The dipeptidyl-peptidase-4 (DPP-4) inhibitors: a new class of oral therapy for patients with type 2 diabetes mellitus

*MA Elrishi, K Khunti, J Jarvis, MJ Davies**

ABSTRACT

The observation that an oral glucose load is more effective at releasing insulin, compared with the same amount of glucose given intravenously, has been called the incretin effect, and is due to the augmentation of glucose-stimulated insulin secretion by intestinally derived peptides.

Glucagon-like peptide-1 (GLP-1), in particular, has been shown to stimulate insulin release in a glucose-dependent manner in humans, but it is rapidly metabolised by dipeptidyl-peptidase-4 (DPP-4). Inhibition of DPP-4 activity enhances fasting and post-prandial GLP-1 which, in turn, improves glycaemic control by increasing glucose-dependent insulin secretion and by decreasing glucagon concentration.

Current oral antidiabetic drugs (OADs) for type 2 diabetes are limited by adverse effects such as gastrointestinal problems, weight gain, oedema, or hypoglycaemia. In addition, there are recent concerns about rosiglitazone and cardiovascular outcomes, and with the thiazolidinediones in general regarding excess fracture rate in women and increased risk of heart failure. Thus the introduction of a new class of OADs, the DPP-4 inhibitors, is welcome.

This review article discusses the most clinically relevant data published on DPP-4 inhibitors based on Medline literature searches (1966 to August 2007) and posters and oral presentations from the American Diabetes Association Scientific Sessions in 2006 and 2007. We have concentrated our review on two DPP-4 inhibitors: sitagliptin (Januvia) and vildagliptin (Galvus).

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KEY WORDS

type 2 diabetes; gliptins; dipeptidyl-peptidase-4 (DPP-4) inhibitors; glycaemic management; HbA_{1c}; incretin effect; oral antidiabetic drugs (OADs)

Introduction

The incretins are peptide hormones that are released from the gut in response to the ingestion of food and enhance glucose-stimulated insulin secretion from the pancreas.[1]

Oral glucose intake stimulates insulin release to a greater extent than does a comparable glucose challenge delivered intravenously.[2] This augmentation of insulin secretion following an oral glucose challenge is known as the 'incretin effect'. The incretin effect is mediated via gut hormones that cause insulin secretion as a response to hyperglycaemia.[1,3] Glucose-dependent insulinotropic polypeptide (GIP) was the first incretin hormone isolated.[4] GIP inhibits gastric acid secretion and regulates fat metabolism in adipocytes. Glucagon-like peptide-1 (GLP-1) was the second incretin hormone isolated.[4] GIP is predominantly produced in jejunal K cells whereas GLP-1 is produced by the L cells in the ileum.[1,5]

Incretins and type 2 diabetes

It has been shown that the incretin effect is diminished in patients with type 2 diabetes mellitus (T2DM)[6] (Figure 1). T2DM patients have reduced circulating GLP-1 and GIP concentrations by as much as 54% compared to normal subjects.[7] Studies show that GIP has lost most of its insulinotropic abilities in patients with T2DM; this implies that GLP-1 is a more effective therapeutic target for T2DM.[8] GLP-1 has a half life of <two minutes because it is rapidly inactivated by the enzyme dipeptidyl-peptidase. Dipeptidyl-peptidase-4 was first reported in 1966 as glycyl-prolyl-β-naphthylamidase[9] and later named dipeptidyl peptidase (DPP-4). DPP-4 is the archetypal member of its six member gene family. Four members of this family – DPP-4, FAB (fibroblast activation protein), DPP-8 and DPP-9 – have a rare substrate specificity: hydrolysis of a prolyl bond two residues from the N-terminus. The ubiquitous DPP-4 glycoprotein has proved interesting in the fields of immunology, endocrinology, haematology and endothelial cell biology and has become a novel target for T2DM therapy.[10]

Mechanism of action

DPP-4 inhibitors suppress the degradation of a variety of bioactive peptides, including GLP-1, thereby

MA Elrishi, MRCP, MMedSci/MSc, Specialist Registrar, Diabetes and Endocrinology, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, UK
K Khunti, MD, FRCGP, Professor of General Practice and Primary Health Care, Department of Health Sciences, University of Leicester, Leicester General Hospital, UK
J Jarvis, MSc, BSc(Hons), RN, Nurse Research Fellow, Department of Diabetes Research, University Hospitals of Leicester NHS Trust, UK
MJ Davies, FRCP, MD, Professor of Diabetes Medicine, Department of Cardiovascular Sciences, University of Leicester and Honorary Consultant, University Hospitals of Leicester, UK
***Correspondence to**: Professor Melanie Davies, FRCP, MD, Department of Cardiovascular Sciences, University of Leicester, c/o Victoria Building, Leicester Royal Infirmary, Leicester LE1 5WW, UK; e-mail: melanie.davies@uhl-tr.nhs.uk

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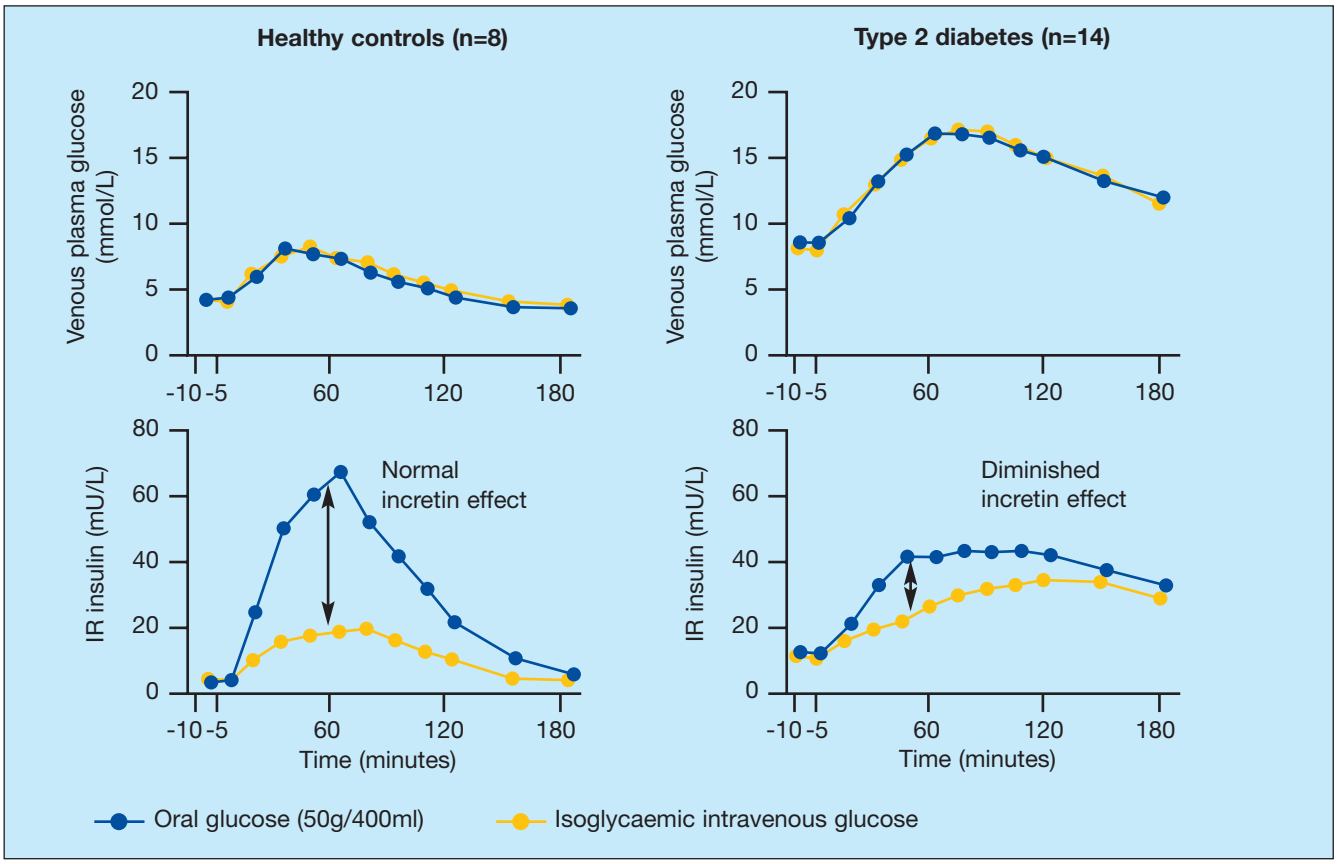
Figure 1. Incretin effect in type 2 diabetes. (Adapted from Nauck M, *et al*. *Diabetologia* 1986; **29:** 46–52[6] by Merck Sharp & Dohme. Permission has been granted by MSD to reproduce this figure, © MSD)



extending their period of action, and work by acting as competitive antagonists of the DPP-4 enzyme.[11]

In addition to the impact on GLP-1 action, they may affect other peptides, including peptide YY, neuropeptide Y, growth hormone releasing hormone and vasoactive intestinal polypeptide.[12] In T2DM subjects, the continuous infusion of GLP-1 has been shown to decrease plasma glucose and HbA1c levels, and increase β-cell mass.[13]

Selectivity with DPP-4 inhibitors

DPP-4 inhibitors have demonstrated efficacy in animal models, but also result in toxicities. Some, but not all DPP-4 inhibitors, have been reported to produce skin lesions in studies in monkeys.[14] It has been proposed that the toxic effect associated with these inhibitors arises from the inhibition of DPP-8 and/or DPP-9, and not DPP-4. Selective inhibition of DPP-8/9-attenuated T-cell activation suggests that these enzymes are involved in the immune system. A study by Lankas *et al.* demonstrated that a selective inhibition of DPP-8/9 was toxic, whilst a selective inhibition of DPP-4 was not.[15]

Sitagliptin

Sitagliptin (Januvia, Merck Pharmaceuticals) is a potent, highly specific DPP-4 inhibitor that is rapidly absorbed orally, and inhibits plasma DPP-4 activity by 90%.[16] It is the first in this new class of OADs to gain regulatory approval, by the Food and Drug Administration (FDA) in October 2006 and by the European Union in March 2007, for the treatment of T2DM.[17,18] In North America it is licensed for use as monotherapy and for use in combination with metformin or thiazolidinediones (TZDs). In the European Union its use is recommended in combination with metformin when diet and exercise plus metformin do not provide adequate glycaemic control, or for combined use with TZDs.[18]

In single dose studies in non-diabetic subjects, sitagliptin was well absorbed with about 80% of the administered dose excreted unchanged in the urine.[19] Sitagliptin induced a two-fold increase in active GLP-1 following a meal; similar results were seen following a divided dosage.[20]

Monotherapy vs *placebo*

(See Table 1: summary of clinical trials with sitagliptin.) A trial of sitagliptin monotherapy decreased glycosylated haemoglobin (HbA1c) levels compared to placebo ($p<0.001$).[21] Patients with a baseline HbA1c ≥9% had a greater reduction in placebo-subtracted HbA1c of about -1.50%. Sitagliptin (100mg and 200mg) significantly decreased two-hour post-prandial glucose (placebo-subtracted -2.6mmol/L and -3.0mmol/L, respectively; $p<0.001$).[21]

In a trial by Raz *et al.*, patients with T2DM were randomised to receive placebo, or sitagliptin 100mg or 200mg. After 18 weeks, HbA1c was significantly reduced with sitagliptin.[22]

Combination therapy

See Table 1.

Table 1. Summary of clinical trials with sitagliptin

Source	Trial duration (weeks)	No. of subjects	Treatment and dose	Duration of diabetes (years)	Mean baseline HbA_{1c} (%)	Change in HbA_{1c} (%) (placebo subtracted*)	P-value	Change in weight
Aschner, *et al.*[21]	24	741	Sitagliptin 100mg od Sitagliptin 200mg od *Vs* placebo	4.4	8.0	-0.79* -0.94*	<0.001	-0.2kg -0.1kg -1.1kg
Raz, *et al.*[22]	18	521	Sitagliptin 100mg od Sitagliptin 200mg od *Vs* placebo	4.5	8.1	-0.60* -0.48*	<0.001	-0.6kg -0.2kg -0.7kg
Goldstein, *et al.*[23]	24	1091	Sitagliptin 100mg od Metformin 1000mg Metformin 2000mg Sitagliptin 50mg bd + metformin 1000mg Sitagliptin 50mg bd + metformin 2000mg Placebo	4.5	8.8%	-0.83* -0.99* -1.30* -1.57* -2.07* –	<0.001	0.0kg -0.6–1.3kg -0.6–1.3kg -0.6–1.3kg -0.6–1.3kg -0.9kg
Charbonnel, *et al.*[24]	24	701	Sitagliptin 100mg + metformin ≥ 1500mg *Vs* metformin + placebo	6.2	8.0	-0.65*	<0.001	-0.6–0.7kg in both groups
Nauck, *et al.*[25]	52	1172	Metformin ≥ 1500mg + sitagliptin 100mg *Vs* metformin ≥ 1500mg + glipizide 5–20mg	6.5 6.2	7.7 7.6	-0.51 -0.56	Similar reduction	-1.5kg +1.1kg
Hermansen, *et al.*[26]	24	441	Sitagliptin 100mg + glimepiride ≥ 4mg *vs* glimepiride ≥ 4mg + placebo Glimepiride ≥ 4mg + metformin ≥ 1500mg + sitagliptin 100mg *vs* glimepiride ≥ 4mg + metformin ≥ 1500mg + placebo	8.8	8.3	-0.57* -0.89*	<0.001	+0.8kg for sitagliptin groups -0.4kg for placebo groups
Rosenstock, *et al.*[27]	24	353	Pioglitazone + sitagliptin 100mg *vs* pioglitazone + placebo	6.1	8.1 8.0	-0.7*	<0.001	+1.8kg +1.5kg

Added to metformin

In a randomised, double-blind, placebo-controlled, parallel-group study, patients with T2DM were randomised to six arms which included combination (metformin plus sitagliptin) treatment, metformin alone, sitagliptin alone or placebo. The placebo-subtracted HbA_{1c} changes are shown in Table 1. The incidence of hypoglycaemia was low (0.5–2.2%) across active treatment groups and was not significantly different from that in the placebo group (0.6%).[23]

In a study in T2DM subjects treated with metformin ≥1500mg, addition of sitagliptin led to a placebo-subtracted reduction in HbA_{1c} (-0.65%), fasting plasma glucose (-1.4mmol/L), and two-hour post-meal plasma glucose (-2.8mmol/L) ($p<0.001$ for all three measures).[24]

Added to metformin and compared with glipizide

Subjects who failed to reach target HbA_{1c} on metformin were ran-

domised to either sitagliptin 100mg or glipizide 5–20mg.[25] Reductions in HbA1c levels in the two groups were similar at 52 weeks. A significantly lower rate of hypoglycaemia occurred in subjects treated with sitagliptin (5%) than in those on glipizide (32%) (p<0.001).

Added to glimepiride alone or to glimepiride and metformin

The addition of sitagliptin to glimepiride-treated patients as dual therapy, and glimepiride plus metformin-treated patients as triple therapy, has been examined. In the entire cohort, patients on sitagliptin had a placebo-adjusted HbA1c reduction of -0.74% (p<0.001). The study also showed that sitagliptin decreased fasting and post-prandial glucose and increased homeostasis model assessment-β (HOMA-β), a marker of β-cell function, by 12% (p<0.05) relative to placebo. The addition of sitagliptin was generally well tolerated; however, there was a higher incidence of hypoglycaemia (12% *vs* 2%) and drug-related adverse experiences (15% *vs* 7%) in the sitagliptin group compared with the placebo group. In addition, the body weight increased with sitagliptin compared to placebo (+0.8kg *vs* -0.4kg; p<0.001).[26]

Added to pioglitazone

Rosenstock *et al.* conducted a 24-week study of sitagliptin added to pioglitazone therapy. T2DM subjects on pioglitazone (30 or 45mg) were randomised to receive sitagliptin 100mg daily or placebo. The addition of sitagliptin produced a significant reduction in HbA1c compared to the placebo plus pioglitazone group.[27]

Sitagliptin use in the elderly population

Preliminary information on the efficacy and tolerability of sitagliptin in subjects with T2DM aged ≥65 years compared to subjects aged <65 years, from pooled data of four studies, shows that the overall incidence of adverse events were generally similar among older and younger patients.[28]

Vildagliptin

Vildagliptin (Galvus, Novartis International) is a potent, selective, bioavailable DPP-4 inhibitor; it is rapidly absorbed orally.[29] It improves glycaemic control by increasing α- and β-cell responsiveness to glucose and suppressing inappropriate glucagon secretion.[30] Vildagliptin is not yet approved by the FDA. However, the European Union granted approval for vildagliptin to be used in combination with metformin, sulphonylurea or TZDs.[31]

Monotherapy

See Table 2: summary of clinical trials with vildagliptin.

Monotherapy vs *placebo*

A double-blind, randomised, multicentre, placebo-controlled parallel study in drug naive subjects with T2DM looked at the efficacy and tolerability of vildagliptin 50mg od, 50mg bd or 100mg od. HbA1c reduced in all treatment arms.[32]

Monotherapy vs *metformin*

Schweizer *et al.*[33] performed a 52-week, multicentre, randomised, double-blind study comparing vildagliptin 50mg bd to metformin 1000mg bd in patients with T2DM. Both vildagliptin and metformin decreased HbA1c but the reduction was significantly greater for metformin (p<0.001) The incidence of hypoglycaemia was 0.6% with vildagliptin *vs* 0.4% with metformin.

Monotherapy vs *rosiglitazone*

Rosenstock *et al.* compared vildagliptin with rosiglitazone in a 24-week trial of patients with T2DM. Both vildagliptin and rosiglitazone resulted in comparable reductions in HbA1c of more than 1% from baseline (p<0.001).[34] Patients using rosiglitazone, however, had an average increase in body weight of 1.6kg at the end of the study, while patients using vildagliptin had an average decrease in weight of -0.3kg (p<0.001).

Combination therapy

See Table 2.

Added to metformin

In a multicentre, randomised, double-blind, placebo-controlled trial vildagliptin was added to a stable dose of metformin; the 12-week study was followed by a 40-week extension. At 12 weeks, the vildagliptin plus metformin group demonstrated a decrease in HbA1c compared with the placebo plus metformin group (p<0.0001). Fasting plasma glucose was reduced by -1.2mmol/L (p=0.0057) in the vildagliptin group, and the mean post-prandial glucose was reduced by -2.2mmol/L (p<0.0001). At the end of 52 weeks, between-group differences in change in HbA1c, fasting plasma glucose, and mean post-prandial glucose were -1.1% (p<0.0001), -1.1mmol/L (p=0.0312), and -2.4mmol/L (p=0.0001), respectively.[35] A further study, in which either placebo or vildagliptin 50mg od or 100mg od given in divided doses was added to metformin, showed significant reduction in HbA1c (p<0.001).[36]

In a study of 416 patients, vildagliptin 50mg od or 50mg bd was added to metformin and compared with placebo. HbA1c was reduced by 0.7% and 1.1% in the 50mg and 100mg vildagliptin groups, respectively, with no weight gain seen.[37]

Added to sulphonylurea

In another study,[38] vildagliptin was added to sulphonylurea monotherapy (glimepiride). This study compared vildagliptin 50mg od and 50mg bd *vs* placebo in patients continuing glimepiride treatment (4mg od). Starting from a mean HbA1c of 8.5%, vildagliptin 50mg od reduced HbA1c by 0.6% with twice daily vildagliptin giving little additional efficacy. Vildagliptin 50mg od was not associated with increased hypoglycaemia (1.2% *vs* 0.6% for vildagliptin and placebo, respectively) or weight gain (-0.1kg *vs* placebo 0.3kg, p=0.409).

Added to insulin

In a multicentre, 24-week, double-blind, randomised, placebo-controlled trial in 296 patients with T2DM (inadequately controlled on insulin, with a baseline HbA1c of 8.4%), subjects were given 50mg of vildagliptin twice a day in addition to insulin (n=144). In those patients aged ≥65 years, the adjusted mean change from baseline to endpoint HbA1c was -0.7% in the vildagliptin group *vs* -0.1% in the placebo group (p<0.001).[39]

Table 2. Summary of clinical trials with vildagliptin

Source	Trial duration (weeks)	No. of subjects	Treatment and dose	Duration of diabetes (years)	Mean baseline HbA_{1c} (%)	Change in HbA_{1c} (%) (placebo subtracted*)	P-value	Change in weight
Pi-Sunyer, *et al*.[32]	24	354	Vildagliptin 50mg od *Vs* vildagliptin 50mg bd *Vs* vildagliptin 100mg od *Vs* placebo	1.8 2.4 2.1 2.5	8.4	-0.5* -0.7* -0.8*	=0.011 <0.001 <0.001	-0.4kg 0.0 -0.4kg -1.4kg
Schweizer, *et al*.[33]	52	780	Vildagliptin 50mg bd *vs* metformin 1000mg bd	1	8.7	-1.0 -1.4	<0.001	+0.3kg -1.9kg
Rosenstock, *et al*.[34]	24	786	Vildagliptin 50mg bd *vs* rosiglitazone 8mg od	2.3 2.7	8.7	-1.1 -1.3	Similar reduction	-0.3kg +1.6kg
Ahren, *et al*.[35]	12	107	Vildagliptin 50mg od + metformin *Vs* metformin + placebo	5.6 5.5	7.7 7.8	-0.6* at 12/52 -1.1* at 52/52	<0.001 both	-0.4kg at 12/52 -0.2kg at 52/52 -0.5kg at 12/52 -0.2kg at 52/52
Bosi, *et al*.[36]	24	544	Vildagliptin 50mg od + metformin ≥ 1500mg Vildagliptin 100mg od + metformin ≥ 1500mg Metformin *vs* placebo	6.2	8.4	-0.7* -1.1*	<0.001 <0.001	-0.4kg +0.2kg -1.0kg
Garber, *et al*.[37]	24	416	Vildagliptin 50mg od + metformin ≥ 1500mg *vs* metformin + placebo Vildagliptin 50mg bd + metformin ≥ 1500mg *vs* metformin + placebo	6.2	8.4	-0.7 -1.1	<0.001	No weight gain in either group
Garber, *et al*.[38]	24	408	Vildagliptin 50mg od + glimepiride 4mg od Vildagliptin 50mg bd + glimepiride 4mg od Placebo + glimepiride 4mg od	7–8	8.5	-0.6* -0.7*	<0.001 <0.01	-0.1kg -0.1kg +0.3kg
Fonseca, *et al*.[39]	24	296	Vildagliptin 50mg bd + unspecified insulin *vs* placebo + insulin	14.5	8.4	-0.3*	<0.01	+1.3kg +0.6kg

DPP-4 inhibitors' *vs* other OADs' effect on lipid profiles

In a head-to-head comparison of vildagliptin 50mg bd with rosiglitazone 8mg od over 24 weeks, the lipid profile improved with vildagliptin compared to the rosiglitazone group, as demonstrated by decreased total cholesterol (-14%, p<0.001), LDL (-16%, p<0.001), triglycerides (-9%, p=0.010), and VLDL (-8%, p=0.007), and a small increase was observed in HDL (+4 *vs* +9%, p=0.003).[34]

Matikainen *et al.* evaluated the effects of vildagliptin on the post-prandial lipid profile. Vildagliptin therapy produced a significant reduction in triglycerides by 22% (p=0.037) with a favourable change in triglycerides compared with metformin.[40]

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