Once- and Twice-Daily Dosing With Rosiglitazone Improves Glycemic Control in Patients With Type 2 Diabetes

LAWRENCE S. PHILLIPS, MD
GEORGE GRUNBERGER, MD
ELIZABETH MILLER, RN, BA
RITA PATWARDHAN, PHD
ELIZABETH B. RAPPAPORT, MD
ALAN SALZMAN, MD, PHD
FOR THE ROSIGLITAZONE CLINICAL TRIALS STUDY GROUP

OBJECTIVE — To determine the efficacy of rosiglitazone compared with placebo in reducing hyperglycemia.

RESEARCH DESIGN AND METHODS — After a 4-week placebo run-in period, 959 patients were randomized to placebo or rosiglitazone (total daily dose 4 or 8 mg) for 26 weeks. The primary measure of efficacy was change in the HbA_{1c} concentration.

RESULTS — Rosiglitazone produced dosage-dependent reductions in HbA_{1c} of 0.8, 0.9, 1.1, and 1.5% in the 4 mg o.d., 2 mg b.i.d., 8 mg o.d., and 4 mg b.i.d. groups, respectively, compared with placebo. Clinically significant decreases from baseline in HbA_{1c} were observed in drug-naive patients at all rosiglitazone doses and in patients previously treated with oral monotherapy at rosiglitazone 8 mg o.d. and 4 mg b.i.d. Clinically significant decreases from baseline in HbA_{1c} were also observed with rosiglitazone 4 mg b.i.d. in patients previously treated with combination oral therapy. Approximately 33% of drug-naive patients treated with rosiglitazone achieved $HbA_{1c} \leq 7\%$ at study end. The proportions of patients with at least one adverse event were comparable among the rosiglitazone and placebo groups. There was no evidence of hepatotoxicity in any treatment group. There were statistically significant increases in weight and serum lipids in all rosiglitazone treatment groups compared with placebo. For LDL and HDL cholesterol, the observed increase appeared to be dose related.

CONCLUSIONS — Rosiglitazone at total daily doses of 4 and 8 mg significantly improved glycemic control in patients with type 2 diabetes and was well tolerated.

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Type 2 diabetes is often characterized by hyperglycemia as a result of increased insulin resistance in hepatic/peripheral tissues and pancreatic β-cell dysfunction (1–3). Improved glycemic control is associated with reductions in long-term microvascular complications (4) and improved survival rates (5). However, monotherapy with sulfonylureas or metformin is often insufficient to sustain glycemic control, indicating a need for additional therapeutic agents (6).

Thiazolidinediones, a new class of oral antidiabetic agents, reduce hyperglycemia by decreasing insulin resistance in peripheral tissues (3,7). They act by binding to the peroxisome proliferator–activated receptor-γ (PPAR-γ) (8) and altering expression of components that influence insulin signaling and glucose transport systems (3). Rosiglitazone is a potent member of the thiazolidinedione class, with a binding affinity for PPAR-γ that is ~100-fold greater than that of pioglitazone and 190-fold greater than that of troglitazone (9).

The primary objectives of this study were to examine the efficacy of rosiglitazone in reducing HbA_{1c} and to evaluate the therapeutic equivalence of once-daily and twice-daily dosing regimens.

RESEARCH DESIGN AND METHODS

Study design

The efficacy of rosiglitazone was assessed in a multicenter double-blind randomized placebo-controlled trial in 65 centers in the U.S. Oral antihyperglycemic agents were discontinued at least 14 days before a 4-week placebo run-in period. Patients were then randomly assigned to receive placebo or rosiglitazone 4 mg o.d., 2 mg b.i.d., 8 mg o.d., or 4 mg b.i.d. for 26 weeks. The study was conducted in accordance with the Declaration of Helsinki (as amended in 1989), Title 21 of the U.S. Code of Federal Regulations, and Good Clinical Practice guidelines. Each center's institutional review board approved the protocol, and the subjects gave written informed consent.

Patients

Eligibility requirements included the following: age 40–80 years, BMI 22–38 kg/m^2, type 2 diabetes as defined by the National Diabetes Data Group (10), fasting plasma glucose 7.8–16.7 mmol/l (140–300 mg/dl), and fasting C-peptide ≥0.27 nmol/l (≥0.8 ng/ml) at the time of screening. Patients with clinically significant renal disease, New York Heart Association (NYHA) class III/IV coronary insufficiency or congestive heart failure, symptomatic

From the Division of Endocrinology (L.S.P.), Emory University School of Medicine, Atlanta, Georgia; the Center for Molecular Medicine and Genetics and the Department of Internal Medicine (G.G.), Wayne State University, Detroit, Michigan; and SmithKline Beecham Pharmaceuticals (E.M., R.P., E.B.R., A.S.), Collegeville, Pennsylvania.

Address correspondence and reprint requests to Lawrence S. Phillips, MD, Division of Endocrinology, Emory University School of Medicine, 1639 Pierce Dr., 1301 Woodruff Memorial Bldg., Atlanta, GA 30322. E-mail: medlsp@emory.edu.

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Abbreviations: ALT, alanine aminotransferase; HOMA, homeostasis model assessment; PPAR-γ, peroxisome proliferator–activated receptor-γ.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline characteristics (intent-to-treat population)*

	Treatment group				
	Placebo	RSG 4 mg o.d.	RSG 2 mg b.i.d.	RSG 8 mg o.d.	RSG 4 mg b.i.d.
n	173	181	186	181	187
Age (years)	57.7 ± 9.2	57.5 ± 9.9	56.8 ± 9.4	58.9 ± 9.9	56.5 ± 9.7
Sex					
Male	119 (68.8)	106 (58.6)	110 (59.1)	119 (65.7)	122 (65.2)
Female	54 (31.2)	75 (41.4)	76 (40.9)	62 (34.3)	65 (34.8)
Race					
White	137 (79.2)	138 (76.2)	145 (78.0)	145 (80.1)	133 (71.1)
Black	16 (9.2)	23 (12.7)	15 (8.1)	13 (7.2)	20 (10.7)
Other	20 (11.6)	20 (11.0)	26 (14.0)	23 (12.7)	34 (18.2)
Previous treatment					
Diet only	39 (22.5)	40 (22.1)	46 (24.7)	53 (29.3)	47 (25.1)
Oral monotherapy	107 (61.8)	111 (61.3)	104 (55.9)	99 (54.7)	121 (64.7)
Oral combination therapy	27 (15.6)	30 (16.6)	36 (19.4)	29 (16.0)	19 (10.2)
BMI (kg/m^2)	29.1 ± 4.2	29.9 ± 4.1	30.0 ± 4.2	30.0 ± 4.3	29.9 ± 4.3
Baseline HbA_{1c} (%)	8.9 ± 1.5	8.9 ± 1.6	8.9 ± 1.5	8.9 ± 1.5	9.0 ± 1.5
Baseline fasting plasma glucose (mmol/l)	12.5 ± 3.2	12.7 ± 3.4	12.5 ± 3.1	12.7 ± 3.2	12.7 ± 3.2
Duration of diabetes (years)	6.6 ± 6.9	5.4 ± 6.1	5.5 ± 4.9	6.1 ± 6.7	5.9 ± 6.1

Data are means ± SD, or *n* (%). RSG, rosiglitazone. At baseline, the patients who were withdrawn from prior antihyperglycemic therapy had been off medication for 6 weeks.

diabetic neuropathy, or elevations in total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), or aspartate aminotransferase >2.5 times the upper limit of the reference range were excluded.

Efficacy and safety measurements

The change from baseline (end of the 4-week placebo run-in period) after 26 weeks of treatment was assessed for the primary efficacy parameter of HbA_{1c} and the secondary efficacy parameters of fasting plasma glucose, immunoreactive insulin, C-peptide, and lipid levels.

Clinical chemistry, hematology, liver enzymes, and urinalysis were performed at SmithKline Beecham Clinical Laboratories (Van Nuys, CA) on fasting samples obtained at weeks −4, −2, 0 (baseline), 4, 8, 12, 18, and 26. Plasma glucose, total cholesterol, HDL cholesterol, and triglycerides were measured by an Olympus analyzer (Olympus Clinical Instruments Division, Lake Success, NY), HbA_{1c} by Variant high-performance liquid chromatography (Bio-Rad, Hercules, CA), C-peptide by radioimmunoassay (Diagnostic Products, Los Angeles, CA), insulin by radioimmunoassay (Pharmacia, Uppsala, Sweden), and free fatty acids by enzymatic/colorimetric analysis (Wako Diagnostic, Richmond, VA) using a COBAS analyzer (Roche Diagnostic Systems, Indianapolis, IN). LDL cholesterol concentrations were estimated using the Friedewald equation (11) when triglycerides were >400 mg/dl. Overall, 14% of patients were excluded from the LDL calculation: 1.0% due to baseline triglyceride levels >400 mg/dl; 9.0% due to week 26 triglyceride levels >400 mg/dl; 0.8% due to week 26 HDL values missing; 3.0% due to baseline and week 26 triglyceride levels >400 mg/dl; and 0.3% due to week 26 triglyceride levels >400 mg/dl. Exclusions were 12.0% with placebo, 12.0% with rosiglitazone 4 mg o.d., 8.0% with rosiglitazone 2 mg b.i.d., 20.0% with rosiglitazone 8 mg o.d., and 19.0% with rosiglitazone 4 mg b.i.d. Estimates of insulin resistance and β-cell function were derived from fasting plasma glucose and immunoreactive insulin using the homeostasis model assessment (HOMA) (12). HOMA has been validated by comparison with glucose clamps (13,14) and intravenous glucose tolerance tests with minimal model analysis (12,14, 15) and has been used to assess both insulin resistance and β-cell function in epidemiological studies (16,17).

Data analysis

So that changes in glycemic control could be assessed, the primary efficacy population consisted of all patients who had at least one postbaseline data point for any efficacy parameter, carrying forward the last observation in the case of missing data or early withdrawals. The lipid and safety assessments were based on observed data for all randomized patients.

Treatment groups were compared using analysis of covariance with terms for baseline, treatment, and geographic region. Since the lipid data did not meet normality and homogeneity of variance assumptions required for parametric analysis, a nonparametric assessment was based on the distribution of the percentage change in lipid values; medians and 95% CIs were estimated, and pairwise comparisons to placebo were conducted using Dunnett's multiple comparison procedure to maintain a two-sided 0.05 significance level. Lipid subset analyses used the same nonparametric methods.

Equivalence between rosiglitazone 4 mg o.d. and rosiglitazone 2 mg b.i.d. and between rosiglitazone 8 mg o.d. and rosiglitazone 4 mg b.i.d. with respect to changes in HbA_{1c} concentration were assessed using Bonferroni-adjusted 95% CIs. Treatments were defined as equivalent if the 95% CI fell within ±0.5%.

Safety parameters, including clinical laboratory tests, vital signs, and body weight, were examined using one-way analysis of variance.

HOMA estimates were expressed relative to values in a lean nondiabetic reference population that was 18–25 years of age (13,14).

RESULTS

Baseline characteristics

Of the 1,503 patients screened, 959 were randomized to treatment. Among those patients excluded, 77% failed to meet the inclusion criteria; the remainder experienced adverse events before randomization (7.5%), withdrew consent (10%), deviated from the protocol (2.2%), or were lost to follow-up (5%). Baseline characteristics were similar in all treatment groups (Table 1). In addition, the baseline characteristics of patients who achieved an HbA_{1c} concentration ≤7% were similar to those patients who did not. Before the study, ~25% of patients were treated with diet alone, 60% with a single antihyperglycemic agent, and 15% with multiple agents.

Glycemic control

All rosiglitazone-treated groups had significant decreases in HbA_{1c} compared with

the placebo group ($P < 0.0001$). Mean treatment effects were −0.8, −0.9, −1.1, and −1.5% with rosiglitazone 4 mg o.d., rosiglitazone 2 mg b.i.d., rosiglitazone 8 mg o.d., and rosiglitazone 4 mg b.i.d., respectively. Reductions in HbA_{1c} began at week 8 and continued through week 18 with rosiglitazone treatment. In contrast, mean HbA_{1c} increased from baseline through week 26 with placebo (Fig. 1*A*). Rosiglitazone 4 mg o.d. and rosiglitazone 2 mg b.i.d. were therapeutically equivalent, whereas rosiglitazone 4 mg b.i.d. produced greater improvements than did rosiglitazone 8 mg o.d. All rosiglitazone regimens also decreased fasting plasma glucose compared with placebo ($P < 0.0001$), beginning at week 4 and reaching maximal effects by weeks 8–12.

Changes in serum insulin did not differ significantly between rosiglitazone and placebo. Compared with placebo, C-peptide decreased significantly with rosiglitazone 4 mg b.i.d. (−0.084 nmol/l; $P = 0.0122$) but not in the other treatment groups. HOMA estimates of insulin resistance decreased with rosiglitazone 4 mg o.d., rosiglitazone 2 mg b.i.d., rosiglitazone 8 mg o.d., and rosiglitazone 4 mg b.i.d. (mean change: −0.7, −11.3, −8.0, and −18.6%, respectively) but increased with placebo (15.8%). HOMA estimates of β-cell function increased in all groups, with the greatest increase occurring with rosiglitazone 4 mg b.i.d. (84.0%) and the smallest with placebo (8.3%).

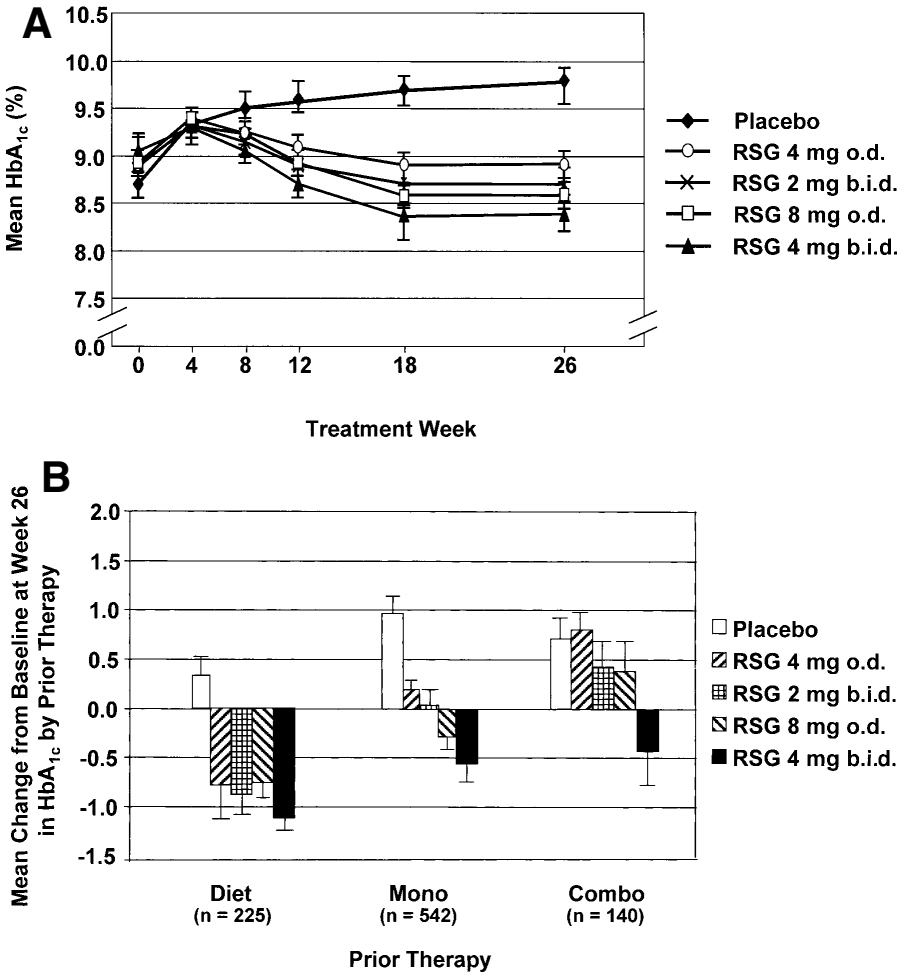

Figure 1—*Mean concentration of HbA_{1c} over time* (A) *and mean change from baseline in HbA_{1c} by prior therapy at week 26* (B) *(intent-to-treat population). Error bars = SEM.*

Glycemic control: analysis by prior therapy

In drug-naive patients, rosiglitazone 4 mg o.d., rosiglitazone 2 mg b.i.d., rosiglitazone 8 mg o.d., and rosiglitazone 4 mg b.i.d. produced mean decreases in HbA_{1c} from baseline of −0.85, −0.89, −0.80, and −1.11%, compared with an increase of 0.35% with placebo treatment (Fig. 1*B*); at study end, HbA_{1c} concentration ≤7.0% was achieved by 38, 25, 31, and 40% of patients in each group, respectively, compared with 17% using placebo.

In patients who had received prior oral monotherapy, rosiglitazone 4 mg o.d., rosiglitazone 2 mg b.i.d., rosiglitazone 8 mg o.d., and rosiglitazone 4 mg b.i.d. altered HbA_{1c} concentration from baseline by +0.14, +0.02, −0.26, and −0.54%, respectively, compared with an increase of 0.98% with placebo (Fig. 1*B*). At study end, HbA_{1c} concentration ≤7% was achieved by 21, 21, 13, and 25% of patients in each group, respectively, compared with 6% of patients in the placebo group.

In patients who had previously received a combination of oral antihyperglycemic agents, only rosiglitazone 4 mg b.i.d. produced a decrease from baseline in HbA_{1c} concentration (−0.43%, Fig. 1*B*); at study end, 33% of these patients achieved HbA_{1c} concentration ≤7%, compared with 0% of patients taking placebo.

Serum lipids

In general, statistically significant dosage-ordered decreases in free fatty acid levels were observed in all rosiglitazone treatment groups, compared with baseline and with placebo (except in the rosiglitazone 4 mg o.d. group) in patients who completed 26 weeks of treatment (Table 2). Small but statistically significant increases in total cholesterol and LDL cholesterol were observed in all treatment groups (including placebo) as compared with baseline, as well as in rosiglitazone treatment groups compared with placebo (Table 2). Statistically significant increases in HDL cholesterol, compared with baseline, were observed in all treatment groups (Table 2). The median percentage changes from baseline for the LDL cholesterol:HDL cholesterol ratio were small and were generally not statistically significant. In comparison with placebo, there were small but statistically significant increases in the rosiglitazone 4 mg b.i.d., 8 mg o.d., and 4 mg b.i.d. treatment groups. Small but significant increases in triglyceride levels compared with baseline were observed in all treatment groups except the rosiglitazone 4 mg b.i.d. group (including placebo); none of these increases within rosiglitazone treatment groups reached statistical significance in comparison with placebo.

Table 2—*Change in lipid parameters at week 26 (intent-to-treat population without last observation carried forward)*

	Treatment group				
	Placebo	RSG 4 mg o.d.	RSG 2 mg b.i.d.	RSG 8 mg o.d.	RSG 4 mg b.i.d.
Free fatty acids					
n	110	145	158	142	158
Baseline (mmol/l)	0.59	0.57	0.56	0.62	0.58
Week 26 (mmol/l)	0.57	0.52	0.48	0.49	0.44
Median % difference from baseline	3.9	−6.6	−12.4	−16.9	−19.0
95% CI	−3.2 to 11.8	−12.9 to −0.1	−18.2 to −5.9	−22.0 to −11.7	−24.9 to −12.8
Median % difference from placebo	—	−10.0	−16.1	−19.5	−22.5
95% CI	—	−22.3 to 1.5	−27.4 to −4.3	−30.2 to −9.3	−33.6 to −11.6
Total cholesterol					
n	110	145	158	142	158
Baseline (mmol/l)	5.50	5.33	5.47	5.43	5.37
Week 26 (mmol/l)	5.48	5.95	6.08	6.28	6.12
Median % difference from baseline	3.0	12.4	9.6	17.5	13.5
95% CI	0.8 to 4.9	9.8 to 15.1	7.2 to 12.1	13.9 to 21.0	10.6 to 16.5
Median % difference from placebo	—	9.3	6.4	14.9	10.1
95% CI	—	5.2 to 13.4	2.6 to 10.6	9.8 to 19.9	5.7 to 14.9
LDL cholesterol					
n	97	128	146	113	128
Baseline (mmol/l)	3.28	3.23	3.36	3.34	3.23
Week 26 (mmol/l)	3.21	3.60	3.72	3.88	3.62
Median % difference from baseline	1.7	10.6	9.5	18.3	14.3
95% CI	−1.6 to 4.9	7.1 to 14.4	6.2 to 13.3	12.6 to 24.2	10.3 to 18.6
Median % difference from placebo	—	8.7	7.4	16.5	12.2
95% CI	—	2.8 to 14.7	1.7 to 13.6	8.3 to 24.7	5.7 to 18.8
HDL cholesterol					
n	110	143	156	140	156
Baseline (mmol/l)	1.09	1.14	1.19	1.11	1.09
Week 26 (mmol/l)	1.22	1.24	1.29	1.22	1.24
Median % difference from baseline	8.1	10.7	10.2	11.8	13.9
95% CI	5.3 to 10.9	7.8 to 13.7	7.7 to 12.7	8.9 to 14.9	10.9 to 17.1
Median % difference from placebo	—	2.6	2.1	3.6	5.7
95% CI	—	−2.3 to 7.6	−2.5 to 6.8	−1.3 to 8.7	0.6 to 11.1
LDL cholesterol:HDL cholesterol ratio					
n	97	128	146	113	128
Baseline (ratio)	2.87	2.98	2.95	2.89	2.92
Week 26	2.57	2.73	2.90	3.02	2.90
Median % difference from baseline	−0.22	−0.04	−0.03	0.14	0.02
95% CI	−0.34 to −0.11	−0.14 to 0.08	−0.13 to 0.09	−0.05 to 0.31	−0.09 to 0.14
Median % difference from placebo	—	0.19	0.19	0.38	0.24
95% CI	—	−0.01 to 0.39	0.00 to 0.40	0.10 to 0.65	0.04 to 0.45
Triglycerides					
n	110	145	158	142	158
Baseline (mmol/l)	1.97	1.82	1.89	2.09	2.18
Week 26 (mmol/l)	1.93	2.12	2.12	2.38	2.18
Median % difference from baseline	7.2	19.6	10.9	17.6	5.2
95% CI	0.3 to 14.6	12.5 to 27.3	4.2 to 18.1	8.4 to 28.0	−2.1 to 13.2
Median % difference from placebo	—	11.9	2.8	7.6	−3.0
95% CI	—	−0.8 to 24.5	−9.0 to 14.7	−5.5 to 20.9	−15.0 to 9.1
Baseline LDL cholesterol ≤3.36 mmol/l					
n	53	71	76	60	75
Baseline (mmol/l)	2.77	2.79	2.91	2.77	2.82
Week 26 (mmol/l)	2.87	3.08	3.17	3.57	3.10
Median % difference from baseline	6.4	14.0	15.3	31.4	17.8

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Table 2—*Continued*

	Treatment group				
	Placebo	RSG 4 mg o.d.	RSG 2 mg b.i.d.	RSG 8 mg o.d.	RSG 4 mg b.i.d.
95% CI	2.5 to 10.7	8.8 to 19.6	8.8 to 22.5	23.0 to 39.9	11.6 to 25.4
Median % difference from placebo	—	6.9	6.6	24.4	9.7
95% CI	—	−1.3 to 15.1	−2.5 to 17.0	12.5 to 36.3	−0.2 to 20.1
Baseline LDL cholesterol >3.36 mmol/l					
n	44	57	70	53	53
Baseline (mmol/l)	3.94	3.85	3.85	3.90	3.72
Week 26 (mmol/l)	3.74	4.24	4.32	4.34	4.14
Median % difference from baseline	−4.4	6.7	5.7	6.3	10.4
95% CI	−9.4 to 0.6	2.4 to 11.7	2.6 to 8.9	−0.7 to 12.7	6.0 to 15.6
Median % difference from placebo	—	11.8	10.2	11.5	15.6
95% CI	—	3.2 to 20.2	3.2 to 18.0	0.5 to 21.3	6.6 to 24.2
Baseline triglycerides ≤5.17 mmol/l					
n	64	91	97	82	81
Baseline (mmol/l)	1.51	1.39	1.50	1.47	1.35
Week 26 (mmol/l)	1.55	1.60	1.80	1.67	1.63
Median % difference from baseline	8.3	24.2	21.0	22.5	13.6
95% CI	0.3 to 17.2	16.2 to 33.1	11.5 to 31.2	10.8 to 35.2	3.6 to 25.5
Median % difference from placebo	—	15.3	10.8	10.2	3.6
95% CI	—	0.7 to 30.7	−3.9 to 25.9	−5.9 to 28.9	−11.5 to 19.0
Baseline triglycerides >5.17 mmol/l					
n	46	54	61	60	77
Baseline (mmol/l)	3.17	3.04	3.04	3.35	3.51
Week 26 (mmol/l)	3.45	3.65	2.89	3.97	3.40
Median % difference from baseline	5.4	10.8	−3.7	9.9	−3.9
95% CI	−6.7 to 18.8	−4.5 to 25.5	−13.3 to 6.0	−1.7 to 26.9	−14.3 to 7.2
Median % difference from placebo	—	4.2	−8.8	3.6	−9.9
95% CI	—	−20.8 to 27.7	−27.6 to 9.0	−17.1 to 25.5	−29.5 to 9.3

Data are medians unless otherwise indicated. All laboratory values are fasting and intent-to-treat; no last observation carried forward. RSG, rosiglitazone.

In patients with baseline LDL cholesterol ≤3.36 mmol/l (130 mg/dl) (the LDL cholesterol cutoff of 3.36 mmol/l for subgroup analysis was chosen based on the guidelines of the National Cholesterol Education Program), both placebo and rosiglitazone treatments resulted in statistically significant increases in LDL cholesterol compared with baseline. When compared with placebo, these changes were generally not significant. In patients with baseline levels >3.36 mmol/l, the changes in LDL cholesterol were smaller in magnitude (Table 2).

In general, the rosiglitazone treatment groups demonstrated small but significant increases in triglyceride levels, with greater increases observed in patients with baseline levels ≤5.17 mmol/l (200 mg/dl); however, these changes were not dosage related. When compared with placebo treatment, only increases observed with rosiglitazone 4 mg o.d. were significant. In patients with baseline triglyceride levels >5.17 mmol/l, no change was significant in any treatment group (Table 2).

Safety

Rosiglitazone was well tolerated; the percentages of patients with at least one adverse event during therapy were comparable for rosiglitazone (75%) and placebo (71%). Hyperglycemia and headache were the most commonly cited reasons for withdrawal. Withdrawals were more common among placebo (38.4%) than among rosiglitazone (20.7%) recipients, and withdrawals due to lack of efficacy were more common with placebo (16.8%) than with rosiglitazone (6.6%). The remaining withdrawals in the placebo- and rosiglitazone-treated patients were due to adverse experience (10.8 and 5.6%, respectively), protocol deviation (1.1 and 1.4%, respectively), loss to follow-up (2.2 and 2.4%, respectively), and others (7.6 and 4.7%, respectively). The patients who withdrew from treatment were more poorly controlled at baseline (mean HbA_{1c} concentration 9.4%).

There were 46 patients who had adverse events related to edema: 3 (1.6%) in the placebo group, 10 (5.2%) in the rosiglitazone 4 mg o.d. group, 12 (6.4%) in the rosiglitazone 8 mg o.d. group, 8 (4.1%) in the rosiglitazone 2 mg b.i.d. group, and 13 (6.6%) in the rosiglitazone 4 mg b.i.d. group. One patient in the placebo group withdrew from the study because of mild edema. Body weight decreased with placebo (−0.9 kg) but increased in a dosage-dependent manner with rosiglitazone (1.2, 1.5, 2.6, and 3.3 kg with rosiglitazone 4 mg o.d., rosiglitazone 2 mg b.i.d., rosiglitazone 8 mg o.d., and rosiglitazone 4 mg b.i.d., respectively; all $P \leq 0.0001$ compared with both placebo and baseline). The waist-to-hip ratio did not change significantly in any group.

Two randomized patients (one treated with placebo and one with rosiglitazone 4 mg b.i.d.) had asymptomatic elevations in

serum ALT that were more than three times the upper limit of the reference range. In both patients, ALT values returned to normal as treatment continued. Small but statistically significant dosage-dependent decreases in Hb (−0.5 to −0.9 g/dl) and hematocrit (−1.6 to −2.5 percentage points) occurred in all rosiglitazone groups ($P \leq 0.0001$ compared with placebo and baseline).

CONCLUSIONS — Rosiglitazone significantly improved glycemic control in a dosage-dependent manner after 26 weeks of treatment. At 4 mg per day, therapeutically equivalent effects on HbA_{1c} were observed with administration once or twice daily; at 8 mg per day, administration twice daily was more effective. Patient responses to rosiglitazone depended on prior antihyperglycemic therapy. Drug-naive patients, who are presumed to have less severe disease, demonstrated clinically significant responses to rosiglitazone at all doses and regimens. Patients previously treated with oral monotherapy or oral combination therapy demonstrated the most marked response to rosiglitazone 4 mg b.i.d. HOMA estimates revealed decreases in insulin resistance and potentially improved estimated β-cell function in all rosiglitazone treatment groups. These findings are consistent with rosiglitazone's insulin-sensitizing action and support preclinical studies that have demonstrated rosiglitazone's β-cell–sparing effects (18). However, it should be noted that although HOMA is validated as a measure of insulin sensitivity, it is less well established as a measure of β-cell function.

A dosage-dependent reduction in free fatty acid levels was observed with all regimens of rosiglitazone. Since free fatty acids may contribute to insulin resistance and impaired insulin secretion (19), decreases in free fatty acid levels may contribute to the observed improvements in insulin sensitivity and glycemic control. Total cholesterol, LDL cholesterol, and HDL cholesterol increased from baseline levels in all treatment groups, with the greatest increases observed in rosiglitazone-treated patients; the increases in LDL cholesterol may be partially offset by corresponding increases in HDL cholesterol. The LDL cholesterol:HDL cholesterol ratio is often considered a better predictor of cardiovascular risk than LDL cholesterol or HDL cholesterol alone (20,21). Changes in the LDL cholesterol:HDL cholesterol ratio with rosiglitazone treatment were small and only modestly different from placebo. Alterations in serum triglyceride levels were small and comparable among all treatment groups, including placebo, possibly dissociating these changes from a true rosiglitazone effect. More long-term experience will be needed to determine consistent effects on lipid levels and the impact of lipid changes on cardiovascular outcomes.

Rosiglitazone was generally well tolerated. Statistically significant dosage-related decreases in Hb and hematocrit were observed in all rosiglitazone treatment groups; however, these changes generally occurred within the first 90 days of treatment and remained stable thereafter. This effect is consistent with plasma volume expansion leading to fluid retention and hemodilution, observed during treatment with other thiazolidinediones (22,23). Rosiglitazone therapy was also associated with significant increases in weight, which may be attributed to thiazolidinedione-associated fluid retention (22–24), adipocyte differentiation (22,25), and increased appetite (26). Since there was no increase in waist-to-hip ratio, it is possible that these weight increases primarily reflect fluid retention and/or subcutaneous fat accumulation, both of which confer less cardiovascular risk than intra-abdominal fat (27). Rosiglitazone treatment was not associated with hepatic side effects.

The decrease in HbA_{1c} of 1.5% with maximum rosiglitazone dosage (4 mg b.i.d.) compares well with the effects of sulfonylureas or metformin in patient groups with comparable initial HbA_{1c} concentrations (~9%) (28–31). Thus, because rosiglitazone has efficacy comparable to that of these agents and is not associated with either hypoglycemia or gastrointestinal intolerance, the benefits of rosiglitazone in reducing glucose levels should apply to a wide spectrum of patients with type 2 diabetes.

Overall, rosiglitazone significantly improved glycemic control and was well tolerated. Because responses varied by patients' treatment history, it appears that once-daily rosiglitazone may be sufficient as first-line therapy for patients with recent diagnoses, whereas 4 mg b.i.d. may be needed for patients with more advanced diabetes.

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Appendix

Rosiglitazone Clinical Trials Study Group

John D. Bagdale, MD, Oregon Research Group, Eugene, OR; Joseph Barrera, MD, East Bay Internal Medicine, Berkeley, CA; Kathleen Baskett, MD, Northwest Physicians Research Network, Missoula, MT; Bruce T. Bowling, MD, Endwell Family Physicians, Endwell, NY; Daniel H. Brune, MD, Creve Coeur Family Practice, Peoria, IL; Mark R. Burge, MD, University of New Mexico Hospital, Albuquerque, NM; Gregory V. Collins, MD, Charlotte Clinical Research, Charlotte, NC; Paresh Dandona, MBBS, DPhil, FRCP, Millard Fillmore Hospital, Buffalo, NY; G. Stephen DeCherney, MD, Medical Center of Delaware, Newark, DE; Harry K. Delcher, MD, Georgia Baptist Medical Center, Atlanta, GA; John K. Earl, MD, Unifour Medical Research Associates/Medical Arts Clinic, Hickory, NC; Mildred V. Farmer, MD, Clinical Studies, Florida, St. Petersburg, FL; Jeffrey S. Freeman, DO, Philadelphia College of Osteopathic Medicine, Philadelphia, PA; John D. Gabriel, MD, North Hills Medical Research, North Richland Hills, TX; W. Thomas Garland, MD, Lawrence Clinical Research, Lawrenceville, NJ; Ronald C. Gove, MD, Jersey Foundation Group, Inc., Pleasantville, NJ; Daniel E. Gremillion, MD, Nashville Research Associates, Nashville, TN; George Grunberger, MD, Wayne State University School of Medicine, Detroit, MI; William J. Henry, MD, MedQuest, Inc., Greer, SC; Jeffrey R. Herbst, MD, Hill Top Research, Inc., Portland, OR; Robert K. Hippert, DO, Fleetwood Medical Associates, Fleetwood, PA; John A. Holmes, MD, Sunflower Medical Group, Mission, KS; Steven D. Hsi, MD, Albuquerque, NM; Abbas E. Kitabchi, PhD, MD, University of Tennessee Hospital, Memphis, TN; Leslie J. Klaff, MD, PhD, Rainier Clinical Research Center, Renton, WA; Andrew J. Lewin, MD, National Research Institute, Los Angeles, CA; Frank P. Maggiacomo, DO, Silver Lake Medical, Inc., Providence, RI; John Matlock, MD, Diagnostic Clinic of San Antonio, San Antonio, TX; Ronald Eric McAllister, DPhil, MD, Ukiah, CA; David J. Miller, DO, Bucks County Clinical

Research, Morrisville, PA; Sam S. Miller, MD, San Antonio, TX; Barbara C. Mitchell, MD, Division of Clinical Research, Mobile, AL; Katikineni Mohan, MD, Riverside Clinical Research Center of Washington, Riverdale, MD; Paul B. Moore, MD, Center for Clinical Research of Austin Diagnostic Clinic, Austin, TX; David J. Morin, RPh, MD, Tri Cities Medical Research, Bristol, TN; William S. Mullican, MD, MediSphere Medical Research Center, Evansville, IN; Daniel A. Nadeau, MD, Eastern Maine Medical Center, Bangor, Maine; John D. Norton, MD, Internal Medical Specialists Research, Colorado Springs, CO; Robert J. Noveck, MD, PhD, Clinical Research Center, New Orleans, LA; Robert Zorba Paster, MD, Dean Medical Center, Oregon, Oregon, WI; Andres Patron, DO, South Florida Clinical Research Center, Hollywood, FL; Lawrence S. Phillips, MD, The Emory Clinic, Atlanta, GA; Julio C. Pita, MD, Miami, FL; Geoffrey P. Redmond, MD, Foundation for Developmental Endocrinology, Inc., Cleveland, OH; Claudio Renjifro-Romero, MD, San Juan, PR; Harvey Resnick, MD, R/D Clinical Research, Inc., Lake Jackson, TX; L. Raymond Reynolds, MD, Lexington Clinic, Lexington, KY; Stephen R. Richard, MD, Richmond Family Practice, Richmond, VA; Sid Rosenblatt, MD, The Irvine Clinical Research Center, Irvine, CA; Seymour J. Rosenbloom, PhD, MD, Endocrinology and Internal Medicine Specialists, Marietta, GA; Corbin P. Roudebush, MD, Diabetes & Endocrinology Associates, Indianapolis, IN; George A. Scharyj, MD, Tucker, GA; Emil M. Skobeloff, MD, Crozer-Chester Medical Center, Upland, PA; William B. Smith, MD, New Orleans Center for Clincial Research, New Orleans, LA; Martin J. Stevens, MD, University of Michigan Medical Center, Ann Arbor, MI; John D. Stokes, MD, Florida Pharmaceutical Research Corp., Palm Harbor, FL; Carol B. Teutsch, MD, Northside Internists and Endocrinologists, Atlanta, GA; Phillip D. Toth, MD, Midwest Institute for Clinical Research, Indianapolis, IN; Jaime E. Trujillo, MD, Salem Research Group, Inc., Winston-Salem, NC; Richard M. Tucker, MD, Wenatchee Valley Clinic, Wenatchee, WA; Richard L. Weinstein, MD, Diablo Clinical Research, Inc., Walnut Creek, CA; Stuart R.Weiss, MD, San Diego Endocrine and Medical Clinic, San Diego, CA; Carol Wysham, MD, Rockwood Clinic, P.S. & Future Scripts, Spokane, WA; and William D. Zigrang, MD, Burlingame, CA.

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