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Original Article

Internal Medicine Section

Role of Saroglitazar in Non Diabetic Non Alcoholic Fatty Liver Disease Patients: A Retrospective Observational Study

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ABSTRACT

Introduction: Non Alcoholic Fatty Liver Disease (NAFLD) is a commonly encountered problem which affects one third of the general population. Saroglitazar, a Peroxisome Proliferator Activated Receptor (PPAR) alpha α and gamma γ agonist has been recently approved for treatment of NAFLD.

Aim: To assess the efficacy of saroglitazar in non diabetic NAFLD patients.

Materials and Methods: It was a retrospective observational study, conducted from October 2020 to March 2021 on 45 non diabetic NAFLD patients, at a tertiary care centre in north-eastern India. Liver enzymes, liver fibrosis and liver fat content were compared before and after receiving saroglitazar for 24 weeks. Multiple regression analysis was used to assess percent change in Alanine Transaminase (ALT), Aspartate Transaminase (AST), ALP, bilirubin, Liver Stiffness Measurement (LSM) and Controlled Attenuation Parameter (CAP). The p-values <0.05 were considered as statistically significant.

Results: Mean age of the study population was 46±8.20 years, and there were 24 males and 21 females. Reduction in liver enzymes like Alanine Transaminase (ALT) and Aspartate Transaminase (AST) and fibroscan parameters like Liver Stiffness Measurement (LSM) and Controlled Attenuation Parameter (CAP) were seen. Mean values of ALT and AST at pretreatment status were 85.52±17.12 U/L and 70.02±19.10 U/L, and after treatment were 40.20±12.11 U/L and 37.32±8.31 U/L, respectively (p-value <0.0001 for both ALT and AST). Pretreatment and post-treatment mean values for LSM and CAP were 8.11±2.18 kPa (kilopascal), 365.84±56.22 d/m (decibel/metre) and 7.20±1.80 kPa, 345.21±35.22 d/m, respectively (p-value=0.021 for LSM and 0.036 for CAP).

Conclusion: Twenty four weeks saroglitazar was effective in treatment of non diabetic NAFLD. It not only reduces hepatocellular inflammation, but also liver fibrosis and liver fat.

Keywords: Alanine transaminase aspartate transaminase, Controlled attenuation parameter, Fibroscan, Liver stiffness measurement, Peroxisome proliferator activated receptor

INTRODUCTION

Non Alcoholic Fatty Liver Disease (NAFLD) is a manifestation of metabolic syndrome which is characterised by fat deposition in liver associated with variable degree of inflammation and fibrosis. NAFLD is a wide spectrum of chronic liver illness, which ranges from non alcoholic fatty liver to non alcoholic steatohepatitis and cirrhosis. It affects approximately one third of the general population and associated with 70-75% patients with diabetes and obesity [1,2].

Various models assessed that prevalence of NAFLD patients, is expected to rise exponentially in near future because of disproportionate increasing cases of obesity and T2DM [3]. NAFLD often develops with background of diabetes and obesity [4]. Our understanding regarding the aetiopathogenesis and natural history of NAFLD has significantly improved in the last few decades. According to most widely accepted "multiple hit hypothesis", insulin resistance plays a crucial role in pathogenesis of NAFLD by increasing availability of free fatty acids to liver, which is responsible for fatty liver and lipotoxicity [5,6]. Lipotoxicity and endotoxemia secondary to altered gut-liver axis and altered gut microbiota related hepatocellular inflammation is responsible for NAFLD [7]. Inflammation activates fibrogenic activity ultimately leading to cirrhosis. Despite numerous trials that has been conducted in the past decade, therapeutic options for treatment of NAFLD is still limited due to low efficacy or significant side effects for the available drugs [8,9].

Primary objective for developing a pharmaceutical agent is a rational molecular target. Therapeutic targets can act either on fat deposition or on inflammatory cascade [10-12]. On the basis of currently available data, only obeticholic acid and saroglitazar showed promising results with minimal side-effects [13,14]. Peroxisome Proliferator Activated Receptor (PPAR) are a group of superfamily of nuclear hormone receptor proteins which act as a transcription factor and include PPAR-α, PPAR-β/δ and PPAR-γ [15].

Saroglitazar, a PPAR-α/γ agonist, has been recently approved for treatment of NAFLD. Proposed mechanism of action of saroglitazar is that it improves insulin sensitivity and lipid oxidation by acting on PPAR-γ and PPAR-α respectively. Therefore, saroglitazar decreases lipotoxicity by dual mechanism like decreasing availability of fat in liver and increasing metabolism of fat inside liver [16,17]. It has shown promising results in both animal based NAFLD models and human trials like decreasing hepatic steatosis, hepatocellular inflammation and fibrogenic activity [16,17]. In last few years, multiple studies conducted and reported beneficial role of saroglitazar in NAFLD with T2DM or NAFLD irrespective of glycaemic status [14,16]. Data regarding the role of saroglitazar in non diabetic NAFLD patients is not available. Hence, this study aimed to evaluate the effects of saroglitazar in non diabetic NAFLD patients in terms of inflammation, fibrosis and reduction in fat content.

MATERIALS AND METHODS

It was a retrospective observational study, conducted from October 2020 to March 2021 (analysis was done April 2021) in a tertiary care centre in north-eastern India (ILS Hospital, Agartala, Tripura, India). The study followed the principles of Declaration of Helsinki and Good clinical Practice as laid down by Indian Council of Medical Research.

Total 45 non diabetic NAFLD patients were retrospectively reviewed. They received saroglitazar magnesium 4 mg for the treatment of NAFLD from hepatology and gastroenterology clinic of the hospital.

Sample size calculation: Sample size was calculated using Cochrane sample size estimation formula: $Z \times p \times q / L^2$. The calculation was based on 9% prevalence of NAFLD in India [2], 10% margin of error and 95% confidence interval. Minimum sample size required was 32.76 (33) patients.

Inclusion criteria: Patients who received 24 weeks treatment of saroglitazar and did follow-up for investigations at the end of therapy, patients with age >18 years, absence of T2DM (fasting blood sugar <100 mg/dL) and presence of fatty liver on ultrasound were included.

Exclusion criteria: Patients with history of T2DM or of receiving medications for T2DM in last 6 months, history of receiving medication for dyslipidaemia, presence of chronic hepatitis B or C infection (positive Hbs Ag or anti HCV ab) or with evidence of chronic liver disease on abdominal ultrasound and portal doppler, significant alcohol intake (>20 gm/ day for males and >10 gm/day for females) and with history of intake of anti-obesity medication in last six months were excluded from study. Cases with a history of intake of hepatotoxic drugs or drugs leading to hepatic fibrosis were also excluded. Patients having others co-morbidities like hypothyroidism, ischaemic heart disease or chronic kidney disease were not included.

Parameters

Data for Liver Function Tests (LFT) like serum bilirubin, ALT, AST, Alkaline Phosphatase (ALP), with ultrasound abdomen and fibroscan were collected. Inclusion criteria for fat liver on ultrasound in study was increased echogenicity of liver along with the presence of any two of the three features:

(a) Increased liver-kidney contrast (brightness of liver in contrast to kidney parenchyma);

(b) Vascular blurring (blurring of hepatic vasculature, mainly hepatic vein trunk);

(c) Deep attenuation of echo-beam (attenuation of echo-beam in the deep portion of right lobe of liver) [18]. Fibroscan (transient elastography by Echosens; Paris, France) was used for assessment of LSM and CAP.

STATISTICAL ANALYSIS

The data collected was entered in MS Excel-2010 and statistical analysis was performed with the help of Epi Info (™) 7.2.2.2 which is a trademark of the Centre for Disease Control and Prevention (CDC). Categorical data were shown as proportions and continuous data were shown as mean and standard deviation (parametric data) along with median and interquartile range (non parametric data). Analysis of Variance (ANOVA) test or Friedman test was performed, where required, to compare before and after treatment data. Multiple regression analysis was used to assess percent change in ALT, AST, ALP, bilirubin, LSM and CAP. The p-values <0.05 were considered as statistically significant.

RESULTS

Total 45 non diabetic NAFLD patients who received 24 weeks saroglitazar therapy, were included in study. Demographic data is shown in [Table/Fig-1]. Out of 45 patients, 55.5% were males. The mean age was 46±8.20 years. Ultrasound was done to diagnose NAFLD. So all the patients included in the study, had fatty liver on ultrasound. Fibroscan was done to assess two parameters i.e., LSM and CAP.

Significant reduction in both ALT and ALT with a trend towards normalcy was noted. The p-value for both ALT and AST were <0.0001. Similarly improvement in LSM and CAP were seen (p-value were 0.021 and 0.036, respectively) [Table/Fig-1].

Parameters	Pretreatment (Mean±SD)	Post-treatment (Mean±SD)	p-value
Age (years)	46±8.20		
Gender (M/F)	24:21		
Alanine Aminotransferase (U/L)	85.52±17.12	40.20±12.11	<0.0001*
Aspartate Aminotransferase (U/L)	70.02±19.10	37.32±8.31	<0.0001*
Alkaline phosphatase (U/L)	156.85±17.22	143.58 ±14.31	0.12
Total Bilirubin (mg/dL)	1.10±0.31	1.16±0.20	0.17
Serum Protein (gm/dL)	6.60±2.22	6.91±2.15	0.11
Serum Albumin (gm/dL)	4.52±1.82	4.60±1.64	0.15
Fasting blood sugar (mg/dL)	95.21±5.86	97.12±4.12	0.18
Liver Stiffness Measurement (LSM) (kp)	8.11±2.18	7.20±1.80	0.021*
Controlled Attenuation Parameter (CAP) (d/m)	365.84±56.22	345.21±35.22	0.036*

[Table/Fig-1]: Comparison of demographic, biochemical and fibroscan values. p-values <0.05 were considered as statistically significant

DISCUSSION

The present study represents the efficacy of saroglitazar in non diabetic NAFLD patients, by comparing pretreatment and post-treatment improvement in liver enzymes and fibroscan parameters. Saroglitazar 4 mg was prescribed to all patients as approved and recommended on the basis of currently available data [14,19]. As per our knowledge, it is the first study from India, which shows beneficial role of saroglitazar specifically in non diabetic NAFLD patients. An ideal pharmaceutical target for managing NAFLD is expected to show beneficial effects on insulin sensitivity, liver fat, hepatocellular inflammation, oxidative stress, mitochondrial dysfunction and liver fibrosis [10].

Previously, multiple drugs were evaluated for the treatment of NAFLD with limited success. The most crucial event in NAFLD is the deposition of fat in hepatocytes. PPARs are key mediators of lipid homoeostasis. PPAR α expression is mostly seen in hepatocytes in the liver, where its stimulation prevents steatosis and steatohepatitis by inhibiting intrahepatic fatty acid accumulation. On the other hand, PPAR γ is predominantly expressed in adipocytes, where its activation improves insulin sensitivity, and so decreases fatty acid availability to the liver [20]. PPAR γ agonist pioglitazone showed histological improvement in NAFLD patients because of antifibrotic properties, but did not get approval because of multiple side effects like heart failure, headache, blurring of vision, bladder cancer and weight gain [21]. PPAR α agonists like fibrates did not show any promising results in trials on NAFLD patients [13]. Elafibrinor, a PPAR-α/δ agonist is under trial for assessing response in NAFLD patients [22]. Metformin, ursodeoxicholic acid and vitamin E were used in the past for treatment of NAFLD, but current data did not show beneficial role of these drugs [8,9]. Recently, promising data published regarding role of obeticholic acid in NAFLD patients, although larger data is required for assessing safety and efficacy of this drug before getting approval for treatment of NAFLD [23]. Saroglitazar is a dual α and γ PPAR agonist, which was recently approved for treatment of NAFLD. Jain N et al., reported that saroglitazar reduces dyslipidemic changes and reduces insulin resistance by reducing glucolipotoxicity and by agonistic effect on PPARγ in patients of diabetes with dyslipidaemia [24]. Elevated ALT and AST levels are markers of hepatocellular inflammation and aids to diagnose NASH without histology. Saroglitazar is effective in reducing liver inflammation, which can be measured by ALT and AST changes. In the present study, author found a significant reduction in liver enzymes after 24 weeks of therapy. Similar results were noted from previous studies. Kaul U et al., reported significant reduction in ALT after receiving saroglitazar for 12 to 58 weeks [19]. Another study mentioned 60% reduction in ALT and 43% reduction in AST after 12 weeks saroglitazar treatment in NAFLD animal models [16]. Similarly Goyal O et al., notified significant reduction in ALT and AST after 24 weeks saroglitazar therapy [14].

So, authors concluded that 24 weeks therapy helps in resolution of transaminitis reflects improving hepatocellular inflammation. Reversal of liver fibrosis is ideal end point for pharmacological treatment. Ideally, accurate assessment is possible only on histopathology by liver biopsy, which is not always possible because of its invasive nature. LSM analysis by fibroscan gives us a non invasive method for assessment of liver fibrosis and cirrhosis. In last few years, multiple studies showed good efficacy of fibroscan for assessment of liver fibrosis [25,26]. Our study reported significant reduction in fibrosis measured by LSM in fibroscan. Goyal O et al., mentioned significant reduction in LSM after 24 weeks treatment with saroglitazar [14]. Another study also reported reduction in liver fibrosis, measured by shear wave elastography after receiving saroglitazar for a period of 9 month [27].

Liver fat assessment is also another important parameter, to assess the response of therapy for NAFLD. Although, ultrasound abdomen is a screening tool for diagnosis of fatty liver, but efficacy of ultrasound is limited for moderate liver fat content alteration. CAP by fibroscan is a reasonable alternative for diagnosis of fatty liver. Simultaneously, there is a good accuracy of CAP for change in liver fat content [28,29]. The present study analysis showed significant liver fat reduction measured by CAP by fibroscan. According to Goyal O et al., reduction in CAP values noted after 24 weeks saroglitazar treatment in NAFLD. Kaul U et al., also reported similar findings with significant improvement in liver fat measured by CAP after 12-58 weeks saroglitazar treatment [19]. Side-effects like hypoglycaemia, nausea, chest discomfort related to saroglitazar are mentioned in literature. No side-effects related to saroglitazar including hypoglycaemia was noted in any of the present study patients. Animal model studies did not show any side-effects [30]. Similarly, no significant side effects noted in human trials also [24].

Limitation(s)

Study was limited by a retrospective nature of study and there was a lack of histological analysis.

CONCLUSION(S)

Authors conclude and recommend that saroglitazar is effective not only in diabetic NAFLD, but non diabetic NAFLD also. Twenty four weeks course treatment efficiently reduces hepatocellular inflammation, liver fibrosis and fat content measured by liver enzymes, LSM and CAP respectively.

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