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ORIGINAL ARTICLE

Rosiglitazone reduces urinary albumin excretion in type II diabetes

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This study examines the effect of rosiglitazone on urinary albumin excretion (UAE) in patients with type II diabetes. Urinary albumin : creatinine ratio (ACR) was measured in a 52-week, open-label, cardiac safety study comparing rosiglitazone and glyburide. Patients were randomised to treatment with rosiglitazone 4 mg b.i.d. or glyburide. ACR was measured at baseline and after 28 and 52 weeks of treatment. Statistically significant reductions from baseline in ACR were observed in both treatment groups at week 28. By week 52, only the rosiglitazone group showed a significant reduction from baseline. Similar results were observed for the overall study population and for the subset of patients with baseline microalbuminuria. For patients with microalbuminuria at baseline, reductions in ACR did not correlate strongly with reductions in glycosylated haemoglobin, or fasting plasma glucose, but showed strong correlation with changes in mean 24-h systolic and diastolic blood pressure for rosiglitazone-treated patients (ΔACR *vs* Δmean 24-h systolic blood pressure, $r=0.875$; ΔACR *vs* Δmean 24-h diastolic blood pressure, $r=0.755$; $P<0.05$ for both). No such correlation was observed for glyburide-treated patients. In conclusion, rosiglitazone treatment was associated with a decrease in urinary albumin excretion. These findings suggest a potential beneficial effect of rosiglitazone in the treatment or prevention of renal and vascular complications of type II diabetes.
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Introduction

Microalbuminuria, defined as a urinary albumin excretion (UAE) rate between 30 and 300 mg/24 h,[1] is widely considered to be a marker of impaired vascular integrity in type II diabetic patients. It is considered to be an early indicator of renal and cardiovascular disease risk,[2,3] as well as of an increased risk of all-cause mortality.[4,5] Thus, microalbuminuria is an indication for aggressive intervention to improve glycaemic and blood pressure (BP) control and to reduce cardiovascular risk factors.

The thiazolidinediones are a class of compounds that improve glycaemic control by enhancing insulin sensitivity in skeletal muscle, liver, and adipose tissue through activation of their target receptor, peroxisome proliferator-activated receptor gamma (PPARγ).[6] This property has led to their current utility as antidiabetic drugs. The activation of PPARγ by thiazolidinediones has been shown to have a range of beneficial vascular effects, including vasorelaxation via blockade of K^+ channels[7] and reduction of voltage-gated Ca^{2+} current,[8] inhibition of the proliferation and migration of vascular smooth muscle cells,[9,10] inhibition of angiogenesis,[11] and improvement in markers of inflammation and fibrinolysis.[12–14] These observations indicate a potential for thiazolidinediones to modify risk of vascular complications in diabetes.

Rosiglitazone (RSG) was shown to reduce UAE (as assessed by the urinary albumin : creatinine ratio [ACR]) in a 26-week, randomised, placebo-controlled study.[15] In this study, RSG treatment produced statistically significant reductions in ACR compared with both baseline and placebo. In the present study, we confirm and extend these results by examining the effects of RSG on urinary ACR in a 52-week, open-label, cardiac-safety study comparing RSG and glyburide (GLB).[16]

Research design and methods

Experimental design and patients

This was a multicentre, randomised, cardiac-safety study. The primary study variable was change from

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baseline in left ventricular mass index. Men and women 40–80 years of age with type II diabetes were eligible. Prior (within 12 months of screening) or concomitant use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, beta-blockers, or calcium-channel blockers was prohibited due to the potential for these compounds to affect cardiac remodelling and confound the interpretation of the primary study end point. Other classes of antihypertensive compounds were permitted. Prior antidiabetic therapy was discontinued at screening and a 4-week placebo run-in period ensued. Patients were subsequently randomised to treatment with RSG 4 mg b.i.d. ($n=104$) or GLB ($n=99$). The sample size was chosen to give 90% power to demonstrate noninferiority of RSG to GLB in the primary study variable, based on a criterion set at 10% of the mean baseline value. GLB dosage was adjustable for the first 8 weeks to optimise glycaemic control, after which the dosage was held constant (mean dose level 10.5 mg/day, median dose level 10 mg/day).[16]

The study was conducted in accordance with the Declaration of Helsinki (1989 amendment), Title 21 of the US Code of Federal Regulations, and Good Clinical Practice Guidelines. The Institutional Review Board at each centre approved the protocol, and participants provided informed consent prior to study enrolment.

Assessments

All patients received a physical examination at screening and at the end of the treatment period. Interim medical histories, adverse event reports, and standard laboratory assessments were obtained at each visit. BP was measured in triplicate at each visit using the patient's nondominant arm and following a 10 min rest using a standard mercury sphygmomanometer. The 24-h ambulatory (A)BP was also measured at baseline and at weeks 28 and 52. The ABP data were analysed by Spacelabs Medical Devices, Inc. (Redmond, WA, USA).

Study visits were conducted in the morning, with patients in the fasting state. Urinary ACR was measured from random morning-voided specimens at baseline and after 28 and 52 weeks of treatment. Microalbuminuria was defined as ACR $\geqslant 30\,\mu$g/mg to $<300\,\mu$g/mg and normoalbuminuria as ACR $<30\,\mu$g/mg.

All laboratory tests were performed by SmithKline Beecham Clinical Laboratories (Van Nuys, CA, USA). Glycosylated haemoglobin (HbA_{1c}) was measured by high-performance liquid chromatography (Bio-Rad Variant™). Fasting plasma glucose (FPG) was measured by an Olympus analyser (Bio-Rad, Hercules, CA, USA). Urinary albumin was measured using radioimmunoassay. Urinary creatinine was determined using the modified Jaffe alkaline picrate method, and ACR was calculated.

Statistical analyses

ACR data were $\log_e$-transformed and changes from baseline and between treatment groups examined by analysis of covariance, with adjustment for $\log_e$-transformed baseline values. Results of the analysis were exponentiated to obtain the ratio of post-treatment to pretreatment ACR, and then expressed as percentage change from baseline (with 95% confidence intervals).

Statistical analyses were performed on all randomised patients with an ACR measurement at baseline and at week 52 (for GLB treatment group, $n=64$; for RSG treatment group, $n=57$). For ACR changes at week 28, ACR patients with data at baseline and at both weeks 28 and 52 were measured (for GLB treatment group, $n=62$; for RSG treatment group, $n=54$). Separate analyses were performed for all randomised patients and for those with microalbuminuria at baseline.

Results

Patients

Baseline and demographic characteristics of patients in this study are presented in Table 1. Patient characteristics were comparable between treatment groups.

Urinary albumin excretion (UAE)

After 28 weeks of treatment, both treatment groups showed reduced UAE. Statistically significant reductions from baseline in ACR were observed for the RSG and GLB treatment groups (Figure 1a). The magnitude of the reduction in both groups was similar. At week 52, however, only the RSG treatment group demonstrated a statistically significant reduction from baseline ACR. No significant difference between treatment groups for reduction from baseline in ACR was observed at either time point (Figure 1b). Similar results were observed for the all randomised population and for patients with microalbuminuria at baseline. The fact that no significant difference was observed between treatment groups may have been due to the low power of the study to detect such differences (see the Discussion).

A greater proportion of RSG-treated patients achieved normoalbuminuria (ACR $<30\,\mu$g/mg) than did GLB-treated patients (Table 2). In the RSG 4 mg b.i.d. group, 43% of patients with baseline microalbuminuria had achieved normoalbuminuria at week 52, compared with 6% of those in the GLB group. Moreover, fewer patients in the RSG group developed microalbuminuria during the treatment course. Although these differences were not shown to be statistically significant (exact Cochrane–Mantel–Haenszel trend test, $P=0.51$), they are

Table 1 Summary of baseline demographic and metabolic characteristics

	Treatment group	
	GLB	*RSG 4 mg b.i.d.*
Age (years, mean ± s.d.)	56.1 ± 8.94 (*n*=99)	55.1 ± 8.96 (*n*=104)
Gender (male:female, %)	71:29 (*n*=99)	75:25 (*n*=104)
Prior therapy (diet:mono:combination, %)	18:70:12 (*n*=99)	21:70:9 (*n*=104)
HbA_{1c} (%, mean ± s.d.)	9.5 ± 1.59 (*n*=99)	9.1 ± 1.68 (*n*=104)
24-h ambulatory systolic BP (mmHg, mean ± s.d.)	129.5 ± 13.51 (*n*=66)	131.7 ± 11.73 (*n*=63)
24-h ambulatory diastolic BP (mmHg, mean ± s.d.)	76.3 ± 7.65 (*n*=66)	78.0 ± 7.65 (*n*=63)

GLB=glyburide; RSG=rosiglitazone; s.d.=standard deviation; HbA_{1c}=glycosylated haemoglobin; BP=blood pressure.

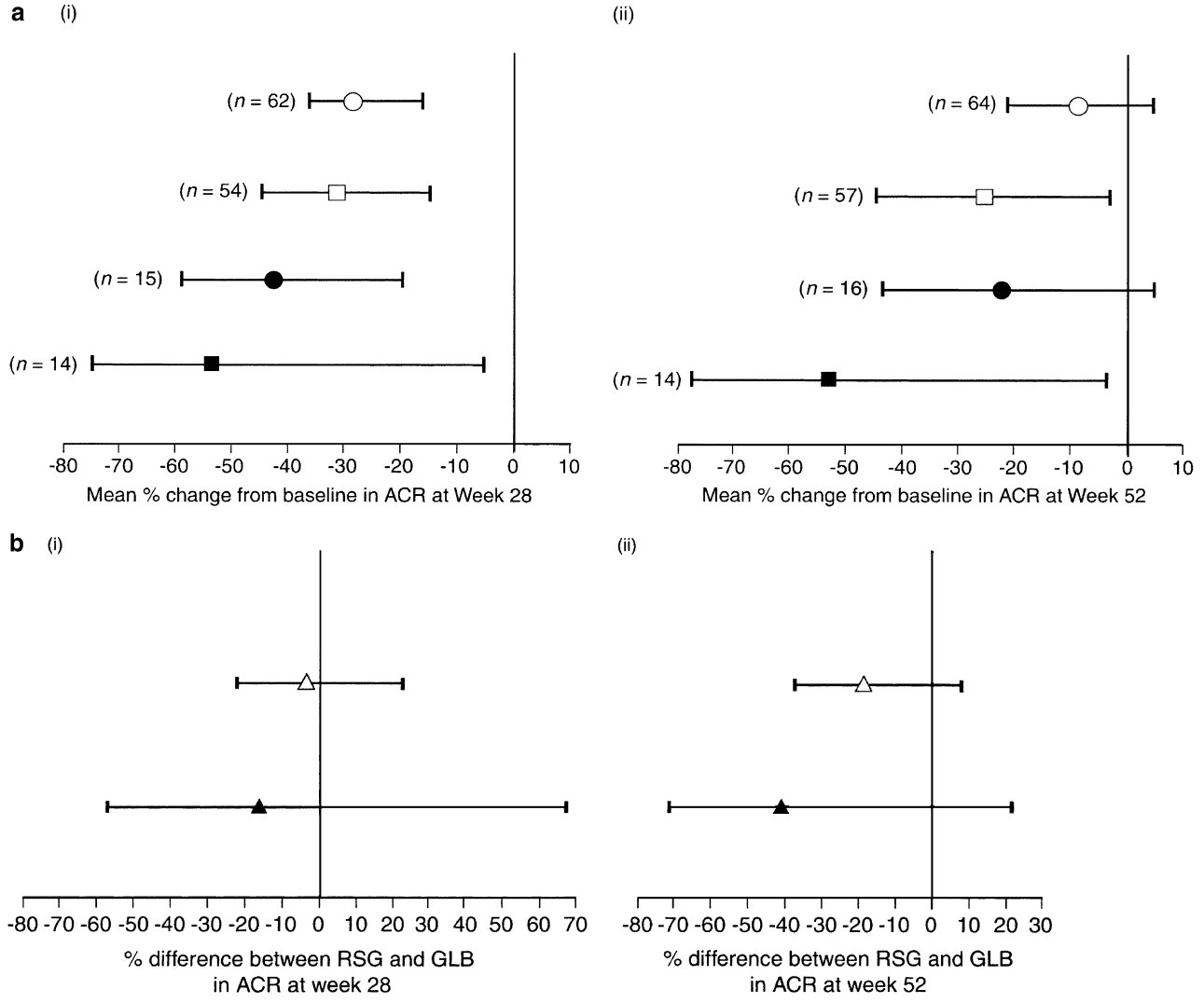

Figure 1 (a) Percentage change (95% confidence interval) from baseline in ACR (from geometric mean of ratio). (i) week 28 (ii) week 52. All patients: ○: GLB; □: RSG. Patients with baseline microalbuminuria: ●: GLB; ■: RSG; ACR=albumin : creatinine ratio; GLB=glyburide; RSG=rosiglitazone. (b) Percentage difference (95% confidence interval) between RSG and GLB in ACR (from geometric mean of ratio). (i) week 28 (ii) week 52. △: all patients; ▲: patients with baseline microalbuminuria; RSG=rosiglitazone; GLB=glyburide; ACR=albumin : creatinine ratio.

Table 2 Outcome of patients with baseline microalbuminuria and normoalbuminuria at study completion[a]

Treatment group	*Baseline microalbuminuria*	*Baseline normoalbuminuria*	*Baseline microalbuminuria normalised by study end (%)*	*Baseline normoalbuminuria progressed by study end (%)*
GLB[b] (*n*=64)	16	47	1 (6.3)	5 (10.6)
RSG 4 mg b.i.d. (*n*=57)	14	43	6 (42.9)	3 (7.0)

[a]Patients with albumin : creatinine ratio values at baseline and at week 52.
[b]One patient in the GLB group had macroalbuminuria at baseline and study completion.
GLB=glyburide; RSG=rosiglitazone.

consistent with the greater reduction from baseline in urinary ACR observed in the RSG treatment group at week 52.

Correlation analysis

Management of microalbuminuria is generally focused on treatment of factors contributing to the development of this condition, such as hyperglycaemia and/or hypertension. With this in mind, we set out to determine whether changes in ACR could be correlated with changes in glycaemic parameters (HbA_{1c} and FPG), sitting BP, or 24-h ABP in this study.

RSG treatment yielded significant decreases from baseline in mean HbA_{1c}, (change from baseline $\pm$ standard deviation (s.d.), $-0.9 \pm 1.38\%$), FPG (change from baseline $\pm$ s.d., -65.1 ± 51.2 mg/dl), and mean 24-h diastolic BP (change from baseline $\pm$ s.d., -2.3 ± 5.58 mmHg) following 52 weeks of treatment. Glycaemic control was similar in the two treatment groups (for GLB treatment group, change from baseline in HbA_{1c} [$\pm$ s.d.], $-0.9 \pm 1.39\%$; change from baseline in FPG [$\pm$ s.d.], -56.0 ± 58.0 mg/dl). There was a statistically significant treatment effect on ABP parameters favouring RSG: mean 24-h systolic (S) BP showed a decrease of 3.5 mmHg, and mean 24-h DBP showed a decrease of 2.7 mmHg, for RSG treatment relative to GLB ($P<0.05$ for both differences).[16]

Correlation analysis revealed weak or inconsistent associations between changes in glycaemic parameters or mean sitting BP and changes in urinary ACR (Table 3). A statistically significant correlation between change in ACR and change in HbA_{1c} was observed in the RSG treatment group for the total study population but not the baseline microalbuminuria subgroup. No statistically significant correlation with changes in FPG was observed.

There were statistically significant correlations between changes in ACR and mean 24-h SBP and DBP for RSG-treated patients in both the all randomised group and the subset with microalbuminuria at baseline. Correlations between these parameters were especially strong for patients with baseline microalbuminuria ($r=0.875$ for ΔACR *vs* Δmean 24-h SBP; $r=0.755$ for ΔACR *vs* Δmean 24-h DBP; $P<0.05$ for both correlations). In the GLB treatment group there was a relatively small but statistically significant correlation between change in ACR and change in mean 24-h SBP for the all randomised group. There was no such correlation in the microalbuminuric subset for these parameters, nor was any statistically significant correlation observed between changes in mean 24-h DBP and ACR in the GLB treatment group.

Table 3 Correlation between change from baseline to study end point in ACR and study parameters: all patients

Parameter	*Correlation coefficient for change from baseline in ACR*	
	GLB (n)[a]	*RSG* (n)[a]
All randomised patients		
HbA_{1c}	0.074 (62)	0.356* (54)
Fasting plasma glucose	0.122 (62)	0.262 (54)
Sitting SBP	0.157 (59)	0.241 (52)
Sitting DBP	0.169 (59)	−0.023 (52)
MASBP	0.283* (58)	0.415* (52)
MADBP	0.238 (58)	0.317* (52)
Randomised patients with baseline microalbuminuria		
HbA_{1c}	0.484 (15)	0.397 (14)
Fasting plasma glucose	0.291 (15)	0.344 (14)
Sitting SBP	−0.193 (15)	0.515 (14)
Sitting DBP	0.092 (15)	−0.037 (14)
MASBP	0.083 (15)	0.875* (12)
MADBP	0.248 (15)	0.755* (12)

[a]Patients with values for ACR and designated parameters at baseline, weeks 28 and 52.
GLB=Glyburide; RSG=rosiglitazone; HBA_{1c}=glycosylated haemoglobin; ACR=albumin : creatinine ratio; SBP=systolic blood pressure; DBP=diastolic blood pressure; MASBP=mean ambulatory systolic blood pressure; MADBP=mean ambulatory diastolic blood pressure.
*$P<0.05$.

Discussion

In a randomised open label clinical study, RSG therapy significantly reduced the ACR from baseline. Given similar levels of glucose control, the mean reduction in ACR was greater in the RSG treatment group than in the GLB group. Moreover, a

greater proportion of participants in the RSG treatment group with baseline microalbuminuria achieved normalisation of the ACR by the end of the study than did participants in the GLB group. This study also showed improvement in mean 24-h SBP and DBP in the RSG treatment group compared with the GLB group, suggesting a salutary effect of RSG on BP (although this should not be taken as an indication of the utility of RSG in managing hypertension). Moreover, while the changes in ACR did not correlate with changes in glycaemic parameters (HbA_{1c} or FPG), strong correlations were noted with reductions in ABP.

The reductions from baseline in ACR in both groups at week 28 were of similar magnitude, and there was no statistically significant difference between the RSG and GLB treatment groups. Although the change from baseline to week 52 in ACR observed in the RSG treatment group was of greater magnitude than that seen in the GLB treatment group, the differences between the two treatment groups at this time point were also not statistically significant. The study was designed to examine potential effects of RSG treatment on cardiac structure; while urinary ACR was a prospectively defined secondary end point, the study was underpowered to detect differences between treatment groups in effects on this parameter (for all randomised patients, the study provides 80% power to detect a 25% reduction from baseline [within-a treatment comparison] and 52% power to detect a 25% difference in the reduction from baseline between RSG and GLB [between-treatment comparison]). The power to detect differences for those patients with microalbuminuria at baseline is 19% for the within-treatment comparison and 12% for the between-treatment comparison.

Because of the relatively low power of the study to detect differences in treatment groups, care must also be taken in interpreting results of correlation analyses. Our inability to detect a relationship between changes in glycaemic control and changes in ACR may reflect the low power of the study to show correlations rather than an actual lack of correlation. At the same time, we consider that the low power of the study provides further confidence in the strong and consistent correlations observed for changes in ABP parameters and changes in ACR.

The results of the present study are in agreement with observations from a placebo-controlled, double-blind study of RSG monotherapy.[15] In this study, RSG therapy produced significant decreases from baseline in ACR. There was no change from baseline in ACR in the placebo group. As in the present study, correlation analysis showed no statistically significant association between changes in ACR and changes in glycaemic parameters or sitting BP. ABP was not measured in the double-blind study, so agreement with the present study in this area cannot be assessed.

Microalbuminuria in diabetic patients is frequently associated with hypertension and poor glycaemic control.[17] Both conditions are thought to create stress on vascular cells, leading to increased vascular permeability, which is manifested as microalbuminuria.[18] Current treatment of microalbuminuria is therefore directed towards lowering BP and improving glycaemic control. Several studies have shown that both tight glycaemic and BP control can lead to improvements in UAE in type II diabetic patients.[19–22] Other studies, however, fail to show a clear relationship between improved glycaemic control and decreases in UAE in participants with microalbuminuria.[23] This may indicate that improvement of the patient's metabolic state may not be sufficient to allow for repair of vascular damage once such damage is established. There are numerous studies showing the utility of antihypertensive compounds, especially ACE inhibitors, in the treatment of microalbuminuria.[24] Interestingly, ACE inhibitors have been shown to lower UAE even in nonhypertensive patients.[25] This may indicate that increased UAE and hypertension share a common underlying pathology that is addressed through ACE inhibition.

Our findings support the results of previous animal studies indicating a role for the thiazolidinedione receptor, PPARγ, in the maintenance of vascular and endothelial integrity.[26,27] The lack of correlation between changes in ACR and changes in glycaemic parameters suggest that the effect of RSG on UAE is independent of its metabolic effects. Instead, improvement in UAE and BP may be a consequence of improvement in vascular integrity and tone resulting from RSG treatment. Ongoing studies are examining the effects of RSG treatment on markers of inflammation and vascular cell damage and their relationship to improvement in cardiovascular outcomes.[28] These studies will provide a clearer picture of the potential benefits of RSG in management of metabolic status as well as cardiovascular complications of type II diabetes.

Conclusions

In an open-label clinical study, RSG reduced UAE, as shown by a reduction in the ACR. Changes in the ACR were strongly correlated with changes in ambulatory SBP and DBP and had little relation to changes in FPG or HbA_{1c}. These findings are in agreement with observations from an earlier double-blind study and suggest a potential benefit of RSG in treatment or prevention of renal and vascular complications of type II diabetes.

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