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REVIEW

Alogliptin: A DPP-4 Inhibitor for the Treatment of Type 2 Diabetes Mellitus

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Abstract: Alogliptin benzoate is a DPP-4 inhibitor currently in Phase 3 clinical trials in the United States for treatment of T2DM. Alogliptin is approved and available for use in Japan for the treatment of T2DM. Alogliptin has been studied clinically as initial therapy in treatment naïve patients with T2DM, as initial therapy in combination with pioglitazone, and as add-on therapy to T2DM patients with inadequate control on metformin, glyburide, pioglitazone, and insulin. Clinical trial data with alogliptin demonstrate clinical efficacy in terms of A1C and FPG reductions when used both as monotherapy and in combination with other oral antidiabetic medications. Overall, alogliptin is generally well tolerated when used as monotherapy and in combination with concomitant oral antidiabetic therapy. Comparative studies are needed to determine the clinical advantages, if any, of alogliptin when compared with other currently available DPP-4 inhibitors.

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

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Introduction

According to the most recent estimates, there are 24 million people living with diabetes in the United States (US), of which 17.9 million have already been diagnosed and the approximate 6.1 million remaining are unaware of their condition.[1,2] This figure has been growing over the years and the trend is expected to continue to rise, especially when considering the approximate 57 million individuals with prediabetes in the US.[1,2]

Uncontrolled diabetes, a harsh reality for many diabetics, is associated with severe complications leading to clinically significant morbidity and mortality. Diabetes is the leading cause of kidney failure, retinopathy, blindness, ketoacidosis, and hyperosmolar coma.[3] Diabetes is associated with a higher risk of osteoporosis, periodontal disease, severe neurological damage leading to amputations, and 2 to 4-fold higher rates of death from heart disease and stroke.[3,4] In addition to the aforementioned comorbidities, elderly individuals with diabetes are additionally prone to the development of hypoglycemia-associated dementia.[5]

The good news is that conscientious blood glucose management and achievement of glycemic goals can lower the incidence of retinopathy, nephropathy and neuropathy.[6] Additionally, data from the United Kingdom Prospective Diabetes Study (UKPDS) showed that just one percentage drop in A1C can reduce the risk of myocardial infarctions and microvascular complications such as eye, kidney, and nerve disease.[3,7] While studies have shown that treating patients to as close to normoglycemia as possible can reduce the onset and progression of diabetic complications, doing so does not come without its risks. Hypoglycemic episodes, defined as intervals of a sudden drop in blood glucose, are highly unpleasant to patients and are associated with both morbidity and mortality. Evidence suggests that the fear of experiencing hypoglycaemia alone is a major barrier to adherence to traditional drug therapy and thus achieving desired blood glucose levels.[9]

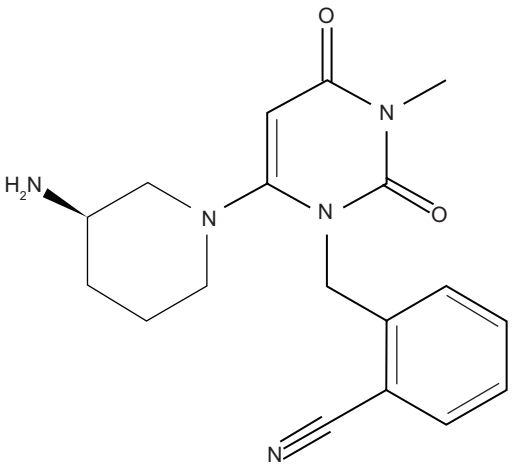

Figure 1. Structure of Alogliptin. Wikimedia Commons. File:Alogliptin.svg. Available at: http://commons.wikimedia.org/wiki/File:Alogliptin.svg. Accessed February 9, 2011.[8]

The Incretin Effect

Incretin-based therapies, a relatively new group of agents used for the treatment of type 2 diabetes (T2DM), were developed based on the observation that patients with T2DM may have a reduced or even non-existent response to natural incretin hormones within the body, thus contributing to abnormally high postprandial blood glucose levels.[10–12] Incretin hormones are naturally secreted from enteroendocrine cells into the blood stream to regulate the secretion of insulin in response to food. Incretin hormones were initially discovered by comparing insulin release in response to oral versus intravenous glucose administration. The insulin response to oral glucose intake was found to be higher than that achieved with intravenous glucose administration, thus indicating that signaling from the gastrointestinal tract is important in modulating insulin secretion from the pancreas.[13,14] In fact, incretin-induced insulin secretion, coined the incretin effect, accounts for at least 50% of the total insulin secreted following a meal.[15] There are two main incretin hormones currently recognized: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). Fasting GLP-1 plasma levels range from 5–10 pmol/L, which increase rapidly after eating, reaching up to 15–50 pmol/L during the postprandial period.[16] The mechanism of action of GIP and GLP-1 rely on binding to structurally distinct G-protein-coupled receptors. This leads to activation of incretin receptors on β cells, which cause a rapid increase of cAMP and intracellular calcium levels leading to insulin secretion.[17] GIP receptors are predominantly expressed on β cells, and to a lesser extent, in adipose tissue and in the central nervous system. GLP-1 receptors, in contrast, are expressed on α and β cells of the pancreas and in peripheral tissues such as the central and peripheral nervous systems, heart, kidneys, lungs, and gastrointestinal tract.[16]

In people with T2DM, GLP-1 administration has demonstrated sustained insulinotropic abilities, and has such become a drug target in this population.[15] GLP-1 secretion is stimulated primarily through ingestion of fat- and carbohydrate-rich meals. Foods containing glucose and other sugars, sweeteners, fatty acids, amino acids, and dietary fiber, can also stimulate GLP-1 secretion, but to a lesser extent.[18] Although there is a strong correlation between secretion of GLP-1 and insulin production, GLP-1 has other benefits not directly tied to its insulin producing properties. These benefits are listed in Table 1. Immediately following secretion, GLP-1 is rapidly deactivated by an enzyme called dipeptidyl peptidase 4 (DPP-4).[12,15] Due to the rapid enzymatic degradation of GLP-1, several pharmacotherapeutic strategies have been devised to take advantage of the potential benefits of GLP-1 augmentation in people with T2DM. One such strategy was the development of GLP-1 receptor agonists such as exenatide and liraglutide. The second approach, was the development of DPP-4 inhibitors to slow the enzymatic degradation of endogenously secreted incretin hormones. DPP-4 inhibitors act by binding to the DPP-4 enzyme and preventing the enzymatic cleavage of endogenous GLP-1 and GIP.[19] Inhibition of the DPP-4 enzyme by DPP-4 inhibitors has been shown to increase postprandial GLP-1 concentrations up to 2 to 3 times normal physiological levels.[20] Currently, sitagliptin and saxagliptin are the only two DPP-4 inhibitors approved for use in the US, while vildagliptin, alogliptin and linagliptin are currently in clinical study. This paper will focus on clinical safety and efficacy data currently available for the DPP-4 inhibitor alogliptin.

Table 1. Physiological effects of GLP-1.[16]

Organ	GLP-1 effect
Brain	Increase satiety Reduce appetite Decrease food and water intake
Stomach	Delayed gastric emptying Reduced acid secretion
Liver	Decreased glucagon secretion Decreased hepatic glucose production Increased glucose uptake
Pancreas	Increased glucose-dependent insulin secretion Decreased glucagon secretion Improved β-cell function Increased somatostatin secretion
Adipose/muscle tissue	Increased glucose uptake

Alogliptin

Alogliptin benzoate is a DPP-4 inhibitor currently in Phase 3 clinical trials in the US for treatment of T2DM. Alogliptin is a quinazolinone-based noncovalent DPP-4 inhibitor, with selectivity for the DPP-4 enzyme being >10,000-fold higher than for related proteases such as DPP-8 and DPP-9.[21] Alogliptin is approved and available for use in Japan for the treatment of T2DM in combination with a thiazolidinedione.[22] While a new drug application (NDA) was submitted to the FDA prior to the December 2008 release of the FDA guidance "Guidance for Industry: Diabetes Meillitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes", the FDA did not deem that the existing cardiovascular data for alogliptin was sufficient to meet the requirements of this guidance. The FDA subsequently requested that the manufacturer conduct additional cardiovascular safety trials prior to approval in the US.

Pharmacodynamics

Alogliptin is a selective (>10,000-fold selectivity for DPP-4 compared to DPP-8/DPP-9) DPP-4 inhibitor.[23,24] In vitro data demonstrate the mean 50% maximal inhibitory concentration of alogliptin to be 6.9 nmol/L, while that for sitagliptin and vildagliptin were 12.1 nmol/L and 23.8 nmol/L, respectively.[21] DPP-4 activity is inhibited greater than 80% at 24 hours post-dosing on day 14 across all doses, with enzyme inhibition sustained up to 168 hours following administration.[25]

Pharmacokinetics

The pharmacokinetic and pharmacodynamic profiles of alogliptin are supportive of once-daily oral dosing.[25,26] In patients with T2DM, alogliptin was absorbed rapidly, with a mean T_{max} of approximately one to two hours across doses tested.[25–27] Administration with food had no effect on the absorption of alogliptin when tested in healthy adults.[28] The AUC and C_{max} increased in a dose proportionate manner on days 1 and 14 when measured. Alogliptin is primarily eliminated renally as unchanged drug,[26] but is partially

metabolized by cytochrome P450 (CYP) 2D6 to the active metabolite M-I and by acetylation to the inactive metabolite M-II.[28] The mean $t_{1/2}$ on day 14 ranged from 12.5 to 21.1 hours, with therapeutic plasma concentrations sustained for over 24 hours.[25] In vitro data demonstrate that alogliptin is 28%–38% bound to plasma proteins.[28]

Clinical studies

Alogliptin has been studied clinically as initial therapy in treatment naïve patients with T2DM,[29] as initial therapy in combination with pioglitazone,[30] and as add-on therapy to T2DM patients with inadequate control on metformin,[31] glyburide,[32] pioglitazone,[33] and insulin.[34] The following sections will focus on efficacy data to date from 26-week trials with alogliptin. Please see Table 2 for a summary of select efficacy outcomes from these studies.

Alogliptin as monotherapy

In a multicentre study enrolling 329 participants, drug naïve patients with T2DM inadequately controlled with diet and exercise (baseline A1C of 7%–10%) were randomized to receive alogliptin 12.5 mg daily (n = 133), alogliptin 25 mg daily (n = 131) or placebo (n = 65).[29] This double blind, placebo controlled study assessed a series of efficacy and safety endpoints following 26-weeks of treatment. In terms of efficacy outcomes, at 26-weeks, the mean change in A1C from baseline was –0.56, –0.59 and –0.02% in the alogliptin 12.5 mg, alogliptin 25 mg and placebo groups, respectively ($P < 0.001$ for alogliptin groups vs. placebo). Likewise, fasting plasma glucose (FPG) levels decreased to a significantly greater extent ($P < 0.001$) for both alogliptin groups relative to placebo from baseline to week 26, with differences noted as early as week 1 of treatment. Alogliptin was considered weight neutral when used as monotherapy in this study, with small weight reductions seen in the alogliptin groups that were not significantly different from that seen in the placebo group.

Alogliptin plus pioglitazone as initial combination therapy

Another study involving T2DM patients naïve to T2DM drug therapy was conducted by Rosenstock and colleagues.[30] The study was performed to assess the efficacy and tolerability of alogliptin in combination with pioglitazone for the initial treatment of drug naïve patients with inadequate glycemic control (baseline A1C of 7.5%–11%). This 26-week, double-blind, parallel group study enrolled 655 participants in total who were randomized to receive alogliptin 25 mg daily (n = 164), pioglitazone 30 mg daily (n = 163), alogliptin 12.5 mg daily plus pioglitazone 30 mg daily (n = 163), or alogliptin 25 mg daily plus pioglitazone 30 mg daily (n = 164). Mean reductions in A1C from baseline at 26 weeks were –0.96, –1.15, –1.56, and –1.71% in the four groups, respectively. In addition to seeing more A1C reduction in the alogliptin plus pioglitazone groups, a greater percentage of participants receiving combination therapy also achieved an A1C of <7% at 26 weeks, as noted in Table 2. Likewise, a statistically significant reduction in FPG was seen in the alogliptin 25 mg daily plus pioglitazone 30 mg daily group when compared to either of the monotherapy groups. When looking at changes in body weight over 26 weeks in the four groups, a statistically significant weight gain was seen in the alogliptin 25 mg daily plus pioglitazone 30 mg daily group when compared to either the alogliptin 25 mg daily or pioglitazone 30 mg daily groups. While the reason for this increase in body weight was not discussed within the research report, it raises the question of additive edema when these agents are used in combination. Given these results, the authors concluded that the combination of alogliptin and pioglitazone appears to be an effective initial treatment option in patients with T2DM.

Alogliptin as add-on to metformin

Another 26-week, double-blind, placebo controlled study enrolleing 527 participants tested the efficacy of alogliptin as add-on to baseline metformin therapy in T2DM patients with inadequate glycemic control, as defined by a baseline A1C of 7%–10%.[31] Participants continued their stable dose of metformin (≥1500 mg) and were randomized to either receive the addition of placebo (n = 104), alogliptin 12.5 mg (n = 213), or alogliptin 25 mg (n = 210). Placebo-subtracted A1C reductions from baseline for both alogliptin groups were –0.5%. In addition, more participants in the alogliptin groups achieved an A1C of <7% after 26 weeks compared to the placebo group. When used as

Table 2. Summary of 26-week clinical efficacy data with alogliptin.

	Pts (N)	Tx period (weeks)	Tx		A1C change (%)	% Reaching A1C <7% (%)	BW change (Kg)
			Baseline (daily dose)	Intervention			
DeFronzo et al[29]	329	26	Tx Naïve	ALO 12.5 mg	–0.56 ($P < 0.0001$)[a]	47.4 ($P = 0.001$)[a]	–0.09
				ALO 25 mg	–0.59 ($P < 0.0001$)[a]	44.3 ($P = 0.008$)[a]	–0.22
				PBO	–0.02	23.4	+0.18
Rosenstock et al[30]	655	26	Tx Naïve	ALO 25 mg	–0.96	24.4	–0.29
				PIO 30 mg	–1.15	33.7	+2.19
				ALO 12.5 mg + PIO 30 mg	–1.56 ($P < 0.0001$)[e]	53.4[e]	+2.51
				ALO 25 mg + PIO 30 mg	–1.71 ($P < 0.0001$)[d]	62.8[e,f]	+3.14[e,f]
Nauck et al[31]	527	26	MET (≥1.5 g)	ALO 12.5 mg	–0.6 ($P < 0.0001$)[a]	52 ($P < 0.0001$)[a]	–0.0 (–0.7, 0.7)[c]
				ALO 25 mg	–0.6 ($P < 0.0001$)[a]	44 ($P < 0.0001$)[a]	–0.3 (–0.9, 0.4)[c]
				PBO	–0.1	18	NA
Pratley et al[32]	500	26	GLY (mean = 12 mg)	ALO 12.5 mg	–0.39 ($P < 0.001$)[a]	29.6	+0.6 ($P = 0.018$)[a]
				ALO 25 mg	–0.53 ($P < 0.001$)[a]	34.8 ($P = 0.002$)[a]	+0.68 ($P = 0.010$)[a]
				PBO	+0.01	18.2	–0.2
Pratley et al[33]	493	26	PIO[b]	ALO 12.5 mg	–0.66 ($P < 0.001$)[a]	44.2 ($P \leq 0.016$)[a]	+0.42 (–0.37, 1.22)[c]
				ALO 25 mg	–0.80 ($P < 0.001$)[a]	49.2 ($P \leq 0.016$)[a]	+0.05 (–0.74, 0.84)[c]
				PBO	–0.19	34.0	NA
Rosenstock et al[34]	390	26	INS ± MET	ALO 12.5 mg	–0.63 ($P < 0.001$)[a]	NA	+0.68
				ALO 25 mg	–0.71 ($P < 0.001$)[a]	NA	+0.60
				PBO	–0.13	NA	+0.63

Notes: [a]Versus Placebo; [b]patients could be on PIO (23%), PIO + MET (56%), or PIO + SU (21%); [c]least squares mean differences in weight from baseline relative to Placebo (95% CI); [d]versus either monotherapy; [e]versus PIO monotherapy; [f]versus ALO 25 mg monotherapy.

Abbreviations: A1C, hemoglobin A1C; ALO, alogliptin; BW, body weight; Kg, kilograms; MET, metformin; NA, data not available; PBO, Placebo; PIO, pioglitazone; Pts, patients; SU, sulfonylurea; Tx, treatment.

add-on the baseline metformin, alogliptin therapy was weight neutral from baseline to 26 weeks. Of note, less participants in the alogliptin groups required rescue therapy for hyperglycemia, with 24%, 9% and 8% of participants requiring rescue therapy in the three groups, respectively.

Alogliptin as add-on to sulfonylurea

Pratley and colleagues enrolled 500 participants with T2DM with inadequate glycemic control on baseline sulfonylurea therapy.[32] Participants, with a mean baseline A1C of 8.1%, were screened and entered into a 4-week run-in, stabilization period where they were switched from their current sulfonylurea to an equivalent dose of glyburide plus placebo. Following the run-in period, participants were randomized to receive alogliptin 12.5 mg daily (n = 203), alogliptin 25 mg daily (n = 198), or placebo (n = 99). A1C changes from baseline to 26 weeks were –0.38, –0.52 and +0.01 in the three treatment groups, respectively. When further looking at A1C reductions with alogliptin treatment, proportionally more patients in the alogliptin 12.5 mg group (47.3%) and alogliptin 25 mg group (50.5%) achieved A1C reductions of $>0.5\%$ from baseline compared to those receiving placebo (26.3%) ($P < 0.001$). Statistically significant increases in weight were seen in the alogliptin groups after 26 weeks of treatment, with placebo-subtracted weight changes being +0.8 kg and +0.88 kg in the alogliptin 12.5 mg and 25 mg groups, respectively. The authors concluded from these results that the addition of alogliptin to sulfonylurea background therapy resulted in clinically significant reductions in A1C without an added risk of hypoglycemia (please see Table 3 for hypoglycemia rates).

Alogliptin as add-on to pioglitazone plus or minus metformin or a sulfonylurea

The efficacy and safety of alogliptin as add-on to pioglitazone plus or minus concomitant metformin or a sulfonylurea was assessed in a double-blind, placebo controlled study.[33] Participants, aged 18–80, had inadequate glycemic control at the time of enrolment (A1C of 7%–10%). Participants were randomized to receive add-on therapy of alogliptin 12.5 mg (n = 197), alogliptin 25 mg (n = 199), or placebo (n = 97) for 26 weeks. Following 26 weeks of treatment, mean A1C reductions from baseline were –0.66, –0.8

Table 3. Summary of select 26-week clinical safety data with alogliptin.

	Pts (N)	Tx period (weeks)	Tx		Pts reporting ≥1 AE (n[%])	DC due to AE (n[%])	HYPO (n[%])	UTI (n[%])	Any GI AE (n[%])	HA (n[%])	Infections and infestations (n[%])	Skin AEs (n[%])
			Baseline (daily dose)	Intervention								
Nauck et al[31]	527	26	MET (≥1.5 g)	ALO 12.5 mg	134 [63]	7 [3]	2 [1]	14 [7]	22 [10]	8 [4]	68 [32]	26 [12]
				ALO 25 mg	118 [57]	4 [2]	0 [0]	6 [3]	26 [13]	4 [2]	53 [26]	24 [12]
				PBO	69 [66]	1 [1]	3 [3]	4 [4]	16 [15]	2 [2]	28 [27]	8 [8]
Pratley et al[32]	500	26	GLY (mean = 12 mg)	ALO 12.5 mg	129 [64]	5 [3]	32 [16]	9 [4]	26 [13]	5 [3]	54 [27]	22 [11]
				ALO 25 mg	125 [63]	4 [2]	19 [10]	10 [5]	36 [18]	11 [6]	50 [25]	25 [13]
				PBO	53 [54]	2 [2]	11 [11]	3 [3]	14 [14]	3 [3]	30 [30]	12 [12]
Pratley et al[33]	493	26	PIO[a]	ALO 12.5 mg	138 [70]	6 [3]	10 [5]	NA	33 [17]	8 [4]	69 [35]	23 [12]
				ALO 25 mg	144 [72]	6 [3]	14 [7]	NA	22 [11]	10 [5]	67 [34]	24 [12]
				PBO	63 [65]	3 [3]	5 [5]	NA	13 [13]	4 [4]	36 [37]	15 [16]
Rosenstock et al[34]	390	26	INS ± MET	ALO 12.5 mg	89 [68]	1 [1]	35 [27]	8 [6]	19 [15]	7 [5]	43 [32]	15 [12]
				ALO 25 mg	86 [67]	6 [5]	35 [27]	9 [7]	27 [21]	4 [3]	38 [30]	14 [11]
				PBO	95 [74]	4 [3]	31 [24]	10 [8]	22 [17]	6 [5]	40 [31]	14 [11]

Note: [a]Patients could be on PIO (23%), PIO + MET (56%), or PIO + SU (21%).
Abbreviations: AE, adverse event; ALO, alogliptin; DC, trial discontinuation; GI, gastrointestinal-related; HA, headache; HYPO, proportion of patients experiencing hypoglycemia; MET, metformin; NA, data not available; PBO, placebo; PIO, pioglitazone; Pts, patients; SU, sulfonylurea; Tx, treatment; UTI, urinary tract infection.

and −0.19% in the alogliptin 12.5 mg, 25 mg, and placebo groups, respectively ($P < 0.001$ for both alogliptin groups versus placebo). A significantly larger ($P \leq 0.016$) proportion of participants in the alogliptin groups achieved an A1C of ≤7% at 26 weeks when compared to the placebo group. FPG reductions from baseline were additionally greater in the alogliptin groups, with mean reductions of −19.7, −19.9, and −5.7 mg/dL noted in the three treatment groups, respectively.

Alogliptin as add-on to insulin

In a 26-week, double-blind, placebo-controlled study conducted by Rosenstock and colleagues, 390 participants with inadequate glycemic control (mean baseline A1C of 9.3%) on background insulin alone or insulin combined with metformin were enrolled.[34] Participants were randomized to receive alogliptin 12.5 mg (n = 131), alogliptin 25 mg (n = 129), or placebo (n = 130). Following 26 weeks of treatment, mean A1C reductions from baseline were −0.63, −0.71 and −0.13% for the three treatment groups, respectively. A significantly greater proportion of participants in the alogliptin groups achieved A1C reductions from baseline of ≥0.5, ≥1.0 and ≥1.5% when compared to the placebo group. Throughout the study, insulin doses remained unchanged, and no difference in the proportion of participants experiencing hypoglycemia (27%, 27% and 24% in the alogliptin 12.5 mg, alogliptin 25 mg, and placebo groups, respectively) were noted in the three treatment groups. Additionally, no differences were noted in regard to weight change from baseline in the alogliptin or placebo groups. The investigators concluded that alogliptin as add-on to background insulin therapy results in improvements in glycemic control without causing additional weight gain or increasing the incidence of hypoglycemia.

Adverse events

In one study, the incidence of adverse events (67.4%–70.3%) and the proportion of patients discontinuing due to adverse events (1.5%–2.3%) were similar across treatment groups.[29] Serious adverse events occurred without relation to alogliptin dose or treatment group (alogliptin 12.5 mg = 3.8%, alogliptin 25 mg = 0.8%, placebo = 3.1%). Skin reactions were reported in alogliptin-treated patients at a rate of 12.8–15.2%, which was more frequently than in placebo-treated subjects (6.3%).[29] In another study, the rates of edema, infection, and gastrointestinal symptoms were similar in alogliptin- and placebo-treated patients when added to pioglitazone background therapy.[32] Rates of hypoglycemia were generally low in clinical trials.[29–34] When added to background insulin treatment, alogliptin-treated groups showed similar rates of hypoglycemia when compared to the placebo group (alogliptin 12.5 mg = 27%, alogliptin 25 mg = 27%, placebo = 24%).[34] Phase 3 data has not, to date, revealed statistically significant changes in hematological endpoints.[29–34] Please refer to Table 3 for a summary of adverse event data from select 26-week trials with alogliptin.

Drug interactions

Alogliptin has been studied as add on therapy to metformin, glyburide, and pioglitazone without any interactions noted in clinical trials.[31–33] Because alogliptin undergoes active renal secretion, potential interactions are possible with other renally excreted drugs.[26] Alogliptin has been studied when coadministered with both digoxin, a P-glycoprotein substrate, and cyclosporine, a P-glycoprotein inhibitor.[35,36] Clinically meaningful changes in pharmacokinetic parameters were not noted.[35,36]

Alogliptin was coadministered with atorvastatin and assessed for interactions in another study.[37] Although the AUC, C_{max}, and C_{min} of atorvastatin were slightly increased when administered with alogliptin, the mean ratios were within or slightly outside the prespecified 80% to 125% range, thus investigators did not consider the changes to be clinically meaningful. Likewise, there were no meaningful changes in alogliptin exposure in the presence of atorvastatin, indicating these agents are acceptable for coadministration.[37] In another interaction study, healthy female subjects were administered alogliptin in combination with norethindrone and ethinyl etradiol. Following 21 days, mean AUC and C_{max} ratios for ethinyl estradiol/norethindrone tested within the 90% to 125% range, demonstrating a lack of interaction with alogliptin.[38]

Special populations

In a study by Karim and colleagues, patients were stratified by age, race, and gender and administered

alogliptin 25 mg on day 1 and days 4 through 8.[39] Clinically significant changes in alogliptin exposure were not seen between groups, although exposure was increased in the elderly when compared to the young, in Whites when compared to Blacks, and in female subjects relative to male subjects. Age, race, and gender did not appear to alter DPP-4 inhibition, however, indicating that dosage adjustment are not needed based on these patient characteristics.[39]

Regarding the treatment of older adults with alogliptin, a pooled analysis from six randomized, double blind, placebo controlled studies of alogliptin was performed to compare the efficacy of alogliptin in patients ≥65 years of age versus those <65 years old.[40] Participants included in the analysis were 18–80 years old with inadequately controlled T2DM at baseline. The mean age of participants in the "Elderly" group was 70 years (n = 455), with a mean age of 51.8 years (n = 1,911) in the "Younger" group. Participants received either alogliptin 25 mg, alogliptin 12.5 mg or placebo for 26 weeks. When examining change in A1C from baseline, a least squares mean reduction of 0.7% and 0.8% were seen for alogliptin 12.5 mg and 25 mg, respectively, in the elderly group ($P < 0.001$ for both alogliptin doses vs. placebo). In comparison, reductions of 0.5% and 0.6% were seen in the younger group for each respective alogliptin dose ($P < 0.001$ for both alogliptin doses vs. placebo). Similar outcomes were observed for fasting plasma glucose (FPG) outcomes, indicating similar effectiveness for alogliptin in both age groups. Likewise, the incidence of hypoglycemia during the 26-week treatment period was ≤8.3% for all alogliptin groups, compared to ≤10.5% for placebo groups. No significant differences in the risk of hypoglycemia or other safety parameters (adverse events reported or changes in blood pressure) were noted based on age stratifications.

Dosage and administration

Two studies of alogliptin pharmacokinetics and pharmacodynamics investigated doses ranging from 25 mg to 800 mg.[25,26] Both of these studies supported a once daily administration of alogliptin to achieve up to 99% DPP-4 inhibition over 24 hours. Most clinical trials have studied 12.5 mg and 25 mg once daily doses of alogliptin.[29–34] Alogliptin is currently approved for the treatment of adult patients with T2DM in Japan.[28] The approved dosing in Japan is for 25 mg once daily in patients with normal renal function. Dose reductions are warranted in individuals with renal dysfunction, with a dose reduction to 12.5 mg daily recommended for individuals with moderate renal impairment (creatinine clearance of 30–50 ml/min). For individuals with a creatining clearance <30 ml/min or end stage renal disease, the dose should be further lowered to 6.25 mg daily. While these are the dosing guidelines for alogliptin in Japan, local dosing guidelines should be checked in the event that alogliptin is approved for use in other countries.

Conclusion

By inhibiting DPP-4, the enzyme responsible for degrading GIP and GLP-1, DPP-4 inhibitors cause a reduction in ambient blood glucose. Clinical trial data with alogliptin demonstrate clinical efficacy in terms of A1C and FPG reductions when used both as monotherapy and in combination with other oral antidiabetic medications.[29–34] Overall, alogliptin is generally well tolerated when used as monotherapy and in combination with concomitant oral antidiabetic therapy. Clinical guidance from the American College of Endocrinology/American Association of Clinical Endocrinologist recommends DPP-4 inhibitor's as a preferred choice for initial therapy in patients with type 2 diabetes and HbA_{1c} of 6%–7%. and is recommended to be used in combination with other oral antidiabetic medication when HbA_{1c} rises above 7%.[41] Some evidence exists for risk of serious skin-related allergies and hypersensitivity reactions with use of the DPP-4 inhibitor sitagliptin, and risk of immunological adverse events with the use of sitagliptin or vildagliptin.[42] Because events such as these are rarely seen in clinical trials, diligent post-marketing surveillance and increased clinical experience with DPP-4 inhibitors in diverse heterogeneous patient populations is needed to monitor for these adverse events and determine what patient groups, if any, may be at risk.

While there are subtle differences in $A1_C$, FPG, and PPG changes depending on background therapy and dose, there are no obvious advantages for one DPP-4 inhibitor over another. In terms of safety, DPP-4 inhibitors are generally well tolerated and demonstrate similar side effect profiles in clinical

trials. Additional safety concerns have recently arisen, however, regarding a potential link between sitagliptin treatment and the occurrence of pancreatitis.[43] While there is ongoing debate regarding whether the reported cases of pancreatitis were in fact attributable to sitagliptin use, the FDA recommends that patients be monitored carefully for the development of pancreatitis during the initiation and upward titration of the drug.[43] The implication that these reports have in regard to alogliptin use are as of yet unknown.

In conclusion, additional clinical experience and study of alogliptin will yield more robust efficacy and safety data for the use of alogliptin for the treatment of T2DM. Comparative studies are needed to determine the clinical advantages, if any, of alogliptin when compared with other currently available DPP-4 inhibitors.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest.

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