A Comparison of the Effects of Rosiglitazone and Glyburide on Cardiovascular Function and Glycemic Control in Patients With Type 2 Diabetes

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OBJECTIVE — This open-label, active-controlled study investigated the cardiac safety and antihyperglycemic effect of rosiglitazone (RSG) in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Of the 203 patients randomly assigned to RSG (4 mg b.i.d.) or glyburide (GLB) (titrated to achieve optimal glycemic control for the first 8 weeks only to limit the risk of hypoglycemia; mean 10.5 mg/day), 118 had an echocardiogram performed at week 52. Left ventricular (LV) mass index, ejection fraction, and left ventricular end-diastolic volume were assessed by M-mode echocardiography at baseline and weeks 12, 28, and 52; 24-h ambulatory blood pressure was assessed at baseline and at weeks 28 and 52. Glycemic control was assessed by measuring fasting plasma glucose (FPG) and HbA_{1c}.

RESULTS — Neither treatment produced an increase in LV mass index that exceeded 1 SD. Ejection fraction did not change in either group. Both groups had clinically insignificant increases in LV end-diastolic volume. RSG, but not GLB, caused a statistically significant reduction in ambulatory diastolic blood pressure. Both treatments reduced HbA_{1c} and FPG.

CONCLUSIONS — A total of 52 weeks of therapy with RSG (4 mg b.i.d.) did not adversely affect cardiac structure or function in patients with type 2 diabetes and produced significant and sustained reductions in hyperglycemia. Decreases in ambulatory diastolic blood pressure with RSG were superior to those with GLB.

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Rosiglitazone (RSG) is a member of the thiazolidinedione class of oral antidiabetic agents and reduces insulin resistance by sensitizing adipose, liver, and muscle tissues to the actions of circulating insulin (1). Clinical studies show that RSG significantly reduces insulin resistance, improves β-cell function, and improves glycemic control in patients with type 2 diabetes as monotherapy (2,3) or combination therapy (4).

Preclinical studies of the first approved thiazolidinedione, troglitazone, found reversible increases in heart weight in Wistar rats after chronic treatment with doses exceeding seven times those recommended in humans (5,6). In clinical trials, however, treatment with troglitazone produced no significant changes in left ventricular mass index (LVMI) after 48 weeks of surveillance (7,8). The present study assessed the effect of long-term RSG treatment on cardiac structure/function and glycemic control in patients with type 2 diabetes compared with glyburide (GLB), a second-generation sulfonylurea.

RESEARCH DESIGN AND METHODS

— This 52-week, randomized, open-label, active-control study compared the effects of RSG with GLB in patients with type 2 diabetes. It was conducted at 19 centers throughout the U.S. (see Appendix) in accordance with the Declaration of Helsinki (as amended in 1989 and 1996), 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.

The protocol consisted of a 2-week screening period, a 4-week placebo run-in period (single-blind, with diet maintenance), and a 52-week open-label treatment period. Patients aged 40–80 years were eligible if they met the National Diabetes Data Group definition for type 2 diabetes, with endogenous insulin production (fasting C-peptide concentration ≥0.8 ng/ml at screening). Female patients had to be postmenopausal, surgically sterile, or currently using hormonal contraceptives or intrauterine devices.

Patients were excluded from participation if they had clinically significant renal disease (serum creatinine level >1.8 mg/dl) or hepatic disease (alanine transaminase, aspartate transaminase,

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Abbreviations: ACEI, ACE inhibitor; AE, adverse event; BP, blood pressure; ECG, electrocardiogram; EF, ejection fraction; FPG, fasting plasma glucose; GLB, glyburide; ITT, intent to treat; LOCF, last observation carried forward; LV, left ventricular; LVEDV, LV end-diastolic volume; LVM, LV mass; LVMI, LV mass index; MR, mitral regurgitation; RSG, rosiglitazone.

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

total bilirubin, or alkaline phosphatase levels >2.5 times the upper limit of the normal laboratory range); previous treatment for myocardial infarction; New York Heart Association (NYHA) class III/IV coronary insufficiency or congestive heart failure; previous or existing treatment with ACE inhibitors (ACEIs), angiotensin II receptor antagonists, β-blockers, or calcium-channel blockers; echocardiographic evidence of marked left ventricular (LV) hypertrophy at baseline; or uncontrolled blood pressure (BP) (>160/>100 mmHg). Whereas patients taking diuretics and lipid-lowering agents were not excluded from the study, doses were not to be changed during the study unless deemed medically appropriate.

Previous oral antidiabetic medications (including GLB) were discontinued at the screening visit, at which time all patients received placebo and dietary instruction. Patients were reevaluated at 2-week intervals during the placebo run-in period. Those with fasting plasma glucose (FPG) ≥140 mg/dl but ≤300 mg/dl at visits 2 and 3 were eligible to enter the treatment period.

Eligible patients were randomly assigned to receive RSG (4 mg b.i.d.) or GLB (q.i.d. or b.i.d.), which was titrated at the discretion of the investigator to optimal glycemic effect over the first 8 weeks and then held constant for the duration of the study period. The dose of GLB did not exceed 20 mg/day. The randomization was stratified according to age (<65 years vs. ≥65 years), BMI (<27 kg/m^2 vs. ≥27 kg/m^2), and mean systolic BP (<140 vs. ≥140 mmHg).

The primary study end point was the change from baseline in LVMI at weeks 28 and 52, with the between-groups difference as the primary comparison of interest. In addition, the study assessed changes from baseline to weeks 28 and 52 in LV end-diastolic volume (LVEDV) and ejection fraction (EF), as well as mean values of BP, heart rate, arterial pressure, and pulse pressure (from 24-h ambulatory monitoring); glycemic control (HbA_{1c} and FPG); and serum lipids.

LV mass and cardiac function parameters

LVMI was assessed by M-mode echocardiography at baseline and after treatment weeks 12, 28, and 52. Echocardiograms were performed with a simultaneously recorded electrocardiogram (ECG) lead II or alternative limb lead with clear QRS deflection, at a recording speed of 50 mm/s for structures and 100 mm/s for timing of cardiac events. Measurements of LV end-diastolic dimensions were made at the onset of the QRS complex of the ECG, and end-systolic dimensions as the smallest dimension between the septum and posterior LV wall. Calibration markers included on the tracing were 0.5–1 cm apart in depth and 0.5 s apart in width (9,10). LV mass (LVM) was calculated using the American Society for Echocardiography convention (9), and LVMI was calculated by normalizing LVM to body surface area.

Echocardiograms were performed on-site at participating centers, and data were recorded on videotape and sent to a central site (Allegheny University, Pittsburgh, PA) for a blinded reading by an image analyst. The majority (98%) of echocardiogram measurements were made by a single image analyst; the remainder by a second image analyst. All measurements were reviewed for technical quality and clinical abnormalities by one of two physicians.

Standard 12-lead ECGs were performed at initial screening, baseline, and after weeks 12, 28, and 52 and read at each site.

Cardiovascular parameters

Within 7 days before baseline and at treatment weeks 28 and 52, 24-h ambulatory monitoring of BP, heart rate, arterial pressure, and pulse pressure was conducted. The cuff and monitor (Spacelabs model 90207; Spacelabs Medical, Redmond, WA) were placed on each patient at the study site, and each patient was instructed on its proper use.

Laboratory studies

Fasting clinical laboratory tests, including chemistry, hematology, and urinalysis, were performed at all study visits. All tests were performed by SmithKline Beecham Clinical Laboratories (Quest Diagnostics).

Safety assessments

Safety was assessed using the all-randomized patient population, defined as all patients who received at least one dose of medication. Clinical interpretation of safety was based on review of ECG and echocardiographic data, adverse event (AE) reports, and laboratory values.

Statistical methods

Descriptive statistics were calculated for both treatment groups for all primary and secondary parameters. Baseline was defined as time of randomization (visit 4).

For continuous variables, i.e., LVMI, LVEDV, EF, HbA_{1c}, FPG, and 24-h ambulatory BP assessments, an ANCOVA with terms for treatment, baseline, age (<65 and ≥65 years), baseline BMI (<27 and ≥27 kg/m^2), and baseline systolic BP (<140 and ≥140 mmHg) was performed to assess between-group differences. Based on this analysis, changes from baseline in echocardiographic measurements (LVMI, EF, and LVEDV) were analyzed using a 95% CI for the difference in treatment means. If the upper limit of the CI for the difference in LVMI or LVEDV was not >10% of the mean baseline across treatment groups (for EF the lower limit of the CI was greater than −10%), it was concluded that RSG did not cause more of an increase in LVMI or LVEDV or a decrease in EF than GLB and was therefore not inferior (11). A target sample size of 60 patients per treatment group was determined to provide a 90% power to detect this. In line with a similar study with troglitazone, a variation of 10 g/m^2 was considered as a conservative estimate of data variability (7). For echocardiographic parameters, the significance level used to calculate the 95% CI was 0.048, to adjust for a prior interim analysis. For nonechocardiographic parameters, the equality of the two treatment groups was tested using a 0.05 significance level. Differences between treatment groups at week 52 in hematocrit and hemoglobin were analyzed using one-way ANOVA, with unadjusted *P* values and a significance level of 0.05.

RESULTS — A total of 351 patients were recruited and entered the placebo run-in phase; 110 patients were withdrawn before randomization because they did not meet study criteria, 18 patients withdrew consent, and 20 patients were withdrawn (7 due to AEs, 1 due to lack of efficacy, 5 due to protocol deviation, 2 due to failure of ambulatory BP monitoring, 1 due to wrong medication, and 4 were lost to follow-up). A total of 203 patients (57.8%) were randomized to active treatment: 99 to GLB and 104 to RSG (4 mg b.i.d.) and were included in safety analyses. In addition, those who had at least one valid observation for any

Table 1—*Baseline characteristics (all randomized [observed case])*

	GLB	RSG
n	99	104
Gender (M/F)	71/29	75/25
Age (years)	56.1 ± 8.9	55.1 ± 9.0
Range	40–76	40–77
Race		
White/black/other	76/3/21	73/5/22
BMI ≥27 kg/m^2	65.7	67.3
Weight (kg)	85.1 ± 13.6	86.2 ± 15.6
Duration of diabetes (years)	6.2 ± 6.3	5.3 ± 6.2
HbA_{1c} (%)	9.5 ± 1.6	9.1 ± 1.7
Previous antidiabetic treatment		
Diet only	18.2	21.2
Single agent	69.7	70.2
Combination therapy	12.1	8.7
Concomitant hypertension	7.0	7.7

Data are % and means ± SD.

primary or secondary study variable were included in the intent-to-treat (ITT) population ($n = 196$), and those who had an observation at a given study time point were considered part of the all-randomized (observed case) population.

Demographic profile, baseline clinical characteristics, and history of diabetes were similar for the two treatment groups (Table 1). Of 203 patients randomized to treatment, 130 (64%) had any efficacy value at week 52, including 118 (58%) with a week-52 echocardiogram reading. Reasons for withdrawal from GLB or RSG included lack of efficacy (12%, $n = 12$ vs. 14%, $n = 15$), AE (4%, $n = 4$ vs. 8%, $n = 8$), protocol deviation (2%, $n = 2$ vs. 4%, $n = 4$), lost to follow-up (3%, $n = 3$ vs. 2%, $n = 2$), and other, e.g., invalid echocardiogram (13%, $n = 13$ vs. 11%, $n = 11$). The median dose following GLB titration (during the first 8 weeks of the study only) was 10.5 mg/day.

LVM and cardiac function parameters

At week 52, a change in LVMI of 3.4 ± 12.5 g/m^2 was observed in the RSG group, most of which occurred by week 28, compared with a change of −0.2 ± 9.1 g/m^2 for the GLB group (Table 2). Analysis of the ITT last observation carried forward (LOCF) population showed similar quantitative and qualitative effects (week 28: GLB 75.6 ± 17.0 g/m^2 vs. RSG 77.8 ± 17.8 g/m^2, week 52: GLB 75.6 ± 16.9 g/m^2 vs. RSG 78.2 ± 17.4 g/m^2). The adjusted mean difference of RSG compared with GLB was 2.7 g/m^2 (95% CI −0.2 to 5.6) and 2.9 g/m^2 (−0.7 to 6.5) for the ITT and all randomized population, respectively. In neither population was the upper 95% CI limit of the adjusted mean difference >10% of both treatment groups (7.6 and 7.7 g/m^2, respectively). Therefore, according to the statistical analysis testing for noninferiority, RSG was no different from GLB in terms of change from baseline LVMI. In addition, the 95% CI included 0, indicating that the traditional test for treatment differences is not statistically significant. No patient in either group started with a low or normal baseline LVMI or developed a high LVMI while on therapy. Furthermore, no patient exhibited an on-therapy increase in LVM of >60 g.

Both treatment groups exhibited an increase from baseline in LVEDV at week 52 (Table 2). The effects were comparable in the ITT (LOCF) population (week 28: GLB 88.0 ± 20.0 ml vs. RSG 95.2 ± 24.2 ml, week 52: GLB 88.3 ± 20.5 ml vs. RSG 95.9 ± 22.2 ml). Unlike LVMI, there were two significant baseline-by-treatment interactions. Among patients with baseline BMI <27 kg/m^2, a greater increase in LVEDV was observed in the GLB group than in the RSG group (12.8 ± 4.8 ml and 8.1 ± 4.9 ml for GLB and RSG, respectively). When baseline BMI was ≥27 kg/m^2, mean changes in LVEDV were 6.2 ± 2.8 ml and 16.4 ± 3.6 ml for GLB and RSG, respectively. Similarly among patients with a baseline systolic BP <140 mmHg ($n = 104$), RSG-treated patients appeared to have a greater increase in LVEDV (15.0 ± 3.3 ml) than GLB-treated patients (7.3 ± 2.4 ml). In those with a baseline systolic BP ≥140 mmHg ($n = 14$), a greater increase in LVEDV was observed in the GLB treatment group (16.5 ± 9.8 ml) than in the RSG treatment group (6.7 ± 3.7 ml).

There were no changes from baseline in EF in either treatment group at weeks 28 or 52 (Table 2) or according to the ITT (LOCF) analysis (week 28: GLB 66.9 ± 5.0% vs. RSG 66.1 ± 6.0%, week 52: GLB 66.6 ± 4.8% vs. RSG 65.6 ± 5.9%). The lower boundary of the 95% CI for the adjusted mean difference of rosiglitazone compared with GLB (ITT: −2.2 to 0.6%, all randomized: −2.4 to 0.9%) was within −10% of the mean baseline EF of both treatments combined (−6.6%), indicating that the effect of RSG on EF was not different from that of GLB.

Table 2—*LVM and cardiovascular function for all randomized patients with assessments at baseline, week 28, or week 52*

	GLB	RSG
LVMI (g/m^2)		
Baseline	75.8 ± 18.4 (81)	75.5 ± 19.9 (86)
Week 28	75.8 ± 17.2 (71)	78.2 ± 17.9 (72)
Week 52	78.0 ± 16.5 (63)	79.5 ± 17.9 (58)
LVEDV (ml)		
Baseline	81.0 ± 25.8 (78)	83.7 ± 23.8 (86)
Week 28	88.4 ± 20.5 (68)	98.3 ± 24.5 (72)
Week 52	90.8 ± 20.3 (60)	99.7 ± 20.5 (58)
EF (%)		
Baseline	65.7 ± 5.6 (78)	65.4 ± 6.7 (86)
Week 28	66.9 ± 5.3 (68)	66.1 ± 6.0 (72)
Week 52	66.6 ± 4.8 (60)	65.9 ± 5.9 (58)

Data are means ± SD (*n*).

Table 3—*Changes in 24-h ambulatory parameters at week 52 (all-randomized population)*

	GLB	RSG
*n**	66	63
Heart rate (bpm)		
Baseline	77.8 ± 8.4	78.3 ± 10.0
Change from baseline at week 52	2.2 ± 6.3	1.0 ± 6.2
P (paired *t* test)	0.0057	0.2049
Mean difference from GLB		−1.1
P		0.2811
Systolic BP (mmHg)		
Baseline	129.5 ± 13.5	131.2 ± 11.7
Change from baseline at week 52	3.8 ± 8.7	−0.1 ± 9.0
P (paired *t* test)	0.0006	0.9113
Mean difference from GLB		−3.5
P		0.0219
Diastolic BP (mmHg)		
Baseline	76.3 ± 7.7	78.0 ± 7.7
Change from baseline at week 52	0.7 ± 5.3	−2.3 ± 5.6
P (paired *t* test)	0.2801	0.0016
Mean difference from GLB		−2.7
P		0.0046
Pulse pressure (mmHg)		
Baseline	53.4 ± 11.0	53.7 ± 9.3
Change from baseline at week 52	3.1 ± 4.8	2.3 ± 5.0
P (paired *t* test)	<0.0001	0.0006
Mean difference from GLB		−0.9
P		0.2856
Mean arterial pressure (mmHg)		
Baseline	94.8 ± 8.9	96.4 ± 8.1
Change from baseline at week 52	1.9 ± 6.4	−1.4 ± 6.5
P (paired *t* test)	0.0189	0.0823
Mean difference from GLB		−2.8
P		0.0110

Data are means ± SE unless otherwise indicated. *Patients with values at baseline and week 52.

Cardiovascular assessments

Twenty-four–hour ambulatory monitoring revealed statistically significant differences in systolic BP, diastolic BP, and mean arterial pressure between the two treatment groups (Table 3). Changes were similar between day and night hours within either treatment group for any variable.

Laboratory assessments

By week 52, patients receiving RSG exhibited mean decreases in hemoglobin and hematocrit values of 1.0 ± 0.75 g/dl and 3.1 ± 2.82%, respectively, compared with decreases of 0.1 ± 0.75 g/dl and 0.7 ± 2.43% in GLB patients. The hemoglobin decrease occurred over the first 16 weeks and was nonprogressive. Small, clinically insignificant changes in white blood cell count (0.86×10^9/l from baseline) and platelet count were observed with RSG.

Glycemic control

Both RSG and GLB produced clinically and statistically significant reductions in HbA_{1c} and FPG at week 52 compared with baseline values. Twice as many patients achieved HbA_{1c} <7% at week 52 in the RSG group compared with GLB (28 vs. 13%). The temporal pattern of these decreases, however, differed between the two treatment groups. GLB treatment resulted in an initially rapid reduction in HbA_{1c} from week 0 through week 16, after which glycemic control progressively deteriorated. The progressive reductions in HbA_{1c} were sustained with RSG such that HbA_{1c} was comparable between treatment groups at week 52 (Fig. 1).

In RSG-treated patients, mean FPG decreased rapidly from 236.4 to 186.6 mg/dl between weeks 0 and 8, and it continued to decrease through week 52 to 161.1 mg/dl. Among GLB-treated patients, mean FPG decreased more dramatically than with RSG between weeks 0 and 8 from 245.5 to 170.8 mg/dl, remained stable from week 8 to week 16, and gradually increased through week 52 to 188.3 mg/dl.

Lipid parameters

Statistically significant median increases in both HDL and LDL cholesterol were observed in the RSG group (7.7 mg/dl for each). LDL cholesterol increased from 140.2 to 146.5 mg/dl in the RSG group and decreased from 135.4 to 126.5 mg/dl in the GLB group. The proportion of patients with LDL cholesterol >100 mg/dl at week 52 was 89% in the RSG group and 77% in the GLB group. The increase in LDL cholesterol was observed during the first 4–8 weeks of therapy, whereas the increase in HDL cholesterol progressed through week 52, at which time total cholesterol–to–HDL cholesterol and LDL cholesterol–to–HDL cholesterol ratios were reduced from baseline values in the RSG treatment group (from 5.2 to 4.8 and from 3.1 to 2.9, respectively). Triglyceride levels did not significantly change in either treatment group at week 52 compared with baseline (RSG group: from 226.6 to 223.8 mg/dl, GLB group: from 189.6 to 175.8 mg/dl).

Safety parameters

The absolute number and percentage of patients with at least one AE while on therapy were similar between the two treatment groups. Four patients on GLB and eight patients on RSG were withdrawn due to an AE. No AE, apart from hyperglycemia and nocturia in the RSG group only, caused the withdrawal of more than one patient. The overall incidence of cardiac-related AEs also was similar in the GLB (12.1%) and RSG (15.4%) groups. Heart disorder was reported in nine patients in the RSG group compared with five patients in the GLB group; cardiomegaly was reported in five patients in the RSG group compared with two patients in the GLB group. All other cardiac-related events (including mitral insufficiency, tachycardia, myocardial infarction, and palpitation) occurred in fewer than three patients in each treatment group. One RSG-treated patient developed clinical heart failure after 20 days of treatment with RSG, and underlying causality was attributed to coronary artery disease. There were no patients with an investigator-reported history of mitral re-

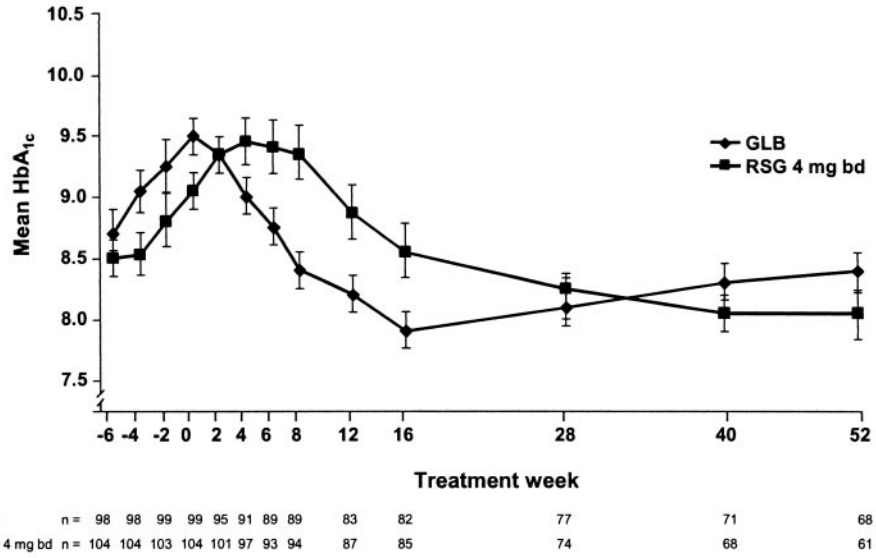

Figure 1—*Mean HbA_{1c} over time (all-randomized [observed case] population). Error bars = SE.*

gurgitation (MR) at randomization. One RSG-treated patient had MR noted on the baseline echocardiogram with a subsequent on-therapy AE of MR reported. A second RSG-treated patient and two GLB-treated patients had on-therapy events of MR. In no case was it concluded that MR was worsened during the study for either therapy. RSG-treated patients had more reports of edema and anemia (6.7% each) than patients in the GLB group (1 and 2%), but no cases led to withdrawal. There were no changes in dose among patients receiving concomitant diuretics or lipid-lowering therapy. No ACEIs or α-2 blockers were used during the study. However, two RSG-treated patients initiated diuretic therapy as a result of a fluid-related event.

Data from patients with both baseline and week-52 values showed that mean body weight increased by 3.4 kg (95% CI 2.7–4.1 kg) with GLB and by 5.0 kg (3.7–6.2 kg) with RSG. The largest magnitude of change was observed through week 28 for both treatment groups. With continued exposure, modest weight gain was observed in both groups. Signs and symptoms of hypoglycemia were reported more commonly in GLB-treated patients (7.1%) than in RSG-treated patients (1.9%); three of the seven GLB-treated patients who reported hypoglycemia required corrective action, but there was no need for withdrawal. No RSG-treated patient had liver function parameters that were of potential clinical concern.

CONCLUSIONS — Cardiac safety is important for any agent used in patients with type 2 diabetes. Up to 30% of patients with type 2 diabetes have clinically significant hypertension (12), and cardiovascular disease is a major complication and the leading cause of death for patients with type 2 diabetes.

The current study assessed the effects of 52 weeks of treatment with RSG at a maximum therapeutic dosage on cardiac safety in patients with type 2 diabetes. The study population was not reflective of patients with type 2 diabetes who generally present to physicians in the U.S. in that the majority of patients were Caucasian men who were drug naive. As a safety study, the primary analysis was performed more conservatively, using observed cases in order to maximize the chances of detecting any treatment effect on cardiac structure or function. Analyzing the data on the basis of noninferiority of RSG against GLB was considered the most appropriate method of accounting for influences of the natural history of diabetes. The results demonstrated that patients treated with RSG for 1 year experienced no greater incidence of adverse cardiac effects or echocardiographic changes compared with patients treated with GLB, a commonly prescribed sulfonylurea, that had been maximally titrated to achieve glycemic control up to week 8. Furthermore, whereas RSG showed comparable effects to GLB on HbA_{1c} at week 52, the magnitude of reduction in HbA_{1c} and FPG achieved with GLB deteriorated from week 16, whereas the glycemic response to RSG was more durable, such that reductions in FPG were diverging between treatment groups by week 52.

After 28 and 52 weeks of treatment, small but significantly different increases from baseline in LVMI were observed in the RSG group. The changes occurred primarily by week 28 but did not progress further to week 52. However, the change in LVMI in the RSG group was not statistically significantly different to that in the GLB group, with mean values in both groups staying within 1 SD of the mean value in healthy patients (9). Analysis of both ITT and all randomized populations was consistent with this finding, thereby addressing the potential for a survival bias. Using two-dimensional echocardiography, Ghazzi et al. (7) showed that treatment with troglitazone was also not associated with any clinically or statistically significant change in LVMI. The use of M-mode echocardiography for these estimates for RSG precluded an assessment of diastolic function such that changes in ventricular compliance could not be evaluated. Small increases in LVEDV were observed in both groups at weeks 28 and 52 as well as a relation between baseline BMI and BP, but none of these were considered clinically relevant because the final values did not exceed the mean normal value plus 1 SD (10). Despite the increase in intravascular volume reflected by the increase in LVEDV, there was a small but statistically significant decrease in ambulatory diastolic BP relative to baseline in the RSG-treated group that was not observed in the GLB-treated group. Increases in fluid retention and plasma volume are a well-described class effect associated with the thiazolidinediones that may be associated with a corresponding increase in LVEDV and a small increase in LVMI (13–15). The increase in systolic BP observed in GLB-treated patients is not unexpected, as this effect has been shown in animal studies with this treatment (16). In line with observations with troglitazone, RSG but not GLB has shown vasodilatory effects on forearm blood-flow resulting in reduced peripheral vascular resistance and consequent lowering of diastolic BP (13,17,18). Reductions in BP accompanied by a decrease in total peripheral resistance have also been recorded in patients treated with troglitazone (13,19,20), and BP re-

ductions have also been shown with pioglitazone in patients (21). Estimates of peripheral vascular resistance were not obtained in this study, but observations were consistent with effects shown by troglitazone. The reduction in peripheral vascular resistance potentially stimulates sodium absorption and may explain the increase in LVEDV observed in this study. One may also postulate that the greater effect of RSG on LVEDV observed in patients with BMI $\geq$27 kg/m^2 could be explained by plasma volume expansion that may be more prominent in obese patients. This is based on the hypothesis that the decrease in vascular resistance is related to restored insulin sensitivity and vasodilatory responses in resistance vessels (22). The reason why LVMI increased slightly in the RSG group is not so clear.

The two effects of RSG on LVMI and diastolic BP might be comparable with the physiological effects of pregnancy, whereby plasma volume expansion is also associated with an increase in cardiac mass (23). Both troglitazone and RSG have been shown to exert a suppressive effect on reactive oxygen species generation and oxidative stress and to improve postischemic flow-mediated vasodilatation (17,24). Reduction in superoxide generation may improve the bioavailability of nitric oxide to cause vasodilatation.

The overall frequency of AEs was similar in the two treatment groups and characteristic of previous observations (2,3,25). In accord with the study objectives, the use of drugs with potential effects on cardiac mass were excluded. As a result, few patients with a previous history of hypertension were studied, and therefore while not altering the interpretation of the results, the study population was not totally representative of patients with type 2 diabetes. The effects of RSG in hypertensive patients with type 2 diabetes, preexisting LVH, and increased LVMI are unknown. As expected, signs or symptoms of hypoglycemia were more frequent in the GLB group (26). The limitations on dose titration of GLB were imposed not only to minimize the risk of hypoglycemia occurring, but also to explore the potential durability of therapeutic effects of these two antidiabetic agents. Although this study is rather an inexact comparison of the two agents, it does highlight the differences in stability of the responses at fixed dosages (dosage of the sulfonylurea was fixed after an 8-week period of titration to maximal glycemic control) (26). The weight gain observed in patients treated with RSG was consistent with that previously reported and could be attributable to increased adipocyte differentiation or fluid retention (4,27–29).

In summary, this open-label study of cardiac safety and antihyperglycemic effect of 52 weeks of treatment with RSG demonstrated small but clinically insignificant effects of RSG on cardiac mass. These changes were no different than those observed with GLB treatment (at a dosage titrated to achieve maximum glycemic control during the first 8 weeks of the study). This was combined with predictably minor changes in hemoglobin and hematocrit, sustained reductions in hyperglycemia, characteristic effects on lipid profile, an increase in LVMI statistically no different from GLB, and reductions in ambulatory diastolic BP compared with GLB.

APPENDIX

RSG Clinical Trials Study Group

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