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Fixed-dose combination of alogliptin/pioglitazone improves glycemic control in Japanese patients with type 2 diabetes mellitus independent of body mass index

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ABSTRACT

This study investigated the effects of switching from combination therapy with either alogliptin (Alo) or pioglitazone (Pio) to fixed-dose combination therapy (FDCT) with alogliptin and pioglitazone (Alo-Pio FDCT). The usefulness and efficacy of Alo-Pio FDCT were investigated. A total of 50 outpatients with type 2 diabetes mellitus (T2DM) treated with Alo and 47 outpatients with T2DM treated with Pio were switched to Alo-Pio FDCT, and its efficacy and usefulness were evaluated. Significant improvements were observed in hemoglobinA1c (HbA_{1c}), alanine transaminase (ALT), and γ-glutamyl transpeptidase (GGT) levels after switching to Alo-Pio FDCT for 16 weeks in both groups. Only the group switching from Alo to Alo-Pio FDCT showed significant improvements in high-density lipoprotein cholesterol (HDL) levels and triglyceride levels. In a multivariate logistic regression model of the variation in the change of HbA_{1c} at 16 weeks, ALT and GGT were independent predictors of the change of HbA_{1c} at 16 weeks. In addition, the switch to Alo-Pio FDCT improved glycemic control to a certain degree regardless of BMI. Switching from either Alo or Pio to Alo-PIO FDCT may, unlike monotherapy with a DPP-4 inhibitor, be effective for patients with T2DM regardless of whether they are obese or lean.

Key Words: type 2 diabetes mellitus, fixed-dose combination therapy, pioglitazone, dipeptidyl peptidase-4 inhibitor, alogliptin

INTRODUCTION

Dipeptidyl peptidase 4 (DPP-4) inhibitors are a new class of antihyperglycemic agents that are now available for the treatment of type 2 diabetes mellitus (T2DM).[1,2] We have reported that DPP-4 inhibitors seem to be less effective for T2DM with obesity and increased alanine transaminase (ALT) and γ-glutamyl transpeptidase (GGT) levels, representing a subset of patients who may have nonalcoholic fatty liver disease.[3,4] Furthermore, a previous study demonstrated that plasma DPP-4 activity is increased in obese patients.[5] In these cases, it is assumed that

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DPP-4 inhibitors might not show significant efficacy.

Meanwhile, pioglitazone (Pio), a peroxisome proliferator activated receptor γagonist, is known to reduce serum DPP-4 activity.[6] Combination therapy with a DPP-4 inhibitor plus pioglitazone can be a theoretically attractive combination. DPP-4 inhibitors improve β-cell function[7] and have been shown to increase β-cell mass in animal models,[8] whereas pioglitazone improves both peripheral and hepatic insulin resistance and preserves β-cell function.[9] Collectively, the use of alogliptin (Alo) in combination with pioglitazone instead of the single use of Alo or Pio raises the possibility of further effects in T2DM patients. Of note, Alo is the only currently available DPP-4 inhibitor available in fixed-dose combination therapy (FDCT) with Pio (Alo-Pio FDCT).[10] FDCT allows multiple medications, often with complementary mechanisms of action, to be given in a single formulation.[11] In recent years, FDCT was introduced in multiple drug classes and disease states, including T2DM.[12] Melilian *et al*. showed that glyburide-metformin FDCT increased subjects' medication adherence rates compared with dual therapy with the two agents.[12,13] Therefore, to switch to Alo-Pio FDCT from combination therapy with either Alo or Pio in T2DM might provide better clinical outcomes by ensuring good medication adherence rates.

The present study assessed the efficacy and tolerability of fixed-dose combination therapy with alogliptin (25 mg qd) and pioglitazone (15 mg qd) by switching obese and lean patients with T2DM who had been treated with either Alo or Pio to the fixed-dose combination. The independent predictors of the efficacy of Alo-Pio FDCT were also examined.

MATERIALS AND METHODS

Subjects

Ninety-seven outpatients with T2DM who had received combination therapy of anti hyperglycemic agent with either Alo or Pio for diabetes mellitus were enrolled. All patients had visited the outpatient clinic of Green Clinic. They were eligible to participate if they were >20 years old and had treatment with antihyperglycemic agents. Use of medications for hypertension or dyslipidemia was permitted. Exclusion criteria were as follows: type 1 diabetes mellitus, severe complications of diabetes, renal insufficiency (serum creatinine >1.5 mg/ dL in men or >1.3 mg/ dL in women), pregnant or nursing women, those who might be pregnant, alcoholism, and any patient whom the investigator judged to be inappropriate for this study.

Study design

A total of 47 T2DM patients (27 men and 20 women) were switched from 15 mg/day Pio to the fixed-dose combination of alogliptin 25 mg/pioglitazone 15 mg (Takeda Pharmaceutical Company, Osaka, Japan). In the other group, 50 T2DM patients (32 men and 18 women) were switched from 25 mg/day Alo to the fixed-dose combination of Alo 25 mg/Pio15 mg. Of these, all of 97 outpatients were completed following the current study protocol. Each group was followed for 16 weeks with monthly reviews. No changes were made to statins, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers during the study period to avoid possible influences on lipid profiles, and blood pressure. Furthermore, the dose of other oral antidiabetes drugs except for Alo or Pio did not change during the study periods and for at least 6 months before the study.

Venous blood samples were collected before switching to Alo-Pio FDCT and every 4 weeks until the end of the study.

All subjects were given an explanation of the details of this clinical study and provided their written, informed consent. This study was approved by the Ethics Committee of Dokkyo Medical

University (#28074, approved date: August, 12, 2016) and the local ethics committee of Green Clinic (approved date: May 28, 2013).

Statistical analysis

All statistical analyses were performed using GraphPad Prism version 6 for Mac (GraphPad Software, San Diego, CA) or Stat mate V (Nihon 3B Scientific Inc., Niigata, Japan). Data are presented as means ± standard deviation (SD). Differences between groups were analyzed by Student's paired or unpaired *t*-test. Differences in non-parametric data were analyzed using the Mann-Whitney U-test and Wilcoxon's matched pairs test. Univariate and multivariate logistic regression analyses were performed to assess whether each clinical marker was correlated with improvement in HbA1c (ΔHbA1c or change in HbA1c: after 4 months – before switching medication). Values of $p < 0.05$ were considered significant.

RESULTS

Patients' clinical data are shown in Table 1. There were no significant differences between groups in any clinical or biochemical parameter, including the number of patients in each group with hypertension, being treated for hypertension, with dyslipidaemia, or being treated for dyslipidaemia at baseline.

As shown in Table 2, HbA1c and fasting glucose levels were significantly improved after treatment with Alo-Pio FDCT ($p < 0.001$) in both groups. Blood pressure did not deteriorate. Regarding lipid profiles, significant changes were observed in the group of patients who switched from alogliptin to Alo-Pio FDCT, including increases in high-density lipoprotein cholesterol (HDL-C) and decreases in triglyceride (TG) and LDL-C levels. ALT and GGT levels were also significantly decreased after treatment with Alo-Pio FDCT in both groups. Regarding body weight increases with pioglitazone, although an increase was seen in the group of patients who switched from Alo to Alo-Pio FDCT (before, 71.7 ± 14.6 kg; after, 72.8 ± 15.2 kg; $p < 0.0001$), no significant increase was seen between before and after the switch for the overall group of 97 patients (before, 71.7 ± 13.8 kg; after, 72.1 ± 14.1 kg; $p = 0.5751$). Fig. 1 shows decreases over time in HbA1c after switching to Alo-Pio FDCT. The 97 patients were divided into three

Table 1 Baseline characteristics of the study subjects

	Pioglitazone→Alo-Pio FDCT	Alogliptin→Alo-Pio FDCT	P value
Age (years)	60.4 ± 10.4	58.4 ± 10.7	0.229
Sex (M/F)	27/20	32/18	0.41
Body mass index (kg/m^2)	27.5 ± 3.6	27.0 ± 4.7	0.349
Duration of diabetes (years)	13.6 ± 8.8	11.9 ± 6.8	0.286
Sulfonylurea (%)	21 (44.6)	19 (38)	0.504
Glinide (%)	9 (19.1)	7 (14.0)	0.495
Biguanide (%)	32 (68.1)	31 (62.0)	0.671
αGI (%)	12 (17.0)	8 (20.0)	0.072
ARBs (%)	24 (51.1)	32 (64.0)	0.197
Statins (%)	19 (40.4)	26 (52.0)	0.253

Data are means ± SD.
αGI, α-glucosidase inhibitors
ARBs, angiotensin II receptor blockers

Table 2 Changes in parameters after fixed-dose combination alogliptin/pioglitazone treatmen

	Pioglitazone→Alo-Pio FDCT (n=47)		P value	Alogliptin→Alo-Pio FDCT (n=50)		P value
	Baseline	16 weeks		Baseline	16 weeks	
HbA1c, % (NGSP) at admission	7.0 ± 0.9	6.4 ± 0.7	< 0.0001**	7.3 ± 1.0	6.4 ± 0.6	< 0.0001**
Non fasting glucose levels (mg/dL)	182.0 ± 61.3	143.2 ± 41.9	0.0001**	188.2 ± 81.9	142.0 ± 44.9	< 0.0001**
Systolic Blood pressure (mmHg)	128.0 ± 19.9	128.6 ± 16.9	0.8626	128.6 ± 16.9	129.0 ± 13.9	0.176*
Diastolic Blood pressure (mmHg)	71.9 ± 12.1	72.1 ± 10.8	0.9302	75.1 ± 13.9	74.1 ± 10.1	0.6502
Total cholesterol (mg/dL)	190.5 ± 33.3 (n=37)	181.6 ± 27.7 (n=37)	0.0339*	180.5 ± 35.6 (n=43)	182.4 ± 29.0 (n=43)	0.3811
HDL – cholesterol (mg/dL)	56.1 ± 12.5 (n=37)	56.1 ± 13.2 (n=37)	0.8631	48.4 ± 11.7 (n=43)	53.3 ± 12.7 (n=43)	0.0001**
LDL – cholesterol (mg/dL)	106.8 ± 31.8 (n=37)	98.3 ± 27.0 (n=37)	0.0488*	94.1 ± 34.8 (n=43)	103.2 ± 28.0 (n=43)	0.1353
Triglyceride (mg/dL)	144.6 ± 61.1 (n=37)	141.8 ± 77.2 (n=37)	0.8084	179.0 ± 96.4 (n=43)	144.2 ± 57.7 (n=43)	0.0015**
AST (U/L)	25.2 ± 10.0	23.5 ± 8.3	0.0604	28.7 ± 18.4	24.7 ± 9.5	0.0726
ALT (U/L)	28.5 ± 16.8	23.1 ± 12.9	< 0.0001**	35.0 ± 22.7	27.0 ± 14.9	0.0034**
GGT (U/L)	47.8 ± 53.0	38.7 ± 37.8	0.0154*	51.2 ± 43.7	35.1 ± 19.1	0.0019**
Weight (kg)	71.8 ± 13.1	71.4 ± 13.0	0.5751	71.7 ± 14.6	72.8 ± 15.2	0.0001**

Data are mean ± SD.
HbA1c, hemoglobin A1c; NGSP
HDL, high-density lipoprotein cholesterol
LDL, low-density lipoprotein cholesterol
AST, aspartate transferase
ALT, alanine transferase
GGT, glutamyltranspeptidase
*P value: <0.05, **P value: <0.01, comparison of respective data between baseline and after 16 weeks for each group

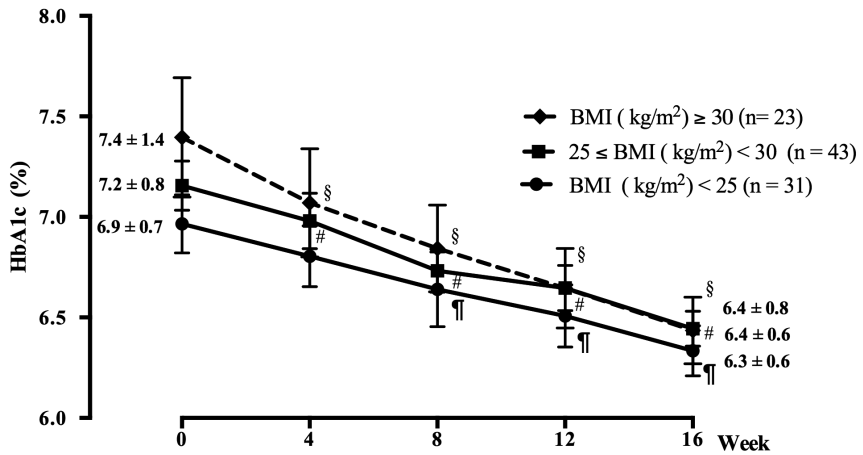

Fig. 1 The effect of Alo-Pio FDCT on changes in HbA1c from baseline to 16 weeks for each BMI subgroup
*#§P value: <0.05, comparison of respective data between baseline and after Alo-Pio FDCT treatment for each group

Table 3 Univariate and multivariate analyses of the association of each variable with improvement in HbA1c levels

Variable	Univariate		Multivariate	
	r	*P* value	*β*	*P* value
ΔNon fasting glucose levels per mg/dL	0.459	<0.001	0.00264	0.0096
ΔTotal cholesterol per mg/dL	0.058	0.612	---	---
ΔLDL – cholesterol per mg/dL	0.121	0.285	---	---
ΔHDL – cholesterol per mg/dL	–0.099	0.382	---	---
ΔTriglyceride per mg/dL	0.059	0.606	---	---
ΔAST per U/L	0.100	0.339	---	---
ΔALT per U/L	0.553	<0.001	0.01254	0.0299
ΔGGT per U/L	0.636	<0.001	0.01136	0.0001
ΔBody weight per kg	–0.700	<0.001	–0.05140	0.0699
R^2			0.720	

HDL, high-density lipoprotein cholesterol
LDL, low-density lipoprotein cholesterol
AST, aspartate transferase
ALT, alanine transferase
GGT, glutamyltranspeptidase

groups by body mass index (BMI): BMI < 25 kg/m^2 (n = 31), 25 ≤ BMI < 30 kg/m^2 (n = 43), and BMI ≥ 30 kg/m^2 (n = 23). Alo-Pio FDCT resulted in significant improvements in HbA1c in all groups, regardless of BMI.

To identify factors with an independent effect on ΔHbA1c in these T2DM patients, a stepwise regression analysis including significant variables was performed. ΔGGT (β = 0.01136, *P* = 0.0001) and ΔALT (β = 0.01254, *P* = 0.0299) were independent determinants of ΔHbA1c (Table 3).

DISCUSSION

People with T2DM are two to four times more likely to develop a serious cardiovascular outcome compared with those without T2DM.[14] It is believed that most of this increased risk is caused by a proatherothrombotic state (i.e. lipid abnormalities, hypertension, obesity, chronic vascular inflammation).

Pioglitazone stimulates the peroxisome proliferator-activated receptor gamma, signaling changes in hepatic, adipose, and skeletal muscle tissues.[15] Two large prospective studies have demonstrated that insulin resistance is a strong independent predictor of cardiovascular disease.[16,17] The PROactive study also demonstrated that pioglitazone significantly reduced the risk of subsequent myocardial infarction by 28%, acute coronary syndrome by 38%, and the chance of a second stroke by 48%.[14,18] Given the results of the PROactive study, it is certainly the relatively best drug in T2DM patients already presenting with cardiovascular disease such as stroke and myocardial infarction. Additionally, pioglitazone has been shown to increase HDL cholesterol, decrease fasting triglycerides, and decrease fasting plasma free fatty acids.[19] The current study also showed increased levels of HDL-C and decreased levels of TG and LDL-C by switching from alogliptin to Alo-Pio FDCT. These results also indicated that pioglitazone may suppress atherosclerosis, linked to its ability to increase HDL-C and decrease LDL-C levels.[20]

It has been reported that Alo-Pio FDCT improved fasting and postprandial glucose levels by addressing partly overlapping and complimentary core defects of T2DM, which are impairment of α, β-cell function, increased insulin sensitivity, and increased DPP-4 activity, and was well tolerated.[21] In the current study involving patients with T2DM using either alogliptin or pioglitazone, Alo-Pio FDCT enabled better glycemic control, regardless of BMI (Fig. 1). With respect to the reason for this effect, the current study also showed a positive correlation between the changes in HbA1c (ΔHbA1c) and ΔGGT or ΔALT in patients with T2DM and both factors were independent determinants of the efficacy of Alo-Pio FDCT in these patients (Table 3). These results indicated that alogliptin treatment may reduce hepatic glucose production by reducing glucagon levels and/or improve insulin secretion, while pioglitazone treatment improved fasting and postprandial insulin sensitivity and decreased visceral abdominal fat. McLaughlin *et al*. have also reported that pioglitazone treatment increased subcutaneous fat but decreased visceral abdominal fat.[22] Therefore, the fact that positive correlations were observed between ΔHbA1c and ΔGGT or ΔALT strongly suggests that there was a major improvement in glycemic control in patients in whom visceral fat decreased.Another advantage of combination therapy with DPP-4 inhibitors and pioglitazone is that side effects may be minimized. There are a number of critical side effects of pioglitazone, such as bone fractures,[23] increased risk of bladder cancer,[24] and the well-known water retention. Although the evidence on the association between pioglitazone use and bladder cancer is contradictory, the cumulative use of pioglitazone was not asscosiated with the incidence if bladder cancer in the large international analysis.[25,26] Further analysis are needed to fully resolve this controversy.

These side effects are mostly related to the dosage, so by combining with alogliptin, efficacy can be expected even with a low dose of pioglitazone. Additionally, combination therapy with DPP-4 inhibitors and pioglitazone may decrease the side effect of water retention because DPP-4 inhibitors diminish renal tubule sodium reabsorption.[27] In the present study, the increase in mean body weight was barely 1.1 kg for 16 weeks in the group switching from pioglitazone to Alo-Pio FDCT. No patients complained of edema.

It has been reported that fixed-dose combinations have the potential to improve compliance and reduce pill burden. Fixed-dose combinations might be considered in patients with T2DM to improve medication compliance, which can translate into better clinical outcomes.[28] No patients discontinued fixed-dose combinations after switching to Alo-Pio FDCT, and, in the present study as well, the usefulness of fixed-dose combinations may have had a positive effect on treatment efficacy.

The current study has several limitations. First, the number of subjects enrolled was relatively small, and the differences detected may have been found to be significant had more patients been included, especially regarding lipid profiles and blood pressure. Second, there was no control group, and a cross-over study design was not used. A large-scale clinical trial should be performed to confirm the results of this study in patients with T2DM.

In conclusion, the current study showed that Alo-Pio FDCT was effective in both obese and lean T2DM patients after switching from either alogliptin or pioglitazone. Alogliptin in fixed-dose combination with pioglitazone offers a welcome option for all T2DM patients and providers wishing to simplify complex medication regimens.

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AUTHOR DISCLOSURE STATEMENT

The authors declare that they have no competing interests.

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