Novel combination treatment of type 2 diabetes DPP-4 inhibition + metformin

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Abstract: Inhibition of dipeptidyl peptidase-4 (DPP-4) as a novel therapy for type 2 diabetes is based on prevention of the inactivation process of bioactive peptides, the most important in the context of treatment of diabetes of which is glucagon-like peptide-1 (GLP-1). Most clinical experience with DPP-4 inhibition is based on vildagliptin (Galvus^{R}, Novartis) and sitagliptin (Januvia^{R}, Merck). These compounds improve glycemic control both in monotherapy and in combination with other oral hyperglycemic agents. Both have also been shown to efficiently improve glycemic control when added to ongoing metformin therapy in patients with inadequate glycemic control. Under that condition, they reduce HbA_{1c} levels by 0.65%–1.1% (baseline HbA_{1c} 7.2–8.7%) in studies up to 52 weeks of duration in combination versus continuous therapy with metformin alone. Sitagliptin has also been examined in initial combination therapy with metformin have; HbA_{1c} was reduced by this combination by 2.1% (baseline HbA_{1c} 8.8%) after 24 weeks of treatment. Both fasting and prandial glucose are reduced by DPP-4 inhibition in combination with metformin in association with improvement of insulin secretion and insulin resistance and increase in concentrations of active GLP-1. The combination of DPP-4 inhibition and metformin has been shown to be highly tolerable with very low risk of hypoglycemia. Hence, DPP-4 inhibition in combination with metformin is an efficient, safe and tolerable combination therapy for type 2 diabetes.

Keywords: DPP-4 inhibition, sitagliptin, vildagliptin, metformin, type 2 diabetes

Introduction

It is known that both the level and the duration of hyperglycemia in type 2 diabetes are closely related to the risk of developing diabetic complications (Stratton et al 2000). Therefore, achieving glycemic control is a prerequisite for prevention of cardiovascular and microvascular complications in type 2 diabetes. Lifestyle interventions, including dietary adjustments and increased physical activity, are cornerstones of the therapy. For most patients, however, pharmacological intervention is required and present guidelines suggest metformin to be a first line treatment (Inzucchi 2000; Nathan et al 2006). Metformin is an inexpensive compound with documented glucose-lowering effect in both obese and non-obese subjects with type 2 diabetes (Inzucchi 2002; Hundal and Inzucchi 2003; Setter et al 2003; Consoli et al 2004; Donnelly et al 2006). Metformin reduces glycemic levels primarily by inhibiting hepatic glucose output (Bailey and Turner 1996; Leverve et al 2003; Stumvoll et al 1995). Metformin has also been shown to improve insulin sensitivity in liver and muscle (Ginnarelli et al 2003). Additional suggested mechanistic effects of metformin are inhibition of glucose absorption in the gut (Ikeda et al 2000) and increase in plasma levels of GLP-1 (Mannucci et al 2001). As has been reviewed (Bailey and Turner 1996), metformin reduces HbA_{1c} levels in the range of 1%–1.5%, depending on the baseline HbA_{1c} levels and the compound is well tolerated, although gastrointestinal adverse events are quite common during the initiation of the therapy. Hypoglycemia is rarely seen during metformin therapy, and the

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potential fatal adverse event of lactic acidosis is uncommon; nevertheless cautious should always be exercised when treating subjects with renal insufficiency with metformin.

Add-on treatment to metformin often required

In spite of the beneficial effects of metformin in improving glycemic control, very often, however, metformin alone is insufficient for achievement of good metabolic control. Often, also, glycemic control deteriorates in metformin-treated patients. This necessitates combination therapy by adding a secondary compound to metformin. Most often, sulphonylureas are added (Inzucchi 2002; Nathan et al 2006). The rationale for this combination is that sulphonylureas stimulate insulin secretion, which is a complimentary mechanism to the improvement in insulin sensitivity by metformin. Other combinations with metformin include thiazolidinediones and insulin (Hundal and Inzucchi 2003; Setter et al 2003; Charbonnel et al 2005; Derosa et al 2006; Umpierrez et al 2006). However, the combinations with sulphonylureas and thiazolidinediones have faced problems, in that sulphonylureas increase the risk of hypoglycemia (Del Prato and Pulizzi 2006; Green and Feinglos 2007) and thiazolidinediones result in weight gain and potential problems of cardiovascular adverse events and increase in the risk of bone fractures in women (Kahn et al 2006; Levetran 2007; Nissen and Wolski 2007). Also the novel GLP-1 based therapy has been found to be successful in combination with metformin. This applies both to the strategy of activating the GLP-1 receptors by exenatide (DeFronzo et al 2005) or liraglutide (Feinglos et al 2005), and by the strategy of preventing the inactivation of endogenous GLP-1 by inhibiting dipeptidyl peptidase-4 (DPP-4) (Ahrén et al 2004; Charbonnel et al 2006; Bosi et al 2007; Brazg et al 2007; Goldstein et al 2007). This review summarizes the experience of combining metformin and a DPP-4 inhibitor in the treatment.

GLP-1 as a target for treatment of type 2 diabetes

The rationale for the development of DPP-4 inhibition in the treatment of type 2 diabetes relies on augmentation of the incretin effect (Holst and Deacon 1998). The incretin effect is the exaggerated insulin secretion that follows oral glucose administration when compared to intravenous glucose administration and it is attributed to gut hormones augmenting glucose-stimulated insulin secretion (Drucker and Nauck 2006). The two most important incretin hormones are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) (Drucker and Nauck 2006). GLP-1 is produced in L-cells, which are located mainly in the distal portion of the ileum. GLP-1 is released during meal ingestion and stimulates insulin secretion in a glucose-dependent manner (Drucker and Nauck 2006). GLP-1 also inhibits glucagon secretion (Dunning et al 2005), delays gastric emptying (Nauck et al 1997) and induces satiety (Gutzwiller et al 1999). In addition, animal studies have presented evidence that GLP-1 increases beta cell mass by stimulating proliferation and inhibiting apoptosis (Perfetti and Hui 2004), although it should be emphasized that such an effect has not been demonstrated in humans. Because all these effects would be important in the treatment of type 2 diabetes, GLP-1 has been developed as a novel therapy (Ahrén and Schmitz 2004). The development of GLP-1 as a therapy has, however, been complicated by its rapid inactivation, which is due to removal of the N-terminal dipeptide end through DPP-4, which inactivates GLP-1 (Mentlein 1999). To overcome this, two strategies have been used. One strategy is the development of GLP-1 receptor agonists (GLP-1 mimetics such as exenatide and liraglutide), which are resistant to DPP-4 (Ahrén and Schmitz 2004). The other strategy is the development of inhibitors of DPP-4, which prevent the inactivation of GLP-1 and thereby enhance and prolong the action of the endogenous incretin hormone (Ahrén and Schmitz 2004; Mari et al 2005; Ahrén 2007a, 2007b). DPP-4 inhibition also prevents the inactivation of the other incretin hormone, GIP, and therefore the concentrations of the active form also of this hormone are increased during DPP-4 inhibition (Mari et al 2005). However, since the action of GIP to stimulate insulin secretion is almost entirely lost in type 2 diabetes (Vilsbøll et al 2002), this raise of GIP concentrations is of less importance.

DPP-4 inhibition as a target for treatment of type 2 diabetes

The rational of DPP-4 inhibition for the treatment of type 2 diabetes was outlined already in 1998 (Holst and Deacon 1998). The first proof-of-concept study of DPP-4 inhibition showed improved metabolic control with reduced fasting and prandial glucose levels and reduction of HbA_{1c} after 4 weeks of treatment of the DPP-4 inhibitor, NVP-DPP728 (Ahrén et al 2002). Improved glycemic control by DPP-4 inhibition has been confirmed in many studies with other compounds and today several DPP-4 inhibitors are in the progress of development (Ahrén 2007a, 2007b). Most experience exists for vildagliptin (LAF237, Galvus^{R}, Novartis) and sitagliptin (MK-0431, Januvia^{R}, Merck), which are orally active

compounds, which efficiently inhibit DPP-4 activity (Ahrén 2006; Kim et al 2005). Both compounds inhibit plasma DPP-4 activity for more than 16 hours after a single administration and are therefore both possible to administer once daily. Furthermore, they have both been shown to improve glycemic control when used in monotherapy as well as in combination therapy with metformin and thiazodilidinedione (Ahrén 2006; Deacon 2007; Gallwitz 2007). Sitagliptin has been approved for treatment of type 2 diabetes in the US and in Europe in combination with metformin and vildagliptin has been approved for treatment of type 2 diabetes in Europe. Of particular importance is that DPP-4 inhibitors are safe and tolerable and that this in combination with their efficiency allow them to be used in early stages of the disease. One such early indication would be to use DPP-4 inhibitors in combination with metformin.

Rationale for combining metformin with DPP-4 inhibition

Type 2 diabetes develops when insulin secretion is insufficiently raised to match insulin resistance (Kahn 2001; DeFronzo 2004). In addition, glucagon levels are inappropriately elevated, which enhances hepatic glucose output and increases fasting glucose (Dunning et al 2005). Therefore, diabetes is a disease with at least three main defects, which need to be corrected: impaired insulin secretion, insulin resistance and hypersecretion of glucagon. The rationale for combining metformin with DPP-4 inhibitors is the complimentary mechanism of action of the two strategies. Thus, metformin acts primarily by reducing hepatic glucose output and improving insulin sensitivity in liver and muscle (Stumvoll et al 1995; Bailey and Turner 1996; Hundal and Inzucchi 2003; Leverve et al 2003; Setter 2003) whereas DPP-4 inhibitors act by increasing GLP-1 levels and thereby stimulating insulin secretion and inhibiting glucagon secretion (Ahrén 2007a; Ahrén 2007b). The two strategies therefore have the potential to improve different mechanisms, which are defective in type 2 diabetes and therefore an additive or synergistic action when used in combination is anticipated. In addition, metformin has been shown to increase GLP-1 levels (Mannucci et al 2001), which would be a potential for an additional synergistic action with DPP-4 inhibitors. The mechanism underlying the increase in GLP-1 levels by metformin remains to be finally established; it has been suggested to be caused by inhibition of DPP-4 (Lindsay et al 2005; Mannucci et al 2001), although there are also findings that metformin does not affect DPP-4 activity (Hinke et al 2002). Instead, more recent findings suggest that metformin stimulates the secretion of GLP-1 from the gut (Migoya et al 2007). Hence, from a mechanistic point of view, there is a clear rationale for combining metformin with DPP-4 inhibitors. Another important information is that the pharmacokinetics of metformin and a DPP-4 inhibitor do not change by combining the two, as shown for sitagliptin, which further indicates the feasibility of the combination (Herman et al 2006).

Vildagliptin and sitagliptin as monotherapy

Both vildagliptin and sitagliptin reduce fasting and prandial glucose as well as HbA_{1c} when used in monotherapy for the treatment of type 2 diabetes; HbA_{1c} has been shown to be reduced by these compounds by 0.65%–1.1% after study periods of 3–12 months from baseline levels of 7.2%–8.7% (Ahrén et al 2004b; Ristic et al 2005; Aschner et al 2006; Pratley et al 2006; Raz et al 2006; Rosenstock et al 2007; Schweizer et al 2007; Scott et al 2007). Furthermore, these studies have shown that both vildagliptin and sitagliptin are safe and tolerable with incidences of adverse events not different from what is seen after placebo treatment and that there is a very low rate of hypoglycemia during the treatment with the DPP-4 inhibitors. Recent reviews have summarized these monotherapy studies in more detail (Ahrén 2007a, 2007b).

DPP-4 inhibition as add-on therapy to metformin

Several studies have reported the experience of treatment with a DPP-4 inhibitor in combination with metformin. The first combination study was a 52 week trial, in which vildagliptin at 50 mg daily or placebo was added to ongoing treatment with metformin (1.5–3 g daily) in patients with a mean baseline HbA_{1c} of 7.8% (Ahrén et al 2004a). The patients had a mean diabetes duration of 5.5 years and they had been on metformin treatment for 29 months as a mean. The results are illustrated in Figure 1 and show that following the initial 12 week study period, HbA_{1c} was reduced by 0.7% by vildagliptin in combination with metformin compared to metformin alone. After the first 12 weeks of study, patients were followed for another 40 weeks. During this period, HbA_{1c} increased by 0.066%/month in patients given metformin alone versus only by 0.013%/month after vildagliptin plus metformin. The between-group difference in change of HbA_{1c} after 52 week of treatment was 1.1%, showing a clinically important improvement of the glycemic control by adding vildagliptin to metformin. Furthermore, fasting glucose was also reduced by vildagliptin in combination with metformin compared to

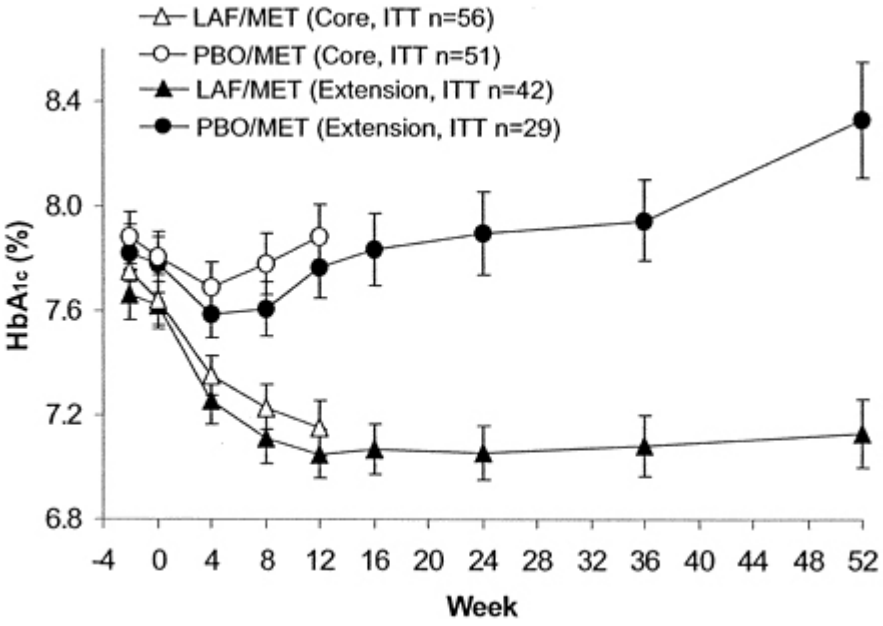

Figure 1 Time course of HbA_{1c} in a 12 week core study and a 40 week extension study when vildagliptin (LAF; 50 mg once daily) was given as add-on to metformin (MET). PBO = placebo. Reproduced from Ahrén et al 2004a after permission from the American Diabetes Association.

metformin alone. Thus, from a mean baseline fasting glucose of 9.8 mmol/l across all patients, the between-group difference in fasting glucose after 52 weeks of treatment was 1.1 mmol/l. The study therefore suggests that addition of vildagliptin to metformin prevents the deterioration of glycemic control seen in these patients when given metformin alone. The study also shows that the combination of vildagliptin and metformin is safe and highly tolerable with an overall incidence of any adverse event being similar in the two groups.

A second study in 416 patients added vildagliptin at 50 mg once or twice daily to on-going treatment with metformin for a study period of 24 weeks (Bosi et al 2007). The patients in this study had a mean diabetes duration of 6 years and had been treated with metformin for a mean of 16 months, their mean daily metformin dose was 2.1 g (inclusion criteria >1.5 g daily). They had a mean baseline HbA_{1c} was 8.4%. Figure 2 shows the HbA_{1c} levels in this study. It is seen that HbA_{1c} was reduced by 0.5% in patients given vildagliptin at 50 mg daily and 0.9% in patients given vildagliptin at 100 mg daily, both in combination with metformin, versus an increase by 0.2% in patients given placebo with on-going metformin. The placebo-adjusted mean reduction in HbA_{1c} was therefore 0.7% by vildagliptin at 50 mg and 1.1% by vildagliptin at 100 mg daily. The data were also analysed with respect to how many patients who experienced improved glycemic control or had a deterioration of glycemic control. The analysis revealed that in the group given metformin alone, 35% of patients had a deterioration of glycemic control and 31% had no meaningful change in glycemic control. In contrast, of the patients given vildagliptin at 50 mg in combination with metformin, 38% showed a meaningful improvement in glycemic control and 29% had a marked improvement in glycemic control (defined as reduction in HbA_{1c} by more than 1%). Also fasting plasma glucose was reduced by vildagliptin in combination with metformin. Baseline fasting glucose was 9.7 mmol/l across all groups. In the group given metformin alone, fasting glucose increased by 0.7 mmol/l and the placebo-adjusted reduction in fasting glucose was 0.8 mmol/l in subjects given vildagliptin at 50 mg daily and 1.7 mmol/l in subjects given vildagliptin at 100 mg in combination with metformin. Except for fasting triglycerides, lipid values were not significantly altered in any of the groups. However, fasting triglycerides increased from a mean value of 2.3 mmol/l by 19% in subjects given metformin alone but only by 1% in subjects given vildagliptin at 50 mg in combination with metformin and by 5% in the group given vildagliptin at 100 mg in combination with metformin. Mean body weight was 94 kg as a mean across all study groups and did not change significantly in the subjects given vildagliptin at either 50 or 100 mg daily in combination with metformin, whereas body weight was reduced by 1.0 kg in subjects given metformin alone. Finally, total number of adverse events was not significantly different between the groups; the only difference was a reduction in gastrointestinal adverse events in the subjects given vildagliptin at 50 mg in combination with metformin (9.6%) versus in those given metformin alone (18.2%). In

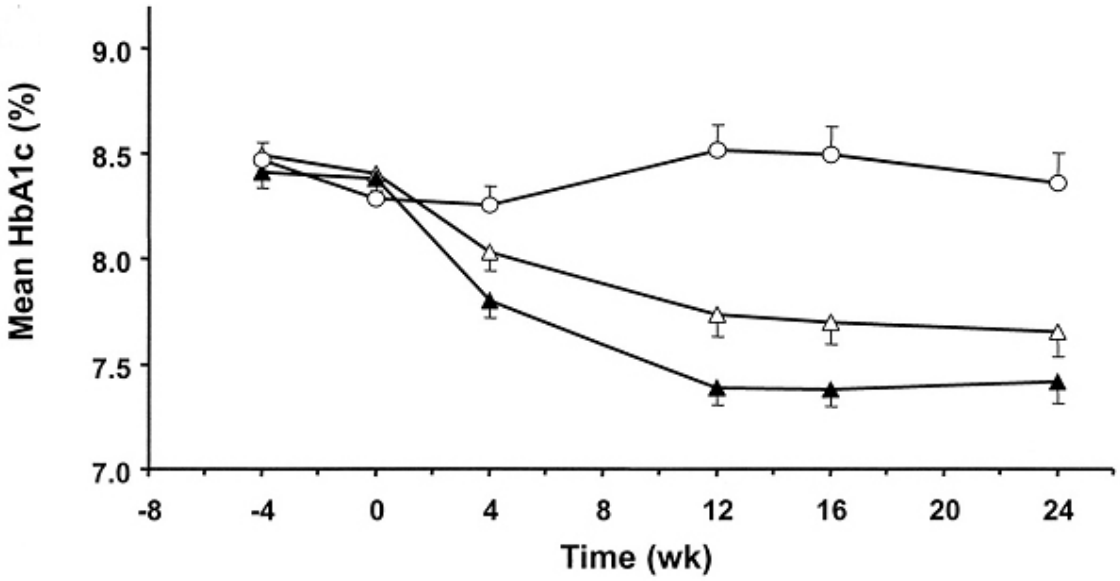

Figure 2 Time course of mean HbA_{1c} levels during 24 week treatment with vildagliptin at 50 mg daily (Δ) or 100 mg daily (▲) or placebo (❍) in patients with type 2 diabetes continuing stable metformin treatment (≥1.5 g daily). Reproduced from Bosi et al 2007 after permission from the American Diabetes Association.

conclusion, this large study showed that vildagliptin is well tolerated when given as add-on to metformin for a study period of 24 weeks and that vildagliptin shows a clinically meaningful improvement in glycemic control as verified by dose-related reductions in HbA_{1c} and fasting glucose.

The first study on the effect of sitagliptin as add-on therapy to patients with inadequate glycaemic control on metformin monotherapy was a four week study in 28 patients (Brazg et al 2007). The patients had a mean duration of diabetes of 6.6 years, the mean baseline HbA_{1c} was 7.7% and the mean fasting plasma glucose was 8.4 mmol/l. The study showed that fasting glucose was reduced by 1.3 mmo/l by sitagliptin in combination with metformin versus only by 0.4 mmol/l by metformin alone. The study also included a 24 hr measurement of glucose after the four week treatment period, and this showed a reduction of glucose by approximately 1–1.5 mmol/l throughout the entire 24 h period. Both fasting and prandial glycemia were reduced by this degree. Furthermore, the number of adverse events was not different when sitagliptin was given in combination with metformin versus when metformin was given alone. Hence, this short-term study verified the efficient improvement in glycemic control by the addition of DPP-4 inhibition to on-going metformin therapy in association with safety and tolerability of the combination therapy.

In a long-term study on the effect of sitagliptin as add-on to metformin in subjects with inadequate glycemic control, sitagliptin (100 mg once daily) was added to metformin (>1.5 g daily) for 24 weeks (Charbonnel et al 2006). The study comprised a total of 701 patients who had a mean diabetes duration of 6.2 years, a mean baseline HbA_{1c} of 8.0% and a mean baseline fasting glucose of 9.5 mmol/l. Figure 3 shows the HbA_{1c} in this study. It is seen that addition of sitagliptin significantly reduced the HbA_{1c} levels after the 24 week treatment period. The placebo-subtracted reduction in HbA_{1c} by sitagliptin was 0.65%. A total of 47% of the patients treated with sitagliptin in combination with metformin reached the target of <7% in HbA_{1c} while the target was reached by only 18% of the subjects given metformin alone. Also fasting glucose was reduced by sitagliptin in combination with metformin versus metformin alone; the placebo-subtracted reduction by sitagliptin was 1.4 mmol/l. The study also showed that sitagliptin in combination with metformin slightly, although significantly, reduced total cholesterol and triglycerides, whereas HDL-cholesterol was slightly increased. Body weight was slightly reduced in both groups, with no difference between the groups, and, similarly, the degree of adverse events did not differ between the groups. Hence, this 24 week trial in a large number of patients showed that sitagliptin when added to on-going therapy with metformin efficiently reduces HbA_{1c} and fasting glucose in combination of being a safe and highly tolerable combination therapy. Following the end of the 24 week trial, patients who did not receive glycemic rescue medication continued to an extension study. During this extension, 387 patients continued with the combination of sitagliptin with metformin throughout a 54 week study period. It was found that the mean HbA_{1c} remained stable at 7.1% during

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