REVIEW

Anagliptin in the treatment of type 2 diabetes: safety, efficacy, and patient acceptability

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Abstract: Anagliptin is a novel dipeptidyl peptidase-4 inhibitor that has been available in Japan since 2012. Because anagliptin is not generally used in countries other than Japan, there are only a small number of reports investigating the effects of anagliptin. In the present article, we review the safety and efficacy of anagliptin according to data obtained from preclinical trials and postmarketing studies. The usual dose of anagliptin is 200 mg daily, and increases in the dose up to 400 mg daily have been approved in cases in which the blood glucose–lowering effect is insufficient. In a Phase II trial, the reduction in the HbA_{1c} values from baseline after 12 weeks monotherapy with 200 mg and 400 mg of daily anagliptin was 0.75%±0.50% and 0.82%±0.46%, respectively, and more than 40% of the subjects receiving anagliptin at a dose of 200 mg or 400 mg daily achieved an HbA_{1c} level below 6.9%. Furthermore, the levels of HbA_{1c}, fasting blood glucose, and postprandial blood glucose were significantly decreased at 52 weeks compared with the baseline values in a Phase III trial investigating the effects of anagliptin included in combination therapy with other oral antidiabetic agents. In a pooled analysis of Phase II and Phase II/III trials, the goal achievement rates for an HbA_{1c} level below 7.0% at 12 weeks were 40.3%, 39.4%, 30.0%, and 34.8% in the patients treated with anagliptin combined with α-glucosidase inhibitors, thiazolidinediones, sulfonylureas, and biguanides, respectively. Meanwhile, the serum lipid concentrations significantly improved after the administration of anagliptin in a pooled analysis of Phase III trials, and no serious adverse effects have been reported in preclinical trials. Therefore, the use of anagliptin in patients with type 2 diabetes is considered to be safe and effective for both monotherapy and combination therapy.

Keywords: dipeptidyl peptidase-4 inhibitor, type 2 diabetes mellitus, monotherapy, combination therapy, adverse effect

Introduction

Treatment with dipeptidyl peptidase-4 (DPP-4) inhibitors, novel oral antidiabetic agents (OADs), results in improvements in the blood glucose levels in patients with type 2 diabetes mellitus following the stimulation of endogenous insulin secretion, inhibition of glucagon release, and reduction of gastric emptying via the enhanced production of incretin hormones (glucagon-like peptide-1 [GLP-1] and gastric inhibitory polypeptide). Sitagliptin, the first DPP-4 inhibitor, was approved for use by the US Food and Drug Administration in 2006 and has been available in Japan since 2009. Seven drugs belonging to this class are currently available for prescription in the clinical setting under the medical insurance law at the time of December 2014 in Japan (Table 1).

Recent trends in the rates of antidiabetic agent prescriptions in our facility are shown in Figure 1. While the number of patients prescribed α-glucosidase inhibitors, sulfonylureas, thiazolidinediones, and glinides has been on the decline,

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Table 1 Pharmacological characteristics and use in the clinical setting in Japan and efficacy of DPP-4 inhibitors in patients with type 2 diabetes based on the data for Phase III clinical trials

	Sitagliptin	Vildagliptin	Alogliptin	Linagliptin	Teneligliptin	Saxagliptin	Anagliptin
IC_{50} (nmol/L)	17.9	9.7	10	1–3.6	0.9	1.3	3.3
T_{max} (h)	2–5	1.3–2.8	1.0–1.4	6	1.0–1.8	0.8	0.9–1.8
$T_{1/2}$ (h)	9.6–12.3	1.5–5.3	14.3–21.8	97–105	2,124	6.0–6.8	5.8–6.2
Inhibition of plasma DPP-4 activity (%)	≥80	≥80	≥80	≥80	≥70	≥80	≥80
Increase in active GLP-1 levels	≥2-fold	1.8-fold	2-fold	Increase	≥2-fold	≥2-fold	≥2-fold
Dosing							
Frequency	QD	BID	QD	QD	QD	QD	BID
Usual dose (daily)							
Normal kidney function	50 mg	100 mg	25 mg	5 mg	20 mg	5 mg	200 mg
Ccr 30–50 mL/min	25 mg	50 mg	12.5 mg	5 mg	20 mg	2.5 mg	200 mg
Ccr <30 mL/min	12.5 mg	50 mg	6.25 mg	5 mg	20 mg	2.5 mg	100 mg
Efficacy as monotherapy							
Study duration (weeks)	24	24	26	24	12	24	52
Baseline mean HbA_{1c} (%)	8.01	8.4	7.9	8.0	7.8	7.9	8.22
Change in HbA_{1c} (%)	−0.79*	−0.7	−0.59	−0.69	−0.8	−0.46	−0.63
Reference number	11	12	13	14	15	16	17

**Notes:** IC_{50}, T_{max}, $T_{1/2}$, the inhibition of plasma DPP-4 activity, and the increase in active GLP-1 levels were based on the drug information of the corresponding agent published by the pharmaceutical company. *The dose of sitagliptin was 100 mg daily (QD).
Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; IC_{50}, half-maximal inhibitory concentration; T_{max}, maximum drug concentration time; $T_{1/2}$, half-life period; Ccr, creatinine clearance rate.

the rate of prescription of DPP-4 inhibitors has increased markedly in recent years, reaching 50%–60%. In contrast, the rate of prescription of insulin and biguanides has remained stable at approximately 30%. This trend is similar to that observed for data obtained from databases in Japan[1] and the United States.[2] Therefore, it is not an exaggeration to state that the introduction of DPP-4 inhibi-

tors has changed the treatment strategies for patients with type 2 diabetes.

Metformin, an OAD in the family of biguanides, is recognized to be the first-line drug among antidiabetic agents.[3] Metformin administration is superior in the glucose-lowering effect for patients with type 2 diabetes, and regardless of the presence or absence of obesity,[4] the prescription rate has
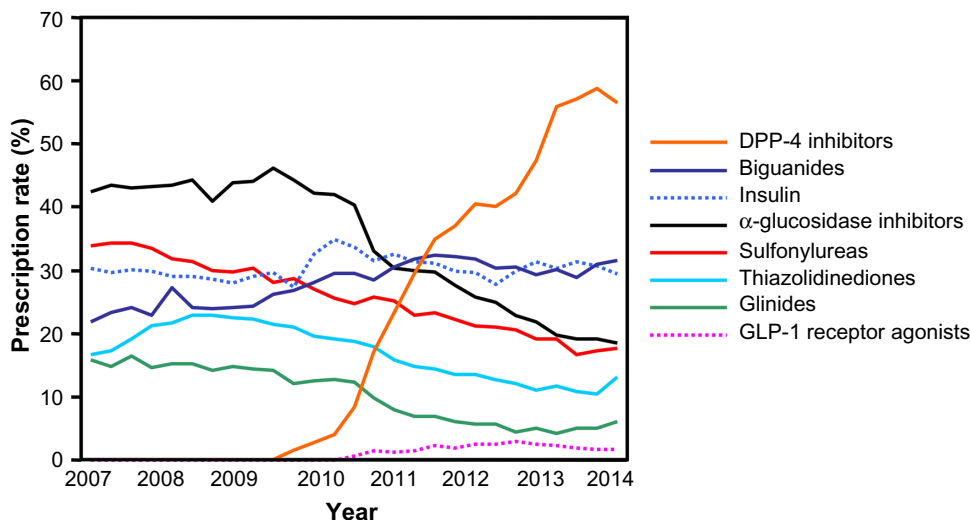
Figure 1 Prescription rates of antidiabetic agents.
Notes: The data were obtained from the database of Edogawa Hospital over three months. The prescription rate was calculated as the number of patients prescribed each class of antidiabetic agent divided by the total number of patients prescribed any type of antidiabetic agent. The number of patients prescribed α-glucosidase inhibitors, sulfonylureas, thiazolidinediones, and glinides has declined continuously since the release of dipeptidyl peptidase-4 (DPP-4) inhibitors. The rate of prescription of dipeptidyl peptidase-4 inhibitors increased steadily to more than 50% in 2013. In contrast, the use of insulin and biguanides has remained relatively stable at approximately 30%. Copyright ©2013. Journal of Japan Diabetes Society. Adapted from Ando S, Tsugami E, Suzuki S, et al. Recent trend in the prescription rates of antidiabetic agents in our facility. *Journal of Japan Diabetes Society*. 2013; 56 Suppl 1: S164.[45]
Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.

remained unchanged at approximately 30% (Figure 1). This observation is considered to account for the relatively lower prescription rates among patients with type 2 diabetes who received consecutive treatments in our department, including many elderly subjects and individuals with renal impairment[5,6] who are contraindicated for biguanide administration.[7–9] Patients with type 2 diabetes tend to demonstrate a decreased renal function, as indicated by the estimated glomerular filtration rate and reduced endogenous insulin secretion along with the long-term duration of diabetes and aging (Figure 2). When selecting antidiabetic agents for patients with type 2 diabetes and renal dysfunction, it is necessary to use various OADs, including biguanides, sulfonylureas, and thiazolidinediones, carefully due to their side effects. On the other hand, it is a major advantage of DPP-4 inhibitors that agents in this class may be administered continuously, even in elderly subjects or patients with renal dysfunction, including those receiving maintenance dialysis.[10]

Whereas linagliptin and teneligliptin do not require dose adjustment, it is recommended that the dose of other DPP-4 inhibitors is reduced depending on the degree of renal dysfunction (Table 1). The lowering effect on the

HbA$_{1c}$ level obtained in Phase III clinical trials[11–17] does not differ significantly based on the drug. Anagliptin (Suiny®), a novel DPP-4 inhibitor, was developed by Sanwa Kagaku Kenkyusho Co, Ltd (Nagoya, Japan) and Kowa Pharmaceutical Co, Ltd (Tokyo, Japan) and has been available in Japan since November 2012. Because anagliptin was released relatively recently and this drug is not generally used in countries other than Japan (at the time of December 2014), there are only a small number of reports investigating the effects of anagliptin. However, it has been reported that anagliptin demonstrates serum lipid–lowering and antiatherogenic effects, which have not yet been observed in other DPP-4 inhibitors. We herein describe the effects of anagliptin primarily in Japanese patients with type 2 diabetes.

Efficacy of anagliptin in patients with type 2 diabetes
Efficacy of monotherapy after 12 weeks of treatment
The recommended dose of anagliptin is 200 mg daily (100 mg, BID) in Japan.[18] Because treatment with anagliptin exhibits
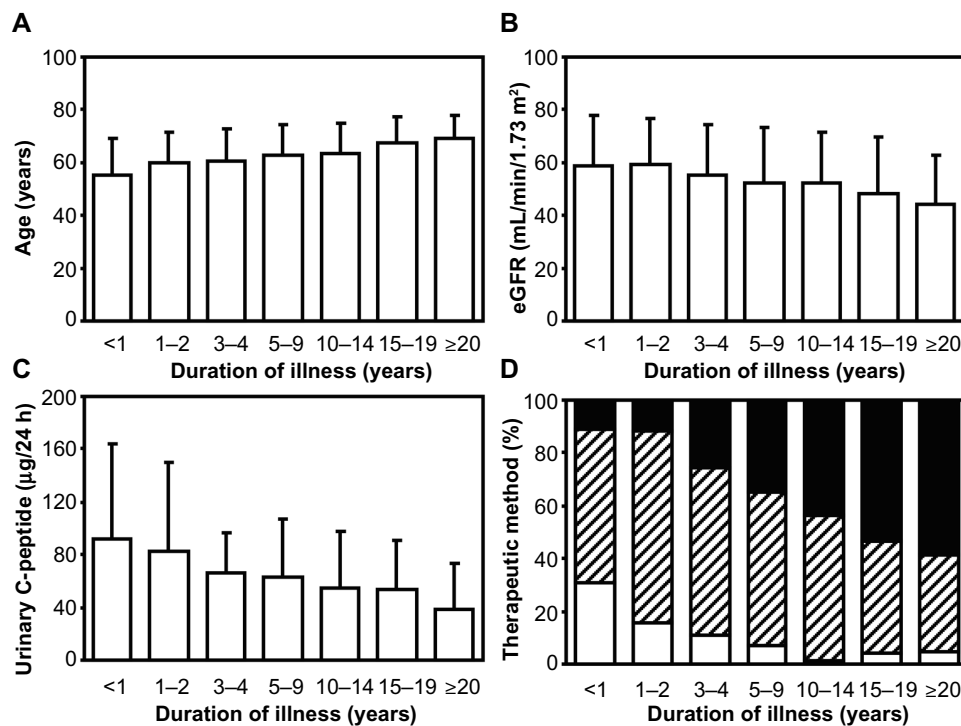

Figure 2 Data for (**A**) patient age, (**B**) estimated glomerular filtration rate (eGFR), (**C**) urinary C-peptide, and (**D**) therapeutic methods for type 2 diabetes among the groups divided according to the duration of illness.
Notes: A population of 1,436 patients diagnosed with type 2 diabetes mellitus whose duration of illness was described in their medical records and who were treated for more than 6 months at the Department of Diabetes, Metabolism and Kidney Disease of Edogawa Hospital between 2008 and 2011 was examined. While the patient ages significantly increased in association with a longer duration of illness ($P<0.0001$, analysis of variance), both the estimated glomerular filtration rate ($n=1436$) and urinary C-peptide ($n=424$) values were significantly reduced ($P<0.0001$, analysis of variance). The proportion of patients receiving insulin treatment increased in association with a longer duration of illness ($P<0.0001$, χ^2 test). The data are shown as the means ± standard deviation. Filled, hatched, and open bars indicate insulin (including the combination of insulin and oral antidiabetic agents), oral antidiabetic agents, and nonpharmacological therapies, respectively.

dose-dependent improvements in the HbA_{1c} and blood glucose levels according to the results of a Phase II trial including a dose-ranging study (50–400 mg daily),[19] increases in the dose up to 400 mg daily (200 mg, BID) have been approved.[18] In one study, the reduction in the HbA_{1c} values from baseline after 12 weeks monotherapy with 200 mg (*n*=69) and 400 mg (*n*=68) of daily anagliptin was 0.75%±0.50% and 0.82%±0.46%, respectively, and more than 40% of the subjects receiving anagliptin at a dose of 200 mg or 400 mg daily achieved an HbA_{1c} level below 6.9%.[19] In another Phase II/III trial, the administration of monotherapy for 12 weeks demonstrated a reduction of 0.66%±0.50% and 0.75%±0.55% in the HbA_{1c} levels with 200 mg (*n*=63) and 400 mg (*n*=58) of daily anagliptin, respectively.[20] The differences in the HbA_{1c} levels versus the placebo group among the subjects receiving 200 mg and 400 mg of anagliptin daily were −0.72% and −0.82%, respectively.[20]

According to a pooled analysis of the data obtained from Phase II and Phase II/III trials, the goal achievement rate of an HbA_{1c} level less than 7.0% was 51.1% in the group treated with anagliptin at a dose of 200 mg (100 mg, BID) at 12 weeks, which was significantly superior to that attained with voglibose, an α-glucosidase inhibitor.[21]

Long-term efficacy of monotherapy

Kaku[17] reported that the use of monotherapy with anagliptin at a daily dose of 200 mg (with dose increases up to 400 mg permitted if the glucose-lowering effect was insufficient) showed continuous improvements in the HbA_{1c} levels over 52 weeks in 150 patients with type 2 diabetes whose blood glucose levels were poorly controlled (6.9%≤ HbA_{1c}<10.5%) even after receiving nonpharmacological therapy. The changes in the HbA_{1c}, fasting blood glucose, and postprandial 2-h blood glucose levels were −0.63%±0.85% (baseline value: 8.22%±1.06%), −12.5±32.2 mg/dL (baseline value: 166.1±38.4 mg/dL), and −31.0±47.8 mg/dL (baseline value: 255.1±60.3 mg/dL), respectively. Furthermore, improvements were noted in the levels of 1,5-AG, glycoalbumin, serum insulin, proinsulin, homeostatic model assessment-β, total cholesterol, and low-density lipoprotein (LDL)–cholesterol.

Combination therapy

The changes in the HbA_{1c} levels observed in a Phase III trial[22] of anagliptin as an add-on therapy to α-glucosidase inhibitors (acarbose 20.2%, voglibose 43.6%, and miglitol 36.2%), biguanides (metformin), sulfonylureas (glimepiride 73.5%, gliclazide 10.3%, and glibenclamide 16.2%), and

thiazolidinediones (pioglitazone) are shown in Table 2. In this trial, treatment with anagliptin at a dose of 200 mg daily (100 mg, BID) or a placebo was administered for an initial 12 weeks in patients with type 2 diabetes whose HbA_{1c} levels were between 6.9% and 10.4%, even after treatment with other OADs. Anagliptin was subsequently administered at a dose of 200 mg daily for 40 weeks in both groups. Increases in the dose of anagliptin up to 400 mg daily (200 mg, BID) were allowed if the HbA_{1c} level was >6.9% at 28 weeks. Consequently, the improvements in parameters indicating glycemic control at 12 weeks were significantly greater in the anagliptin/anagliptin group than in the placebo/anagliptin group, regardless of whether OADs were administered before the trial. Furthermore, the levels of HbA_{1c}, fasting blood glucose, and postprandial blood glucose were significantly decreased at 52 weeks compared with the baseline values.

As it has been reported that metformin increases the plasma-active GLP-1 in humans[23] via the inhibitory effects of DPP-4,[24] combination therapy with anagliptin and metformin is considered to be suitable for the treatment of type 2 diabetes based on the enhanced endogenous GLP-1 activity. Furthermore, combination therapy with anagliptin and α-glucosidase inhibitors also has advantages, as it has been reported that GLP-1 secretion is prolonged by acarbose.[25] On the other hand, the maximum drug concentration (C_{max}) and area under the blood concentration–time curve (AUC) from time zero to 24 h after dosing (AUC_{0-24h}) for anagliptin are reduced with the concomitant administration with miglitol,[26] whereas both the C_{max} and AUC_{0-24h} values for anagliptin are elevated in subjects under treatment with the combination therapy consisting of metformin and anagliptin.[27] The degree of improvement in glycemic control achieved with combination therapy using anagliptin and sulfonylureas appears to be lower than that attained with α-glucosidase inhibitors, biguanides, or thiazolidinediones. Nevertheless, there is concern regarding the potential for hypoglycemia in patients with type 2 diabetes treated with DPP-4 inhibitors and sulfonylureas.[28] This issue should be investigated in detail in a real clinical setting.

According to the results of a pooled analysis of the data obtained from Phase II and Phase II/III trials,[21] the goal achievement rates of an HbA_{1c} level less than 7.0% at 12 weeks in patients receiving combination therapy with anagliptin and other OADs are 40.3%, 39.4%, 30.0%, and 34.8% for α-glucosidase inhibitors, thiazolidinediones, sulfonylureas, and biguanides, respectively.

Table 2 Changes in the levels of HbA$_{1c}$, fasting blood glucose, and postprandial blood glucose in the groups treated with combination therapy with anagliptin and other oral antidiabetic agents in a Phase III clinical trial

	Parameters	Treatment group	12 weeks (n)	52 weeks (n)
α-gucosidase inhibitors	HbA$_{1c}$ (%)	Placebo/anagliptin	0.12±0.58 (32)	−0.87±0.81 (94)[###]
		Anagliptin/anagliptin	−0.83±0.56 (62)[***]	
	Fasting blood glucose (mg/dL)	Placebo/anagliptin	5.9±39.5 (32)	−15.6±29.3 (94)[###]
		Anagliptin/anagliptin	−18.5±25.7 (62)[***]	
	Postprandial blood glucose (mg/dL)	Placebo/anagliptin	5.9±47.5 (32)	−38.5±48.9 (92)[###]
		Anagliptin/anagliptin	−43.1±38.3 (62)[***]	
Biguanides	HbA$_{1c}$ (%)	Placebo/anagliptin	0.45±0.91 (36)	−0.67±1.15 (104)[###]
		Anagliptin/anagliptin	−0.62±0.67 (69)[***]	
	Fasting blood glucose (mg/dL)	Placebo/anagliptin	10.9±35.2 (36)	−15.0±37.5 (104)[###]
		Anagliptin/anagliptin	−13.6±26.8 (69)[***]	
	Postprandial blood glucose (mg/dL)	Placebo/anagliptin	15.6±43.5 (36)	−24.9±56.7 (100)[###]
		Anagliptin/anagliptin	−30.4±45.1 (67)[***]	
Sulfonylureas	HbA$_{1c}$ (%)	Placebo/anagliptin	0.24±0.59 (45)	−0.36±0.84 (135)[###]
		Anagliptin/anagliptin	−0.53±0.48 (90)[***]	
	Fasting blood glucose (mg/dL)	Placebo/anagliptin	2.0±27.8 (45)	−6.7±27.0 (135)[##]
		Anagliptin/anagliptin	−10.3±29.2 (90)[*]	
	Postprandial blood glucose (mg/dL)	Placebo/anagliptin	1.9±40.6 (45)	−8.7±43.5 (134)[#]
		Anagliptin/anagliptin	−25.1±40.1 (90)[***]	
Thiazolidinediones	HbA$_{1c}$ (%)	Placebo/anagliptin	0.32±0.67 (31)	−0.88±0.89 (102)[###]
		Anagliptin/anagliptin	−0.52±0.68 (71)[***]	
	Fasting blood glucose (mg/dL)	Placebo/anagliptin	6.3±21.3 (31)	−19.8±26.9 (102)[###]
		Anagliptin/anagliptin	−15.9±34.9 (71)[**]	
	Postprandial blood glucose (mg/dL)	Placebo/anagliptin	10.5±38.1 (31)	−42.4±50.3 (100)[###]
		Anagliptin/anagliptin	−34.4±52.7 (69)[***]	

Notes: Mean ± standard deviation. *$P<0.05$, **$P<0.01$, ***$P<0.001$ vs placebo group. #$P<0.05$, ##$P<0.01$, ###$P<0.001$ vs baseline value. Copyright © 2012. Japanese Pharmacology and Therapeutics. Adapted from Kaku K. Efficacy and safety of anagliptin add-on therapy in Japanese patients with type 2 diabetes. *Jpn Pharmacol Ther*. 2012;40(9):745–770.[22]

Daily blood glucose profile

Uchino and Kaku[29] investigated the daily blood glucose profiles using continuous glucose monitoring in 20 patients with type 2 diabetes under treatment with 200 mg of anagliptin (100 mg, BID) or 50 mg of sitagliptin (QD) in an open-label, two-period crossover study. The area under the curve for the blood glucose level (4,421.9±1,187.0 mg h/dL), average 24-h blood glucose level (184.10±49.39 mg/dL), M-value (29.4±32.7 mg/dL), and mean amplitude of glycemic excursion (104.97±32.71 mg/dL) during the anagliptin administration period were significantly lower than the corresponding values obtained in the control period (4,906.0±924.9 mg h/dL, 204.25±38.53 mg/dL, 39.54±26.27 mg/dL, and 126.50±19.03 mg/dL, respectively), whereas these parameters were not significantly different from the corresponding values noted during the sitagliptin administration period (4,469.2±1,125.7 mg h/dL, 186.06±46.83 mg/dL, 30.35±12.42 mg/dL, and 110.35±30.95 mg/dL, respectively).

Lipid-lowering effect

Managing the serum lipid concentrations is important in patients with type 2 diabetes as dyslipidemia is an important risk factor for diabetic macroangiopathy in Japanese subjects.[30] According to a pooled analysis of data obtained from Phase III trials, the serum LDL-cholesterol, triglyceride, total cholesterol and non–high-density lipoprotein (HDL)-cholesterol levels significantly improved after the administration of anagliptin at a dose of 200 mg (100 mg, BID) or 400 mg (200 mg, BID) (Table 3).[31] Meanwhile, the serum concentrations of HDL-cholesterol increased significantly in the subjects with an HDL-cholesterol level less than 40 mg/dL and decreased in the entire patient population. These observations suggest that there is an additional mechanism independent of the lipid-lowering effect of these drugs that occurs secondary to improvements in the blood glucose level, as the correlation coefficient between the change in the HbA$_{1c}$ level and the LDL-cholesterol ($r=0.112$, $P=0.003$) or triglyceride ($r=0.075$, $P=0.07$) levels was rather small. Therefore, treatment with anagliptin is expected to prevent atherosclerotic diseases in addition to diabetic microangiopathy by improving glycemic control in patients with type 2 diabetes.

Antiatherogenic effect

DPP-4 inhibitors are thought to reduce the risk of cardiovascular events, particularly myocardial infarction, in patients with

Table 3 Changes in the serum lipid concentrations in a Phase III trial

	Baseline	12 weeks	52 weeks	P
LDL-cholesterol				
n	577	556	388	
Measured value (mg/dL)	121.1±1.2	117.0±1.2	111.9±1.3	<0.001
Amount of change (mg/dL)	–	–3.6±0.9	–9.7±1.1	
Rate of change (%)	–	–1.8±0.7	–6.5±0.9	
Triglycerides				
n	585	571	399	
Measured value (mg/dL)	119.0	115.0	107	0.005
Amount of change (mg/dL)	–	–5.0	–5.0	
Rate of change (%)	–	–4.7	–5.4	
Total cholesterol				
n	585	571	399	
Measured value (mg/dL)	204.8±1.4	200.5±1.4	195.1±1.6	<0.001
Amount of change (mg/dL)	–	–4.2±1.0	–10.1±1.3	
Rate of change (%)	–	–1.5±0.5	–4.1±0.6	
HDL-cholesterol				
n	585	571	399	
Measured value (mg/dL)	56.2±0.6	55.9±0.6	55.9±0.7	<0.001
Amount of change (mg/dL)	–	–0.4±7.7	–0.1±0.4	
Rate of change (%)	–	0.2±0.6	0.6±0.6	
HDL-cholesterol (in subgroup with baseline value <40 mg/dL)				
n	63	61	43	
Measured value (mg/dL)	34.5±0.5	36.1±0.7	37.6±0.8	<0.001
Amount of change (mg/dL)	–	1.6±0.6	2.3±0.6	
Rate of change (%)	–	5.4±2.0	6.9±1.9	
Non HDL-cholesterol				
n	585	571	399	
Measured value (mg/dL)	148.6±1.4	144.5±1.5	139.2±1.5	<0.001
Amount of change (mg/dL)	–	–3.9±0.9	–10.0±1.3	
Rate of change (%)	–	–1.7±0.7	–5.2±0.8	

Notes: Mean ± SE. The *P*-value was measured according to a repeated-measures analysis of variance. Copyright © 2012. Japanese Pharmacology and Therapeutics. Adapted from Kaku K. Effects of anagliptin on serum lipids in Japanese patients with type 2 diabetes – a pooled analysis of long-term therapy with anagliptin. *Jpn Pharmacol Ther*. 2012;40(9):771–784.[31]
Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein.

type 2 diabetes.[32] Recently, Ervinna et al[33] reported that the administration of anagliptin attenuates atherosclerosis secondary to suppression of the proliferation of vascular smooth muscles and monocyte inflammatory reactions in apo-E–deficient mice, an animal model of progressive atherosclerosis.

Kakuda et al[34] showed that oxidative stress markers, such as urinary 8-OHdG and serum high-sensitivity-CRP, are

ameliorated and the plasma level of high–molecular weight adiponectin, which has an antiatherogenic effect, increases after the initiation of therapy with 200 mg of anagliptin daily, in addition to observed improvements in blood glucose control and the serum LDL-cholesterol, triglyceride, non–HDL-cholesterol and remnant-like particle-cholesterol levels. Imai et al[35] also reported that treatment with anagliptin or miglitol reduces the oral sucrose load–inducible gene expression of inflammatory cytokines, such as interleukin-1β and interleukin-18, and tumor necrosis factor-α, in the peripheral leukocytes of Otsuka Long-Evans Tokushima fatty rats. However, it remains unclear which of these anti-inflammatory effects is specifically caused by anagliptin and which occurs secondary to improvements in postprandial hyperglycemia, which is commonly seen in patients with glucose impairment.

Mimura et al[36] demonstrated that treatment with anagliptin facilitates the restoration of mucosal damage in mice exhibiting experimental colitis induced by dextran sulfate sodium. The authors suggested the possibility of applying anagliptin administration as a novel therapeutic approach for the treatment of inflammatory bowel disease. Further investigations are required to confirm this hypothesis in both basic and clinical research.

Safety and patient acceptability
Safety in preclinical trials
The frequency of adverse effects (AEs) is not significantly different between subjects administered anagliptin and those administered a placebo according to the results of a Phase II trial performed over 12 weeks.[19] Most AEs were mild and no events resulting from increases in the dose of anagliptin were observed.

AEs were noted in 23.5% (19 of 81 patients) and 15.7% (11 of 70 patients) of subjects receiving preprandial and postprandial administration, respectively, during treatment with long-term monotherapy consisting of 200–400 mg of daily anagliptin (100–200 mg, BID) for 52 weeks.[17] In that study, the complications observed in more than 2% of the subjects included constipation (4.9%) and gastritis (4.9%), whereas only one patient (0.7%) showed mild hypoglycemia. Although statistically significant changes were detected in some laboratory data and vital signs compared with the baseline values, they were not considered to be meaningful due to the small variation within the normal ranges. Furthermore, no serious AEs were reported in another Phase III trial investigating the effects of combination therapy with anagliptin and other OADs.[22] Side effects observed in more than 2% of the subjects in that trial are shown in Table 4. Because the frequency of hypoglycemia was relatively high in the

Table 4 Side effects observed in more than 2% of subjects treated with anagliptin and other oral antidiabetic agents in a Phase III trial in Japan

	Biguanides	**α-Glucosidase inhibitors**	**Sulfonylureas**	**Thiazolidinediones**
n	104	94	135	102
Total number	25 (24.0%)	22 (23.4%)	43 (31.9%)	23 (22.5%)
Abdominal fullness				2 (2.0%)
Constipation	3 (2.9%)	2 (2.1%)	7 (5.2%)	2 (2.0%)
Nasopharyngitis		2 (2.1%)		
ALT elevation	7 (3.8%)		6 (4.4%)	
AST elevation	3 (2.9%)			
Serum amylase elevation	3 (2.9%)			
γGTP elevation			3 (2.2%)	
Hematocrit reduction		3 (4.2%)		
Hemoglobin reduction		4 (4.3%)		
Red blood cell count reduction		2 (2.1%)		
Occult blood in stool	5 (4.8%)		5 (3.7%)	
Hypoglycemia			10 (7.4%)	3 (2.9%)

Note: Copyright © 2012. Japanese Pharmacology and Therapeutics. Adapted from Kaku K. Efficacy and safety of anagliptin add-on therapy in Japanese patients with type 2 diabetes. *Jpn Pharmacol Ther*. 2012;40(9):745–770.[22]
Abbreviations: ALT, aspartate aminotransferase; AST, alanine transaminase; γGTP, γ-glutamyltransferase.

sulfonylurea group, it is important to pay attention to the potential for hypoglycemia in patients receiving combination therapy with anagliptin and sulfonylureas, as described earlier. Other than hypoglycemia, no side effects of concern have been documented. Therefore, treatment with anagliptin is considered to be superior in terms of safety and tolerability for both monotherapy and combination therapy.

Safety in the real clinical setting

One case of hypokalemia and muscle weakness was reported as serious side effects of anagliptin during postmarketing surveillance by Sanwa Kagaku Kenkyusho Co, Ltd.[37] In addition, a small number of nonserious events, including gastrointestinal symptoms (*n*=9) and somnolence (*n*=3), were observed among approximately 20,000 diabetic patients treated with anagliptin for 6 months after the drug's release. The case of a 60-year-old Japanese male with type 2 diabetes complicated by the onset of angioedema 4 days after the initiation of anagliptin was reported by Hamasaki and Yanai.[38] Although an increased risk of angioedema has been described in patients using both DPP-4 inhibitors and angiotensin-converting enzyme inhibitors,[39] no medications other than anagliptin were given in this case. Because DPP-4 influences the rate of degradation of bradykinin, the authors suggested that DPP-4 inhibitors may increase the half-life of bradykinin.

Currently, the biggest clinical concern with DPP-4 inhibitors is the increased incidence of new heart failure with these medications.[40,41] Although alogliptin, another DPP-4 inhibitor, did not demonstrate an increased risk for cardiovascular disease and heart failure,[42,43] there have not

yet been any studies on the association between anagliptin treatment and heart failure.

Safety in patients with renal impairment

The ratio of AUC from time zero to infinity after dosing ($AUC_{0-\infty}$) in subjects with a normal kidney function following the single administration of anagliptin at a dose of 400 mg is 1.65 ng h/mL, 1.76 ng h/mL, 2.70 ng h/mL, and 3.22 ng h/mL for those with mild renal impairment (*n*=6, 60 mL/min/1.73 m^2 ≤ creatinine clearance <90 mL/min/1.73 m^2), moderate renal impairment (*n*=6, 30 mL/min/1.73 m^2 ≤ creatinine clearance <60 mL/min/1.73 m^2), severe renal impairment (*n*=6, 15 mL/min/1.73 m^2≤ creatinine clearance <30 mL/min/1.73 m^2), and end-stage kidney disease under maintenance hemodialysis (*n*=6), respectively.[18] Because AUC values are greater in the progressive stages of renal dysfunction, the dose of anagliptin is usually reduced to 100 mg once daily in patients with severe renal impairment (Table 1). There are currently no studies investigating safety or patient acceptability in subjects with type 2 diabetes and renal impairment. However, treatment with anagliptin may have a glucose-lowering effect at half-doses in patients with renal dysfunction, similarly to linagliptin,[44] which does not require dose reduction.

Conclusion

Anagliptin is thought to be a potent DPP-4 inhibitor demonstrating safety and tolerability in patients with type 2 diabetes. Treatment with anagliptin improves glycemic control for both monotherapy and combination therapy, and it is possible that anagliptin prevents atherosclerotic disease as well as diabetic

microangiopathy. However, there are too few reports of the effects of anagliptin. There is currently no data on the use of this drug for more than 1 year or the application of combination therapy with anagliptin and insulin. Additionally, the antiatherogenic effect of anagliptin was not supported by any comprehensive clinical data. Further investigation is therefore necessary to clarify the safety, efficacy, and patient acceptability of anagliptin in subjects with type 2 diabetes.

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Disclosure

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