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Observational Study

An Observational, Real Time Clinical Study of Saroglitazar in Type 2 Diabetes with Dyslipidaemia

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Abstract

Aim: The objective of this study was to evaluate the safety and efficacy of saroglitazar 4 mg once daily in clinical practice.

Methods: This was a retrospective, observational, single centre, post marketing study. Patients with type 2 diabetes (with on-going antidiabetic medication), age above 18 years and triglycerides (TG) >200 mg/dL were included.

Results: A total of 69 patients with a mean duration of diabetes of 5.42 years were included in this analysis. The baseline demographic profile was: mean age of 56 years, mean body weight of 68 kg and 56.5% patients were male. All 69 patients were on antidiabetic and lipid lowering therapy at baseline. The baseline triglycerides and HbA1c values were 232.8 mg/dL and 7.7%, respectively. At 6 months follow-up, use of saroglitazar 4 mg led to significant reduction in TG (144.7 mg/dL), LDL-C (97 mg/dL) and non- HDL-C (126 mg/dL). Addition of saroglitazar to baseline antidiabetic therapy showed a significant 0.6% absolute reduction in HbA1c with significant improvements in fasting and post prandial plasma glucose. No serious adverse events, alteration in liver or renal enzymes and oedema or weight gain were reported.

Conclusion: Saroglitazar is a promising therapeutic option in type 2 diabetic patients with high TG levels, not controlled by statins, for comprehensive control of lipid and glycaemic parameters with a favourable safety profile.

Keywords: Diabetic dyslipidaemia, saroglitazar, hypertriglyceride, PPAR alfa/gamma, diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is amongst the most common metabolic disorders that also has deleterious cardiovascular outcomes.[1] As per the International Diabetes Federation (IDF), the total number of diabetic patients is estimated to be around 77.0 million in India. This is further set to increase to almost 134.2 million by the year 2045.[2] The increased morbidity and mortality seen with T2DM could be due to the complex interaction of multiple comorbidities like chronic hyperglycaemia, dyslipidaemia and hypertension.[3]

Dyslipidaemia is among the most common comorbidities associated with T2DM and poses as a major cardiovascular risk too.[4] Diabetic dyslipidaemia, is characterized by the existence of an altered lipid profile in a diabetic patient and is reflected by an elevated serum triglyceride (TG) levels (>150 mg/dL), reduced high-density lipoprotein (HDL) cholesterol levels (<40 mg/dL in males and <50 mg/dL in females) and normal or elevated levels of low-density lipoprotein (LDL) cholesterol (>100 mg/dL).[5] Multiple studies have shown that intensive glycaemic control has little or no effect on preventing macrovascular complications.[6] Consequently, a lot of significance has been assigned to control diabetes and its associated comorbidities like dyslipidaemia simultaneously. Which would lead to a decrease in the macrovascular complications and the long run, reduce mortality rates associated with T2DM.

The benefits of targeting multiple risk factors has been demonstrated in the Steno Diabetic Study, which has shown that a target-driven, long term and intensified intervention aimed at multiple risk factors (hyperglycaemia, dyslipidaemia, hypertension) in patients with T2DM reduces the risk of macrovascular and microvascular events by 50%.[7]

Statins are without doubt, the first line therapy for dyslipidaemia to decrease not only LDL-C levels, but also the risk of cardiovascular disease (CVD) in patients with or without diabetes.[8] But despite statin therapy, a significant residual risk remains which can be potentially attributed to increased TG levels and low HDL cholesterol, a typical feature of dyslipidaemia seen in diabetics.

A meta-analysis of 14 trials involving statins that included 18,686 people with diabetes proved that presence of low HDL and high triglyceride limits the efficacy of statin therapy alone in reducing the vascular events despite achieving target LDL-C levels.[9] Multiple studies have shown that in comparison to Caucasians, Indians have higher TG levels and an associated low HDL-C.[10,11] High TG has long been deliberated to be a major risk factor for CVD and there is growing evidence which associates higher TG levels with an increased CVD risk.[12]

The PROVE IT-TIMI 22 trial, has shown a reduced risk of coronary heart disease (CHD) with low on-treatment TG (<150 mg/dL) and this was independent of the level of LDL-C. For each 10 mg/dL decline in on treatment TG, there was a 1.6% lower risk of the composite end point ($p<0.001$) after adjustment for LDL-C and other covariates. Moreover, the combination of low LDL-C (<70 mg/dL) and low TG (<150 mg/dL) was associated with the lowest event rates compared with higher LDL-C, higher TG or both.[13]

In 2015, a study analysed the results of two trials, the Dalcetrapib in Patients with a Recent Acute Coronary Syndrome (dal-OUTCOME) and Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL), to predict long and short term effects of fasting TGs on recurrent ischemic evens in acute coronary syndrome (ACS) patients already on statins. Results indicated that high TG levels (>175 mg/dL on long term and >195 mg/dL on short term) despite statin therapy in post-acute coronary artery syndrome (ACS) patients led to an increased CVD risk (60% and 50% higher on long and short term respectively) compared to those patients who had lower TG levels (≤80 mg/dL on long term and ≤135 mg/dL on short term). This relationship of triglycerides to CVD risk was independent of LDL-C in both studies.[14]

The Bezafibrate Infarction Prevention (BIP) trial, a study analysed the 22-year mortality data for patients with severe hypertriglyceridaemia from 15355 patients and showed that 22-year mortality risk for patients with severe hypertriglyceridaemia was found to be increased by 68% when compared with patients with low-normal triglycerides ($p<0.001$).[15] Statin therapy alone does not eliminate CVD risk (residual risk) associated with high triglycerides, therefore, triglyceride-rich lipoproteins may be a meaningful additional target for therapy, especially in patients of diabetic dyslipidaemia.

In a recently published REDUCE-IT study, the risk of the primary composite end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina, assessed in a time-to-event analysis, was significantly lower, by 25%, among the patients who received 2 gm of icosapent ethyl (TG lowering drug) twice daily than among those who received placebo, corresponding to an absolute between-group difference of 4.8 percentage points in the rate of the end point and a number needed to treat to avoid one primary end-point event was 21 (95% CI, 15 to 33) over a median follow-up of 4.9 years. This study has proven that among patients with elevated triglyceride levels who were receiving statin therapy, the risk of major ischemic events, including cardiovascular death, can be reduced through TG lowering agent like icosapent ethyl.[32]

Saroglitazar is a novel dual PPAR α/γ agonist, with a predominant PPAR α agonistic activity approved in 2013 by the Drug Controller General of India (DCGI) for management of diabetic dyslipidaemia and hypertriglyceridaemia in T2D patients not controlled by statins alone. It has been found to have excellent pre-clinical and clinical safety profile together with a higher efficacy in optimizing lipids (especially high triglycerides and non-HDL-C) and glycaemic targets.[16-18] It could be suitable and safe option as add on after statin therapy, for a comprehensive management of dyslipidaemia, along with possible glycaemic benefits. This retrospective analysis aimed to evaluate the safety and effectiveness of saroglitazar for the treatment of hypertriglyceridaemia in type 2 diabetes at our centre and contribute to nationwide existing data of saroglitazar's use in real time clinical practice.

Methodology

This was a retrospective, observational, single centre and post marketing study to evaluate the safety and effectiveness of saroglitazar in the treatment of hypertriglyceridaemia in patients of type 2 diabetes, who were prescribed saroglitazar

4 mg once daily as per the approved indication (diabetic dyslipidaemia and hypertriglyceridaemia in type 2 diabetes not controlled with statin). Saroglitazar was prescribed at the discretion of the treating physician, as per prescribing information of saroglitazar. Patients with type 2 diabetes (with on-going antidiabetic medication), age above 18 years and triglycerides >200 mg/dL were prescribed. The exclusion criteria were pregnancy, lactating mothers, active liver disease, the New York Heart Association (NYHA) class III or IV heart failure, malignancy, or patients with history of hypersensitivity to saroglitazar or any of the excipients used in the formulation. There was no experimental intervention done. Data of patients with diabetic dyslipidaemia who received saroglitazar treatment were collected and included in this analysis.

In this retrospective observational analysis, 69 patients were found to have been prescribed saroglitazar 4 mg once daily before breakfast in addition to lipid lowering and anti-diabetic agents at this centre. Information on concomitant therapy (type of therapy) was noted along with their demographic details (age, gender, body weight), clinical profile (duration of disease) and laboratory measurements (lipid, glycaemic and safety parameters at baseline and 6 months). The laboratory tests were conducted at centres recommended by treating physicians. The LDL-C values were direct, not calculated from the Friedewald equation. Also, any available information on associated adverse events morbidities was recorded. Data of only those patients which had baseline and 6 month follow up details were considered for analysis. The SAS® system for Windows was used for statistical analysis. Significant differences in the means from baseline to post baseline were assessed by paired t-tests. A p-value of <0.05 was considered as significant. A total of 69 type 2 diabetes dyslipidaemia patient's data on demographic and clinical profile was collected and analysed.

Results

This study was initiated just after approval of saroglitazar in management of diabetes dyslipidaemia (DD). And data of 69 patients who were prescribed saroglitazar 4 mg once daily was recorded at baseline and 6 months and analysed. All patients were on statin therapy [moderate to high dose of atorvastatin (20-80 mg OD) or rosuvastatin (10-40 mg OD)] and optimal anti-diabetic therapy. The age of the patients was between 26 and 77 years and the mean age was 56 years. The patients had a mean weight of 68 kg and mean body mass index (BMI) was 26.5 kg/m^2. Majority of the patients were male (56.5%) (**Table 1**). All patients had T2DM and concomitant dyslipidaemia, with an average duration of diabetes of 5.42 years.

Table 1. Patient demographics. Abbreviations: N- Number of subjects in specified treatment; n- Number of subjects at specified category.

Baseline demographic profile of patients on saroglitazar 4 mg (N=69)		
Age (years)	Mean±SD	55.9±10.4
	Range	26-77
Gender n (%)	Male	39 (56.5%)
	Female	30 (43.4%)
Weight (kg)	Mean±SD	68±11.2

Saroglitazar in addition to oral antidiabetic and lipid lowering medication showed significant improvement in all lipid and glycaemic parameters at 6 month follow-up. The mean baseline TG was 232.8 mg/dL vs. 144.7 mg/dL at 6 month follow-up ($p<0.001$). Non-HDL-C levels also reported a significant reduction (baseline- 167.5 mg/dL vs. 125.9 mg/dL at 6 month follow-up). A statistically significant reduction in LDL-C levels and a significant improvement in HDL-C levels were also noted as compared to baseline values. Analysis of glycaemic parameters revealed a statistically significant 0.6% absolute reduction in HbA1c from baseline value of 7.7% to 7.1% at 6 month follow-up. A significant reduction in fasting plasma glucose level from a mean baseline of 127.1 mg/dL to mean follow-up value of 104 mg/dL and a significant reduction in post-prandial plasma glucose level from mean baseline level of 179.1 mg/dL to mean follow-up value of 133.5 mg/dL was also observed at 6 months (**Table 2**).

Table 2. Change from baseline in lipid and glycaemic variables at 6 months. All values in mean±SD. Abbreviations: N- Number of subjects in specified treatment; n- Number of subjects having non-missing values at baseline and post-baseline visits; TG- Triglyceride; LDL-C- Low-density lipoprotein cholesterol; HDL-C- High-density lipoprotein cholesterol; HbA1c- Haemoglobin A1c. The p-values are calculated from paired t-test.

Summary of efficacy parameters for patients on saroglitazar (N=69), p-value <0.0001		
Efficacy parameters	**Baseline**	**6 month follow-up**
TG (mg/dL); n=68	232.82±33.67	144.79±24.77
LDL-C (mg/dL); n=68	121.02±16.04	96.98±14.22
HDL-C (mg/dL); n=68	39.48±6.27	46.26±5.41
Non-HDL-C (mg/dL); n=68	167.59±18.15	125.94±16.64
HbA1c (%); n=69	7.77±0.26	7.11±0.25
Fasting plasma glucose (mg/dL); n=69	127.11±15.09	104.07±10.48
Post-prandial plasma glucose (mg/dL); n=69	179.18±21.36	133.52±17.62

Saroglitazar administration did not lead to weight gain. The mean body weight at baseline was 68 kg and at 6 month follow-up was 64.5 kg. There were no significant changes observed either in the liver enzymes [alanine transaminase (ALT), aspartate aminotransferase (AST)] or the kidney function test (serum creatinine). No serious adverse events were reported (**Table 3**).

Table 3. Change from baseline in weight, alanine transaminase, aspartate aminotransferase and serum creatinine at 6 months. All values in mean±SD. Abbreviations: N- Number of subjects in specified treatment; n- Number of subjects having non-missing values. The p-values are calculated from the paired t-test. # Non-significant.

Summary of safety parameters for patients on saroglitazar (N=69)			
Safety parameter	**Baseline**	**6 month follow-up**	**p-value**
Body weight (kg)	68.08±11.21 n=67	64.55±12.35 n=62	0.09#
Alanine transaminase (IU/L)	35.78±14.21 n=37	38±10.35 n=15	0.5#
Aspartate aminotransferase (IU/L)	35.24±16.05 n=37	40.13±11.56 n=15	0.2#
Serum creatinine (mg/dL)	0.98±0.29 n=45	1.18±1.02 n=28	0.3#

Discussion

The extent of dyslipidaemia, especially in T2DM patients is increasing worldwide at a disturbing rate.[2] The more worrisome aspect is the associated increase in CVD risk seen along with both diabetes as well as dyslipidaemia.[4] Despite the availability of multiple lipid lowering and anti-diabetic agents, the present arsenal of therapeutic strategies have their respective limitations. The treatment of diabetic dyslipidaemia with predominant hypertriglyceridaemia, which is highly prevalent in our country, is far from satisfactory.[19] Statins are recognized as first-line therapy for cholesterol lowering, and their benefits have been shown to extend to patients with diabetes.[20,21] Statins alone are inadequate in addressing the CV risk a person faces and adequate statin

therapy, residual risk remains.[22-25] Effectiveness of conventional agents in treatment of hypertriglyceridaemia is also inadequate and there is a concern about their safety.[26, 27]

Therefore, a need for newer therapeutic targets and newer drugs is always omnipresent. 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 diabetic dyslipidaemia with relative absence of adverse events, especially with no increase of body weight. This retrospective analysis was carried out to evaluate the safety and effectiveness of saroglitazar for the treatment of hypertriglyceridaemia in type 2 diabetes at our centre and contribute to nationwide existing data of saroglitazar's use in real time clinical practice.

Though international and western guidelines are preferring statin as first line therapy at irrespective of TG level, but recent European Society of Cardiology (ESC) dyslipidaemia guidelines consider to add TG lowering agents to statin in high risk patients with TG level between 135-499 mg/dL.[19] For primary prevention, ESC also recommends to use TG lowering drug along with statin when TG is more than 200 mg/dL.[28] The present post marketing surveillance study has shown that use of saroglitazar with statins helps in achieving a better control of all lipid parameters, especially non HDL-C and TGs which are common lipid abnormalities seen in diabetic dyslipidaemia patients. There were significant TG and non-HDL-C reductions observed at the end of 6 month follow-up. Other lipid parameters like LDL-C and HDL-C also improved significantly. Saroglitazar being a dual PPAR α/γ agonist also has insulin sensitizing properties and this was reflected by significantly better reductions observed in the glycaemic parameters. There was a significant reduction 0.6% in HbA1c in these diabetic dyslipidaemia patients after 6 months of saroglitazar use (these patients were on their on-going anti-diabetic medications). At 6 months saroglitazar was found to be well tolerated, with no weight gain or oedema and no significant alterations in liver or renal enzymes and oedema or weight gain. Finally, there were no serious adverse events reported in this analysis.

Our present study shows significant reduction of triglyceride, which in accordance with the phase III clinical trials (PRESS V and PRESS VI) with favourable glycaemic control and safety profile. Though saroglitazar is TG reducing agent, but this reduction which could be because of the weight loss (not statistically significant, though numerically less), improvement in HbA1c level and to prove that more randomized, controlled clinical trials with longer duration of follow-up will be necessary.[17,18,29-31]

Limitations of the Study

This is not a randomized, controlled, comparative clinical trial and these analyses consist of retrospective data obtained from real time clinical practice. The data was analysed at a short follow-up of 6 months. Adherence to therapy could not be assessed in this analysis. Laboratory tests were not conducted at specific assigned laboratory.

Conclusion

In patients with diabetic dyslipidaemia, the use of saroglitazar 4 mg once daily for 6 month is associated with significant improvement of lipid and glycaemic parameters. Saroglitazar was safe, well tolerated and there was no serious adverse event reported.

Declaration of conflicting interests

The authors declare no conflict of interest.

Funding

No funds were received for conducting the study.

Ethical approval

Since this study is an observational study, there is no need of ethics committee approval.

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