

Alogliptin: a new addition to the class of DPP-4 inhibitors

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Background: Alogliptin is an oral antihyperglycemic agent that is a selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4). Inhibition of DPP-4 elevates levels of the incretin hormones glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) by preventing their degradation.

Objective: To review the evolution of alogliptin and its pharmacokinetics, pharmacodynamics, clinical efficacy and adverse effects. In addition, we compared alogliptin to other DPP-4 inhibitors.

Methods: A comprehensive literature search was performed using the term 'alogliptin'. Original research articles and review articles as well as scientific abstracts were included.

Results: Alogliptin raises postprandial levels of GLP-1. It has excellent bioavailability exhibiting a median T_{max} ranging from 1 to 2 hours and a mean half-life of 12.4 to 21.4 hours across all doses. When given as monotherapy, mean hemoglobin A_{1c} (HbA_{1c}) reductions achieved were 0.5% to 0.6%. Combination therapy yielded similar reductions (−0.5% with metformin, −0.6% with glyburide, −0.8% with pioglitazone and −0.6% with insulin). Administration of alogliptin does not promote weight loss but has not resulted in weight gain. The agent is relatively well tolerated with few adverse effects, the major finding being a marginally higher rate of skin events, primarily pruritus.

Conclusions: Alogliptin causes significant reductions in HbA_{1c} when used alone or in combination with other oral agents in patients with type 2 diabetes similar to other DPP-4 inhibitors in current clinical use. The side effect profile also does not differ from that of other DPP-4 inhibitors. However, long-term studies are necessary before the place of alogliptin in the management of type 2 diabetes can be established.

Keywords: alogliptin, DPP-4 inhibitors, GLP-1, vildagliptin, sitagliptin, saxagliptin

Introduction

Type 2 diabetes mellitus is a disorder of blood glucose control owing to multiple metabolic abnormalities, including insufficient insulin secretion, impaired response of liver and peripheral tissues to insulin (insulin resistance), progressive loss of beta-cell function, dysregulation of glucagon secretion and disturbed incretin hormone physiology.¹ The prevalence of diabetes is increasing worldwide from estimated 2.8% in 2000 to 4.4% in 2030.² The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030.² While tight control of diabetes substantially decreases the risk of microvascular complications,³ only 37% of patients currently reach the target hemoglobin A_{1c} (HbA_{1c}) of <7%, goal set by the American Diabetes Association.⁴ The choice of agents to improve blood glucose

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levels includes metformin, sulfonylureas, disaccharidase inhibitors, thiazolidinediones and insulin. Two new classes of agents which target the incretin system have recently come into clinical use. These are the GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors.

The incretin system

Incretins are hormones secreted by the gut in response to oral nutrient intake. Incretin secretion results in an augmentation of insulin secretion over and above the response solely attributable to the rise in intravenous glucose concentration. Two incretin hormones are of particular interest: glucagon-like polypeptide (GLP-1) and glucose-dependent insulinotropic peptide, also known as gastric inhibitory polypeptide (GIP). GIP and GLP-1 are both secreted within minutes of food consumption and act through distinct receptors.^{5,6,7} Both peptides act on pancreatic beta-cells to stimulate glucose-dependent insulin secretion, induction of beta-cell proliferation, and enhance resistance to apoptosis. Both GIP and GLP-1 are rapidly degraded by the enzyme DPP-4.

GIP is the first incretin to be discovered.⁸ It is secreted proximally from the K cells of the gut in response to oral ingestion of food containing glucose and fat. GIP promotes a glucose-dependent insulin secretion. GIP also promotes energy storage by adipocytes and enhances bone formation via stimulation of osteoblast proliferation and inhibition of apoptosis.⁶ Effects of GIP include incorporation of fatty acids into triglycerides, stimulation of lipoprotein lipase activity, modulation of fatty acid synthesis⁸ and promotion of beta-cell proliferation and survival.^{9,10} Plasma concentrations of GIP are reported to be normal or increased in diabetes,^{11,12} but the insulinotropic effect is deficient. This is thought to be due to downregulation of GIP expression/activity.^{13,14}

GLP-1 is a 30/31 amino acid peptide secreted from the L cells of the distal gut into the capillaries and then into the blood stream. It is quickly metabolized by DPP-4 giving active GLP-1 a half-life of only 1 to 2 minutes. Despite its short life, GLP-1 reaches the pancreatic beta-cell causing a glucose-dependent increase in insulin secretion. Other effects of GLP-1 include suppression of glucagon secretion, slowing of gastric emptying time and promotion of satiety.¹⁵ GLP-1 also promotes differentiation and proliferation of beta-cells and inhibition of apoptosis, thus offering the potential to reverse the effects of diabetes on beta-cell mass. GLP-1, but not GIP, controls glycemia via additional actions on inhibition of gastric emptying, food intake and glucagon secretion.⁷ Postprandial GLP-1 release is about 25% to 30%

lower in patients with type 2 diabetes and those with impaired glucose tolerance.¹⁶ In addition, the insulinotropic effect of GLP-1 is blunted in diabetes,^{17,18} perhaps in part related to glucagon levels.^{19,20} GLP-1 infusions have shown more promising results than those of GIP in lowering plasma glucose in diabetes.^{21,22} GLP-1 also promotes satiety, and sustained GLP-1-receptor activation is associated with weight loss in both preclinical and clinical studies.

Incretin pathway effects can be enhanced in two ways: by administering GLP-1 agonists, or by slowing their degradation with DPP-4 inhibitors. Several studies have now shown that GLP-1 can lower glucose levels even in patients with severe beta-cell impairment, presumably as a result of lowered glucagon levels and other non insulin related effects.²³ Subcutaneous infusion of GLP-1 resulted in lower overall glycemic levels than pioglitazone treatment, and the effect was additive.²⁴ Treatment with the long acting GLP-1 derivative liraglutide significantly reduced overall 24-hour glucose levels as well as those of glucagons.²⁵ Continuous subcutaneous infusion of GLP-1 for 3 months lowered capillary blood glucose levels in elderly type 2 diabetic subjects.²⁶ The glycemic effects of GLP-1 are associated with improvement in endothelial function.²⁷

Exendin is a reptilian peptide with affinity for the mammalian GLP-1 receptor and relative resistance to degradation, resulting in a relatively long-lasting effect.²⁸ Exenatide treatment has shown promising effects either as monotherapy²⁹ or in combination with other agents.³⁰⁻³² Treatment with exendin-4 has reduced postprandial hyperglycemia in Type I diabetes, confirming that the mechanism of action does not rely solely on insulin secretion.³³ In 272 metformin treated patients with initial HbA_{1c} of $8.2 \pm 1.1\%$, HbA_{1c} levels dropped by $0.8 \pm 0.1\%$ and weight decreased by 2.8 ± 0.5 kg after 30 weeks of treatment with 10 μ g of exenatide.³¹ In 377 sulfonylurea treated subjects with initial HbA_{1c} of $8.6 \pm 1.2\%$ given exenatide 10 μ g twice daily, HbA_{1c} dropped $-0.9 \pm 0.1\%$ and weight was reduced -1.6 ± 0.3 kg from baseline ($P < 0.05$ vs placebo).³² Exenatide is injectable and needs to be taken twice daily. There are considerable gastrointestinal side effects in up to 40% of patients.

An alternative to supplementation of GLP-1 is to inhibit the rapid degradation of this hormone by DPP-4.^{33,34} Several DPP-4 inhibitors have been developed and have come into clinical use.^{35,36} Currently, sitagliptin is the only DPP-4 inhibitor available in the United States.³⁷ Sitagliptin is effective as monotherapy^{38,39} and in combination with metformin.⁴⁰⁻⁴² Sitagliptin is generally well tolerated with an overall incidence of adverse experiences comparable to

placebo, a low risk of hypoglycemia and gastrointestinal problems, and a neutral effect on body weight.⁴³

Vildagliptin is approved in Europe and in Latin America.⁴⁴ It is efficacious as monotherapy⁴⁵ and in combination with metformin.⁴⁶ In a comparison study of vildagliptin vs metformin in drug-naïve patients with type 2 diabetes, metformin treatment resulted in greater weight loss and a superior glucose-lowering effect, but had a higher incidence of gastrointestinal side effects.⁴⁷ Vildagliptin added to metformin therapy provides a modest reduction in HbA_{1c} comparable to that of glimepiride but without the significant weight gain and hypoglycemia which occurs with the sulfonylureas.⁴⁸ Inhibition of GLP-1 and GIP by DPP-4 inhibitors such as vildagliptin and sitagliptin result in significant improvements in glucose levels in patients with type 2 diabetes. The glucose-lowering effect of currently available DPP-4 inhibitors appears to be somewhat less than those of exenatide and, unlike exenatide, there is no beneficial weight loss.^{49,50}

Recently a new DPP-4 inhibitor alogliptin has been developed. It is our purpose to review the properties of alogliptin and its potential benefits in treating diabetes.

Pharmacokinetics and pharmacodynamics of alogliptin

Alogliptin benzoate is an orally available quinazolinone-based noncovalent inhibitor of DPP4.⁴⁹ It is a highly potent, highly selective, orally available DPP-4 inhibitor. Its selectivity for DPP-4 is >10,000-fold greater than that of the other DPP isozymes 2/8/9.^{51,52}

Metabolism

Disposition of alogliptin was studied in eight healthy volunteers given a dose of 25 mg.⁵³ It is rapidly absorbed as early as 15 minutes with a T_{max} of 2 hours. The mean volume of distribution of alogliptin was 60.9 L, greater than that of body water (42 L), indicating that it is well distributed in all tissues. Approximately 85% of plasma radioactivity, 95% of urine radioactivity and 88% of fecal radioactivity was accounted for by the parent compound suggesting minimal metabolism.⁵³ It is metabolized to two minor metabolites. M-1, an N-demethylated metabolite and M-2, an N-acetylated metabolite. M-1 and M-2 are formed and represent <2% and 6% respectively, of parent drug concentrations in plasma and urine.

The pharmacokinetic and pharmacodynamic profiles of alogliptin in healthy subjects were evaluated with single doses of 6.25 mg, 12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg,

400 mg, and 800 mg.⁵⁴ Multiple-dose studies were done in subjects with type 2 diabetes and doses of 25 mg, 100 mg and 400 mg were given for 14 days.⁵⁵ Alogliptin is rapidly absorbed after oral administration with median T_{max} ranging from 1 to 2 hours across all doses. Mean half-life was 12.4 to 21.4 hours across all doses.⁵⁴

DPP-4 inhibition

DPP-4 enzyme activity and active GLP-1 levels were measured in human studies after single and multiple doses of alogliptin.^{54,55} Mean plasma DPP-4 inhibition after a single dose of alogliptin (25 mg to 800 mg) ranged from 74.3% to 94% at 24 hours and 47.5% to 83% at 72 hours.⁵⁴ After 14 days of dosing (25 mg to 400 mg), mean peak DPP-4 inhibition ranged from 94% to 99% and mean inhibition at 24 hours after dosing ranged from 82% to 97% across all doses. Plasma DPP-4 activity was inhibited by >80% after 24 hours, supporting a once daily regimen.⁵⁵ An increase of 2- to 4-fold in active GLP-1 levels in response to alogliptin occurs and is most evident after meals.⁵⁵ This is similar to GLP-1 values observed with sitagliptin treatment.³⁷

Excretion

Alogliptin is primarily excreted unchanged in the urine accounting for ~60% to 71% of the administered dose. Mean clearance (165 to 254 mL/min) across doses slightly exceeded the GFR (glomerular filtration rate) suggesting some renal secretion.⁵³ The fact that it is excreted unchanged through the kidney raises concern for possible interaction with other renally excreted drugs like metformin. However, a multiple-dose drug interaction study done with alogliptin and metformin found no pharmacokinetic interaction.⁵⁶

Drug interaction studies

In addition to metformin, drug interaction studies were done with other common antidiabetic agents (glyburide,⁵⁷ and pioglitazone.⁵⁸ Studies with CYP inhibitors disclosed no significant interactions with fluconazole, ketoconazole and gemfibrozil.⁵⁹ Other interaction studies with warfarin,⁶⁰ cyclosporine,⁶¹ ethinylestradiol and norethindrone,⁶² atorvastatin,⁶³ and digoxin⁶⁴ were also reassuring.

Efficacy

Alogliptin monotherapy

Alogliptin has been studied as both monotherapy and in combination with other oral agents in type 2 diabetes patients with HbA_{1c} between 7% and 10%. DeFronzo et al evaluated alogliptin as monotherapy for treatment-naïve patients

with type 2 DM for 26 weeks.⁶⁵ Mean HbA_{1c} decreased significantly with 12.5 mg (−0.56%) and 25 mg (−0.59%) compared with placebo (−0.02%). Fasting plasma glucose improved within a week and HbA_{1c} within 4 weeks. Differences in fasting plasma glucose from placebo at week 26 were significant at −22 mg/dL and −28 mg/dL with 12.5 mg and 25 mg respectively.⁶⁵

Sulfonylurea add-on

Pratley et al evaluated combination therapy of alogliptin added to glyburide (mean dose was 11.2 to 12.4 mg) and showed significant HbA_{1c} reductions across increasing doses of alogliptin: −0.39% with 12.5 mg, and −0.53% with 25 mg compared with placebo (+0.01%).⁶⁶ Reductions were seen as early as 4 weeks and continued throughout the 26-week period. More patients in the alogliptin group achieved HbA_{1c} reductions of >0.5% (26.3% with placebo, 47.3% with 12.5 mg and 50.5% with 25 mg of alogliptin; $P < 0.001$). Similarly more patients in the alogliptin arm had HbA_{1c} reductions of >1% compared with placebo (13.1% with placebo, 18.7% with 12.5 mg and 29.8% with 25 mg of alogliptin; $P < 0.001$ for 25 mg and 0.149 for 12.5 mg). The improvement was noted primarily in postprandial glucose since the mean change in fasting plasma glucose was small and non significant across all groups.⁶⁶

Metformin add-on

Nauck et al assessed the efficacy of alogliptin as an add-on to metformin therapy for 26 weeks.⁶⁷ Mean HbA_{1c} reductions noted with placebo, alogliptin 12.5 mg and 25 mg were −0.1%, −0.6% and −0.6% respectively ($P > 0.001$). Reductions in fasting plasma glucose were observed at all metformin doses and were significant in patients receiving either dose of alogliptin compared with placebo: 0 mg/dL, −19 mg/dL and −17 mg/dL with placebo, alogliptin 12.5 mg and 25 mg respectively.⁶⁷

Pioglitazone (TZD) add-on

Alogliptin was utilized as add-on therapy for patients on thiazolidinediones (pioglitazone) with or without metformin and sulfonylurea and followed for 26 weeks.⁶⁸ Reductions in HbA_{1c} were: −0.19%, −0.66% and −0.80% for placebo, 12.5 mg and 25 mg of alogliptin respectively ($P < 0.001$). Meaningful reductions were seen regardless of the dose of pioglitazone and with or without sulfonylurea or metformin. Mean differences in fasting plasma glucose from placebo were −14 mg/dL with both 12.5 mg and 25 mg ($P < 0.001$).⁶⁸

Insulin add-on

In a double-blind placebo-controlled study, 390 subjects on insulin with or without metformin were randomized to receive alogliptin at 12.5 mg or 25 mg and followed for 26 weeks.⁶⁹ Subjects on very high insulin doses (>100 units/day) and HbA_{1c} < 8% were excluded. The mean dose of insulin was 56.5 units/day and mean HbA_{1c} was >9% at the entry. The addition of alogliptin resulted in HbA_{1c} reduction of −0.51% and −0.59% and was significant ($P < 0.001$ for both doses). Reductions were seen regardless of the insulin dose and whether or not they were on metformin. Mean FPG reductions from placebo were −4 mg/dL and −18 mg/dL for 12.5 mg and 25 mg respectively.⁶⁹

Effects on pancreatic beta-cell function

In the 26-week randomized double-blind placebo-controlled study done by DeFronzo with alogliptin, modest apparent increases in proinsulin:insulin ratio and beta-cell function determined by homeostasis model assessment (HOMA-β) did not achieve statistical significance.⁶⁵ Similar results were observed by Pratley et al evaluating efficacy of alogliptin with glyburide. Improvements in measurement of beta-cell function (as measured by fasting insulin concentration, proinsulin to insulin ratio and HOMA-β) were not clinically significant ($P \geq 0.124$) (66). In the study evaluating metformin and alogliptin by Nauck et al a trend towards lower proinsulin:insulin ratio was observed with alogliptin.⁶⁷ In summary, alogliptin, like other DPP-4 inhibitors, could theoretically preserve beta-cell function, but long-term studies will be needed to prove this to be true.

Effects on lipids

Effects on lipid parameters, evaluated across the alogliptin studies, have been minor. Changes in LDL were −3.2 mg/dL compared with placebo and +3.9 mg/dL ($P = 0.044$) in monotherapy and in combination therapy with glyburide.^{65,66} The effects on other lipid parameters were non significant.⁶⁵ In add-on therapy to metformin, there have been no significant effects on lipid profiles.⁶⁷

Effects on weight

Weight changes noted when alogliptin was used in monotherapy in doses of 12.5 mg or 25 mg have not been clinically or statistically significant.⁶⁵ Minor increases in weight were seen when alogliptin was added to the background of sulfonylurea: −0.2 kg placebo, +0.6 kg alogliptin 12.5 mg ($P = 0.018$) and +0.68 kg for alogliptin 25 mg ($P = 0.010$).⁶⁶

Alogliptin proved to be weight neutral when added to metformin. Mean differences in weight relative to placebo were 0.0 kg and -0.3 kg for 12.5 mg and 25 mg respectively.⁶⁷ These results showing minor increases in mean weight are consistent with the results from previous studies done with other DPP-4 inhibitors, sitagliptin (+0.7 kg, $P = 0.008$) and vildagliptin (+0.8 kg, $P = 0.009$).⁷⁰

A summary of the clinical efficacy of alogliptin as monotherapy and combination therapy is included in Table 1.

Efficacy of alogliptin compared to other DPP-4 inhibitors

There is much experience with the other available DPP-4 inhibitors sitagliptin and vildagliptin. However, 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. A meta-analysis comparing sitagliptin and vildagliptin with placebo showed that they resulted in significant reduction of HbA_{1c} values, -0.6% with sitagliptin (95% CI -0.8 to -0.4, $P < 0.00001$) and -0.7% with vildagliptin (95% CI -0.9 to -0.6, $P < 0.001$).⁷⁰ Combination therapy resulted in additional lowering of HbA_{1c} with both agents. However, monotherapy with either DPP-4 inhibitor proved inferior in comparison to monotherapy with either metformin or sulfonylureas.⁷⁰ Saxagliptin is another DPP-4 inhibitor undergoing phase 3 trials and is also showing placebo-adjusted HbA_{1c} reductions of -0.45% to -0.63%.^{71,72}

The improvements in HbA_{1c} seen with alogliptin appear to be in the same range as with the alternative DPP-4 inhibitors.

Clinical safety

Clinical safety of alogliptin has been evaluated in multiple studies with doses ranging from 6.25 to 800 mg. It has also been studied in patients with renal and hepatic impairment.

Monotherapy

Single-dose study

Covington et al studied single increasing doses of alogliptin in 36 subjects.⁵⁴ Thirty received alogliptin in doses ranging from 25 mg to 800 mg and 6 received placebo. Asymptomatic hypoglycemia was reported in 5 subjects (1 on 50 mg, 2 on 200 mg, 1 on 400 mg of alogliptin and 1 on placebo). Other adverse events reported in one subject each include: dizziness (100 mg), syncope (200 mg), constipation (200 mg), viral infection (400 mg), hot flush (placebo) and nausea (placebo).⁵⁴

Multiple-dose study

In a multiple-dose study of 56 subjects given alogliptin in doses ranging from 25 mg to 400 mg for 14 days, commonly reported adverse events included headache (6/16), dizziness (4/16) and constipation in 3/16. These events occurred primarily at the highest dose of alogliptin. There were no discontinuations from the study due to side effects.⁵⁵

Phase 3 studies

In a 26-week study examining 329 subjects on alogliptin monotherapy, DeFronzo et al showed an overall incidence of adverse events (AEs) of 68.4% with 12.5 mg, 67.4% with 25 mg and 70.3% with placebo.⁶⁵ However, only 17.2%, 23.3% and 22.7% were considered drug related in the placebo, alogliptin 12.5 mg and 25 mg groups, respectively. Discontinuation of therapy due to side effects occurred in similar proportions of patients across the treatment groups (1.5 to 2.3%). Serious AEs occurred without relation to dose (12.5 mg: 3.8%; 25 mg: 0.8%; placebo: 3.1%) and were considered unrelated to the drug. Most common AEs were nasopharyngitis (7.8%, 9.0% and 7.6%; with placebo, 12.5 mg and 25 mg, respectively), headache (4.7%, 7.5% and 6.8%; with placebo, 12.5 mg and 25 mg, respectively) and upper respiratory tract infection (9.4%, 3.8% and 4.5%; with placebo, 12.5 mg and 25 mg). The incidence of hypoglycemia was low and similar across groups (1.6% with placebo and 3.0%, 1.5% with 12.5 mg and 25 mg). Hypoglycemic events were not severe and did not require assistance. Skin-related AEs, primarily pruritus, were higher in the treated groups (12.5 mg, 3%; 25 mg, 1.5%; 0 with placebo).⁶⁵

Pratley et al studied 500 patients using alogliptin as add-on therapy to glyburide (66). AEs were reported in 64% of patients treated with alogliptin 12.5 mg, and 63% of patients on 25 mg dose, compared with 54% in the placebo group. Most AEs were mild in intensity and not considered treatment-related. Serious AEs were reported in 2% of placebo-treated patients, 5.4% of patients on alogliptin 12.5 mg and 5.6% of patients treated with the 25 mg alogliptin dose. AEs that occurred in $\geq 5\%$ of patients in any treatment group (including placebo) included upper respiratory infection, urinary tract infection, headache and hypertension. There was also an increased incidence of skin-related events, mainly pruritus (0%, 3% and 6% with placebo, 12.5 mg and 25 mg). Gastrointestinal side effects occurred with the same frequency in the placebo and 12.5 mg groups, with a nominally higher incidence at 25 mg. The incidence of hypoglycemia was 11.1% for placebo, 15.8 for alogliptin 12.5 mg and 9.6%

Table 1 Summary of the clinical efficacy of alogliptin as mono and combination therapy

Study	N	Wks	Baseline HbA _{1c} (%)	Intervention	Change from baseline				Hypoglycemia (%) ^a	Severe hypoglycemia (%) ^b
					HbA _{1c} (%)	FPG (mg/dL)	Weight (kg)			
DeFronzo et al 2008 ⁵⁵	329	26	7.9	placebo	0	+11	+0.2	1.6	0	
				alogliptin 12.5 mg	-0.6	-10.3	-0.1	3	0	
				alogliptin 25 mg	-0.6	-16.4	-0.2	1.5	0	
Nauck et al 2009 ⁵⁷	527	26	7.9	placebo + metformin	-0.1	0	-0.4	2.9	0	
				alogliptin 12.5 mg + metformin	-0.6	-19	-0.4	0.9	0	
				alogliptin 25 mg + metformin	-0.6	-17	-0.7	0	0	
Pratley et al 2008 ⁵⁶	500	26	8.1	placebo + glyburide	0	+2.2	-0.2	11.1	0	
				alogliptin 12.5 mg + glyburide	-0.4	-4.7	+0.6	15.8	0	
				alogliptin 25 mg + glyburide	-0.5	-8.4	+0.7	9.6	0	
Pratley et al 2008 ⁵⁸	493	26	8.0	placebo + pioglitazone ± metformin/sulfonylurea	-0.2	-5.7	+1.0	5.2	0	
				alogliptin 12.5 mg + pioglitazone ± metformin/sulfonylurea	-0.7	-19.7	+1.5	5.1	0	
				alogliptin 25 mg + pioglitazone ± metformin/sulfonylurea	-0.8	-19.9	+1.1	7.0	0	
Rosenstock et al 2008 ⁵⁹	390	26	9.3	placebo + insulin ± metformin	-0.1	5.8	0.6	24	0.5	
				alogliptin 12.5 mg + insulin ± metformin	-0.6	2.3	0.7	26.7	0	
				alogliptin 25 mg + insulin ± metformin	-0.7	-11.7	0.6	27.1	0.25	

^aHypoglycemia defined as blood glucose <70 mg/dL.^bSevere hypoglycemia defined as symptomatic hypoglycemia requiring another person's assistance.**Abbreviation:** FPG, fasting plasma glucose.

for alogliptin 25 mg. Thus, addition of alogliptin did not increase the risk of hypoglycemia attributable to glyburide therapy.⁶⁶

In a study of alogliptin in combination with metformin in 201 patients, Nauck et al found that the majority of AEs were unrelated to the study drug.⁶⁷ The incidence of serious AEs was similar across treatment groups (2.8% to 3.9%). The incidence of hypoglycemia was low ($\leq 1\%$) across all groups and there were no severe hypoglycemic events requiring assistance. Skin-related events occurred in 7.7% of patients in the placebo group, 12.2% in the 12.5 mg group and 11.6% in the 25 mg group. These included dry skin, rash, eczema and pruritus.⁶⁷

In a study of alogliptin added to pioglitazone, the AE rates among 372 patients completing the study were: 64.9% with placebo, 69.7% with alogliptin 12.5 mg and 72.4% with alogliptin 25 mg.⁶⁸ The incidence of hypoglycemia was low (5.2%, placebo; 5.1%, 12.5 mg; 7%, 25 mg).

Alogliptin was studied as an addition to insulin therapy in 390 patients. Patients experiencing ≥ 1 AE (73.6%, placebo; 67.9%, 12.5 mg; 66.7%, 25 mg) and ≥ 1 serious AE (4.7%, placebo; 6.1%, 12.5 mg; 5.4%, 25 mg) were similar across treatment groups. The incidence of severe hypoglycemia was low (1.6%, placebo; 0%, 12.5 mg; 0.8%, 25 mg) and similar across groups.⁶⁹

Skin toxicity

Preclinical studies done with other DPP-4 inhibitors, vildagliptin and saxagliptin, have raised the concern of necrotic skin lesions observed in monkeys, the mechanism of which is unclear.⁷³ However such skin lesions have not been observed in humans, or in preclinical or clinical studies with sitagliptin⁷⁴ or alogliptin. The relationship of the monkey skin lesions to DPP-4 inhibition vs DPP-8/9 inhibition remains unresolved.⁷⁵ Serious allergic and hypersensitivity reactions such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome were reported in patients treated with sitagliptin in post-marketing reports.⁷⁶ The alogliptin studies have incorporated a search for skin lesions, with a marginally higher rate than in placebo, the major finding being pruritus.

Safety profile of alogliptin compared with other DPP-4 inhibitors

Like other DPP-4 inhibitors, alogliptin is well tolerated overall. Severe hypoglycemia requiring third-party assistance has not been reported in studies done on DPP-4 inhibitors. This is not surprising, because secretion of incretins is glucose-dependent.⁷⁷ Meta-analysis of all the available studies on

sitagliptin and vildagliptin showed a risk of gastrointestinal side effects comparable to placebo. Risk of all-cause infections (nasopharyngitis, upper respiratory infection, urinary tract infection, sinusitis) was higher with sitagliptin (odds ratio 1.34, 95% CI 1.10 to 1.64, $P = 0.004$), but not for vildagliptin.⁷⁰ Since this side effect may be related to the prolonged action of another DPP4 substrate, substance P,⁷⁸ it is possible that the same side effects will be noted with alogliptin as well. Vildagliptin is also reported to cause pedal edema which is not reported with alogliptin.^{79,80} Rare cases of hepatic dysfunction and hepatitis have been reported with vildagliptin, and it is recommended to monitor liver function tests every 3 months for the first year of therapy.⁷⁰ Liver enzyme abnormalities have not been observed with alogliptin thus far. It is not known whether DPP4 selectivity of alogliptin and sitagliptin, compared to vildagliptin (which inhibits both DPP-4 and DPP-8 enzymes), has clinical significance. While DPP-4 protein has a role in T-cell mediated immune response, DPP-8 and DPP-9 enzymes (located in leukocytes) are involved in T-cell activation and the processes of cell adhesion, migration and apoptosis. It has been shown⁸¹ that inhibition of DPP-8 and 9 suppresses mitogen-stimulated T-cell responses but DPP-4 selective inhibition does not. Again, the clinical significance (if any) of the DPP-4 vs DPP-8 selectivity is not clear at this point, and long-term clinical follow up data are needed.⁸² At this time, it is unclear whether there have been sufficient cardiac events in the alogliptin-treated populations in the research studies to date to satisfy potential cardiac safety concerns.

Special populations Patients with renal and hepatic impairment

Alogliptin 50 mg administered to patients with renal impairment did not cause any increase in AEs.⁸³ It was given to 6 subjects in each group of mild, moderate, severe and end stage renal disease, and 25% experienced at least one AE, but were judged to be mild and unrelated to drug. This incidence of AEs was similar to their respective healthy age- and sex-controlled controls. Based on this study, no dose adjustments were recommended in patients with renal insufficiency.⁸³ Administration of 25 mg of alogliptin to 8 subjects with moderate hepatic impairment did not result in any serious AEs.⁸⁴

Theoretical issues

There are theoretical concerns⁸⁵ stemming from the ubiquitous nature of DPP-4 enzyme presence: namely, this membrane-associated protein is present in many tissues including kidneys, intestine, hepatocytes, vascular endothelium, T-cells, B cells

and natural killer cells.⁸⁶ DPP-4 has two major functions: a) enzymatic action that includes cleavage of oligopeptides and b) messenger action by activation of intracellular signaling pathways.⁸⁷ While DPP-4 inhibitors do not affect the signaling action, there is a concern that inhibition of enzymatic action on regulatory peptides may produce unforeseeable AEs. Enzymatic action involves cleavage of oligopeptides and regulating metabolism and activation of peptides such as YY (involved in gastrointestinal functions), neuropeptide Y (involved in regulation of food intake) and brain-derived natriuretic peptide (BNP) (involved in vasodilatation, natriuresis). Clinical consequences of blockade of these peptides are not obvious at this time but warrant long-term follow up. In addition, DPP-4 protein has a role in T-cell mediated immune response. This raises concerns of possible side effects, related to reduced NK and T-cell function.⁷⁵

Conclusions

Alogliptin is a new addition to incretin based therapies for type 2 diabetes. Like other agents in the DPP-4 inhibitor class, it offers good tolerability, lack of severe hypoglycemia, and weight neutrality as major advantages. In addition, thus far it appears to be safe for use in patients with co-morbidities such as heart failure and renal failure. In as much as endogenous GLP-1 has a beneficial effect on beta-cell mass, there is a hope that the DPP-4 inhibitor class might have such a benefit. That, however, has yet to be proven, not only for alogliptin but for other members of the DPP-4 class.⁸⁵ On the other hand, alogliptin, like other DPP-4 inhibitors, is a new and hence costly agent of only modest efficacy. Mean HbA_{1c} reductions of 0.5% to 0.8% seen with alogliptin and other DPP-4 inhibitors are markedly inferior to the 1.0% to 2.0% reductions seen with metformin or sulfonylurea therapy and 1.5% to 3.5% reductions with addition of insulin therapy. The weight loss seen with GLP-1 agents does not occur with the current DPP-4 inhibitors. However, because of the low incidence of hypoglycemia and other side effects, the DPP-4 inhibitors have a place in treatment of vulnerable patients, such as the elderly.

At this time, there is a lack of long-term safety data for alogliptin and other DPP-4 inhibitors, especially those related to generalized DPP-4 inhibition. Studies of longer duration and careful postapproval surveillance are needed to assess the safety of alogliptin. Undoubtedly such studies will proceed to assess long-term cardiac events in alogliptin-treated patients. Such large-scale studies should clarify the role of alogliptin in the armamentarium of therapies we use to treat type 2 diabetes mellitus.

Disclosure

The authors disclose no conflicts of interest.

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