A Study to Evaluate the Effect of Saroglitazar in Type 2 Diabetes

Jaswant Goyal[1], Sudhir Bhandari[2], Sengupta Kushan Kaushik[3], Barkha Goyal[4], Saloni Chandalia[5], Rashmi Attri[6]

ABSTRACT

Introduction: Type 2 diabetes mellitus is a common condition characterized by high blood sugar level. This risk gets inflated by lipid abnormalities additionally. Diabetics have high risk of developing dyslipidemia (Atherogenic Diabetic Dyslipidemia-ADD) which is characterized by high triglycerides and/or low HDL-C and/or small dense LDL-C. Study aimed to assess difference in mean Fasting plasma glucose (FPG), Post prandial plasma glucose (PPPG), Lipid parameters [triglycerides (TG), total cholesterol (TC), very low density lipoprotein (VLDL), low density lipoprotein (LDL), high density lipoprotein (HDL) and non-HDL] before and after adding saroglitazar in patients of type 2 diabetes.

Material and Methods: A total of 36 cases with Diabetes Mellitus Type 2 aged between 18 and 65 years with their BMI> 25kg/m2, HbA1c between 7 and 9% and total cholesterol levels >150mg/dl were enrolled. Their baseline glycemic and lipid parameters were measured and they were given Saroglitazar 4mg every day for 3 months and their parameters were checked again at the end of 3 months.

Results: It was found that the mean Fasting plasma glucose (FPG), Post prandial plasma glucose (PPPG), Lipid parameters decreased after 3 months of Saroglitazar therapy and this decrease was found to be statistically significant (P<0.001).

Conclusion: Thus, addition of Saroglitazar to the drug regimen of the patients with Diabetic Dyslipidemia can bring about significant improvement in the glycemic and lipid parameters with the added advantage of insignificant adverse effects, thus proving beyond doubt the efficacy and safety of this drug in the treatment of Diabetic Dyslipidemia.

Keywords: Diabetes Mellitus, FPG, Glycated Hemoglobin, Glycemic Control, HBA1c, Macrovascular, Microvascular, PPPG, Saroglitazar

INTRODUCTION

Diabetes mellitus (DM), commonly known as diabetes is an endocrinal disorder in which there are elevated blood sugar levels over a long period.[1] The common symptoms of high blood sugar are frequent urination, increased thirst, and increased hunger.[2] However, diabetes can cause many complications also if left undertreated.[2] Some of the complications are diabetic ketoacidosis and hyperosmolar hyperglycemic state.[3] There can be long term serious complications such as cardiovascular disease, stroke, kidney disease, ulcers in the foot, and damage to the eyes.[2]

India accounts for 21% of the world's global burden of disease. About two-third of total morbidity and 53% of total mortality in India is because of Non-communicable diseases (NCDs). Cardiovascular disease and diabetes are two out of four leading non communicable diseases in India. It is accounted that every fourth diabetic in the world is an Indian. The prevalence of diabetes has increased as reported by Indian Council of Medical Research (ICMR, 2011): Urban India (12-18%), Rural India (3-6%) and Pre Diabetes (14%). Increased cardiac risks have found to be associated with diabetes. Additionally, lipid abnormalities inflate this risk. Diabetics have high risk of developing dyslipidemia (Atherogenic Diabetic Dyslipidemia-ADD) which is characterized by high triglycerides and/or low HDL-C and/or small dense LDL-C.

Studies have suggested that insulin resistance and a relative insulin secretory defect are the main pathophysiological defects that lead to Type 2 Diabetes. Other aetiological risk factors are obesity, age, physical inactivity and family history. Dietary risk factors have recently emerged: risk is increased by high consumption of red and processed meat[8] and sugar-sweetened beverages,[9] and reduced by intake of fruit and vegetables,[10] some types of dairy products,[11] and some overall dietary patterns.[12] Novel strategies to use quantifiable nutritional biomarkers are paving the way for more detailed understanding of the association between diet and diabetes. Type 2 diabetes has high heritability (30-70%) and more than 60 genetic variants related with diabetes risk have now been identified,[13] the individual effects of genetic variants are modest, and even when combined into a genetic score, known genes contribute little to the diabetes prediction. Better discrimination for diabetes has been presented by Phenotype-based risk models, and the addition of genotypic information adds no more than 5–10% improvement in prediction. It can be said that genetic variants gives insights into biological pathways and pathogenesis of

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diabetes, but not its prediction. It is likely that interactions between the environment/lifestyle and genetic factors provide the account for the possibility of type 2 diabetes, but representing such interaction is challenging. Encouraging research findings have recently shown higher absolute risk of diabetes associated with obesity at any level of genetic risk.[14] For diabetes management, secretagogues such as insulin cause hypoglycaemia, and the secretagogues might lead to the pancreatic beta cells exhaustion. Only Metformin is not always enough, and the other insulin sensitizers such as pioglitazone, act by stimulating the nuclear peroxisome proliferator-activated receptors-γ (PPAR-γ) receptors, are in the shade for their side effect profile.

The world's first approved dual PPAR-α/γ agonist; Saroglitazar was introduced in and for diabetic dyslipidemia patients, it displayed efficacy in improving the glycemic as well as the lipid parameters both, and also an excellent safety profile.

An observational, multicenter, post-marketing study (phase IV) involving 2804 subjects by Shetty R et alrevealed that saroglitazar in addition to oral antidiabetic medication (at outpatient clinics) showed significant improvement in all lipid and glycemic parameters at 3 month follow-up. The mean baseline TG was 312.3 mg/dL*vs.* 188.7 mg/dL at 3 month follow-up, a significant reduction of 35.8% (mean of % change from baseline). Non-HDLC levels also reported a significant 23.4% mean reduction at 3 month follow-up.[15]

PPARs (Peroxisome Proliferator-Activated Receptors) are nuclear lipid-activated transcription factors that control of lipid and lipoprotein metabolism by regulating the expression of genes, inflammatory processes and glucose homeostasis.[16] The first approved glitazar class compound by therapeutic agent is Saroglitazar. Structurally, saroglitazar is a non-fibrate molecule and a non-TZD which belongs to aryl alkoxy propionic acid class. Saroglitazar was intended as dual PPAR-α/γ agonist having strong PPAR-α effect with moderate PPAR-γ effect.[17] Its Chemical name (IUPAC) is (S)-a-ethoxy-4-[2-[2-methyl-5-[4-(methylthio) phenyl]-1H-pyrrol-1-yl]ethoxy] benzenepropanoic acid magnesium salt (2:1)[17,18]

During conduction of safety pharmacology studies it has been demonstrated that Saroglitazar doses several fold higher than therapeutic doses does not affect cardiovascular system (CVS), central nervous system (CNS), gastrointestinal (GI) functions and respiratory system (RS).[19]

Study aimed to assess difference in mean Fasting plasma glucose (FPG), Post prandial plasma glucose (PPPG), Lipid parameters [triglycerides (TG), total cholesterol (TC), very low density lipoprotein (VLDL), low density lipoprotein (LDL), high density lipoprotein (HDL) and non-HDL] before and after adding saroglitazar in patients of type 2 diabetes.

MATERIAL AND METHODS

The current observational study was conducted at the Out-Patient Department (OPD) of Tertiary Care Hospital, Jaipur city, Rajasthan. The study was approved by the Institutional Ethics Committee. A total of 36 patients were enrolled in the study who fulfilled the inclusion and exclusion criteria, consent from all the enrolled patients were taken in writing.

Hematological Investigations such as after 8 hours fasting, various samples were collected with patients lying supine, avoiding stress and hemolysis. Post prandial venous samples were taken 2 hours after a 75 gram oral glucose load. Following investigations were carried out. Serum fasting plasma glucose, Serum post prandial glucose, GlycatedHemoglobin (HbA1c), Blood urea, Serum creatinine, S.G.O.T, S.G.P.T, Total lipids, Phospholipids, Triglycerides, Total Cholesterol, HDL Cholesterol, LDL Cholesterol, VLDL Cholesterol.

On registration of a patient, identification details, socio-demographic profile, presenting complaints and precipitating events were recorded. Out of the 50 patients, 12 patients were on only on Metformin, 20 patients were on Metformin and Sulfonylurea, 11 patients were on Metformin and insulin and 7 patients were on Metformin, Sulfonylurea and DPP4 inhibitors. 32 out of the 50 patients were on Statin therapy. The treatment regimen for all the patients remained the same for the next 3 months. The average duration of diabetes was 2 years. Patients with triglycerides 150 mg/dl were started on Saroglitazar 4mg daily and instructed to continue on diet modification, exercise and OHA.

After 12 weeks of therapy, patients were again assessed on the basis of parameters of HbA1c, FBG, PPPG and lipid profile.

STATISTICAL ANALYSIS

Data was entered in MS excel sheet and analysed using appropriate statistical test. SPSS 10.0 statistical package (SPSS, Chicago, Illinois, USA) was applied to analyze the data. Mean±SD were applied to present the continuous and interval related data, frequency distribution and percentages to present the categorical variables. Qualitative data were analyzed using the Chi-square test or Student's t test.

RESULTS

The age distribution of study subjects were40-49 years age (42%) followed by 50-59 years age group (30%). Only 5 (10%) subjects were ≥ 60 years of age.

The Baseline clinical parameters of study subjects were the mean weight of the subjects was 71.98±4.49 Kg with a maximum of 80 kg. Height of the study subjects ranged from 1.55 to 1.76 meters. Mean BMI of the study participants was 26.63±1.3 Kg/m^2 with a range of 23.5 to 29.7 Kg/m^2. The mean systolic blood pressure was 146 ±7.4 mmHg and Diastolic blood pressure was 88.16±5.7 mm Hg.

The baseline Lab parameters of the study participants were the mean Hb of the subjects was 13.37±1.6 mg/dl. TLC was within normal range in all subjects with mean of 7.7±1.9 thousand/ml. Platelet count ranged from 1.26 to 3.88 lakh/ml. Serum SGOT and SGPT were also within a normal range in most subjects with mean value of 32.68±6.41 U/L and 41.5±16 U/L respectively. Blood urea level in the study subjects ranged from 15 to 38 mg/dl.

The mean HBA1c decreased from 7.8% at start of study to 6.75% after 3 months of Saroglitazar therapy and this

decrease in HBA1c was found to be statistically significant (P<0.001) on application of paired t test. The trend of HBA1c before and after treatment with Saroglitazar clearly reflects visible decrease in HB1Ac.

The baseline FPG was 149.5±37.25 mg/dl. After 3 months of Saroglitazar mean FPG decreased to 105.9 mg/dl with a mean decrease of 43.56 mg/dl. Application of unpaired t test showed that this decrease in mean FPG was statistically significant (P<0.001).

The baseline PPPG was 230.9±62.02 mg/dl. After 3 months of Saroglitazar mean PPPG decreased to 161 mg/dl with a mean decrease of 69.9 mg/dl. Application of unpaired t test showed that this decrease in mean PPPG was statistically significant (P<0.001). There was change in FBG and PPBG after treatment with Saroglitazar.

The baseline Total cholesterol was 215±33.6 mg/dl. After 3 months of Saroglitazar the cholesterol reduced to 163.7±29.25 mg/dl. There was a mean decrease of 51.3 mg/dl in cholesterol level and this decrease in Total cholesterol level was statistically significant (p<0.001)

The mean baseline Triglycerides was 318±82.3 mg/dl. After 3 months of Saroglitazar the cholesterol reduced to 193.3±57.32 mg/dl. There was a mean decrease of 124.7 mg/dl in serum TG level and this decrease in Serum TG level was statistically significant (p<0.001)

the mean High Density Lipoprotein level decreased only marginally from 38.72 mg/dl at baseline to 38.62 mg/dl after 3 months of Saroglitazar and this decrease was not found to be statistically significant (P>0.05).

The mean Non-High Density Lipoprotein level at baseline was 176.4 mg/dl which decreased significantly to 133.7 mg/dl after 3 months of therapy with Saroglitazar and the difference was significant (P<0.001).

The mean Low Density Lipoprotein level at baseline was 125.9 mg/dl which decreased significantly to 90.48 mg/dl after 3 months of therapy with Saroglitazar and the difference was significant (P<0.001).

The mean VLDL at baseline was 50.42 mg/dl which decreased to 35.28 mg/dl after 3 month of therapy with Saroglitazar, and application of Paired t test shows that the decrease was significant (P<0.001).

Table 2 shows the mean TG/HDL ratio at baseline was 8.527 which decreased to 5.153 after 3 month of therapy with Saroglitazar, and application of Paired t test shows that this decrease was statistically significant (P<0.001).

DISCUSSION

Treatment of DD with predominant hypertriglyceridaemia is far from satisfactory. Effectiveness of conventional agents in treatment of hypertriglyceridaemia is inadequate and there is concern about safety.

Hence, there is always need for newer therapeutic targets and newer drugs. Saroglitazar is a dual PPAR- α/γ agonist, the first glitazar approved in the world and has emerged with a new hope to effectively treat DD with relative absence of AEs, especially with no increase of body weight[20,21]

In our study, the mean HbA1c decreased from 7.8% at start of study to 6.75% after 3 months of Saroglitazar therapy and this decrease in HbA1c was found to be statistically significant (P<0.001) on application of paired t test. In the study done by Chatterjeeet al[22] the baseline HbA1c was 8.34±1.58%, at the end of 3months it was 7.21±1.33% with a difference of 1.13±0.43%. The reduction is in concordance with our study. In the study by Ghoshet al[23], the baseline HBA1c was 6.9±0.56% and it reduced to 5.6±0.23% at the end of 12 weeks. Due to lower baseline FPG and PPPG in the study of Ghosh et al, probably the baseline HbA1c was also lower as compared to our study but the reduction in HbA1c was similar in both studies. In a study by Shetty et al[17] it was found that the safety and efficacy of saroglitazar in Indian diabetic dyslipidemia patients, analysis of glycemic parameters revealed a statistically significant 0.9% absolute reduction in HbA1c from baseline value of 8.3% to 7.4% at 3 month follow-up.

In the study by Joshi et al, on Saroglitazar in Diabetic Dyslipidemia[24], there was a reduction in HbA1c from 8.5% at baseline to 6.9% at the end of one year. This shows there is additional reduction in the HbA1c when given for a longer duration. In another study by Joshi et al, on the Efficacy and Safety of Saroglitazar in Indian Diabetics, there was a reduction of 1% in the HbA1c at the end of 2 year follow up. In a study by Saboo et al.[25] on the effect of Saroglitazar 4mg in Patients of diabetic dyslipidemia with non alcoholic fatty liver disease for 24 weeks at diabetes care centre, the baseline was 9.04±1.2% and at the end of 24 weeks it was 8.2%.

Thus, Saroglitazar, a dual PPAR-α/γ agonist was proved to be a very effective drug in the treatment regimen of patients with Diabetic Dyslipidemia. Its addition in the armamentarium of the anti-diabetic drugs and statins was found to have several additional benefits over the lipid and glycemic profile of the patients.

In our study, Saroglitazar brought about significant reductions in glycemic parameters of Fasting Plasma Glucose, Post Prandial Plasma Glucose and HbA1c.

CONCLUSION

It was found that addition of Saroglitazar to the drug regimen of the patients with Diabetic Dyslipidemia can bring about significant improvement in the glycemic and lipid parameters with the added advantage of insignificant adverse effects, thus proving beyond doubt the efficacy and safety of this drug in the treatment of Diabetic Dyslipidemia.

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