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

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Objective—To assess efficacy and tolerability of alogliptin plus pioglitazone for initial combination therapy in drug-naïve type 2 diabetes 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: alogliptin 25 mg qd monotherapy, pioglitazone 30 mg qd monotherapy, or alogliptin (A12.5 or A25 mg qd) plus pioglitazone (P30 mg qd) combination therapy. Primary efficacy was HbA1c change from baseline with the high-dose combination (A25+P30) versus each monotherapy.

Results—Combination therapy with A25+P30 resulted in greater reductions in HbA1c (-1.7±0.1% from an 8.8% mean baseline) versus A25 (-1.0±0.1%, P<0.001) or P30 (-1.2±0.1%, P<0.001) and in FPG (-2.8±0.2 mmol/L) versus 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.

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), 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.

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 to 80 years, with type 2 diabetes, HbA1c 7.5%-11%, BMI 23-45 kg/m², 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: alogliptin 25 mg (A25) monotherapy; pioglitazone 30 mg (P30) monotherapy; alogliptin 12.5 mg plus pioglitazone 30 mg (A12.5+P30) combination therapy; or alogliptin 25 mg plus pioglitazone 30 mg (A25+P30) combination therapy. (See Supplementary Figure 1 in the online appendix at http://care.diabetesjournals.org.)

The primary efficacy endpoint was HbA1c change from baseline to week 26 or to study-end in the intent-to-treat (ITT) population with last observation carried forward (LOCF). Secondary glycemic control variables included HbA1c and FPG changes from baseline at each study visit, percentage of patients achieving specific HbA1c goals, and frequency of glycemic rescue according
to protocol when above specific FPG or HbA1c values. Subgroup analyses by baseline HbA1c, gender, 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 to P30 and to A25, with a two-sided significance level of 0.05; if both comparisons were statistically significant, A12.5+P30 was then compared to 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 years, BMI ~31 kg/m², diabetes duration ~3 years, baseline mean HbA1c 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 Figure 2 in the online appendix). Fewer patients in the combination therapy groups required hypoglycemic 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 HbA1c and FPG that were sustained throughout the 26 weeks (see Supplementary Figure 3a and b in the online appendix).

Combination therapy with A25+P30 produced significantly larger reductions from baseline in HbA1c (-1.7%) and FPG (-2.8 mmol/L) than either component monotherapy (Table 1 and Supplementary Figure 3c and d in the online appendix). Furthermore, A12.5+P30 resulted in significantly greater HbA1c and FPG changes from baseline versus P30. Overall, combination therapy was consistently more efficacious than either component monotherapy regardless of age, gender, race, ethnicity, or baseline BMI.

Both subgroups of patients with HbA1c <8.5% or ≥8.5% had significantly greater reductions with combination A25+P30 in HbA1c than those observed with either monotherapy. As expected those with baseline HbA1c >8.5% experienced greater reductions with A25+P30 (-2.1 %) than with A25 or P30 alone (-1.2% and –1.5%; respectively). Target HbA1c ≤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 SAE occurred with A25 and 1 with A12.5+P30, while 6 SAEs (3.7%) occurred with P30, and 8 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
Alogliptin/pioglitazone initial combination therapy

A25+P30 group (5 patients [3.0%]), and 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 HbA1c, this treatment strategy allowed nearly 2/3 of the patients to achieve HbA1c ≤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 diabetes patients not achieving adequate glycemic control with lifestyle changes alone or in those who cannot tolerate metformin therapy.

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compared with component monotherapy in patients with type 2 diabetes. Diabetes Obes Metab 2007;9:175-185


Table 1— Results of glycemic control end points

<table>
<thead>
<tr>
<th>Alogliptin 25 mg qd</th>
<th>Pioglitazone HCl 30 mg qd</th>
<th>Alo 12.5 + Pio 30</th>
<th>Alo 25 + Pio 30</th>
</tr>
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<tbody>
<tr>
<td>N = 164</td>
<td>N = 163</td>
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<td>N = 164</td>
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</table>

Baseline Values, mean ± SD

<table>
<thead>
<tr>
<th></th>
<th>Alogliptin 25 mg qd</th>
<th>Pioglitazone HCl 30 mg qd</th>
<th>Alo 12.5 + Pio 30</th>
<th>Alo 25 + Pio 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>8.80 ± 0.988</td>
<td>8.76 ± 1.005</td>
<td>8.85 ± 1.039</td>
<td>8.80 ± 0.962</td>
</tr>
<tr>
<td>FPG (mmol/L)</td>
<td>10.5 ± 2.84</td>
<td>10.5 ± 3.01</td>
<td>11.0 ± 3.34</td>
<td>10.2 ± 2.76</td>
</tr>
</tbody>
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Changes from Baseline at Week 26 (a)

<table>
<thead>
<tr>
<th></th>
<th>Alogliptin 25 mg qd</th>
<th>Pioglitazone HCl 30 mg qd</th>
<th>Alo 12.5 + Pio 30</th>
<th>Alo 25 + Pio 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>-0.96 ± 0.081</td>
<td>-1.15 ± 0.083</td>
<td>-1.56 ± 0.081*</td>
<td>-1.71 ± 0.081*†</td>
</tr>
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| HbA1c by baseline HbA1c 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, HbA1c:
  ≤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†  |

(a) Results shown 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 P30 alone.
†P<0.05 vs A25 alone.