A Randomized Trial of Rosiglitazone Therapy in Patients With Inadequately Controlled Insulin-Treated Type 2 Diabetes

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OBJECTIVE — To determine the efficacy and safety of rosiglitazone (RSG) when added to insulin in the treatment of type 2 diabetic patients who are inadequately controlled on insulin monotherapy.

RESEARCH DESIGN AND METHODS — After 8 weeks of insulin standardization and placebo (PBO) run-in, 319 type 2 diabetic patients with mean baseline HbA_{1c} ≥7.5% (8.9 ± 1.1 to 9.1 ± 1.3) on twice-daily insulin therapy (total daily dose ≥30 U) were randomized to 26 weeks of additional treatment with RSG (4 or 8 mg daily) or PBO. Insulin dose could be downtitrated only for safety reasons. The primary end point was reduction of HbA_{1c} from baseline.

RESULTS — RSG 4 and 8 mg daily significantly improved glycemic control, which was unchanged on PBO. By intent-to-treat analysis, treatment with RSG 8 mg plus insulin resulted in a mean reduction from baseline in HbA_{1c} of 1.2% ($P < 0.0001$), despite a 12% mean reduction of insulin dosage. Over 50% of subjects treated daily with RSG 8 mg plus insulin had a reduction of HbA_{1c} ≥1.0%. Neither total:HDL cholesterol nor LDL:HDL cholesterol ratios significantly changed with RSG treatment. Serious adverse events did not differ among groups.

CONCLUSIONS — The addition of RSG to insulin treatment results in significant improvement in glycemic control and is generally well tolerated.

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Type 2 diabetes is a common and serious disorder that accounts for >$100 billion in annual health care expenditures in the U.S. alone (1), mostly because of chronic complications associated with the condition. It is characterized by an impaired sensitivity of target tissues to insulin and impaired insulin secretion by pancreatic β-cells, which leads to hyperglycemia and, over time, to microvascular and macrovascular complications (2–6). Results of the U.K. Prospective Diabetes Study (UKPDS) have shown that improvement of glycemic control reduces these complications and that progressive β-cell failure usually leads to the need for combination therapy to maintain glycemic control (7–10). The UKPDS demonstrated that even insulin-treated patients were unable to sustain adequate glycemic control.

The insulin-sensitizing effects of the thiazolidinedione (TZD) class of oral antidiabetic agents may alter the natural history of type 2 diabetes. By improving insulin sensitivity at the level of the target tissues, including adipose and muscle tissues, TZDs enhance the effectiveness of both endogenous and exogenous insulin (11), thereby improving glycemic control and perhaps slowing the decline of β-cell function. Rosiglitazone (RSG) is a potent TZD that binds to the peroxisome proliferator–activated receptor-γ and improves insulin action in isolated tissues (11), β-cell function in animals (12,13) and humans (14), and glycemic control in patients with type 2 diabetes (15,16).

This article reports the results of the efficacy and safety of RSG added to previously ineffective insulin monotherapy in patients with type 2 diabetes who participated in a multicenter randomized double-blind trial. The aim of this trial was to demonstrate the therapeutic effect of the addition of RSG 4 or 8 mg daily while attempting to keep insulin dosage constant, unless dose reduction was required to avoid hypoglycemia.

RESEARCH DESIGN AND METHODS

— This randomized double-blind placebo (PBO) controlled study was conducted at 38 centers in the U.S. and consisted of a screening visit, a 4-week insulin standardization period, a 4-week PBO run-in period, a 26-week treatment period, and a follow-up visit.

Patients deemed eligible at screening entered a standardization period, during which their insulin regimen was stan-

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Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CHF, congestive heart failure; FPG, fasting plasma glucose; I, insulin; PBO, placebo; RSG, rosiglitazone; TZD, thiazolidinedione; UKPDS, U.K. Prospective Diabetes Study; WHR, waist-to-hip ratio.

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

dardized to twice-daily injections. Insulin dose could be adjusted at the investigator's discretion during this period, but remained constant thereafter, unless dose reduction was required to avoid hypoglycemia. Subsequent reductions in insulin dosage were made at the discretion of the investigator.

After completion of the 4-week insulin standardization period, there was a 4-week single-blind PBO run-in period, during which the insulin dose was held constant and patients took RSG-matched PBO tablets twice daily. Patients were not eligible for subsequent randomization unless they had a fasting plasma glucose (FPG) of 7.8–16.7 mmol/l on insulin monotherapy. Eligible individuals were then randomly assigned to PBO, RSG 2 mg bid (4 mg total daily dose), or RSG 4 mg bid (8 mg total daily dose) in a 1:1:1 ratio. Patients continued their established insulin dose for the duration of the study, and alterations were permitted only in patients with sustained low glucose values (7-day mean capillary glucose level of <5.6 mmol/l on home monitoring), or in those with severe or recurrent hypoglycemic episodes. No other antidiabetic medications were allowed.

Double-blind study medication taken during the treatment period consisted of RSG or matched PBO tablets. Randomization codes were generated with an internal software system, and each bottle was labeled only with study number, medication code, and instructions for use. No patients, investigators, or SmithKline Beecham personnel directly involved in the study were aware of treatment allocation until the code was broken and the data analyzed.

Male and female patients 18–80 years of age were eligible if they met the National Diabetes Data Group definition for type 2 diabetes (17), if they were receiving ≥30 U insulin/day, and if they had a fasting C-peptide level ≥0.13 nmol/l and an HbA_{1c} ≥7.5% at the initial screening. Female patients had to be postmenopausal, surgically sterile, or using adequate contraception.

Patients were excluded from participation if they had any of the following at baseline: elevated liver enzymes (≥2.5 times the upper limit of the reference range), serum creatinine >160 mmol/l, anemia (Hb <11 g/dl for men or <10 g/dl for women), BMI <22 or >42 kg/m^2, a history of ketoacidosis, angina/New York Health Academy class III/IV cardiac insufficiency, electrocardiographic evidence of marked left ventricular hypertrophy, uncontrolled hypertension, or hemoglobinopathy. In addition, patients with a variation in body weight >10% while receiving insulin during the run-in period were excluded. Patients with FPG ≥19.4 mmol/l on two consecutive study visits were withdrawn from the study.

Each eligible patient gave written informed consent before initiation of any study-related procedures. Both the statement of informed consent and the study protocol were approved by an institutional review board at each study location before the center's initiation into the study. The study was conducted according to the U.S. Code of Federal Regulations Good Clinical Practice Guidelines and the Declaration of Helsinki (amended).

End points and safety parameters

The primary end point was change in HbA_{1c} from baseline after 26 weeks of treatment. Secondary end points included mean change from baseline in FPG, lipids, and total daily insulin dose and percent change from baseline in daily insulin dose. At each visit, laboratory specimens were collected before the patients' first daily doses of insulin and study medication.

Medical history, a complete physical examination, and an electrocardiogram were conducted before and after the treatment period. Blood pressure (BP), heart rate, body weight, glucose meter values, and compliance were monitored at all study visits. Vital signs, diabetes-related symptoms, hypoglycemic events, adverse events, and routine laboratory tests (including blood chemistry, hematology, urinalysis, and lipid profile) were assessed at weeks 4, 8, 12, 18, and 26. Liver function was monitored via aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and total bilirubin.

SmithKline Beecham Clinical Laboratories performed all laboratory tests except insulin assays. HbA_{1c} was assessed by Variant, a high-performance liquid chromatography method (Bio-Rad, Hercules, CA). Linco Research (St. Charles, MO) assayed insulin samples. Upon collection, samples for insulin assay were frozen immediately and shipped to SmithKline Beecham Clinical Laboratories for storage. The frozen samples were then shipped in bulk to Linco for analysis.

Statistical methods

The primary population for statistical inferences was the intent-to-treat population, defined as randomized patients with at least one on-therapy data point for the specified efficacy parameter. For patients who were withdrawn before the end of the 26-week study period, analyses were based on the last on-therapy value carried forward.

To assess differences between the treatment groups with regard to continuous variables (e.g., HbA_{1c}), an analysis of covariance procedure was used to account for the variability caused by regions, treatments, and baseline. The treatment comparisons of least-square means (adjusted treatment means) were performed using PROC MIXED in SAS. There were no statistically significant treatment-by-region interactions. Some secondary end points (total:HDL cholesterol ratio and LDL cholesterol) violated normality assumptions and were analyzed by Wilcoxon's rank-sum test.

Change and percent change from baseline in insulin dose were calculated by treatment groups. In addition, the extent of change in total daily insulin dose was also analyzed as ordered outcomes (decrease, no change, and increase in dose), and the pairwise comparisons between treatment groups were made using the extended Mantel-Haenszel χ^2 test (mean score statistic) (18). Comparisons among all three pairs of treatments were performed using Hochberg's modification to the Bonferroni multiple-comparison procedure with $P = 0.05$.

RESULTS — Of the 370 patients screened, 367 met the inclusion criteria and entered the PBO run-in phase. At the end of the run-in period, 319 patients (86.9%) were randomized to treatment. Of the 48 patients withdrawn before randomization, 29 failed to meet entry criteria, 7 were lost to follow-up, 4 were withdrawn because of protocol deviations, 4 were withdrawn because of adverse events, and 4 withdrew by personal choice. Six of the randomized patients were dispensed study medication but withdrew before valid postbaseline measurements could be obtained. Thus, the intent-to-treat population comprised 313 patients.

Table 1—*Baseline characteristics (all randomized patients)*

Characteristic	Treatment group		
	I+PBO	I+RSG 4 mg/day	I+RSG 8 mg/day
n	104	106	103
Age (years)	55.6 ± 10.3	57.1 ± 10.0	57.7 ± 10.2
Range	32–79	29–80	26–77
Sex (M/F)	58/46	60/46	56/47
Race (white/black/other)	71/19/14	76/20/10	73/16/14
BMI (kg/m^2)	32.7 ± 4.5	32.1 ± 4.8	32.3 ± 4.9
Years since diagnosis of diabetes	11.7 ± 6.2	12.7 ± 7.3	12.5 ± 8.0

Data are means ± SD or *n* unless otherwise indicated.

Demographic and baseline metabolic characteristics were comparable among the three treatment groups (Table 1). Similar proportions of the groups completed the study: 79, 81, and 77% in the insulin plus placebo (I+PBO), insulin plus rosiglitazone (I+RSG) 4 mg/day, and I+RSG 8 mg/day treatment groups, respectively. The most common reasons for withdrawal in the I+PBO group were deviation from protocol (7 of 107, 7%), lack of efficacy (5 of 107, 5%), and loss to follow-up (5 of 107, 5%). In the RSG groups, the most common reasons were adverse experiences (17 of 212, 8%) and protocol deviations (9 of 212, 4%).

Therapeutic efficacy

The patterns of HbA_{1c} and FPG values over the 26-week treatment period are illustrated in Fig. 1. Substantial reductions in glucose levels were evident as early as 2 weeks of dosing at 8 mg/day. In the RSG groups, maximal reductions in FPG and HbA_{1c} occurred between treatment weeks 8 and 12 (Fig. 1).

I+RSG twice daily resulted in statistically significant dose-related decreases in HbA_{1c} at week 26 compared with baseline or with insulin alone (Table 2). At week 26, more patients treated with I+RSG 4 or 8 mg/day versus patients treated with I+PBO demonstrated a decrease in HbA_{1c} of ≥0.7% (45.3 and 68.0 vs. 17.5%, respectively) or a decrease of ≥1% (34 and 59 vs. 11%, respectively). There were significant differences in change from baseline in mean FPG, which dropped steadily through week 8 in both I+RSG groups but increased to a small extent in the I+PBO group (Fig. 1*B*).

Patients with baseline HbA_{1c} ≥9% who were treated with I+RSG 4 or 8 mg/day had mean changes from baseline HbA_{1c} of −0.9 and −1.52%, respectively. This compares with a mean change of −0.2% for patients treated with I+PBO. Patients with HbA_{1c} ≥9% experienced a reduction from baseline in FPG levels of −0.14 and −0.17 mmol/l for I+RSG 4 and 8 mg/day, respectively, whereas FPG increased by 0.09 mmol/l in the I+PBO group.

In patients with baseline HbA_{1c} <9%, treatment with I+RSG 4 or 8 mg/day resulted in reductions from baseline of −0.4 and 0.9%, respectively. FPG levels decreased from baseline by 0.12 and 0.10 mmol/l in patients treated with I+RSG 4 or 8 mg/day, respectively. In the I+PBO group, HbA_{1c} increased by 0.3%, and FPG did not change in patients with baseline HbA_{1c} <9%.

Despite the intended restrictions in insulin dose reductions, total daily insulin dose was reduced for significantly more patients in the I+RSG 4 and 8 mg/day groups (36 of 106 patients, $P \leq 0.001$, and 45 of 103 patients, $P \leq 0.001$, respectively) than in the I+PBO group (14 of

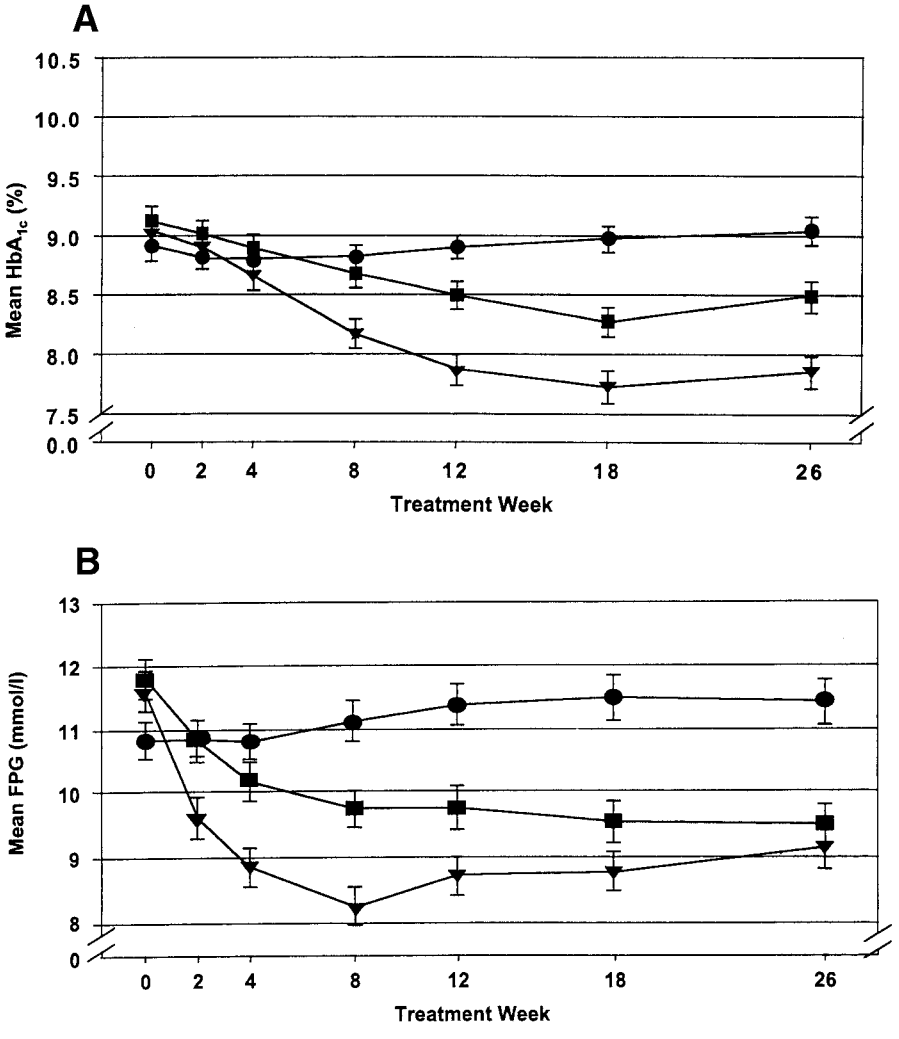

Figure 1—A: *HbA_{1c} over time.* —●—, *I+PBO;* —■—, *I+RSG 4 mg daily;* —▼—, *I+RSG 8 mg daily.* B: *FPG over time.* —●—, *I+PBO;* —■—, *I+RSG 4 mg daily;* —▼—, *I+RSG 8 mg daily. Error bars = SE.*

Table 2—*Changes in glycemic parameters at week 26*

	Treatment group		
	I+PBO	I+RSG 4 mg/day	I+RSG 8 mg/day
HbA_{1c} (%)*			
n†	103	106	103
Baseline	8.9 ± 1.1	9.1 ± 1.3	9.0 ± 1.3
Week 26	9.0 ± 1.2	8.5 ± 1.4	7.9 ± 1.4
Change from baseline	0.1 ± 1.0	−0.6 ± 1.1	−1.2 ± 1.1
P‡	0.2032	<0.0001	<0.0001
Difference from PBO§	—	−0.7	−1.3
P‖	—	<0.0001	<0.0001
FPG (mmol/l)¶			
n†	103	106	103
Baseline	10.8 ± 2.9	11.8 ± 3.2	11.6 ± 3.2
Week 26	11.4 ± 3.6	9.5 ± 3.2	9.1 ± 3.3
Change from baseline	0.6 ± 3.8	−2.3 ± 3.9	−2.5 ± 3.3
P‡	0.1273	<0.0001	<0.0001
Difference from PBO§	—	−2.2	−2.6
P‖	—	<0.0001	<0.0001
Insulin dose			
n†	104	106	103
Baseline (U)	70.1 ± 30.4	71.3 ± 43.8	77.7 ± 36.4
Week 26 (U)	69.7 ± 31.1	66.5 ± 38.2	68.3 ± 36.7
Change from baseline (U)	−0.4 ± 5.6	−4.8 ± 14.6	−9.4 ± 16.7
Percent change from baseline (%)	−0.6 ± 8.2	−5.6 ± 15.9	−12.0 ± 20.2

Data are means ± SD unless otherwise indicated. *Reference range: <6.5; †intent-to-treat population, last observation carried forward; ‡paired *t* test; §adjusted mean difference, pairwise comparison; ‖from comparisons of least-squares means within generalized linear model; ¶reference range: 13–50 years, 3.9–6.4 mmol/l; ≥50 years, 3.6–6.9 mmol/l.

104 patients). Mean total daily insulin dose reductions were 12, 5.6, and 0.6% for the I+RSG 8 mg/day, I+RSG 4 mg/day, and I+PBO groups, respectively (Table 2).

At week 26, RSG treatment was associated with significant decreases from baseline in free fatty acids in both the I+RSG 4 and 8 mg/day treatment groups. In both I+RSG treatment groups, these changes were significantly different from the slight increase in free fatty acids observed in the I+PBO group ($P < 0.01$) (Table 3).

Mean serum triglyceride levels did not significantly change from baseline in either I+RSG group compared with a significant increase in patients receiving I+PBO. Mean total cholesterol, LDL cholesterol, and HDL cholesterol increased in both RSG treatment groups. However, median total:HDL cholesterol and LDL:HDL cholesterol ratios were without changes from baseline in either I+RSG group and were similar across all treatment groups (ratios presented as medians because they required nonparametric analyses) (Table 3).

Safety parameters

Overall, treatment with RSG in combination with insulin was safe and well tolerated. The most common adverse event (AE) was symptoms consistent with hypoglycemia, which was reported in 57 of 107 patients (53%) of the I+RSG 4 mg group and 70 of 105 (67%) of the I+RSG 8 mg group compared with 41 of 107 (38%) in the I+PBO group. In all but four of these patients, the investigator classified the hypoglycemia as mild or moderate. Documented hypoglycemia, confirmed by an at-home capillary blood glucose concentration ≤2.8 mmol/l, was observed in 6% (I+PBO), 12% (I+RSG 4 mg), and 14% (I+RSG 8 mg) of patients. Three patients withdrew as a result of signs or symptoms of hypoglycemia; one was receiving I+PBO, and two were receiving I+RSG 8 mg/day. In the two groups receiving I+RSG, the proportion of patients having hypoglycemic events increased in the early months of the study. By 6 months, however, the monthly rate of hypoglycemia was the same as at baseline for these groups. In general, patients were managed by insulin dose reductions. More patients in the I+RSG groups reported edema (13.1% with I+RSG 4 mg and 16.2% with I+RSG 8 mg) than in the I+PBO group (4.7%). Investigators classified these events as mild to moderate, and none were considered serious. Congestive heart failure (CHF) was reported in two patients in each I+RSG group and in one patient in the I+PBO group. Of these, one patient in each I+RSG group had a prior documented history of CHF.

Small but statistically significant decreases in Hb (0.5 g/dl with I+RSG 4 mg and 1.0 g/dl with I+RSG 8 mg vs. 0.0 g/dl with I+PBO) and in hematocrit (1.9% with I+RSG 4 mg and 3.0% with I+RSG 8 mg vs. 0.3% with I+PBO) occurred during RSG treatment. A total of 36 patients (5, 14, and 17 in the I+PBO, I+RSG 4 mg, and I+RSG 8 mg treatment groups, respectively) had at least one episode of one type of edema during the double-blind treatment period. Four of these patients (two in each I+RSG treatment groups) entered the study with edema. No case of edema was considered to be a serious AE; therefore, no patients were withdrawn. BP was unchanged in the I+PBO and I+RSG 4 mg/day groups. There was a decrease of 2.6 mmHg in diastolic pressure in the I+RSG 8 mg/day group ($P < 0.005$). Body weight increased significantly in all treatment groups (mean increase 0.9, 4.0, and 5.3 kg in I+PBO, I+RSG 4 mg, and I+RSG 8 mg groups, respectively). There was no significant change in mean waist-to-hip ratio (WHR) relative to baseline or to the I+PBO group in either I+RSG treatment group. No patients showed an increase of AST, ALT, or alkaline phosphatase values >2.5 times the upper limit of the reference range or total bilirubin >1.5 times the upper limit of the reference range.

CONCLUSIONS — The results of this study demonstrate the efficacy of RSG in improving glycemic control in inadequately controlled insulin-treated patients with type 2 diabetes. RSG treatment resulted in a significant dose-related decrease in HbA_{1c} values and in a significant improvement in FPG concentrations. The effect of RSG on FPG concentrations was apparent within 2 weeks of initiating treatment. Its effect on HbA_{1c} values reached its nadir at 18 weeks and was sustained for the remainder of the study period. The

Table 3—*Change from baseline in secondary end points at week 26*

	Treatment group		
	I+PBO	I+RSG 4 mg/day	I+RSG 8 mg/day
FFAs (g/l)			
Reference range: 0.05–0.25			
*n**	101	104	103
Baseline	0.16 ± 0.08	0.17 ± 0.08	0.16 ± 0.07
Week 26	0.18 ± 0.08	0.15 ± 0.80	0.15 ± 0.07
Change from baseline	0.01 ± 0.08	−0.02 ± 0.07	−0.02 ± 0.08
P†	0.165	0.0066	0.0138
Triglycerides (mmol/l)			
Reference range: <2.26			
*n**	102	104	103
Baseline	2.57 ± 2.27	2.66 ± 2.92	2.45 ± 2.13
Week 26	3.10 ± 3.70	2.91 ± 2.53	2.50 ± 2.27
Change from baseline	0.53 ± 2.30	0.25 ± 3.24	0.05 ± 1.72
P†	0.0211	0.4253	0.7527
Total cholesterol (mmol/l)			
Reference range: <5.17			
*n**	102	104	103
Baseline	5.36 ± 0.93	5.48 ± 1.06	5.43 ± 1.24
Week 26	5.54 ± 1.29	5.99 ± 1.28	6.18 ± 1.51
Change from baseline	0.19 ± 0.85	0.51 ± 1.15	0.75 ± 1.36
P†	0.0262	<0.0001	<0.0001
HDL cholesterol (mmol/l)			
Reference range: >0.88			
*n**	102	104	103
Baseline	1.20 ± 0.34	1.21 ± 0.38	1.18 ± 0.39
Week 26	1.26 ± 0.35	1.28 ± 0.36	1.34 ± 0.50
Change from baseline	0.06 ± 0.2	0.17 ± 0.36	0.16 ± 0.46
P†	0.0006	0.0674	0.0005
LDL cholesterol (mmol/l)‡			
Reference range: 0–3.36			
*n**	95	98	98
Baseline	3.10 ± 0.84	3.19 ± 0.79	3.23 ± 0.98
Week 26	3.10 ± 0.94	3.43 ± 0.85	3.73 ± 1.18
Change from baseline (median)	0.01	0.28	0.38
P†	0.7598	0.0001	<0.0001
Total cholesterol:HDL ratio‡			
*n**	102	104	103
Baseline	4.75 ± 1.497	4.81 ± 1.407	4.92 ± 1.595
Week 26	4.63 ± 1.546	5.07 ± 1.890	5.08 ± 2.062
Change from baseline (median)	−0.13	0.11	0.06
P†	0.063	0.2522	0.6999
LDL:HDL ratio‡			
Reference range: N/A			
*n**	95	98	98
Baseline	2.67 ± 0.923	2.85 ± 0.986	2.83 ± 0.956
Week 26	2.53 ± 0.959	2.89 ± 1.048	3.00 ± 1.124
Change from baseline (median)	−0.13	0.05	0.07
P†	0.0106	0.4138	0.4199

Data are means ± SD unless otherwise indicated. FFA, free fatty acid. *Intent-to-treat population, last observation carried forward; †from paired *t* test; ‡parameter required nonparametric analysis.

improvements in FPG were evident despite decreases in the insulin dose of 6 and 12% in the RSG 4 and 8 mg/day treatment groups, respectively, and the design constraints, which attempted to minimize insulin dose reduction. However, owing to the robust glycemic reductions in some subjects, numerous patients required insulin dose reductions; 25 patients (24%) treated with RSG 8 mg/day and 15 patients (14%) treated with RSG 4 mg/day required a dose reduction of >20%. This is consistent with previous reports on the impact of adding a TZD to insulin therapy in patients with type 2 diabetes (19,20). There was no relationship between demographic or metabolic characteristics and improvements in glycemia. In addition, there were no predictors of response to RSG treatment.

These findings indicate that insulin-treated patients with type 2 diabetes may experience improved glycemic control with the addition of RSG. These data also suggest that the signs or symptoms of hypoglycemia might be anticipated when RSG is administered in combination with insulin and are easily managed with insulin dose reduction.

RSG was generally well tolerated. The proportion of patients reporting at least one on-therapy AE was increased in the I+RSG–treated patients. These differences are largely accounted for by the greater proportions of patients in the I+RSG treatment groups who had hypoglycemia, anemia, edema, arthralgia, weight gain, and hyperlipidemia. In all groups, the most frequently reported AE was hypoglycemia, an expected event by virtue of RSG's mechanism of action, which can be managed expectantly (as needed) with cautious RSG titration and insulin dose reduction as needed. An increased incidence of edema and decreases in mean Hb and hematocrit were also observed in patients treated with I+RSG. These effects are consistent with expansion of plasma volume and hemodilution, which has been observed during treatment with all members of the TZD class (11,21). The incidence of edema was greater than that observed with monotherapy or in combination with metformin and sulfonylureas (11,22,23). This increased incidence of edema has also been observed with use of pioglitazone in combination with insulin (24). The mechanism by which this occurs is unknown; plausible hypotheses for the increased incidence of edema with this combination include enhancement of the antinatriuretic or peripheral vasodilatory effects of insulin (25) as well as other host factors that might increase susceptibility. In this study, the incidence of heart failure was low in the groups treated with RSG and not clearly differ-

ent from the group treated with insulin alone. However, since TZDs and insulin can cause fluid retention, patients at risk for heart failure should be closely monitored. RSG treatment was also associated with significantly greater increases in weight as compared with patients treated with I+PBO. These increases may be attributable to several factors previously reported with TZDs, including improvement in glycemic control, fluid retention (11,21), adipocyte differentiation (11,26), and increased appetite (27). It is notable that despite weight increases observed with RSG treatment, no significant differences in WHR were observed between the I+RSG and I+PBO groups. There was no evidence of hepatotoxicity in this trial.

The changes in lipoprotein values seen during this study require additional comment. The observed reduction of plasma free fatty acid levels probably reflects a primary site of action, including the suppression of lipolysis and RSG at the adipose tissues (11). This change could contribute to improvement of insulin sensitivity in other tissues. RSG treatment had little effect on plasma triglyceride concentration. The ratios of serum HDL:LDL cholesterol and total:HDL cholesterol, predictors of cardiovascular risk (28,29), did not change because of the increase in HDL cholesterol concentrations, which was offset by an increase in total cholesterol levels.

Prescribers should be aware of the gradual onset of action of this agent, with maximal effects on HbA_{1c} occurring up to ≥3 months after treatment begins. Insulin dosage may need to be adjusted to avoid or manage hypoglycemia. Customary dose titration of RSG should be used, and insulin dosage should be adjusted. Furthermore, as reported with other TZDs, awareness of the potential for fluid retention in combination use with insulin is required.

These findings conclude that the coadministration of RSG with insulin results in a sustained improvement in glycemic control when administered to patients with type 2 diabetes who are poorly controlled on insulin therapy alone. In addition, these findings support early studies suggesting that RSG improves glycemic control by increasing insulin sensitivity in patients with type 2 diabetes.

APPENDIX

Rosiglitazone Clinical Trials Study Group

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