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ORIGINAL ARTICLE

Saroglitazar improves nonalcoholic fatty liver disease and metabolic health in liver transplant recipients

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Abstract

NAFLD is common after liver transplantation (LT) and is associated with an increased metabolic burden. Currently, there is a paucity of investigations into the treatment of post-LT NAFLD. In the present study, we evaluated the safety and efficacy of saroglitazar, a novel dual peroxisome proliferator–associated receptor α/γ agonist, on the treatment of post-LT NAFLD and metabolic burden. This is a phase 2A, single-center, open-label, single-arm study in which patients with post-LT NAFLD received saroglitazar magnesium 4 mg daily for 24 weeks. NAFLD was defined by a controlled attenuation parameter ≥ 264 dB/m. The primary endpoint was the reduction in liver fat as measured by MRI proton density fat fraction (MRI-PDFF). Secondary MRI-based metabolic endpoints included visceral adipose tissue, abdominal subcutaneous adipose tissue volumes, muscle fat infiltration, and fat-free muscle volume. Saroglitazar treatment led to a reduction in MRI-PDFF from $10.3 \pm 10.5\%$ at baseline to $8.1 \pm 7.6\%$. A relative 30% reduction from baseline MRI-PDFF value was noted in 47% of all patients and 63% of patients with baseline MRI-PDFF $> 5\%$. Reduction in serum alkaline phosphatase was an independent predictor of MRI-PDFF response. Saroglitazar did not decrease fat-free muscle volume nor increase muscle fat infiltration, but did lead to a mild increase in visceral adipose tissue and abdominal subcutaneous adipose tissue. The study drug was well tolerated and a mild nonsignificant increase in serum creatinine was noted. Saroglitazar did not affect the weight. The study provides preliminary data demonstrating the safety and metabolic benefits of saroglitazar in LT recipients and underscores the importance of future studies to establish its efficacy after LT.

Abbreviations: ASAT, abdominal subcutaneous adipose tissue; CAP, controlled attenuation parameter; eGFR, estimated glomerular filtration rate; LT, liver transplantation; MFI, muscle fat infiltration; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; PPAR, peroxisome proliferator-activated receptors; VAT, visceral adipose tissue;

INTRODUCTION

The prevalence of cirrhosis associated with NASH, the clinically aggressive variant of NAFLD, is increasing rapidly.[1] NASH-associated cirrhosis is now becoming a leading indication for liver transplantation (LT) as patients with NASH develop decompensated cirrhosis,[2,3] and is now the leading indication for LT among women and the elderly.[4,5] Recurrence of NAFLD following LT is nearly universal and associated with rapid fibrosis progression.[6] Moreover, nearly a third of patients transplanted for non-NASH indications will develop *de novo* NAFLD following LT, increasing the risk of fibrosis progression and graft cirrhosis.[7]

As the liver plays a central role in glucose, energy, and lipid homeostasis, perturbations leading to the development of NAFLD also increase the risk of insulin resistance, obesity, and dyslipidemia, respectively.[8,9] In LT recipients, this is of paramount importance as these factors accelerate cardiovascular disease, which is the leading cause of long-term mortality among LT recipients and is considerably higher than in matched non-LT cohorts.[10–14] Despite the high prevalence and significant impact of NAFLD, there is no approved therapy for the treatment of NASH in either the general or LT population. Moreover, lifestyle measures in LT recipients aimed at weight loss are less effective partly due to inefficient fatty acid oxidation in LT recipients with NAFLD.[15,16] This underscores the importance of the investigation of potential therapeutic strategies for the treatment of NAFLD and associated metabolic comorbidities in LT recipients.

Saroglitazar is a novel peroxisome proliferator–associated receptor (PPAR) γ/δ ligand that has shown efficacy for the treatment of NASH in phase 2 clinical trials.[17] Moreover, saroglitazar improves atherogenic dyslipidemia and insulin resistance.[18] Given the beneficial effects of saroglitazar on NAFLD as well as its beneficial cardiometabolic risk profile, we conducted the current study of saroglitazar magnesium in LT recipients with NAFLD to (1) demonstrate safety, (2) efficacy on fatty liver, and (3) impact of weight and body composition.

METHODS

Study design

The current study is a phase 2A, single-center, open-label, single-arm study to evaluate the safety and efficacy of saroglitazar 4 mg daily for 24 weeks in patients with evidence of NAFLD after LT (ClinicalTrials.gov identifier: NCT03639623). The study protocol was reviewed and approved by the Western Internal Review Board (IRB). The Food and Drug Administration (FDA) Investigational New Drug (IND) was obtained by Zydus Therapeutics (IND-138352). The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki.

Study population

The study enrolled adult LT recipients between the age of 18 and 75 years, who had received an LT at least 24 weeks prior, had a body mass index of at least 18 kg/m^2, and had evidence of post-LT NAFLD based on a controlled attenuation parameter (CAP) value of 264 dB/m or greater before enrollment.[19] The key exclusion criteria included pregnant or lactating females, graft cirrhosis or failure, poorly controlled diabetes mellitus, defined as HbA1c $>8.5\%$, unstable cardiovascular disease, more than 5% change in body weight 3 months before enrollment, and active or history of malignancy within the past 5 years with the exception of resolved superficial nonmelanoma skin cancer. Patients with acute cellular rejection, chronic rejection, clinically significant biliary strictures, or recurrence of non-NAFLD chronic liver diseases (eg, hepatitis C, autoimmune, or cholestatic liver disease) were also excluded. Patients consuming more than mild alcohol use, defined by $\geq$21 U of alcohol per week in males and $\geq$14 U of alcohol per week in females for 2 years before enrollment, were excluded. Finally, while there are renal safety data with saroglitazar, in this proof-of-concept study in LT recipients, an estimated glomerular filtration rate (eGFR) of <60 was exclusionary. Detailed inclusion and exclusion criteria are provided in the Supplemental Material (http://links.lww.com/LVT/A356). All patients provided written, informed consent before participating in the study procedures.

Study procedures

The study was conducted over a 33-week period that included a 5-week screening period, a 24-week treatment period, and a 4-week follow-up safety visit. The patients were followed every 4 weeks while on therapy with a routine assessment that included history, physical examination, and laboratory. During the study duration, the patients were advised not to alter their diet or exercise. Patients were also advised to minimize alcohol consumption as it is considered the standard of care in patients with chronic liver disease who may be at risk for disease progression.

MRI was performed for body composition profiling, and magnetic resonance elastography (MRE) was performed at enrollment and end of treatment (EOT) using a Philips Ingenia 3.0 T MR-scanner. MRI-based body composition profiling was performed using AMRA Researcher (AMRA Medical AB) for liver fat content via the MRI proton density fat fraction (MRI-PDFF), visceral adipose tissue

(VAT) volume, abdominal subcutaneous adipose tissue (ASAT) volume, thigh fat-free muscle volume (FFMV), and muscle fat infiltration (MFI) as described.[20]

Pharmacokinetics was measured in 6 patients following the first and last dose with sample collection at predose (0), 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hours after the dose. The pharmacokinetics parameters evaluated included C_{max}, T_{max}, the area under plasma concentration versus time curve in the 24-hour dosing interval (AUC_{tau}), the elimination half-life ($t_{1/2}$), apparent volume distribution, and apparent clearance.

Outcomes

The primary efficacy endpoint was the percentage change from baseline in MRI-PDFF at week 24. Secondary efficacy endpoints included change from baseline in serum aminotransferases, alkaline phosphatase, and bilirubin. Additional endpoints included change in body composition from baseline to week 24 including VAT, ASAT, and MFI. Safety endpoints included medication tolerability, renal function, body weight, immunosuppression, 12-lead electrocardiogram, and echocardiography.

Funding source

The study was fully funded by Zydus Therapeutics Inc. and the study protocol was developed in collaboration with the study authors. All authors had full access to study data and are responsible for data analysis, interpretation, and manuscript preparation.

Statistical analysis

The descriptive statistics are reported as means ± SDs for continuous variables, and frequencies and percentages for categorical variables. The primary endpoint was change in MRI-PDFF value from baseline to the end of study, which was evaluated using 2-sided paired *t* tests. As prior studies have documented a >30% reduction in MRI-PDFF with improvement in histological findings, a 30% reduction in MRI was also evaluated. To determine if baseline factors could predict the response (ie, reduction in MRI-PDFF value), a simple linear regression model was constructed that included a hepatic panel (alkaline phosphatase, aminotransferases, and bilirubin). The aim of the secondary analysis was to evaluate the impact of saroglitazar on metabolic burden; thus, the key endpoints evaluated included fat volumes (ASAT and VAT), muscle health (FFMV and MFI), insulin resistance (HbA1c and fasting glucose), serum lipids (HDL-C, LDL-C, and triglycerides), and body weight. A nominal *p*-value <0.5 was considered statistically significant.

RESULTS

Study population

A total of 30 patients were screened from March 2019 to May 2021 for study enrollment; 18 patients were enrolled in the study and received at least one dose. Of these, 3 patients could not continue with the study and 15 patients completed the study procedures. Briefly, the study cohort consisted of 15 LT recipients (n = 13 males) with a mean age of 58 ± 12 years (Table 1). The body mass index of the study cohort was 37.4 ± 7.4 kg/m^2 and the prevalence of diabetes,

TABLE 1 Baseline characteristics of the study cohort at study enrollment

	Value ± SD or proportions (%)
Demographics	
Age (y)	58 ± 12
Gender (% male)	13 (86.7)
Ethnicity (%)	
Non-Hispanic White	12 (80)
Black	3 (20)
Etiology of cirrhosis (%)	
Alcohol induced	2 (13.3)
Hepatitis C	1 (6.7)
NASH	10 (66.7)
Cholestatic liver disease	2 (13.3)
Medical comorbidities	
Body mass index (kg/m^2)	37.4 ± 7.4
Diabetes (%)	4 (26.7)
Hypertension (%)	14 (93.3)
Hyperlipidemia	4 (26.7)
Laboratory values	
Sodium (mg/dL)	138.2 ± 1.9
Creatinine (mg/dL)	0.97 ± 0.13
Alanine aminotransferase (mg/dL)	45.7 ± 36.0
Aspartate aminotransferase (mg/dL)	33.7 ± 14.0
Alkaline phosphatase (mg/dL)	99 ± 35
Bilirubin (mg/dL)	0.83 ± 0.38
International normalized ratio	1.01 ± 0.08
HDL cholesterol (mg/dL)	42.9 ± 13.9
LDL cholesterol (mg/dL)	72.7 ± 23.7
Total cholesterol (mg/dL)	142.0 ± 23.1
Triglycerides (mg/dL)	164.1 ± 172.7
Time from liver transplantation (mo)	72.2 ± 99.4
Tacrolimus (%)	15 (100)

dyslipidemia, and hypertension was 27%, 27%, and 93%, respectively. All patients were on tacrolimus for immunosuppression.

Impact of saroglitazar on liver-related parameters

The mean MRI-PDFF value at baseline was 10.3 ± 10.5%. Treatment with saroglitazar improved MRI-PDFF after 24 weeks of therapy with a reduction in MRI-PDFF to 8.1 ± 7.6% (Figure 1A). A relative 30% reduction in MRI-PDFF was observed in 47% of all study participants, which was more pronounced in patients who had higher MRI-PDFF values at baseline. In the subgroup analysis of patients with MRI-PDFF > 5%, the relative reduction in MRI-PDFF value from baseline to end of study was 63%. The mean MRE value at study entry was 2.59 ± 0.69 kPa compared with 2.78 ± 0.79 kPa at study completion ($p = 0.96$).

A trend toward a decrease in serum aminotransferases was noted over time; however, this did not reach significance (Figure 1B, C). In contrast, a highly significant decrease in serum alkaline phosphatase was noted after initiation of saroglitazar, and the alkaline phosphatase level improved from 99 ± 35 to 54 ± 18 IU/L ($p < 0.001$) from study entry to study completion (Figure 1D). The reduction in serum alkaline phosphatase from baseline to end of study was associated with a relative reduction in MRI PDFF (adjusted $R^2 = 0.328$, $p = 0.02$). Serum bilirubin improved from 0.83 ± 0.38 to 0.75 ± 0.28 mg/dL ($p = 0.09$) after treatment with saroglitazar.

Impact of saroglitazar on body composition

Treatment with saroglitazar did not significantly increase the body weight. The mean ASAT in the study population was 14.5 ± 4.6 L at baseline and treatment with sargoglitazar resulted in a mild increase to 14.9 ± 4.2 L at EOT ($p = 0.046$) (Figure 2A and Supplemental Table 1, http://links.lww.com/LVT/A356). A significant increase in VAT from 8.9 ± 3.3 to 9.5 ± 3.5 L ($p < 0.01$) was noted with saroglitazar treatment (Figure 2B). Similarly, the MFI did not significantly change from baseline to EOT (9.2 ± 2.7% to 9.5 ± 2.8%, $p = 0.10$) (Figure 2C). Serum adiponectin, a protective adipokine, significantly improved with saroglitazar therapy (Figure 2D). Skeletal muscle volume was not affected by saroglitazar treatment (Figure 2E). The reduction in liver fat was independent of changes in VAT, ASAT, and MFI.

Pharmacokinetic analysis

Saroglitazar was rapidly absorbed with a median T_{max} of 1.0 hours (range: 1.0–3.0 h) on day 1 and 2.5 hours

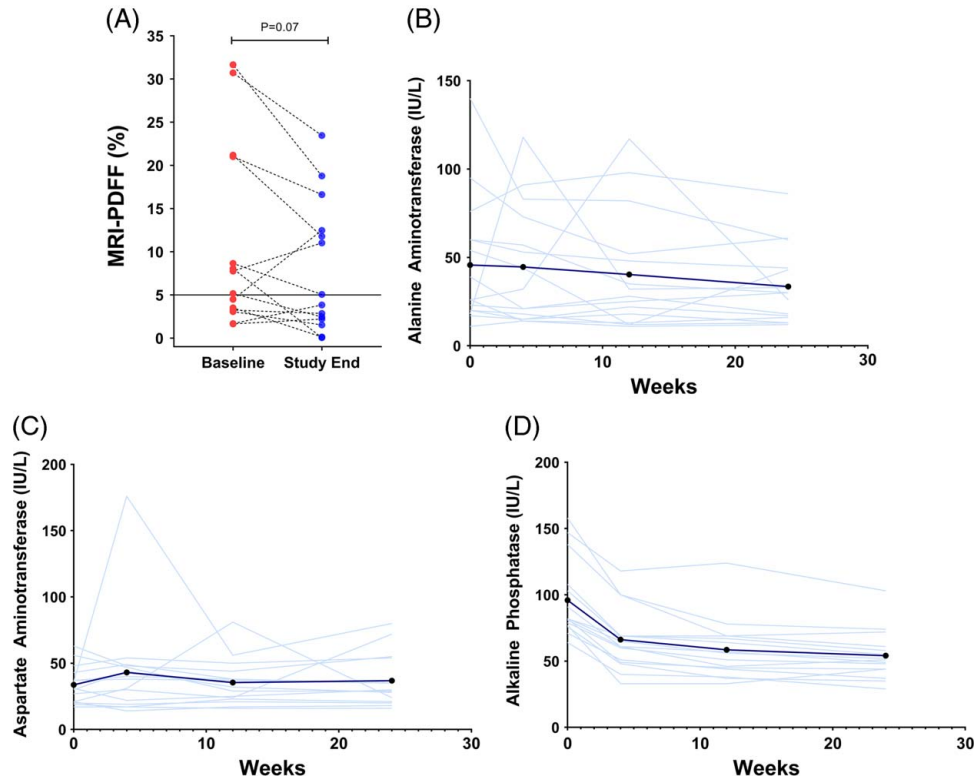

FIGURE 1 Impact of saroglitazar on liver fat content (A), alanine aminotransferase (B), aspartate aminotransferase (C), and alkaline phosphatase (D).

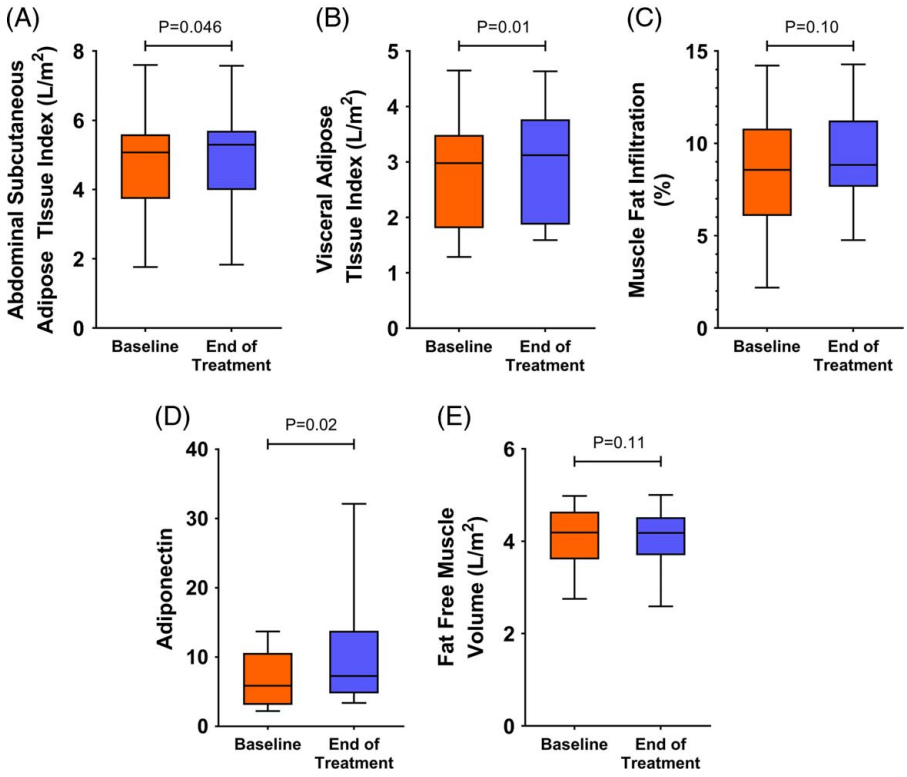

FIGURE 2 Impact of saroglitazar on body composition profile including abdominal subcutaneous adipose tissue (A), visceral adipose tissue (B), muscle fat infiltration (C), serum adiponectin (D), and fat-free muscle volume (E).

on the last day (range: 0.5 and 4.0). The C_{max} ranged from 110 to 244 ng/mL on first day of dosing to 45–196 mg/dL on the last day of dosing. The elimination half-life of saroglitazar ranged from 3.56 to 4.81 hours.

Safety profile

Saroglitazar was well tolerated throughout the study and there was no drug discontinuation or dose reduction over the study duration. There was a total of 15 treatment-emergent adverse event reports, with the most common adverse events being reduction in eGFR, increase in aspartate aminotransferase, and an increase in alanine aminotransferase. The increase in aminotransferases was transient and improved without drug discontinuation (Figure 1B, C). In one patient, the serum eGFR dropped from 62 mL/min/1.73 m^2 at study enrollment to 57 mL/min/1.73 m^2 over the 3 months of therapy. The second patient had a screening eGFR of 61 mL/min/1.73 m^2 and baseline eGFR of 62 mL/min/1.73 m^2. Before taking any study medication, his eGFR decreased to 45 mL/min/1.73 m^2, and on repeat testing his eGFR improved to 54 mL/min/1.73 m^2 (deemed to be unrelated to the study as eGFR decreased before taking the study drug). According to the prespecified stopping rule, a reduction in eGFR to <60 mL/min/1.73 m^2 necessitated study termination in both patients. Overall, a mild increase in serum creatinine was noted in the study cohort (1.0 ± 1–1.1 ± 0.2 mg/dL; $p < 0.01$). The third patient had a history of porto-mesenteric thrombus but was not anticoagulated due to patient preference. After nearly 12 weeks of therapy, the patient developed symptoms of intestinal ischemia necessitating the need for anticoagulation. While this was deemed not to be related to the study drug, the decision was made to stop the study drug.

No statistically significant change in weight was noted from baseline to EOT (118 ± 24 kg at baseline vs. 119 ± 23 kg at end of study; $p = 0.90$). Otherwise, no serious adverse events related to the study drug were noted in the study. No patients in the trial required adjustment of their immunosuppressive therapy. Safety labs including serum bilirubin and aminotransferases did not significantly vary from baseline to the end of study. No patients developed edema. Cardiac function as measured by echocardiography did not change from baseline to the end of therapy.

DISCUSSION

Liver transplant recipients are at significantly higher risk for metabolic diseases including the development of post-LT NAFLD.[12,21] Development of NAFLD after LT synergizes with metabolic diseases to further promote cardiovascular disease, an important cause of long-term mortality following LT.[14] However, there are

currently no therapeutics for the management of post-LT NAFLD aside from lifestyle modifications, which have proven to be of limited value to LT recipients.[6,15] The present study presents data from a phase 2, open-label clinical trial demonstrating the beneficial impact of saroglitazar on the treatment of post-LT NAFLD and improving the metabolic risk.

As there are currently no pharmacological trials aimed at improving NAFLD in LT recipients, the current study aimed to establish the safety of the study drug. Historically, PPAR-γ agonists have demonstrated significant benefits for the treatment of NAFLD and metabolic diseases in the general (ie, non-LT) population, but their use has been limited over safety concerns regarding heart failure exacerbations, adipose tissue expansion, weight gain, edema, and bone loss. This would be of particular concern in LT recipients, in whom the risk of these conditions is higher than in the general population. In the present study, no significant impact of saroglitazar on cardiac function, weight gain, peripheral edema, or bone loss was noted. This is in part because of the fact that saroglitazar has predominant PPAR-α agonist effects and only modest PPAR-γ effects.[22] Thus, the adverse metabolic effects from strong PPAR-γ activation can be avoided with saroglitazar. Saroglitazar did increase VAT; however, it led to a significant increase in serum adiponectin level, demonstrating a beneficial effect on adipose tissue composition. Moreover, as this is a single-arm, unblinded study, it is unclear if this was an effect of saroglitazar or natural history of LT patients as weight gain and adiposity are common following LT. This is further confounded by the fact that the study enrolled patients through the COVID-19 pandemic, which was associated with the worsening of metabolic comorbidities including weight gain. The drug was well tolerated and showed no clinically evident interaction with immunosuppression or other commonly used medications in the LT setting such as antihypertensives or lipid-lowering agents, underscoring the safety of its use in the LT setting. Treatment with saroglitazar did have a statistical increase in serum creatinine; however, this was not clinically significant as the rise in serum creatine was only 0.1 mg/dL from baseline to EOT.

The study also aimed to provide more guidance in the construction of clinical trials with NAFLD in the setting of LT. As CAP was used as the inclusion criteria for the presence of post-LT NAFLD, those patients with lower CAP values had lower MRI-PDFF values at study entry and were, therefore, less likely to have a significant reduction in liver fat content at EOT. This has significant implications for clinical trial design, where MRI-PDFF rather than CAP values should be used as inclusion criteria for noninvasive diagnosis of post-LT NAFLD. If CAP is to be used as a screening tool, higher CAP measurements should be utilized.[19,23]

Saroglitazar, a dual PPAR-α/γ agonist, has shown benefit for not only the treatment of NAFLD but also common metabolic comorbidities such as dyslipidemia and insulin resistance.[17,18,24] After treatment, MRI demonstrated significant improvement in the severity of hepatic steatosis. The absolute reduction in liver fat was mitigated by enrollment of patients with low MRI-PDFF values at baseline, and a subgroup analysis of patients with higher PDFF values demonstrated a much larger effect size. Moreover, a $>30\%$ reduction in MRI-PDFF, which has been associated with improvement in several histological parameters in non-LT patients with NAFLD,[25] occurred in nearly half of all patients; however, these results must be tempered as this was not a double-blinded randomized controlled trial (RCT). Unlike the non-LT population, the LT patients did not have a significant improvement in serum aminotransferases after treatment with saroglitazar. As serum aminotransferases in LT recipients are not able to distinguish between the presence and severity of fatty liver, it is not surprising that serum aminotransferases did not significantly improve.[6,26] Moreover, several patients on treatment had relatively normal serum aminotransferases at study entry, thus making it difficult to improve on normal baseline aminotransferases. Regardless, a trend toward improvement in serum alanine aminotransferase was noted. In contrast to serum aminotransferases, patients treated with saroglitazar had a marked reduction in serum alkaline phosphatase. This is not unexpected as saroglitazar has a significant anticholestatic effect and is currently under investigation for the treatment of primary biliary cholangitis.[27] Therefore, it is likely that serum aminotransferases may not be a reliable biomarker in LT recipients to determine the treatment effect, unlike the non-LT population.

Saroglitazar provided significant metabolic benefits to the study cohort, including improvement in dyslipidemia and glycemic control (Figure 3). The activation of PPAR-α leads to increased hepatic mitochondrial and peroxisomal oxidation of fatty acids, thereby improving the serum lipid concentration.[22] The PPAR-γ activation on the other hand improves glucose homeostasis, thereby improving the indices of insulin resistance. This is germane to the LT population, particularly those with NAFLD, in whom the burden from metabolic diseases such as dyslipidemia and diabetes is disproportionately higher.[6,21,28] Given the multiple metabolic benefits, saroglitazar is a potentially attractive agent for the treatment of post-LT NAFLD to reduce the overall metabolic burden.

The current study was a single-arm, open-label study; thus, the true impact of saroglitazar on post-LT NAFLD and metabolic health requires further validation in RCT. However, given the difficulty with weight loss and impaired body fuel utilization that promotes weight gain and the development of NAFLD in LT

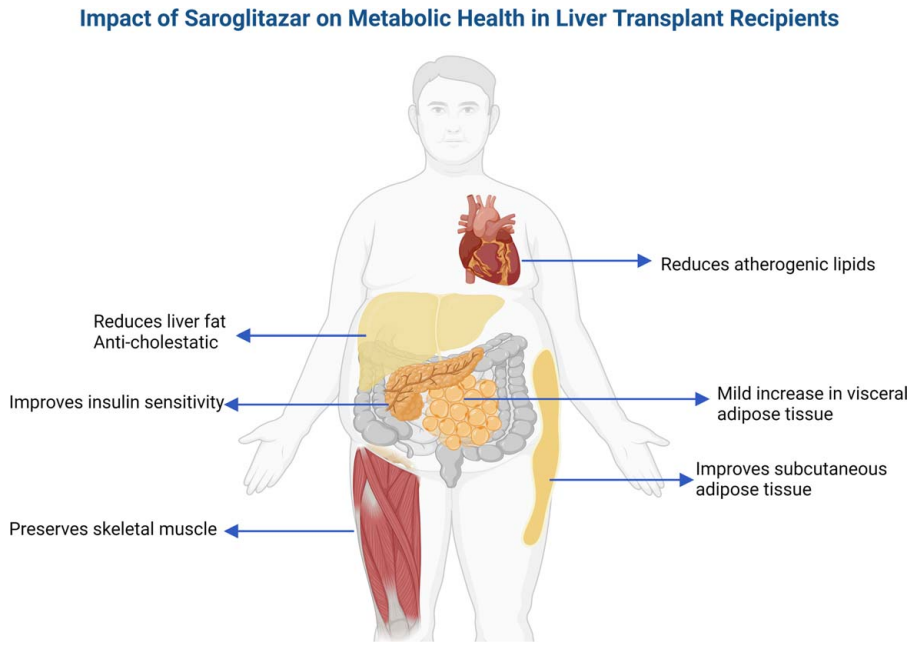

FIGURE 3 Summary of the metabolic effect of saroglitazar in liver transplant recipients.

recipients, the positive treatment effect observed is likely due to saroglitazar. This treatment effect is further supported by similar findings in double-blinded, placebo-controlled, RCTs that have been conducted in non–liver transplant populations.[17,24] Finally, the study cohort consisted primarily of non-Hispanic Caucasians and males; thus, the study results cannot be readily extrapolated to females or other ethnicities, where the adipose tissue distribution and liver fat content might be significantly different. Future studies in larger and diverse cohorts with double-blinded RCTs are needed to better understand the impact of saroglitazar on LT with a different propensity to the distribution of adiposity.

In summary, in this single-arm, open-label clinical trial, saroglitazar was safe and well tolerated among LT recipients. Saroglitazar was also associated with improvement in post-LT NAFLD, insulin resistance, and dyslipidemia. These findings suggest that saroglitazar has the potential to positively affect the natural history of patients who had post-LT NAFLD; however, the study findings require further validation in well-designed prospective double-blinded RCTs.

AUTHOR CONTRIBUTIONS

Mohammad Shadab Siddiqui, Deven Parmar, Arun J. Sanyal, and Farheen Shaikh: conceptualization. Mohammad Shadab Siddiqui, Samarth Patel, Vaishali Patel, and Sherry Boyett: patient recruitment. Anh Tuan Bui: statistical analysis. Mohammad Shadab Siddiqui, Anh Tuan Bui, Farheen Shaikh, and Deven Parmar: manuscript preparation. Mikael Forsgren interpreted MRIs and reviewed the final manuscript.

FUNDING INFORMATION

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CONFLICT OF INTEREST

Mohammad Shadab Siddiqui advises ARMA Medical AB. He is on the DSMB for Sagimet. Deven Parmar is employed by Zydus Therapeutics. Farheen Shaikh is employed by Zydus Therapeutics. Mikael Forsgren is employed by ARMA Medical AB. Arun J. Sanyal owns stock in and consults for GenFit. He consults for and received grants from Gilead, Malinkrodt, Boehringer Ingelheim, Novarits, Bristol Myers Squibb, Merck, Lilly, Novo Nordisk, Madrigal, and Inventiva. He owns stock in Exhalenz, Durect, Indalo, Northsea, Tiziana, and Rivus. He consults for Intercept, Pfizer, Salix, Sequana, Hemoshear, Terns, Albireo, Jannsen, Poxel, 89 Bio, Siemens, AstraZeneca, NGM Bio, Amgen, Regeneron, GenenTech, Alynylam, Roche, Covance, Prosciento, Histoindex, and Path AI. He received grants from Fractyl. He received royalties from Elsevier and Up-To-Date. The remaining authors have no conflicts to report.

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