

Dipeptidyl peptidase-4 inhibitors in type 2 diabetes therapy – focus on alogliptin

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Abstract: Type 2 diabetes mellitus is a complex and progressive disease that is showing an apparently unstoppable increase worldwide. Although there is general agreement on the first-line use of metformin in most patients with type 2 diabetes, the ideal drug sequence after metformin failure is an area of increasing uncertainty. New treatment strategies target pancreatic islet dysfunction, in particular gut-derived incretin hormones. Inhibition of the enzyme dipeptidyl peptidase-4 (DPP-4) slows degradation of endogenous glucagon-like peptide-1 (GLP-1) and thereby enhances and prolongs the action of the endogenous incretin hormones. The five available DPP-4 inhibitors, also known as ‘gliptins’ (sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin), are small molecules used orally with similar overall clinical efficacy and safety profiles in patients with type 2 diabetes. The main differences between the five gliptins on the market include: potency, target selectivity, oral bioavailability, long or short half-life, high or low binding to plasma proteins, metabolism, presence of active or inactive metabolites, excretion routes, dosage adjustment for renal and liver insufficiency, and potential drug–drug interactions. On average, treatment with gliptins is expected to produce a mean glycated hemoglobin (HbA_{1c}) decrease of 0.5%–0.8%, with about 40% of diabetic subjects at target for the HbA_{1c} goal <7%. There are very few studies comparing DPP-4 inhibitors. Alogliptin as monotherapy or added to metformin, pioglitazone, glibenclamide, voglibose, or insulin therapy significantly improves glycemic control compared with placebo in adult or elderly patients with inadequately controlled type 2 diabetes. In the EXAMINE trial, alogliptin is being compared with placebo on cardiovascular outcomes in approximately 5,400 patients with type 2 diabetes. In clinical studies, DPP-4 inhibitors were generally safe and well tolerated. However, there are limited data on their tolerability, due to their relatively recent marketing approval. Alogliptin will be used most when avoidance of hypoglycemic events is paramount, such as in patients with congestive heart failure, renal failure, and liver disease, and in the elderly.

Keywords: type 2 diabetes, DPP-4 inhibitors, alogliptin

Introduction

In 2011, there were 366 million people with diabetes worldwide, and this is expected to rise to 552 million by 2030, rendering previous estimates very conservative.¹ Excluding accidents, diabetes is the fifth cause of death for women and the fourth for men in the USA.² Tight glycemic control, to maintain a hemoglobin A1c (HbA_{1c}) concentration of 7% or lower, is recommended for many nonpregnant adults with diabetes to minimize the risk of long-term vascular complications.³ As a consequence, current diabetes guidelines⁴ suggest adjustment of therapy based on HbA_{1c} level. However, there is little evidence about the relative effects of various antihyperglycemic therapies on clinical outcomes,

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with the possible exception of metformin, which appears moderately protective on cardiovascular (CV) outcomes.⁵

Although there is general agreement on the first-line use of metformin in most patients with type 2 diabetes, the ideal drug sequence after metformin failure is an area of increasing uncertainty,⁶ given the panoply of diabetes medications so far available for treatment of hyperglycemia. There are 45 rational and US Food and Drug Administration-permissible combinations that can be used in dual therapy.⁷ A recent estimate claims 150 therapeutic options for triple therapy and 600 options for quadruple therapy, not including the different options within each class, for example, basal vs premixed insulin.⁸

The failure to achieve glycemic goals in a large portion of this population is, in part, due to limitations in the current treatment options available to patients with type 2 diabetes. Many oral diabetes medications are associated with side effects that limit their use, including hypoglycemia (sulfonylureas, insulin, meglitinides), weight gain (sulfonylureas, thiazolidinediones, insulin), gastrointestinal side effects (metformin, exenatide, α -glucosidase inhibitors), and fluid retention (thiazolidinediones and insulin). Even if these medications are initially effective, glycemic control gradually worsens over time in most patients owing to a steady and progressive decline in pancreatic β -cell function. There is at present no robust evidence that a single therapeutic agent can address all pathogenetic factors associated with the progressive exhaustion of beta cells. As a corollary, most type 2 diabetic patients require more than one pharmacological option to achieve glycemic target. Ultimately, most patients will require insulin therapy.⁹

Antihyperglycemic agents also have the potential to contribute to therapeutic inertia, defined as the failure of health care providers to initiate or intensify therapy when indicated,¹⁰ via factors inherent to the drugs themselves, such as treatment-related adverse effects, perception of long-term safety profiles, and the complexity of the treatment regimen. Perhaps it is not by chance that the position statement from the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) on the management of hyperglycemia in type 2 diabetes is subtitled 'a patient-centered approach'.⁴ This statement highlights the clinical judgment (a mixture of clinical experience, knowledge, and skill) of physicians together with the patients' values and preferences. However, physician feeling and conviction about the willingness to reach the HbA_{1c} target (now tailored on the patient) remain paramount to reduce unnecessary therapeutic inertia.¹¹

An improved understanding of the pathogenesis of type 2 diabetes, including postprandial control of glucose homeostasis, has led to the emergence of new treatment strategies that target pancreatic islet dysfunction, in particular those that target gut-derived incretin hormones.

The incretin system

More than 20 years ago, Gutniak et al¹² suggested that glucagon-like peptide-1 (GLP-1) might be a potential target in the treatment of type 2 diabetes, as they demonstrated that its intravenous infusion reduced the insulin requirement to meal ingestion in subjects with diabetes. At that time, it was already known that oral glucose ingestion elicited a greater insulin response than did intravenous glucose infusion, at the same level of attained glycemia.¹³ Later, this was called the incretin effect, and attributed to an increased glucose-stimulated insulin secretion induced by the gut incretin hormones released after glucose ingestion.¹⁴

The two incretin hormones with the greatest effect on glucose control are GLP-1 and glucose-dependent insulinotropic peptide (GIP). Both peptides are secreted within minutes of food consumption and act on pancreatic beta cells, through distinct receptors, to stimulate insulin secretion with dependency on blood glucose concentration; when glucose levels are normal, incretin-stimulated insulin secretion is suppressed.¹⁵ GLP-1 is a product of the proglucagon gene and is secreted from the L cells located in the distal gut into the capillaries and then into the blood stream. Activation of the GLP-1 receptors (G_{os} protein-coupled receptors) expressed on the pancreatic β -cells elevates cAMP levels, which in turn activates protein kinase A and Epac 1 and 2, resulting in a glucose-dependent increase of insulin secretion by the β -cell.¹⁶ GLP-1 infusions have shown more promising results than those of GIP in lowering plasma glucose in diabetes. Other effects of GLP-1 include suppression of glucagon secretion, also exerted in a glucose-dependent manner, slowing of gastric emptying time, and promotion of satiety. The net effect of enhanced insulin secretion and suppressed glucagon secretion is decreased fasting and postprandial glucose levels. GLP-1 also increases β -cell mass through differentiation and proliferation of β -cells and inhibition of apoptosis, as shown in rodents.¹⁷ Since all of these effects are of potential value in the treatment of type 2 diabetes, GLP-1 has intensively been explored as a pharmacological therapy for the disease.

The incretin effect is greatly reduced in patients with type 2 diabetes – this plays an important contributory role in the insulin insufficiency and chronic hyperglycemia characteristic of the disease.¹⁸ The short half-life (1–2 minutes) of GLP-1 is a consequence of its rapid inactivation by the enzyme dipeptidyl

peptidase-4 (DPP-4) that truncates the peptide by removal of the N-terminal dipeptide end. GLP-1 effects can be provided therapeutically by giving supplemental GLP-1 agonists, which are largely resistant to the action of DPP-4; the other approach is to inhibit the enzyme DPP-4, which slows degradation of endogenous GLP-1, and thereby enhances and prolongs the action of the endogenous incretin hormone.

DPP-4 inhibitors: pharmacology, mode of action, pharmacokinetics

DPP-4 (also known as lymphocyte cell surface protein CD26) is a membrane-spanning, cell-surface aminopeptidase ubiquitously expressed in many tissues, such as gut, lymphocyte, liver, kidney, lung, and endothelial cells.¹⁷ DPP-4 enzyme is a member of the DPP family, which also includes the structurally related enzymes DPP-2, DPP-8, DPP-9, and fibroblast activation protein; DPP-4 has several substrates, such as gastrointestinal hormones, neuropeptidase, cytokines, and chemokines.¹⁹

The five available DPP-4 inhibitors, also known as ‘gliptins’ (sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin), are small molecules used orally with similar overall clinical efficacy and safety profiles in patients with type 2 diabetes. Sitagliptin was the first gliptin licensed by the US Food and Drug Administration (FDA) in 2006 (Table 1) and is now available worldwide;²⁰ vildagliptin and saxagliptin were approved in 2007 and 2009, respectively.^{21,22} More recent compounds are alogliptin (available only in Japan in 2010) and linagliptin (authorized by the FDA and EU in 2011).^{23,24} DPP-4 inhibitors may be used as monotherapy or in double or triple combination with other oral glucose-lowering agents, as metformin, thiazolidinediones, or sulfonylureas. The authorized combined therapies in EU are reported in Table 2. Sitagliptin, vildagliptin, and saxagliptin are currently available as single agents or in a fixed-dose combination with metformin.

DPP-4 inhibitors reduce plasma DPP-4 activity by 70%–90% in a sustained manner for 24 hours with an increase of GLP-1 levels (1.5- to 4-fold). They do not pass the blood–brain barrier, have no direct central effect on satiety, and in contrast with GLP-1 agonists (incretin mimetics), did not alter gastric emptying.²⁵ Although DPP-4 inhibitors have the same mode of action, they differ by some important pharmacokinetic and pharmacodynamic properties that may be clinically relevant in some patients.¹⁹ The main differences between the five gliptins on the market include: potency, target selectivity, oral bioavailability, long or short half-life, high or low binding to plasma proteins, metabolism, presence of active or inactive metabolites, excretion routes, dosage adjustment for renal and liver insufficiency, and potential drug–drug interactions (Table 3).

Table 1 DPP-4 inhibitors-based medicines authorized through central procedure by the European Medicines Agency (EMA)

DPP-4 inhibitors	Medicines	Date of authorization
Sitagliptin	Januvia®	21/03/2007
	Xelevia®	21/03/2007
	Tesavel®	10/01/2008
	Ristaben®*	15/03/2010
Sitagliptin + metformin	Effcib®	16/07/2008
	Janumet®	16/07/2008
	Velmetia®	16/07/2008
	Ristfor®	15/03/2010
Vildagliptin	Galvus®	26/09/2007
	Jalra®*	19/11/2008
	Xiliarx®*	19/11/2008
Vildagliptin + metformin	Eucreas®	14/11/2007
	Icandra®	01/12/2008
	Zomarist®*	01/12/2008
Saxagliptin	Onglyza®	01/10/2009
Saxagliptin + metformin	Komboglyze®	24/11/2011
Linagliptin	Trajenta®*	24/08/2011
Linagliptin + metformin	Jentaduet®	20/07/2012

Note: *Not available in Italy. Data from European Medicines Agency [homepage on the Internet]. European public assessment reports (EPAR). [updated August, 2013]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WVC0b01ac058001d124. Accessed August 29, 2013.⁷²

Abbreviation: DPP, dipeptidyl peptidase.

Pharmacodynamic properties

Regarding potency, linagliptin, compared with sitagliptin, alogliptin, saxagliptin, and vildagliptin demonstrated the highest potency of DPP-4 inhibition (IC₅₀ values of 1 nM, 19 nM, 24 nM, 50 nM, and 62 nM, respectively).^{19,26,27} The duration of action of DPP-4 inhibitors with comparatively shorter half-lives may be strongly influenced by binding strength and reversibility with the receptor.²⁸ All gliptins exhibit a greater selectivity for DPP-4 enzyme, ranging from 30- to 40,000-fold superior to the other enzymes, ie, DPP-8 and DPP-9.^{28,29} However, because DPP-8 and DPP-9 are proteases responsible for T-cell activation which play an important role in immune function, the off-target inhibition of selective DPP-4 inhibitors is responsible for toxicity (immune dysfunction, impaired healing, and skin reactions).²⁹

Pharmacokinetic properties

After oral administration in humans, all DPP-4 inhibitors are well absorbed with oral bioavailability ranges

Table 2 The combinations between DPP-4 inhibitors and other oral glucose-lowering agents authorized by the European Medicines Agency (EMA)

Indications	Sitagliptin	Sita + Met	Vildagliptin	Vilda + Met	Saxagliptin	Saxa + Met	Linagliptin	Lina + Met
Alone	Yes	Yes	Yes	Yes	–	Yes	Yes	Yes
+ Met	Yes	–	Yes	–	Yes	–	Yes	–
+ TZD	Yes	Yes	Yes	–	Yes	–	–	–
+ SU	Yes	Yes	Yes	Yes	Yes	–	–	Yes
+ Met and SU	Yes	–	Yes	–	–	–	Yes	–
+ Met and TZD	Yes	–	–	–	–	–	–	–
+ Insulin and ± Met	Yes	Yes	Yes	Yes	Yes	Yes	–	–
Previous gliptin + Met (separately)	–	Yes	–	Yes	–	Yes	–	Yes
Dose adjustment in kidney impairment	Yes	Yes	Yes	Yes	Yes	–	–	–

Abbreviations: DPP, dipeptidyl peptidase; Lina, linagliptin; Met, metformin; Saxa, saxagliptin; Sita, sitagliptin; Vilda, vildagliptin; SU, sulfonylurea; TZD, thiazolidinedione.

from approximately 30% with linagliptin to 75%–87% for all others and are not significantly influenced by food intake.³⁰ Linagliptin has the longest half-life (120–184 hours), followed by alogliptin (12.4–21.4 hours), and sitagliptin (8–14 hours), whereas saxagliptin and vildagliptin have shorter half-lives (2.2–3.8 hours and 2–3 hours, respectively). Due to a sustained DPP-4 enzyme inhibition and a long half-life, sitagliptin, alogliptin, and linagliptin are generally prescribed once a day. Saxagliptin is also administered once daily due to the presence of an active metabolite (5-hydroxy saxagliptin) which is half as potent as the parent compound. Due to the shorter half-life, vildagliptin needs twice-daily dosing.³¹ The apparent volumes of distribution (Vd) among the gliptins range from 70 to 918 L.²⁵ Moreover, the distribution of DPP-4 inhibitors is strongly influenced by protein binding. All gliptins are not extensively bound to plasma proteins,

except for linagliptin, which has the highest binding level to proteins.³²

DPP-4 inhibitor metabolism is widely variable. While sitagliptin does not appear to undergo extensive metabolism, both vildagliptin and saxagliptin are extensively metabolized in the liver. However, vildagliptin produces a large amount of inactive metabolites through several pathways (hydrolysis, glucuronidation, and oxidation) not mediated by the cytochrome P450 (CYP) system, while saxagliptin is mainly metabolized by the CYP3A4/5 isoforms to a major active metabolite, 5-hydroxy saxagliptin (which is 2-fold less potent than its parent molecule).^{32–34} Both saxagliptin and its major metabolite are not inhibitors or inducers of various CYP isoforms.³² Although the potential for drug interactions with saxagliptin and its metabolite is low, their pharmacokinetic profile may be influenced in co-administration with strong CYP3A4/5 inducers (such as rifampicin) or inhibitors (such

Table 3 Main pharmacokinetic and pharmacodynamic properties of DPP-4 inhibitors available on the European market

Parameters	Sitagliptin	Vildagliptin	Saxagliptin	Alogliptin	Linagliptin
Pharmacodynamics					
In vitro DPP-4 inhibition (IC ₅₀ in nM)	19	62	50	24	1
DPP-4 selectivity (vs DPP-8 and DPP-9)	>2,600	<100	<100	>14,000	>10,000
Pharmacokinetics					
Oral bioavailability (%)	87	85	75	70	30
Volume distribution (L)	198	71	151	300	368–918
Fraction bound to proteins (%)	38	9.3	<10	20	70
Half life (T _{1/2}) (h)	8–14	2–3	2.2–3.8	12.4–21.4	120–184
Liver excretion (%)	13	4.5	22	13	85
Kidney excretion (%)	87	85	75	76	5
Proportion excreted unchanged (%)	79	23	24	95	~90
Substrate for CYP3A4/5	Low	No	Yes	No	No
Drug–drug interactions	Unknown	Unknown	CYP3A4/5 inducers and inhibitors	Unknown	Unknown

Note: Data were obtained from references 19, 25, 28, 29, 32.

Abbreviations: DPP, dipeptidyl peptidase; CYP, cytochrome P450.

as ketoconazole); in these cases, it is recommended to modify the dosage of saxagliptin.^{34,35} The pharmacokinetic profiles of the other DPP-4 inhibitors suggest a low risk of drug–drug interactions,³² which is especially favorable in patients older than 65 years.³⁵

All DPP-4 inhibitors predominantly (75%–87%) undergo renal excretion, with 76%–87% of each dose eliminated as unchanged parent compound in the urine. In contrast, linagliptin is excreted mostly (~90%) unchanged in feces via biliary excretion,^{19,25} and therefore appears to be safe in diabetic patients suffering from renal complications.^{29,34} An appropriate dose reduction of the gliptins with predominantly renal excretion (sitagliptin, saxagliptin, and alogliptin, but not vildagliptin) is required in case of renal impairment.^{25,29,32} In patients with mild to severe liver impairment, no dose adjustment seems necessary for linagliptin despite its liver excretion.²⁵

Efficacy studies

In a meta-analysis of randomized controlled trials (RCTs) through September 2010,³⁶ we assessed the effectiveness of different DPP-4 inhibitors to reach the recommended HbA_{1c} target of <7% in people with type 2 diabetes. Of the 1,438 citations identified, we selected 43 studies, with 10,467 patients treated with a DPP-4 inhibitor. All studies were published between 2005 and 2010; all studies were of parallel groups, and most studies were of double-

triple-blind design. The duration of the studies ranged from 12–52 weeks, and most arms were of 24–26 weeks.

There were 14 RCTs testing vildagliptin, with 4,288 subjects. The direct random effect meta-analysis of RCTs showed that 37% of subjects achieved the HbA_{1c} goal of <7% at the end of treatment, without differences between the four arms in which vildagliptin was added to metformin and the nine arms in which vildagliptin was used in monotherapy (Figure 1). The mean decrease in HbA_{1c} was 0.88%, body weight change was 0.165 kg, and the frequency of hypoglycemia was 1.4% (Figure 2).

There were 18 RCTs testing sitagliptin, with 3,646 subjects. The meta-analysis showed that 37% of subjects achieved the HbA_{1c} goal of <7% at the end of treatment, without differences between the eight arms in which sitagliptin was added to metformin and the seven arms in which sitagliptin was used in monotherapy (Figure 1). The mean decrease in HbA_{1c} was 0.71%, body weight change was –0.254 kg, and the frequency of hypoglycemia was 3.1% (Figure 2).

There were nine RCTs testing saxagliptin, with 1,608 subjects. The meta-analysis showed that 38% of subjects achieved the HbA_{1c} goal of <7% at the end of treatment, without differences between the six arms in which saxagliptin was used at the 5 mg dose, and the three arms in which it was used at the 10 mg dose (Figure 1). The mean decrease in HbA_{1c} was 0.8%, body weight change was –0.20 kg, and the frequency of hypoglycemia was 3.4% (Figure 2).

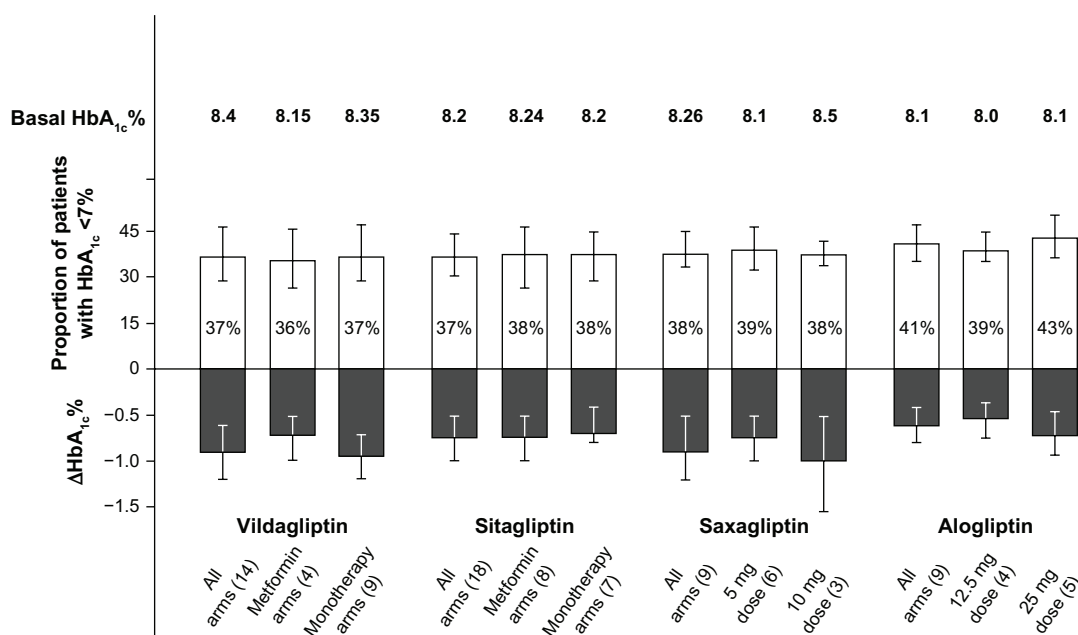


Figure 1 Proportion of patients with HbA_{1c} <7%, and absolute decrease of HbA_{1c} from baseline at endpoint in patients with type 2 diabetes on gliptins after failure of previous treatments.

Note: Basal HbA_{1c} represents the mean baseline HbA_{1c} level at randomization.

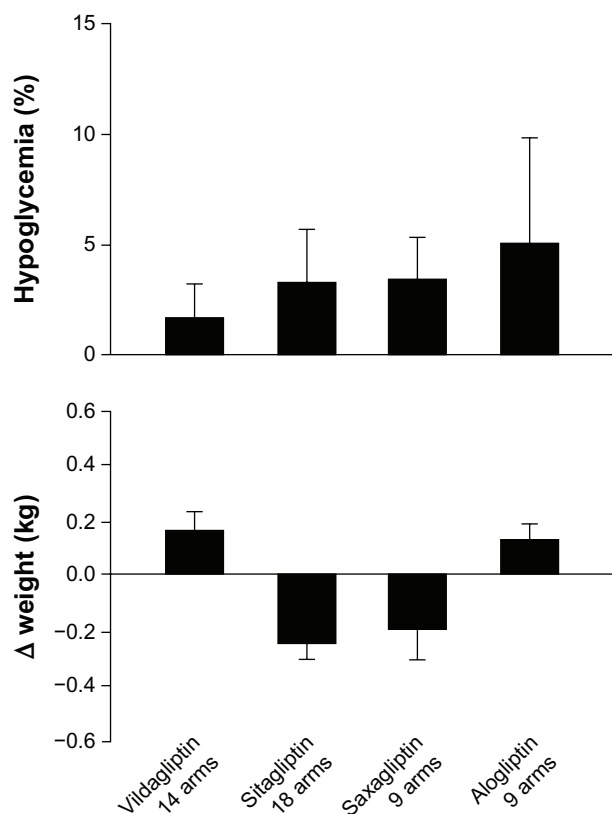


Figure 2 Proportion of patients with hypoglycemia (%) and changes in weight (kg) in patients with type 2 diabetes on gliptins after failure of previous treatments.

There are few studies comparing DPP-4 inhibitors. There are no head-to-head studies reported comparing sitagliptin and vildagliptin, nor have there been studies comparing alogliptin with these currently approved DPP-4 inhibitors. Caution must therefore be exercised in judging relative efficacy. There is one head-to-head study showing no difference in the effect of saxagliptin combined with metformin as compared with sitagliptin plus metformin.³⁷ The improvements in HbA_{1c} seen with alogliptin seem to be in the same range as those seen with other DPP-4 inhibitors.³⁶

Focus on alogliptin

In the pivotal, 26-week, Phase III monotherapy trial³⁸ in drug-naïve type 2 diabetic patients inadequately controlled with diet and exercise, alogliptin treatment resulted in significantly greater improvements in glycemic control than placebo, in terms of changes from baseline in HbA_{1c} and fasting glucose levels, and achievement of prespecified target levels of HbA_{1c} (HbA_{1c} <6.5% or 7%). Moreover, fewer alogliptin (12.5 and 25 mg/day groups) than placebo recipients required hyperglycemic rescue. There were no statistically or clinically meaningful changes in body weight in both alogliptin groups versus the placebo group. There were also

significant ($P < 0.006$) improvements in total cholesterol levels in the alogliptin groups after 26 weeks of treatment, but no difference in HDL-cholesterol, LDL-cholesterol, or triglyceride levels.

Alogliptin plus metformin,³⁹ pioglitazone,⁴⁰ glibenclamide,⁴¹ voglibose,⁴² or insulin⁴³ therapy significantly improved glycemic control compared with placebo in adult patients with inadequately controlled type 2 diabetes. After 26 weeks, changes from baseline in HbA_{1c} levels, which were apparent from week 4 onwards, were all significantly greater in the alogliptin 12.5 mg group (range -0.4% to -0.7%) and 25 mg group (range -0.5% to -0.8%) than in placebo recipients (range -0.2% to +0.01%). Consistent with these findings, significantly more patients in the alogliptin groups than in the placebo groups achieved HbA_{1c} target levels (HbA_{1c} <6.5% or <7.0%).

The efficacy of alogliptin in elderly patients with inadequately controlled diabetes has been evaluated in a pooled analysis.⁴⁴ The elderly people (aged ≥65 years; n = 455) were compared to younger people (aged <65 years; n = 1911). There were no statistically significant differences between the two age groups in terms of improvements in glycemic control (HbA_{1c} or fasting blood glucose decrease from baseline), irrespective of whether patients had a baseline HbA_{1c} level of ≤8% or >8%. In addition, 37% of younger patients achieved an HbA_{1c} level of ≤7% at week 26 (both alogliptin doses). In elderly patients, this target HbA_{1c} level was achieved by 45% of patients on both alogliptin doses. There were no significant differences between treatment groups or between younger and elderly patients in terms of body weight changes from baseline, or lipid parameters. Table 4 shows the characteristics of the studies^{38-42,45-51} hitherto published evaluating the efficacy and tolerability of alogliptin at different doses in type 2 diabetic patients not adequately controlled on previous treatments.

The EXAMINE trial

As a result of concerns regarding the association of antidiabetic agents with adverse CV outcomes,⁵² the FDA released a guidance in December 2008 titled, 'Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes'.⁵³ This guidance outlines requirements for CV safety assessment before and after approval of all new antidiabetic therapies. Specifically, sponsors must rule out an upper 95% confidence interval (CI) of the hazard ratio (HR) of 1.8 before approval and 1.3 after approval. Alogliptin has been studied in 3,489 diabetic patients and 1,213 patients on placebo in seven 26-week

Table 4 Characteristics of the studies with alogliptin

Studies (author, year, reference)	No	Mean age (years)	FU (weeks)	Alogliptin dosage	Add-on to	Mean HbA _{1c} basal (%)	HbA _{1c} Δ (%)	HbA _{1c} <7%	Weight Δ (kg)	Overall hypoglycemia (%)	Any AE (drug-related) %
DeFronzo et al ³⁸	133	53.4	26	12.5 mg	Naïve	7.9	-0.56	47.4	-0.09	3	23
Nauck et al ³⁹	213	55	26	12.5 mg	Met	7.9	-0.6	52	0	1	11
Pratley et al ⁴⁰	197	55.5	26	12.5 mg	Pio/+Met/+Su	8.1	-0.66	44	0.42	5.1	19
Pratley et al ⁴¹	203	56.5	26	12.5 mg	Su	8.1	-0.39	29.6	0.6	15.8	15
Seino et al ⁴²	76	61.0	12	12.5 mg	Voglibose	8.02	-0.96	46	0.19	0	9
Seino et al ^{45,*}	84	58.7	12	12.5 mg	Naïve	7.99	-0.68	35.7	0.45	1	14.3
Kaku et al ^{46,*}	111	60.8	12	12.5 mg	Pio	7.9	-0.91	49.5	0.48	1	7.2
DeFronzo et al ⁴⁷	128	55.2	26	12.5 mg	Met	8.6	-0.65	20	-0.02	1	20.3
Seino et al ^{48,*}	92	53.4	12	12.5 mg	Met	7.9	-0.55	28.3	0.17	1	8.3
DeFronzo et al ³⁸	131	53.4	26	25 mg	Naïve	7.9	-0.59	44.4	0.22	2	23
Nauck et al ³⁹	210	54	26	25 mg	Met	7.9	-0.6	43.8	-0.3	0	13
Pratley et al ⁴⁰	198	56.5	26	25 mg	Su	8.1	-0.53	34.8	0.68	9.6	18
Pratley et al ⁴¹	199	55.4	26	25 mg	Pio/+Met/+Su	8	-0.80	49.2	0.05	7	19
Rosenstock et al ⁴⁹	164	53	26	25 mg	Naïve	8.8	-0.96	24.5	-0.29	2	18.8
Seino et al ⁴²	79	62.9	12	25 mg	Voglibose	7.91	-0.91	50.6	-0.19	0	12
Seino et al ^{45,*}	80	59.7	12	25 mg	Naïve	7.9	-0.77	44.3	0.2	1	32
Bosi et al ⁵⁰	404	54.3	52	25 mg	Met + Pio	8.2	-0.7	33.2	1.1	4.5	21.8
Kaku et al ^{46,*}	113	59.3	12	25 mg	Pio	7.9	-0.97	49.6	0.46	1	8.8
DeFronzo et al ⁴⁷	129	53.1	26	25 mg	Met	8.6	-0.92	28	-0.7	1	22.1
Seino et al ^{48,*}	96	52.3	12	25 mg	Met	8.02	-0.64	27.1	-0.09	2	10
Kutoh and Ukai ⁵¹	25	47.9	12	25 mg	Naïve	10.5	-1.77	7	-0.7	16	NR

Note: *HbA_{1c} target <6.9%.

Abbreviations: AE, adverse events; FU, follow-up; Met, metformin; NR, not reported; Pio, pioglitazone; Su, sulfonylurea.

studies and one 12-week study (Phase III studies). Compared with placebo, treatment with alogliptin was associated with a reduced risk (HR: 0.61, 95% CI: 0.24–1.56) of adjudicated major adverse CV events (MACE), defined as death from CV disease, nonfatal myocardial infarction, or nonfatal stroke.⁵⁴ However, the CV event rate was too low to rule out a concern in patients with higher baseline risk.

EXamination of cArdiovascular outcoMes with alogliptin versus standard of care (EXAMINE)⁵⁵ is a Phase III, multicenter, prospective, double-blind randomized trial in which alogliptin is being compared with placebo on CV outcomes in approximately 5,400 patients with type 2 diabetes and a well-defined acute coronary syndrome event (myocardial infarction or hospitalization with unstable angina). The primary objective of EXAMINE is to demonstrate the noninferiority of MACE on alogliptin versus placebo in the treatment of type 2 diabetes in a high-risk CV patient group. The study consists of a screening period of up to 2 weeks and a follow-up period of 4.75 years. The length of the study participation will vary but is estimated to be a median of 2 years of study drug treatment. The statistical plan for the trial uses a design that evaluates the HR of alogliptin to placebo first based on the primary CV composite end-point after accrual of 80–150 primary CV events and again when there are 550–650 primary CV events. Long-term CV safety of alogliptin is being established using an analytical approach that has both an interim and final assessment. In the first series of analyses, the upper boundary of a group-sequential 1-sided repeated CI for the HR must be ≤ 1.8 for registration in the USA. At the end of the study, the upper boundary of a subsequent group-sequential 1-sided repeated CI for the HR must be ≤ 1.3 .

Safety and tolerability

In clinical studies, DPP-4 inhibitors were generally safe and well-tolerated.⁵⁶ However, there is limited data on their tolerability, in particular on onset of rare events, due to their relatively recent marketing approval. As a drug class, the DPP-4 inhibitors have become accepted in clinical practice due to their excellent tolerability profile, with a low risk of hypoglycemia, a neutral effect on body weight, and once-daily dosing.⁵⁷

In many clinical studies, the most common adverse events (AEs) with incretin therapy were gastrointestinal events, such as vomiting and diarrhea, which generally diminish over time or with a dose-escalation strategy.^{28,56} Nausea, which is the most common AE observed with GLP-1 receptor agonist therapy, is not frequently observed in treatment with DPP-4 inhibitors.⁵⁶ Moreover, both GLP-1 agonists and

metformin were associated with a higher discontinuation rate than DPP-4 inhibitors, which is probably related to their higher incidence of gastrointestinal reactions (diarrhea, nausea, and vomiting).⁵⁸ So far, no characteristic pattern of adverse events has been associated with the DPP-4 inhibitors despite the large number of potential substrates for DPP-4.^{17,28} DPP-4 inhibitors are less associated with several specific AEs of traditional antidiabetic treatments.²⁶ The neutral effect on body weight of DPP-4 inhibitors can be useful in overweight or obese patients with type 2 diabetes, while the low risk of hypoglycemia may be an advantage in the elderly.²⁵ Hypoglycemic events are mainly observed when DPP-4 inhibitors are associated with sulfonylureas (in 20% of the patients treated in combination) than without sulfonylureas.^{25,28}

In clinical trials, other AEs commonly correlated to DPP-4 inhibitors are of mild severity and include nasopharyngitis, headache, and urinary tract infections (UTIs).^{59–61} Another meta-analysis failed to find differences in the incidence of nasopharyngitis, upper respiratory tract infections (URTIs), and UTIs between DPP-4 inhibitors and the other hypoglycemic drugs.⁵⁸ The biological plausibility of the risk associated with this class of drugs may be related to the important role DPP-4 plays in the immune system, being a T-cell co-stimulator.^{26,62} In post-marketing, new AEs have been reported, including hypersensitivity reactions (angioedema, skin toxicity such as Stevens–Johnson syndrome),^{26,63} and also increased rates of infections.⁵⁹ In a nested case–control study conducted using VigiBase, the World Health Organization's Adverse Drug Reactions database, the spontaneous reporting of infections (primarily URTIs) was higher for patients using DPP-4 inhibitors (sitagliptin, vildagliptin, and saxagliptin) compared with users of other antidiabetic drugs (in particular metformin).⁶⁴ Regarding the newer gliptins (alogliptin and linagliptin), close post-marketing vigilance is required because of a limited exposure to these agents at this time.³¹

Although a rare event, pancreatitis has been reported in sitagliptin- and exenatide-treated patients.³⁴ However, patients with type 2 diabetes have a near three-fold baseline risk of suffering from acute pancreatitis.⁶⁵ In particular, in 2006, the US FDA received 88 reports of acute pancreatitis in patients who received sitagliptin treatment (as monotherapy or in combination with metformin), including two cases of fatal hemorrhagic or necrotizing pancreatitis, and serious nonfatal cases.⁶⁶ Besides these reports, six patients with hemorrhagic or necrotizing pancreatitis treated with exenatide required hospitalization, and two of them died.⁶⁷ The attention on this concern is still strong. As emphasized

on the FDA website,⁶⁸ a recent population-based, case–control study, conducted on a large administrative database in the US from 2005 to 2008, and including 1,269 hospitalized cases with acute pancreatitis, showed that treatment with incretin-based therapy (sitagliptin and exenatide) is associated with a doubled risk of developing acute pancreatitis in comparison with nonusers.⁶⁹

A previous study has examined the FDA adverse event reporting system (AERS) database, and has noted a 6-fold risk for pancreatitis with the use of sitagliptin or exenatide as compared with other therapies. Moreover, this analysis showed the reported event rate for pancreatic cancer was 2.9-fold greater in patients treated with sitagliptin and exenatide compared with other therapies. Unlike patients treated with GLP-1 agonists (in particular liraglutide), the reported event rate for thyroid cancer did not reach statistical significance in sitagliptin-treated patients. These observations have been explained as being due to incomplete data and reporting bias in the FDA database.⁷⁰ In preclinical toxicology studies, GLP-1 activation promoted the development of C-cell hyperplasia and medullary thyroid cancer, while this action on human C-cells is uncertain.⁷¹ In addition, there is evidence in animal models that DPP-4 inhibition is related to melanoma, prostate cancer, ovarian cancer neuroblastoma, and lung cancer. In malignancy, low levels of DPP-4 seems to be associated with dissemination or metastasis.⁷² Immunomodulatory effects of DPP-4 inhibition might explain the increased risk for all cancers.⁷² Examination of pancreata from age-matched organ donors with type 2 diabetes (DM) treated by incretin therapy resulted in a marked expansion of the exocrine and endocrine pancreatic compartments, with increased proliferation and dysplasia, and α -cell hyperplasia.⁷³ Therefore, careful long-term surveillance on the safety profile of DPP-4 inhibitors is mandatory.⁷⁴

Diabetic patients are at increased risk of CV disease. Rosiglitazone was been withdrawn from the market in the European Union (EU) in 2010,⁷⁵ because of a possible increased risk of ischemic heart disease associated with its use.⁷⁶ Several preclinical⁷⁷ and clinical studies have suggested a possible beneficial effect on CV risk associated with DPP-4 inhibitors, which also seem to possess a direct effect on the heart, independent of the incretin system.⁷⁸ They may exert some favorable effects on risk factors, resulting in a reduction of blood pressure, an improvement of postprandial lipid levels, and a reduction of high-sensitivity C-reactive protein (hsCRP).^{25,78} The endothelial dysfunction is also improved by gliptins.⁷⁹ Several large randomized Phase III

trials are ongoing and will increase our knowledge about the effect on CV outcomes and safety.^{80–83}

Focus on alogliptin

Overall, the tolerability profile of alogliptin, used alone or in association with other antidiabetic agents, did not differ from that of placebo. Severe hypoglycemia has never been reported; however, skin-related adverse events (especially pruritus) were more common in patients treated with alogliptin compared with other treatment groups.^{84,85} Although in preclinical studies, the use of other DPP-4 inhibitors, such as saxagliptin and vildagliptin, have been associated with necrotic skin lesions in monkeys,^{84–86} these events have not been observed in clinical trials. In the post-marketing phase, some patients treated with sitagliptin presented Stevens–Johnson syndrome and other exfoliative skin reactions, besides serious allergic reactions and anaphylaxis.⁸⁷

The combination of alogliptin and metformin is well tolerated. Nasopharyngitis was the most commonly reported adverse event in one study,⁴⁸ and the overall incidence of infections was highest among the other adverse events. Alogliptin is also safe when added to pioglitazone in metformin-treated patients. The incidence of skin events was similar among treatment groups, while the incidence of infections was slightly greater in patients treated with alogliptin 25 mg plus pioglitazone than pioglitazone alone or with alogliptin 12.5 mg.⁴⁷ Kaku et al⁴⁶ observed that nasopharyngitis, even if of mild severity, was the most commonly reported adverse event when alogliptin was added to pioglitazone in naïve patients. The combination of alogliptin (25 mg) and pioglitazone induced edema–related events (incidence $\geq 3\%$), which were not observed with a lower dosage of alogliptin.⁴⁶ The safety profile of the combination alogliptin and sulfonylurea is also favorable, without an increased incidence of hypoglycemia, as compared with placebo.⁴¹ Finally, alogliptin added to insulin also shows an acceptable tolerability profile, characterized by gastrointestinal, skin, and infection-related events, without increasing weight gain and the incidence of hypoglycemia.⁴³ The frequency of hypoglycemia with alogliptin reported in Figure 2 is that obtained from four studies;^{38–41} in two of these studies,^{40,41} alogliptin was added to a previous sulfonylurea treatment, which was associated with higher prevalence of hypoglycemia, which is not different from placebo. The analysis of data from Table 4 shows that the overall frequency of hypoglycemia is 3.57 (mean, where SD: 4.76) or 1.0 (median, where interquartile range: 1.0–4.6).

No clinically meaningful changes in laboratory test results have been reported.^{39,43,46} Moreover, few patients died, but the fatal events were not considered to be related to study medication.^{39,46,47} In the study of Nauck et al,³⁹ two patients in the alogliptin (25 mg) + metformin group reported severe pulmonary embolism and congestive heart failure, which were considered 'possibly related' to the study drug. On the other hand, alogliptin seems to have anti-atherosclerotic effects, including decreasing cholesterol and low density lipoproteins,⁸⁸ both alone and in association with pioglitazone, with a potential reduction of CV risk in patients with type 2 diabetes.^{55,88} Moreover, a pool analysis of six studies showed that the tolerability of alogliptin was similar in younger and elderly patients.⁴⁴

Patient-focused perspectives

Unlike incretin mimetics, which need subcutaneous injections, DPP-4 inhibitors are administered by oral ingestion. The different route of administration could influence patients' compliance, leading to possible increased adherence to therapy in patients treated with DPP-4 inhibitors. However, some evidence suggests higher patient satisfaction with GLP-1 analogs than gliptins.^{89,90} A review on patient-reported outcomes of incretin-based therapies showed that patients' satisfaction when treated with GLP-1 receptor agonists was greater in comparison with DPP-4 inhibitors, probably due to greater efficacy and weight loss.⁹⁰ Patients' perception of hypoglycemic condition was similar between the two groups. In a study comparing exenatide and sitagliptin, both groups experienced significant improvements on psychological well-being, although exenatide improved patients' satisfaction more than sitagliptin.⁹¹ Moreover, weight-related quality of life also improved in patients treated with incretin-based therapies.⁹⁰ Overall, patients were highly satisfied with an incretin-based treatment compared with traditional antidiabetic treatments.

Place in therapy

The recent Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes states that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent.⁴ If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a DPP-4 inhibitor. With a distinct paucity of long-term comparative-effectiveness trials available, uniform recommendations on the best agent to be combined with metformin cannot be made.¹¹ Thus, the advantages and disadvantages of specific drugs for each patient should be considered.

The DPP-4 inhibitors represent a highly promising, novel class of oral agents for the treatment of type 2 diabetes. Their novelty lies in their dual action on α - and β -cell function, leading to an improved profile of glucagon and insulin secretion patterns after meal. These drugs are weight-neutral, do not provoke hypoglycemia, and are not associated with gastrointestinal adverse events. Long-term clinical trial data are not yet available to assess the sustainability of glycemic control and protection of β -cell mass. The interference of the DPP-4 inhibitors with immune function is poorly understood and warrants further research. Another potential disadvantage is a higher cost per day of clinical use as compared to insulin, metformin, or pioglitazone, which is an economic drawback for the DPP-4 inhibitors.⁹²

Like other DPP-4 inhibitors, alogliptin is a novel, and hence, costly agent of modest to moderate efficacy. Even then, the DPP-4 inhibitors have found a place in the treatment of vulnerable elderly patients because of minimal risk of hypoglycemia and lack of significant drug-drug interactions. Its primary use will presumably be as an adjunct to other hypoglycemic agents rather than as a first-line agent, although its primary use can be foreseen for patients who are metformin intolerant or in those with renal insufficiency where metformin is contraindicated. Alogliptin will be used most in patients in whom it is especially important to avoid hypoglycemic events: in patients with congestive heart failure, renal failure, and liver disease, hypoglycemia can be more severe and refractory to treatment. In the elderly, hypoglycemic events increase the risk of injurious falls as well as coronary events. Alogliptin and other DPP-4 inhibitors could potentially replace the sulfonylureas in such vulnerable patients. Moreover, due to the paucity of head-to-head clinical data between DPP-4 inhibitors,⁹³ indirect comparisons assessing their efficacy or safety do not allow us to establish if one agent is superior to another within the class. Longer duration studies with careful post-approval surveillance are needed to assess the safety of alogliptin. Such large-scale, long-duration studies not only will characterize the long-term safety of alogliptin but should also shed light on possible β -cell preservation.

Disclosure

The authors report no conflicts of interest in this work.

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