

An Investigator Initiated Prospective, Single Arm Observational Study to Evaluate the Safety and Efficacy of Saroglitazar 4 mg in Patients with Non-Alcoholic Fatty Liver Disease (NAFLD)/Non-Alcoholic Steatohepatitis (NASH)

Santosh D Hajare¹, Varadaraj P Gokak², Sandesha Ghorpade³, Amar Patil⁴, Arvind Jadhav⁵

ABSTRACT

Introduction: Saroglitazar is known to safely and effectively improve dyslipidemia by reducing triglyceride (TG), low density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, non-high-density lipoprotein (non-HDL) cholesterol and increasing high density lipoprotein (HDL) cholesterol. In addition, saroglitazar can improve glycemic indices in diabetic patients by reducing fasting plasma glucose (FPG) and glycosylated haemoglobin (HbA1c). Aim of the study was to evaluate the hospital based clinic-pathological profile, diagnosis, treatment and follow up of Indian patients with Non-alcoholic fatty liver disease and to evaluate the safety and efficacy of Saroglitazar 4 mg in patients with Non-alcoholic fatty liver disease /Non-alcoholic Steatohepatitis in real life setting.

Material and methods: This was an ongoing observational study with the sample size of 52 patients having Non-alcoholic fatty liver disease and dyslipidaemia with or without Type 2 Diabetes Mellitus and treatment follow up for a period of 1 year in the Department Of Gastroenterology. The data was collected from eligible patients who have been prescribed Saroglitazar 4 mg once daily in routine clinical practice. Primary endpoints were to see liver stiffness. Secondary endpoints were to measure serum alanine aminotransferase, aspartate aminotransferase level and Serum triglycerides level.

Results: There was a significant decrease in Serum alanine aminotransferase (p <0.001), aspartate aminotransferase (p value < 0.001), triglycerides (p value <0.001) and triglycerides (p value 0.01), levels after the treatment as compared to the baseline.

Conclusion: Saroglitazar treatment is effective and there is a significant difference in Serum alanine aminotransferase and aspartate aminotransferase, triglycerides and Liver Stiffness Measurement levels after treatment. The drug can be successfully administered for the treatment of Non-alcoholic fatty liver disease.

Keywords: Non-alcoholic Fatty Liver Disease, Triglycerides, Dyslipidemia, Insulin, Alanine Aminotransaminase

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a range of disease which extends from simple steatosis through inflammation and fibrosis. Type 2 diabetes and obesity are the risk factors for the development of NAFLD, It also a risk factor for development of cirrhosis.¹

Prevalence of NAFLD in Indian population is found to be around 9-32%.² It develops into four stages which are simple fatty liver (steatosis), non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis.³

It is identified by excessive hepatic fat accumulation which is associated with insulin resistance (IR) and it is defined by the presence of steatosis in more than 5% of hepatocytes according to histological analysis or more than 5.6% proton density fat fraction assessed by proton magnetic resonance spectroscopy (¹HMRS) or quantitative fat or water selective magnetic resonance imaging (MRI).³ This is highly prevalent and there are considerable adverse outcomes that are related to liver-specific mortality and morbidity but there are more cardiovascular and metabolic-related adverse outcomes.¹

Saroglitazar is a dual peroxisome proliferator-activated receptor (PPAR)- α/γ agonist. It has been approved in India since 2013 for the treatment of dyslipidaemia in patients with diabetes. Saroglitazar reduced alkaline phosphatase as well as triglyceride levels in patients with hypertriglyceridemia (>200 and <500 mg/dL) and type 2 diabetes mellitus (T2DM) in a three-arm phase III, 16-week prospective, multicenter, randomized, double-blind, placebo-controlled study.⁴

Considering the association between insulin resistance, dyslipidemia and the development of NAFLD/NASH, saroglitazar could potentially benefit patients with NAFLD including those with borderline NASH. Therefore, the

¹Professor and HOD, Department of Gastroenterology,

²Assistant Professor, Department of Gastroenterology, ³Medical Officer, Department of Gastroenterology, ⁴Senior Resident, Department of Gastroenterology, ⁵Medical Officer, Department of Gastroenterology, Kaher, Jawaharlal Nehru Medical College, Department of Gastroenterology, Belagavi, Belgaum, Karnataka, India

Corresponding author: Dr. Santosh D Hajare, Department of Gastroenterology, KLES, DR Prabhakar Kore Hospital and MRC, 2nd Floor, Jawaharlal Nehru Medical College, Belagavi, Belgaum, Karnataka, India

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purpose of the present study was to examine the efficacy of saroglitazar in improving NAFLD Fibrosis Score and liver biochemistry in patients with NAFLD/NASH.

MATERIAL AND METHODS

This was an ongoing observational study with the sample size of 52 patients having NAFLD and dyslipidaemia with or without Type 2 Diabetes Mellitus (DM) and treatment follow up for a period of 1 year who presented to the Department Of Gastroenterology.

This was an investigator initiated prospective, single arm observational study to evaluate the safety and efficacy of Saroglitazar 4 mg in patients with NAFLD/NASH in real life setting.

The data was collected from eligible patients who were prescribed Saroglitazar 4 mg once daily in routine clinical

practice.

Primary Endpoints

1. Liver stiffness as measured by transient elastography/ FibroScan (Time frame: Baseline and 12 months)
- To evaluate after Baseline and 12 months of daily administration of Saroglitazar 4 mg the change from baseline, through Fibroscan / Transient Elastography (TE).

Secondary Endpoints

2. Serum alanine aminotransferase (ALT) and; aspartate aminotransferase (AST) level
3. Serum triglycerides (TG) level.

To evaluate after Baseline 6 months and 12 months of daily administration of Saroglitazar 4 mg the change from baseline Patients with diabetes were on standard orally administered antihyperglycemic agents (OHA) or Insulin therapy and other drugs for comorbid illness were continued. All patients received saroglitazar 4mg once daily till one year.

RESULTS

In the study, there were total of 52 patients. Out of 52 patients 37 were males and 15 were females. Only 17.31% of the subjects suffered from hypertension and 28.85% of the subjects suffered from diabetes mellitus. All the subjects underwent initial BMI assessment. In the study, and we observed that 19 subjects were overweight and 15 subjects had obesity. (table 1)

In the analysis of the AST and ALT Levels are compared between baseline, at 6 months and one year. In ALT and AST

Variable	Sub-category	Mean \pm SD/ Frequency
Age		45.88 \pm 11.66
Gender	Male	37 (71.15%)
	Female	15 (28.85%)
Hypertension	Present	9 (17.31%)
Diabetes Mellitus	Present	15 (28.85%)
BMI (Kg/m ²)		27.84 \pm 5.97
BMI category	Normal (< 25 Kg/m ²)	18 (34.62%)
	Overweight (25-30 Kg/m ²)	19 (36.54%)
	Obese (\geq 30 Kg/m ²)	15 (28.85%)

Table-1: Demographic details.

Enzymes	Baseline	After 6 months	After 1 year	p-value	% reduction after 6 months	% reduction after one year
ALT	56.19 \pm 30.92	36.14 \pm 19.27	33.55 \pm 16.58	<0.001 ^{B0.5} <0.001 ^{B1}	35.68%	40.29%
AST	46.73 \pm 22.38	32.53 \pm 14.54	29.48 \pm 11.19	<0.001 ^{B0.5} <0.001 ^{B1}	30.38%	36.91%

Abbreviations: B0.5- p-value corresponding to mean comparison between baseline and after 6 months of
B1- p-value corresponding to mean comparison between baseline and after a year of treatment.

Table-2: Comparison of levels of different enzymes at different time points

	Baseline	After 1 year	p-value	% reduction after one year
Triglycerides (mg/dL)	193 \pm 56.76	133.12 \pm 37.05	<0.001	31.02%
Fibrosis (kPa)	12.33 \pm 9.99	9.62 \pm 4.53	0.01972	21.97%

Table-3: Comparison of triglycerides and fibrosis before and after treatment

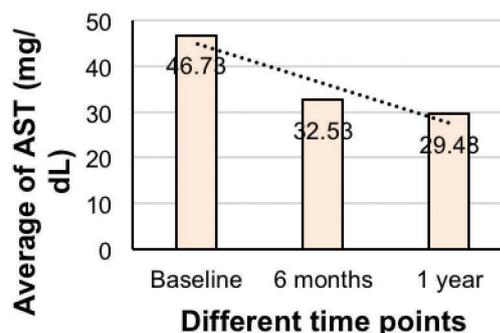
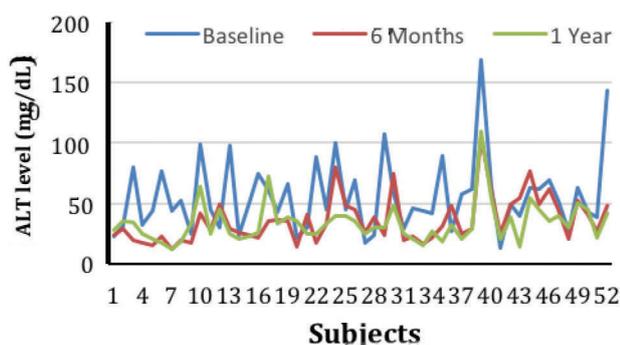


Figure-1: Comparison of ALT and AST level at different time points.

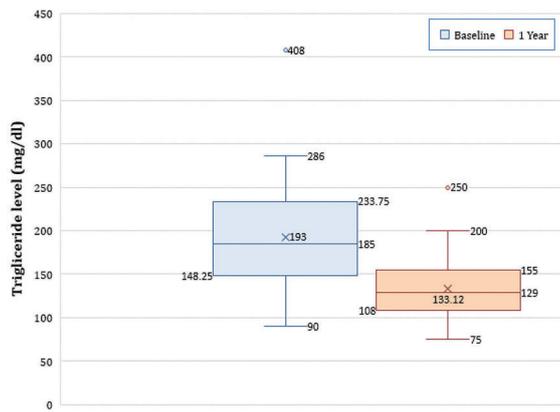


Figure-2: Comparison of triglycerides level at different time points

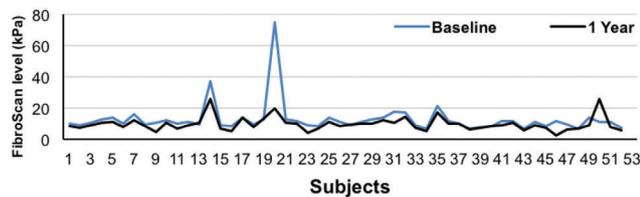


Figure-3: Comparison of FibroScan level at different time points.

after the treatment both the enzyme levels have decreased significantly compared to the baseline (table-2).

Fibrosis was measured by Fibroscan. Triglyceride level and Fibrosis are significantly reduced after treatment, p-value for the paired t-test was significant (table-3, figure-1).

In the figure-2, 193 mg/dL, 133.12 mg/dL are the mean of triglycerides at baseline and triglycerides level at 1 year after treatment respectively. Median triglycerides in baseline and after one-year treatment were 185 mg/dL and 129 mg/dL respectively. There were 2 outliers, that is, the data points which are far from others. Figure 3 shows comparison of FibroScan level at different time points.

DISCUSSION

Chatterjee S et al. (2015), conducted an observational study to see the effects of Saroglitazar on Glycaemic and Lipid Parameters in Indian Patients with Type 2 Diabetes in which they had taken total 34 patients out of which 23 were male. In the present study out of 52 patients 37 were male. The mean age was 45.88 ± 11.66 in the present study whereas in their study it was 52.33. In their study all patients had diabetes mellitus 34 (100%), and 20(58.8%) patients were having hypertension whereas in our study 15 (28.85%) patients had diabetes mellitus and 9(17.31%) patients had hypertension.⁵ Hegazy et al. (2019), conducted a study and found that 8 ($24.21b \pm 0.14$) patients had normal BMI for diabetics and 10 ($30.67a \pm 0.83$) patients had diabetics with high BMI. In the present study 18 (34.62%) had normal BMI, 19 (36.54%) patients were overweight (25-30 Kg/m²) and 15 (28.85%) were Obese (≥ 30 Kg/m²).⁶

Kyung-Soo Kim et al.(2019), mentioned in his review article that Saroglitazar reduced alkaline phosphatase as well as triglyceride levels.⁴ A review article by Kaul et al.(2019), also stated that Saroglitazar was found effective in lowering ALT levels and improving fatty liver (evaluated by

sonographic (Fibroscan) investigation) in NAFLD patients with diabetic dyslipidemia as well as reduction TG levels was also observed. These results were similar to our study.⁷ Joshi et al. (2016), conducted a prospective, study in which they screened patients for the NAFLD through ultrasound elastography (fibroscan) and they found that 86 patients out of 221 showed sonographic improvement in fatty liver. They also found that triglycerides and ALT levels are reduced in patients.⁸

CONCLUSION

It was a pilot study that was conducted to see effect of saroglitazar in patients with NAFLD and it was seen that after giving the treatment there is decrease in specific enzyme levels like ALT, AST, triglycerides, and even fibroscan (TE levels). So, we conclude that the saroglitazar treatment is effective and there is significant difference in ALT, AST, triglycerides and fibroscan levels before and after treatment. The drug can be successfully administered for the treatment of NAFLD.

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