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Management of type 2 diabetes patients: current perspective and futuristic promise of combination therapies with DPP-IV inhibitors.

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ABSTRACT

Mechanism of action of the currently available therapeutic drugs for treatment of T2DM varies from being insulin secretogogues to insulin sensitization or reduction in insulin requirement. Often the diabetes treatment goals are not met due to adverse effects of current therapies like hypoglycemia, cardiovascular risks, weight gain etc. Metformin-based combination therapy with DPP-IV inhibitors vildagliptin has shown more efficacy than monotherapy for effective T2DM treatment as the two acts synergistically and using altogether different mechanisms of actions leading to augmentation of incretin effect and increased β- cell mass as well as increased sensitivity to insulin leading to improved hyperglycaemic control, has no adverse effects and is relatively safe.

Keywords: Vildagliptin, secretagogues, insulin, diabetes mellitus, DPP-IV inhibitors

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the most common form of diabetes accounting for 90 to 95% patients. It is a dual heterogeneous metabolic syndrome characterized by islet (alpha and beta) cell dysfunction in the setting of insulin resistance leading to decreased insulin-mediated glucose transport, enhanced endogenous glucose production by the liver and impaired pancreatic insulin secretion, fasting and postprandial hyperglycemia due to peripheral insulin resistance (Mathieu & Degrande; 2008, Dineen *et al*., 1992, Firth *et al*., 1986; Butler & Rizza 1991). The incidence of T2DM patients is rapidly increasing worldwide and also appearing in patients in their 30s and even younger (NCCD & ADA Data). According to World Health Organization (WHO), the number of diabetes patients in 2000 is 171 million which will increase to more than 300 million by 2030. Disease progression follows a silent course; often diagnosed late and is associated with micro and macrovascular complications like neuropathy, nephropathy, and retinopathy attributing to the increased mortality.

The levels and duration of hyperglycemia in T2DM is key factor in developing the diabetes complications (Stratton *et al*., 2000). As a result, the achievement of glycemic control becomes an essential prerequisite for the prevention of T2DM associated cardiovascular and microvascular complications. Life style interventions, dietary adjustments and enhanced physical activity are also important key factors in therapy.

Postprandial hyperglycemia is one of the reasons for suboptimal glycemic control.
Control of the disease requires management of blood glucose, lipid levels, and thrombotic status. Glycated haemoglobin (HbA1c), fasting and post prandial blood glucose levels can be monitored for the measurement of metabolic control. Results of the UK Prospective Diabetes Study (UKPDS), 1998 and Kumamoto Study (Ohkubo *et al*., 1995) conducted in T2DM have been interpreted differently by various professionals and there is no common consensus amongst the treatment guidelines (ADA 2000; EDPC 1999; McIntosh *et al*., 2001; Kahn, 2001; DeFronzo *et al*., 2005). Desirable glycated haemoglobin (HbA1c) levels vary widely from approximately 6.2% to as high as 7.5% but, based on data from the UKPDS, the general consensus is an HbA1c level of 7% or lower. Less than 12% of people with diagnosed diabetes meet the recommended goals for blood glucose, blood pressure, and cholesterol, despite a great deal of research showing that controlling these conditions dramatically delays or prevents diabetes complications. It has therefore become the need of hour that treatment goals should be decided for the individual patient depending upon stage of disease, their commitment and capability for carrying out selfcare and the risk of hypoglycemia.

I Monotherapy

There are three ways in which the currently available therapy works toward improving glycemic control:

1. Increasing insulin secretion (insulin secretagogues),
2. Increasing insulin action (insulin sensitizers), and
3. Decreasing insulin need (inhibitors of glucose absorption).

A. Increasing Insulin Secretion (Secretagogues)

Sulphonylureas (SUs)

Introduced in mid-1950s, these are relatively cheap and quite effective in blood glucose lowering, with an almost instant onset of the effect after start of therapy. Drops in level of glycated haemoglobin by 1–2% can be expected as mean, with the higher the baseline HbA1c, bigger the drop. These drugs work by binding to a regulatory protein (SU receptor) on pancreatic β-cells, which in turn, results in closure of ATP-dependent potassium (KATP) channels leading to membrane depolarization and influx of calcium through voltage-dependent channels, which subsequently leads to insulin secretion (Zimmerman, 1997).

The most common side effect of the SUs is hypoglycemia, which is due to increased duration of binding to the SU receptor. Weight gain is variable, but tends to be greatest with glyburide, which relates to its greater propensity to induce hypoglycemia mainly as a result of edema and reduction of the osmotic diuresis caused by hyperglycemia. Other side effects are: abdominal upset, headache and hypersensitivity reactions. Sulfonylureas are potentially teratogenic and cannot be used in pregnancy or in patients who may become pregnant. Impairment of liver or kidney function increases the risk of hypoglycemia. Second generation SUs have a neutral effect on lipid profile or blood pressure and unlike their predecessors but are more expensive.

Glinides

Glinides are short-term insulin secretogogues. Glinides act by stimulating β- cells and hence increasing insulin. These are relatively expensive and also mechanism of action is different from that of SUs. They have rapid onset and short-term action attributed to their shorter circulating half-lives. Insulin release by glinides is partly regulated by glucose (Krentz and Bailey, 2005).

Their potential to reduce the glycated haemoglobin is slightly lesser compared to SUs, with less effect on fasting glycemia. They are more suitable for the people with irregular lifestyles and predominantly suffer from postprandial hyperglycemia and are not widely used.

Gliptins

The gliptins are a new group of agents called DPP-IV inhibitors. DPP are enzymes which breakdown glucogon like peptide-1 (GLP-1). By delaying the degradation of GLP-1, they prolong the action of insulin and delay the release of glucagon. Both of these actions will reduce sugar. Gliptins also contribute to an improvement in beta-cell function and an increase in hepatic and peripheral insulin sensitivity. Vildagliptin and Sitagliptin are the two currently available gliptins (Green *et al*., 2008).

In general, gliptins appear to be safe and well tolerated, with few reported side-effects, and the overall incidence of side-effects being similar to placebo. With vildagliptin, the most common side-effects were cold/flu-like symptoms, headache and dizziness. With sitagliptin, the most common side-effects were stuffy or runny nose, sore throats, headache, diarrhoea, upper respiratory infection and joint pains (Bosi *et al*., 2007).

B. Increasing Insulin Action (Insulin Sensitizers)
Thiazolidinediones (TZD)

These agents bind to peroxisome proliferator activator receptor-gamma (PPAR-γ) nuclear receptors affecting gene regulation in adipocytes. This altered transcription of the genes that primarily regulate fatty acid metabolism results in decreased serum FFA by approximately 20% to 40% (Fonseca *et al*., 2000 & Yamasaki *et al*., 1997) The reduction in FFA, in turn, improves insulin action in muscle tissue and β-cell function by decreasing lipotoxicity, a process whereby elevated serum FFA eventually leads to β-cell death. Their main target is fat tissue, inducing differentiation of adipocytes into small but insulin sensitive cells, but PPAR-γ receptors are present in cells throughout the body, including β- cells.

TZDs are contraindicated in patients with liver disease as they can lead to hepatitis, Water retention, leading to edema and eventual decompensation of potentially previously unrecognized heart failure is another point of concern for those with New York Heart Association class III or IV cardiac status. Recent studies have shown there may be an increased risk of coronary heart disease and heart attacks with rosiglitazone, though from a therapeutic standpoint, there is likely no significant difference between these agents in terms of glucose-lowering effect and they may be slightly less potent than the SUs or biguanides (Boyle *et al*., 2002, LaCivita & Villarreal, 2002 & Khan *et al*., 2002).

Metformin

Metformin is an insulin sensitizing biguanide used for treatment of T2DM. It has been shown to be as effective as insulin or sulfonylureas when used as monotherapy (Hermann *et al*., 1994, DeFronzo & Goodman, 1995, Johansen, 1999 and Garber *et al*., 1997). Actual mechanism of metformin action is not fully known but its main effect is to reduce the rate of hepatic gluconeogenesis, thereby improving fasting hyperglycemia (Hundal & Inzucchi, 2003). In conjunction with diet, metformin reduces fasting glucose concentration accounting for 1.3% to 2.0% reduction in HbA1c values (Garber *et al*., 1997, Selby, 1999, Davidson *et al*., 1997 and Hundal & Inzucchi, 2003) The effectiveness of metformin therapy has been shown to be independent of age, body weight, ethnicity, duration of diabetes, and insulin and C-peptide levels (DeFronzo & Goodman, 1995). Metformin may have special benefits in overweight patients with type 2 diabetes. Significant reductions in total body fat and visceral fat have been observed in women with pre-existent abdominal or visceral obesity treated with metformin (Pasquali, 2005). There is also a peripheral effect of improved insulin action in muscle tissue, which may be related to metformin's ability to lower free fatty acids (FFA) **(**Prato *et al*., 1995 & Abbasi *et al*., 1998) and/or its induction of mild weight loss through decreased caloric intake. Weight loss during metformin treatment has been attributed to reduced caloric intake (Rvinen & Kimmatilla, 1999), probably through suppression of appetite, an effect that is largely independent of gastrointestinal side effects of metformin (such as nausea and diarrhoea) (Hundal & Inzucchi, 2003).

Metformin is contraindicated in people with any condition that could increase the risk of lactic acidosis, including kidney disorders (creatinine levels over 150 μmol/l), lung disease and liver disease. It is recommended that metformin be temporarily discontinued before any radiographic study involving iodinated contrast (contrast-enhanced CT scan or angiogram), due to temporary impairment of kidney function, leading to lactic acidosis by causing retention of metformin in the body. Gastrointestinal upset, including diarrhea, cramps, nausea, vomiting and increased flatulence; are more commonly associated with metformin than most other anti-diabetic drugs. Long-term use of metformin has been associated with increased homocysteine levels and malabsorption of vitamin B_{12}. Also metformin alone is insufficient for achievement of good metabolic control and glycemic control deteriorates in metformin treated patients. This necessitates combination therapy by adding a secondary compound to metformin.

C. Decreasing Insulin Need (Inhibitors of Glucose Absorption)
α-Glucosidase Inhibitors (AGIs)

The two agents in this class currently available, acarbose and miglitol, were released in 1996. These

drugs only affect post prandial glucose levels by competitively inhibiting the binding of oligosaccharides to the alpha-glucosidase enzyme in the small intestine that cleaves oligosaccharides to monosaccharides and delay the absorption of carbohydrates. These drugs do not cause hypoglycemia or weight gain.

However, because they only affect PPG levels the potency of the AGIs is significantly less than most other agents. For this reason and for the often significantly troublesome side effects of flatulence, abdominal pain and diarrhoea, these agents are limited in practice, used often sparingly.

II Combination Therapy

Lack of effectiveness of the monotherapy using drugs having different mechanistic actions has lead to the development of combinational therapy. The rationale for the combination therapy is complementation of mechanism of actions of one drug to other for achieving treatment goals. However, the combinations with sulphonylureas and thiazolidinediones have faced problems as sulphonylureas increase the risk of hypoglycemia (Prato & Pulizzi, 2005, Green & 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). Also the recent GLP-1 based therapy has been found to be successful in combination with metformin. This can be achieved by either activating the GLP-1 receptors by exenatide (Fenglos *et al*., 2005) or liraglutide, and by the strategy of preventing the inactivation of endogenous GLP-1 by inhibiting dipeptidyl peptidase-IV (DPP-IV) (Ahrén & Schmitz, 2004, Charbonnel *et al*., 2006, Bosi *et al*., 2007, Brazg, 2007 & Holst & Deacon, 1998). The rationale for the development of DPP-IV inhibition in the treatment of type 2 diabetes relies on augmentation of the incretin effect that is the exaggerated insulin secretion after oral glucose administration when compared to intravenous glucose administration and is attributed to gut hormones augmenting glucose-stimulated insulin secretion (Drucker & Nauck, 2006). The two most important incretin hormones are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) (Drucker & Nauck, 2006). GLP-1 also inhibits glucagon secretion, delays gastric emptying and induces satiety. In addition, animal studies have presented evidence that GLP-1 increases beta cell mass by stimulating cell proliferation and inhibiting apoptosis (Perfetti & Hui 2004), even though such an effect is yet to be 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 (Rao *et al*., 2008). 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-IV, which inactivates GLP-1 (Perfetti & Hui 2004). Two strategies used to overcome this are the development of GLP-1 receptor agonists (GLP-1 mimetics such as exenatide and liraglutide), which are resistant to DPP-IV (Ahrén & Schmitz, 2004) and other strategy is the development of inhibitors of DPP-IV, which prevent the inactivation of GLP-1 and thereby enhance and prolong the action of the endogenous incretin hormone (Ahrén & Schmitz, 2004, Mari, 2005 & Ahren, 2007). DPP-IV 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-IV inhibition (Ahren, 2007).

A. Rationale for Combining Metformin with Vildagliptin

Type 2 diabetes is a disease with at least three main defects that needs to be corrected: impaired insulin secretion, insulin resistance and hypersecretion of glucagon. The rationale for combining metformin with Dipeptidyl peptidase-IV inhibitor vildagliptin is that the two strategies follow a complimentary mechanism of action to each other. Metformin acts primarily by reducing hepatic glucose release and improving insulin sensitivity in liver and muscle (Leverve, 2003 & Setter, 2003), while DPP-IV inhibitors act by increasing GLP-1 levels and thereby stimulating insulin secretion and inhibiting glucagons release (Ahrén, 2007a).

The combination of two strategies therefore has the potential to improve different mechanisms that are impaired in T2DM 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, 2001), which would be a potential for an additional synergistic action with DPP-IV inhibitors. The mechanism underlying the increase in GLP-1 levels by metformin is yet to be finally established; it has been suggested to be caused by inhibition of DPP-IV (Lindsay, 2005, Mannucci, 2001, Hinke, 2002). Instead, more recent findings suggest that metformin stimulates the secretion of

GLP-1 from the gut (Migoya, 2007). It has also been reported that pharmacokinetics of metformin and DPP-IV inhibitors are not altered by the combination of the two (Herman, 2006). Hence, an incretin based therapy acts by different mechanisms than metfomin, combined therapy with metformin and vildagliptin has shown high potential. Apart from synergism in action of the two, the combination of metformin and vildagliptin achieves the desired target without the exacerbating side effects of metformin in GI tract, without enhanced risk of hypoglycemia or weight gain. The fact that Vildagliptin substantially enhances the incretin effect in patients receiving concomitant metformin may underlie the pronounced efficacy of Vildagliptin to reduce FPG, PPG and HbA1c.

Hence, from a mechanistic point of view, there is a clear rationale for using combinatorial therapy of metformin with DPP-IV inhibitors for effective treatment of T2DM.

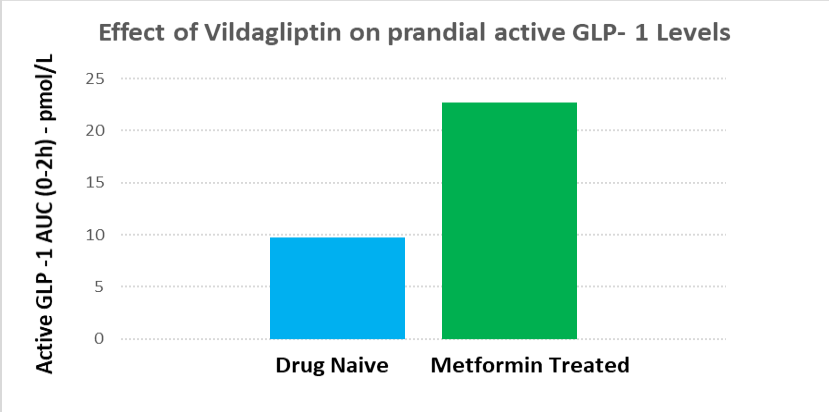


Figure 1. Effect of vildagliptin on prandial active GLP-1 levels in drug-naive (5) versus metformin-treated patients (13).

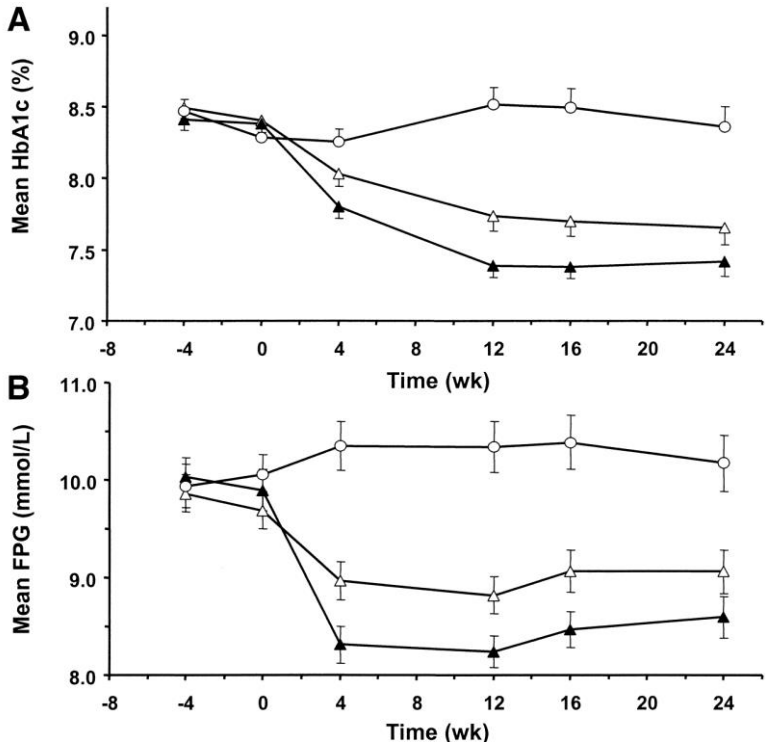


Figure 2. A) Mean ± SE HbA1c during 24 weeks of treatment with vildagliptin daily or placebo in patients with type2 diabetes continuing stable metformin dose regimen (1,500mg/day). B) Mean ± SE FPG during 24 weeks of treatment with vildagliptin daily or placebo in patients with type2 diabetes continuing stable metformin dose regimen (1,500mg/day).

Pharmacokinetics/Pharmacodynamics of Metformin and Vildagliptin

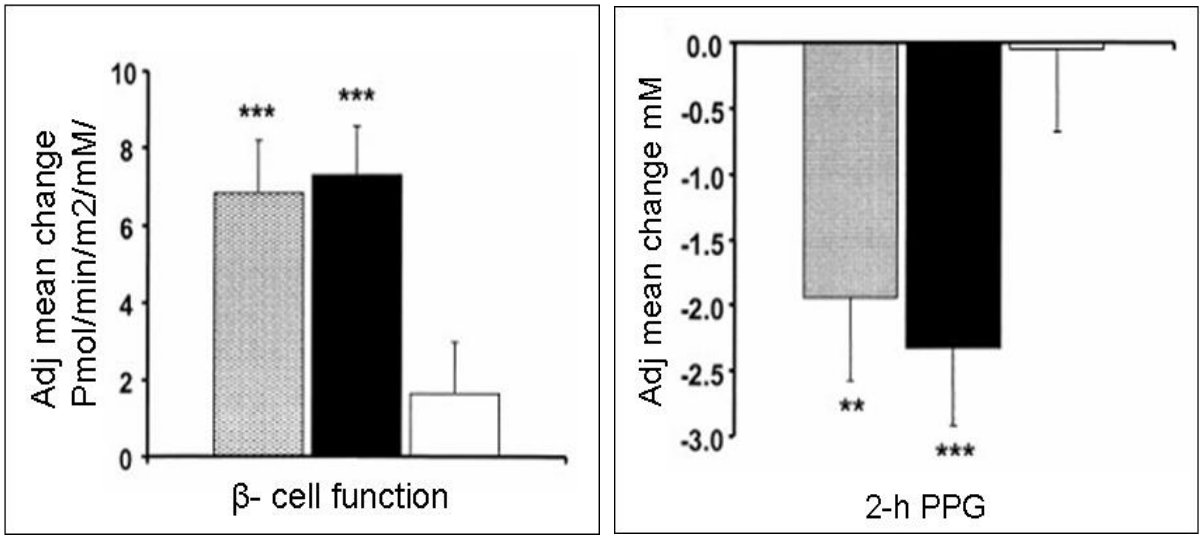
Metformin has a bioavailability of approximately 60% and is mainly absorbed from the small intestine. It's not significantly metabolized and >90% of it is eliminated unchanged in urine through glomerular filtration and tubular secretion. Mechanism of metformin action is not clearly understood but is related to action on AMP kinase. The glucose lowering effect of metformin is mainly due to reduced hepatic glucose output and to enhanced sensitivity for uptake of peripheral glucose (by muscles).

On the other hand, Vildagliptin is rapidly absorbed after oral administration and approximately 70% of orally administered drug is hydrolyzed. Excretion of the metabolites occurs through kidney with relatively lower concentrations being eliminated in unchanged form (23%). Vildagliptin doesn't induce or inhibit major P450 enzymes and shows no drug interaction with metformin. Pharmacokinetics of Vildagliptin is unaltered by factors like age, gender, BMI and race. Vildagliptin selectively inhibits DPP-IV activity resulting in increased levels of two incretin hormones GLP-1 and GIP thereby allowing pancreatic islets for better response to raised glucose levels.

Clinical Data on Vildagliptin Induced DPP-IV Inhibition as Add-on Therapy to Metformin

Efficacy of the metformin and vildagliptin combination has been supported by the clinical research and results from one year combination study with vildagliptin at 50 mg daily or placebo in combination to metformin (1.5–3 g daily) (Ahrén & Schmitz, 2004, Bosi *et al*., 2007 & Brazg, 2007) show the reduction in HbA1c 0.7% by vildagliptin in combination with metformin compared to metformin alone.

Both long term as well as short term studies with the metformin and vildagliptin combination therapy shows a clinically significant improvement of the glycemic control and combination of vildagliptin and metformin is safe and highly tolerable with an overall incidence of any adverse event being similar in the two groups. Improvement in the triglycerides is also moderately observed without any increase in the mean body weight. Also metformin and vildagliptin action is synergistic on the post meal concentration of active GLP-1 (Migoya *et al*, 2007). The combination of vildagliptin and metformin versus metformin alone showed a marked improvement in β- cell function and a slight improvement in insulin sensitivity which together results in improved β- cell adaptation ability to insulin resistance, a measure that correlated to the reduction in HbA1c levels.



3a 3b

Figure 3. Adjusted mean change ± SE in β-cell function (a) and 2-h postprandial glucose (b) after 24-week treatment with 50 and 100 mg vildagliptin daily or placebo in patients with type 2 diabetes continuing stable metformin dose regimen (1,500 mg/day). ***P < 0.001 **P = 0.001 vs. placebo. (Bosi *et al.*)

Reduction in proinsulin levels was observed and a reduction in the proinsulin to insulin ratio under fasting conditions has also been reported when used in combination, However, fasting proinsulin levels per se were not altered and the homeostasis model assessment of insulin resistance (HOMA-IR) was not altered (61).

The most common AEs observed in the trial are shown in table 1 with types and frequencies of AEs with combination treatment were similar to those observed with metformin monotherapy. Among the gastrointestinal AEs characteristic of metformin therapy, diarrhoea and abdominal pain appeared to occur with lower frequency in both the low-dose and high-dose combinations compared with metformin monotherapy. Bosi *et al* has also suggested that gastrointestinal AEs of metformin may be reduced with the addition of vildagliptin to metformin; in that trial, gastrointestinal AE rates were 9.6% with vildagliptin 50 mg qd as add-on treatment (p ¼ 0.02 vs. metformin plus placebo), 14.8% with vildagliptin 50 mg bid as add on treatment and 18.2% with metformin plus placebo (Bosi *et al*., 2007).

Finally, there has been increased concern over the cardiovascular safety of widely used oral antidiabetic drugs especially due to potential cardiovascular AEs associated with sulfonylurea treatment. have long been the subject of investigation and debate, and recent reports have emphasised increased risk when the thiazolidinedione rosiglitazone is used in combination with a sulfonylurea or metformin (Rao *et al*., 2008). It is now critical that the cardiovascular safety of new antidiabetic agents be demonstrated. pooled safety analysis of cardiovascular events during up to 24 weeks of vildagliptin treatment in 11 monotherapy trials and 8 combination therapy trials found a nonsignificant trend for lower risk in patients receiving vildagliptin than with placebo or any other comparator (Kothny, 2008).

Table 1 : Most common AEs (3.0% in any group, listed in order of frequency in low-dose combination group) in trial comparing vildagliptin, metformin, low-dose combination and high-dose combination for 24 weeks in treatment-naive patients.

Event%	Vildagliptin 50mg bid (n = 297)	Metformin 1000mg bid (n = 292)	Vildagliptin/ Metformin 50/500mg bid (low dose) (n = 290)	Vildagliptin/ Metformin 50/ 1000 mg bid (high dose) (n = 292)
Diarrhoea	2.4	11.0	7.2	6.5
Headache	5.4	4.5	6.2	5.5
Nasopharyngytia	3.7	4.8	5.5	7.5
Dizziness	2.7	4.1	4.8	5.1
Nausea	2.4	5.8	4.8	5.1
Pain in extremity	1.7	2.4	3.1	1.4
Upper respiratory tract infection	3.4	2.7	3.1	1.4
Fatigue	2.0	5.1	2.4	2.4
Dyspepsia	1.0	1.7	2.1	3.4
Asthenia	1.3	1.4	1.4	3.1
Cough	2.7	3.1	1.4	1.7
Vomiting	0.3	2.4	1.4	3.1
Back pain	2.0	3.8	1.0	3.8
Hypertension	2.4	3.4	1.0	2.1
Abdominal pain	2.0	3.4	0.7	0.7
Constipation	3.4	1.7	0.7	2.1

In summary, there is enough clinical evidence that combination therapy of vildagliptin with metformin shows statistically significant reduction in HbA1c, fasting and PP glucose levels and improved β- cell function. The effects were neutral for fasting lipid levels and did not lead to the weight gain. Tolerability of the combination was good, in particular to GI tolerability without any additional risk of induced hypoglycemia with the combination of the two drugs.

CONCLUSION

Combination of metformin with vildagliptin has shown superior efficiency in meeting the T2DM treatment goals. The mechanism of action of the two is complementary and act by preventing the inactivation of the incretin hormone GLP-1 through stimulation of insulin secretion and reduction in glucagon secretion and increased β-cell mass and sensitivity to insulin without increasing the risk of hypoglycemia, cardiovascular risks factors (hypertension and lipid profile), without exposing to weight gain.

Combination therapy using vildagliptin and metformin will be of highest value for mildly hyperglycaemic patients relatively closer to target HbA1c (between 6.5% - 7.5% on metformin treatment) and in older individuals for meeting the diabetes treatment goals.

REFERENCES

Abbasi F, Carantoni M, Chen YD, Reaven GM. Further evidence for a central role of adipose tissue in the antihyperglycemic effect of metformin. Diabetes Care 1998; 21: 1301-1305.

Ahrén B, Pacini G, Tura A, *et al*. Improved meal-related insulin processing contrib utes to the enhancement of B-cell function by the DPP-4 inhibitor vildagliptin in pa tients with type 2 diabetes. Horm Metab Res 2007; 39: 826–829.

Ahrén B, Schmitz O. GLP-1 receptor agonists and DPP-4 inhibitors in the treatment of type 2 diabetes. Horm Metab Res 2004; 36: 867–76.

Ahrén B.Dipeptidyl peptidase-4 inhibitors – clinical data and clinical implications. Diabetes Care 2007a; 30:1344–1350.

American Diabetes Association. Facts and Figures. <diabetes.org/>.

American Diabetes Association. Clinical Practice Recommendations 2000. Diabetes Care 2000; 23 (Suppl 1): S1–S116.

Asian-Pacific Type 2 Diabetes Policy Group. Type 2 diabetes. Practical targets and Treatments, edn 3. Sydney: Health Communications Australia Pty Ltd and In vivo, 2002.

Bosi E, Camisasca RP, Collober C, *et al*. Effects of vlidagliptin on glucose control over 24 weeks in patients with type 2 diabetes in adequatelycontrolled with met formin. Diabetes Care 2007; 30: 890–895.

Boyle PJ, King AB, Olansky L, Marchetti A, Lau H, Magar R, Martin J. Effects of pioglitazone and rosiglitazone on blood lipid levels and glycemic control in patients with type 2 diabetes mellitus: a retrospective review of randomly selected medical records. Clin Ther 2002; 24: 378-396

Brazg R, Xu L, Dalla Man C, *et al*. Effect of add ingsitagliptin, a dipeptidyl peptidase-4 inhibitor, to metformin on 24-h glycaemic control and β-cell function in patients with type 2 diabetes. Diabetes Obes Metab 2007; 9: 186–193.

Butler PC, Rizza RA. Contribution to postprandial hyperglycemia and effect on initial splanchnic glucose clearance of hepatic glucose cycling in glucose-intolerant or NIDDM patients. Diabetes 1991; 40: 73-81.

Center for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion. Frequently Asked Questions. <cdc.gov/diabetes/faqs.htm>.

Chantal Mathieu Evy Degrande, Vildagliptin: a new oral treatment for type 2 diabetes mellitus. Vascular Health and Risk Management 2008:4(6) 1349–1360.

Charbonnel B, Wu M, Karasik A, *et al*. Efficacy and safety of the dipeptidyl pepti dase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. Diabetes Care 2006; 29: 2638–43.

Davidson MB, Peters AL. An overview of metformin in the treatment of type 2 diabetes mellitus. Am J Med 1997; 102: 99-110.

DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med 1995; 333: 541-549.

DeFronzo RA, Ratner RE, Han J, *et al*. Effects of exenatide (exendin on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care 2005; 28:1092–100.

Del Prato S, Marchetto S, Pipitone A, Zanon M, Vigili de Kreutzenberg S, Tiengo A. Metformin and free fatty acid metabolism. Diabetes Metab Rev 1995; 11: S33-S41.

Del Prato S, Pulizzi N. The place of sulfonylureas in the therapy for type 2 diabetes mellitus. Metabolism 2006; 55: S20–S27.

Dinneen S, Gerich J, Rizza R. Carbohydrate metabolism in non-insulin dependent diabetes mellitus. N Engl J Med 1992; 327: 707-713.

Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4

inhibitors in type 2 diabetes. Lancet 2006; 368: 1696–1705.

Dunning BE, Foley J, Ahrén B. Alpha-cell function in health and disease: influence of GLP-1. Diabetologia 2005; 48:1700–1713.

Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352: 854-865.

European Diabetes Policy Group. A desktop guide to Type 1 (insulin-dependent) diabetes mellitus. Diabetic Medicine 1999; 16: 253–266.

Fenglos MM, Saad MF, Pi-Sinyer FX, *et al*. Effects of liragflutide (NN2211) , a long-acting GLP-1 analogue, on glycaemic control and bodyweight in subjects with type 2 diabetes. Diabet Med 2005; 22: 1016–1023.

Firth RG, Bell PM, Marsh HM, Hansen I, Rizza RA. Postprandial hyperglycemia in patients with noninsulin-dependent diabetes mellitus: role of hepatic and extrahepatic tissues. J Clin Invest 1986; 77: 1525-1532.

Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. JAMA 2000; 283: 1695-1702.

Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose response trial. Am J Med 1997; 103: 491-497.

Green Brian, Flatt Peter, Bailey Clifford. Gliptins: DPP-4 inhibitors to treat type 2 diabetes. Future prescriber, 2008; 8: 6-12.

Green JB, Feinglos MN. Are sulphonylureas passé? Curr Diabet Rep 2007; 6: 373–377.

Herman GA, Bergman A, Yi B, *et al*. Tolerability and pharmacokinetics of metformin and the dipeptidyl peptidase 4 inhibitor sitagliptin when co-adminis tered in patients with type 2 diabetes. Curr Med Res Opin 2006; 22: 1939–1947.

Hermann LS, Scherste ´n B, Bitze ´n PO, Kjellstro ¨m T, Lindga ¨rde F, Melander A. Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations. A double-blind controlled study. Diabetes Care 1994; 17: 1100-1109.

Hinke SA, Kuhn-Wache K, Hoffman T, *et al*. Metformin effects on dipeptidylpeptidase IV degradation of glucagon-like peptide-1. Biochem Biophys Res Commun 2002; 291: 1302–1308.

Holst JJ, Deacon CF. Inhibition of the activity of dipeptidyl-peptidase- IV as a treatment for type 2 diabetes. Diabetes 1998; 47: 1663-1170.

Hundal RS, Inzucchi SE. 2003. Metformin: new understandings, new uses Drugs 63:1879–94.

Johansen K. Efficacy of metformin in the treatment of NIDDM. Meta analysis. Diabetes Care 1999; 22: 33-37.

Kahn SE, Haffner, SM, Helse MA, *et al*. Glycemic durabil ity of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006; 355:2427–2443.

Kahn SE. The importance of beta-cell failure in the development and progression of type 2 diabetes. J Clin Endocrinol Metab 2001; 86:4047–58.

Khan MA, St Peter JV, Xue JL. A prospective, randomized comparison of the metabolic effects of pioglitazone or rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone. Diabetes Care 2002; 25: 708- 711.

Kothny W, Gimpelewicz CR, Byiers S, Mills D, Fitchet M. Cardiovascular safety profile of vildagliptin, a new DPP-4 inhibitor for the treatment of type 2 diabetes. Poster presented at: European Association for the study Diabetes–44th Annual Scientific Sessions; September 7–11, 2008; Rome, Italy. Poster P-915.

Krentz AJ, Bailey CJ, Oral antidiabetic agents. Current role in type 2 diabetes mellitus, Drugs 2005; 65: 385–411.

LaCivita KA, Villarreal G. Differences in lipid profiles of patients given rosiglitazone followed by pioglitazone. Curr Med Res Opin 2002; 18: 363-370.

Leverve KM, Guigas B, Detaille D, *et al*. Mitochondrial metabolism and type-2 diabetes: a specific target of metformin. Diabetes Metab 2003; 29: 6S88–94.

Levetran C. Oral antidiabeti agents in type 2 diabetes. Curr Med Res Opin 2007; 23:945–952.

Lindsay JR, Duffy NA, McKillop AM, *et al*. Inhibition of dipeptidyl peptidase IV activity by oral metformin in type 2 diabetes. Diabet Med 2005; 22: 654–657.

Mannucci E, Pierazzuoli E, Ognibene A, *et al*. Effect of metformin on glucagon-like peptide 1 (GLP-1) and leptin levels in obese nondiabetic subjects. Diabetes Care 2001;24:489–494.

Mari A, Sallas WM, He YL, *et al*. Vildagliptin, a dipeptidyl peptidase-IV inhibitor, improves model-assessed beta-cell function in patients with type 2 diabetes. J Clin Endocrinol Metab 2005; 90: 4888–94.

Matthews DR, Hosker JP, Rudenski AS, *et al*. Homeostasis model assessment: insulin resistance and beta cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412–419.

McIntosh A, Hutchinson A, Home PD, Brown F, Bruce A, Damerell A, Davis R, Field R, Frost G, Marshall S, Roddick J, Tesfaye S, Withers H, Suckling R, Smith S, Griffin S, Kaltenthaler E, Peters J & Feder G. Clinical guidelines and evidence review for Type 2 diabetes: management of blood glucose. Sheffield: ScHARR, University of Sheffield, 2001.

Migoya EM, Miller J, Larson P, *et al*Sitagliptin, a selective DPP-4 inhibitor, and metformin have complementary effects to increase active GLP-1 concentrations. Diabetes 2007; 56(Suppl 1): A74.

Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima , Furuyoshi N & Shichiri M. Intensive insulin therapy prevents the progression of diabetic

microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Research and Clinical Practice 1995; 28; 103–117.

Pasquali R, Gambineri A, Biscotti D, Vicennati V, Gagliardi L, Colitta D. Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. J Clin Endocrinol Metab 2000; 85: 2767-2774.

Perfetti R, Hui H. The role of GLP-1 in the life and death of pancreatic beta cells. Horm Metab Res 2004; 36: 804–810.

Rao AD, Kuhadiya N, Reynolds K, Fonseca VA. Is the combination of sulfonylureas and metformin associated with an increased risk of cardiovascular disease or all cause mortality? A meta-analysis of observational studies. Diabetes Care 2008; 31: 1672–1678.

Selby JV, Ettinger B, Swain BE, Brown JB. First 20 months' experience with use of metformin for type 2 diabetes in a large health maintenance organization. Diabetes Care 1999; 22: 38-44.

Setter SM, Iltz JL, Thams J, *et al*. 2003. Metformin hydrochloride in the treatment of type 2 diabetes mellitus: a clinical review with a focus on dualtherapy. Clin Ther 25:2991–3026.

Stratton IM, Adler AI, Neil HA, Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. Br Med J 2000; 321: 405–12.

UK Prospective Diabetes Study Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352 837–853.

United Kingdom Prospective Diabetes Study (UKPDS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. BMJ 1995; 310: 83-88.

US) FDA News. FDA issues safety alert on Avandia, May 21, 2007. Available from URL: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01636.html.Last accessed on 01 December 2008.

WHO, http://www.who.int/diabetes/facts/world_figures/en/index.html

Yamasaki Y, Kawamori R, Wasada T, Sato A, Omori Y, Eguchi H, Tominaga M, Sasaki H, Ikeda M, Kubota M, Ishida Y, Hozumi T, Baba S, Uehara M, Shichiri M, Kaneko T; Glucose Clamp Study Group, Japan. Pioglitazone (AD-4833) ameliorates insulin resistance in patients with NIDDM. AD-4833 Tohoku J Exp Med 1997; 183: 173-183.

Yki-Ja ¨rvinen H, Nikkila ¨K,Ma ¨kimattila S. Metformin prevents weight gain by reducing dietary intake during insulin therapy in patients with type 2 diabetes mellitus. Drugs 1999; 58 Suppl 1: 53-54; discussion 75-82.

Zimmerman BR. Sulfonylureas. Endocrinol Metab Clin North Am 1997; 26: 511-522.