

Alogliptin benzoate for management of type 2 diabetes

Yoshifumi Saisho

Department of Internal Medicine,
Keio University School of Medicine,
Tokyo, Japan

Abstract: Dipeptidyl peptidase-4 (DPP-4) inhibitors, a new class of oral hypoglycemic agents, augment glucose-dependent insulin secretion and suppress glucagon levels through enhancement of the action of endogenous incretin by inhibiting DPP-4, an incretin-degrading enzyme. DPP-4 inhibitors are generally well tolerated because of their low risk of hypoglycemia and other adverse events. Moreover, with their potential to improve beta cell function, a core defect of type 2 diabetes, DPP-4 inhibitors are becoming a major component of treatment of type 2 diabetes. Alogliptin benzoate is a newly developed, highly selective DPP-4 inhibitor which has been approved in many countries throughout the world. Once-daily administration of alogliptin as either monotherapy or combination therapy with other oral antidiabetic drugs or insulin has a potent glucose-lowering effect which is similar to that of other DPP-4 inhibitors, with a low risk of hypoglycemia and weight gain. The cardiovascular safety of this drug has been confirmed in a recent randomized controlled trial. This review summarizes the efficacy and safety of alogliptin, and discusses the role of DPP-4 inhibitors in the treatment of type 2 diabetes.

Keywords: dipeptidyl peptidase-4 inhibitor, type 2 diabetes, efficacy, safety, alogliptin

Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors, a new class of oral hypoglycemic agents, augment glucose-dependent insulin secretion through enhancement of the action of endogenous incretin (ie, glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide) by inhibiting DPP-4, a degrading enzyme of incretin. DPP-4 inhibitors also suppress glucagon secretion via elevation of glucagon-like peptide-1. They are generally well tolerated because of their low risk of hypoglycemia and other adverse events.¹

Alogliptin benzoate is a newly developed DPP-4 inhibitor developed by Takeda Inc (Osaka, Japan) that was approved for clinical use in the treatment of type 2 diabetes (T2DM) in Japan in April 2010 with the trade name Nesina®. Alogliptin was also approved by the US Food and Drug Administration and the European Medicines Agency in January 2013 and September 2013, respectively (with the trade name Vipidia® in Europe) and, as of September 2014, is available in 39 countries. In Japan, sitagliptin was the first approved DPP-4 inhibitor in December 2009, and first approved by the US Food and Drug Administration in 2006. Currently, seven DPP-4 inhibitors, ie, sitagliptin, vildagliptin, alogliptin, linagliptin, teneligliptin, anagliptin, and saxagliptin, have been approved in Japan.

Alogliptin was developed by structure-based design and proved to have high selectivity for DPP-4.² The efficacy and safety of alogliptin has been confirmed to be similar

Correspondence: Yoshifumi Saisho
Department of Internal Medicine,
Keio University School of Medicine,
35 Shinanomachi, Shinjuku-ku,
Tokyo 160-8582, Japan
Tel +813 3353 1211 ext 62383
Fax +813 3359 2745
Email ysaisho@keio.jp

to that of other DPP-4 inhibitors in recent clinical trials.³ This updated review of a previous publication⁴ focuses on the clinical efficacy and safety of alogliptin for the treatment of T2DM. The pharmacokinetics and pharmacodynamics of alogliptin have also been reviewed elsewhere.^{5,6}

Methods

This review is based upon a MEDLINE search and personal experience with alogliptin. A MEDLINE search (1966 to December 2014) for published clinical trials and pertinent review articles published in English was conducted with the keywords “alogliptin”, “incretin”, and “DPP-4 inhibitor”. References of identified articles were searched for additional relevant sources. Relevant articles were also obtained from the author’s personal list of references.

Chemistry

The chemical structure of alogliptin is shown in Figure 1. Alogliptin shows high selectivity for DPP-4 (>10,000-fold over other DPP isozymes such as DPP-2, DPP-8, and DPP-9.^{2,7} High selectivity of alogliptin for DPP-4 has also been confirmed in a DPP-8/9-expressing cell model.⁸ A recent study using X-ray crystallography revealed that alogliptin interacts with the S1 and/or S2 subsites in addition to the S1 and S2 subsites of DPP-4, where vildagliptin interacts, suggesting that alogliptin offers more potent DPP-4 inhibition compared with vildagliptin.⁹

Pharmacokinetics

Alogliptin is rapidly absorbed after oral administration, with a median time taken to reach peak plasma concentration of 2 hours and a mean half-life of 12–21 hours across various doses (6.25–800 mg). Food does not affect the absorption of alogliptin.^{10–12}

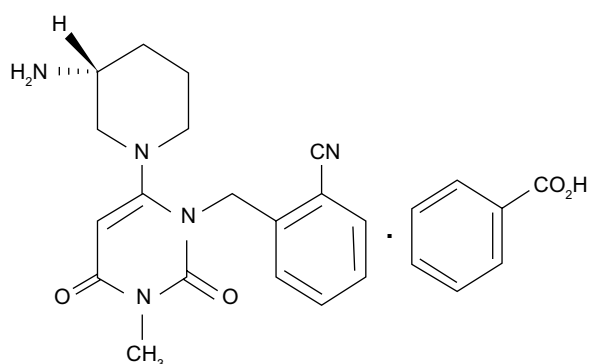


Figure 1 Chemical structure of alogliptin benzoate: 2-((6-((3R)-3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl) benzonitrile monobenzoate.

To date, no drug interaction with alogliptin has been reported, although among the DPP-4 inhibitors, the level of saxagliptin may be affected by inhibitors or inducers of the cytochrome P450 3A4/5 isozyme (eg, ketoconazole, diltiazem, and rifampicin).

The pharmacokinetics of alogliptin have also been evaluated in subjects with renal and hepatic impairment. Following administration of a single 50 mg dose of alogliptin, 1.7-fold, 2.1-fold, 3.2-fold, and 3.8-fold increases in alogliptin exposure in subjects with mild, moderate, severe renal insufficiency, and end-stage renal disease, respectively, were observed compared with levels in healthy volunteers.^{6,13} Thus, dose adjustment of alogliptin, as well as sitagliptin and saxagliptin, is recommended for patients with renal dysfunction (Table 1).

A single 25 mg dose of alogliptin was administered to eight patients with moderate hepatic impairment based on the Child-Pugh Scale, and there was no significant increase in serum concentration of alogliptin when compared with that in healthy volunteers. Thus, dose adjustment of alogliptin is not needed in patients with hepatic impairment.^{6,13}

Pharmacodynamics

Mean plasma DPP-4 inhibition after a single dose of alogliptin (25–800 mg) ranged from 74% to 94% at 24 hours and 48% to 83% at 72 hours. After 14 days of dosing (25–400 mg/day), mean peak DPP-4 inhibition ranged from 94% to 99%, with mean inhibition at 24 hours after dosing of 82%–97%, supporting once-daily administration.^{10,11} A recent qualitative model of DPP-4 inhibition showed that with once-daily administration of alogliptin 25 mg, the usual recommended dosage of alogliptin, the percentage of time when DPP-4 inhibition was >80% was 88%, the percentage of DPP-4 inhibition at trough was 80%, and the percentage of weighted average DPP-4 inhibition over 24 hours was 88%, which is comparable with the results with once-daily administration of sitagliptin 100 mg.¹⁴

Table 1 Dosage modification of alogliptin for patients with renal impairment in Japan

Mild (CCr $\geq$ 50 mL/min): no dosage adjustment required (25 mg once daily)
Moderate (CCr $\geq$ 30 to < 50 mL/min): decrease dose to 12.5 mg once daily
Severe (CCr < 30 mL/min): decrease dose to 6.25 mg once daily*

Note: *Can be administered without regard to timing of hemodialysis.

Abbreviation: CCr, creatinine clearance.

Clinical efficacy

Glucose-lowering effect

The glucose-lowering effect of alogliptin has been evaluated in double-blind, placebo-controlled Phase II and III trials and also in recent Phase IV trials. The results of major clinical trials assessing the clinical efficacy of alogliptin compared with placebo or active comparators are summarized in Table 2.

Monotherapy

To evaluate the efficacy of alogliptin as monotherapy, 329 drug-naïve patients with poorly controlled T2DM (mean HbA_{1c} 7.9%) were randomized to once-daily treatment with alogliptin 12.5 mg, alogliptin 25 mg, or placebo for 26 weeks.¹⁵ At week 26, the reduction in HbA_{1c} from baseline was -0.56% and -0.59% in the alogliptin 12.5 mg and 25 mg groups, respectively, compared with 0.02% in the placebo group ($P<0.001$). Another dose-ranging study examined the efficacy of alogliptin (6.25–50 mg) in 480 drug-naïve Japanese patients with T2DM.¹⁶ HbA_{1c} at week 12 was dose-dependently reduced by alogliptin, and the reduction in HbA_{1c} from baseline was -0.68% and -0.77% in the alogliptin 12.5 mg and 25 mg groups, respectively, compared with 0.05% in the placebo group ($P<0.0001$).

Combination with other antidiabetic medications

Sulfonylureas

The efficacy of alogliptin in combination with sulfonylureas has also been evaluated.¹⁷ In one study, 500 patients with T2DM inadequately controlled by sulfonylurea monotherapy (mean HbA_{1c} 8.1%) were randomized to treatment with glyburide plus alogliptin 12.5 mg or 25 mg or placebo for 26 weeks. At week 26, the reduction in HbA_{1c} was -0.38% and -0.52% with alogliptin 12.5 mg and 25 mg, respectively, compared with 0.01% for placebo ($P<0.001$). In another study, 312 Japanese patients with T2DM inadequately controlled by sulfonylurea monotherapy (mean HbA_{1c} 8.5%) were randomized to alogliptin 12.5 mg or 25 mg or placebo in addition to glimepiride 1–4 mg for 12 weeks.¹⁸ The HbA_{1c} reduction at week 12 was -0.59% and -0.65% with alogliptin 12.5 mg and 25 mg, respectively, compared with 0.35% for placebo ($P<0.0001$).

Metformin

The efficacy of alogliptin in combination with metformin was evaluated in a study that included 527 patients with T2DM inadequately controlled on metformin monotherapy (mean HbA_{1c} 8%).¹⁹ The patients were randomized to add-on

treatment with alogliptin 12.5 mg or 25 mg or placebo for 26 weeks. At week 26, the reduction in HbA_{1c} with either dose of alogliptin was -0.6% ($P<0.001$ versus placebo). In another Japanese study, a total of 288 patients with T2DM inadequately controlled with metformin 500 or 750 mg/day (mean HbA_{1c} 8.0%) were randomized to receive alogliptin 12.5 mg or 25 mg or placebo in addition to metformin for 12 weeks.²⁰ At week 12, the reduction in HbA_{1c} was -0.55% and -0.64% with alogliptin 12.5 mg and 25 mg, respectively, compared with 0.22% for placebo ($P<0.0001$).

Two more studies have been published recently. One trial was designed to evaluate the efficacy of initial therapy with alogliptin plus metformin.²¹ A total of 784 drug-naïve patients (mean HbA_{1c} 8.45%) were randomized to receive placebo, alogliptin 12.5 mg twice daily or 25 mg once daily, metformin 500 mg or 1,000 mg twice daily, or a combination of alogliptin 12.5 mg plus metformin 500 mg or 1,000 mg twice daily. The reduction in HbA_{1c} at week 26 was -1.22% and -1.55% with the combination of alogliptin 12.5 mg plus metformin 500 mg or 1,000 mg twice daily, respectively, compared with -0.52% and -1.11% with alogliptin 25 mg once daily and metformin 1,000 mg twice daily, respectively ($P<0.001$). The number of patients who achieved HbA_{1c} <7% was greater for combination therapy compared with monotherapy (47.1%–59.5% versus 20.2%–34.3%). The second study was designed to compare the long-term efficacy and safety of alogliptin plus metformin with that of glipizide plus metformin.²² A total of 2,639 patients with a mean age 55.4 years, a mean duration of diabetes of 5.5 years, and a mean HbA_{1c} of 7.6% were randomized to receive alogliptin 12.5 mg or 25 mg once daily or glipizide 5–20 mg once daily in addition to metformin for 104 weeks. The HbA_{1c} reduction at week 104 was significantly greater with alogliptin 25 mg than with glipizide (-0.72% versus -0.59%, $P=0.010$), with less hypoglycemia (1.4% versus 23.2%) and weight gain (-0.89 versus 0.95 kg, $P<0.001$).

Thiazolidinediones

The efficacy of alogliptin in combination with a thiazolidinedione (TZD) was also evaluated. A total of 493 patients with T2DM inadequately controlled on a TZD (mean HbA_{1c} 8.0%) were randomized to treatment with pioglitazone plus alogliptin 12.5 mg, alogliptin 25 mg, or placebo for 26 weeks.²³ At week 26, the reduction in HbA_{1c} was -0.66% with alogliptin 12.5 mg and -0.80% with alogliptin 25 mg, compared with -0.19% for placebo ($P<0.001$). In another Japanese study,²⁴ 339 patients with T2DM inadequately controlled on pioglitazone (mean HbA_{1c} 7.9%) were randomized

Table 2 Selected efficacy outcomes from clinical trials of alogliptin

Study	Patients (n)	Background treatment (mg)	Treatment group (intervention, mg)	Treatment period (weeks)	Baseline HbA _{1c} (%)	HbA _{1c} change (%)	Achievement of HbA _{1c} ≤7.0% (%)	Body weight change (kg)	Hypoglycemia (%)
DeFronzo et al ¹⁵	329	Drug-naïve	PBO ALO 12.5 ALO 25	26	7.9	0.02 -0.56 -0.59	23.4 47.4 44.3	0.18 -0.09 -0.22	1.5–3.0
Seino et al ¹⁶	480	Drug-naïve	PBO ALO 6.25 ALO 12.5 ALO 25 ALO 50 VOG 0.2 tid ALO 25 PIO 30 ALO 12.5 + PIO 30 ALO 25 + PIO 30	12	7.93	0.05 -0.52 -0.68 -0.77 -0.80 NA -0.96 -1.15 -1.56	8.0* 29.1* 35.7* 44.3* 38.0* 19.3* 24.4 33.7 53.4	-0.04 0.12 0.45 0.20 0.47 -0.46 -0.29 2.19 2.51	1.3 [#] 1.2 [#] 0 0 0 1.2 [#] NA NA NA
Rosenstock et al ²⁵	655	Drug-naïve	PBO ALO 25 QD ALO 12.5 bid M 500 bid M 1,000 bid ALO 12.5 + M 500 bid ALO 12.5 + M 1,000 bid	26	8.45	0.15 -0.52 -0.56 -0.65 -1.11 -1.22 -1.55	3.9 20.2 20.2 27.2 34.3 47.1 59.5	-0.87 0.13 -0.01 -0.80 -1.25 -0.57 -1.17	0.9 1.8 5.5 1.8 6.3 1.9 5.3
Pratley et al ²¹	784	Drug-naïve	GLB + PBO GLB + ALO 12.5 GLB + ALO 25 GLM 1–4 + PBO GLM 1–4 + ALO 12.5 GLM 1–4 + ALO 25 PBO ALO 12.5 ALO 25 PBO ALO 12.5 ALO 25 PIO 15–45 PIO 15–45 + ALO 12.5 PIO 15–45 + ALO 25 ALO 12.5 ALO 25 GLP 5–20 PIO 45 PIO 30 + ALO 25 PBO	26	8.1	0.01 -0.38 -0.52 0.35 -0.59 -0.65 -0.1 -0.6 -0.6 0.21 -0.54 -0.64 -0.9 -1.4 -1.4 -0.68 -0.72 -0.59 -0.29 -0.70 -0.19	18.2 29.6 34.8 0* 9.6* 7.7* 18 52 44 2.0 28.3 27.1 30.5 54.6 55.9 45.6 48.5 42.8 21.3 33.2 34.0	-0.20 0.60 0.68 -0.37 0.27 0.56 – -0.0† -0.3† -0.23 0.17 -0.09 1.5 1.8 1.9 -0.7† -0.9† 0.9† 1.6 1.1 –	11.1 15.8 9.6 1.0 [#] 0 1.9 [#] 3 1 0 0 1.1 [#] 2.1 [#] 2.1 1.0 1.5 2.5 1.4 23.2 1.5 4.5 5.2
Pratley et al ¹⁷	500	SU							
Seino et al ¹⁸	312	SU							
Nauck et al ¹⁹	527	M ≥1,500 or MTD							
Seino et al ²⁰	288	M 500 or 750							
DeFronzo et al ²⁶	1,554	M ≥1,500							
Del Prato et al ²²	2,639	M ≥1,500 or MTD							
Bosi et al ⁴⁹	803	M ≥1,500 or MTD + PIO 30							
Pratley et al ²³	493	PIO ± M/SU							

[illegible]

Notes: ^aAchievement of $HbA_{1c} < 6.9\%$; ^bcalculated from the number of subjects; ^cleast square mean differences relative to PBO; ^destimated from the graph; ^eamong patients who completed the study. The readers should refer to the text or original article for statistical significance.

Abbreviations: DPP-4, dipeptidyl peptidase-4; PBO, placebo; ALO, alogliptin; VOG, voglibose; PLO, pioglitazone; GLP, glipizide; MTD, maximum tolerated dose; OAD, oral antidiabetic agent; GLP-1, glucagon-like peptide-1; NA, not available; HbA_{1c}, glycated hemoglobin.

to add-on treatment with alogliptin 12.5 mg, alogliptin 25 mg, or placebo for 12 weeks. At week 12, the reduction in HbA_{1c} was -0.91% with alogliptin 12.5 mg and -0.97% with alogliptin 25 mg compared with -0.19% for placebo ($P<0.001$).

Initial combination therapy of alogliptin and pioglitazone in drug-naïve patients with T2DM was also evaluated. A total of 655 drug-naïve patients with inadequately controlled diabetes (mean HbA_{1c} 8.8%) were randomized into four treatment arms: alogliptin 25 mg monotherapy, pioglitazone 30 mg monotherapy, or alogliptin 12.5 mg or 25 mg plus pioglitazone 30 mg combination therapy for 26 weeks.²⁵ At week 26, combination therapy with alogliptin 25 mg plus pioglitazone 30 mg resulted in a greater reduction of HbA_{1c} (−1.7%) versus alogliptin 25 mg monotherapy (−1.0%) or pioglitazone 30 mg monotherapy (−1.2%; *P* < 0.001).

Combination therapy with alogliptin and pioglitazone in addition to metformin monotherapy was evaluated in another study.²⁶ A total of 1,554 patients with T2DM inadequately controlled on metformin monotherapy (mean HbA_{1c} 8.5%) were randomized to add-on treatment with alogliptin (12.5 mg or 25 mg) alone or combined with pioglitazone (15, 30, or 45 mg) for 26 weeks. At week 26, the reduction in HbA_{1c} was -0.9% in the pioglitazone alone group and -1.4% in the alogliptin 12.5 mg and alogliptin 25 mg plus pioglitazone groups ($P<0.001$).

The efficacy of a combination of alogliptin and pioglitazone was also evaluated in another study.²⁷ Seventy-one patients with well-controlled T2DM (mean HbA_{1c} 6.7%) treated with metformin, sulfonylurea, or glinide monotherapy were randomized to receive alogliptin 25 mg plus pioglitazone 30 mg, alogliptin 25 mg monotherapy, or placebo for 16 weeks. The reduction in HbA_{1c} at week 16 was -0.9%, -0.4%, and 0.4%, respectively (*P* < 0.001 versus placebo).

Insulin

The efficacy of alogliptin when added to insulin therapy in patients with T2DM was assessed in two trials. In one study, 390 patients with T2DM inadequately controlled with insulin alone or combined with metformin (mean HbA_{1c} 9.3%) were randomized to receive add-on therapy with alogliptin 12.5 mg, alogliptin 25 mg, or placebo for 26 weeks.²⁸ At week 26, the reduction in HbA_{1c} was -0.63% with alogliptin 12.5 mg and -0.71% with alogliptin 25 mg, compared with -0.13% for placebo ($P<0.001$). In another Japanese study, 179 patients with T2DM inadequately controlled with insulin monotherapy were randomized to receive alogliptin 25 mg or placebo in addition to insulin

therapy for 12 weeks.²⁹ The HbA_{1c} reduction at week 12 was -0.96% for alogliptin compared with -0.29% for placebo ($P < 0.0001$). The proportion of patients who achieved HbA_{1c} $< 7\%$ was greater with alogliptin than with placebo (23.3% versus 5.7%).

Lastly, the large-scale, randomized, controlled EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) study was conducted to assess the cardiovascular safety of alogliptin.³⁰ In this study, treatment with alogliptin on top of other antidiabetic medications showed a significant reduction in HbA_{1c} (-0.36% , $P < 0.001$) compared with placebo during a median follow-up of 18 months.

Recently, Berhan et al conducted a meta-analysis of ten randomized controlled trials to assess the efficacy of alogliptin in T2DM.³ The pooled standardized mean difference for the reduction in HbA_{1c} in patients treated with alogliptin 12.5 mg was -0.81% (95% confidence interval [CI] -1.11 , -0.51) and that in patients treated with alogliptin 25 mg was -0.98% (95% CI -1.30 , -0.66). The standardized mean difference of the reduction in fasting plasma glucose in patients treated with alogliptin 25 mg was -0.51 mmol/L (95% CI -0.68 , -0.34).

Although there has been no head-to-head trial comparing the efficacy of alogliptin with that of other DPP-4 inhibitors, the improvement of HbA_{1c} seen with alogliptin seems to be in the same range as that seen with other DPP-4 inhibitors,^{31,32} with the exception of vildagliptin 50 mg twice daily, which was reported to have a small advantage in glucose-lowering effect compared with other DPP-4 inhibitors.^{33–35}

Predictors of HbA_{1c} reduction by DPP-4 inhibitors

Recent meta-analyses of randomized controlled trials have shown that the efficacy of DPP-4 inhibitors is mainly related to baseline HbA_{1c} level, as is seen with other antidiabetic medications.^{36,37} Esposito et al examined the clinical characteristics that predict the HbA_{1c} response to DPP-4 inhibitors in their meta-regression analysis of 78 randomized controlled trials with 20,053 patients, and found a greater absolute reduction of baseline HbA_{1c} in patients with higher baseline HbA_{1c} and lower fasting glucose levels.³⁷

Recent meta-analyses have also suggested the efficacy of incretin therapy differs between ethnic groups. It has been shown that the efficacy of HbA_{1c} reduction by DPP-4 inhibitors or glucagon-like peptide-1 receptor agonists is greater in Asian populations than in non-Asian populations,^{38,39}

suggesting that lower body mass index is associated with a better HbA_{1c} response to incretin therapy.

The long-term glycemic durability of DPP-4 inhibitors in patients with T2DM has also been reported. A meta-analysis of 12 trials with 14,829 patients showed that the effect of DPP-4 inhibitors on HbA_{1c} declined significantly by $\sim 0.2\%$ during the second year of treatment,⁴⁰ while a greater HbA_{1c} reduction at 2 years was reported for alogliptin compared with glipizide in the above-mentioned trial.²²

Efficacy in the elderly

The efficacy of alogliptin in the elderly was evaluated in a randomized, double-blind, active-controlled study.⁴¹ In this study, 441 elderly type 2 diabetic patients of mean age 70 (range 65–90) years and with mild hyperglycemia on diet/exercise therapy alone or combined with oral antidiabetic monotherapy (mean HbA_{1c} 7.5%) were randomized to alogliptin 25 mg or glipizide 5–10 mg for 52 weeks. The reduction in HbA_{1c} at the end of study was -0.42% with alogliptin and -0.33% with glipizide, demonstrating no inferiority of alogliptin to glipizide. A post hoc analysis using this cohort showed that the proportion of patients achieving HbA_{1c} $\leq 7.0\%$ without hypoglycemia or weight gain was significantly higher with alogliptin than with glipizide (24% versus 13%, $P < 0.03$).⁴² It has also been shown that patients with baseline HbA_{1c} $< 8.0\%$ receiving alogliptin are also more likely to achieve HbA_{1c} $\leq 7.0\%$ without hypoglycemia or weight gain than those receiving glipizide (29% versus 13%, $P < 0.03$).⁴²

A pooled analysis of Phase II and III studies to assess the efficacy of alogliptin in elderly patients with T2DM has also been reported.⁴³ Analysis of six randomized controlled trials of alogliptin showed a similar improvement in HbA_{1c} in elderly patients (mean age 70 years) compared with younger patients (mean age 52 years).

Efficacy in hemodialysis patients

Since alogliptin is excreted by the kidney, the dose of alogliptin should be reduced in patients with moderate to severe renal impairment, as shown in Table 1. In a single-arm study, treatment with alogliptin 6.25 mg reduced HbA_{1c} and glycated albumin levels from $7.1\% \pm 0.2\%$ to $5.8\% \pm 1.6\%$ and from $22.5\% \pm 0.7\%$ to $19.6\% \pm 0.6\%$, respectively, after 24 months in 16 hemodialysis patients with T2DM.⁴⁴

Effect on beta cell function

Alogliptin has been shown to improve beta cell function and increase beta cell mass in rodents.^{45–48} In humans, it

was reported that there was no or only modest improvement of beta cell function assessed by proinsulin to insulin ratio or homeostasis model assessment (HOMA)- β by alogliptin monotherapy or combination therapy with metformin or a sulfonylurea.^{15,17,19} On the other hand, significant improvement of beta cell function was reported when patients were treated with alogliptin combined with pioglitazone.^{24,26,49} It has been reported that treatment with a combination of alogliptin 25 mg and pioglitazone 30 mg for 16 weeks significantly improved beta cell glucose sensitivity and fasting secretory tone compared with placebo, while alogliptin 25 mg monotherapy did not change beta cell function parameters.²⁷ A recent study has shown that treatment with alogliptin improved the function and proliferation of adult human beta cells engrafted in diabetic immunodeficient mice;⁵⁰ however, the effect of DPP-4 inhibitors on beta cell mass in humans remains unclear.⁵¹

Effect on lipids

Eliasson et al reported a change in postprandial lipids during treatment with alogliptin.⁵² Seventy-one patients with inadequately controlled T2DM were randomized to treatment with alogliptin 25 mg, alogliptin 25 mg plus pioglitazone 30 mg, or placebo for 16 weeks. At 16 weeks, a significant reduction in postprandial triacylglycerol and triacylglycerol-rich lipoproteins was observed with alogliptin monotherapy and alogliptin plus pioglitazone combination therapy compared with placebo. A meta-analysis of 17 studies⁵³ also showed a significant reduction in total cholesterol (-0.18 mmol/L [-7 mg/dL]) and triacylglycerol (-0.15 mmol/L [-13 mg/dL]) on treatment with a DPP-4 inhibitor, although the reduction was small. A separate analysis of the effect of individual DPP-4 inhibitors showed a significant reduction in total cholesterol with alogliptin and vildagliptin, but not with sitagliptin.⁵³ However, in the EXAMINE study, no significant difference in lipoprotein levels was found between the alogliptin and placebo groups.³⁰

Effect on atherosclerosis and cardiovascular events

In animal studies, it was reported that alogliptin suppressed the progression of atherosclerosis in diabetic mice through downregulation of proinflammatory cytokines.^{54,55} It was also reported that alogliptin reduced the volume of the infarct lesion and neurological deficit after the induction of temporary focal ischemia in nondiabetic male C57BL/6J mice,⁵⁶ suggesting that the neuroprotective effect of alogliptin is independent of its glucose-lowering effect.

The effect of DPP-4 inhibitors on atherosclerosis in humans is unclear. In a preliminary study of ten healthy volunteers, treatment with alogliptin 25 mg for 1 week significantly suppressed the postprandial elevation in serum triacylglycerol and improved postprandial endothelial dysfunction, as assessed by brachial artery flow-mediated dilation.⁵⁷

Effect on kidney function

Although a protective effect of DPP-4 inhibitors against renal injury has been reported in rodent studies,^{58–61} the presence of such an effect remains to be established in humans. It has been reported that switching from sitagliptin to alogliptin, combined with an angiotensin II type 1 receptor blocker, resulted in a significant reduction in the urinary albumin to creatinine ratio in 12 patients with T2DM and albuminuria.⁶² This improvement in albuminuria was accompanied by an elevated plasma level of stromal cell-derived factor-1 alpha and a decrease in urinary 8-hydroxy-2'-deoxyguanosine, an oxidative stress marker, suggesting that alogliptin ameliorated albuminuria by reducing oxidative stress. Sakata et al reported that treatment with alogliptin for 12 weeks significantly reduced the urinary albumin to creatinine ratio, as well as HbA_{1c} and the circulating soluble form of the receptor for advanced glycation end products, in 61 patients with T2DM.⁶³

In the EXAMINE trial, no difference in change in estimated glomerular filtration rate was reported between alogliptin and placebo.³⁰ On the other hand, fewer patients showed worsened urinary albumin to creatinine ratio with saxagliptin versus placebo in the SAVOR (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus)-TIMI (Thrombolysis in Myocardial Infarction) 53 trial,⁶⁴ although it remains unclear whether this effect of a DPP-4 inhibitor is independent of its glucose-lowering effect.

The effect of DPP-4 inhibitors on other types of microangiopathy such as retinopathy and neuropathy in humans remains largely unknown.⁶⁵

Safety

In general, the incidence of adverse events with DPP-4 inhibitors is reported to be low, and these agents are well tolerated.

Hypoglycemia

The risk of hypoglycemia is low on treatment with alogliptin. The incidence of hypoglycemia with alogliptin was reported to be as low as that with placebo or metformin monotherapy

and lower than that with sulfonylureas.^{15,17,19,41} Adding alogliptin to insulin therapy resulted in improvement of HbA_{1c}, without increasing hypoglycemia compared with insulin therapy alone.^{28,29} However, use of a DPP-4 inhibitor as combination therapy with a sulfonylurea can increase the risk of hypoglycemia.¹ Therefore, caution is needed when a DPP-4 inhibitor is added to a sulfonylurea, especially in patients at risk of hypoglycemia, such as the elderly, patients with renal impairment, patients treated with a high dose of sulfonylureas, and patients with autonomic neuropathy.

Effect on body weight

The effect of DPP-4 inhibitors on body weight is generally reported to be neutral.¹ Treatment with alogliptin has shown less weight gain compared with sulfonylureas.^{22,41} It was reported that alogliptin neither prevented nor exacerbated weight gain when it was combined with pioglitazone.^{23–26,49}

Cardiovascular safety

Recently, regulatory agencies have created cardiovascular safety guidelines for the development of therapies for diabetes. A pooled analysis of alogliptin trials including 4,168 patients showed no sign of increased cardiovascular risk with alogliptin in patients with T2DM (hazard ratio, 0.635, 95% CI 0.0–1.41).⁶⁶

The results of the EXAMINE study assessing the long-term cardiovascular safety of alogliptin were published in September 2013.³⁰ In this study, 5,380 patients with T2DM and recent acute coronary syndrome were randomized to receive alogliptin or placebo in addition to existing antihyperglycemic therapy. During a median follow-up period of 1.8 years, the rate of major adverse cardiovascular events, a composite of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke, was not increased with alogliptin compared with placebo (11.3% versus 11.8%, hazard ratio 0.96; upper boundary of one-sided repeated CI, 1.16; $P < 0.001$ for noninferiority).

Another cardiovascular outcome trial of a DPP-4 inhibitor was published at the same time. The SAVOR-TIMI 53 trial⁶⁴ was designed to evaluate the safety and efficacy of saxagliptin with respect to cardiovascular outcomes in patients with T2DM and at risk of a cardiovascular event. A total of 16,492 patients were randomized to receive saxagliptin or placebo and followed for a median of 2.1 years. There was no significant difference in incidence of a primary endpoint event, a composite of cardiovascular death, myocardial infarction, and ischemic stroke, between the groups (hazard ratio 1.00, 95% CI 0.89–1.12; $P = 0.99$ for superiority; $P < 0.001$ for noninferiority).

The results of these two randomized controlled trials confirmed the cardiovascular safety of DPP-4 inhibitors. However, in the SAVOR-TIMI 53 trial, more patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (3.5% versus 2.8%; hazard ratio 1.27, 95% CI 1.07–1.51, $P = 0.007$).⁶⁴ Meta-analyses of trials using different DPP-4 inhibitors including alogliptin also suggested an increased risk of heart failure with DPP-4 inhibitor treatment,^{67,68} although in the EXAMINE study the incidence of heart failure was not significantly increased in the alogliptin group (hazard ratio 1.19, 95% CI 0.89–1.58, $P = 0.24$).³⁰ Further investigation is needed to clarify whether DPP-4 inhibitors are associated with a risk of heart failure.

Other adverse events

Angioedema has been reported as an adverse event of DPP-4 inhibitors, especially when combined with an angiotensin-converting enzyme inhibitor.⁶⁹ We have had a patient who developed facial angioedema after the introduction of vildagliptin, which improved after switching from vildagliptin to alogliptin.⁷⁰ The incidence of angioedema due to DPP-4 inhibitors is generally low, and no difference in its incidence was reported between the alogliptin and placebo groups in the EXAMINE trial.³⁰

To date, no meta-analyses of clinical trials or large-scale, randomized controlled trials of DPP-4 inhibitors suggest any increase in specific adverse events, such as nasopharyngitis, upper respiratory tract infection, skin reaction, hepatotoxicity, or pancreatitis, with the exception of heart failure as described above.^{1,30,64,71,72} Concern has been raised regarding the risk of pancreatitis or pancreatic cancer associated with incretin therapy;^{73,74} however, no increase in the incidence of acute pancreatitis has been reported in patients treated with incretin therapy in recent health insurance claims database and case-control studies,^{75,76} or in randomized controlled trials.^{30,64} Although case reports of liver injury in patients treated with alogliptin have raised the question of possible hepatotoxicity with this agent, no evidence of liver injury was reported in the EXAMINE trial.^{30,77} Completion of pooled analysis of ongoing long-term, large-scale clinical trials is needed to determine the longer-term safety profile, such as the incidence of cancer (Table 3).

Table 3 Issues concerning dipeptidyl peptidase-4 inhibitors in need of further clarification

- Hepatotoxicity
- Heart failure
- Pancreatitis
- Pancreatic cancer

Role of DPP-4 inhibitors in treatment of T2DM

It is now well appreciated that not only type 1 diabetes but also T2DM is characterized by a deficit of beta cells.^{78–81} Beta cell dysfunction is a strong predictor of future development of T2DM,^{82–87} suggesting that beta cell dysfunction is a core pathogenetic feature of the disease. Further, beta cell function in patients with T2DM progressively declines with duration of disease and is negatively associated with glycaemic control.^{88–92} Thus, preservation or recovery of beta cell function is an important treatment strategy in T2DM.⁹³

Despite recent advances in the treatment of T2DM, several issues remain to be resolved (Table 4), all of which are related to nonphysiological, inappropriate insulin supplementation by treatment, such as with sulfonylureas or insulin. In contrast, DPP-4 inhibitors have benefits with respect to all these issues (Table 4). Further, DPP-4 inhibitors improve the dynamics of glucagon,^{94,95} whereas raised plasma glucagon levels and a paradoxical increase in postprandial glucagon are another major defect in diabetes.⁹⁶ Therefore, one of the most important characteristics of DPP-4 inhibitors is recovery of endogenous insulin (and glucagon) secretion in a more physiological fashion compared with previous antidiabetic medications.

A proposed concept with regard to a treatment strategy for T2DM in relation to beta cell function is shown in Figure 2. T2DM is a progressive disease, and usually medication needs to be uptitrated with time.⁹⁷ Currently, the most effective strategy to preserve or restore beta cell function is to reduce the beta cell workload.⁹⁸ Since metformin reduces the insulin demand and beta cell workload by lowering hepatic glucose production, use of metformin in addition to lifestyle modification should be considered at as early a stage of diabetes as possible, unless contraindicated. In addition to the glucose-lowering efficacy of metformin, the less weight gain

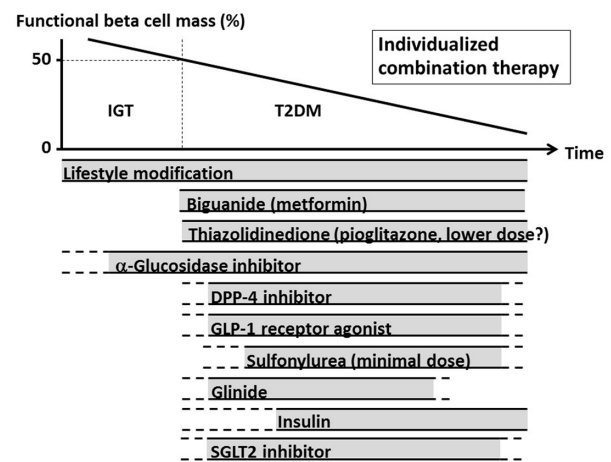


Figure 2 Proposed concept of treatment strategy for T2DM in relation to beta cell function.

Notes: T2DM is a progressive disease, and usually medication needs to be uptitrated with time. Currently, the most effective way to preserve or restore beta cell function is to reduce beta cell workload. Since metformin reduces insulin demand and beta cell workload through lowering hepatic glucose production, the use of metformin in addition to lifestyle modification should be considered at as early a stage of diabetes as possible, unless contraindicated. In Japan, alpha-glucosidase inhibitors are approved for clinical use in patients with impaired glucose tolerance and metabolic syndrome, in addition to T2DM. Since DPP-4 inhibitors are expected to improve beta cell function in addition to their glucose-lowering effect, the use of DPP-4 inhibitors can also be considered for a broad range of disease stages. In contrast, the use of insulin secretagogues, sulfonylureas, may not be considered as initial therapy but rather for use at a lower dose to support the insulinotropic effect of incretin therapy. Since to date no drug can cure diabetes, combination therapy should be considered in most cases. Triple combination therapy with metformin, pioglitazone, and alogliptin has been shown to be effective in reducing HbA_{1c} and improving beta cell function. Medications not approved in Japan are not included in the figure. Copyright © 2015. The Author. Reproduced from Saisho Y. Beta cell dysfunction: its critical role in prevention and management of type 2 diabetes. *World J Diabetes*. 2015;6(1):109–124.⁹³

Abbreviations: IGT, impaired glucose tolerance; T2DM, type 2 diabetes; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter 2.

or modest weight loss, low risk of hypoglycemia, and low cost of this drug support metformin as a first-line treatment for T2DM, as recommended in most guidelines.^{99–101} Other non-insulin secretagogues, such as TZDs, alpha-glucosidase inhibitors, and sodium-glucose cotransporter 2 inhibitors should also be considered as treatment options to reduce beta cell workload, in addition to their clinical utility, ie, low risk of hypoglycemia.

On the other hand, although DPP-4 inhibitors are “insulin secretagogues”, they are expected to improve beta cell function in addition to having a glucose-lowering effect and other advantages, as described in Table 4. Therefore, use of DPP-4 inhibitors can be considered for a broad range of disease stages. Combination therapy with metformin and a DPP-4 inhibitor is expected to have high glucose-lowering efficacy, a low risk of hypoglycemia, less weight gain or modest weight loss, and a low risk of adverse events, except for the gastrointestinal side effects of metformin, as described in a meta-analysis.¹⁰²

Table 4 Remaining issues in the treatment of type 2 diabetes and potential of DPP-4 inhibitors

Remaining issues	Potential of DPP-4 inhibitors
Hypoglycemia	Low risk of hypoglycemia
Weight gain	Neutral effect on body weight
Postprandial hyperglycemia	Reduce glycemic variability
Concern about increased risk of malignancy and/or atherosclerosis due to systemic (peripheral) hyperinsulinemia (especially with insulin therapy)	Restore endogenous insulin secretion in a more physiological manner
Progressive decline in beta cell function	Improve beta cell function

Abbreviation: DPP-4, dipeptidyl peptidase-4.

Table 5 Summary of characteristics of antidiabetic medications when combined with metformin

	DPP-4 inhibitors	TZD	Sulfonylureas	AGIs	Glinides	SGLT2 inhibitors	GLP-1 receptor agonists	Insulin
Efficacy of HbA _{1c} reduction	Moderate	Moderate	Moderate	Modest to moderate	Modest to moderate	Moderate	High	High (Highest)
Risk of hypoglycemia	Low	Low	High	Low	Moderate to high	Low	Low	High
Other side effects		Edema, heart failure, bone fracture, bladder cancer?		Abdominal bloating, flatulence, constipation, diarrhea		Genitourinary infection, polyuria, volume depletion	Nausea/vomiting, constipation, diarrhea	
Inhibitory effect of weight gain	±	–	–	+	± to –	++	++	–
Preservation of effect on beta cell function	+	+	– to ±	± to +	±	+	+	+
Other additional effects	Improvement of postprandial hyperglycemia, suppression of glucagon secretion, extra-pancreatic effects of incretin	Improvement of lipid profile, antiatherosclerotic effect, CV protective effects	Microvascular complications ↓ (UKPDS)	Improvement of postprandial hyperglycemia, CV protective effect	Improvement of postprandial hyperglycemia	Improvement of blood pressure and lipid profile	Improvement of blood pressure and lipid profile, suppression of glucagon secretion, extra-pancreatic effects of GLP-1	Microvascular complications ↓ (UKPDS)
Cost	\$ \$ \$	\$ to \$ \$	\$	\$ \$	\$ \$	\$ \$	\$ \$ \$	\$ \$ to \$ \$ \$

Note: ±, plus minus; +, plus; –, minus; ↓, reduced; \$, low cost; \$\$, moderate cost; \$\$\$, high cost; ?, unconfirmed.

Abbreviations: DPP-4, dipeptidyl peptidase-4; TZD, thiazolidinedione; AGI, alpha-glucosidase inhibitor; SGLT2, sodium-glucose cotransporter 2; GLP-1, glucagon-like peptide-1; CV, cardiovascular; UKPDS, UK Prospective Diabetes Study; HbA_{1c}, glycated hemoglobin.

The glucose-lowering effect of TZDs has been shown to have greater durability compared with that of sulfonylureas or even metformin.¹⁰³ Thus, combination therapy with a DPP-4 inhibitor and a TZD is also expected to have a glucose-lowering effect with high efficacy and durability and a low risk of hypoglycemia, and to effectively improve beta cell function.²⁷ However, since TZDs are associated with weight gain, weight reduction should not be expected. In addition, a risk of bladder cancer and bone fractures are a concern with TZDs, although a recent large cohort study showed no increased risk of bladder cancer in patients treated with pioglitazone.¹⁰⁴ Thus, it might be advisable to use TZDs such as pioglitazone at a lower dosage to reduce the risk of adverse effects.

Fixed-dose combination tablets of alogliptin and metformin (Kazano[®]) or pioglitazone (Liovel[®] or Oseni[®]) are now available in many countries. It has been reported that use of fixed-dose combination tablets improves patient adherence to treatment and treatment satisfaction,^{105,106} possibly resulting in improved glycemic control. Thus, fixed-dose combinations containing alogliptin will be an important option for the treatment of T2DM. A combination of a DPP-4 inhibitor and another non-insulin secretagogue such as an alpha-glucosidase inhibitor or sodium-glucose cotransporter 2 inhibitor has also been shown to be effective for improving HbA_{1c} and glycemic variability,^{107,108} with a low risk of hypoglycemia and weight neutrality or modest weight loss, although gastrointestinal disturbance with alpha-glucosidase inhibitors often limits their use. The long-term efficacy and safety of the combination of a DPP-4 inhibitor and a sodium-glucose cotransporter 2 inhibitor remains to be established.

In contrast, sulfonylureas (insulin secretagogues) may not be considered as initial therapy, but rather for use at a lower dose to support the insulinotropic effect of incretin therapy, because of their risk of hypoglycemia and weight gain. Glinides, short-acting insulin secretagogues, correct postprandial hyperglycemia. Although the glucose-lowering effect of glinides is modest, the risk of hypoglycemia with glinides is lower than that with sulfonylureas. Therefore, combined use of a DPP-4 inhibitor and a glinide may be useful to manage postprandial hyperglycemia while minimizing the risk of hypoglycemia and weight gain.

Insulin shows the greatest efficacy in reducing HbA_{1c}, and has been shown to improve beta cell function.^{109,110} Thus, combination of a DPP-4 inhibitor and insulin should be considered for patients with various stages of T2DM, although the risk of hypoglycemia, weight gain, and fear

or unwillingness to carry out injections may limit this combination. The efficacy of combination of a DPP-4 inhibitor and a glucagon-like peptide-1 agonist remains to be determined.

Since there is no drug to date that can cure diabetes, combination therapy should be considered in most cases. To date, on top of metformin, each combination of antidiabetic medication has its advantages and disadvantages (Table 5). The results of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study have warned us not to simply intensify medical treatment to reduce HbA_{1c} to near-normal levels.¹¹¹ Hospital admission rates for hypoglycemia now exceed those for hyperglycemia among older adults.¹¹² The burden of medical treatment may rather result in reducing the patient's quality-adjusted life years.¹¹³ Therefore, each combined drug should be selected for each individual patient with consideration of the patient's preference.^{99,114} Although studies suggest that initial combination therapy reduces HbA_{1c} more effectively than monotherapy in the short term,^{21,25} the longer-term efficacy remains unknown.

It has been reported that the glucose-lowering effect of DPP-4 inhibitors is more potent in Asians than in Caucasians.³⁸ Moreover, recent studies suggest that there is a difference in the pathophysiological features of T2DM according to ethnicity.^{115–117} Thus, the above-mentioned treatment strategy may not be applicable to other ethnicities or countries, and may need to be modified in each situation.

Conclusion

Alogliptin, a highly selective DPP-4 inhibitor, has a glucose-lowering effect, the degree of which is similar to that of other DPP-4 inhibitors, with a low risk of hypoglycemia and weight gain. The safety of alogliptin, including cardiovascular adverse events, has been confirmed in a large-scale trial. Having a low risk of hypoglycemia, weight neutrality, and the potential to improve beta cell function, DPP-4 inhibitors are expected to become an important component of the treatment of T2DM. In Japan, currently more than half of patients with T2DM are treated with DPP-4 inhibitors. The cost-effectiveness of DPP-4 inhibitors needs to be assessed in future trials.

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Disclosure

The author reports no conflicts of interest in this work.

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