and reduced glycaemic excursions\(^{(9,10)}\). Vildagliptin is usually well tolerated with a low rate of adverse effects seen in clinical trials. Headache, dizziness and nasopharyngitis have been the adverse effects most commonly reported in clinical trials, with an incidence similar to placebo\(^{(5-9)}\). Hypoglycaemia occurred in less than 1% in patients treated with vildagliptin. Perhaps of concern with vildagliptin are the elevated liver enzymes, and it is recommended that liver function should be monitored during vildagliptin therapy. The above clinical studies have shown that vildagliptin is an effective therapy for patients with type 2 diabetes. It improves blood glucose control resulting in a significant reduction in A1c plus fasting and postprandial blood glucose levels. Vildagliptin has also been shown to be weight neutral, improves beta-cell function and does not significantly increase the incidence of hypoglycaemia when used in patients with type 2 diabetes as monotherapy or in combination therapy.

**Sitagliptin**

Sitagliptin was the first of DPP-4 inhibitor to be launched for clinical use. Sitagliptin inhibits DPP-4 activities by 95% for 12 hours and by 80% after 24 hours, and thus can be given as once daily medication, however, its effects are rapidly lost on discontinuation of treatment\(^{(11)}\). Eighty percent of sitagliptin is excreted by the kidneys, and therefore, a dose reduction is needed for patients with renal impairment (creatinine clearance <50 ml/min)\(^{(11)}\). The preliminary clinical trials of Phase III that preceded its launch involved both its use as monotherapy in placebo
controlled trials and in combination with other anti-diabetic agents. Aschner et al (2006)\(^{(12)}\) in a randomized and controlled placebo study assessed the effect of varying doses of sitagliptin monotherapy in 741 patients with type-2 diabetes, who had an average HbA1c of 8% at baseline, and were randomized to either sitagliptin 100mg or 200mg or placebo for 24 weeks. The study showed that sitagliptin resulted in a significant reduction in HbA1c. In patients with baseline HbA1c of ≥ 9%, A1c was reduced by 1.52 and 1.50% on sitagliptin 100 mg and 200 mg respectively. Those subjects with a baseline of HbA1c < 8% or those whose baseline HbA1c was 8% to 9% had lesser reduction of A1c (-0.65 - 1.13%). The average reduction in fasting plasma glucose was 1.0 mmol/l and that of post-prandial glucose was 2.6 mmol/l. The sitagliptin group showed improved parameters of beta cell function assessed by, C-peptide, proinsulin to insulin ratio and HOMA model. Sitagliptin also resulted in no weight change, but there was higher incidence of gastrointestinal side effects and hypoglycaemia. A similar study\(^{(13)}\) in design and outcome measures involved 551 subjects who failed to achieve a satisfactory glycaemic control on diet and exercise and who had had similar average HbA1c to the study by Aschner et al (2006)\(^{(12)}\). This study\(^{(13)}\) confirmed the finding of Aschner et al with far greater reduction of HbA1c in those who were at the higher A1c quartile (≥ 9%) at baseline\(^{(13)}\). The reduction in fasting plasma glucose and improvement in markers of beta cell function assessed by HOMA, C-peptide levels and pro-insulin/insulin ratio were also reported in patients on sitagliptin treatment. However, the incidence of hypoglycaemia and GI side effects was no different between the active and placebo group.

Several studies have examined the effect of sitagliptin in combination with metformin therapy. Goldstein et al (2007) assessed the addition of sitagliptin to various doses of metformin in a randomized, double-blind, placebo controlled study of 24 weeks duration\(^{(14)}\). A total of 1091 patients with type 2 diabetes who had a range of HbA1c of 7.5-11% were randomized in a double blind manner to receive one of six treatments of metformin and sitagliptin. Patients received metformin 1g or 2g alone or in combination with sitagliptin 100 mg. Two other groups of patients received sitagliptin alone or placebo. Combination of sitagliptin 100mg with either metformin 1g or 2g per day resulted in significant reduction of HbA1c (-2.7% and 1.57% respectively). Sixty six percent in the former and 44% in the later achieved the target A1c of ≤7%. The combination regimen had similar side effects profile to those who took metformin monotherapy. In another study, Charbonnel et al evaluated the effect of 24 weeks of sitagliptin therapy in patients who were inadequately controlled on stable dose of metformin monotherapy\(^{(15)}\). Sitagliptin added to metformin therapy led to an additional reduction of HbA1c of 0.65% compared to those receiving placebo.

The effect of combining sitagliptin and metformin was also compared to the combination of sulphonylurea (glipizide) and metformin in a randomized trial\(^{(16)}\). From a mean baseline of 7.5%, HbA1c changes from baseline were -.67% at week 52 in both groups, confirming non-inferiority of sitagliptin to sulphonylurea, glipizide. Similar proportion of patients achieved HbA1c of less than 7% on sitagliptin and glipizide. Sitagliptin led to weight loss of -1.5 kg compared to weight gain of + 1.1kg with glipizide. Furthermore; the glipizide group suffered more episodes of hypoglycaemia than the sitagliptin group (32% vs 5%). The addition of sitagliptin to other combination regime of oral antidiabetic agents was examined in several studies. Rosenstock et al (2006)\(^{(17)}\) studied a group of patients who failed to achieve a satisfactory glycaemic control ( HbA1c ≥7% to <=10%) after been

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**References:**

3. Charbonnel et al
treated with pioglitazone (30mg or 45mg). The study lasted for 24 weeks and patients were randomized to receive either sitagliptin or placebo, in a double blind placebo control manner, in addition to their usual pioglitazone dose. Those who received sitagliptin had a mean HbA1c reduction of -0.7%, significant improvement in FPG, and favourable effects on indices of beta cell function. Furthermore, 45% achieved the target HbA1c <7% vs. only 23% in the placebo group. The drug was well tolerated and there was no significant increase in the incidence of hypoglycemia.

The combination of sitagliptin with a sulphonylurea agent was also assessed in the study by Hermansen et al (2007)(18). This double-blind placebo-controlled trial studied the addition of sitagliptin to patients who were on a combination of glimepride (4mg) plus metformin (1.5g) and a third group taking glimepride alone. A total number of 441 patients aged 18-75 years, whose baseline HbA1c was ≥7%-10.5%, participated. Pioglitazone was used as a rescue therapy in those exceeding the pre-specified HbA1c glycaemic target during the double blind run in period till the end of the study, which lasted for 24 weeks. The sitagliptin group achieved a mean reduction of A1c of 0.74% relative to placebo. In those with the combination of glimepride and metformin the reduction of A1c was 0.89% compared to that of placebo of 0.57% in the subset of patients taking glimepride alone. In this study, there were 12% excess episodes of hypoglycaemia vs. 2% in the placebo group, and a modest increase in body weight (+ 0.8 kg) in the sitagliptin group vs. reduction of 0.4kg in the placebo group.

The above studies and others in patients with type 2 diabetes have shown that sitagliptin improves blood glucose control and results in significant reduction of A1c, fasting and postprandial blood glucose levels. The addition of sitagliptin to metformin, SU, or pioglitazone monotherapy for 24 weeks improves blood glucose control compared to monotherapy plus placebo with more patients achieving target A1c of ≤7.0% with sitagliptin treatment. The use of sitagliptin monotherapy or in combination with metformin, or pioglitazone has been shown to be weight neutral and did not increase the incidence of mild hypoglycaemia(12-18).

Saxagliptin
Saxagliptin is the most recent addition to the oral anti-diabetic agents, and it is a reversible, competitive, selective inhibitor of the DPP-4 enzyme. The inhibition of DPP-4 is thought to be due to the combined inhibition of saxagliptin and its metabolites. In patients with type 2 diabetes, administration of saxagliptin leads to inhibition of DPP-4 activity for a 24-hour period, and thus it can be used as a once daily preparation. Saxagliptin is rapidly absorbed after oral administration, with maximum plasma concentration attained within 2-4 hours. The efficacy and safety of saxagliptin in patients with type 2 diabetes have been evaluated in multiple clinical studies(19-22). These studies have shown that treatment with saxagliptin 5 mg daily produced clinically relevant and statistically significant improvement in HbA1c, fasting blood glucose, postprandial blood glucose levels compared with placebo, in combination with metformin, in combination with SU and in combination with TZD. Saxagliptin is weight neutral, and has low risk of hypoglycaemia, however, when combining saxagliptin with SU, the dose of SU should be monitored as the risk of hypoglycaemia may increase. Saxagliptin is well tolerated with no increase risk of adverse effects compared to placebo. It also has renal plus hepatic excretion.

Alogliptin
Alogliptin is a DPP-4 inhibitor, which is currently under development for treatment of type 2 diabetes. The short-term efficacy of Alogliptin monotherapy has been demonstrated in doses ranging from 25 to 50 mg once daily(23). In this study, 14-day
Treatment with alogliptin reduced HbA1c by 0.2-0.4% compared to no change with placebo. The efficacy of alogliptin as monotherapy or in combination with metformin, combination with SU or combination with TZD have been evaluated in randomized studies in patients with type 2 diabetes\textsuperscript{(23-25)}. These studies showed that alogliptin is an effective treatment for patients with type 2 diabetes, and results in significant improvement in glycaemic control and significantly reduces A1c, without increasing the incidence of hypoglycaemia. Alogliptin is also generally tolerated and well tolerated.

**Which one is more effective, the incretin-mimetic or the DPP-4 inhibitors (gliptins)?**

This is an intriguing question to answer. A recently published randomized double-blind cross-over study compared the incretin-mimetic, exenatide with sitagliptin in a head to head study. The study involved a group of patients with type 2 diabetes who were on metformin. Two hours postprandial glucose, insulin and glucagon secretion, gastric emptying (assessed by acetaminophen absorption) and caloric intake were used as the study endpoint\textsuperscript{(26)}. The study showed that exenatide is superior to sitagliptin in reducing 2-hour postprandial glucose excursions, reducing insulinogenic index of insulin secretion, and reducing glucagon secretion. Exenatide was also superior in reducing postprandial triglyceride concentration, caloric intake and slowing gastric emptying. However, both agents were equally effective in reducing the net fasting blood glucose level. The study was limited by its short duration, so further studies are needed.

**References**


