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Observational Study of Saroglitazar on Metabolic Parameters in Indian Patients with Diabetic Dyslipidaemia – A Fifty Eight Weeks of Clinical Experience

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Abstract

Background: Earlier we had reported results of our study of treatment with Saroglitazar, in a dose of 4 mg daily, for 14 weeks in 34 patients with diabetic dyslipidemia., and showed significant improvement in both glycemic and lipid parameters. We conducted this 58 weeks follow-up study in 158 patients to determine whether the improvement in glycemic and lipid parameters persisted in long-term follow-up and whether long-term therapy had any effect on the blood pressure, weight, renal and liver functions.

Methods: We have studied follow-up data of 158 patients collected from the authors' clinic databases and analyzed the effect of saroglitazar on metabolic parameters. Data of patients having both baseline and follow-up data were included in the analysis. The mean duration of follow-up was 58 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 58 weeks of 158 patients with diabetic dyslipidemia, there was significant reduction in triglycerides from 319.88 ± 178.75 mg/dl (mean ± SD) to 174.03 ± 113.62 mg/dl (reduction of 145.84 ± 186.59 mg/dl; p<0.001). Glycosylated hemoglobin (HbA1c) was reduced from 7.91 ± 1.53% (mean ± SD) to7.25 ± 1.38% (reduction of 0.65 ± 1.37%; 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 long-term follow-up study showed that dual PPAR α+γ agonist, 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 and may confer an additional beneficial effect on blood pressure and liver function as well.

Keywords: Saroglitazar; Diabetic Dyslipidemia; India; Real World

Significant Findings of the Study

The significant improvements in glycemic and lipid parameters persisted even in long-term in a larger sample size with an additional benefit on blood pressure and liver function without any adverse effect on renal function, thereby demonstrating the efficacy and safety of the dual PPAR α+γ agonist, saroglitazar.

What this Study Adds

The current study is a long term follow up and establishing for the first time the 58 weeks clinical safety and efficacy of Saroglitazar 4 mg once daily in patients with diabetes and hypertriglyceridemia in a real world scenario.

Introduction

Type 2 Diabetes Mellitus (T2DM) is a major global health burden affecting millions across the globe leading to various complications causing cardiovascular morbidity and mortality. Dyslipidaemia is an important risk factor for cardiovascular diseases (CVD) found to be inherently associated with diabetes.

Diabetic dyslipidaemia (DD) is a particular laboratory phenotype of the lipid profile observed in patients with T2DM: hypertriglyceridaemia with low serum high-density lipoprotein cholesterol (HDLc) concentrations, normal or, moderately elevated serum low-density lipoprotein (LDLc) levels with increased small dense LDL (sdLDL) particles [1-3]. The prevalence of DD reported in various studies varied between 35 and 50% and is strongly associated with increased cardiovascular risk [4].

Despite statin therapy and LDL-lowering, a residual risk of cardiovascular events still persists in all patients. Nevertheless, the residual CVD risk is especially higher in patients with diabetes as demonstrated in an analysis by the collaborators of the Cholesterol Treatment Trialists' (CTT) [5]. Several genome-wide association studies indicate an independent causal role of triglyceride (TG)-rich lipoproteins (TRL) in CVD [6-8]. Additionally, severe hypertriglyceridaemia is associated with an increased risk of acute pancreatitis [9]. Some international guidelines recommend treatment of TG at levels more than 200 mg/dl despite the use of high-intensity statin therapy [10]. The current treatment options available for reducing hypertriglyceridaemia are fibrates, niacin, long chain omega 3 fatty acids and saroglitazar.

Saroglitazar is approved in India for treating hypertriglyceridaemia in patients with diabetes and it has a potential role in reducing both lipid and glycaemic parameters being a dual (α+γ) peroxisome proliferator-activated receptor (PPAR) agonist. Phase III, controlled clinical trials have shown that saroglitazar 4 mg once daily, when added to statin, leads to significant decrease in triglyceride (45-46.7%) and non HDLc (32.5%) and resulted in significant decrease in HbA1c (0.3%) [11,12].

This study was aimed at evaluating effectiveness and safety of Saroglitazar in real time clinical settings. We had earlier reported, the use of saroglitazar on patients with diabetic dyslipidemia and observed significant changes in both lipid and glycemic parameters [13]. This study is an extension of our earlier observation on more number of patients and with more prolonged duration of treatment.

Methods

Saroglitazar was prescribed at a dose of 4 mg daily, as per the 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. Data of only those patients were considered for final evaluation having both baseline and follow-up values of fasting plasma glucose, post-prandial plasma glucose, glycated hemoglobin (HbA1c) and lipid profile. A total of 158 patients' data analyzed for study. Out of 158 patients, 118 patients received statins. Patients' data was collected from the authors' clinic databases.

The patients' physical parameters (weight, blood pressure etc.), serum lipid profile and glycaemic parameters (fasting plasma glucose, post-meal plasma glucose,HbA1c) were determined at baseline and at last follow-up visit. Descriptive data analytics has been carried out in the present study. Results on continuous measurements are presented as mean ± SD and results on categorical measurements are represented in counts (%). Significance is assessed at a level of 5%.

Normality of data was tested by simultaneous Anderson Darling test, Shapiro-Wilk test and graphically by QQ plot. Paired t-test was applied to detectany significance change of study parameters measured on two occasions for same group of patients. A p value of <0.05 was considered as statistically significant.

Ethical Approval

The current study was a retrospective study retrieving and analyzing data from author's clinic database. All the included patients received treatment as per approved guidelines of regulatory authorities without any experimentation on any patient. The identity of none of the patients was disclosed at any place of the manuscript and patients' confidentiality was not compromised. Hence, all the authors felt that Approval of Ethics Committee is not necessary and also Informed Consent was not necessary.

Statistical Software

The Statistical software namely SAS (Statistical Analysis System) version 9.2 for windows, SAS Institute Inc. Cary, NC, USA and Statistical Package for Social Sciences (SPSS Complex Samples) Version 21.0 for windows, SPSS, Inc., Chicago, IL, USA were used for the analysis of the data. Microsoft word 2010 and Microsoft Excel 2010 (Microsoft Corp, Redmond, WA, USA), have been used to generate graphs and tables.

Results

A total of 158 patients' data was analyzed in this observational study, which had a male preponderance (67.72% males versus 32.28% females). The mean age was 51.34 ± 10.87 years and average weight was 70.52 ± 2.13 kgs (Table 2). All were T2DM patients and had dyslipidemia (TG>150 mg/dl). A total of 53.16% patients were overweight/ obese and 58.86% patients were hypertensive. Other significant co-morbidities are enlisted in Table 1. Baseline parameters of patients are documented in Table 2.

Comorbidities	Number (n)	Percentage (%)
Overweight/Obesity	84	53.16
Hypertension	93	58.86
Microalbuminuria	35	22.15
Diabetic Nephropathy	9	5.7
CHD	8	5.06
Hypothyroidism	15	9.49
Fatty Liver(by USG)	14	8.86
Statin Usage	118	74.68
Alteration in Medication	101	63.92

Table 1: Comorbidities (N=158).

Demographic Profile , N=158	
Male(number)	107
Female(number)	51
Age, Mean ± SD (years)	51.34 ± 10.87
Weight, Mean ± SD (Kgs)	70.52 ± 2.13
SBP, Mean ± SD (mmHg)	131.24 ± 12.2
DBP, Mean ± SD (mmHg)	80.79 ± 7.02
Laboratory data	
FPG, Mean ± SD(mg/dL)	160.31 ± 58.3
PPPG, Mean ± SD(mg/dL)	234.93 ± 94.3
HbA1c, Mean ± SD (%)	7.98 ± 1.58
Total Cholesterol, Mean ± SD(mg/dL)	180.67 ± 50.94
Triglycerides, Mean ± SD(mg/dL)	315.4 ± 176.31
HDL, Mean ± SD(mg/dL)	38.38 ± 10.17
LDL, Mean ± SD(mg/dL)	101.77 ± 41.91
Non-HDL, Mean ± SD(mg/dL)	139.52 ± 56.28
TG/HDL ratio, Mean ± SD	8.28 ± 5.15
ALT, Mean ± SD(IU/L)	42.15 ± 26.62
Serum Creatinine, Mean ± SD(mg/dL)	0.98 ± 0.29

Table 2: Baseline characteristics.

After 58 weeks, the mean blood pressure was significantly reduced, both systolic (P= 0.004) and diastolic (P=0.001) (Table 3).

Mean follow-up period (14 weeks) in 34 patients[Ref:13]					Mean follow-up period (58 weeks) in 158 patients			
Parameters	**Baseline values**	**At Follow up**	**Mean change**	**P value (two-tailed)**	**Baseline values**	**At Follow up**	**Mean change**	**P value (two-tailed)**
Weight, Mean ± SD (Kgs)	69.14 ± 9.56	69.85 ± 10.52	+ 0.71 ±0.78	0.07	70.61 ± 12.13	71.69 ± 12.93	1.09 ± 4.40	0.002
SBP, Mean ± SD (mmHg)	131.70 ± 14.81	127.77 ± 10.71	- 4.35 ± 4.20	0.06	131.24 ± 12.2	127.13 ± 17.53	-4.21 ± 17.70	0.004
DBP, Mean ± SD (mmHg)	80.67 ± 5.94	79.00 ± 4.87	- 1.39 ± 0.54	0.2	80.79 ± 7.02	79.03 ± 5.76	-1.76 ± 6.68	0.001

Table 3: Effect of saroglitazar on Physical Parameters.

After the completion of 58 weeks mean follow-up, HbA1c was significantly reduced (P< 0.001) from 7.91% to 7.25%.The other glycaemic parameters namely fasting plasma glucose and post prandial plasma glucose were also significantly reduced (P< 0.001) (Table 4).

The addition of saroglitazar favorably modified the lipid profile of the patients, regardless of concomitant statin therapy. Serum triglycerides level was significantly reduced from 319.88 mg/dl at baseline to 174.03 mg/dl at 58 week follow up (P< 0.001). All of the other lipid parameters such as total cholesterol (TC), LDLc, non-HDLc and triglyceride/HDLc ratio were significantly reduced after 58 weeks of Saroglitazar therapy. The substantial drop in non-HDLc level in our study may have a favorable effect on residual CV risk-reduction with addition of Saroglitazar therapy. Mean HDLc increased, however the values were not significant (Table 4). Another interesting finding of the present study is the robust decrease in triglyceride/HDLc ratio, and this may have a well-disposed effect on LDL particle size. The LDL particle size is better indicated by TG/HDL ratio than triglyceride level. 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 [13].

Mean follow-up period (34 weeks)[Ref:13]					**Mean follow-up period (58 weeks)**			
Parameters	**Baseline values**	**At Follow-up**	**Mean change**	**P value**	**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	0.0007	160.46 ± 58.37	134.67 ± 45.51	-25.79 ± 61.10	<0.001
PPPG Mean ± SD (mg/dL)	243.68 ± 114.59	177.39 ± 60.87	- 66.29 ± 34.71	0.0005	235.42 ± 95.05	191.55 ± 66.52	- 43.87 ± 94.62	<0.001
HbA1c Mean ± SD (%)	8.34 ± 1.58	7.21 ± 1.33	- 1.13 ±0.43	< 0.0001	7.91 ± 1.53	7.25 ± 1.38	- 0.65 ± 1.37	<0.001
Cholesterol Mean ± SD (mg/dL)	195.91 ± 56.97	147.75 ± 36.08	- 48.16 ± 17.32	< 0.0001	181.02 ± 51.70	148.4 ± 38.55	- 32.61 ± 47.76	<0.001
Triglycerides Mean ± SD (mg/dL)	346.78 ± 246.01	154.00 ± 127.73	-192.78 ±91.06	0.0001	319.88 ± 178.75	174.03 ± 113.62	- 145.84 ± 186.59	<0.001
HDL-C Mean ± SD (mg/dL)	38.88 ± 9.79	39.34 ± 11.37	+ 0.47 ± 3.45	0.78	38.27 ± 10.51	38.55 ± 10.8	0.28 ± 8.33	0.69
LDL-C Mean ± SD (mg/dL)	108.34 ± 46.94	84.31 ± 23.26	- 24.04 ± 16.14	0.0048	102.05 ± 42.35	90.54 ± 49.88	- 11.51 ± 56.4	0.016
Non HDL-C Mean	157.34 ±	108.63 ±	- 48.72 ±	<0.0001	140.14 ± 55.4	104.52 ± 49.7	- 35.63 ± 58.99	<0.001

± SD (mg/dL)	53.44	34.47	17.09					
TG/HDL-C Mean ± SD (mg/dL)	9.60 ± 7.84	4.30 ± 4.12	- 5.30 ± 2.82	0.0006	7.46 ± 4.34	4.23 ± 2.80	- 3.23 ± 3.42	<0.001

Table 4: Effect of saroglitazar on Metabolic Parameters.

Saroglitazar was found to be safe with no major adverse events reported throughout the entire duration of 58 weeks. Liver enzymes ALT and AST were both reduced from baseline, the ALT reduction being significant (P<0.001). Serum creatinine was not adversely affected during this observational study (Table 5).

Mean follow-up period (34 weeks) [Ref:13]					Mean follow-up period (58 weeks)			
Parameters	**Baseline values**	**At Follow-up**	**Mean change**	**P value**	**Baseline values**	**At Follow-up**	**Mean change**	**P value**
AST Mean ± SD (U/L)	Not Captured in previous Study				31.63 ± 17.11	27.63 ± 10.35	-4.00 ± 15.54	0.15
ALT Mean ± SD (U/L)	52.83 ± 31.96	43.17 ± 27.84	- 9.69 ± 9.05	0.03	42.15 ± 26.62	30.19 ± 20.36	- 12.64 ± 27.34	<0.001
Creatinine Mean ± SD (mg/dL)	0.95 ± 0.21	1.04 ± 0.24	+ 0.098 ± 0.10	0.06	0.98 ± 0.29	1.00 ± 0.29	0.022 ± 0.18	0.20

P<0.05 considered as statistically significant

Table 5: Safety and Tolerability of saroglitazar.

Discussion

Elevated plasma TG (TG>150 mg/dl) and non-HDLc levels have been found to be independently associated with increased cardiovascular disease (CVD) risk and severe hypertriglyceridaemia (TG>500 mg/dl) have been associated with an increased risk of acute pancreatitis [14,15]. Likewise, 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 [16]. While no large clinical trials have been designed to test this objective, observational data and retrospective analyses support long term dietary and lipid management of hypertriglyceridaemia for prophylaxis against or treatment of acute pancreatitis [16].

Theoretically, Non–high-density lipoprotein cholesterol (non-HDLc) level poses to be an important predictor of coronary heart disease (CHD) risk than LDLc for it comprehensively corresponds to total cholesterol carried in all potentially atherogenic lipoprotein particles namely low-density lipoprotein (LDL), very low density lipoprotein (VLDL), VLDL remnants, intermediate-density lipoprotein (IDL), and lipoprotein(a) . To investigate the same, Cui and associates examined the data obtained from the Lipid Research Clinics (LRC) Program Follow-up Study, whether the non-HDLc level would predict cardiovascular disease (CVD) mortality, and how it equates to LDLc in this prediction. A total of 4,462 men and women, who were followed up for 19 years in the LRC Program Follow-up Study, were analyzed for CVD death. The CVD mortality (both in men and women) were better predicted by baseline non-HDLc and HDLc levels as compared to LDLc level [17]. In the same line, a pooled post-hoc analysis of outcomes using data from four large landmark studies had underlined the limited utility of LDLc to represent the long-established cardio-metabolic lipid load in patients with diabetic dyslipidaemia [18]. In a recent review by Ramjee et al., non–HDLc have been stated to be twice as good as LDLc in predicting risk reduction, and to demonstrate dose-dependent effects in predictive models of CVD more consistently than LDLc [19].

Additionally, a recent article concluded that even non-fasting mild-to-moderate hypertriglyceridemia from 177mg/dL (2 mmol/L) and above is associated with a high risk of acute pancreatitis, with hazard ratio estimates higher than that for myocardial infarction [20]. Triglycerides are predominantly carried in TG-rich lipoproteins (chylomicrons carries exogenous TG and VLDL carries endogenous TG) remnants [14], and it is the cholesterol content of these TG-rich lipoproteins that is mainly believed to lead to atherosclerosis. A study demonstrated that a 1 mmol/L (39 mg/dL) increase in non-fasting remnant cholesterol is associated with a 2.8-

fold increase in the risk of ischaemic heart disease [8]. These elevated levels of TG-rich lipoproteins and their remnants have been shown to be linked to accumulation of intimal cholesterol, plaque formation and progression [21]. TG-rich lipoprotein remnants are also hypothesized to contribute to the progression of atherosclerosis by indirect mechanisms such as impaired vasodilation and increased inflammation [21-25].

The results from 22 year follow-up of the Bezafibrate Infarction Prevention (BIP) study and registry showed that increased levels of serum triglycerides in patients with established CHD are associated with a long-term mortality risk which is independent of HDL-C levels. The results also detected the higher risk of mortality even in subjects with triglycerides >100 mg/dL. Severe hypertriglyceridemia (triglycerides >500 mg/dL) was found to be associated with 68% increase in the risk of mortality over 22-years follow-up [26].

The results of Strong Heart Study also established the association between high triglyceride and increased risk of CHD. Total 3,216 American Indians participants (free of cardiovascular disease at baseline) participated in this study with a median follow-up of 17.7 years. 41% participants were having diabetes. Participants with diabetes and high TG (≥150 mg/dL) plus low HDL (<40 mg/dL for men and <50 mg/dL for women) levels had a 1.54-fold greater HR (95% CI1.15–2.06) for CHD than those with diabetes having normal TG and HDL levels. The HR for stroke was 2.13 fold greater in diabetes with high TG and low HDL compared to diabetes subjects with normal TG and HDL values [27].

Therefore, the management of hypertriglyceridaemia is important not just in the prevention of pancreatitis, but also in reducing the risk of CVD in patients with mild to moderate hypertriglyceridaemia. In a recent study the authors quoted "Numerous studies consistently showed that pharmacological interventions that target the dyslipidemia and hypertension associated with T2DM, reduce risk of macrovascular complications in such patients" [28].

Lifestyle modification in the form of diet and exercise can be considered vital to start with. However, lifestyle interventions alone are often insufficient to achieve the strict lipid goals. The addition of niacin, fibrates, or long-chain omega-3-fatty acids to statin therapy has been advocated for those patients who have failed to attain normal TG levels [29-33]. However, these agents have been found to differ substantially in their TG lowering effects and they are also burdened by their gamut of side effects. Attempts to reduce TG levels, with addition of fibrates in specific patients' subgroups, have shown modest benefit. In a recently published article of 9.7 years follow-up data of the Action to Control Cardiovascular Risk in Diabetes Lipid Study (ACCORD Lipid Arm), fenofibrate therapy when added to statins was found to reduce the hazards of CVD by 27 percentage points (HR, 0.73; 95% CI, 0.56-0.95) in subjects with triglyceride levels greater than 204 mg/dL and high-density lipoprotein cholesterol levels less than 34 mg/dL. This post-trial finding demonstrates that fenofibrate can reduce cardiovascular disease risk in this subgroup of statin-treated patients with type 2 diabetes [34].

Saroglitazar is a dual PPAR α and γ agonist approved in India for the treatment of hypertriglyceridaemia in T2DM uncontrolled with statin therapy. A phase 3, controlled clinical trial has shown that saroglitazar 4 mg once daily, when added to statin, leads to significant decrease in triglyceride (46.7%) and non HDLc (32.5%). In another phase 3 controlled clinical trial use of saroglitazar 4mg once in patients with diabetic dyslipidemia, daily for 24 weeks' treatment resulted in significant decrease in HbA1c (0.3%) in addition to lowering of lipid parameters. In these controlled clinical trials, saroglitazar was found to be safe and well tolerated. Saroglitazar was not associated with weight gain, hepatotoxicity, renal toxicity or muscle related toxicity when co-prescribed with statin [11,12].

In an open label randomized study conducted in India, saroglitazarwas evaluated against fibrates as an add on therapy to metformin in diabetic dyslipidemia, saroglitazar was found to cause statistical significant reduction not only in triglycerides levels but also in all the glycemic parameters viz. FPG, PPPG and HbA1c [35].

A post-marketing, observational, multicenter, single arm study was conducted in India involving patients (2804 patients) of diabetic dyslipidemia. At 3 months follow-up, saroglitazar 4 mg led to significant reduction in TG (35.8%), LDLc (16.4%), total cholesterol (19%) and non-HDLc (23.4%). Addition of saroglitazar to baseline anti-diabetic medications showed a significant 0.9% absolute reduction in HbA1c with no serious adverse events reported. This study reiterated the potent lipid lowering and anti-hyperglycaemic effects of Saroglitazar in alignment with the above trial results [36].

A part of this study was earlier published with follow-up data of only 34 patients for a period of 14 weeks. The present study is a continuation to the above, with 158 patients with a follow-up period of 58 weeks showing similar reductions in glycemic and lipid parameters. We had also noticed, in our earlier studies, favorable effects on serum ALT level and no significant change in serum creatinine level following therapy with saroglitazar. Though, our earlier observations had shown a trend towards slight but insignificant change (gain) in weight, 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; hence the weight-gain cannot be solely attributable to saroglitazar alone [13,37,38].

Conclusion

Raised TG levels are an inherent part of diabetic dyslipidaemia and considered independent risk factor for CVD. Current international guidelines recommend treatment of TG>200 mg/dl if not controlled by intensive statin therapy. The use of dual PPAR alpha/gamma agonist, saroglitazar, for a period of 58 weeks, was associated with significant improvement in both glycaemic and lipid parameters among Indian patients with diabetic dyslipidaemia. Overall saroglitazar was well tolerated and there was no serious adverse event reported.

Limitations and Strength of this study

The study has many limitations and the results should be interpreted in view of the limitations. As with any observational study, this study lacks the vigilance of a controlled environment and adverse events are under reported. Larger and more comprehensive trials are required to establish and further validate our findings.

Secondly, the sample size is small. The number of patients studied is 158 which is a relatively small group.

The strength of this study lies being a real world observational study with longest duration so far on record and this adds to the present body of medical literature on the usage of saroglitazar therapy where the long term data of this medication usage is only up to 24 weeks.

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