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Original Article

Long term safety and efficacy of Saroglitazar on diabetic dyslipidemia with very high triglyceride in Indian subjects: Real world evidence

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ABSTRACT:

Background: Diabetic dyslipidemia (DD) is an important factor contributing to the increased risk of CVDs.The objective of this study was to evaluate the long-term safety and efficacy of Saroglitazar on diabetic dyslipidemia with very high triglyceride (>500 mg/dl) in real world clinical practice. **Materials & Methods:** 150 patients with type 2 diabetes on antidiabetic medications and statins, age above 18 years and triglycerides >500 mg/dL were included. Patients were treated with Saroglitazar 4 mg once daily and the follow-up data were available for 12 months after Saroglitazar treatment. Serum fasting plasma glucose, Serum post prandial glucose, Glycated hemoglobin (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 was assessed. **Results:** There was significant reduction of TG and LDLcholesterol was observed from baseline to 12th weeks 669.93±81.22 to 268.72±82.32 mg/dl and from 167.68±10. to 118.88±12 mg/dl ($p< 0.01$). The mean HbA1c was reduced from 8.02±0.3 to 7.71±0.5% ($p< 0.01$). This reduction in lipid and glycemic parameters were continued till 52 weeks. At 52 weeks mean TG, LDL-cholesterol and HbA1c was reduced to 221.51±61.81 mg/dl, 118.88±12.16 mg/dl and 7.12±0.2 % ($p< 0.01$). No major adverse event reported during the study period. CPK, liver enzymes and creatinine did not alter significantly. **Conclusion:** The addition of Saroglitazar in patients on existing baseline antidiabetic medications showed a significant 0.9% absolute reduction in HbA1c and significant improvement in fasting and post prandial plasma glucose. There were no serious adverse events or alteration in liver enzymes or serum creatinine and edema or weight gain reported in this study. Saroglitazar is a very effective therapeutic option in diabetic dyslipidemia with very high triglycerides level, not controlled by statins. It is very safe for long term use.

Key words: Diabetes, Saroglitazar, Triglycerides

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INTRODUCTION

Diabetes and diabetic dyslipidemia with high triglycerides (TGs) are commonly associated. Diabetic dyslipidemia (DD) is an important factor contributing to the increased risk of CVDs.[1] Studies have shown that three out of four diabetes patients globally have associated dyslipidemia. DD, also known as atherogenic dyslipidemia, is the triad of high triglycerides (TG), higher proportion of small dense low density lipoprotein cholesterol (sd-LDL-C) and low high density lipoprotein cholesterol (HDL-C).

Cardiovascular disease (CVD) is the major cause of morbidity and mortality in individuals with type 2 diabetes mellitus and responsible for 75% of deaths among type 2 diabetes patients. There is also 2- to 4-fold increase in cardiovascular events (coronary heart disease, stroke and peripheral vascular disease) when compared with nondiabetic patients.[2]

Currently statins, fibrates, niacin and omega 3 fatty acids are the available drugs in the armamentarium for the treatment of dyslipidemia. Saroglitazar is the novel molecule approved in India for the management of DD.[3] Saroglitazar is the first dual PPAR α/γ agonist approved in India for the management of diabetic

dyslipidemia. Randomized trials have shown that Saroglitazar when added to statin leads to a significant decrease in TG (−46.7%) and non-HDL cholesterol (−32.5%). Saroglitazar effectively reduces triglyceride, blood glucose, non high-density lipoprotein cholesterol (non-HDL-C) and small, dense low-density lipoprotein sd-LDL particles in patients with diabetic dyslipidaemia.[4] 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).[5] The objective of this study was to evaluate the long-term safety and efficacy of Saroglitazar on diabetic dyslipidemia with very high triglyceride (>500 mg/dl) in real world clinical practice.

MATERIALS & METHODS

This is a real-world retrospective observational study in which 150 patients with type 2 diabetes on antidiabetic medications and statins, age above 18 years and triglycerides >500 mg/dL were included. All enrolled patients were informed regarding the study and their written consent was obtained.

Demographic data such as name, age, gender etc. was recorded. 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, Glycated hemoglobin (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. Patients were treated with Saroglitazar 4 mg once daily and the follow-up data were available for 12 months after Saroglitazar treatment. At baseline, all patients were on stable dose of antidiabetic and statin therapy. Descriptive statistics was used to compare the demographic and baseline disease characteristics. P value less than 0.05 was considered significant.

RESULTS

Table I Distribution of patients

Total- 150		
Gender	**Males**	**Females**
Number	90	60

Table I shows that out of 150, males were 90 and females were 60.

Table II Assessment of parameters

Parameters	Baseline (0 week)	12 weeks	P value	52 weeks	P value
Triglyceride	669.93±81.22	268.72±82.32	0.001	221.51±61.81	0.001
Total cholesterol	310.2 ± 33.04	240.7 ± 23.41	0.001	171.1 ± 21.82	0.001
Non- HDL- C	270.8 ± 34.08	198.6 ± 28.02	0.001	128.3 ± 27.69	0.001
LDL- C	167.68±10.881	118.88±12.16	0.001	103.17±5.51	0.001
HDL- C	40.42±5.87	41.16±6.13	0.059	42.33±5.79	0.02
HbA1C	8.02±0.3	7.71±0.5	0.001	7.12±0.2	0.001
FPG	160.52±7.23	132.47±5.81	0.001	119.62±4.11	0.001
PPG	269.62±24.39	174.16±16.31	0.001	161.18±16.91	0.001
SGOT	42.15±3.18	41.14±3.5	0.21	40.11±3.4	0.31
SGPT	37.34±4.5	37.34±4.5	0.23	36.32±4.7	0.21
S. Creatinine	0.7 ± 0.24	0.7 ± 0.22	0.53	0.7 ± 0.19	0.51
CPK	76.3 ± 19.4	71.8 ± 24.2	0.62	65.3 ± 18.1	0.51

Table II shows that there was significant reduction of TG and LDLcholesterol was observed from baseline to 12th weeks 669.93±81.22 to 268.72±82.32 mg/dl and from 167.68±10. to 118.88±12 mg/dl ($p< 0.01$). The mean HbA1c was reduced from 8.02±0.3 to 7.71±0.5% ($p< 0.01$). This reduction in lipid and glycemic parameters were continued till 52 weeks. At 52 weeks mean TG, LDL-cholesterol and HbA1c was reduced to 221.51±61.81 mg/dl, 118.88±12.16 mg/dl and 7.12±0.2 % ($p< 0.01$). No major adverse event reported during the study period. CPK, liver enzymes and creatinine did not alter significantly.

DISCUSSION

Diabetes mellitus (DM), commonly known as diabetes is an endocrinal disorder in which there are elevated blood sugar levels over a long period. The common symptoms of high blood sugar are frequent urination, increased thirst, and increased hunger.[6] However, diabetes can cause many complications also if left undertreated. Some of the complications are diabetic

ketoacidosis and hyperosmolar hyperglycemic state.[7] There can be long term serious complications such as cardiovascular disease, stroke, kidney disease, ulcers in the foot, and damage to the eyes. The cardiovascular diseases (CVDs) burden globally and as well in India is rising sharply and presently is the number one cause of mortality.[8] INTERHEART study, a major Canadian-led global study identified easily measured risk factors (smoking, lipids, hypertension, diabetes, obesity, diet, physical activity, alcohol consumption, and psychosocial factors) that account for over 90% of the risk of acute myocardial infarction (AMI) and dyslipidemia being the strongest risk predictor globally.[9] The objective of this study was to evaluate the long-term safety and efficacy of Saroglitazar on diabetic dyslipidemia with very high triglyceride (>500 mg/dl) in real world clinical practice.

In present study, there were 150 patients (males- 90, females- 60). Shetty et al[10] evaluated the safety and efficacy of saroglitazar 4 mg once daily in clinical practice. Patients with type 2 diabetes (with on-going antidiabetic medication), age above 18 years, and triglycerides ≥200 mg/dL were included. A total 2804 patients with a mean duration of diabetes 6.29 yrs were included in this analysis. The baseline demographic profile was: mean age of 53 yrs, mean body weight 72.3 kg and mean BMI of 27 kg/m2. 62.5% patients were male and 57.8% were reported to be on statin therapy at baseline. All 2804 patients were on antidiabetic medications with 15.4% patients on monotherapy and rest were on two or more than two antidiabetic medications at baseline. The baseline triglycerides and HbA1C values were 312.3 mg/dL and 8.3% respectively. At 3 months follow-up, use of saroglitazar 4 mg led to significant reduction in TG (35.8%), LDL-C (16.4%), total cholesterol (19%) and non-HDL-C (23.4%). Addition of saroglitazar to baseline antidiabetic medications showed a significant 0.9% absolute reduction in HbA1c with significant improvement in fasting and post prandial plasma glucose. No serious adverse events, alteration in liver or renal enzymes and edema or weight gain were reported.

We found that that there was significant reduction of TG and LDL-cholesterol was observed from baseline to 12th weeks 669.93±81.22 to 268.72±82.32 mg/dl and from 167.68±10. to 118.88±12 mg/dl. Goyal et al[11] studied 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. 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. 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).

We observed that the mean HbA1c was reduced from 8.02±0.3 to 7.71±0.5% (p< 0.01). This reduction in lipid and glycemic parameters were continued till 52 weeks. At 52 weeks mean TG, LDL-cholesterol and HbA1c was reduced to 221.51±61.81 mg/dl, 118.88±12.16 mg/dl and 7.12±0.2 % (p< 0.01). No major adverse event reported during the study period. CPK, liver enzymes and creatinine did not alter significantly. Pai et al[12] conducted a study in which diabetic patients who received at least a single dose of saroglitazar were included for safety evaluation. The efficacy analysis included 109 patients (n = 37 in saroglitazar 2 mg; n = 39 in saroglitazar 4 mg; n = 33 in pioglitazone). Saroglitazar 2 mg and 4 mg significantly reduced (P < .001) plasma triglyceride from baseline by 26.4% (absolute change ± SD: −78.2 ± 81.98 mg/dL) and 45% (absolute change ± SD −115.4 ± 68.11 mg/dL), respectively, as compared to pioglitazone -15.5% (absolute change ± SD: −33.3 ± 162.41 mg/dL) at week 24. Saroglitazar 4 mg treatment also demonstrated marked decrease in low-density lipoprotein (5%), very-low-density lipoprotein (45.5%), total cholesterol (7.7%), and apolipoprotein-B (10.9%). 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. Saroglitazar appeared to be an effective and safe therapeutic option for improving hypertriglyceridemia in patients with type 2 diabetes mellitus.

CONCLUSION

The present study shows that Saroglitazar in addition to statins led to a significant improvement in all the lipid parameters. At 52 week there was a significant reduction in TG of 66.9%, LDL-C of 38.47%, total cholesterol of 44.84 % and non- HDL-C of 52.62 %. The addition of Saroglitazar in patients on existing baseline antidiabetic medications showed a significant 0.9% absolute reduction in HbA1c and significant improvement in fasting and post prandial plasma glucose. There were no serious adverse events or alteration in liver enzymes or serum creatinine and edema or weight gain reported in this study. Saroglitazar is a very effective therapeutic option in diabetic dyslipidemia with very high triglycerides level, not controlled by statins. It is very safe for long term use.

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