Original research

Saroglitazar and its impact on Diabetic Dyslipidemia: A Real life Observational study from Eastern India

[1]Dr Sayantani Bhattacharyya, [2]Dr Supratik Bhattacharyya*, [3]Dr Kingshuk Bhattacharyya

[1]MD Post Graduate Trainee, Department of Physiology, RG Kar Medical College, Kolkata, 1, Khudiram Bose Sarani, Kolkata-700004

[2]Consultant Endocrinologist, Department of Endocrinology, AMRI Hospital, Saltlake, Jc 16 & 17, Kb Block, Saltlake,Kolkata-700098

[3]PhD, Independent Medical writer and Biostatistician, Kolkata-700055

Corresponding author*

Abstract:

Background: As per the randomized trials conducted by manufacturers, Saroglitazar appeared to be an effective and safe therapeutic option for improvinghypertriglyceridemia in patients with type 2 diabetes mellitus.

Methods: We have studied follow-up data of 60 patients collected from the authors' clinic databases and analyzed the effect of saroglitazar on metabolic parameters. The mean duration of follow-up was 12 weeks. Saroglitazar was prescribed at a dose of 4 mg daily, in accordance with approved indication and prescribing information, to patients of T2DM and having hypertriglyceridemia (serum TG level ≥150 mg/dl). Patients received treatment as per routine standard of care. The patients' physical parameters (weight, blood pressure etc.), serum lipid profile and glycemic parameters (fasting plasma glucose, post-meal plasma glucose,HbA1C) were determined at baseline and at end of 12 weeks.

Results: After a mean study duration period of 12 weeks of 60 patients with diabetic dyslipidemia, there was significant reduction in triglycerides from 219.88 ± 178.75 mg/dl (mean ± SD) to 74.03 ± 113.62 mg/dl ($p<0.001$). Glycosylated hemoglobin (HbA1c) also reduced from 7.91 ± 1.53% (mean ± SD) to7.15 ± 1.38%($p<0.001$). Other lipid and glycemic parameters such as total cholesterol, low-density lipoprotein, non-high-density lipoprotein, triglyceride/HDLc ratio, fasting and postprandial plasma glucose were also significantly reduced. There were no major adverse events observed or, reported during the entire study period.

Conclusion: Our short-term follow-up study showed that saroglitazar, could be an effective and safe therapeutic option in adult patients with diabetic dyslipidemia with a persistent and significant improvement in glycemic and lipid parameters.

Background:

Cardiovascular risk reduction is an important issue in the management of patients with Type 2 diabetes mellitus (T2DM). India is estimated to have approximately 65 million people with diabetes, with more than 80% of them suffering from diabetic dyslipidaemia. It is also found that about 30% of deaths in the world are caused by CVD, and diabetes is one of the major causes associated with CVD. Almost 80% of diabetic populations have associative dyslipidemia (low high density lipoprotein (HDL), increased triglycerides (TG), and postprandial lipemia) which necessitates a drug therapy for treatment. This pattern is mostly seen in diabetes mellitus type 2 (T2DM) and may be a treatable risk factor for consequent cardiovascular diseases.[2]

Peroxisome proliferator activated receptor (PPAR) agonists favourably influenceglycaemic and lipid parameters in patients with T2DM and a dual PPAR agonist is expected to have favourable effect on both parameters.Drugs

which are dual agonists of both PPAR-alpha and PPAR-gamma are being developed with the hope of improving glycaemic and lipid parameters and therebyreducing cardiovascular risk in Type 2 diabetes patients. This group of drugs has been named saroglitazar.Saroglitazar, is [(S)-a-ethoxy-4-{2-[2-methyl-5-(4-methylthiophenyl)]-1H-pyrrol-1-yl]-ethoxy})-benzenepropanoic acid magnesium salt]. Saroglitazar treatment was generally safe and well tolerated. No serious adverse events were reported in saroglitazar treatment arm and no persistent change in laboratory parameters.

Hypertriglyceridemia and reduced HDL commonly occur in poorly controlled diabetes mellitus type-1 and even ketoacidosis. The leading cause of diabetic dyslipidemia is the increased free fatty-acid (FFA) release from insulin resistant fat cells.[4] The inability of insulin to suppress FFA release leads to augmented hepatic very low density lipoprotein(VLDL) cholesterol production, which parallels the extent of hepatic fat accumulation. Activation of peroxisome proliferator-activated receptors (PPAR)-γ (predominantly expressed in adipose tissue) by thiazolidinedione (TZDs i.e. rosiglitazone and pioglitazone) may appear to lessen hepatic and skeletal insulin resistance through one or several mechanisms that control adipocyte signaling and metabolism.[5]

Statins are considered a first-line treatment for lowering LDL-C in patients with atherogenic diabetic dyslipidemia (ADD). These drugs decrease the LDL-C levels by as much as 50% with additional benefit on HDL-C and TG levels. But the most common problem with statins use is their effect on muscle function. Muscle symptoms range from myalgia to myositis. Hepatic function is also known to be affected by statins use.[6] Recent studies also shows that statins therapy for long term, especially in high dose can worsen the glycemic control and can lead to new onset of T2DM. Fibrates are another class of drugs which have been used in the treatment of dyslipidemia, particularly useful in raising HDL-C and reducing TG. However, the efficacy of the current fibrates are subjected to limitations, owing to the incertitude relating to the optimal level of PPARα-agonistic activity, agonist-specific biologic responses, the side effects of current synthetic agonists and of course the relevance for patients already on statin therapy, particularly in view of increased risk of muscle-related adverse events.[1]

Saroglitazar has shown to optimize glycemic control and lipid parameters, and minimize PPAR-related adverse effects in the treatment of patients with T2DM. Saroglitazar treatment produced significant dose-dependent improvements in HbA1c, Fasting Plasma Glucose concentration and significant improvements in all lipid parameters, including LDL-C.[7]

Methods:

We have studied follow-up data of 60 patients collected from the authors' clinic databases and analyzed the effect of saroglitazar on metabolic parameters. The mean duration of follow-up was 12 weeks. Saroglitazar was prescribed at a dose of 4 mg daily, in accordance with approved indication and prescribing information, to patients of T2DM and having hypertriglyceridemia (serum TG level ≥150 mg/dl). Patients received treatment as per routine standard of care without any experimentation on any patient. The patients' physical parameters (weight, blood pressure etc.), serum lipid profile and glycemic parameters (fasting plasma glucose, post-meal plasma glucose,HbA1C) were determined at baseline and at last follow-up visit.

Results: After a mean study duration period of 12 weeks of 60 patients with diabetic dyslipidemia, there was significant reduction in triglycerides from 219.88 ± 178.75 mg/dl (mean ± SD) to 74.03 ± 113.62 mg/dl ($p<0.001$). Glycosylated hemoglobin (HbA1c) was reduced from 7.91 ± 1.53% (mean ± SD) to7.15 ± 1.38%($p<0.001$). Other lipid and glycemic parameters such as total cholesterol, low-density lipoprotein, non-

high-density lipoprotein, triglyceride/HDLc ratio, fasting and postprandial plasma glucose were also significantly reduced. There were no major adverse events observed or, reported during the entire study period.

Table 1: Effect of saroglitazar on Anthropometric Parameters

Mean follow-up period (12 weeks) in 60 patients				
Parameters	Baseline values	At Follow up	Mean change	P value (two-tailed)
Weight, Mean ± SD (Kgs)	79.14 ± 9.56	79.85 ± 10.52	+ 0.71 ±0.78	0.07
SBP, Mean ± SD (mmHg)	141.70 ± 14.81	137.77 ± 10.71	- 4.35 ± 4.20	0.06
DBP, Mean ± SD (mmHg)	90.67 ± 5.94	89.00 ± 4.87	- 1.39 ± 0.54	0.20

P<0.05 considered as statistically significant

Table 2: Effect of saroglitazar on Metabolic Parameters

Mean follow-up period (12 weeks)				
Parameters	Baseline values	At Follow- up	Mean change	P value
FPG Mean ± SD (mg/dL)	160.53 ± 53.71	123.82 ± 54.91	- 36.71 ± 20.06	0.014
PPPG Mean ± SD (mg/dL)	243.68 ± 114.59	177.39 ± 60.87	- 66.29 ± 34.71	0.013
HbA1c Mean ± SD (%)	7.91 ± 1.53	7.15 ± 1.38	- 0.76 ±0.43	< 0.001
Cholesterol Mean ± SD (mg/dL)	175.91 ± 56.97	127.75 ± 36.08	- 48.16 ± 17.32	0.001
Triglycerides Mean ± SD (mg/dL)	219.88 ± 178.75	74.03 ± 113.62	-192.78 ±91.06	<0.001
HDL-C Mean ± SD (mg/dL)	38.88 ± 9.79	39.34 ± 11.37	+ 0.47 ± 3.45	0.98
LDL-C Mean ± SD (mg/dL)	108.34 ± 46.94	84.31 ± 23.26	- 24.04 ± 16.14	0.0038
Non HDL-C Mean ± SD (mg/dL)	157.34 ± 53.44	108.63 ± 34.47	- 48.72 ± 17.09	0.0001
TG/HDL-C Mean ± SD (mg/dL)	8.60 ± 7.84	3.30 ± 4.12	- 5.30 ± 2.82	0.002

P<0.05 considered as statistically significant

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Discussion:

Peroxisome proliferator–activated receptors (PPARs) are transcription factors belonging to the superfamily of nuclear receptors. Their natural activating ligands are fatty acids and lipid-derived substrates. Three isoforms, alpha, gamma & delta have been described. They act on DNA response elements as heterodimers with the nuclear retinoic acid receptor. On November 26, 2013, the American Diabetes Association (ADA) posted a press release with comments on ACC/AHA guidelines on lipid management. ADA commented "Diabetes patients often have a unique pattern of dyslipidemia that may require specific consideration".

In our cases, the benefits were elicited beyond marked TG reduction with regards to therapy switchover from insulin to OADs, reduction in blood pressure, decrease in dosage of anti-hypertensive drugs. It was demonstrated bya plethora of randomized controlled trials that despite statin therapy, there was still about 60% residual risk of cardiovascular events Residual CVD risk remains in all patients treated with statins; however, residual CVD risk is particularly high in patients with diabetes treated with statins. The Cholesterol Treatment Trialists' (CTT) Collaborators analyzed data from 18 686 individuals with diabetes in the context of a further 71 370 patients without diabetes in 14 randomized trials of statin therapy. During a mean follow-up of 4.3 years, there were 3247 major vascular events (nonfatal MI, CHD death, stroke, or coronary revascularization) in people with diabetes. Although there was a substantial relative reduction in major vascular events per 1 mmol/L reduction (39 mg/dL) in LDL-cholesterol in participants with a prior history of CHD with diabetes and in participants with a prior history of CHD but without diabetes, the CVD event rate (ie, residual CVD risk) in patients with diabetes treated with statins was higher than the CVD event rate of those patients without diabetes on placebo. Thus, statin therapy does not eliminate the increased CVD risk associated with diabetes.

With regards to triglyceride reduction, statins have been found to reduce TG by around 7%-30% but has associated risk of myalgias, muscle weakness, hepatotoxicity, myopathy, propensity to increase creatinine levels and teratogenicity. Fibrates though are more potent in TG reduction by 20-30% but has side effects viz. dyspepsia, hepatotoxicity, myopathy and gallstones. Furthermore fibrates may cause pancreatitis as well.

Recently, Chatterjee et al. after a mean follow-up period of 14 weeks in 34 patients, treatment with Saroglitazar, in a dose of 4 mg daily, reported significant mean reductions of fasting plasma glucose (36.71 mg/dl), post-prandial plasma glucose (66.29 mg/dl),glycosylated hemoglobin (1.13%), total cholesterol (48.16 mg/dl), LDL-cholesterol (24.04 mg/dl), triglyceride (192.78 mg), non-HDL-cholesterol (48.72 mg/dl) and the ratio of triglyceride and high density lipoprotein cholesterol (5.30).

Saroglitazar, which is a dual PPAR alpha/gamma agonist has shown impressive results in clinical trials with regard to TG reduction. At Week 12, saroglitazar 4 mg tablets significantly reduced mean plasma triglyceride levels by -46.7 $\pm$3.02% (mean $\pm$SE), and the difference was significant (P< 0.001) compared with placebo. Saroglitazar treatment was associated with a mean HbA1c reduction of 0.3%. Saroglitazar was found to be safe and well tolerated by patients.[3]

Triglyceride was identified as important predisposing factor for cerebrovascular accidents and CVD.[13]Dyslipidemia is associated with significantly increased risk of thrombosis in younger patients who develop venous thromboembolism (VTE) (OR: 2.13; 95%CI: 1.08-4.18; p=0.0266.[8]Meta-analysis of eleven studies (8 case-control and 3 cohort studies) by Angeno et al found that patients with VTE had higher triglyceride levels than that of the control population, with a mean difference of 21.0 mg/dL (95% CI, 11.0 to 31.0) in the case-control studies and 8.6 mg/dL (95% CI, 1.2 to 16.0) in the cohort studies. Patients with

alterations in the lipid profile had a higher risk of VTE (OR: 1.62, 95%CI: 1.04-2.52, p= 0.03)[9] Wang et al reported the case of a child suffering from acute lymphoblastic leukemia which illustrated the strong correlation of the rare thrombotic complication, superior sagittal sinus thrombosis and hypercoagulable status secondary to combination use of L-asparaginase and corticosteroid.[10] The mean peak triglyceride level was significantly higher than the level before therapy, which provides a plausible relationship between elevated triglyceridemia and CVA.[10]Doggen and colleagues conducted a case-control study in post-menopausal women and concluded that elevated triglyceride levels were associated with a doubling of venous thrombosis risk.[11]Candelaria and associates demonstrated that the odds ratio for the occurrence of deep vein thrombosis in patients with triglyceride levels ≥300 mg/dL was 3.14.[12]

Dyslipidemia in diabetes has some unique features and may require specific consideration. Our case series of clinical use of a dual PPAR alpha/gamma agonist on Type 2 diabetic patients with dyslipidemia has observed the significant improvement in both glycemic and lipid parameters among Indian patients with type 2 diabetes. In the cases described above, we have observed a benefit on lipid parameters especially with a marked reduction in triglycerides as found in clinical trials. We observed a mean reduction of 853 ± 80.43 mg/dl in triglycerides level with a mean follow-up duration of 46 days. Overall saroglitazar was well tolerated and there was no serious adverse event reported in all of the cases.

Conclusion:

Saroglitazar, the only glitazar approved for clinical use, has shown good efficacy and safety in short-term use. In the studydescribed above, we have observed substantial benefit on lipid parameters,especially with a marked reduction in triglycerides by more than 50% in few weeks.If such early response were to be found in a randomized controlled trial carried out in patients with very extremely high triglycerides levels, this may have huge implication in reducing the incidence of CVA and CVD as well as acute pancreatitis in this high risk subgroup of patients. Our study highlights the need for clinicians to consider saroglitazar among patients with uncontrolled hypertriglyceridemia.

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