

Rosiglitazone and Metformin in Patients with Type-2 Diabetes Mellitus Who are Inadequately Controlled on Metformin Alone

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Type 2 Diabetes Mellitus is almost reaching epidemic levels. With tight hyperglycemic control the risk reduction is 24% for any diabetes related end-point and 32% for death related to diabetes, against only 0.9% decrease in HbA1c level. Complementary mode of actions of Rosiglitazone and Metformin can be used to maximize the therapeutic effect and to decrease the side effects. We evaluated the efficacy, safety and tolerability of the combination of Rosiglitazone and Metformin on change in HbA1c levels from baseline over a period 24 weeks in patients with type 2 diabetes mellitus. Twenty eight type 2 diabetes mellitus patients were recruited randomly presenting to West Medical Ward, Mayo hospital Lahore, through OPD, Diabetic Clinic and Emergency, who were on Metformin alone and were poorly controlled from September 2003 to July 2004. They were given Rosiglitazone 4 mg/day or 8 mg/day with metformin for a period of 24 weeks. Only 2 patients were dropped and 26 patients completed the study (46% were males and 54% were females), and none of patient was dropped due to adverse effects. Their fasting blood sugar measured at baseline and at 4, 8, 16 and 24 week. HbA1c was measured at start and at 24 weeks. The fasting blood glucose responders were 84.6%, with mean fall of 46 mg/dl. HbA1c responders were 73% patients. Average weight gain was 1.125 kg over 24 weeks. Out of 26 patients, 89% showed a mild decrease in hemoglobin concentration but none reaching anemic levels. Only 10% patients had a rise in liver enzymes, which was less than 2 times the normal. Addition of rosiglitazone, in patients with type 2 diabetes mellitus, who are inadequately controlled on metformin alone, resulted in better glycaemic control but a large scale study is required and other combinations with Rosiglitazone like sulphonylurea and insulin should be compared.

Key words: Type 2 Diabetes, Rosiglitazone, Metformin, Better, Combination

Diabetes Mellitus is a very common problem worldwide and almost reaching epidemic levels. It is a metabolic syndrome characterized by hyperglycemia and has 2 types: Type 1 is due to deficiency in production of insulin and type 2 the most common one having 90% prevalent rate, is caused by decreased insulin production or insulin resistance. Therefore, drugs that improve insulin resistance are very important group for treating this type of diabetes. In 1998, an estimated 135 million people worldwide had diabetes, but their number has increased to 170 million in 2003. This figure is expected to double up to 300 million by year 2025 with maximum brunt of disease increase (upto 200%) in the developing countries. According to WHO estimate, Pakistan ranked eighth for the number of persons having diabetes in 1995 and is estimated to be fourth in year 2025 with 14.5 million diabetics at that time. We have prevalence of diabetes as 16.2% in males and 11.7% in females^{1,2,3}. In another local study, 6.3% prevalence was reported⁴.

With tight hyperglycemic control the risk reduction is 24% for any diabetes related end- point, 32% for death related to diabetes, 21% for MI, 44 % for stroke and 37% for microvascular complications. Only 0.9% change in HbA1c signifies all above mentioned changes⁵. Various guidelines are being established that call for aggressive management of hyperglycemia in type 2 diabetics to reduce its complications. Despite tight hyperglycemic control with combination therapy, it may often be associated with potential risk of hypoglycemia⁶.

Role of metformin in treatment of type 2 diabetes mellitus is well established. It decreases hyperglycemia but has no effect on fasting blood glucose in normal subjects and is being used for type 2 diabetic alone or in combination especially in obese ones and in those where insulin resistance is suspected. It is contraindicated when serum creatinine level is more than 1.5 mg/dl⁶.

Rosiglitazone {[4-[2-(methyl-2- pyridimylconino) ethoxy] methyl]-24 thiazolidinedione} belongs to thiazolidinediones which, are antihyperglycemic agents, sensitize peripheral tissues to insulin. It consistently lowers fasting and postprandial glucose concentration as well as free fatty acids^{7, 8, 9, 10}. It is accompanied by weight gain and increase in the subcutaneous adipose tissue mass^{11, 12, 13, 14}. Rosiglitazone leads to an increase in body weight of 2-3 kg for every 1% decrease in HbA1c. The magnitude of this increase in weight is similar in monotherapy or in combination with metformin^{15, 16}. Rosiglitazone can lower fasting insulin concentration¹⁷. It is moderately effective in achieving hyperglycemic control, on average decrease in HbA1c upto 1-1.2% in type 2 diabetes mellitus, which is its only approved indication. It decreases ratio of urinary albumin to creatinine¹⁸. Its side effects include weight gain and edema in 4-6% patients resulting in some increase in the incidence of heart failure. There is associated slight decrease in hemoglobin level and haematocrit without clinical consequence¹⁹. Rosiglitazone also causes increase in serum ALT levels upto more than 10 times in only 0.68%²⁰.

Rosiglitazone and metformin lower plasma glucose concentrations by different mechanisms. When combined together they may offer benefit and because of their complementary mode of action they can be used to maximize the therapeutic effect and to decrease the side effects.

Purpose of study:

To evaluate the efficacy, safety and tolerability of the combination of Rosiglitazone and Metformin on change in HbA1c levels from baseline over a period 24 weeks in patients with type 2 diabetes mellitus.

Material and methods:

Study Population: Twenty eight patients were recruited randomly presenting to West Medical Ward, Mayo hospital Lahore, through OPD, Diabetic Clinic and Emergency, who were on Metformin alone and were poorly controlled. Study was conducted in West Medical Ward of Mayo Hospital, Lahore from September 2003 to July 2004.

Inclusion Criteria: Males and females of 40 to 80 years of age, with type 2 diabetes mellitus (defined by WHO criteria) for 3 or more months, having fasting plasma glucose of >140 mg/dl and <300 mg/dl at screening and baseline visits, and BMI of >22 and <38 kg/sq.m², taking metformin 1.5 to 2.5 gm/day, were included in the study. The females were either post- menopausal, surgically sterile or using effective contraceptives.

Exclusion Criteria: The patients excluded were either pregnant/lactating, having any uncontrolled diseases e.g. unstable ischemic heart disease, congestive cardiac failure, uncontrolled hypertension (Systolic BP >180 mmHg or Diastolic >110 mmHg), liver dysfunction (ALT and AST >2 times than normal range), diabetic nephropathy (S/Cr >1.6), present or past history of diabetic ketoacidosis, hyperosmolar non-ketotic coma, significant anemia or serious psychological disorder. Patients with BMI of <22 or >38 kg/m² were also excluded.

Study Design and Methodology: In this open labeled, Quazi experimental study, 28 patients were recruited who were taking metformin for their diabetes (1.5-2.5 g/dl) and were not properly controlled. At baseline visit their inclusion and exclusion criteria were determined. At second baseline visit all the patients were looked for eligibility for Add-on Rosiglitazone Treatment period. The study consisted of following phases:

i) **Screening visit:** To determine eligibility for study.

ii) **Metformin maintenance period:** Patients already on metformin dose (1.5-2.5 g/d) were given a 2 weeks trial of diet plus metformin in order to confirm they are inadequately controlled and the dose of metformin remain unchanged during the whole study.

iii) **Add-on Rosiglitazone period/ baseline visit.**(Week 0).

1. Rosiglitazone started at dose of 4 mg/OD with constant dose of metformin for next 8 weeks.

2. BSF and HbA1c were checked.

iv). **BSF rechecked at 4 weeks.**

v). **Rosiglitazone dose adjustment visit:** At 8 weeks, the patient's response to treatment was evaluated by their

Fasting Plasma Glucose (FPG) measurements. Patients were divided in 2 groups depending on Blood Sugar Fasting (BSF) level:

a) BSF < 160 mg/dl – Rosiglitazone 4 mg OD for next 16 weeks

b) BSF > 160 mg/dl – Rosiglitazone 4 mg BID for next 16 weeks

vi). **End of Treatment (week 24):** The patients were then followed up for upto 24 weeks for response or withdrawal. BSF and HbA1c were measured at 24 weeks. Baseline signs and symptoms were noted and clinical examination done at every visit. Diet check and medical history were also obtained at every visit. The history and examination to determine side effects were also done.

Efficacy Outcome Variables: Primary efficacy parameter was set as change in HbA1c from baseline (visit 2) to End of Treatment Period i.e. week 24 for all patients.

The main secondary efficacy parameter was change from baseline in FPG at End of Treatment Period i.e. week 24 for all patients. Other secondary parameters were percentage change from baseline in weight, fasting lipid profile and LFT.

Safety Parameter: Safety and tolerability of Rosiglitazone was defined through assessment of changes in physical examination, vital signs, body weight, waist circumference, clinical laboratory tests, adverse experiences and ECG.

Results:

A total of 85 patients were screened. Twenty eight patients were included in the study and 26 completed the study. Two were lost to follow up. Males were 46% and 54% were females. Most of patients fell in range of 45 to 60 years of age. The **fasting blood glucose responders** were 84.6% (**normalized BSF or fall of BSF > 30 mg/dl from baseline**) and 14.4% were non-responders. Out of 84.6% responders, 64% (14) had normal level of BSF i.e.<126mg/dl, and 36% (08) had fall of BSF >30 mg/dl from baseline. Mean fasting blood glucose fall was 46 mg/dl (table 1).

HbA1c responders (HbA1c < 7 % or decrease of HbA1c \geq 0.7 % from baseline) were 73% (19) patients and out of them 68% (13) had decrease of > 0.7% from baseline and 32% (06) had HbA1c < 7 %. All Patients had > 0.5% decrease (table 1).

Seventy six percent (20) patients gained weight of 1 to 3 Kg over 24 weeks (average weight gain was 1.125 kg), while in 16% (04) patients' weight remained unchanged from baseline and 8%(02) patients even lost weight. Out of 26 patients, 89 % showed a mild decrease in hemoglobin (Hb.) concentration (<2 g/dl) but none of them had significant anemia. On an average Hb. decreased

was 0.9 gm/dl. Only 3 (11%) patients had derangement in ALT and AST but increase did not rise >2 times and none called for drug withdrawal. No patient had rise in serum bilirubin in the abnormal range. As for as fasting lipid profile was concerned, 46% (12) patients had elevated triglycerides (TGs) from baseline and no significant increase in LDL level or HDL levels was noted.

Table 1 Mean change in BSF and HbA1c

	Baseline Value	End of treatment	Net Change Over 24-weeks
BSF(mg/dl)	176	130	46
HbA1c	8.7%	7.8%	0.9%

Discussion:

The epidemic of type 2 diabetes has created a need for new hypoglycemic therapies, but very few agents have been introduced during the past 20 years. The thiazolidinediones represent a potentially important new group of drugs with a mechanism of action differing from and perhaps complementary to existing therapies²¹.

In the UKPDS trial the investigators demonstrated that, despite intensive treatment, monotherapy often failed to maintain optimal glycemic control. Many patients (39%) required the addition of insulin or metformin to maintain control²². The addition of rosiglitazone to metformin improves glycemic control in patients with type 2 diabetes, which has already been observed in a study of 384 patients, where a dose dependent statistically significant decrease in HbA1c and FPG noted at 26th week. However, with rosiglitazone addition a small decrease in hemoglobin and hematocrit, presence of more edema and more weight gain were seen. No one in the rosiglitazone arms experienced a clinically significant increase in ALT (greater than 3 times the upper limit of normal) during the study. Mean changes in AST, total bilirubin, and alkaline phosphatase were not different among groups²³. Rosiglitazone is an insulin sensitizer that decreases the HbA1c level by 1%. Metformin is a time tested another insulin sensitizer drug that has long been used for treatment of diabetes²⁴. We in our study hypothesized that combination therapy using two complementary modes of action would maximize therapeutic effect and decrease side effects. In this study we included patients previously uncontrolled on metformin and 84.6% fasting blood glucose responders had more than 30 mg/dl decrease from baseline. The 73% HbA1c responders similarly had a fall of $\geq 0.7\%$ from baseline. The triglycerides level had increased in 46% of patients but there was no significant increase in LDL levels or decrease in HDL. All the patients who were included in this study were taking metformin before for at least 3 months and had settled with adverse effects. The adverse effects which were seen in this study were usually due to Rosiglitazone. Patients had mild adverse effects and no one discontinued the study due to adverse effects. No more than 3 kg weight was gained

during the 24 week study period. Only a few patients (08%) lost 1-2 kg. Most of the patients had a decrease of average 0.9 mg/dl Hb. in hemoglobin level. No patients had significant derangement in liver enzymes and similarly no patient developed edema, therefore on the whole drug is well tolerated and has good hyperglycemic control.

The results of the current study and the study by Wolffebuttal and colleagues (involving rosiglitazone in combination with sulphonylureas) suggest that rosiglitazone can improve glycemic control when used in combination therapy in patients who have experienced secondary failure to one oral hypoglycemic agent²⁵. Although direct comparisons cannot be made between these results and the results from Fonseca et al., it may be hypothesized that the effects would be similar between the two combinations (i.e. metformin and sulfonylurea vs. metformin and rosiglitazone). To date, there have been no trials comparing the effects of the combination of metformin and a sulfonylurea versus the combination of a thiazolidinediones and either metformin or a sulfonylurea.

Conclusion:

Addition of rosiglitazone, in patients with type 2 diabetes mellitus, who are inadequately controlled on metformin alone, resulted in better glycemic control. As the number of patients was small in the present study therefore, a large scale study is required and other combinations with Rosiglitazone like sulphonylureas and insulin should be compared.

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