The efficacy and safety of rosiglitazone with concurrent sulphonylurea therapy in subjects with type 2 diabetes mellitus in Nigeria

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Abstract

An open label study was conducted to asses the efficacy and safety of rosiglitazone when administered concurrently with sulphonylurea compounds. Sixty-three type 2 diabetic patients were enrolled in the study in three different centres across Nigeria, Zaria in the north, Lagos in the southwest and Port Harcourt in the southeast. Nigeria is a large country with multi-ethnic groups. Subjects were randomly divided into two treatment groups; one on only sulphonylurea and the other on rosiglitazone (4 mg daily) for 26 weeks in addition to the current dose of sulphonylurea. Fifty-two subjects (82.5%) completed the study. The addition of rosiglitazone to sulphonylurea therapy resulted in more steady control of fasting plasma glucose (FPG) over time, higher mean change in FPG from baseline and higher proportion of subjects recording HBA1C value of $\leq$7.5. There were no significant adverse events attributable to rosiglitazone therapy during the 26 weeks of therapy. It is concluded that the addition of rosiglitazone to sulphonylurea treatment is safe and has a synergistic effect in controlling glycaemia in type 2 diabetic patients. (Int J Diabetes Metab 15:62-67, 2007)

Keywords: *Rosiglitazone, sulphonylurea, type 2 diabetes, ethnic group, management*

Introduction

There has been a progressive increase in the incidence and prevalence of type 2 diabetes worldwide and this is particularly so in the underdeveloped and developing countries.[1] Changes in lifestyles brought about by urbanization and modernization, as well as genetic factors are responsible for this change. In Nigeria, the national expert committee on non-communicable diseases estimates a national prevalence rate of 2.73% as of 1997, implying that not less than 1.05 million people aged 15 years and above had diabetes mellitus at that time.[2] Even in suburban communities with relatively little urbanization, prevalence rates of as high as 1.6% have been reported.[3]

Considerable debate and controversy have been generated and still continue as to the initiating defect (insulin resistance or pancreatic beta-cell failure) that lead to the development of type 2 diabetes.[4-5] Insulin resistance has been shown using the homeostasis model assessment method (HOMA) [6] to characterise type 2 diabetic Nigerians who are found to be generally hypoinsulinaemic with advancement of the disease.[7]

Although the underlying pathogenic defect may vary between populations and most probably even within the same population, once type 2 diabetes has become established, the resultant hyperglycaemia is known to induce or aggravate insulin resistance.[8-10] This is mediated through glucosamine, a product of glucose metabolism through the hexosamine pathway, which impairs the insulin-mediated translocation of GLUT4 glucose transporter in adipocytes and skeletal muscle.[11]

The thiazolidinediones are a class of oral anti-hyperglycaemic agents that specifically target insulin resistance and improve insulin sensitivity in skeletal muscle, liver and adipose tissue through the activation of peroxisome proliferators-activated receptor gamma (PPARγ) [12] originally developed in the early 1980s in Japan as antioxidants.[13] Controlled clinical trials assessing the efficacy of rosiglitazone as a single therapeutic agent in patients with type 2 diabetes showed an average decrease of fasting plasma glucose levels by about 45 mg/dl and of HbA1c by about 1.0%.[14,15] This effect is dose-dependent, an effect that leveled off when daily doses were greater than 8 mg.

In many African centres, evaluation of control of diabetes using HBA1C is uncommon due to cost considerations and therefore fasting plasma glucose levels as well as the 2-h postprandial (2HPP) blood glucose levels have been used. The 2HPP could identify those with glucose spikes, a significant factor in the aetiopathogenesis of chronic diabetic complications.[16] Investigations using micro-column technique for $HbA1_C$[17] showed that iron deficiency anaemia, sickle cell genotype as well as elevated blood urea conditions which must be determined and which are common in African diabetic patients may affect HBA1values. In some centres like Zaria, measurement of fructosamine values has been introduced. [18]

This study was therefore undertaken to study the efficacy and safety of the addition of rosiglitazone to sulphonylurea

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therapy in type 2 diabetic Nigerian patients with poor glycaemic control while on sulphonylurea monotherapy.

Methods

Patient selection

A total of 63 type 2 diabetic patients (52 males and 11 females) from three centres (Ahmadu Bello University Teaching Hospital Zaria, Lagos University Teaching Hospital, Lagos and University of Port Harcourt University Teaching Hospital, Port Harcourt) were studied.

During the screening visits, information on age, duration of diabetes, concomitant illnesses and medications; complete medical examination and anthropometric measures were obtained from all subjects. Weights (in Kg) were taken with only undergarments to the nearest 0.5 kg. Heights (in metres) were taken to the nearest 0.5 cm with subjects standing erect without shoes or headgear. Body Mass Index (BMI) was derived by dividing the weight by the square of the height[19] and fasting plasma glucose levels were estimated using a glucose oxidase method.[20] The inclusion criteria were the following; age range 40-80 years, having been on sulphonylurea monotherapy for at least 6 months and on a constant dose for at least 2 months prior to the study, fasting plasma glucose ≥ 7.0mmol/L and ≤ 15.0mmol/L at screening visit and HbA1c ≥ 7.5%.

The exclusion criteria were pregnancy, breast feeding, any clinically significant anomaly detected on the screening by physical examination, chest radiograph or electrocardiography. Other exclusion criteria were, sickle cell disease, use of any investigational product within 30 days before study, hypersensitivity to any drug, significant, liver or kidney disease, significant anaemia, leucopaenia, thrombocytopaenia, chronic use of insulin for glycaemic control in the past, past history of ketoacidosis, severe diabetic retinopathy or neuropathy, BMI <19 or >35kg/M^2 or variation of body weight >10% between screening and visit 2. Scheduled visits occurred in the morning with at least 9 hours of fasting.

Information on concomitant illnesses and medications as well as complete medical examination were obtained in all subjects during scheduled visits as follows; visit 2 (baseline within 2 weeks of the screening visit), visit 3 (4 weeks from baseline), visit 4 (8 weeks from baseline), visit 5 (12 weeks from baseline) , visit 6 (20 weeks from baseline) and visit 7 (end of study i.e. week 26 from baseline). Fasting HBA1c, triglycerides HDL, LDL and total cholesterol were estimated using commercially available kits at screening, visit 2 (baseline), visit 5 (12 weeks from baseline) and visit 7 (end of study at week 26 from baseline). Haematological indices, liver enzymes, serum urea and creatinine, serum calcium and phosphate, uric acid were determined using standard laboratory methods.

Statistical analysis

Results were analyzed using Epi Info version 6 statistical software on an IBM compatible computer. Results are presented as mean ± standard deviation. Unpaired student's *t-test* was used to determine the differences between continuous variables while chi-square test was used for categorical variables. The level of statistical significance in each case was taken as $P < 0.05$.

Assessment of efficacy

Efficacy was assessed by the following parameters.

1. Change in baseline $HbA1_C$ at week 26
2. Mean change in FPG from baseline at week 26.
3. Proportion of subjects that achieve ≥ 0.l7% fall in HbA1c from baseline at week 26.
4. Proportion of subjects that achieve ≥ 30mg/dl (≥ 1.6mmol/L) decrease from baseline FPG at week 26.

Results

A total of 63 subjects (52 males and 11 females) were enrolled out of which 52 (82.5%) completed the study. Twenty-nine (55.8%) of these were allocated to the rosiglitazone group while the remaining 23 (44.2%) were allocated to the sulphonylurea only group.

Eleven (17.5%) subjects did not complete the study. These include: seven patients who defaulted from follow-up resulting in withdrawal from study; one patient who was dizzy with a fasting plasma glucose level of 3.0mmol/L, one was diagnosed with prostatic carcinoma; one died of acute-gastroenteritis unrelated to study medication; another had left foot sepsis following injury and required insulin for glycaemic control.

Baseline parameters

Table 1 shows the baseline parameters in the treatment groups. The rosiglitazone group had higher mean fasting plasma cholesterol, fasting plasma glucose and glycosylated haemoglobin levels and higher BMI than the sulphonylurea only group. However, the differences were not statistically significant for these parameters except for total cholesterol.

Assessment of efficacy

a) *Proportion of subjects with FPG decrease of >1.6mmol/L*

Fifteen (51.7%) in the rosiglitazone group and 12 (52.2%) in the sulphonylurea only group demonstrated reduction in FPG of >1.6mmol/L at the end of the 26 weeks treatment period. This difference was however not significant ($p > 0.05$).

b) Proportion of subjects with decrease of >0.7% in HbA1C.

Twenty-one (72.4%) in the rosiglitazone group and 12 (52.2%) in the sulphonylurea only group had a reduction in HbA1C of >0.7% at the end of the 26 weeks treatment period. This was statistically significant ($p<0.05$).

c) Proportion of patients with FPG ≤ 7.7 mmol/L by week 26.

The proportion of subjects with FPG ≤ 7.7 mmol/L significantly increased from 13.8% at baseline to 55.2% among subjects in the rosiglitazone group ($p<0.05$). Similarly, the proportion increased from 21.7% at baseline to 65.2% at week 26 in the sulphonylurea only group ($p < 0.05$).

Table 1: Comparison between baseline parameters of the two treatment groups

	Mean FPG mmol/L	Mean $HbA1_C$ %	Mean BMI Kg/M^2	Mean TCHOL mmol/L	Proportion FPG>7.7mmol /L	Proportion $HbA1_C$ >7.7%
Rosiglitazone + Sulphonylurea	10.59 (SD2.2)	9.94 (SD 1.8)	27.4 (SD 4.5)	4.7 (SD0.99)	86.2	93.1
Sulphonylurea alone	9.38 (SD1.96)	9.72 (SD1.9)	25.97 (SD3.8)	4.24 (SD1.14)	78.3	95.7
P-value	=0.05	>0.05	>0.05	<0.05	>0.05	>0.05

TCHOL = Total Cholesterol; FPG = Fasting plasma glucose; $HbA1_C$ =Glycosylated haemoglobin, BMI = Body Mass Index

d) Proportion of subjects with $HbA1_C \leq 7.5\%$ by week 26.
The proportion of subjects with $HbA1_C \leq 7.5\%$ significantly increased from 6.8% at baseline to 37.9 % ($p<0.05$) at week 26 of treatment among subjects in the rosiglitazone group. Similarly, the proportion increased from 4.3% at baseline to 47.8% at week 26 in the sulphonylurea only group ($p<0.05$).

e) Differences between baseline FPG and FPG at week 26.
The rosiglitazone group (2.69 SD 3.4) demonstrated larger mean differences between baseline and end of study FPG than the sulphonylurea group (1.57 SD 3.4), $P>0.05$.

f) Effect of duration of treatment on FPG (from baseline to week 26)
Figure 1 demonstrates that although both treatment groups recorded falls in FPG overtime, the rosiglitazone group shows more consistent falls in mean FPG.

Assessment of safety
Both treatment groups demonstrated statistically non-significant decreases in weight and BMI, reductions in mean systolic blood pressures. The reduction in diastolic blood pressures was, however, significant in the rosiglitazone group ($p<0.05$). Similarly, there were no clinically important haematological or biochemical derangements of significance noted (Tables 2 and 3). Mean serum uric acid levels decreased though not significantly in both treatment groups.

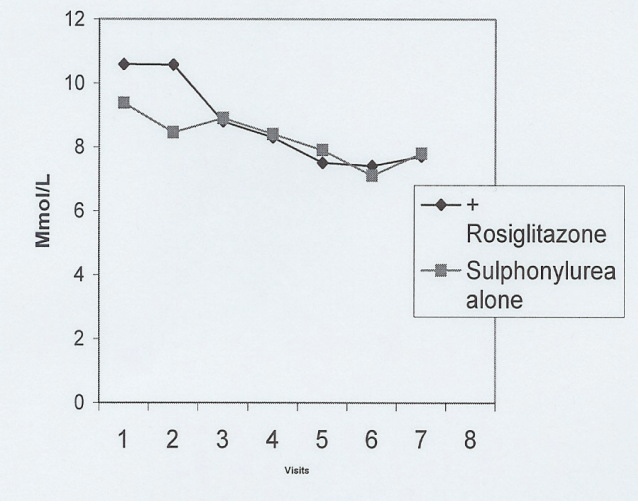

Figure 1: Mean fasting plasma glucose over time by treatment group.

It is noteworthy that mean HDL cholesterol increased although non significantly from 0.84 ± 0.3 to 1.1 ± 0.7 mmol/L while LDL cholesterol decreased in the rosiglitazone group. This was not observed in the sulphonylurea only group (Table 4).

Discussion
The study has demonstrated that both treatment groups showed an improvement in glycaemic control. This could be attributable to the benefits of close clinical monitoring and a constant reminder during each visit on the need to adhere to healthy diets.

The rosiglitazone group started with much higher fasting plasma glucose levels and much higher $HbA1_C$ levels than the sulphonylurea only group but at the end of the study, it had lower mean FPG levels. The results in this study confirm the synergistic effect of a combination of rosiglitazone and sulphonylurea on the therapy of diabetes. This finding is expected and consistent with previous observations in other populations.[14, 15]

It is noteworthy that changes in the fasting plasma glucose levels started manifesting at the end of 4 weeks of therapy (visit 3), but thereafter consistently continued to fall with each subsequent visit. This may be related to the fact that significant length of time may be required to bring about the cellular changes that ultimately improves both insulin sensitivity and pancreatic beta cell function. It also implies that sufficient time needs to be given before making a decision on dose changes. It is also noteworthy that although significant changes in FPG were noted, mean FPG was still higher than 7.0mmol/L, fixed doses of both sulphonylurea and rosiglitazone were used for the purpose of this study. In clinical practice, however, the dosage of the sulphonylurea or rosiglitazone could be increased to achieve the required glycaemic control. The choice of which agent to increase would, however, need to be individualized considering costs especially in depressed economies.

The proportion of subjects with $HbA1_C \leq 7.5\%$ significantly increased from 6.8% at baseline to 37.9 %($p<0.05$) at week 26 of treatment among subjects in the rosiglitazone group. Similarly, the proportion increased from 4.3% at baseline to 47.8% at week 26 in the sulphonylurea only group Furthermore, 72.4% of the group that had rosiglitazone added to sulphonylurea had >0.7% decrease in their $HbA1_C$ from baseline compared to 52.2% in the sulphonylurea only group.

Table 2: Comparison of selected clinical parameters at baseline and after 26 weeks of treatment

Parameter	Baseline	End of study	P value
Mean weight (Kg)			
Rosiglitazone group	72.4 (SD10.4)	67.1 (SD 21.3)	>0.05
Sulphonylurea only group	69.7(SD 9.4)	68.4(SD10.0)	>0.05
Mean systolic BP(mmHg)			
Rosiglitazone group	129.0(SD16.0)	119.8(SD17.2)	>0.05
Sulphonylurea only group	135.6(SD 17.7)	123.5(SD17.0)	>0.05
Mean diastolic BP(mmHg)			
Rosiglitazone group	82.3(SD 9.4)	74.2 (SD 8.5)	<0.05
Sulphonylurea only group	87.2(SD 15.3)	76.3 (SD 9.8)	>0.05
Mean Arterial BP(mmHg)			
Rosiglitazone group	97.1 (SD10.7) (n =32)	89.7(SD9.9)(n=30)	>0.05
Sulphonyl urea only group	103.8(SD13.4)(n=31)	92.8(SD11.3)(n=26)	>0.05
Mean Heart rate(Beats/min)			
Rosiglitazone group	77.5 (SD 15.6)	77.6 (SD7.8)	>0.05
Sulphonyl urea only group	78.4 (SD8.5)	75.1 (SD 7.7)	>0.05
ECG Abnormality (%)			
Rosiglitazone group	0%	0%	>0.05
Sulphonyl urea only group	4.3%	0%	>0.05

Table 3: Comparison of selected Laboratory parameters at baseline and after 26 weeks of treatment*.

Parameter	Baseline	End of study	P-value
ALT (IU/L)			
Rosiglitazone group	26.9 (SD17.4)(n =29)	26.9(SD13.9)(n=30)	>0.05
Sulphonyl urea only group	25.5(SD12.0)(n=28)	25.0(SD11.2)(n=25)	>0.05
AST (IU/L)			
Rosiglitazone group	21.2 (SD14.0)(n =29)	20.1(SD11.5)(n=31)	>0.05
Sulphonyl urea only group	23.7(SD19.2)(n=28)	18.4(SD9.4)(n=25)	>0.05
Total plasma protein(g/L)			
Rosiglitazone group (n =19)	70.4 (SD 5.9)	73.61(SD 8.3)	>0.05
Sulphonylurea only group(n=15)	72.9 (SD 6.9)	73.5 (SD 5.6)	>0.05
Plasma bilirubin (umol/L)			
Rosiglitazone group (n =19)	11.7 (SD4.8)	12.1 (SD4.5)	>0.05
Sulphonylurea only group(n=15)	13.5 (SD3.8)	13.7 (SD4.4)	>0.05
Plasma Uric acid (umol/L)			
Rosiglitazone group (n =19)	264.2 (SD115.2)(n =18)	223.4(SD91.6)(n=20)	>0.05
Sulphonylurea only group(n=15)	277.3(SD98.9)(n=20)	246.5(SD72.3)(n=18)	>0.05
Mean Haematocrit (g/dl)			
Rosiglitazone group (n =19)	40.7 (SD4.2)	38.34(SD 4.4)	>0.05
Sulphonylurea only group(n=15)	41.2 (SD 4.0)	41.8 (SD 7.2)	>0.05

Table 4: Comparison of cholesterol levels baseline and after 26 weeks of treatment*

Parameter	Baseline	End of study	P-value
Mean total cholesterol (mmol/L)			
Rosiglitazone group	4.7 (SD0.96) (n =29)	5.3 (SD1.2) (n =24)	>0.05
Sulphonyl urea only group	4.4(SD1.1) (n =30)	5.3(SD0.9) (n =19)	>0.05
Mean HDL cholesterol (mmol/L)			
Rosiglitazone group	0.84(SD0.3) (n =29)	1.1(SD0.7) (n =21)	>0.05
Sulphonyl urea only group	0.88(SD0.3) (n =31)	0.8(SD0.2) (n =19)	>0.05
Mean LDL cholesterol (mmol/L)			
Rosiglitazone group	3.3 (SD0.96) (n =29)	3.0(SD1.2) (n =31)	>0.05
Sulphonyl urea only group	3.7 (SD1.0) (n =21)	3.9(SD0.87) (n =19)	>0.05
Mean Triglycerides (mmol/L)			
Rosiglitazone group	1.1 (SD0.4) (n =26)	1.9(SD2.5) (n =30)	>0.05
Sulphonyl urea only group	1.2 (SD0.9) (n =21)	1.2(SD0.6)(n=19)	>0.05
Total Cholesterol /LDL Ratio.			
Rosiglitazone group	1.5 (SD0.4) (n =25)	1.5(SD0.4) (n =30)	>0.05
Sulphonyl urea only group	1.5 (SD0.6) (n =21)	1.3(SD0.1) (n =19)	>0.05
LDL /HDL cholesterol Ratio			
Rosiglitazone group	4.5 (SD2.1) (n =26)	4.6 (SD2.3) (n =21)	>0.05
Sulphonylurea only group	3.7(SD1.7) (n =30)	4.5(SD1.6) (n =19)	>0.05

Table 5: Trend of mean total cholesterol /HDL ratio by treatment group

GROUP	Visit 1	Visit 5	Visit 7
Rosiglitazone group	5.59	5.33	4.81
Sulphonylurea only group	5.0	5.11	6.62

Apart from mean diastolic blood pressure, no other significant changes in clinical or laboratory parameters were noted in either group. This attests to the safety of both regimens. However, it is worth noting the tendency of the lipid levels in the two treatment groups, whereas mean HDL cholesterol increased and the total cholesterol/HDL ratio reduced in the rosiglitazone group, this was not observed in the sulphonylurea only group. Such trend is beneficial in the prevention of macrovascular complications and is consistent with earlier studies suggesting that dyslipidaemia is improved by thiazolidinediones. [15, 21] Furthermore, none of the subjects experienced elevation in liver enzymes. This is important considering that troglitazone was withdrawn due to concerns on its safety on the liver. [22]

Interestingly, the rosiglitazone group demonstrated significant reductions in diastolic blood pressures. This could be attributable to the beneficial effects of improving insulin sensitivity on blood pressure,[23] and is in agreement with an open labeled study that showed potential benefits of rosiglitazone in the treatment and prevention of vascular complications in type 2 diabetes mellitus, [24] as well as animal studies suggesting significant roles for the PPARγ receptor in the maintenance of vascular and endothelial integrity.[25]

It is concluded that the addition of rosiglitazone to sulphonylurea treatment is safe, and has a synergistic effect in controlling glycaemia in type 2 diabetic Nigerian patients. It also has the potential to induce better blood pressure control, as well as beneficial changes in uric acid and lipid profiles.

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