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Efficacy and Tolerability of the DPP-4 Inhibitor Alogliptin Combined with Pioglitazone, in Metformin-Treated Patients with Type 2 Diabetes

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Context: Optimal management of type 2 diabetes remains an elusive goal. Combination therapy addressing the core defects of impaired insulin secretion and insulin resistance shows promise in maintaining glycemic control.

Objective: The aim of the study was to assess the efficacy and tolerability of alogliptin combined with pioglitazone in metformin-treated type 2 diabetic patients.

Design, Setting, and Patients: We conducted a multicenter, randomized, double-blind, placebo-controlled, parallel-arm study in patients with type 2 diabetes.

Interventions: The study consisted of 26-wk treatment with alogliptin (12.5 or 25 mg qd) alone or combined with pioglitazone (15, 30, or 45 mg qd) in 1554 patients on stable-dose metformin monotherapy (≥1500 mg) with inadequate glycemic control.

Main Outcome Measure: The primary endpoint was change in glycosylated hemoglobin (HbA_{1c}) from baseline to wk 26. Secondary endpoints included changes in fasting plasma glucose and β-cell function. Primary analyses compared pioglitazone therapy [all doses pooled, pioglitazone alone (Pio alone); n = 387] with alogliptin 12.5 mg plus any dose of pioglitazone (A12.5+P; n = 390) or alogliptin 25 mg plus any dose of pioglitazone (A25+P; n = 390).

Results: When added to metformin, the least squares mean change (LSMΔ) from baseline HbA_{1c} was $-0.9 \pm 0.05\%$ in the Pio-alone group and $-1.4 \pm 0.05\%$ in both the A12.5+P and A25+P groups ($P < 0.001$ for both comparisons). A12.5+P and A25+P produced greater reductions in fasting plasma glucose (LSM$\Delta = -2.5 \pm 0.1$ mmol/liter for both) than Pio alone (LSM$\Delta = -1.6 \pm 0.1$ mmol/liter; $P < 0.001$). A12.5+P and A25+P significantly improved measures of β-cell function (proinsulin:insulin and homeostasis model assessment of β-cell function) compared to Pio alone, but had no effect on homeostasis model assessment of insulin resistance. The LSMΔ body weight was 1.8 ± 0.2, 1.9 ± 0.2, and 1.5 ± 0.2 kg in A12.5+P, A25+P, and Pio-alone groups, respectively. Hypoglycemia was reported by 1.0, 1.5, and 2.1% of patients in the A12.5+P, A25+P, and Pio-alone groups, respectively.

Conclusions: In type 2 diabetic patients inadequately controlled by metformin, the reduction in HbA_{1c} by alogliptin and pioglitazone was additive. The decreases in HbA_{1c} with A12.5+P and A25+P were similar. All treatments were well tolerated. **(*J Clin Endocrinol Metab* 97: 0000–0000, 2012)**

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Abbreviations: A12.5 and A25, Alogliptin at doses of 12.5 and 25 mg; A12.5+P and A25+P, A12.5 and A25 plus any dose of pioglitazone; AE, adverse event; ANCOVA, analysis of covariance; BG, blood glucose; BMI, body mass index; DPP-4, dipeptidyl-peptidase-4; FPG, fasting plasma glucose; HbA_{1c}, glycosylated hemoglobin; HOMA-B, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; LSMΔ, least-squares mean change; OAD, oral antidiabetic drug; P15, P30, and P45, pioglitazone at doses of 15, 30 and 45 mg; PI:IRI, proinsulin-to-insulin ratio; Pio alone, pioglitazone alone; SAE, serious AE; TZD, thiazolidinedione.

Despite an increasing number of therapeutic options, optimal management of hyperglycemia in patients with type 2 diabetes remains an elusive goal for a majority of patients (1). Current treatment guidelines recommend a stepwise approach (2), beginning with lifestyle intervention and metformin, followed by sequential addition of basal insulin or other oral antidiabetic drugs (OAD). Impaired insulin secretion and insulin resistance are the core defects in type 2 diabetes and are present long before the onset of frank diabetes (3–6). Therefore, early intervention with a combination of OAD to target both pathogenic disturbances represents a rational therapeutic approach.

Combination therapy with a dipeptidyl peptidase-4 (DPP-4) inhibitor plus a thiazolidinedione (TZD) is theoretically an attractive combination. DPP-4 inhibitors improve both α- and β-cell function (7, 8) and have been shown to increase β-cell mass in animal models (9), whereas TZD reduce both peripheral and hepatic insulin resistance and, when given early in the course of disease, preserve β-cell function (10–12). DPP-4 inhibitors are effective and well tolerated when given in combination with TZD, whether given as add-on therapy (13, 14) or as initial combination therapy (15). However, the efficacy and tolerability of combination DPP-4 inhibitor/TZD therapy in patients inadequately controlled with metformin monotherapy have yet to be examined. This group represents a large proportion of type 2 diabetic patients (16).

The present study assesses the efficacy and tolerability of two dose levels of alogliptin (12.5 and 25 mg qd), a potent and selective DPP-4 inhibitor (6, 17, 18), combined with one of three doses of pioglitazone (15, 30, or 45 mg qd) in patients with type 2 diabetes inadequately controlled by metformin monotherapy [glycosylated hemoglobin (HbA_{1c}) = 7.5 to 10%].

Subjects and Methods

Study design

A 26-wk, multicenter, randomized, double-blind, placebo-controlled, parallel-arm study was conducted at 327 sites in 20 countries. The study contained 12 treatment groups and was performed in patients with type 2 diabetes inadequately controlled (HbA_{1c} = 7.5 to 10%, inclusive) on metformin 1500 mg/d or greater. Subjects taking any antidiabetic medication other than metformin were excluded. Subjects entered a 2-wk screening period followed by a 4-wk run-in/stabilization period, a 26-wk treatment period, an end-of-treatment visit, and a 2-wk follow-up period. Subjects receiving metformin (1000 mg/d) who had inadequate glycemic control (HbA_{1c} = 7.5 to 12%, inclusive) entered a 2-wk prescreening period, during which the metformin dose was increased to 1500 mg/d if tolerated. An optional 12-wk titration period ensued, followed by the protocol described above. During the run-in/stabilization period, eligible subjects were switched (open label) from their own metformin medication to an equivalent dose of immediate-release metformin formulation.

Following conclusion of the run-in/stabilization period, at baseline visit (d 1), eligible subjects were randomized in equal proportions to one of 12 treatment groups, with study drugs administered in a double-blind, double-dummy fashion. Randomization was balanced within the following stratification factors: HbA_{1c} at wk −1 (<9.0% *vs.* ≥9.0%), and geographic region, defined as follows—1) United States; 2) Mexico and Central and South America; 3) Western Europe, Australia, and New Zealand; and 4) the rest of world. Patients returned for eight additional visits, at wk 1, 2, 4, 8, 12, 16, 20, and 26. The individual treatment groups were: placebo, alogliptin at doses of 12.5 or 25 mg qd (A12.5 and A25), pioglitazone at doses of 15, 30, or 45 mg qd (P15, P30, and P45), the combinations of alogliptin 12.5 mg with 15, 30, or 45 mg pioglitazone (A12.5+P15, A12.5+P30, and A12.5+P45) and alogliptin 25 mg with 15, 30, or 45 mg pioglitazone (A25+P15, A25+P30, and A25+P45). All treatments were given in addition to a stabilized dose of metformin. The study design is illustrated in Supplemental Fig. 1 (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

Study population

The study enrolled male and female subjects [age, 18 to 80 yr; body mass index (BMI), 23 to 45 kg/m^2; fasting C-peptide, ≥0.26 nmol/liter] with diagnosed type 2 diabetes inadequately controlled by metformin monotherapy (stable metformin dose ≥1500 mg/d for ≥2 months). Females of childbearing potential were required to use medically approved birth control methods. Inclusion criteria included a systolic/diastolic blood pressure no greater than 160/100 mm Hg, hemoglobin of at least 12 g/dl for men and at least 10 g/dl for women, alanine aminotransferase no more than 2.5 times the upper limit of normal, TSH no greater than the upper limit of normal, serum creatinine below 133 μmol/liter (for men) or below 124 μmol/liter (for women), and the willingness and ability to perform self-monitoring of blood glucose (BG) and to provide written informed consent. After the run-in/stabilization period, subjects were required to have an HbA_{1c} of 7.5 to 10%, inclusive, and fasting plasma glucose (FPG) no greater than 16.7 mmol/liter. Exclusion criteria included oral or systemically injected glucocorticoids or weight-loss drugs within 3 months of randomization, urine albumin/creatinine ratio greater than 113 mg/mmol, history of laser treatment for proliferative retinopathy within 6 months, treated diabetic gastroparesis, history of New York Heart Association Class III or IV heart failure, cardiac surgery, or myocardial infarction within 6 months.

Study assessments

The primary endpoint was change in HbA_{1c} from baseline (d 1) to wk 26 or last observation, *i.e.* at the time of rescue therapy or at the time the patient was lost to follow-up. Secondary glycemic control endpoints included: 1) change in FPG from baseline to wk 26 or last observation; 2) changes in HbA_{1c} and FPG from baseline to each study visit (FPG was measured at each study visit; HbA_{1c} was measured at all visits except wk 1 and 2); 3) incidence of hyperglycemic rescue (>wk 1 but <wk 4—FPG ≥16.7 mmol/liter confirmed within 5 d; wk 4 but <wk 8—FPG ≥ 15.3 mmol/liter confirmed within 5 d; wk 8 but <wk 12—FPG ≥13.9 mmol/liter confirmed within 5 d; and wk 12 through end of treatment—

HbA_{1c} ≥8.5% and ≤0.5% decrease compared with baseline, confirmed within 5 d); and 4) incidence of wk 26 HbA_{1c} no greater than 7.0%. The medication employed in rescue therapy was left to the discretion of the treating physician. Prespecified subgroup efficacy analyses were stipulated based on gender, age group, BMI group, race, and ethnicity. Other secondary endpoints included changes from baseline in β-cell function [fasting proinsulin-to-insulin ratio (PI:IRI), homeostasis model assessment of β-cell function (HOMA-B)] and insulin resistance [homeostasis model assessment of insulin resistance (HOMA-IR)] and change in body weight from baseline to wk 26 or last observation.

All adverse events (AE) were recorded and judged by an investigator as to severity and possible relationship to study medication. Safety laboratory assessments (hematology and biochemistry) and vital signs were assessed at each study visit. Urinalyses and electrocardiograms were performed at baseline, wk 12, and wk 26. Mild-to-moderate hypoglycemia was defined as BG below 3.3 mmol/liter accompanied by symptoms or BG below 2.8 mmol/liter with or without symptoms. Severe hypoglycemia was defined as any episode requiring assistance of another person associated with documented BG below 3.3 mmol/liter, unless the clinical situation prevented obtaining BG measurement. Patients were provided diaries in which to record BG levels, symptoms, and any assistance received in association with any hypoglycemic events.

Data analysis

Changes from baseline in efficacy variables were analyzed using an analysis of covariance (ANCOVA) model with treatment and geographic region (defined as North America, Mexico, Central and South America, Western Europe, Australia/New Zealand, and rest of world) as class effects and baseline value and baseline metformin dose as continuous covariates (using SAS version 8.2; SAS Institute Inc., Cary, NC). Analyses were performed with the full analysis set, defined as all randomized patients who received at least one dose of double-blind study drug and who had a baseline assessment (defined as the last value before the first dose of study medication) and at least one post-baseline assessment, with last observation carried forward at the time of rescue therapy or at the time the subject was lost to follow-up. The primary analysis compared the least-squares mean change (LSMΔ) in HbA_{1c} from baseline to wk 26 in patients receiving alogliptin (25 mg qd) and any pioglitazone dose (A25+P) to that in patients receiving any dose of pioglitazone alone (Pio alone) at the 0.05 significance level using a contrast derived from the ANCOVA model (the contrast compared the average change across pioglitazone doses for the combination treatment groups with the average change across doses in patients receiving piolitazone alone). If this test was significant, the response in patients receiving alogliptin (12.5 mg qd) plus any pioglitazone dose (A12.5+P) was compared with the response in the Pio-alone group at the 0.05 significance level using a similar contrast. With this step-down strategy, no significance level adjustment was made for multiple comparisons (19).

As supportive analyses, each individual combination treatment group was compared with the alogliptin or pioglitazone therapy group using the same ANCOVA model at the 0.05 significance level with no adjustment for multiple comparisons (*e.g.* A12.5+P15 *vs.* A12.5+placebo and P15+placebo). Each individual combination treatment group was also compared with the placebo group (*i.e.* patients receiving both alogliptin placebo and pioglitazone placebo). This analytical approach was applied to all efficacy variables.

A total of 1440 subjects (120 per treatment group) were planned to be randomized into the study to achieve 95% power to detect a 0.3% difference (1.1% SD) between the HbA_{1c} response in the A25+P or A12.5+P group and that in the Pio-alone group at the two-sided 0.05 significance level. This sample size was also determined sufficient to detect a difference of approximately 0.46% for any pairwise comparison at the two-sided 0.05 significance level.

Ethics and good clinical practice

All patients provided written informed consent. The protocol was approved by the independent ethics committee/institutional review board at each study site. The study was conducted using Good Clinical Practice in accordance with the Declaration of Helsinki.

Results

A total of 1554 patients were randomized, and 1553 patients comprised the full analysis set. Table 1 summarizes the demographics, baseline characteristics, and disposition of all randomized patients. The groups were well balanced at baseline. Patients were predominantly white (71%), with almost half (48%) being of Hispanic or Latino ethnicity. The mean duration of diagnosed diabetes was 6.2 yr, and the mean metformin dose at baseline was 1887 mg/d.

More patients in the placebo group (41 of 129; 31.8%) required hyperglycemic rescue (defined in *Study assessments*) than in any active treatment group. The alogliptin and pioglitazone therapy groups had a higher percentage of patients requiring hyperglycemic rescue (8.5–14.7%) than any combination therapy (1.5–4.6%). Premature discontinuations (other than hyperglycemic rescue) showed no clear trend, ranging from eight of 130 (6.2%) receiving A12.5+P30 to 24 of 130 (18.5%) receiving pioglitazone (15 mg qd) therapy.

Efficacy

When combined with any dose of pioglitazone, both alogliptin doses resulted in reductions in HbA_{1c} and FPG that were sustained throughout the 26-wk treatment period and were greater than those elicited by pioglitazone therapy. The LSMΔ in HbA_{1c} from baseline to wk 26 was −0.9 ± 0.05% in the Pio-alone pooled group *vs.* −1.4 ± 0.05% in both A12.5+P and A25+P groups ($P < 0.001$ for either *vs.* Pio alone). The LSMΔ FPG was −1.6 ± 0.1 mmol/liter in patients receiving pioglitazone *vs.* −2.5 ± 0.1 mmol/liter in both the A12.5+P and A25+P pooled groups ($P < 0.001$ for either *vs.* Pio alone). The time courses for HbA_{1c} and FPG in the three pooled treatment

TABLE 1. Demographic, baseline characteristics, and disposition of patients (randomized population)

				Pioglitazone 15 mg		
	Placebo	Alogliptin		P15	P15+A	
Alogliptin (mg)	0	12.5	25	0	12.5	25
Pioglitazone (mg)	0	0	0	15	15	15
n	129	128	129	130	130	130
Age (yr)	55.2 ± 9.9	53.1 ± 9.6	53.7 ± 9.3	54.1 ± 9.5	53.6 ± 9.9	54.9 ± 9.2
Age <65 yr	106 (82.2)	116 (90.6)	112 (86.8)	113 (86.9)	109 (83.8)	112 (86.2)
Males	61 (47.3)	67 (52.3)	50 (38.8)	61 (46.9)	60 (46.2)	61 (46.9)
Race (%)						
White	72.1	69.5	62.0	65.4	73.1	73.8
Asian	3.9	10.9	11.6	8.5	6.9	5.4
African-American	6.2	4.7	3.9	6.2	3.1	2.3
All other	17.8	14.8	22.5	20.0	16.9	18.5
Hispanic/Latino ethnicity	63 (48.8)	60 (46.9)	63 (48.8)	63 (48.5)	55 (42.3)	57 (43.8)
BMI (kg/m^2)	30.6 ± 4.8	31.0 ± 5.1	31.5 ± 5.7	31.3 ± 5.3	31.5 ± 5.0	30.8 ± 4.7
Diabetes duration (yr)	6.0 ± 5.0	6.2 ± 5.6	5.6 ± 4.9	5.7 ± 4.8	6.1 ± 5.5	6.9 ± 5.5
Metformin dose (mg/d)	1937 ± 428	1902 ± 450	1851 ± 414	1893 ± 411	1910 ± 419	1880 ± 414
HbA_{1c} (%)[a]	8.5 ± 0.6	8.6 ± 0.7	8.6 ± 0.7	8.5 ± 0.7	8.5 ± 0.7	8.5 ± 0.7
FPG (mmol/liter)[a]	9.8 ± 2.6	10.2 ± 2.8	10.2 ± 2.7	9.8 ± 2.6	10.2 ± 2.7	10.0 ± 2.5
Disposition of patients						
Completed	70 (54.3)	97 (75.8)	101 (78.3)	93 (71.5)	115 (88.5)	110 (84.6)
Hyperglycemic rescue	41 (31.8)	18 (14.1)	16 (12.4)	13 (10.0)	6 (4.6)	5 (3.8)
Discontinued[b]	18 (14.0)	13 (10.2)	12 (9.3)	24 (18.5)	9 (6.9)	15 (11.5)

Data are expressed as number (percentage) or mean ± SD, unless otherwise specified.

[a] Full analysis set.

[b] Discontinuations excluding hyperglycemic rescue.

groups used in the primary efficacy analysis are depicted in Supplemental Fig. 2.

Figure 1 depicts changes from baseline in HbA_{1c} (Fig. 1A) and FPG (Fig. 1B) in the 12 individual treatment arms. Each individual combination therapy had significantly greater efficacy at lowering HbA_{1c} and FPG than treatment with either component alone. Maximum efficacy was seen in the A25+P45 group (LSMΔ HbA_{1c} = −1.6 ± 0.1%; LSMΔ FPG = −2.9 ± 0.2 mmol/liter). Dose-related efficacy of either alogliptin or pioglitazone was apparent for both HbA_{1c} and FPG. In combination, alogliptin and pioglitazone had additive efficacy.

The reduction in HbA_{1c} with the 12.5-mg dose of alogliptin was similar to 15 mg of pioglitazone, whereas the reduction in HbA_{1c} with the 25-mg dose of alogliptin was similar to 30 mg of pioglitazone and slightly less than with 45 mg of pioglitazone (Fig. 1).

In the pooled pioglitazone therapy group, the need for hyperglycemic rescue increased with treatment duration, whereas this was not the case for either A12.5+P or for A25+P. Over the 26-wk active treatment period, 43 of 376 (11.4%) patients receiving pioglitazone required rescue. This was significantly higher than in the A12.5+P group (15 of 382; 3.9%; $P = 0.005$) or the A25+P group (13 of 377; 3.4%; $P < 0.001$).

Subgroup and responder analyses

Larger HbA_{1c} decreases were observed in both pooled combination groups than in the pooled pioglitazone therapy group, regardless of baseline HbA_{1c} value, and the magnitude of response increased with increasing baseline HbA_{1c} level. In patients with baseline HbA_{1c} of at least 9.0% (mean baseline for each pooled treatment group = 9.4%), the LSMΔ in HbA_{1c} was −1.1% for pioglitazone (n = 90), −1.9% for A12.5+P (n = 103; $P < 0.001$ *vs.* pioglitazone), and −2.0% for A25+P (n = 105; $P < 0.001$ *vs.* pioglitazone). There were no differences in efficacy in any of the prespecified patient subgroups (based on sex, age, race, ethnicity, baseline BMI) for pioglitazone, A12.5+P, or A25+P. The most pronounced difference observed (0.34%) was for Δ HbA_{1c} in the A12.5+P subgroup of Hispanic/Latino ethnicity (mean Δ = −1.6%; n = 182) *vs.* non-Hispanic/Latino patients in the A12.5+P subgroup (mean Δ= −1.3%; n = 203).

The percentage of patients achieving any prespecified clinical response was significantly higher for both pooled combination therapy groups than for the pooled pioglitazone therapy group. For example, of patients receiving any pioglitazone dose (n = 387), 30.5% achieved HbA_{1c} no greater than 7.0%, whereas 54.6% of 390 patients in the A12.5+P group and 55.9% of 390 patients in the

TABLE 1. Continued

Pioglitazone 30 mg			Pioglitazone 45 mg			
P30	P30+A		P45	P45+A		Overall
0	12.5	25	0	12.5	25	
30	30	30	45	45	45	
129	130	130	129	130	130	1554
56.1 ± 9.4	55.0 ± 9.1	54.4 ± 9.7	54.5 ± 9.7	54.0 ± 9.8	54.2 ± 8.9	54.4 ± 9.5
101 (78.3)	111 (85.4)	107 (82.3)	112 (86.8)	111 (85.4)	112 (86.2)	1322 (85.1)
63 (48.8)	54 (41.5)	55 (42.3)	53 (41.1)	60 (46.2)	52 (40.0)	697 (44.9)
74.4	82.3	65.4	65.9	70.8	71.5	70.5
7.8	3.8	9.2	9.3	6.2	9.2	7.7
4.7	1.5	3.8	7.0	6.9	2.3	4.4
13.2	12.3	21.5	17.8	16.2	16.9	17.4
67 (51.9)	66 (50.8)	62 (47.7)	61 (47.3)	63 (48.5)	65 (50.0)	745 (47.9)
31.4 ± 5.4	31.1 ± 5.1	31.9 ± 5.6	30.7 ± 4.7	31.5 ± 5.2	30.6 ± 4.8	31.2 ± 5.1
7.6 ± 7.1	5.8 ± 5.1	6.6 ± 6.0	5.7 ± 4.2	6.6 ± 5.3	6.2 ± 5.0	6.2 ± 5.4
1854 ± 436	1822 ± 444	1867 ± 456	1919 ± 418	1920 ± 421	1885 ± 439	1887 ± 429
8.5 ± 0.7	8.5 ± 0.7	8.5 ± 0.7	8.5 ± 0.7	8.5 ± 0.7	8.6 ± 0.7	8.5 ± 0.7
9.7 ± 2.4	10.0 ± 2.6	9.9 ± 2.6	10.0 ± 3.0	9.7 ± 2.7	9.9 ± 2.5	10.0 ± 2.6
94 (72.9)	116 (89.2)	113 (86.9)	97 (75.2)	112 (86.2)	114 (87.7)	1232 (79.3)
19 (14.7)	6 (4.6)	6 (4.6)	11 (8.5)	3 (2.3)	2 (1.5)	146 (9.4)
16 (12.4)	8 (6.2)	11 (8.5)	21 (16.3)	15 (11.5)	14 (10.8)	176 (11.3)

A25+P group achieved HbA_{1c} no greater than 7.0% ($P < 0.001$ *vs.* Pio alone for both pooled combination groups).

β-Cell function, insulin sensitivity, and body weight

PI:IRI, HOMA-B, and HOMA-IR for the three pooled treatment groups are depicted in Fig. 2. At baseline, PI:IRI (Fig. 2A) averaged 0.320, 0.312, and 0.318 in patients randomized to pioglitazone, A12.5+P, and A25+P, respectively. PI:IRI decreased modestly in patients receiving pioglitazone therapy; however, in patients receiving A12.5+P and A25+P, the decrease was similar and significantly greater than with Pio alone. At baseline, HOMA-B (Fig. 2B) averaged 60.4, 52.6, and 53.5 in patients randomized to pioglitazone, A12.5+P, and A25+P, respectively. HOMA-B increased in patients receiving pioglitazone therapy. The increase in HOMA-B in patients receiving either A12.5 or A25 in addition to pioglitazone was significantly greater than that with Pio alone, and the effect appeared to be dose related. At baseline, HOMA-IR (Fig. 2C) averaged 6.2, 6.4, and 5.9 in patients randomized to pioglitazone, A12.5+P, and A25+P, respectively. HOMA-IR decreased substantially in all treatment groups, but neither combination dose had a significantly greater effect than Pio alone.

Changes from baseline in indices of β-cell function and insulin resistance in the 12 treatment arms are depicted in Supplemental Fig. 3. In general, alogliptin and pioglitazone had no additive effect to decrease PI:IRI and increase HOMA-B, whereas the effects of combination therapy on HOMA-IR were similar to that of Pio alone.

At baseline, mean body weight ranged from 81.6 to 85.6 kg in the 12 treatment groups. Body weight decreased slightly in patients receiving placebo (LSMΔ = −0.7 kg) or alogliptin (LSMΔ = −0.02 and −0.7 kg for A12.5 and A25, respectively), whereas there were modest but significant increases in body weight in all groups receiving pioglitazone. Alogliptin, when combined with pioglitazone, neither prevented nor exacerbated weight gain. The LSMΔ body weight for the pioglitazone pooled group was 1.5 ± 0.2 kg, which was not significantly different from the LSMΔ body weight in the A12.5+P (1.8 ± 0.2 kg) or A25+P (1.9 ± 0.2 kg) pooled treatment groups.

Tolerability and safety

In general, the combination of alogliptin and pioglitazone was well tolerated. The AE profile for the three pooled active treatment groups is summarized in Supplemental Table 1. The incidence of any treatment-emergent AE was similar across treatment groups. The incidence of any specific AE was low, and there were no differences among the treatment groups. In the system organ class of skin and sc tissue disorders, a similar percentage of patients in each pooled treatment group reported one or more AE (8.0, 7.7, and 8.2% for pioglitazone, A12.5+P, and A25+P, respectively). In the infections and infesta-

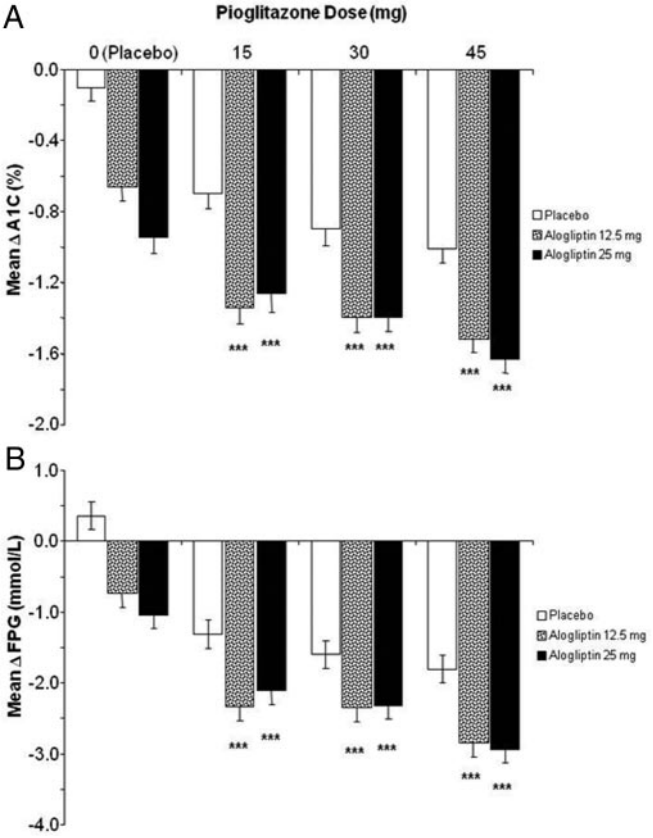

FIG. 1. LSMΔ (±SE) from baseline to last observation in HbA_{1c} (A) and FPG (B) in patients receiving placebo or increasing doses of pioglitazone (*open bars*), or pioglitazone in combination with A12.5 (*stippled bars*) or A25 (*closed bars*) (n = 122 to 130 patients per group). ***, $P \leq 0.001$ *vs.* both component therapies.

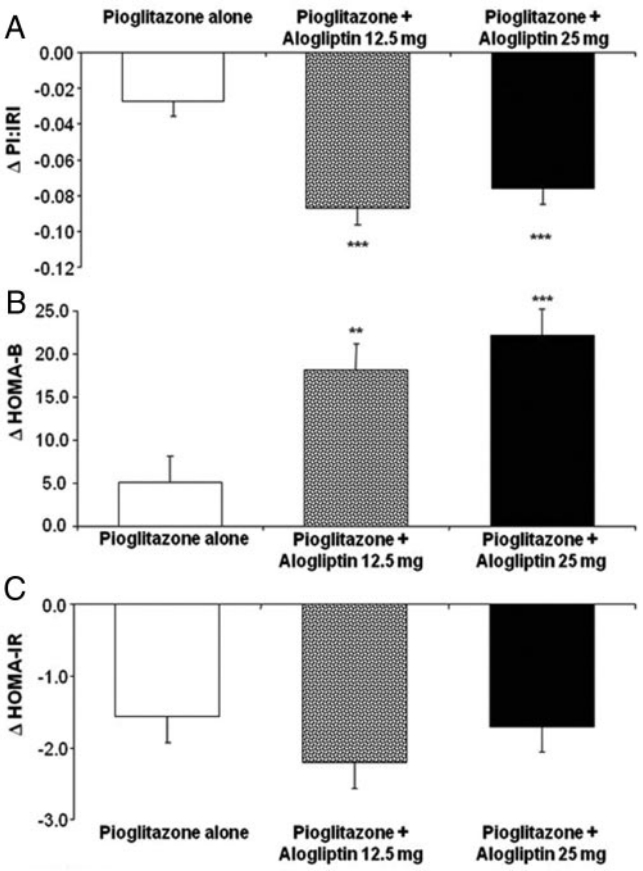

FIG. 2. LSMΔ (±SE) from baseline to last observation in fasting PI:IRI (A), HOMA-B (B) and HOMA-IR (C) (n ≥ 340 in each pooled group). **, $P < 0.01$; ***, $P < 0.001$, *vs.* Pio alone; for HOMA-IR, differences between either combination group and Pio alone were not statistically significant.

tions system organ class, a slightly higher percentage of patients in the A25+P group (30.8%) reported one or more AE than in the pioglitazone (26.6%) or A12.5+P (25.1%) groups. Weight increase was reported as an AE in 2.8, 1.8, and 2.3% of patients in the pioglitazone, A12.5+P, and A25+P groups, respectively. Peripheral edema was reported for 2.6, 2.6, and 3.6% of patients in these three groups, respectively.

The incidence of AE considered related to study medication was slightly higher in both combination groups than in the pioglitazone group. The incidences of discontinuation due to an AE and serious AE (SAE) were higher in the pooled pioglitazone therapy group than in one or both of the pooled combination groups. Nine SAE in eight subjects were considered by the investigator to be related to study medication. These SAE were one cerebrovascular accident (placebo group), one spontaneous abortion (A12.5), one episode of cholecystitis (A25), one case of hepatitis and one lower respiratory tract infection occurring coincidently in the same subject (P45), one episode of acute cholecystitis (A12.5+P15), one episode of gastritis (A12.5+P30), one incident of unstable angina (A12.5+P45), and one episode of pneumonia (A25+P30). One sudden cardiac death occurred on d 156 of treatment with pioglitazone 45 mg. This was not considered by the investigator to be related to the study drug.

Two cases of congestive cardiac failure were reported, neither in subjects receiving alogliptin: one subject in the P30 alone group (considered possibly related), and one subject in the P45 alone group (considered unrelated). No bone fractures related to study drug were observed.

During the 26-wk treatment period, hypoglycemia was uncommon. In the pooled pioglitazone therapy group, 17 hypoglycemic episodes (16 documented) were reported by eight patients (2.1%); two of these episodes, which occurred in two different patients, were severe. In the pooled A12.5+P group, 21 events (all documented) were reported by four patients (1.0%), and none of these were severe. In the pooled A25+P group, 15 events were reported by six patients (1.5%); one patient had three undocumented events, and one patient had one documented severe event.

There were no meaningful changes from baseline or between-treatment differences in serum chemistry, hematology, or urinalysis tests; physical examination findings; electrocardiograms; or vital signs during the study.

Discussion

In patients with inadequate glycemic control (HbA_{1c}, ~8.5%) on maximized metformin therapy, the addition of alogliptin to pioglitazone was well tolerated and produced clinically meaningful and statistically significant reductions in HbA_{1c} and FPG. When added to metformin, the combinations of alogliptin (12.5 or 25 mg qd) and pioglitazone (15, 30, or 45 mg qd) were significantly more effective than either component monotherapy. Relative to pioglitazone therapy, combination therapy was not associated with greater weight gain or increased incidence of hypoglycemia, AE, SAE, or discontinuations due to an AE. As expected, the better completion rate was due to reduced need for rescue therapy in patients receiving combination therapy.

These data are in general agreement with prior studies that have assessed the effects of DPP-4 inhibitors [alogliptin (20), sitagliptin (13), or vildagliptin (14)] added to ongoing pioglitazone therapy or given as initial combination therapy (15) in drug-naive patients with type 2 diabetes. In each of these earlier studies, as in the present study, a DPP-4 inhibitor provided additional efficacy of approximately 0.7% reduction in HbA_{1c} and a greater than 1 mmol/liter decrease in FPG compared with Pio alone. In these studies, combined DPP-4 inhibitor/pioglitazone therapy was well tolerated and allowed a substantial proportion of patients to achieve HbA_{1c} no greater than 7.0%. In the present study, this goal was achieved by approximately 55% of patients receiving the alogliptin/pioglitazone combination. This result compares favorably to the corresponding analyses for vildagliptin (36.4%) (14) or sitagliptin (45.4%) (13) added to ongoing pioglitazone treatment. The present responder rate approaches that reported for initial combination therapy with vildagliptin plus pioglitazone (65%) despite a longer disease duration (>6 yr *vs.* ~2 yr) (15), concomitant metformin treatment, and similar baseline HbA_{1c}. Taken together, these studies indicate that pioglitazone/DPP-4 inhibitor combination therapy adds meaningful efficacy compared with component therapy, with no apparent effect on safety or tolerability.

The efficacy of the DPP-4 inhibitor/TZD combination can be explained by the complementary mechanisms of action of the two agents. In the present study, alogliptin/pioglitazone groups had significantly improved β-cell function relative to pioglitazone therapy (decreased PI:IRI and an increased HOMA-B). HOMA-IR was similarly reduced in pioglitazone and combination treatment groups, suggesting that the DPP-4 inhibitor did not exert an insulin-sensitizing effect. These observations suggest that both alogliptin and pioglitazone contributed to improved β-cell function, whereas pioglitazone was responsible for the improved insulin sensitivity.

In the absence of pioglitazone, A25 demonstrated greater efficacy than A12.5. Both the A12.5 and A25 doses, when combined with pioglitazone, decreased FPG and HbA_{1c}, but no dose-response relationship was apparent. The difference in dose response may have been obscured by the addition of pioglitazone in patients already receiving maximized metformin therapy. However, no conclusions regarding dose response can be drawn because the 12-arm factorial design employed in this study was not intended to compare efficacy results between A12.5 and A25 in either the presence or absence of concomitant pioglitazone.

All treatments appeared safe and similarly well tolerated. Hypoglycemia was very uncommon and was less frequent in patients receiving combination therapy than in those receiving pioglitazone therapy. There is no evidence that the combination of alogliptin and pioglitazone increased the incidence of known or potential side effects of either component. Nonetheless, the present results suggest that the use of A25 combined with the maximal pioglitazone dose of 45 mg will not be necessary except in cases of uncontrolled glycemia.

Metformin is the currently recommended and most commonly used first-line OAD for type 2 diabetes. However, in patients initially achieving glycemic targets with metformin, additional therapy usually is necessary within 5 yr (21). The present results demonstrate that combination therapy with alogliptin plus pioglitazone achieves a degree of glycemic control not feasible with either single agent, without increasing the occurrence of hypoglycemia or other AE.

In view of the established effects of early treatment with pioglitazone to improve and maintain insulin sensitivity and β-cell function in prediabetic subjects (12), preclinical studies demonstrating the ability of DPP-4 inhibition to increase β-cell mass (9), and recent evidence that DPP-4 inhibitor treatment of patients with type 2 diabetes and mild hyperglycemia slows the deterioration of glycemic control (22), the present findings raise hope that even later intervention with the combination of a DPP-4 inhibitor and a TZD may allow long-term maintenance of good glycemic control.

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