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Clinical Case Series on Assessment of Therapeutic Efficacy of Saroglitazar in MASLD Patients

Naresh Dang [a++*] and Tamphasana Wairokpam [b#]

[a] Internal Medicine, Max Super Speciality Hospital, Patparganj, New Delhi, India.
[b] Nottingham University Hospitals, NHS Trust, England, United Kingdom.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Objective: This prospective case series aimed to evaluate the efficacy of saroglitazar 4 mg in improving clinical parameters in patients with type 2 diabetes mellitus (T2DM) with steatotic liver disease (SLD), focusing on glycemic control, lipid profile, liver enzymes, and transient elastography parameters (CAP and LSM scores).
Materials and Methods: Eight T2DM patients having SLD; defined as Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD) were enrolled from a single-center, Dr. Dang's Clinic, Ghaziabad, Uttar Pradesh India. Saroglitazar 4 mg was administered daily, and various clinical parameters were monitored at baseline, 16 weeks, and 32 weeks. Statistical analysis was performed using paired t-tests to assess changes over time.
Results: Saroglitazar treatment significantly reduced HbA1c, Triglycerides (TG), Alanine aminotransferase (ALT), transient elastography parameters (CAP and LSM) along with other lipid

[++] *Senior Consultant;*
[#] *Senior Clinical Fellow;*
**Corresponding author: E-mail: naresh.dang@gmail.com;*

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and glycemic parameters from baseline to weeks 32. These findings underscore potential role of saroglitazar in managing T2DM and associated SLD by improving metabolic parameters and liver health.

Conclusion: Saroglitazar showed significant improvements in glycemic control, lipid profile, liver enzymes, liver fat and fibrosis in MASLD patients, indicating its potential as a therapeutic option for managing metabolic abnormalities and liver complications. Further research is needed to validate these findings.

Keywords: Type 2 diabetes mellitus; saroglitazar; transient elastography, liver fibrosis; liver fat.

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a commonly prevalent metabolic condition which is projected to reach 629 million by 2045 [1]. Insulin resistance is a root cause factor for T2DM which can lead to further complications like cardiovascular disease (CVD), kidney disorders, steatotic liver disease (SLD) etc. SLD with T2DM is known as metabolic dysfunction associated steatotic liver disease (MASLD); which is a revised nomenclature of NAFLD [2]. Almost 7 out of 10 T2DM patients are suffering from SLD and carry higher risk of CV events. Managing T2DM may have an impact on progression of SLD but no anti-diabetic medications are approved for management of MASLD till date [3].

Peroxisome proliferator-activated receptors (PPARα and PPARγ) are crucial for controlling insulin resistance, glucose metabolism, lipid metabolism and liver fat / fibrosis reduction [4]. And newer PPAR agonists continue to be pursued for their potential benefits and effects on glucose and lipid metabolism [5,6]. These agonists can improve glycemic control and address lipid abnormalities in T2DM patients [7]. Saroglitazar, a new dual PPAR α/γ agonist was approved in 2013 for the management of diabetic dyslipidemia and hypertriglyceridemia and in 2020, it received approval for Non-Alcoholic Fatty Liver Disease (NAFLD) and non-cirrhotic non-alcoholic steatohepatitis (NASH) by DCGI in India [8]. Saroglitazar has shown positive benefits in glycemic control and lipid profile, along with reduction of liver fat, fibrosis and elevated liver enzymes in various studies including NAFLD patients [9,10].

To assess the effect of saroglitazar 4 mg in MASLD (SLD with T2DM) patients in routine clinical practice, we performed this study, evaluating various clinical parameters over a 32-week treatment period. We also examined its impact on CAP (controlled attenuation parameter) and LSM (liver stiffness measurement) scores, which are crucial for assessing liver health and fibrosis in patients. The CAP score is vital for measuring liver fat accumulation, while LSM is linked to fibrosis, providing comprehensive insights into liver health.

2. MATERIALS AND METHODS

2.1 Study Design and Participants

This was a prospective case series conducted at Dr. Dang's Diabetes Clinic, Ghaziabad, Uttar Pradesh, as a single-center study, for 32 weeks. Eight patients from the outpatient medical department were enrolled with the known case of T2DM with SLD.

2.2 Inclusion Criteria

The participants included in the study with the age between 18-70 years and known case of type 2 diabetes mellitus as per American Diabetes Association criteria [1], with $\geq$ grade I fatty liver confirmed by ultrasonography along with signed informed consent.

2.3 Exclusion Criteria

Patients were excluded from the study if they had history of liver injury due to chemicals or drugs during the 9 months of assessment. Additionally, use of GLP1 analogues, SGLT2 inhibitors, or pioglitazone during the assessment period or within 3 months prior to assessment was prohibited. Positive status for Hepatitis B or Hepatitis C also led to exclusion. Further, any conditions or factors that could interfere with the study outcomes or patient safety are not mentioned in the inclusion criteria.

2.4 Baseline Examination and Laboratory Investigation

Initially, a comprehensive medical history was obtained from the patients, along with tests for liver function, including aspartate transaminase (AST) and alanine transaminase (ALT), lipid profile (low-density lipoprotein (LDL), triglycerides (TG), total cholesterol (TC), and high-density lipoprotein (HDL)), kidney function, with a specific focus on serum creatinine level. Additionally, postprandial blood glucose (PPBG), fasting blood glucose (FBG), and glycosylated hemoglobin (HbA1c) levels were assessed. Systolic and diastolic blood pressures were measured at each appointment. Basic anthropometric measurements such as waist-to-hip ratio and body mass index (BMI) were also recorded and documented in the case report form.

A dietician recommended diet and lifestyle changes, including exercise, to help people lose weight, and antidiabetic drugs were kept constant during the course of the study. Patients received 4 mg of saroglitazar daily and were monitored for 32 weeks.

2.5 Non-Invasive Test

The patients underwent ultrasonography (USG) to evaluate the liver size and to screen any liver disease. Following that, the patients had FibroScan®, for recording of LSM, and CAP.

2.6 Statistical Analysis

The GraphPad Insta Online Version® (https://www.graphpad.com/quickcalcs/ttest2/) was employed for the statistical analysis, and the paired t test was conducted to analyze the findings. P values of <0.05 were considered statistically significant.

3. RESULTS AND DISCUSSION

3.1 Baseline Characteristics

Basic demographic details of a total 8 patients, whose mean age was 56.9 years are mentioned in Table 1.

3.2 Follow Up Data

Table 2 represents various clinical parameters of patients at baseline, 16 weeks, and 32 weeks, along with changes from baseline at each time point and corresponding p-values indicating the statistical significance of these changes. At end of 32 weeks, saroglitazar has shown significant reduction of PPBG, HbA1c in glycemic parameters; TC and TG in lipid parameters and ALT in Liver enzymes. Transient elastography parameters; CAP and LSM value had been consistently reduces at 16 and 32 weeks with P<0.05. (Table 2).

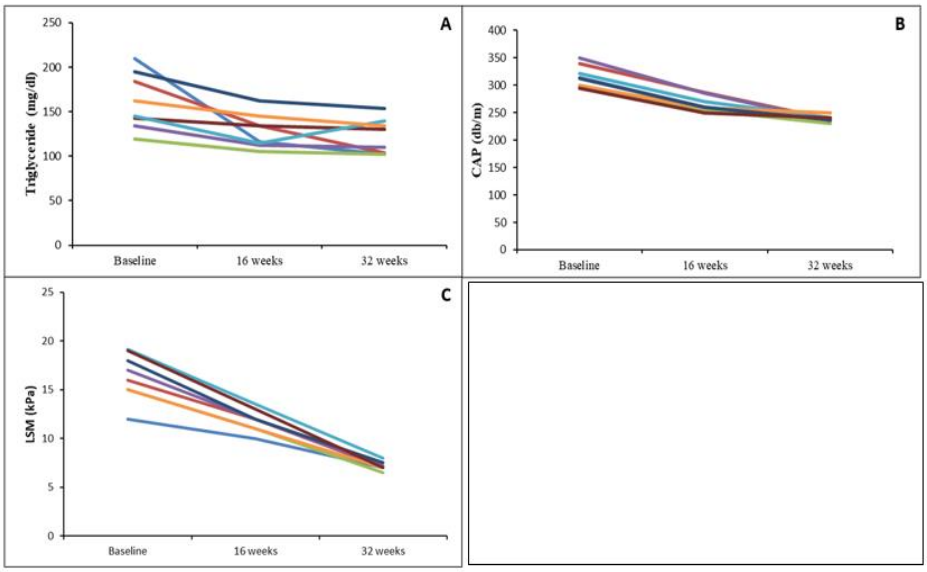

Fig. 1. Reduction in A) TG (mg/dl), B) CAP (dB/m), C) LSM (kPa) of 8 patients from baseline to week 16 and week 32 with saroglitazar treatment

Table 1. Baseline findings

Parameter	Patient No.							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Age (Years)	62	50	67	58	66	64	44	44
Gender	M	F	M	M	F	F	M	M
BMI (kg/m2)	30.1	34	33.5	32.3	30.5	33.8	29.7	30.8
SBP (mmHg)	150	135	122	110	125	130	119	160
DBP (mmHg)	90	88	81	68	90	80	76	100
ALT (U/L)	63	37	14	48.5	52	40	60	14
AST (U/L)	45	62	18	35	40	41	46	21
S. Creatinine (mg/dl)	0.49	0.5	0.6	0.8	0.9	0.53	0.99	0.8
HbA1c (%)	6.4	7.2	7.8	6.8	8.2	8.5	9.2	6.4
FBG (mg/dl)	115	112	95	122	110	84	158	86
PPBG (mg/dl)	142	125	110	125	118	135	158	105
TC (mg/dl)	206	145	110	184	172	212	152	159.3
HDL (mg/dL)	28	36	26	38	52	48	32	75.4
LDL (mg/dl)	94	54	79	64	95	45	81	55.3
TG (mg/dl)	210	184	119	134	145	162	195	142.8
CAP (dB/m)	314	339	296	350	321	300	312	295
LSM (kPa)	12	16	15	17	19.16	15	18	19
USG findings	GRADE 3	GRADE 3	GRADE 3	GRADE 3	GRADE 3	GRADE 2	GRADE 3	GRADE 3

[Abbreviations: ALT-Alanine transaminase, AST-Aspartate transaminase, BMI-Body Mass Index, CAP-Controlled Attenuation Parameter, DBP-Diastolic Blood pressure, dB/m – decibel per meter, FBG - Fasting Blood Glucose, HbA1c - Glycated Hemoglobin, HDL - High Density Lipoprotein, kPa- Kilopascal, LDL- Low Density Lipoprotein, LSM-Liver Stiffness Measurement, PPBG- Post Prandial Blood Glucose, SBP-Systolic Blood Pressure, TC- Total Cholesterol, TG- Triglyceride, USG- Ultrasonography]

Table 2. Effect of saroglitazar in various parameters at weeks 16 and 32

Parameter	Baseline (mean ± SD)	16 weeks (mean ± SD)	Change from baseline to weeks 16	p-value	32 weeks (mean ± SD)	Change from baseline to weeks 32	p-value
FBG (mg/dl)	110.25 ± 23.77	107.88 ± 17.68	- 2.38	0.40	113.00 ± 22.97	2.75	0.74
PPBG (mg/dl)	127.25 ± 17.37	116 ± 17.43	- 11.25	0.01*	113.13 ± 16.39	- 14.13	0.008*
HbA1c (%)	7.56 ± 1.03	6.76 ± 0.66	- 0.8	0.03*	6.11 ± 0.94	- 1.4	0.005*
TC (mg/dl)	167.53 ± 33.54	137.5 ± 18.33	- 30.08	0.04*	134.13 ± 22.56	- 33.41	0.03*
HDL (mg/dl)	41.92 ± 16.28	39.02 ± 10.71	- 2.9	0.48	41.39 ± 12.12	- 0.54	0.90
LDL (mg/dl)	70.91 ± 19	58.01 ± 16.05	- 12.9	0.0002*	64.55 ± 29.34	- 6.36	0.40
TG (mg/dl)	161.48 ± 31.99	127.91 ± 19.30	- 33.56	0.01*	122 ± 20.08	- 39.48	0.01*
ALT (U/L)	41.06 ± 18.89	32.41 ± 14.31	- 8.65	0.04*	26.50 $\pm$ 6.90	- 14.56	0.02*
AST (U/L)	38.50 ±14.13	37.83 ± 11.41	- 0.66	0.68	28.86 $\pm$ 8.70	- 9.63	0.10
CAP (dB/m)	315.88 ± 20.10	265.75 ± 13.71	- 50.13	0.0001*	238.75 $\pm$ 5.68	- 77.13	0.0001*
LSM (kPa)	16.40 ± 2.41	11.81± 1.13	- 4.58	0.0001*	7. 16 ± 0.44	- 9.23	0.0001*
S. Creatinine (mg/dl)	0.70 ± 0.19	0.62 ± 0.26	- 0.08	0.47	0.64 ± 0.26	- 0.07	0.57

*[P value at weeks 16 and 32, is compared with baseline. *p value<0.05, denotes significant data]*

Saroglitazar is predominantly a TG lowering drug, which can be observed in Fig. 1(A) with significant TG reduction in all eight patients. ALT levels decreased significantly from 41.06 ± 18.89 U/L at baseline to 32.41 ± 14.31 U/L at 16 weeks ($p = 0.04$) and further to 26.50 ± 6.90 U/L at 32 weeks ($p = 0.02$). AST levels did not show significant changes. CAP scores showed significant reductions from 315.88 ± 20.10 dB/m at baseline to 265.75 ± 13.71 dB/m at 16 weeks ($p = 0.0001$) and to 238.75 ± 5.68 dB/m at 32 weeks ($p = 0.0001$), indicating decreased liver fat content is depicted in Table 2, Fig. 1B. LSM values also decreased significantly from 16.40 ± 2.41 kPa at baseline to 11.81 ± 1.13 kPa at 16 weeks ($p = 0.0001$) and to 7.16 ± 0.44 kPa at 32 weeks ($p = 0.0001$) shown in Table 2, Fig. 1C, suggesting reduced liver fibrosis. Serum creatinine levels remained stable, with no significant changes observed.

Overall, these findings indicate that the treatment was effective in improving glycemic control, lipid profile, liver enzyme levels, and reducing liver fat and fibrosis in patients over the study period.

This case series explores the potential of saroglitazar in T2DM patients, focusing on its effects on glycemic control, lipid profile, liver enzymes, and transient elastography parameters like CAP and LSM scores. Given the increasing prevalence of T2DM and its association with increased risk of cardiovascular disease, this research provides valuable insights. The findings indicate that the majority of the patients exhibit Grade 3 fatty liver which is the most severe form MASLD [11,12].

Further, results demonstrate a significant improvement in glycemic control among patients treated with saroglitazar. The reduction in HbA1c levels from 7.56% at baseline to 6.11% at 32 weeks is noteworthy, indicating better overall blood glucose management compared to previous study showed the mean HbA1c reduction of 0.3% with saroglitazar treatment [9]. Additionally, PPBG levels showed a significant decrease over the study period, whereas FBG levels, although improved, did not reach statistical significance. In recent comparative study of saroglitazar (2 mg and 4 mg) and pioglitazone treatment groups showed statistically significant reduction in FPG and 2 h PPG at week 12, week 24 and week 56 [7,13]. These findings align with previous studies that suggest PPAR agonists, including saroglitazar, can enhance insulin sensitivity and glycemic control in patients with diabetes [5,9,13,14].

Significant improvements were observed in the lipid profiles of the patients. Total cholesterol and triglyceride levels both showed substantial reductions by the 32-week mark. In comparison with pioglitazone after 24 weeks, saroglitazar 4mg showed significant reduction in TG by 45% from baseline, LDL-C by 5%, VLDL by 45.5%, TC by 7.7% respectively, hence it is best therapeutic option for the hypertriglyceridemia patients with T2DM [13]. Meanwhile, at week 12, saroglitazar 4 mg tablets significantly reduced mean plasma triglyceride levels by −46.7 ± 3.02% [14]. Regarding MASLD, Saroglitazar is the only approved drug in India for NAFLD with co-morbidities and pre-cirrhotic NASH. Gawrieh et al. recorded that in MRI-PDFF driven study, mean percent change from baseline in ALT at week 16 was -45.8% with saroglitazar 4 mg, with additional improvement in liver fat content (LFC), insulin resistance, and atherogenic dyslipidemia in participants with NAFLD/NASH [15]. According to multiple clinical trials, giving individuals with NAFLD or NASH, 4 mg of saroglitazar improved their lipid profile and blood glucose levels, as well as their liver enzymes and liver stiffness [8]. As per Goyal et al, after 24 weeks of follow, ALT score improved from baseline 94 U/L to 39 U/L, and AST from baseline 89 U/L to 37 U/L, it indicates that saroglitazar is effective on liver enzymes levels [5].

Saroglitazar has demonstrated efficacy in reducing inflammation and fibrosis, resulting in improved LSM scores, suggesting a decrease in fibrosis and improved liver health [16]. In this study, findings showed the reduction in CAP and LSM scores, indicating decreased liver fat and fibrosis, respectively. The CAP score was reduced from 315. 88 dB/m to 238.75 dB/m over 32 weeks is consistent with other studies where CAP score reduced from 335 dB/m to 256 dB/m after 24 weeks, demonstrating saroglitazar effectiveness in reducing hepatic steatosis. Similarly, the LSM score reduction from 16.40 kPa to 7.16 kPa aligns with the findings of the previous research where LSM score decreased from 8.4 kPa to 7.4 kPa, suggesting a marked decrease in liver stiffness, correlating with reduced fibrosis [5].

These improvements are critical, as liver fibrosis is a key determinant of morbidity and mortality in NAFLD patients. While the use of CAP and LSM became more popular, results began to diverge,

particularly regarding differences in diagnostic accuracy and cut-off values between different BMI populations and between different probes. Earlier, several meta-analyses had discussed the accuracy of CAP or LSM alone in NAFLD patients, but few studies were included, with only nine studies, which might lead to relatively limited conclusions [8,16].

Overall, the baseline characteristics of the patients, including elevated liver enzymes (ALT and AST), significant liver fat accumulation (indicated by CAP scores), and varying degrees of liver fibrosis (indicated by LSM values), suggest the presence of NAFLD. These findings indicated that these 8 T2DM patients were having MASLD, and the substantial improvements in a number of clinical indices highlighted saroglitazar as a potential multimodal treatment agent for MASLD.

This case-series study represents promising results, but challenges are involved such as single-centre approach, limited sample size, and limited follow-up duration. The interaction between the antidiabetic drugs and saroglitazar along with its combined effects on the overall parameters were not discussed. To validate these findings and assess the long-term effects of saroglitazar on type 2 diabetes mellitus patient with steatotic liver disease, further research with larger, varied cohorts and longer follow-up durations is needed, ensuring broad applicability and long-term safety and efficacy evaluation.

4. CONCLUSION

Saroglitazar considerably reduces liver enzyme levels, glycemic parameter, lipid parameters and the amount of liver fat and fibrosis in MASLD patients. These results demonstrate the drug's potential as a beneficial choice for managing steatotic liver disease, especially when other metabolic disorders are involved.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT AND ETHICAL APPROVAL

The study was carried out in compliance with ICH-GCP ethical standards; before its commencement, participants were informed about the study and received their consent.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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