Open Access　　　　　　　　　　　　　　　　　　　　　　**Mini Review**

Real Time Clinical Safety and Effectiveness of Long Term Use of Saroglitazar in Indian Patients with Diabetic Dyslipidemia Having Abnormal Metabolic Parameters

Sanjay Chatterjee [1]*, Majumder A [2], Ray S [1] and Bhattacharjee K [3].

[1] Apollo Gleneagles Hospital, Kolkata, India.

[2] KPC Medical College, Kolkata, India.

[3] PhD Scholar, JJT University, India.

*Corresponding Author : **Sanjay Chatterjee**, MD Consultant Diabetologist, Apollo Gleneagles Hospital, Kolkata, India.
 Email: Sanjay_doc@yahoo.co.in

Question: Indian patients with type 2 diabetes (T2DM) usually suffer from multiple metabolic abnormalities, such as overweight, obesity, high triglycerides (TG), low HDL-C, increased blood pressure, along with insulin resistance. In India, Saroglitazar is being used in the management of diabetic dyslipidemia since 2013. Randomized controlled clinical trials of Saroglitazar (PRESS V & PRESS VI studies) 1, 2 have established safety and efficacy of Saroglitazar in T2DM patients with dyslipidemia. But the question is "What is the real time clinical safety and effectiveness of Saroglitazar in Diabetic dyslipidemia, if it is used for more than a year?

Review scope: This article reviews the observational study and retrospective analysis of 58 weeks safety and effectiveness data of Saroglitazar in Indian patients having diabetic dyslipidemia [3].

Objective of this review: Phase III randomized controlled clinical trials of Saroglitazar have evaluated the safety and efficacy of this drug for 12-24 weeks follow-up [1, 2]. Previously published post-marketing studies evaluating the clinical safety and effectiveness of Saroglitazar in diabetic dyslipidemia had a shorter duration of follow-up (less than 1 year) [4-6]. We conducted a retrospective analysis of safety and effectiveness data of Saroglitazar 4 mg once daily in Indian patients with T2DM, having metabolic abnormalities (like high TG and low HDL). This analysis included the data from the patients with a mean follow-up duration of 58 weeks [3]. The main objective of this retrospective analysis was to evaluate long-term safety and effectiveness of Saroglitazar in diabetic dyslipidemia.

Methods: We identified 158 patients having type 2 diabetes and dyslipidemia (TG $\geq$150 mg/dl) who had been prescribed Saroglitazar 4 mg once daily as per the prescribing information and the follow-up results were available for 58 weeks duration. Data of only those patients were considered for final evaluation having both baseline and follow-up values of fasting plasma glucose (FPG), post-prandial plasma glucose (PPPG), glycated hemoglobin (HbA1c) and lipid profile. Descriptive data analytics has been carried out in the present study and were analyzed by appropriate statistical tests. A p value of <0.05 was considered as statistically significant.

Results: A total of 158 patients' data was analyzed in this observational study with variable co-morbidities and all were T2DM patients, with high TG (TG>150 mg/dl). A total of 53.16% patients were overweight/ obese and 58.86% patients were hypertensive. After 58 weeks, the mean blood pressure was significantly reduced, both systolic (-4 mmhg, P= 0.004) and diastolic (-2 mmhg, P=0.001).

At end of 58 weeks, metabolic parameters like TG, TC, LDL-C, FPG, PPPG, HbA1c, non HDL-C were reduced significantly from baseline (Table). Significant drop in non HDL-C may have beneficial impact on residual CV risk, while a reduction of both triglyceride and TG/HDL ratio makes a shift of the small dense LDL particles to more buoyant and larger LDL particles which are less atherogenic.

Regarding safety analysis, Saroglitazar was to be found safe without having any major/serious adverse events during 58 weeks of therapy. Liver enzymes ALT and AST were both reduced from baseline, the ALT reduction at 58 weeks was found to be statistically significant (P<0.001). Serum creatinine level was not adversely affected during this observational study. The change in body weight at 58 wees follow-up was found to be statistically significant (increased from 70.61 kg at baseline to 71.69 kg at 58 weeks; p=0.002) in this retrospective analysis.

Parameters	Baseline values	At Follow-up	Mean change	Difference (%)	P value
FPG (mg/dL)	160.5	134.7	-25.8	-16.0	<0.001
PPPG (mg/dL)	235..4	191.6	- 43.9	-18.6	<0.001
HbA1c (%)	7.91	7.25	- 0.65	-	<0.001
Cholesterol (mg/dL)	181.02	148.4	- 32.6	-18.0	<0.001
Triglycerides (mg/dL)	319.9	174.0	- 145.8	-45.6	<0.001
HDL-C (mg/dL)	38.3	38.6	0.2	0.5	0.69
LDL-C (mg/dL)	102.0	90.5	- 11.5	-11.0	0.016
Non HDL-C (mg/dL)	140.1	104.5	- 35.6	-25.4	<0.001
TG/HDL-C (mg/dL)	7.4	4.2	-3.2	-43.2	<0.001

Table.1: Metabolic Parameters: % Changes from baseline at 58 weeks follow-up

HDL-C: High density lipid cholesterol, LDL-C: Low density lipid cholesterol, TG: Triglyceride, FPG: Fasting plasma glucose, PPPG: Post-prandial plasma glucose, HbA1c: glycated hemoglobin

Conclusion:

High TG is considerably associated with diabetes mellitus and it is of utmost importance to reduce TG when it is more than >200 mg/dl. The results of this analysis showed that 58 weeks use of Saroglitazar significantly improves the metabolic abnormalities (lipids and glycemic parameters) in Indian diabetic patients with good safety and tolerability profile.

Commentary

Various recently published large observational and epidemiological studies have strongly established the positive association of High TG (>150 mg/dl) with elevated CV risk [7-9].

The results from 22 year follow-up of the Bezafibrate Infarction Prevention (BIP) study and registry showed that in patients with established CHD, the increased levels of serum triglycerides (TG> 500mg/dL) is associated with a long-term increased risk of mortality by 68% [7]. The results from Strong Heart Study established that in American Indian patients with high TG (>150 mg/dL), Diabetes and low HDL had 54% increased risk of CHD and 2.13 times higher risk of stroke compared to diabetic patients with normal TG and HDL values [8]. So management of high TG is important and as per guidelines recommendations, statins are first line therapy while non-statin TG lowering therapies (Saroglitazar, Fibrates, Niacin, Omega-3 fatty acid) may be considered as add on therapy only in those high risk patients who do not achieve their lipid targets (TG and non HDL-C) in spite of optimal statin therapy.

Studies have also established that even mild to moderate elevation of TG levels are associated with significant increase in the risk of acute pancreatitis [10]. The latest consensus statement by American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) advocates reducing triglyceride levels when severely elevated (>500 mg/dL) to prevent pancreatitis [11].

Saroglitazar is a dual PPAR α and γ agonist approved in India for the treatment of hypertriglyceridemia in patients with T2DM uncontrolled with statin therapy. In two phase 3 trials, Saroglitazar 4 mg once daily showed significant decrease in triglyceride levels (-45 to 46.7%), non HDL-C (-32.5%) and HbA1c (-0.3%) with better safety and tolerability profile over the period of 12-24 weeks follow-up[1, 2]. In one Indian post-marketing, observational study, at 3 months follow-up, Saroglitazar 4 mg led to significant reduction in TG (-35.8%), LDL-C (-16.4%), total cholesterol (-19%), non HDL-C (-23.4%) and significant 0.9% absolute reduction in HbA1c (As an add on to anti-diabetic medications) with no serious adverse events reported [4].

A part of Chatterjee S et al 2018 study of 158 patients with follow-up of 58 weeks is a continuation of earlier published data with follow-up data of only 34 patients for a period of 14 weeks [3, 5]. In 58 weeks follow-up study, it was observed that Saroglitazar 4 mg significantly improves various metabolic parameters (lipid and glycemic parameters) along with favorable effects on serum ALT level and no significant change in serum creatinine level. These 58 weeks follow-up results are in consistent with previous 14 weeks and 40 weeks observational data analysis [5, 6]. Unlike previous observations (of no weight gain associated with Saroglitazar), in this study with much longer duration, the weight-gain has reached a level of statistical significance. However, it should be noted that many patients were on sulfonylureas and/or insulin, which are known to cause weight gain; hence the weight-gain cannot be solely attributable to Saroglitazar alone.

Unique strength of this study is long duration of therapy of 58 weeks but lack of vigilance of control group and small sample size (158 patients) are limitations of it. Larger and more comprehensive randomized controlled clinical trials are required to establish and further validate these findings.

References

1. Pai V, Paneerselvam A, Mukhopadhyay S, Bhansali A, Kamath D et al (2014) Multicenter, Prospective, andomized, Double-blind Study to Evaluate the Safety and Efficacy of Saroglitazar 2 and 4 mg Compared to Pioglitazone 45 mg in Diabetic Dyslipidemia (PRESS V). J Diabetes Sci Technol 8(1): 132-141.

2. Jani RH, Pai V, Jha P, Jariwala G, Mukhopadhyay S et al (2014) A multicenter, prospective, randomized, double-blind study to evaluate the safety and efficacy of Saroglitazar 2 and 4 mg compared with placebo in type 2 diabetes mellitus patients having hypertriglyceridemia not controlled with atorvastatin therapy (PRESS VI). Diabetes Technol Ther 16(2): 63-71.

3. Chatterjee S (2018) Observational Study of Saroglitazar on Metabolic Parameters in Indian Patients with Diabetic Dyslipidaemia – A Fifty Eight Weeks of Clinical Experience. Diabetes Obes Int J, 3(2): 000180.

4. Shetty SR, Kumar S, Mathur RP, Sharma KH, Jaiswal AD (2015) Observational study to evaluate the safety and efficacy of saroglitazar in Indian diabetic dyslipidemia patients. Indian heart journal 67(1): 23-26.

5. Chatterjee S, Majumder A, Ray S (2015) Observational Study of Effects of Saroglitazar on Glycaemic and Lipid Parameters on Indian Patients with Type 2 Diabetes. Sci Rep 5: 7706.

6. Chatterjee S, Majumder A, Ray S (2016) Effect of Saroglitazar on Metabolic Parameters in Indian Patients with Diabetic Dyslipidemia: A 40-Week, Retrospective Analysis. Diabetes 65: A541-A556.

7. Klempfner R, Erez A, Sagit BZ, Goldenberg I, Fisman E et al (2016) Elevated Triglyceride Level Is Independently Associated With Increased All-Cause Mortality in Patients With Established Coronary Heart Disease Twenty-Two–Year Follow-Up of the Bezafibrate Infarction Prevention Study and Registry. Circ Cardiovasc Qual Outcomes 9(2): 100-108.

8. Lee JS, Chang PY, Zhang Y, Kizer JR, Best LG et al (2017) Triglyceride and HDL-C Dyslipidemia and Risks of Coronary Heart Disease and Ischemic Stroke by Glycemic Dysregulations Status. The Strong Heart Study. Diabetes Care 40(4): 529-537.

9. Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG, Tybjærg-Hansen A (2014) Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. N Engl J Med;371:32-41.

10. Pedersen SB, Langsted A, Nordestgaard BG (2016) Non fasting Mild-to-Moderate Hypertriglyceridemia and Risk of Acute Pancreatitis. JAMA Intern Med 176(12): 1834-1842.

11. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT et al (2017) Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2017 Executive Summary. Endocr Pract 23(2): 207-238.