Dipeptidyl Peptidase-4 Inhibitors as Add-on Therapy to Metformin

a report by
Bo Åhrén

Dean, Faculty of Medicine, and Professor of Clinical Metabolic Research, Lund University DOI:10.17925/EE.2007.00.02.60

The incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released after food intake and stimulate insulin secretion in a glucose-dependent manner.[1] GLP-1 also inhibits glucagon secretion[2] and, as evident from animal studies, may increase β-cell mass.[3] GLP-1 also induces satiety and may reduce bodyweight.[4] Therefore, GLP-1 has been developed as a novel treatment for type 2 diabetes.[5] However, GLP-1 is rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4).[6] To overcome this problem, two strategies for GLP-1-based therapy have evolved.[7] One strategy has been the development of DPP-4-resistant GLP-1 receptor agonists such as exenatide,[8] which is approved in both the US and the EU for treatment of type 2 diabetes.

The other strategy uses inhibition of DPP-4.[9] The rationale for DPP-4 inhibition as a treatment for type 2 diabetes is that the inactivation of GLP-1 is prevented, which would increase and prolong the suprabasal levels of endogenously released active GLP-1.[9] This in turn will increase insulin secretion and reduce glucagon secretion, and thereby lower glucose levels. The first study to show efficiency of DPP-4 inhibition in diabetic patients demonstrated that a DPP-4 inhibitor (NVP-DPP728) improved metabolic control in drug-naïve type 2 diabetic patients treated over four weeks.[10] At present, several DPP-4 inhibitors are in clinical development. Sitagliptin (Januvia®, Merck Research Laboratories) and vildagliptin (Galvus®; Novartis Biomedical Research Institutes) are those with the longest experience; sitagliptin has been approved by the US Food and Drug Administration (FDA), and vildagliptin has been approved for use in Europe by the European Medicines Agency (EMEA). The purpose of this short review is to examine the current experience of DDP-4 inhibition in metformin-treated patients.

Mechanism of Action of Dipeptidyl Peptidase-4 Inhibition

Several studies have shown that DPP-4 inhibition improves β-cell function in type 2 diabetes patients. This is demonstrated by the observations that prandial insulin levels are sustained during DPP-4 inhibition even in the presence of lowered glucose levels.[11,12] Furthermore, modelling glucose, insulin and connecting peptide (C-peptide) data show that vildagliptin increases insulin secretion through increasing the glucose sensitivity of the β cells.[13] Moreover, sitagliptin reduces the pro-insulin/insulin ratio,[14] which is a sign of improved β-cell function.

Animal studies have also shown increased β-cell mass after DPP-4 inhibition.[15] Glucagon levels during meal ingestion are reduced in subjects treated with vildagliptin, which suggests inhibition of glucagon secretion.[11] Indirect measures of insulin sensitivity show improved insulin action after treatment with vildagliptin.[13] These results demonstrate that DPP-4 inhibition increases β-cell function, inhibits glucagon secretion and improves insulin sensitivity, all of which may contribute to the improved glycaemia measures during treatment. In contrast to the effect of GLP-1 analogues, DPP-4 does not inhibit gastric emptying[16] or reduce bodyweight.[11,17–24]

Dipeptidyl Peptidase-4 Inhibition as Antidiabetic Treatment

Both sitagliptin and vildagliptin are orally active and inhibit DPP-4 with high specificity.[25,26] The inhibition of DPP-4 activity is rapid and is seen within 30 minutes of oral administration. The duration is long: at 24 hours after administration, DPP-4 is inhibited by >80% by sitagliptin 200mg or vildagliptin 100mg.[11,27]

Several studies have shown that both sitagliptin and vildagliptin improve metabolic control in type 2 diabetes. In one study, once-daily administration of vildagliptin (100mg) as monotherapy to drug-naïve type 2 diabetes patients reduced fasting and post-prandial glucose, and glycated haemoglobin (HbA_{1c}) levels were reduced by 0.53% compared with placebo after four weeks.[11] In another monotherapy study, it was demonstrated that vildagliptin at 50mg or 100mg once daily significantly reduced HbA_{1c} compared with placebo over 12 weeks.[17] Vildagliptin over 12 weeks at 25mg twice daily was shown to reduce both fasting and prandial glucose and HbA_{1c} was reduced by 0.6%.[18] In a 24-week parallel-group study in drug-naïve type 2 diabetes patients, vildagliptin 50mg once daily or 50mg twice daily significantly reduced HbA_{1c} compared with placebo.[28] The groups were well balanced at baseline, with a mean age of ~51 years, a mean HbA_{1c} of 8.4% and a mean fasting plasma glucose (FPG) of 10.6mmol/l. Vildagliptin 50mg twice daily and 100mg once daily produced similar significant reductions in HbA_{1c} compared with placebo (-0.7 and -0.8%, respectively), suggesting that the 100mg dose may be effective as monotherapy. Sitagliptin has been shown to reduce HbA_{1c} over a 12-week study in 552 patients by 0.4% (at 25mg once daily) and 0.6% (at 100mg once daily) as monotherapy from a baseline of 7.7%.[22] Similar effects were reported in a study involving 743 patients over 12 weeks.[23]

DDP-4 inhibition has also demonstrated clinical benefit as monotherapy in comparative trials. In a 24-week study on vildagliptin as monotherapy (50mg

Bo Åhrén is Dean of the Faculty of Medicine and Professor of Clinical Metabolic Research at Lund University. He is also the Chief Physician in the Department of Endocrinology at Lund University Hospital. Between 2004 and 2006 he was the Chief Physician in the County of Skåne in Sweden. His clinical and experimental research in diabetology is primarily focused on the regulation of insulin secretion and incretin actions, with particular emphasis on developing a new treatment for type 2 diabetes using the incretin hormone glucagon-like peptide-1. Professor Åhrén received his MD from Lund University, his Physician Diploma from the Swedish Board of Medicine in 1978 and his PhD in pharmacology from Lund University in 1981.

E: bo.ahren@med.lu.se

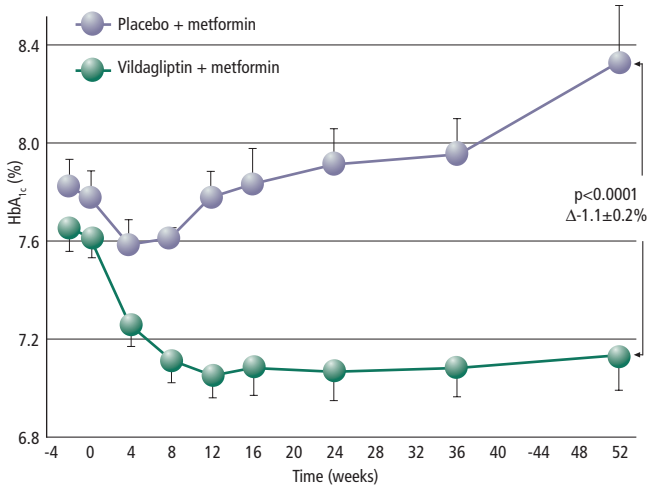
twice daily) in 459 patients, DDP-4 inhibition showed a reduction in HbA_{1c} by 1.1% from a baseline of 8.7% with achievement of non-inferiority versus rosiglitazone.[21] Recently, results of larger, long-term studies on the antidiabetic properties of vildagliptin have been disclosed. A 52-week study using vildagliptin as monotherapy at 50mg twice daily in 526 subjects with type 2 diabetes showed a reduction in HbA_{1c} by 1.0% from a baseline of 8.7%, although non-inferiority to metformin was not reached.[20]

Dipeptidyl Peptidase-4 Inhibition and Its Role as Add-on Therapy to Metformin – Clinical Data and Implications

Due to the progressive nature of type 2 diabetes and the concomitant worsening of glycaemic control, combination therapy usually becomes necessary. In the majority of cases, add-on therapy is included to a metformin regimen, because metformin improves insulin sensitivity, and an agent improving islet function would be of additional benefit. One of the first studies to assess combination therapy with a DDP-4 inhibitor was a 52-week study with vildagliptin versus placebo in 107 type 2 diabetes patients continuing metformin therapy. The study was designed as a 12-week randomised, placebo-controlled trial with a 40-week extension in those patients completing the core 12-week study period. Placebo or vildagliptin 50mg once daily was added to ongoing treatment with metformin 1.5–3.0g daily. The study showed that vildagliptin added to metformin provided clinical benefits compared with the placebo/metformin group.[19] At the end of the 12-week study period, patients randomised to vildagliptin showed a 0.6% reduction in HbA_{1c} from a baseline of 7.7%, whereas the placebo group did not experience a change from baseline. Mean prandial glucose and fasting plasma glucose were significantly reduced in the vildagliptin group compared with placebo ($p<0.0001$ and $p=0.0057$, respectively). These benefits in glycaemic control were maintained in the extension period. At the end-point of the extension, the difference in HbA_{1c} between the groups was 1.1% ($p<0.0001$) (see *Figure 1*). Moreover, at 52 weeks vildagliptin treatment significantly reduced mean prandial glucose and fasting plasma glucose compared with placebo.

A recent phase III study evaluated vildagliptin as an add-on therapy to metformin versus placebo in 544 type 2 diabetes patients. The double-blind, randomised, multicentre, parallel-group study assessed 24-week treatment with vildagliptin 50mg once daily, vildagliptin 50mg twice daily or placebo (n=182) in patients continuing a stable metformin dose regimen (≥1.5g/day) but achieving inadequate glycaemic control (HbA_{1c} 7.5–11%).[29] The result of the study was consistent with the earlier phase II trial[19] and showed that vildagliptin treatment as add-on to metformin monotherapy produces clinically significant and dose-related decreases in fasting plasma glucose and HbA_{1c}. In the current study, the mean baseline HbA_{1c} was 8.4% in both groups of patients randomised to vildagliptin and 8.3% in patients randomised to placebo. Vildagliptin 50mg daily resulted in a placebo-adjusted decrease in HbA_{1c} of 0.8% at week 12. Moreover, HbA_{1c} remained stable for the remainder of the study period compared with placebo, with a placebo-adjusted decrease in HbA_{1c} of 0.7% at week 12 (see *Figure 2*). The higher dose of vildagliptin provided even greater efficacy. At week 12, vildagliptin 100mg daily achieved a between-group reduction in HbA_{1c} of 1.2% compared with placebo, and this reduction was maintained to the end of the 24-week study period (1.1%). Interestingly, the study found that bodyweight did not change significantly after 24 weeks of treatment with vildagliptin 50mg once daily or vildagliptin 50mg twice daily. In comparison, in patients receiving placebo and continuing metformin monotherapy, bodyweight decreased significantly from baseline. One patient in each treatment arm experienced one mild hypoglycaemic event. The results of

Figure 1: Time Course of Glycated Haemoglobin in Patients with Type 2 Diabetes



Patients were given vildagliptin 50mg once daily in combination with metformin (1.5–3g/day; n=42) versus metformin in combination with placebo (n=29). Data are mean ± standard error.
Figure modified after reference 17 with permission from the American Diabetes Association.

this phase III study, and those of the previous phase II study, also suggest that vildagliptin treatment improves meal-related β-cell function.[12,29] These data suggest that DDP-4 inhibition may have important advantages over other currently available antidiabetic agents, especially in terms of efficacy, excellent tolerability profile and negligible impact on bodyweight. A 24-week active, controlled study demonstrated that vildagliptin 50mg twice daily was as effective as pioglitazone 30mg daily in patients with inadequate glycaemic control while receiving a stable metformin dose of ≥1,500mg daily, although only pioglitazone therapy increased bodyweight.[30]

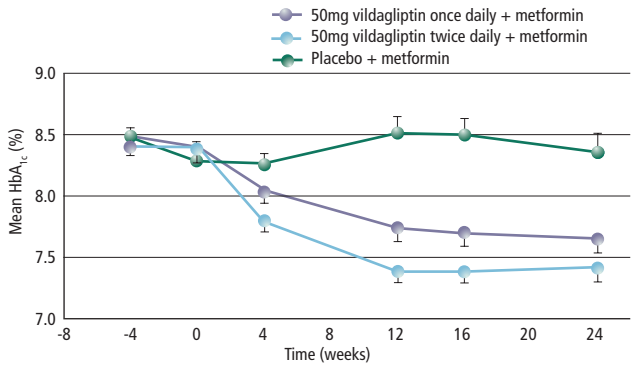
Recently, the results of a study evaluating the efficacy of sitagliptin plus metformin as initial combination therapy were published.[31] The 24-week placebo-controlled, parallel-group study was conducted in patients with type 2 diabetes and inadequate glycaemic control with diet and exercise (HbA_{1c} >7.5%). The trial had five treatment arms plus a placebo arm and patients were then randomised to sitagliptin 100mg daily, metformin 1g or 2g daily, sitagliptin 100mg daily plus either 1g or 2g metformin daily or placebo. All active treatment arms produced statistically significant reductions in HbA_{1c} from baseline to week 24 compared with placebo. However, the combination of sitagliptin plus metformin had a greater effect on HbA_{1c} than the monotherapy arms. The authors of the study concluded that metformin plus sitagliptin has additional effects on diabetic control as measured by HbA_{1c}.

Dipeptidyl Peptidase-4 Inhibition in Other Combination Therapies

A number of studies have evaluated the efficacy of DDP-4 inhibition in combination with other antidiabetic agents, including thiazolidinediones (TZDs) and insulin.

Vildagliptin was evaluated in 463 type 2 diabetes patients failing TZD monotherapy in a 24-week placebo-controlled, multicentre, double-blind, randomised, parallel-group study.[32] Patients were randomised to vildagliptin 50mg or 100mg daily or placebo as add-on therapy to pioglitazone 45mg daily. Both doses of vildagliptin significantly reduced HbA_{1c} from baseline to end-point (between-group differences: 0.8% and 1.0% for vildagliptin 50mg and 100mg daily,

Figure 2: Mean Glycated Haemaglobin During 24 Weeks of Treatment with Vildagliptin as Add-on Therapy



Mean ± standard error HbA_{1c} during 24 weeks of treatment in patients with type 2 diabetes continuing stable metformin dose regimen (≥1,500mg/day). Adapted from Bosi, et al., Diabetes Care*, 2007;30(4):890–95.*[29]

respectively, versus placebo). Furthermore, the authors of the study concluded that, relative to placebo, both doses of vildagliptin in combination with pioglitazone significantly increased the insulin secretory rate/glucose by more than three-fold. Moreover, a 24-week study examining addition of sitagliptin 100mg once daily to ongoing treatment with pioglitazone in subjects with type 2 diabetes showed a reduction in HbA_{1c} by sitagliptin by 0.7% from a baseline of 8.0%.[24]

In another trial, the efficacy of initial combination therapy with vildagliptin and pioglitazone was examined in a 24-week study in 607 drug-naïve type 2 diabetes patients.[33] Vildagliptin combined with pioglitazone 30/100mg daily or 15/50mg daily produced significantly greater reductions in HbA_{1c} (1.9% and 1.7%, respectively) from a baseline of 8.7% compared with both pioglitazone and vildagliptin monotherapy. Both high- and low-dose combinations were also more effective at reducing fasting plasma glucose from baseline than the monotherapy arms of the study.

The efficacy of DDP-4 inhibition as add-on therapy has also been evaluated in a 24-week study in patients with type 2 diabetes that was inadequately controlled (HbA_{1c} 7.5–11%) by insulin.[34] Surprisingly, the addition of vildagliptin 50mg twice daily to the insulin regimen produced a mean reduction in HbA_{1c} of 0.5% from baseline. Furthermore, hypoglycaemic events were less common and less severe in vildagliptin-treated patients.

Dipeptidyl Peptidase-4 Inhibition and Lipidaemia

Whereas marked improvements in glycaemic control are consistently seen after DPP-4 inhibition, most studies on DPP-4 inhibition show only minor effects on fasting lipid levels. However, a recent study demonstrated reduction of prandial triglyceride levels after a fat-rich meal following treatment with vildagliptin.[35] Hence, DPP-4 inhibition may improve lipid metabolism in association with improved glycaemia.

Tolerability and Safety of Dipeptidyl Peptidase-4 Inhibition

The clinical studies reported show that both vildagliptin and sitagliptin are remarkably well tolerated. In most studies, the number of adverse events is not different from that in groups treated with placebo. Furthermore, hypoglycaemia is rarely seen, which is explained by the glucose-dependency of the effects. In particular, studies examining the efficacy and tolerability of DDP-4 inhibitors in combination with metformin, pioglitazone or insulin have shown minimal risk of hypoglycaemia. Moreover, the incidence of adverse events was similar in all treatment groups.

Conclusions

DPP-4 inhibition is efficient in reducing HbA_{1c}. In the monotherapy setting, DDP-4 has produced a reduction of approximately 1% in HbA_{1c} in different studies up to 52 weeks in duration. DPP-4 inhibition is also safe and tolerable, as is evident for both vildagliptin and sitagliptin. Mechanistically, DPP-4 inhibitors improve β-cell function and inhibit α-cell secretion; DPP-4 inhibition may also improve insulin sensitivity, and animal studies have shown increased β-cell mass. Therefore, DPP-4 inhibition is a new, efficient and tolerable treatment of type 2 diabetes that may improve the disease process. It may be suggested that a primary place for DPP-4 inhibition is as a first-line treatment since it is efficient, safe, tolerable and orally active.

Furthermore, the efficiency of DPP-4 inhibition in combination both with metformin and with TZDs suggests that it may be useful as combination therapy. Encouragingly, the safety and tolerability data from combination studies show that addition of a DDP-4 inhibitor to the ongoing monotherapy regimen has similar incidences of adverse effects versus monotherapy. Furthermore, there is a low incidence of hypoglycaemia in the combination regimens. Long-term studies are now warranted to show the durability and long-term safety of this approach to treat type 2 diabetes. ■

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