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Rosiglitazone Monotherapy Is Effective in Patients with Type 2 Diabetes

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ABSTRACT

This study evaluated the efficacy and safety of rosiglitazone monotherapy in patients with type 2 diabetes. After a 4-week placebo run-in period, 493 patients with type 2 diabetes were randomized to receive rosiglitazone [2 or 4 mg twice daily (bd)] or placebo for 26 weeks. The primary end point was change in hemoglobin A_{1c}; other variables assessed included fasting plasma glucose, fructosamine, endogenous insulin secretion, urinary albumin excretion, serum lipids, and adverse events. Rosiglitazone (2 and 4 mg bd) decreased mean hemoglobin A_{1c} relative to placebo by 1.2 and 1.5 percentage points, respectively, and reduced fasting plasma glucose concentrations relative to placebo by 3.22 and 4.22 mmol/L, respectively. Fasting plasma insulin and insulin precursor molecules decreased significantly. Homeostasis model assessment estimates indicate that rosiglitazone (2 and 4 mg bd) reduced insulin resistance by 16.0% and 24.6%, respectively, and improved β-cell function over baseline by 49.5% and 60.0%, respectively. Urinary albumin excretion decreased significantly in the rosiglitazone (4 mg bd) group. There was no increase in adverse events with rosiglitazone. In the short-term, rosiglitazone is an insulin sensitizer that is effective and safe as monotherapy in patients with type 2 diabetes who are inadequately controlled by lifestyle interventions. (*J Clin Endocrinol Metab* **86:** 280–288, 2001)

INSULIN RESISTANCE contributes to the pathophysiology of several major chronic diseases. Insulin resistance precedes the development of type 2 diabetes mellitus and contributes to the hyperglycemic state in about 80–85% of patients with this disorder (1, 2). In addition, evidence suggests that insulin resistance and hyperinsulinemia are also associated with other disease states, such as polycystic ovarian syndrome, an insulin-resistant state that leads to hyperinsulinemia, thus stimulating excessive ovarian androgen production in genetically susceptible individuals (3, 4). Insulin resistance and hyperinsulinemia have also been associated with increased risks of atherosclerosis and hyperten-

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sion (5–7). Therefore, reducing insulin resistance may have wide applicability as a therapeutic approach for the treatment of type 2 diabetes. Preliminary studies with agents that reduce insulin resistance suggest that such therapies may delay or prevent progression from impaired glucose tolerance to overt type 2 diabetes (8, 9) and preserve β-cell function in patients with type 2 diabetes (10) and have potential to treat other diseases associated with insulin resistance (11, 12).

Thiazolidinediones are insulin-sensitizing agents that act as ligands for the γ-subtype of the peroxisome proliferator-activated receptor (PPARγ), which is directly involved in the regulation of genes controlling glucose homeostasis and lipid metabolism (13–16). Troglitazone, the first thiazolidinedione that had been approved for clinical use, was effective in reducing glycemia in patients with type 2 diabetes (17, 18), but was also associated with hepatotoxicity and rare cases of liver failure and death (19–22). As a result, frequent monitoring of hepatic function had been required during troglitazone treatment (19). The U.S. FDA asked Parke-Davis/Warner-Lambert to remove troglitazone from the market as of March 22, 2000. The FDA took this action after its review of recent safety data on troglitazone, rosiglitazone, and pioglitazone had demonstrated that troglitazone is more toxic to the liver than the other two drugs. Data to date show that rosiglitazone and pioglitazone, both approved in the past year, offer benefits similar to troglitazone without the same risk (23).

Rosiglitazone is a potent member of the thiazolidinedione class, with a binding affinity for PPARγ that is approximately 30-fold greater than that of pioglitazone and 100-fold greater than that of troglitazone (24–26). This translates to a clinical dose that is approximately 1/100th that of troglitazone (4–8 *vs.* 400–600 mg) and 1/6th that of pioglitazone (4–8 *vs.* 15–45 mg). This report describes the results of a multicenter study designed to assess the efficacy and safety of rosiglitazone monotherapy in patients with type 2 diabetes whose hyperglycemia was inadequately controlled by diet or an oral antihyperglycemic agent.

Materials and Methods

The study was conducted at 42 centers in the United States in accordance with the Declaration of Helsinki (as amended, 1989), Title 21 of the U.S. Code of Federal Regulations, and Good Clinical Practice guidelines. The institutional review board at each institution approved the protocol, and all patients gave written, informed consent before study enrollment.

Patient population

Patients, 36–81 yr old, with a diagnosis of type 2 diabetes (as defined by the National Diabetes Data Group) (27) were eligible for the study if they had fasting plasma glucose (FPG) between 7.8–16.7 mmol/L, fasting plasma C peptide level greater than 0.26 nmol/L, and a body mass index (BMI) between 22–38 kg/m^2 at screening. Patients with angina or cardiac insufficiency (New York Heart Association class III or IV), renal impairment (serum creatinine, >159 μmol/L), hepatic disease [alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, or total bilirubin, >2.5 times the upper limit of the reference range], history of diabetic ketoacidosis, history of chronic insulin use, symptomatic diabetic neuropathy, a serious major illness that would compromise their participation, and women of childbearing potential were excluded from the study.

Study design

The study was divided into three phases: a screening period of up to 14 days (during which patients discontinued all antidiabetic medications), a 4-week single blind placebo baseline period, and a 26-week double blind treatment period. At the end of the screening period, patients were assessed for inclusion in the placebo baseline period. Eligible patients received instruction on a weight maintenance diet during the placebo baseline phase and reinforcement at all subsequent study visits. After completing the baseline period, patients were randomly assigned to receive placebo, 2 mg rosiglitazone twice daily (bd), or 4 mg rosiglitazone bd. Study medications were matched for weight, shape, and color and dispensed in bottles of 40 tablets (enough for 20 days).

All patients were given a complete physical examination at screening and at the end of the treatment period. Interim medical histories, reports of adverse events, and standard laboratory assessments (including clinical chemistry, hematology, and urinalysis) were obtained at each visit. Electrocardiograms were performed at screening, baseline, and weeks 12 and 26 of the double blind treatment period.

Evaluation of efficacy

The primary end point for evaluating effects on glycemic control was the change in hemoglobin A_{1c} (HbA_{1c}) from baseline to 26 weeks in the rosiglitazone treatment groups compared with the placebo group by an intention to treat analysis. Other measures of efficacy were comparisons of rosiglitazone with placebo for changes from baseline to week 26 in FPG, C peptide, immunoreactive insulin, proinsulin, 32–33 split proinsulin, fructosamine, urinary albumin excretion as determined by urinary albumin/creatinine ratio (ACR), and serum lipids. All of the efficacy parameters were measured at two visits during the run-in period, at baseline (the day of randomization), and at five visits during the treatment phase. The proportions of patients who had a reduction in HbA_{1c} of more than 1 percentage point or a reduction in FPG of more than 1.67 mmol/L at week 26 compared with baseline were determined in each treatment group.

Laboratory measurements

HbA_{1c} was measured by high performance liquid chromatography (Variant Bio-Rad Laboratories, Inc., Richmond, CA), with a normal reference range of 4.1–6.5%; the assay was linear up to 17.89%. FPG was measured by the hexokinase method with an Olympus Corp. analyzer (New Hyde Park, NY). Serum total cholesterol and triglycerides were measured by enzymatic methods with the same analyzer. Fructosamine was measured by colorimetric analysis (RoTAG fructosamine assay, Roche , Indianapolis, IN), C peptide was determined by RIA (Diagnostic Products, Los Angeles, CA), immunoreactive insulin was measured by a one-step immunoenzymatic assay (28, 29) (Access Ultrasensitive Immunoassay System, Sanofi Pharmaceuticals, Inc.; normal reference range, 13–61 pmol/L), and proinsulin and 32–33 split proinsulin were determined by time-resolved fluoroimmunoassay linear to at least 400 pmol/L (Delfia, Wallac, Inc., Turku, Finland). Serum high density lipoprotein (HDL) cholesterol was isolated by precipitation and then measured by enzymatic methods with an Olympus Corp. analyzer. Serum low density lipoprotein (LDL) cholesterol was assayed using the Direct LDL Cholesterol Immunoseparation Reagent Kit (Genzyme, Cambridge, MA). Free fatty acids were measured by enzymatic colorimetric analysis (COBAS analyzer, Roche). SmithKline Beecham Clinical Laboratories (Van Nuys, CA) performed all laboratory tests, with the exception of the insulin assays. Insulin samples were assayed at Addenbrooke's National Health Service Trust (Cambridge, UK).

Statistical analyses

Efficacy analyses were performed for the intention to treat population, defined as all randomized patients who had at least one on-therapy value. In the case of missing data or early withdrawals, the last observation was carried forward to week 26. The safety parameters were assessed based on observed week 26 data without carrying forward the last observation.

Treatment groups were compared using analysis of covariance with terms for baseline, treatment, center, and BMI. Pairwise comparisons to

placebo used Dunnett's multiple comparison procedure to maintain a two-sided 0.05 significance level within each parameter (30, 31) The statistical significance of the within-group change from baseline was tested by a paired *t* test. ACR was log transformed before analysis of covariance with terms for baseline and treatment. Results in the log scale were back-transformed to provide geometric means and corresponding percent change from baseline. Separate analyses were performed for all patients and for those with microalbuminuria.

Estimates of insulin resistance and β-cell function were derived from fasting glucose and insulin using the homeostasis model assessment (HOMA), a mathematical model that relates fasting blood glucose and insulin levels to insulin resistance (IR) and β-cell function (BCF) (32): IR = [fasting insulin (μU/mL) × fasting glucose (mmol/L)]/22.5; and BCF = [20 × fasting insulin (μU/mL)]/fasting glucose (mmol/L) − 3.5]. HOMA estimates of insulin resistance and β-cell function have been validated by comparison with results of glucose clamp studies (33). Estimates of insulin resistance and β-cell function were calculated for all patients at baseline and at weeks 4, 8, 12, 18, and 26 using FPG and insulin values obtained at those times. For patients with missing values at week 26, the last observation was carried forward. Statistical analyses were performed on the percentages of change from baseline to week 26 in insulin resistance and in β-cell function using the SAS statistical package (SAS Institute, Inc., Cary, NC).

Results

Characteristics of the treatment groups

A total of 623 patients entered the placebo baseline phase, and 90 patients withdrew before randomization. Five hundred and thirty-three patients were randomized to treatment; 40 (7.5%) withdrew before having a valid, postbaseline data point. Therefore, the intention to treat population (randomized patients with at least 1 valid postbaseline data point) consisted of 493 patients, 472 of whom had no major protocol violations and comprised the efficacy evaluable population.

Three hundred and sixty-five patients (68.4% of those randomized) completed the 26-week study period. One hundred and sixty-eight patients withdrew during double blind treatment: 77 (44%), 46 (26%), and 45 (25%) from the placebo, 2 mg rosiglitazone bd, and 4 mg rosiglitazone bd groups, respectively. Lack of efficacy was the most common reason for withdrawal, reported for 20.5%, 5.1%, and 8.2% of patients in the placebo, 2 mg rosiglitazone bd, and 4 mg rosiglitazone bd groups, respectively.

Baseline characteristics were similar in all three treatment groups (Table 1). For the entire intention to treat population, mean HbA_{1c} and FPG were 8.9% and 12.49 mmol/L, respectively. The mean BMI was 29.7 kg/m^2, and 74% of patients had a BMI of 27 kg/m^2 or more. Before entering the study, 27% of patients had been managed with diet and exercise alone (drug naive), and 73% had been receiving oral antihyperglycemic agents (primarily sulfonylureas). The mean duration of diagnosed diabetes was approximately 5 yr.

Glycemic control

Rosiglitazone (2 and 4 mg bd) decreased mean HbA_{1c} by 1.2 and 1.5 percentage points, respectively ($P = 0.0001$), compared with placebo (Fig. 1A). At 26 weeks, rosiglitazone (2 and 4 mg bd) reduced mean HbA_{1c} from baseline in the intention to treat population by 0.3 percentage points ($P = 0.0045$) and 0.6 percentage points ($P < 0.0001$), respectively, whereas placebo treatment increased mean HbA_{1c} by 0.9 percentage points ($P < 0.0001$; Fig. 1B). The proportions of patients treated with rosiglitazone (2 and 4 mg bd) who achieved a reduction in HbA_{1c} from baseline of 1 percentage point or more were 29.5% and 36.1%, respectively, *vs.* 3.8% for the placebo-treated population.

Among drug-naive patients receiving placebo, mean HbA_{1c} values remained stable throughout the study (Fig. 2A). In placebo-treated patients previously treated with a single oral antihyperglycemic agent, mean HbA_{1c} rose progressively from week −6 until week 4 and was stable throughout the remainder of the treatment phase (Fig. 2B). In rosiglitazone-treated patients, both the drug-naive and previously treated populations exhibited decreases in mean

TABLE 1. Baseline characteristics

	Placebo (n = 158)	Rosiglitazone, 2 mg daily (n = 166)	Rosiglitazone, 4 mg daily (n = 169)
Mean age (yr)	59 ± 10.9	60 ± 9.8	61 ± 9.5
Sex (M:F)	104:54	107:59	113:56
Race (white:black:other)	117:13:28	125:14:27	124:16:29
Mean BMI (kg/m^2)	29.9 ± 4.1	30.2 ± 4.1	29.1 ± 3.9
Duration of diabetes (yr)	4.6 ± 4.8	4.8 ± 5.8	5.4 ± 6.0
Prior treatment (n [%])			
Drug naive	45 (28.5)	44 (26.5)	45 (26.6)
Prior monotherapy	101 (63.9)	114 (68.7)	111 (65.7)
Prior combination therapy	12 (7.6)	8 (4.8)	13 (7.7)
HbA_{1c} (%)	9.0 ± 1.7	9.0 ± 1.5	8.8 ± 1.6
FPG (mmol/L)	12.71 ± 3.28	12.60 ± 3.44	12.21 ± 3.55
C Peptide (nmol/L)	1.0 ± 0.42	1.0 ± 0.43	1.0 ± 0.47
Lipid parameters			
n[a]	158	164	169
Total cholesterol (mmol/L)	5.53 ± 1.24	5.61 ± 1.39[b]	5.64 ± 1.15
HDL cholesterol (mmol/L)	1.11 ± 0.34	1.09 ± 0.25	1.09 ± 0.26
LDL cholesterol (mmol/L)	3.15 ± 0.96	3.13 ± 0.89[b]	3.21 ± 0.95
Total/HDL ratio	5.32 ± 1.7	5.32 ± 1.5	5.42 ± 1.4
LDL/HDL ratio	2.98 ± 0.988	2.96 ± 0.897	3.03 ± 0.860
Free fatty acids (g/L)	0.19 ± 0.07	0.19 ± 0.08[b]	0.19 ± 0.08
Triglycerides (mol/L)	2.55 ± 2.02	2.85 ± 3.36[b]	2.66 ± 1.77

Values are the mean ± SD.
[a] Patients with valid baseline and week 26 values (last observation carried forward).
[b] n = 166.

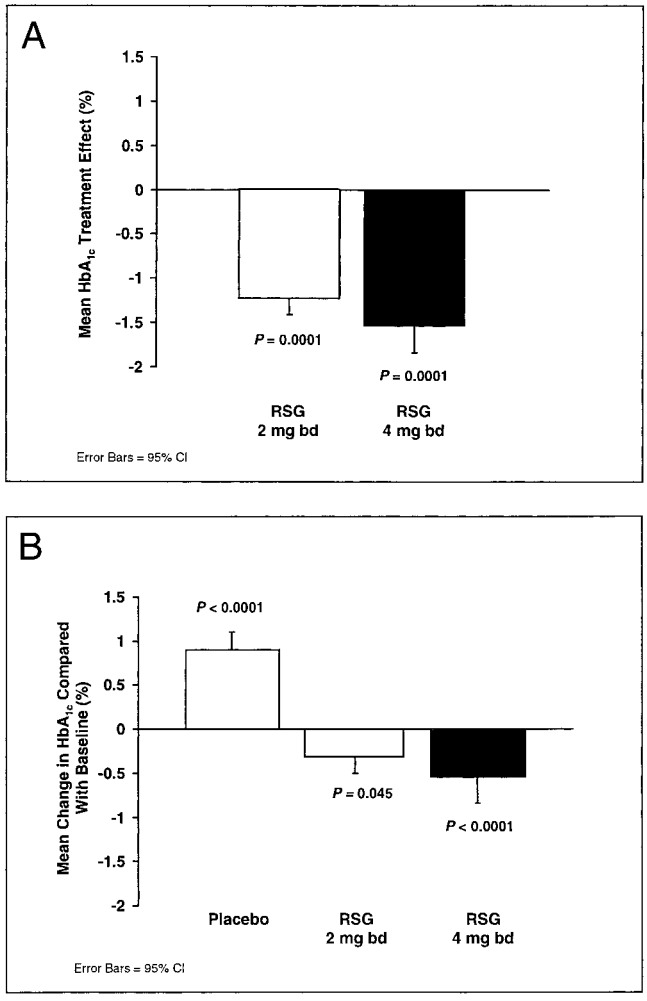

FIG. 1. Mean percent change in HbA_{1c} compared with placebo (A) and baseline (B) at week 26 of rosiglitazone treatment.

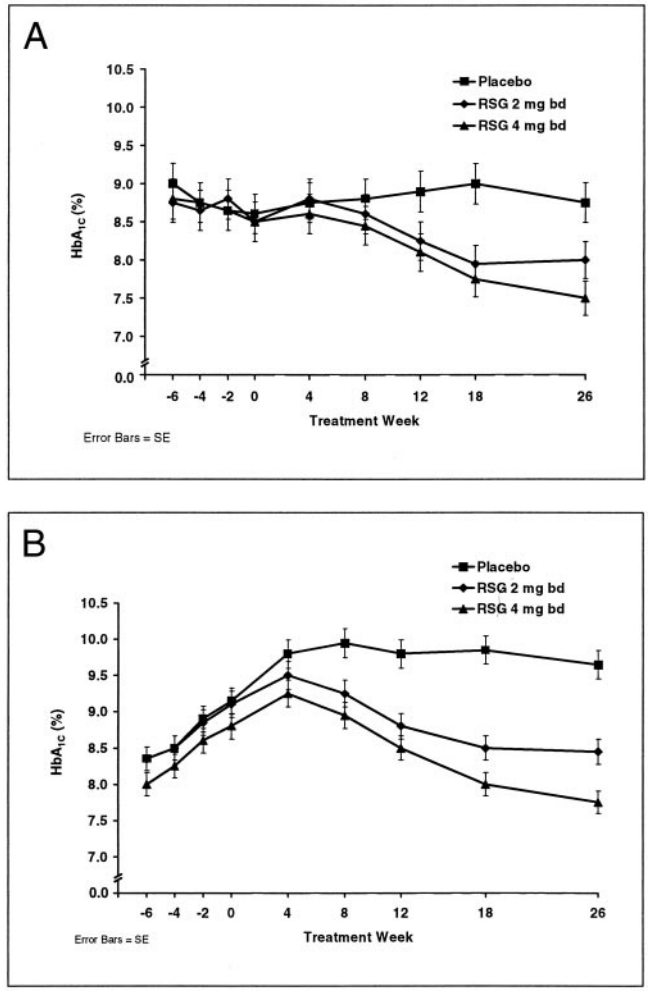

FIG. 2. Mean HbA_{1c} over time in the diet-only population (A) and the prior monotherapy population (B) in patients treated with rosiglitazone.

HbA_{1c} starting at week 8, which were maximal at 18–26 weeks of treatment (Fig. 2, A and B).

Intention to treat analysis of the proportion of patients achieving target HbA_{1c} levels (≤8% and ≤7%) at 26 weeks revealed that a greater number of patients achieved target goals in the rosiglitazone treatment groups than in the placebo group (Table 2). In patients who were above target HbA_{1c} levels at baseline, less than 2% of placebo-treated patients achieved these goals, whereas 39.1% and 19.3% of patients treated with 4 mg rosiglitazone bd achieved HbA_{1c} below 8% and below 7%, respectively.

In the 4 mg rosiglitazone bd group, a higher proportion of previously drug-naive patients achieved target HbA_{1c} levels than patients previously treated with monotherapy. In the drug-naive group, 41% achieved HbA_{1c} of 7% or less, and 71.8% achieved HbA_{1c} of 8% or less. By contrast, 28.2% of patients previously treated with monotherapy achieved HbA_{1c} of 7% or less, and 64.7% achieved HbA_{1c} of 8% or less.

If the data including only those patients who actually completed 26 weeks of treatment are analyzed, 26% and 7% of placebo-treated patients, 52% and 26% of those treated with 2 mg rosiglitazone bd, and 65% and 32% of those treated with 4 mg rosiglitazone bd achieved an HbA_{1c} of 8% or less and 7% or less, respectively.

TABLE 2. Patients achieving a mean HbA_{1c} of 8% or less and 7% or less at week 26 (number achieving target HbA_{1c} goal/number in baseline category

	Placebo	Rosiglitazone	
		2 mg daily	4 mg daily
Target goal HbA_{1c} ≤8%			
All patients	32/158 (20.3)	71/166 (42.8)	99/169 (58.6)
Baseline HbA_{1c} ≤8%	30/52 (57.7)	43/50 (86.0)	56/59 (94.9)
Baseline HbA_{1c} >8%	2/106 (1.9)	28/116 (24.1)	43/110 (39.1)
Target goal HbA_{1c} ≤7%			
All patients	8/158 (5.1)	34/166 (20.5)	50/169 (29.6)
Baseline HbA_{1c} ≤7%	6/14 (42.9)	11/13 (84.6)	22/24 (91.7)
Baseline HbA_{1c} >7%	2/144 (1.4)	23/153 (15.0)	28/145 (19.3)

Data are analyzed for each total treatment population and separately for patients whose mean baseline HbA_{1c} values were already at the target goal and for those whose values exceeded the target goal. Percentages are given in *parentheses*.

Furthermore, responders were defined based on clinically important decreases from baseline at week 26 in HbA_{1c} (≥0.7 percentage point decrease) and FPG (≥1.67 mmol/L de-

crease). The difference in the proportions of HbA_{1c} and FPG responders relative to the placebo group was statistically significant in both rosiglitazone-treated groups.

In both rosiglitazone-treated groups, mean FPG decreased by treatment week 4 and reached a nadir by week 12, remaining stable for the duration of the double blind treatment phase (Fig. 3). At 26 weeks, rosiglitazone (2 and 4 mg bd) produced mean decreases in FPG relative to placebo of 3.22 and 4.22 mmol/L ($P = 0.0001$), respectively, and mean decreases from baseline of 2.11 and 3.00 mmol/L ($P = 0.0001$), respectively (Table 3). Placebo-treated patients showed a progressive rise in mean FPG from baseline (week 0) to week 8 of double blind treatment, after which mean FPG remained stable for the duration of the double blind treatment period.

Rosiglitazone (4 mg bd) reduced FPG by at least 1.67 mmol/L in 63.9% of patients and by 2.78 mmol/L or greater in 50.3% of patients at 26 weeks of double blind treatment. The corresponding data for 2 mg rosiglitazone bd were 54.2% and 34.9%, and those for placebo were 15.8% and 9.5%, respectively.

Effects on β-cell function and insulin resistance

HOMA estimates of β-cell function and insulin resistance showed significant mean increases in β-cell function and reductions in insulin resistance among rosiglitazone-treated patients. At 26 weeks, patients treated with 2 and 4 mg rosiglitazone bd showed increases in estimated β-cell function of 49.5% and 60.0%, respectively ($P < 0.00001$ compared with placebo for both groups), By contrast, estimated β-cell function decreased 4.5% in the placebo group (Fig. 4).

HOMA estimates of insulin resistance showed reductions of 16.0% and 24.6% in the 2 and 4 rosiglitazone mg bd groups, respectively ($P < 0.00001$ compared with placebo for both groups). In the placebo group, estimated insulin resistance increased 7.9% (Fig. 5).

Treatment with 4 mg rosiglitazone bd significantly reduced fasting plasma proinsulin, split proinsulin, and C peptide compared with baseline and placebo (Table 4). Rosiglitazone (2 mg bd) significantly reduced these parameters from baseline, but not compared with placebo.

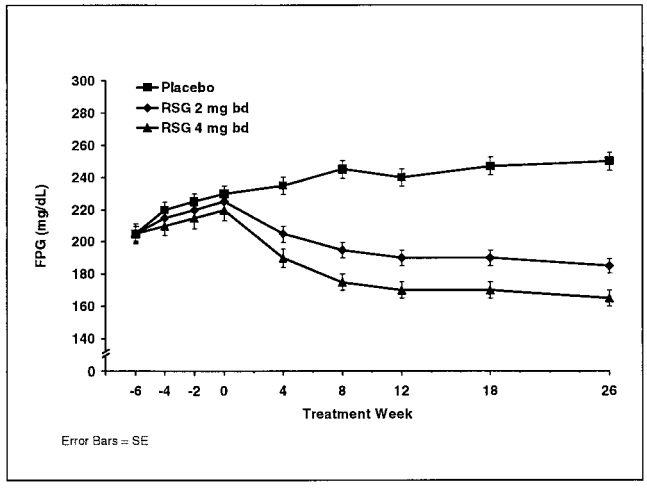

FIG. 3. Mean FPG over time in patients treated with rosiglitazone.

Other metabolic effects

There was a statistically significant mean decrease from baseline in urinary ACR in the 4 mg rosiglitazone bd treatment group (Table 5). The 2 mg rosiglitazone bd treatment group showed a similar decrease. This may be compared with an insignificant increase from baseline in the placebo group. Analysis of ACR in the subgroup of patients with microalbuminuria at baseline showed that both doses of rosiglitazone were associated with reductions from baseline in ACR, ranging from approximately 39–42%. Relative to the placebo group, the rosiglitazone treatment groups showed decreases in ACR of approximately 30% (Table 6).

Both rosiglitazone treatment regimens lowered plasma free fatty acids and increased plasma HDL cholesterol and LDL cholesterol (Table 7). No statistically significant effect on plasma triglycerides was noted with either dose of rosiglitazone. Rosiglitazone-treated patients had significant increases in mean body weight relative to baseline (1.6 and 3.5 kg for 2 and 4 mg rosiglitazone bd, respectively) and relative to placebo-treated patients (2.6 and 4.5 kg for 2 and 4 mg rosiglitazone bd, respectively). This weight gain, however, was coupled with a statistically significant decrease from baseline in the waist/hip ratio. Patients classified as treatment responders (≥0.7 percentage point reduction in HBA_{1c} from baseline) gained more weight than nonresponders.

TABLE 3. Change in FPG and fructosamine at week 26 compared to baseline and placebo

	Placebo	Rosiglitazone	
		2 mg daily	4 mg daily
FPG (mol/L)			
Baseline	12.71 ± 3.30	12.60 ± 3.42	12.21 ± 3.54
Change from baseline	1.05 ± 3.58	−2.11 ± 2.91[a]	−3.0 ± 2.85[a]
Difference from placebo		−3.22[b]	−4.22[b]
95% CI		−3.94, −2.50	−4.94, −3.50
Fructosamine (μmol/L)			
Baseline	391 ± 87.4	383 ± 84.9	382 ± 90.6
Change from baseline	20 ± 72.1	−34 ± 64.8[a]	−51 ± 58.6[a]
Difference from placebo (adjusted mean)		−55[b]	−73[b]
95% CI		−71, −39	−89, −57

Values are the adjusted mean ± SD. CI, Confidence interval.
[a] $P < 0.0001$.
[b] $P = 0.0001$.

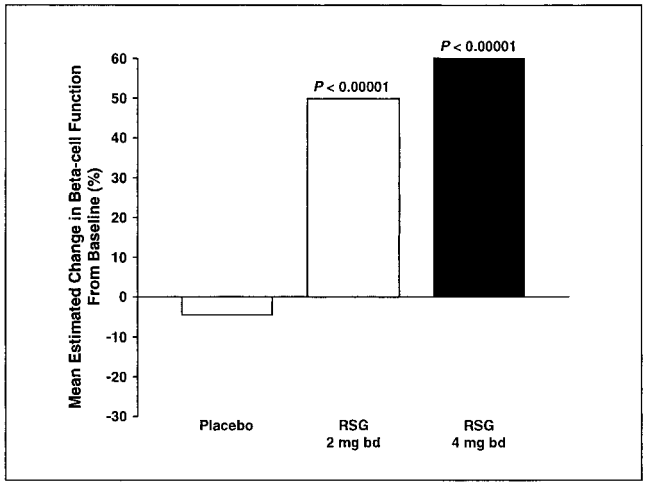

FIG. 4. Estimate of β-cell function as calculated by the HOMA model described in *Materials and Methods*. Data are the percent change compared with the baseline assessment. rosiglitazone treatment resulted in 50% and 60% improvement at 4 and 8 mg/day, respectively.

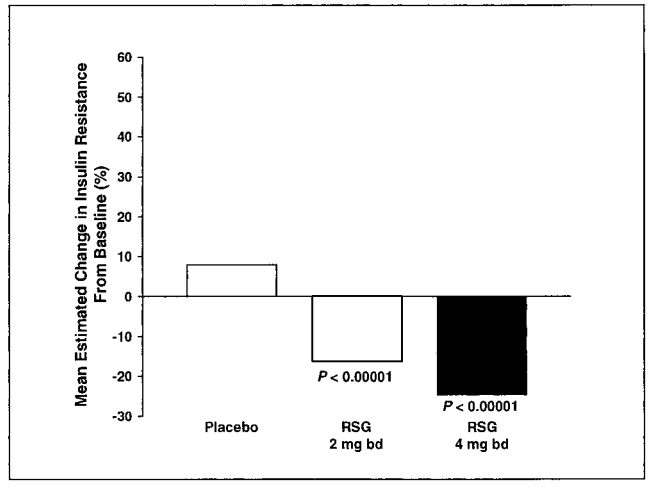

FIG. 5. Estimate in the improvement of insulin resistance as calculated by the HOMA model described in *Materials and Methods*. Data are percent decreases in insulin resistance (improvement in insulin sensitivity) relative to baseline values. Rosiglitazone (4 and 8 mg/day) improved insulin action by 16% and 25%, respectively.

Safety

The proportions of patients with at least one adverse experience during the double blind treatment phase in the rosiglitazone treatment groups (73.1–74.3%) were similar to the proportion in the placebo group (69.9%). The mean decrease in hemoglobin was 6.0 g/L in the 2 mg rosiglitazone bd group and 10.0 g/L in the 4 mg rosiglitazone bd treatment group. Corresponding mean decreases from baseline in hematocrit were 0.8 ($P = 0.0001$) and 2.1 percentage points ($P < 0.0001$), respectively. These hematological changes occurred primarily within the first 8–12 weeks of treatment; hemoglobin remained constant during the second 12 weeks of treatment, whereas hematocrit increased slightly. No patients withdrew due to anemia or decreased hemoglobin or hematocrit.

There were no significant changes from baseline in vital signs or electrocardiogram parameters for rosiglitazone-treated patients compared with placebo-treated patients. Thirty-one patients developed edema during the study: 3 in the placebo group, 10 in the 2 mg rosiglitazone bd group, and 18 in the 4 mg rosiglitazone bd group. All cases of edema were mild (25 cases) or moderate (6 cases), and no patient withdrew due to edema. One patient in the 4 mg rosiglitazone bd treatment group had a transient elevation of aminotransferase level of 217 U/L (reference range, 0–48 U/L) at week 4. However, medication was continued, and the aminotransferase level returned to within the reference range by week 8; the patient completed the study.

Discussion

The data from this large multicenter clinical trial show that rosiglitazone is an effective and well tolerated monotherapy for patients with type 2 diabetes treated for 26 weeks. For the entire study population, rosiglitazone decreased mean HbA_{1c} by 0.3 (2 mg bd) or 0.6 (4 mg bd) percentage points from baseline values after 6 months of treatment. Of patients receiving 4 mg rosiglitazone bd, 58.6% achieved a target mean HbA_{1c} of 8.0% or less and 29.6% achieved a target mean HbA_{1c} of 7.0% or less. In contrast, 6 months of treatment with placebo resulted in an increase in mean HbA_{1c} of 0.9 percentage points from baseline, with only 20.3% of patients achieving HbA_{1c} of 8% or less and 5.1% achieving HbA_{1c} of 7% or less. The absolute treatment effect of rosiglitazone, therefore, was to decrease mean HbA_{1c} by 1.2 percentage points (2 mg bd) and 1.5 percentage points (4 mg bd).

Achievement of glycemic targets was significantly influenced by prestudy glucose management therapy. Patients previously treated with diet and exercise alone responded better than those who were previously treated with monotherapy. In previously drug-naive patients, 4 mg rosiglitazone bd produced a decrease in mean HbA_{1c} from 8.5% at baseline to 7.5% at 26 weeks. By contrast, patients treated with 4 mg rosiglitazone bd who had previously received a single antihyperglycemic medication achieved a mean HbA_{1c} of 7.9%. These findings provide support for the early use of rosiglitazone in the treatment of patients with type 2 diabetes who are poorly controlled with diet and exercise alone.

The effects of rosiglitazone in decreasing plasma insulin levels, increasing body weight, increasing plasma LDL and HDL cholesterol, and lowering plasma free fatty acids are in accord with what is expected from a potent PPARγ agonist (34, 35). Observed reductions (or lack of increase) in plasma immunoreactive insulin, proinsulin, split proinsulin, and C peptide after rosiglitazone treatment reflect a decrease in insulin resistance, which has been demonstrated in previous studies of thiazolidinediones. Applying the HOMA model to the fasting plasma glucose and insulin levels in the trial population confirmed the effect of rosiglitazone in decreasing insulin resistance. Several recent studies have shown that the HOMA model provides a valid assessment of changes in insulin resistance in population-based studies (32, 37, 38). However, this tool is not yet validated for measuring improvements in β-cell function by other independent methods. Therefore, the data that it provides must be viewed as an intriguing estimate that needs further validation.

TABLE 4. Changes in fasting plasma insulin and its precursors at week 26 compared to baseline and placebo

	Placebo	Rosiglitazone	
		2 mg daily	4 mg daily
Immunoreactive insulin (pmol/L)			
Baseline	62.1 ± 44.3	63.6 ± 38.7	59.7 ± 41.0
Change from baseline	−4.1 ± 31.2	−6.6 ± 25.6[a]	−10.5 ± 31.1[b]
Difference from placebo		−2.4	−6.4
Proinsulin (pmol/L)			
Baseline	22.4 ± 26.9	19.3 ± 16.4	18.4 ± 17.0
Change from baseline	0.5 ± 23.9	−2.7 ± 8.3[b]	−5.2 ± 11.8[b]
Difference from placebo		−3.7	−6.6[b]
Split proinsulin (pmol/L)			
Baseline	33.0 ± 36.7	31.5 ± 26.7	30.1 ± 28.4
Change from baseline	−1.4 ± 26.72	−5.6 ± 17.83[b]	−10.5 ± 22.27[b]
Difference from placebo		−4.6	−10.0[b]
C Peptide (nmol/L)			
Baseline	1.00 ± 0.42	1.02 ± 0.43	0.99 ± 0.47
Change from baseline	−0.06 ± 0.40	−0.07 ± 0.31[c]	−0.15 ± 0.34[b]
Difference from placebo		−0.02	−0.09[d]

Values are the adjusted mean ± SD.
[a] $P = 0.0012$.
[b] $P = 0.0001$.
[c] $P < 0.05$.
[d] $P < 0.0271$.

TABLE 5. Mean change from baseline in urinary albumin/creatinine ratio in the entire patient population

Treatment group	Baseline ACR[a] (μg/mg)	% Change from baseline (95% CL)[b]
Placebo (n = 132)	17.8	+3.6 (−9.1, 18.0)
RSG, 2 mg daily (n = 142)	21.0	−14.0 (−25.3, −0.9)
RSG, 4 mg daily (n = 145)	16.0	−21.6 (−30.6, −11.3)[c]

[a] Geometric mean.
[b] Based on geometric means.
[c] By paired t test, $P < 0.001$.

TABLE 6. Mean change from baseline in urinary albumin/creatinine ratio in patients with baseline microalbuminuria

Treatment group	Baseline ACR[a] (μg/mg)	% Change from baseline (95% CL)[b]
Change from baseline		
Placebo (n = 33)	65.0	−13.2 (−36.7, +18.9)
RSG, 2 mg daily (n = 36)	95.7	−39.1 (−53.3, −20.7)
RSG, 4 mg daily (n = 35)	69.7	−42.1 (−56.2, −20.7)
Change *vs.* placebo		
RSG, 2 mg daily		−29.9 (−52.8, +4.2)
RSG, 4 mg daily		−33.3 (−55.2, −0.6)

[a] Geometric mean.
[b] Based on geometric means.

The weight gain observed in rosiglitazone-treated patients may be due to a combination of factors: increased adipocyte differentiation potentially leading to alterations in fat mass (39, 40), fluid retention and edema (39, 41), increased appetite, reductions in physical activity (42), and improved glycemic control. The relative contribution of these is unknown, but will be addressed in future studies. It is interesting to note that the increases in weight were accompanied by decreases in the waist to hip ratio from baseline, suggesting that rosiglitazone treatment leads to increased calorie storage in sc adipocytes, which are not associated with increased cardiovascular risk (43). Several studies measuring regional adiposity by computerized tomography suggest that troglitazone, another thiazolidinedione, decreases visceral and increases sc adipose tissue when given to type 2 diabetic patients (44, 45).

Fluid retention and expanded plasma volume may also contribute to the small decreases observed in hemoglobin and hematocrit in the rosiglitazone-treated groups. There was no significant incidence of elevated liver enzymes associated with rosiglitazone therapy. Furthermore, in approximately 3300 patients with type 2 diabetes treated with rosiglitazone for more than 6 months, there was no significant increase in ALT or other liver enzyme levels, which provides additional support for the hepatic safety of rosiglitazone (46).

Studies using data derived from HOMA calculations have suggested that β-cell function decreases with duration of diabetes in type 2 diabetic patients treated with diet therapy or antihyperglycemic therapy (47–49). In this 6-month study, HOMA estimates of β-cell function indicate that rosiglitazone significantly improves β-cell function. The improvement in β-cell function is probably secondary to the increased insulin sensitivity and the concomitant decrease in hyperglycemia. It will be important to determine whether the improvement in β-cell function that occurs with rosiglitazone therapy persists over several years.

Among rosiglitazone-treated patients who had microalbuminuria at baseline, ACR decreased relative to baseline and placebo. Microalbuminuria in diabetic patients is in part related to insufficient glycemic control and may show significant improvement with glycemic control or antihypertensive therapy (50, 51). As only a small percentage of rosiglitazone-treated patients were receiving concomitant antihypertensive therapy (13.7% and 16.5% of the 2 and 4 mg bd groups, respectively), this decrease is probably the result of either improved glycemic control observed with rosiglitazone or a different effect of thiazolidinediones on mesangial cell function (52).

Rosiglitazone is effective monotherapy for type 2 diabetes when used in patients previously treated with diet and ex-

TABLE 7. Plasma lipids and body weight: changes from baseline to week 26

	Placebo	Rosiglitazone	
		2 mg daily	4 mg daily
Total cholesterol (mmol/L)	0.15 ± 0.72[a]	0.66 ± 1.17[a]	0.73 ± 1.13[a]
HDL cholesterol (mmol/L)	0.06 ± 0.19[a]	0.11 ± 0.18[a]	0.11 ± 0.23[a]
Total/HDL cholesterol ratio	−0.12 ± 1.1	0.21 ± 1.5	0.37 ± 2.1[a]
LDL cholesterol (mmol/L)	0.15 ± 0.65[a]	0.43 ± 0.70[a]	0.61 ± 0.81[a]
Free fatty acids (g/L)	−0.0099 ± 0.076	−0.042 ± 0.079[a]	−0.045 ± 0.08[a]
BW (kg)	−1.0 ± 2.9	1.6 ± 3.1	3.5 ± 3.6
Waist/hip ratio	−0.002	−0.013[b]	−0.009[a]

Values are the mean ± SD.
[a] $P < 0.05$.
[b] $P < 0.02$.

ercise or in patients previously treated with antihyperglycemic monotherapy. The demonstrated effectiveness of rosiglitazone in improving glycemic control while decreasing insulin secretion was well tolerated, and there appears to be no sign of hepatotoxicity (53).

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