A Multicenter, Open-Label, Single-Arm Study to Evaluate the Efficacy and Safety of Saroglitazar in Patients With Primary Biliary Cholangitis

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INTRODUCTION: **Patients with primary biliary cholangitis (PBC) without biochemical response to ursodeoxycholic acid (UDCA) are at increased risk of liver-related mortality. Saroglitazar is a novel peroxisome proliferator-activated receptor (PPAR) agonist with dual PPAR agonistic properties (α/γ). There is a strong mechanistic rationale for studying saroglitazar in PBC because PPARα is a molecular target of fibrates that showed improvements in liver tests in patients with PBC.**

METHODS: **In this 16-week, open-label, phase 3 study, 37 patients were screened across 3 clinical centers to enroll 7 patients. All patients received daily dose of saroglitazar 4 mg for 16 weeks in addition to their ongoing treatment with UDCA. The primary efficacy endpoint was the reduction in alkaline phosphatase (ALP) level at week 16 as compared to baseline.**

RESULTS: **Mean age of the study population was 51.1 ± 10.0 years, all patients were female of Mexican descent, and mean body mass index was 25.5± = 4.8 kg/m². Six (85.7%) patients reported taking ursodiol at baseline and continued throughout the study with a mean daily dosage of 417 mg. Among these, the daily dosage of UDCA 500 mg in 4 and 250 mg in 2 subjects, respectively. The mean baseline ALP level was 230 ± 103 U/L. The primary efficacy endpoint, mean change (reduction) from baseline in ALP concentration at week 16 based on the modified intent-to-treat population was −94 ± 53 U/L ($P = 0.003$), corresponding to a reduction of 48 ± 23%. Treatment with saroglitazar 4 mg resulted in a rapid and sustained decrease of ALP levels at week 4 (−84 ± 47 U/L, $P = 0.003$). Six patients who completed the study achieved mean ALP reduction of at least 40% at week 4 and all subsequent visits.**

DISCUSSION: **Although the study was terminated because of lack of enrollment, saroglitazar daily for 16 weeks resulted in rapid and sustained improvements in ALP with an acceptable safety profile in patients with PBC.**

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INTRODUCTION

Patients with primary biliary cholangitis (PBC) without biochemical response to ursodeoxycholic acid (UDCA) are at increased risk of liver-related mortality (1–3). Currently, there is only 1 approved drug, obeticholic acid, for use in these patients (4). Patients with PBC also suffer from fatigue and pruritus, with no therapies approved to treat either of these symptoms (5–7). Therefore, a treatment option that would address both hepatic and extrahepatic manifestations in patients with PBC is very desirable.

Saroglitazar is a novel peroxisome proliferator-activated receptor (PPAR) agonist with dual agonistic properties—it is a potent and predominant PPARα agonist with moderate PPARγ agonistic activity (8–11). There is a strong mechanistic rationale for studying saroglitazar in PBC because PPARα is a molecular target of fibrates that show improvements in liver enzymes and lipid profiles (1,12,13). Therefore, this study was designed to evaluate the safety, tolerability, and efficacy of saroglitazar in patients with PBC.

MATERIALS AND METHODS

Patients aged 18–75 years at the time of screening with a diagnosis of PBC based on the Practice Guidelines were enrolled in this study (5,6). Patients had to be on therapeutic doses of UDCA for

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≥12 months and on stable therapy for ≥3 months before enrollment. One entry criterion was an alkaline phosphatase (ALP) level of at least 1.67 times the upper limit of the normal (ULN) at both screening 1 and 2 visits with <30% variance between the ALP levels from screening visit 1 to 2 and total bilirubin less than or equal to 2 × ULN. All patients provided written informed consent before the study participation. This was a multicenter, prospective, open-label proof-of-concept study conducted to evaluate the efficacy and safety of saroglitazar 4 mg in patients with PBC treated for 16 weeks. The study protocol was reviewed and approved by the institutional review board at each participating institution. All eligible patients received a daily dose of saroglitazar 4 mg orally for 16 weeks in addition to their ongoing treatment with UDCA. Patients were followed every 4 weeks for clinical and biochemistry assessments. The primary efficacy endpoint was the reduction in ALP concentration level at week 16. It was analyzed using a modified intent-to-treat population that included all enrolled patients who received at least 1 dose of study drug and had at least 1 postbaseline efficacy assessment. Change from baseline in the primary and secondary efficacy parameters was analyzed using a paired *t* test. For this proof-of-concept study, no formal sample size estimation was performed. All statistical analyses were conducted using SAS software (version 9.4; SAS Institute, Cary NC).

RESULTS

A total of 37 patients were screened, and only 7 participants who met the study inclusion and exclusion criteria were enrolled from 3 participating medical centers in Mexico. The top reasons for screen failure include >30% variation of ALP with levels ≥1.67 × ULN between the 2 screening visits, elevated total bilirubin or international normalized ratio, or renal impairment (6 patients met 1 or more of these criteria). The other common reasons include inability to meet the PBC criteria, abnormal creatinine kinase, lipase or amylase levels (5 patients met 1 of more of these criteria), or <30% increase in aminotransferase. International normalized ratio or total bilirubin levels between the 2 screening visits (3 patients met 1 or more of these criteria). The ALP values at baseline for 3 patients were less than 1.67 times of ULN and were enrolled through a protocol exemption. All 7 patients were included in both efficacy and safety analysis. The demographic and baseline characteristics are presented in Table 1. Briefly, the mean age of the study population was 51.1 ± 10.0 years, all (100%) patients were female and of Mexican descent, and mean body mass index was 25.5± = 4.8 kg/m^2. Six (85.7%) patients reported taking ursodiol at baseline and continued throughout the study with a mean daily dosage of 417 mg. Among these, the daily dosage of UDCA 500 mg in 4 and 250 mg in 2 subjects, respectively. The mean baseline ALP level was 230 ± 103 U/L.

The primary efficacy endpoint mean change (reduction) from baseline in ALP concentration at week 16 based on the modified intent-to-treat population was −94 ± 53 U/L (P = 0.003) and corresponds to mean percentage reduction of 48% ± 23%. Treatment with saroglitazar 4 mg resulted in a rapid and sustained decrease of ALP levels at week 4 (−84 ± 47 U/L, P = 0.003) (Figure 1a). Six patients who completed the study achieved mean ALP reduction of at least 40% at week 4 and all subsequent visits (Figure 1b). For 1 patient who discontinued the study after the week 8 assessment, no clinically meaningful changes in ALP concentration were observed at week 8 445 IU/L) compared with baseline (436 IU/L). At week 16, 5 (71%) patients were within the ULN in ALP concentration, and 6 (86%) patients were within 1.67 × ULN.

The mean reduction in gamma-glutamyl transferase concentration, the other cholestasis-associated enzyme, was consistent with the primary efficacy endpoint (1A). No clinically relevant changes in total bilirubin were observed at week 16 (Figure 1c). The total bilirubin level for all patients was within the normal ranges both at baseline and at week 16. No clinically relevant changes in aspartate aminotransferase and alanine aminotransferase (ALT) were observed at week 16. At week 16, the mean reductions in total cholesterol, triglycerides, and low-density lipoprotein were 10.3%, 21.5%, and 14.0%, respectively (Figure 1d).

One patient discontinued the study by withdrawing consent after 8 weeks with no safety concerns. The adverse events occurred in 4 patients, and all of them were mild to moderate in severity. The adverse events that occurred in at least 2 patients were dry mouth, gastritis, gastroesophageal reflux disease, headache, nausea, and pruritus.

One patient had a hepatocellular pattern of liver enzyme elevations with ALT levels <3 × baseline at weeks 12 and 16 that worsened to 5–10 × ULN at week 20 and resolved spontaneously at follow-up. Briefly, this was a 51-year, Hispanic or Latino woman with BMI of 32.3 kg/m^2 enrolled with confirmed diagnosis of PBC. She was continued on UDCA and received saroglitazar for total study duration of 16 weeks. A 2.6× elevation of ALT from baseline was noted. At the safety visit (4 weeks after

Table 1. Select demographic, liver biochemistries, lipid panel, and use of UDCA at baseline

	Saroglitazar 4 mg (N = 7)
Age (yr)	51.1 ± 10.0
Female, n (%)	7 (100)
Race, Mexican, n (%)	7 (100)
BMI (kg/m^2)	25.5 ± 4.8
Liver biochemistries	
ALP (U/L)	230 ± 103
Total bilirubin (mg/dL)	0.5 ± 0.1
AST (U/L)	50 ± 9
ALT (U/L)	57 ± 24
GGT (U/L)	136 ± 60
Lipid panel	
Total cholesterol(mg/dL)	191 ± 36
Triglyceride(mg/dL)	116 ± 16
LDL (mg/dL)	113 ± 33
HDL (mg/dL)	65 ± 13
UDCA, daily dose (mg)	417 ± 129
Pruritus at baseline, n (%)	1 (14.3)

All values are reported in mean ± SD unless otherwise specified.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; UDCA, ursodeoxycholic acid.

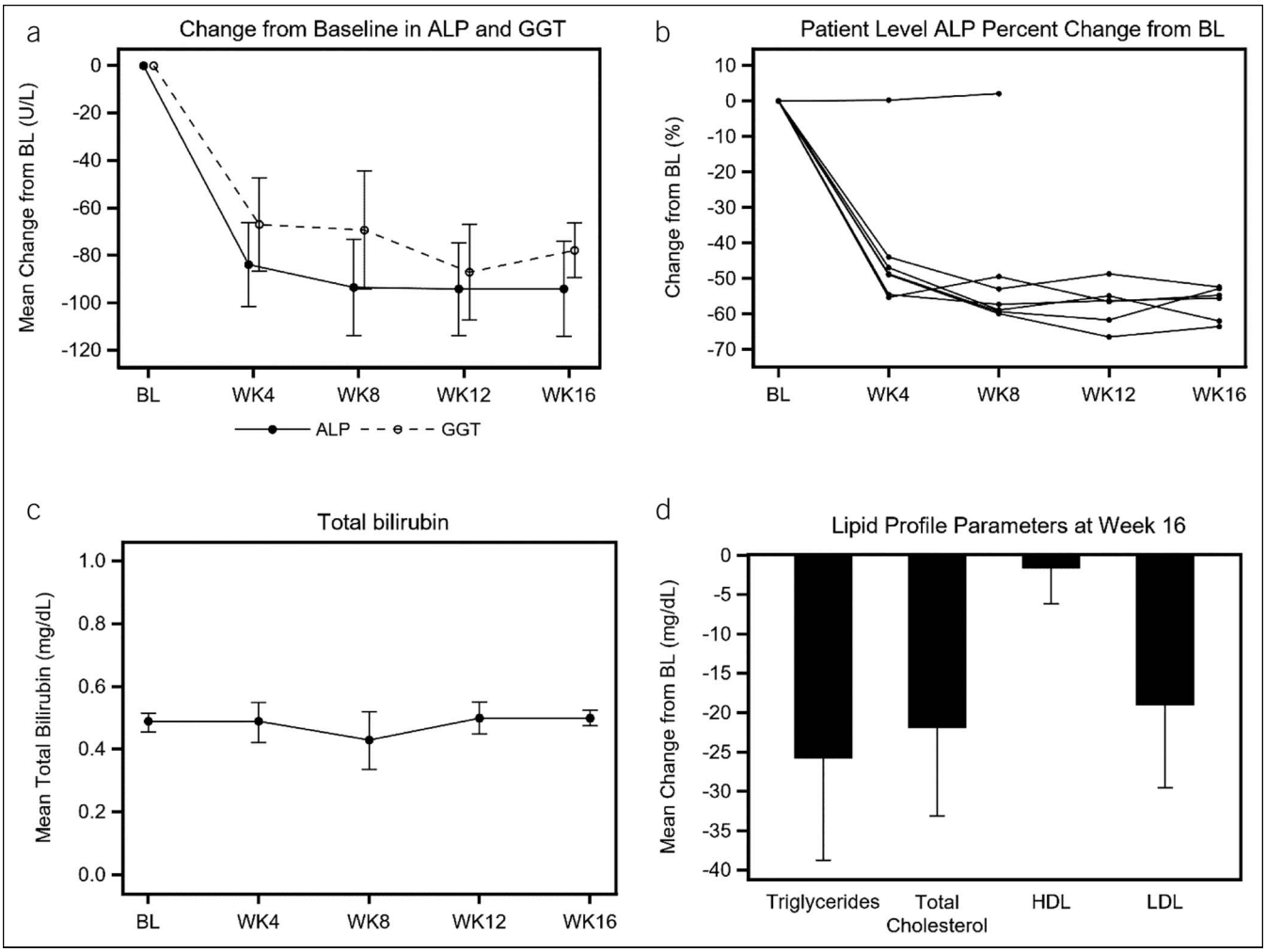

Figure 1. Trends of select liver biochemistries and lipid profile parameters during the study period. (**a**) Mean changes in ALP and GGT levels from BL at various study visits. Treatment with saroglitazar 4 mg resulted in rapid reduction of ALP concentration at week 4 (mean = −83.9 IU/L, SD = 46.9, $P = 0.003$) and sustained throughout the duration of treatment. The mean changes in GGT concentration was −69.2 IU/L (SD = 65.7, $P = 0.032$) and −77.7 IU/L (SD = 28.1, $P = 0.001$) for week 8 and week 16 which corresponds to a reduction of 49.6% and 60.8% at week 8 and week 12, respectively. (**b**) Change in ALP and gamma-glutamyl transferase levels compared with baseline at various study visits expressed as percent change from BL. Six patients who completed the study achieved mean ALP reduction of at least 40% at week 4 and all subsequent visits. For 1 patient who discontinued the study after the week 8 assessment, no clinically meaningful changes in ALP concentration were observed at week 8 (mean = 445 IU/L) compared with baseline (mean = 436 IU/L). At week 16, 5 (71.4%) patients were within the ULN in ALP concentration and 6 (85.7%) patients were within 1.67 × ULN. (**c**) Mean total bilirubin levels (mg/dL) at various study visits. (**d**) Mean changes in lipid panel parameters at week 16 as compared to baseline. At week 16, the mean reduction in total cholesterol was −22 ± 30 mg/dL ($P = 0.10$), triglycerides was −26 ± 34 mg/dL ($P = 0.096$), and low-density lipoprotein was −19 ± 28 mg/dL ($P = 0.122$) which corresponds to a reduction of 10.3%, 21.5%, and 14.0%, respectively. No clinically relevant changes were observed for high-density lipoprotein concentration. ALP, alkaline phosphatase; BL, baseline; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ULN, upper limit of the normal.

discontinuation of saroglitazar), the ALT levels were increased to 545 U/L (see Supplementary Figure 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A525). Serum total bilirubin levels remained well within the reference range throughout the course of the study. Unfortunately, no additional laboratory parameters were available until a year later when she was found to have a normal ALT at 19 U/L. The local study investigator attributed the liver enzyme elevations to underlying nonalcoholic fatty liver disease and intentional weight loss by the study participant. This case of suspected drug-induced liver injury was evaluated by an independent hepatic safety adjudication committee, and the event was considered as possibly related to saroglitazar. Liver enzyme elevations in the 500-U/L range were considered unlikely to be from underlying nonalcoholic fatty liver disease.

Overall, saroglitazar 4 mg was well-tolerated in PBC patients with no potentially life-threatening adverse events. Its effect on pruritus severity could not be assessed as there was only 1 patient with pruritus at baseline.

DISCUSSION

In this proof-of-concept study, saroglitazar seems to be a very promising therapeutic agent with rapid and sustained

biochemical response rates that far exceed any previous treatments for PBC. Its effect on pruritus could not be assessed because only 1 patient reported itching at baseline. Unfortunately, the study was closed because of a lack of enrollment from a high screen failure rate (81%). Although some of the screen failure rate could be inflated from inadequate prescreening such a not meeting the PBC criteria or renal impairment at baseline, most reasons seem to unanticipated and highlight the challenges with study enrollment. These include >30% variation in ALP and other liver test biochemistries. Enrollment into therapeutic clinical trials for PBC is challenging because of it being a rare disease with low prevalence in the general population. Currently, improvement in ALP levels or achieving a composite endpoint of ALP <1/67 × ULN, normal total bilirubin, and >15% decrease in ALP are recommended endpoints to assess therapeutic benefits per regulatory guidelines. This criteria for the most part require the sponsor to make sure that there are at least 2 baseline liver biochemistry values, at least 4 weeks apart with fluctuations that are not more than 30% to establish a stable ALP value at baseline. Unfortunately, this aspect of the study design adds additional challenge with study enrollment as encountered in the current study.

Saroglitazar also seems to be well-tolerated and safe, although the small sample size precludes any definitive conclusions. However, the 1 case of potential drug-induced liver injury observed in this study will likely result in evaluation of lower doses of saroglitazar. The results from an ongoing phase 2 trial in the United States examining 2 and 4 mg daily (ClinicalTrials.gov Identifier: NCT03112681) were recently reported, and there seems to be a dose-dependent increase in the incidence of patients with aminotransferase elevations. It is likely that lower dosage of 1 and 2 mg will be pursued in the phase 3 trial. Interestingly enough, no cases of hepatoxicity were reported in the phase 2 trial that evaluated saroglitazar for treatment of non-alcoholic steatohepatitis (14). The observation in the current trial only emphasizes the caution that must be exercised when similar doses of a study drug are used for drug development in cholestatic and parenchymal liver disorders.

In summary, the current proof-of-concept study supports the potential therapeutic role of saroglitazar as a treatment option for patients with PBC. This study also highlights the challenges associated with recruitment for a PBC trial in Hispanic or Latino population.

CONFLICTS OF INTEREST

Guarantor of the article: Raj Vuppalanchi, MD.

Specific author contribution: The authors of the study were responsible for data analysis, data interpretation, and manuscript preparation. All authors had full access to the study data and approved the manuscript before submission.

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Potential competing interests: None to report.

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Study Highlights

WHAT IS KNOWN

- ✓ Patients with primary biliary cholangitis who do not have biochemical improvement with ursodeoxycholic acid (UDCA) have limited treatment options.
- ✓ Fibrates downregulate bile acid biosynthesis through suppression of cholesterol 7-alpha hydroxylase (CYP7A1), the rate-limiting enzyme in bile acid biosynthesis.
- ✓ In combination with UDCA, fibrates have resulted in the improvement or normalization of alkaline phosphatase (ALP) levels. Saroglitazar, a novel peroxisome proliferator-activated receptor agonist, is an attractive treatment option because of its predominant peroxisome proliferator-activated receptor alpha activity resulting in decreased bile acid biosynthesis.

WHAT IS NEW HERE

- ✓ Saroglitazar in patients who have failed to respond to UDCA showed a significant reduction in ALP levels with approximately 50% decline compared with baseline at 16 weeks.
- ✓ The improvement in ALP was observed as early at 4 weeks and was sustained throughout the treatment duration.

TRANSLATIONAL IMPACT

- ✓ Measurement of fibroblast growth factor 19 and 7alpha-hydroxycholest-4-en-3-one (C4) may allow us to understand the mechanism through which saroglitazar may provide the therapeutic benefit.

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