Initial Combination Therapy With Alogliptin and Pioglitazone in Drug-Naïve Patients With Type 2 Diabetes

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OBJECTIVE — To assess the efficacy and tolerability of alogliptin plus pioglitazone for initial combination therapy in drug-naïve type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — This 26-week, double-blind, parallel-group study randomized 655 patients with inadequately controlled type 2 diabetes to four arms: 25 mg alogliptin (A25) q.d. monotherapy, 30 mg pioglitazone (P30) q.d. monotherapy, or 12.5 (A12.5) or 25 mg alogliptin q.d. plus pioglitazone (P30) q.d. combination therapy. Primary efficacy was A1C change from baseline with the high-dose combination (A25 + P30) versus each monotherapy.

RESULTS — Combination therapy with A25 + P30 resulted in greater reductions in A1C ($-1.7 \pm 0.1\%$ from an 8.8% mean baseline) vs. A25 ($-1.0 \pm 0.1\%$, $P < 0.001$) or P30 ($-1.2 \pm 0.1\%$, $P < 0.001$) and in fasting plasma glucose (-2.8 ± 0.2 mmol/l) vs. A25 (-1.4 ± 0.2 mmol/l, $P < 0.001$) or P30 (-2.1 ± 0.2 mmol/l, $P = 0.006$). The A25 + P30 safety profile was consistent with those of its component monotherapies.

CONCLUSIONS — Alogliptin plus pioglitazone combination treatment appears to be an efficacious initial therapeutic option for type 2 diabetes.

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Because the pathogenesis of type 2 diabetes involves defects in both insulin secretion and insulin action, simplified, well-tolerated, and durably effective combination therapies are being considered as potential standard initial treatment strategies to increase the likelihood of achieving sustained glycemic targets (1–3). Two drug classes that have complementary modes of action and may prove efficacious in combination are thiazolidinediones (TZDs), which are insulin sensitizers that increase peripheral glucose uptake, and dipeptidyl peptidase (DPP)-4 inhibitors, which augment pancreatic insulin secretion and also reduce hepatic glucose output through a suppressive effect on pancreatic glucagon secretion (4,5). This phase 3 study was conducted in drug-naïve patients with type 2 diabetes inadequately controlled with diet and exercise to evaluate the effects of initial combination therapy with the DPP-4 inhibitor alogliptin and the TZD pioglitazone versus either component used alone.

RESEARCH DESIGN AND METHODS

— Eligible subjects were drug-naïve (no current antihyperglycemic medication or ≤6 days of any such agent within 3 months of screening) men and women (aged 18–80 years, with type 2 diabetes, A1C 7.5–11%, BMI 23–45 kg/m^2) who had failed treatment with diet and exercise for ≥2 months prior to screening. Subjects were randomized to 26 weeks of once-daily treatment with 25 mg alogliptin (A25) monotherapy, 30 mg pioglitazone (P30) monotherapy, 12.5 mg alogliptin plus pioglitazone 30 mg (A12.5 + P30) combination therapy, or 25 mg alogliptin plus 30 mg pioglitazone (A25 + P30) combination therapy (see supplementary Fig. 1 in the online appendix, available at http://care.diabetesjournals.org/cgi/content/full/dc10-0159/DC1).

The primary efficacy end point was A1C change from baseline to week 26 or to study end in the intent-to-treat (ITT) population, with the last observation carried forward. Secondary glycemic control variables included A1C and fasting plasma glucose (FPG) changes from baseline at each study visit, percentage of patients achieving specific A1C goals, and frequency of glycemic rescue according to protocol when above the specific FPG or A1C values. Subgroup analyses by baseline A1C, sex, age-group, race, ethnicity, and baseline BMI were also performed.

Changes from baseline were analyzed using ANCOVA, with treatment and geographic region as class effects and baseline value as a continuous covariate. The primary analysis compared A25 + P30 with P30 and with A25, with a two-sided significance level of 0.05; if both comparisons were statistically significant, A12.5 + P30 was then compared with P30.

Adverse events (AEs) were recorded, and hypoglycemia was defined as blood glucose <3.3 mmol/l with symptoms suggesting low blood glucose or <2.8 mmol/l regardless of symptoms. Severe hypoglycemia was defined as any episode requiring assistance from another person.

RESULTS

— The study included 655 randomized patients, 654 of which comprised both the ITT and safety populations. Demographic and baseline characteristics were well balanced (51.1% female, 80.3% Caucasian, mean age ~53

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Table 1—*Results of glycemic control end points*

	25 mg alogliptin q.d.	30 mg pioglitazone HCl q.d.	12.5 mg alogliptin + 30 mg pioglitazone	25 mg alogliptin + 30 mg pioglitazone
n	164	163	163	164
Baseline values				
A1C (%)	8.80 ± 0.988	8.76 ± 1.005	8.85 ± 1.039	8.80 ± 0.962
FPG (mmol/l)	10.5 ± 2.84	10.5 ± 3.01	11.0 ± 3.34	10.2 ± 2.76
Changes from baseline at week 26				
A1C (%)	−0.96 ± 0.081	−1.15 ± 0.083	−1.56 ± 0.081*	−1.71 ± 0.081*†
A1C by baseline A1C subgroups				
<8.5%	−0.67 (*n* = 70)	−0.76 (*n* = 68)	−1.25 (*n* = 67)*	−1.20 (*n* = 63)*†
≥8.5%	−1.15 (*n* = 90)	−1.47 (*n* = 85)	−1.79 (*n* = 91)	−2.07 (*n* = 95)*†
<9.0%	−0.77 (*n* = 97)	−1.00 (*n* = 92)	−1.33 (*n* = 92)*	−1.30 (*n* = 93)*†
≥9.0%	−1.20 (*n* = 63)	−1.38 (*n* = 61)	−1.91 (*n* = 66)*	−2.30 (*n* = 65)*†
Clinical response, A1C				
≤6.5%	19 (11.6)	27 (16.6)	43 (26.4)*	45 (27.4)†
≤7.0%	40 (24.4)	55 (33.7)	87 (53.4)*	103 (62.8)*†
Reduction ≥1.0%	71 (43.3)	89 (54.6)	111 (68.1)	124 (75.6)*†
Reduction ≥2.0%	29 (17.7)	32 (19.6)	54 (33.1)*	56 (34.1)*†
FPG (mmol/l)	−1.4 ± 0.18	−2.1 ± 0.18	−2.7 ± 0.18*	−2.8 ± 0.18*†
Marked hyperglycemia	72/162 (44.4)	60/157 (38.2)	50/162 (30.9)	41/162 (25.3)*†
Hyperglycemic rescue	18/160 (11.3)	10/156 (6.4)	6/160 (3.8)	4/161 (2.5)†
Body weight (kg)	−0.29 ± 0.291	+2.19 ± 0.302	+2.51 ± 0.296	+3.14 ± 0.295*†

Data are least square mean changes ± SE (with *P* values from an ANCOVA model) or *n* (%) (with *P* values from extended Mantel-Haenszel tests comparing overall incidence between treatment groups). *$P < 0.05$ vs. 30 mg pioglitazone HCl alone; †$P < 0.05$ vs. 25 mg alogliptin alone.

years, BMI ~31 kg/m^2, diabetes duration ~3 years, baseline mean A1C 8.8%, and FPG 10.6 mmol/l).

More than 75% of each treatment group completed the study, with the highest percentage (82.9%) in the A25 + P30 group (see supplementary Fig. 2 in the online appendix). Fewer patients in the combination therapy groups required hyperglycemic rescue (3.7 and 2.4% with combination A12.5 + P30 and A25 + P30, respectively) than with either P30 (6.1%) or A25 (11.0%) monotherapy. Each treatment resulted in prompt and progressive reductions in A1C and FPG that were sustained throughout the 26 weeks (see supplementary Fig. 3*A* and *B* in the online appendix).

Combination therapy with A25 + P30 produced significantly larger reductions from baseline in A1C (−1.7%) and FPG (−2.8 mmol/l) than either component monotherapy (Table 1) (supplementary Fig. 3*C* and *D* in the online appendix). Furthermore, A12.5 + P30 resulted in significantly greater A1C and FPG changes from baseline versus P30. Overall, combination therapy was consistently more efficacious than either component monotherapy regardless of age, sex, race, ethnicity, or baseline BMI.

Both subgroups of patients with A1C <8.5 or ≥8.5% had significantly greater reductions in A1C with combination A25 + P30 than those observed with either monotherapy. As expected, those with baseline A1C ≥8.5% experienced greater reductions with A25 + P30 (−2.1%) than with A25 or P30 alone (−1.2 and −1.5%, respectively). Target A1C ≤7.0% was achieved by 24% of patients receiving A25, 34% with P30, 53% with A12.5 + P30 ($P < 0.001$ vs. P30), and 63% with A25 + P30 ($P < 0.001$ vs. either monotherapy). Body weight remained unchanged with A25 (−0.3 ± 0.3 kg) and increased with P30 (+2.2 ± 0.3 kg), A12.5 + P30 (+2.5 ± 0.3 kg), and A25 + P30 (+3.1 ± 0.3 kg; $P < 0.05$ vs. P30 and A25).

Incidence of AEs was lowest with A25 (54.9%) and highest with A25 + P30 (65.2%). Most frequent AEs were headache (all treatment groups), back pain and urinary tract infection (A25 + P30), and peripheral edema (P30). Incidence of study drug–related AEs, as judged by the investigators, was lowest with A25 (13.4%) and highest with A25 + P30 (21.3%). Discontinuations because of AEs were least frequent with A25 (1.8%) and most frequent with P30 (4.3%). One serious AE (SAE) occurred with A25 and one with A12.5+P30, whereas six SAEs (3.7%) occurred with P30 and eight SAEs (4.9%) with A25 + P30. No congestive heart failure or bone fracture events were reported. Hypoglycemia was uncommon, with the highest incidence of mild hypoglycemia in the A25 + P30 group (five patients [3.0%]), and there were no reports of severe hypoglycemia.

CONCLUSIONS — Initial combination therapy with the DPP-4 inhibitor alogliptin (25 mg) plus the TZD pioglitazone (30 mg) once daily for 26 weeks significantly improved glycemic control relative to monotherapy with either component in patients with type 2 diabetes inadequately controlled with lifestyle interventions. Despite a relatively high baseline A1C, this treatment strategy allowed nearly two-thirds of the patients to achieve A1C ≤7.0%. The safety profiles of alogliptin and pioglitazone administered together or separately were generally consistent with those previously reported for these two drug classes individually (6,7).

In summary, initial combination treatment with alogliptin and pioglitazone appears to be safe and was highly effective in short-term exposure and may be considered as an initial therapeutic option for type 2 diabetic patients not achieving adequate glycemic control with lifestyle changes alone or in those who cannot tolerate metformin therapy.

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