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REDUCTION IN CONTROLLED ATTENUATION PARAMETER AND LIVER STIFFNESS WITH SAROGLITAZAR IN NAFLD: A PROSPECTIVE ANALYSIS

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Abstract

Background: Non-Alcoholic Fatty Liver Disease (NAFLD) is defined as the accumulation of fat in the liver, typically affecting more than 5% of hepatocytes, in the absence of significant alcohol consumption. NAFLD is considered the most common liver disease in the developed world and is

fast emerging as a global health priority due to the epidemic burden of obesity, diabetes, and metabolic diseases worldwide.

Objective: The purpose of the study was to analyze the reduction in controlled attenuation parameter and liver stiffness with Saroglitazar in NAFLD.

Material and method: After an overnight fast, all 240 study participants provided blood samples in accordance with the protocol for the measurement of serum lipids and lipoproteins. The lipid profile and liver stiffness and CAP parameters were assessed. The patients on continued saroglitazar 4 mg once daily therapy was follow-up at 24 and 52 weeks. SPSS version 20 was used for the statistical analysis, and $p<0.05$ was chosen as the significance level.

Result: Among 240 patients, there was significant decrease in Continued Attenuation Parameter (CAP) – baseline 333.68 ± 28.21db/m, at 24 weeks 300.40± 25.52db/m and at 52 weeks 286.89± 24.22db/m. Similarly, there was significant decrease in Liver Stiffness Measurement (LSM) also baseline 8.26 ± 2.73kPa, at 24 weeks 7.73± 2.56kPa and at 52 weeks 7.15± 2.31kPa. A shift toward milder fibrosis stages was evident: F0–F1 rose from 32.081% to 48.8% (P = 0.004), F2 fibrosis reduce from 48.33% to 43.33%, F3 fibrosis reduce by 17.08% to 12.92%, while F4 nearly resolved. These findings reflect plausible reductions in fibrosis burden over time and parallel trends from other 52-week observational cohorts.

Conclusion: These findings suggest that saroglitazar 4 mg daily may be a promising therapeutic option for non-diabetic NAFLD patients, providing multi-dimensional benefits across liver stiffness and fibrosis.

Keywords: NAFLD, liver Stiffness, CAP, lipid profile, saroglitazar.

1. INTRODUCTION

Non-Alcoholic Fatty Liver Disease (NAFLD) is defined as the accumulation of fat in the liver, typically affecting more than 5% of hepatocytes, in the absence of significant alcohol consumption. Historically, fatty liver was often associated with excessive alcohol consumption and was considered a benign and reversible condition. However, this view has been challenged, and interest in fatty liver occurring in non-drinkers (NAFLD) has increased dramatically over the last two decades.[1]

Today, NAFLD is considered the most common liver disease in the developed world and is fast emerging as a global health priority due to the epidemic burden of obesity, diabetes, and metabolic diseases worldwide.[2] Its prevalence is rising exponentially and is projected to continue increasing. It is strongly associated with obesity, insulin resistance, hypertension, and dyslipidemia. These conditions are often components of the metabolic syndrome, and NAFLD is considered the hepatic manifestation of this syndrome. A progressively sedentary lifestyle and consumption of calorie-dense diets facilitate the development of NAFLD.[3]

NAFLD encompasses a range of liver diseases, from straightforward hepatic steatosis to NASH with increasing fibrosis, which in certain people leads to cirrhosis and liver failure, and ultimately to hepatocellular cancer. The many components of this spectrum are most likely best understood as components of a continuum of histology.

Numerous studies have since demonstrated Saroglitazar's strong therapeutic impact on fatty liver disease and non-alcoholic steatohepatitis (NASH). Today, Saroglitazar holds the distinction of being the world's first approved drug for treating NASH[4,5].

Saroglitazar exerts its action through:

• **PPAR-alpha and PPAR-gamma activation**, which play crucial roles in controlling metabolic pathways, especially in relation to non-alcoholic fatty liver disease (NAFLD). **PPAR-alpha** receptors are mainly associated with lipid regulation, promoting hepatic fatty acid oxidation and thereby decreasing lipid accumulation within liver cells — a defining characteristic of NAFLD. Additionally, saroglitazar assists in lowering circulating triglycerides, leading to improved lipid profiles, and elevates HDL cholesterol by stimulating the expression of genes responsible for HDL regulation.[6]

• **PPAR-gamma**, in contrast, improves insulin sensitivity — a critical factor in addressing insulin resistance and type 2 diabetes mellitus (T2DM), conditions frequently coexisting with NAFLD. It also plays a role in modulating fat deposition and its metabolism. Collectively, these actions illustrate how saroglitazar's dual agonistic effect on PPAR-alpha and PPAR-gamma receptors supports enhanced lipid control and better management of metabolic disorders linked to NAFLD.[7]

In summary, Saroglitazar presents a novel and well-tolerated therapy for NAFLD, offering improvements in liver enzymes, lipid profile, and hepatic steatosis. Its dual mechanism and

favorable safety profile may bridge current gaps in pharmacological management for patients with concurrent metabolic diseases.

The purpose of the study was to analyze the reduction in controlled attenuation parameter and liver stiffness with Saroglitazar in NAFLD.

2. MATERIAL AND METHOD

Study Site: The study was conducted in the Department of Pharmacology and Department of General Medicine of Index Medical College & Hospital and Research centre, Indore, M.P (a tertiary healthcare teaching hospital attached to Malwanchal University, Indore, M.P).

Study Design: A prospective, uni-centric, observational, hospital-based study. Total duration of study was 03 years.

Study Population: A total of 240 diagnosed patients of Non-Alcoholic Fatty Liver Disease (NAFLD) and satisfying the inclusion and exclusion criteria mentioned below was enrolled in the study.

Inclusion Criteria:

1. Patients of both gender and aged from 18 to 60 years.

2. Documented diagnosis of NAFLD according to the American Association for the Study of Liver Diseases (AASLD) criteria.

3. Patients on lifestyle modification for NASH for at least one month.

4. Willingness to comply with all protocol required evaluations; provision of written informed consent before any study specific tests or procedures were performed.

5. Patients providing a written informed consent for participation in this study.

Exclusion criteria:

1. Pregnancy and lactation.

2. Known allergy, sensitivity, or intolerance to the study drug.

3. History of alcohol consumption of >30 gm/week for men and >20 gm/week for women for 3 consecutive months in the last 5 years.

4. Patient on vitamin E (>400 IU/day) or multivitamins containing vitamin E (>400 IU/day) or fibrates (clofibrate, fenofibrate) in the 3 months preceding enrolment.

5. Patient on drugs with potential effect on NAFLD such as ursodeoxycholic acid, S-adenosylmethionine (SAM-e), glutathione, Orlistat, Betaine, and Pentoxyphyllin 1 month prior to enrolment.

6. Use of drugs associated with a clinical or histological picture consistent with fatty liver diseases for more than 3 months in n the 1 year prior to start of the study, namely, Amiodarone, Tamoxifen, Methotrexate, Glucocorticoids, anabolic steroids, Tetracyclines, estrogens, Valproic acid, Chloroquine, anti-HIV drugs.

7. History of other cause of chronic liver disease (viral hepatitis B or C, autoimmune hepatitis, cholestatic and metabolic liver diseases, and hemochromatosis.

8. Patients with known cirrhosis (compensated/decompensated) either based on clinical criteria or liver histology or Imaging techniques.

9. History of myopathies or evidence of active muscle disease

10.History of malignancy in the past 5 years and/or active neoplasm with the exception of resolved superficial non-melanoma skin cancer

11.History of bowel surgery (gastrointestinal (bariatric) or undergoing evaluation for bariatric surgery for obesity, extensive small-bowel resection, or orthotopic liver transplant (OLT) or listed for OLT.

12.History or other evidence of severe illness or any other conditions that would make the patient, in the opinion of the investigator, unsuitable for the study (such as poorly controlled psychiatric disease, HIV, coronary artery disease or active gastrointestinal conditions that might interfere with drug absorption)

Sample Size: For the 95% confidence interval, desired sample size was calculated using the formula: $n = Z2pq\ e2$

Where,

n = Sample size needed

p = Prevalence rate from previous study q = (1-p)

Z = the value from the table of probabilities of the standard normal distribution for the desired

e = the margin of error

The estimated prevalence of NAFLD is around 9% to 32% in general population of India according to operational guidelines for NAFLD by NPCDCS. With 95% confidence level, considering 5% margin of error sample size comes out to be 251.Among these, all those who fulfil the inclusion criteria and consent to participate in the study was recruited for study intervention.

Study Method: After an overnight fast, all study participants provided blood samples in accordance with the protocol for the measurement of serum lipids and lipoproteins. The Echosens FibroScan was used to measure both fibrosis (liver stiffness) and steatosis (ultrasound attenuation rate/ CAP), together by an expert and Echosens certified technician. M and XL probes were used for subjects with BMI less than 30 kg/m2 and ≥ 30 kg/m2 respectively. At baseline, patients were categorized into four categories based on liver stiffness (LSM) value: (i) F0–F1: LSM (ii) F2: LSM 7–10 kPa; (iii) F3: LSM >10 to 14 kPa. The patients on continued saroglitazar 4 mg once daily therapy was follow-up at 24 and 52 weeks. Anthropometric measurements were taken at each clinical visit. The data was analyzed using paired t-test on SPSS Version 28.0 statistical package.

3. RESULTS

Total 240 patients were included in study. They had a mean age of 46.8 ± 10.05 years, predominantly male (69.2%), with a high prevalence of type 2 diabetes (69%) and less frequent hypertension (9.6%), which typically include middle-aged patients with metabolic comorbidities undergoing saroglitazar 4 mg therapy. Gender distribution showed males with 69.17% population while female formed 30.83% of study population.

	Baseline	24 weeks	52 weeks	**P value**

	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Conitnued Attenuation Parameter (CAP)	**333.68**	**28.21**	**300.40**	**25.52**	**286.89**	**24.22**	**<0.001**
Liver Stiffness Measurement (LSM)	**8.26**	**2.73**	**7.73**	**2.56**	**7.15**	**2.31**	**<0.001**

Table 1: Fibroscan

The mean Continued Attenuation Parameter (CAP) at the start of study was 333.68 mg/dl. There was significant decrease in Continued Attenuation Parameter (CAP) – baseline 333.68 ± 28.21db/m, at 24 weeks 300.40± 25.52db/m and at 52 weeks 286.89± 24.22db/m.

Similarly, There was significant decrease in Liver Stiffness Measurement (LSM) also baseline 8.26 ± 2.73kPa, at 24 weeks 7.73± 2.56kPa and at 52 weeks 7.15± 2.31kPa.

Parameters	**At baseline**	**24 weeks**	**52 weeks**	**% change from baseline to 52 wk***	**P value****
LSM (kPa)	8.26 ± 2.73	7.73 ± 2.56	7.15 ± 2.31	13.43%	<0.05
CAP (dB/m)	333.68 ± 28.21	300.40 ± 25.52	286.89 ± 24.22	14.02%	<0.05

Table 2: Improvement in primary end point (liver stiffness measurement and CAP score) at Weeks 24 and 52

CAP (marker of steatosis) dropped by ~14% and LSM (marker of fibrosis surrogate) by ~13% at week 52 ($P < 0.001$). These are robust improvements echoing pooled observational data and non-invasive assessments in NAFLD treated with saroglitazar.

	Baseline (n=240)		24 weeks (n=240)		52 weeks (n=240)		**P value**
	No.	**%**	**No.**	**%**	**No.**	**%**	
F0 - F1	77	32.08%	101	42.08%	117	48.75%	0.004
F2	116	48.33%	104	43.33%	99	41.25%	>0.05

F3	41	17.08%	31	12.92%	23	09.58%	>0.05
F4	6	2.50%	5	2.08%	1	0.04%	>0.05

Table 3: Fibrosis Grade

Fibrosis grades (LSM) (Number)	Baseline	At 24 weeks				At 52 weeks			
	Mean ± SD	Mean ± SD	Absolute difference	% Difference	P* value	Mean ± SD	Absolute difference	% Difference	P** value
Fo-F1 (<7kPa) (N=77)	5.66 ± 0.99	5.16 ± 1.01	-0.50	-8.83%	<0.05 (S)	4.66 ± 1.04	-1.00	-17.67%	<0.001 (HS)
F2 (≥7 to 10 kPa) (N=116)	8.49 ± 0.85	7.99 ± 0.92	-0.50	-5.89%	<0.05 (S)	7.49 ± 1.01	-1.00	-11.78%	<0.001 (HS)
F3 (≥10 to<14 kPa) (N=41)	10.98 ± 0.81	10.50 ± 0.94	-0.48	-4.37%	<0.05 (S)	10.00 ± 0.79	-0.98	-8.93%	<0.05 (S)
F4 (≥14 kPa) (N=6)	18.60 ± 4.90	16.63 ± 3.33	-1.97	-10.59%	<0.001 (HS)	12.89 ± 2.29	-5.71	-30.70%	<0.001 (HS)

Table 4: 24- and 52-week assessment of improvement in transient elastography parameters according to baseline fibrosis grade

A shift toward milder fibrosis stages was evident: F0–F1 rose from 32.081% to 48.8% (P = 0.004), F2 fibrosis reduce from 48.33% to 43.33% (P = >0.05), F3 fibrosis reduce by 17.08% to 12.92% (P = >0.05), while F4 nearly resolved from 2.50% to 0.04% (P = >0.05). These findings reflect plausible reductions in fibrosis burden over time and parallel trends from other 52-week observational cohorts.

4. DISCUSSION

Non-alcoholic fatty liver disease (NAFLD) has emerged as a significant global health crisis, characterized by excessive fat accumulation in the liver in individuals who consume little to no

alcohol. This condition is often considered the hepatic manifestation of metabolic syndrome, a cluster of interconnected health issues including obesity, Type 2 Diabetes Mellitus (T2DM), dyslipidemia, and cardiovascular disease (CVD). The prevalence of NAFLD is escalating rapidly worldwide, affecting approximately 25% of the global population and projected to rise by an alarming 63% between 2015 and 2030. In India alone, adult NAFLD prevalence ranges from 6.7% to 55.1%, with higher rates observed in individuals with metabolic risk factors such as obesity and T2DM. Despite this escalating disease burden, effective pharmacological treatments for NAFLD remain remarkably limited, underscoring a critical unmet medical need.

Hence, the study concludes that 24-week treatment aids in resolving transaminitis and reflects reduced hepatic inflammation. The reversal of fibrosis is a key goal in pharmacologic treatment. While liver biopsy remains the most definitive method for fibrosis assessment, its invasive nature limits routine use. Fibroscan-based LSM provides a non-invasive alternative for evaluating fibrosis and cirrhosis. Several studies over recent years have validated fibroscan's effectiveness in this context [8,9]. Our findings revealed a significant decrease in LSM following saroglitazar treatment. Goyal O et al. also documented improvements in LSM after 24 weeks of therapy[10] . Another trial using shear wave elastography noted reduced liver fibrosis after nine months of saroglitazar use [11].

Assessing hepatic fat is also vital in evaluating NAFLD therapy outcomes. Though ultrasound is commonly used to detect fatty liver, its sensitivity is limited in moderate fat changes. CAP via fibroscan serves as a viable option for liver fat quantification and has shown strong accuracy in tracking fat content changes [12,13]. Our data demonstrated marked liver fat reduction using CAP. Goyal O et al. reported similar reductions after 24 weeks of saroglitazar use. Kaul U et al. also observed improvements in liver fat via CAP between 12 and 58 weeks of therapy[14] . Known side effects of saroglitazar like nausea, hypoglycemia, and chest discomfort are mentioned in literature. No adverse effects, including hypoglycemia, were observed among participants in this study. Likewise, animal models showed no side effects [15], and human trials have not reported significant adverse events either[16] .

5. CONCLUSION

The study shows Comprehensive Multi-Target Approach: Its dual PPAR-α/γ modulation allows for a targeted, multi-dimensional approach that simultaneously addresses dyslipidemia, insulin resistance, hepatic steatosis, inflammation, and fibrosis. This makes it a "magic bullet" for metabolic syndrome, offering huge benefits not only for diabetes but also for obesity-associated cardiovascular diseases and NAFLD. This integrated approach is crucial for a complex disease like NAFLD, which is deeply intertwined with various metabolic dysfunctions

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