Efficacy and Safety of the Dipeptidyl Peptidase-4 Inhibitor Alogliptin in Patients With Type 2 Diabetes and Inadequate Glycemic Control

A randomized, double-blind, placebo-controlled study

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OBJECTIVE — To evaluate the dipeptidyl peptidase-4 (DPP-4) inhibitor alogliptin in drug-naïve patients with inadequately controlled type 2 diabetes.

RESEARCH DESIGN AND METHODS — This double-blind, placebo-controlled, multicenter study included 329 patients with poorly controlled diabetes randomized to once-daily treatment with 12.5 mg alogliptin ($n = 133$), 25 mg alogliptin ($n = 131$), or placebo ($n = 65$) for 26 weeks. Primary efficacy end point was mean change from baseline in A1C at the final visit.

RESULTS — At week 26, mean change in A1C was significantly greater ($P < 0.001$) for 12.5 mg (−0.56%) and 25 mg (−0.59%) alogliptin than placebo (−0.02%). Reductions in fasting plasma glucose were also greater ($P < 0.001$) in alogliptin-treated patients than in those receiving placebo. Overall, incidences of adverse events (67.4–70.3%) and hypoglycemia (1.5–3.0%) were similar across treatment groups.

CONCLUSIONS — Alogliptin monotherapy was well tolerated and significantly improved glycemic control in patients with type 2 diabetes, without raising the incidence of hypoglycemia.

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Inhibition of dipeptidyl peptidase-4 (DPP-4) increases the concentration of glucagon-like peptide-1, an incretin hormone that stimulates glucose-dependent insulin release, suppresses glucagon production, slows gastric emptying, reduces appetite, and may promote preservation of β-cell function in patients with type 2 diabetes (1). Alogliptin is a novel, high-affinity, high-specificity DPP-4 inhibitor that produces rapid and sustained DPP-4 inhibition and significantly reduces postprandial plasma glucose concentrations in patients with type 2 diabetes (2,3). A phase-three study was conducted to evaluate the efficacy and safety of alogliptin in adults with type 2 diabetes that was inadequately controlled with diet and exercise.

RESEARCH DESIGN AND METHODS

— Eligible patients were treatment-naïve (i.e., no current antidiabetes therapy and <7 days of therapy in the past 3 months) men and women, aged 18–80 years, with type 2 diabetes. Key inclusion criteria included A1C 7–10%, BMI 23–45 kg/m^2, treatment with diet and exercise for ≥1 month, and systolic/diastolic blood pressure ≤180/≤110 mmHg. Patients received counseling on diet and exercise. Patients who completed a 4-week, single-blind run-in period with fasting plasma glucose (FPG) <275 mg/ml (15.27 mmol/l) and ≥75% compliance (by tablet count) were randomized (2:2:1) to 26 weeks of double-blind treatment with 12.5 mg alogliptin, 25 mg alogliptin, or placebo taken once daily before the first meal. Additional antidiabetes agents were prohibited.

Efficacy assessments included all randomized patients who received the double-blind study drug. The primary end point was mean change from baseline in A1C at week 26. Other efficacy measures included changes in FPG, clinical response rates, incidences of marked hyperglycemia (FPG ≥200 mg/dl [11.10 mmol/l]) and hyperglycemic rescue, and changes in body weight. Exploratory end points included changes in measures of pancreatic function (fasting insulin, fasting proinsulin, and homeostasis model assessment of β-cell function) and lipid profiles. Treatment group differences for the primary end point were analyzed through ANCOVA, with treatment and geographic region as variables and baseline A1C and diabetes duration as covariates. The last observation carried forward method was used for imputing missing data; testing was two-sided at a significance level of 0.05. Continuous secondary efficacy analyses were performed as for the primary analysis, except that the baseline covariate corresponds with the tested end point. Incidence variables were compared using nonparametric, extended Mantel-Haenszel X^2 tests; covariates were the same as for the primary end point.

The safety population included patients who took at least one dose of the study drug (double blind). Safety assessments included adverse events, clinical laboratory findings, 12-lead electrocar-

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Table 1—*Results of secondary efficacy end points and exploratory assessments*

Parameter	Placebo	12.5 mg Alogliptin	*P* (vs. placebo)	25 mg Alogliptin	*P* (vs. placebo)
n	64	133	—	131	—
A1C (%)					
≤6.5%	7 (10.9)	23 (17.3)	0.818	27 (20.6)	0.294
≤7.0%	15 (23.4)	63 (47.4)	0.001	58 (44.3)	0.008
Reduction ≥0.5%	19 (29.7)	67 (50.4)	0.005	72 (55.0)	<0.001
Reduction ≥1.0%	7 (10.9)	38 (28.6)	0.003	39 (29.8)	<0.001
FPG	11.3 ± 5.24	−10.3 ± 3.6	<0.001	−16.4 ± 3.7	<0.001
Hyperglycemic rescue	19 (29.7)	13 (9.8)	0.001	10 (7.6)	<0.001
Marked hyperglycemia	30 (46.9)	44 (33.1)	0.110	33 (25.4)	0.005
Body weight (kg)	0.18 ± 0.37	−0.09 ± 0.26	0.539	−0.22 ± 0.26	0.379
Proinsulin-to-insulin ratio	0.046 ± 0.022	−0.040 ± 0.015	0.001	−0.038 ± 0.015	0.002
HOMA-B	−0.26 ± 5.98	7.53 ± 3.99	0.279	9.70 ± 4.08	0.172
Total cholesterol (mg/d)l	10.1 ± 3.3	−1.2 ± 2.3	0.006	−3.9 ± 2.3	<0.001
HDL cholesterol (mg/dl)	1.3 ± 0.9	0.9 ± 0.6	0.724	0.4 ± 0.6	0.417
LDL cholesterol (mg/dl)	4.6 ± 3.0	−0.5 ± 2.1	0.169	−0.4 ± 2.1	0.178
Triglycerides (mg/dl)	26.5 ± 14.8	−5.8 ± 10.2	0.074	−17.8 ± 10.4	0.015

Data are *n* (%) or change in least-squares means ± SE unless otherwise indicated. *HOMA-B, homeostasis model of assessment of β-cell function.

diograms, physical examination findings, vital signs, and hypoglycemic events. Skin and digits were specifically examined because of lesions previously observed in monkeys given DPP-4 inhibitors other than alogliptin (4–6). Safety findings were summarized with descriptive statistics.

RESULTS — Of 420 patients enrolled (see online appendix, available at http://dx.doi.org/10.2337/dc08-1035), 329 were randomized to double-blind treatment. Baseline characteristics were similar among treatment groups. Participants had a mean ± SD age of 53.4 ± 11.1 years and baseline A1C 7.9 ± 0.08% and were predominantly male (53.2%) and white (66.9%).

Mean A1C decreased significantly more with 12.5 mg (−0.56%; $P < 0.001$) or 25 mg (−0.59%; $P < 0.001$) alogliptin than with placebo (−0.02%) by week 26. Significant A1C reductions were observed as early as week 4 ($P < 0.001$). FPG reductions were significantly greater with alogliptin than with placebo at week 26 ($P < 0.001$) and as early as week 1 ($P \leq 0.002$). The percentage of patients who required hyperglycemic rescue was significantly less with alogliptin (12.5 mg, 9.8%; 25 mg, 7.6%; $P \leq 0.001$) than with placebo (29.7%). Minor reductions in weight with alogliptin were neither clinically nor statistically significant relative to placebo. Results for secondary efficacy measures and exploratory assessments are summarized in Table 1.

Overall incidences of adverse events (67.4–70.3%) and proportions of patients who discontinued because of adverse events (1.5–2.3%) were similar across treatment groups. Most adverse events were mild or moderate in intensity. Serious adverse events occurred without relation to dose (12.5 mg, 3.8%; 25 mg, 0.8%; and placebo, 3.1%) and were considered unrelated to treatment. No patient died during the study. Adverse events from the most commonly observed categories occurred with similar or lower frequency in those given alogliptin versus placebo (infection, 28.0–37.6%; gastrointestinal, 12.1–14.3%). Headache occurred more frequently with alogliptin (6.8–7.5%) than with placebo (4.7%). Despite increased surveillance for skin-related adverse events, their overall incidence remained low (12.5%), albeit higher with alogliptin (12.8–15.2%) than with placebo (6.3%), mostly because of pruritic events. Two patients discontinued because of skin-related adverse events: one adverse event was considered possibly related to the study drug (25 mg, moderate subcorneal pustular dermatosis); the other was judged unrelated to the study drug (12.5 mg, moderate exacerbation of contact dermatitis). No skin lesions resembling those noted in nonclinical studies of other DPP-4 inhibitors were observed. Hypoglycemia was rare (1.5–3.0%), and no hypoglycemic event was considered an adverse event or was severe enough to require assistance. No clinically meaningful changes in laboratory test results, vital sign measurements, or electrocardiogram recordings were observed.

CONCLUSIONS — Alogliptin monotherapy administered for 26 weeks to treatment-naïve patients with type 2 diabetes produced significant and clinically meaningful improvements in A1C. Glycemic improvements with alogliptin were rapid, sustained, and independent of age, race, and sex. Alogliptin treatment was well tolerated and was not associated with treatment-related serious adverse events. A low incidence of hypoglycemia occurred with alogliptin and with placebo.

Weight gain is common among patients taking sulfonylureas and thiazolidinediones and may reduce treatment adherence (7,8); thus, the weight neutrality of alogliptin and other DPP-4 inhibitors may offer a therapeutic advantage (9–15). Increases in the proinsulin-to-insulin ratio with alogliptin versus placebo and a trend toward increased homeostasis model assessment of β-cell function suggest that alogliptin, similarly to other DPP-4 inhibitors (9–11,14, 15), may modestly improve pancreatic function.

In summary, the efficacy and safety of alogliptin monotherapy were comparable with those of other DPP-4 inhibitors (9–15). Alogliptin represents an effective treatment option whether given alone or in combination with antihyperglycemic agents from other classes.

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