PPAR agonists in Primary Biliary Cholangitis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Hilária Saugo Faria
Federal University of Santa Maria

Milene Vitória Sampaio Sobral
University of Western São Paulo

Victor Gonçalves Soares
Federal University of Vales do Jequitinhonha e Mucuri

Thainá Torres Cavalheiro
Federal University of Santa Maria

Beatriz Nishimoto
University of Western São Paulo

Rafaela Cunha Pirolla
University of Western São Paulo

Ana Paula Sampaio
Franciscan University

Ocilio Ribeiro Gonçalves
Federal University of Piauí

Daniela Gomez Costa
Federal University of Santa Maria

Eduardo Buzatti Souto
éduardo.souto@ufsm.br

Federal University of Santa Maria

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Abstract

Introduction

Agonists of the peroxisome proliferator-activated receptor (PPAR) have attracted attention for their potential to treat primary biliary cholangitis (PBC). However, individual trials lack sufficient power to detect significant differences in clinical and laboratory outcomes.

Objectives

This meta-analysis aims to compare PPAR agonists versus placebo or standard treatment in patients with PBC.

Methods

We systematically searched PubMed, Embase and Cochrane for studies comparing PPAR agonists with placebo or standard-of-care treatment in PBC. The primary outcomes were pruritus, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and total and direct bilirubin levels. We performed statistical analyses using R 4.1.1. Heterogeneity was examined with the Cochran Q test and $I^2$ statistics. We computed risk ratios (RR), mean differences (MD), and Standardized Mean Differences (SMD), with 95% confidence intervals (CI), using a random-effects model.

Results

Thirteen randomized controlled trials were included in this meta-analysis, comprising 1,124 patients, of whom 687 (57%) received PPAR agonists plus UDCA. When compared with control, PPAR analogs were significantly associated with a reduction in pruritus (RR 0.63; 95% CI 0.41 to 0.96; p = 0.031; $I^2=9\%$), ALP (MD -130.93; 95% CI -156.44 to -105.42; p < 0.01; $I^2=84\%$), GGT (MD -39.83; 95% CI -78.44 to -1.22; p = 0.04; $I^2=94\%$) and total bilirubin levels (SMD − 0.03; 95% CI -0.06 to -0.01; p < 0.01; $I^2=69\%$).

Conclusion

The use of PPAR agonists reduced the incidence of pruritus and the levels of ALP, GGT, and total bilirubin in patients with PBC.

1. Introduction

Primary biliary cholangitis (PBC) is an autoimmune disease characterized by inflammation and destruction of intrahepatic bile ducts. [1] Global prevalence is approximately 35 to 40 people per 100,000 inhabitants, which varies heterogeneously among countries and is predominantly found in females. [2–6] The increasing number of cases raises a public health alert as it can progress to hepatic fibrosis, cirrhosis, and complications such as portal hypertension and hepatocellular carcinoma. [7] The only medications approved by the Food and Drug Administration (FDA) are ursodeoxycholic acid (UDCA) and...
obeticholic acid (OCA), as an adjunctive agent to UDCA or monotherapy in UDCA-intolerant patients. [8, 9] However, 40% of patients do not respond adequately to UDCA and OCA frequently leads to pruritus and treatment discontinuation. [7, 10]

On the other hand, PPAR ligands are receiving much interest due to positive results obtained in clinical trials, especially regarding reduction in pruritus. PPARs, nuclear receptors responsible for regulating the transcription of genes involved in inflammation, inhibit the expression and duration of action of pro-inflammatory cytokines, reducing acute and chronic inflammatory processes. [7] The protective role of PPARs in the regulation of carcinogenesis and metabolic pathways makes them essential molecular targets for cholestatic liver diseases, such as PBC. [7, 11, 12] However, individual trials lack sufficient power to detect significant differences in outcomes, posing significant challenges to the use of PPARs agonists as recommended drugs for PBC treatment. [13]

Previous meta-analyses evaluated the use of fibrates in the treatment of patients with PBC [14–17] and a recent one compared the use of PPAR agonists to UDCA regards alkaline phosphatase levels. [18] However, no previous meta-analysis has focused on investigating the potential outcomes of fibrates and non-fibrate PPAR agonists in a larger population. Therefore, we aimed to perform a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing PPAR agonists versus placebo or standard treatment in patients with PBC.

2. Material and Methods

This systematic review and meta-analysis was performed in accordance with the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines. [19] As such, it was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under protocol CRD42024527779.

2.1 Search strategy and data extraction

MEDLINE, Embase, and Cochrane Central Register of Controlled Trials were systematically searched from inception to March 2024 with the following search terms: ("Primary Biliary Cholangitis" OR PBC) AND (Bezafibrate OR Fenofibrate OR Saroglitazar OR saroglitazar OR Seladelpar OR Elafibranor OR "PPAR agonist" OR "PPAR agonists"). The references from all included studies were also searched manually for any additional studies. Two authors (B.N. and T.T.) independently extracted the data following predefined search criteria and quality assessment. Disagreements were resolved by consensus between the authors.

2.2 Eligibility criteria

Inclusion in this meta-analysis was restricted to studies that met all the following eligibility criteria: (1) RCTs that directly compared PPAR agonists with placebo or standard of care treatment; (2) enrolling patients with PBC. In addition, there was no restriction on follow-up. We excluded studies with (1) no
control group; (2) population overlap (i.e. overlapping institutions and recruitment periods); (3) patients without PBC; (4) no outcomes of interest. Conference abstracts, case reports, editorials or reviews were also excluded. The corresponding authors were contacted in case of missing data from individual studies.

### 2.3 Endpoints and subgroup analyses

The endpoints of interest were the incidence of pruritus and the mean change in alkaline phosphatase levels (ALP), gamma-glutamyltransferase (GGT), and total and direct bilirubin levels. We assessed the incidence of nausea, headache, fatigue, myalgia, diarrhea, abdominal pain, normalization of ALP levels, laboratory abnormalities, and serious treatment adverse events. The mean change in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were also analyzed. The definitions of normalization of ALP levels, laboratory abnormalities, and serious treatment adverse events were described respectively as adequate biochemical response rate, as established by the Barcelona, Paris-I, Paris-II and Toronto I criterias, kidney dysfunction, elevated levels of creatine phosphokinase, rapid elevation of serum levels of creatinine, and aminotransferases in grades 1, 2 and 3, in addition to slight changes in total bilirubin and albumin; and serious adverse events that occurred as a result of the experimental treatment.

### 2.4 Quality assessment

Quality assessment of RCTs was performed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (RoB-2), in which studies are scored as high, low, or unclear risk of bias in 5 domains: selection, performance, detection, attrition, and reporting biases. [20] The risk of bias was performed independently by two authors (M.V.S.S. and O.R.G.). Disagreements were resolved by consensus between authors. Publication bias was assessed with contour-enhanced funnel plot analysis [21] and Egger's test [22] of efficacy endpoints and evaluation for symmetrical distribution of trials with similar weights, using the Pustejovsky and Rodgers [23] approach when standardized mean difference was used for the outcome of interest.

### 2.5 Statistical analysis

Treatment effects were compared using standardized mean differences (SMD), with 95% confidence intervals (CI), for outcomes for which studies reported different measures of units, and mean differences (MD), with 95% CI, for continuous outcomes. risk ratios (RR), with 95% CI, were used for binary endpoints. Given the expected heterogeneity between studies, we adopted the DerSimonian and Laird random-effects model for all outcomes reported. We used the Cochran Q test and $I^2$ statistics to assess for heterogeneity; P values inferior to 0.1 and $I^2 > 40\%$ were considered significant for heterogeneity. R version 4.1.2 (The R Foundation, 2021) was used for statistical analysis.

### 2.6 Sensitivity analysis

We performed a pre-specified sensitivity analysis for efficacy and primary endpoints with (1) a leave-one-out approach to ensure that results were not dependent on a single study and to evaluate studies that
had high contributions to the heterogeneity on efficacy endpoints when $I^2 \geq 40$; (2) several univariable meta-regression analyses to assess any interactions with some covariates (PPAR agonists’ dosages; time of follow up measured in weeks; mean ALP levels at baseline) for the outcomes reported by at least 10 studies[24]. In addition, for outcomes with high heterogeneity, we performed subgroup analysis according to (1) time of follow up (12 to 35 weeks and 52 to 104 weeks) and (2) type of PPAR agonist (benzafibrate, fenofibrate, seladelpar, and elafibranor).

3. Results

3.1 Study selection and characteristics

As detailed in Figure 1, the initial search yielded 913 results. After the removal of duplicate records and ineligible studies, 36 remained and were fully reviewed based on inclusion criteria. Of these, a total of 13 randomized controlled trials (RCTs) [25–38] were included, comprising 1,124 patients. A total of 687 (61.1%) patients were in the intervention group, of which 27 (3.9%) received saroglitazar, 138 (20.1%) received elafibranor, 87 (12.6%) received fenofibrate, 331 (48.2%) received seladelpar and 104 (15.1%) received bezafibrate. Study characteristics are reported in Table 1. The total number of women in the study was 1039 (92.4%). The mean age of participants was 55.6 years. Mean ALP level at baseline was 325.2 units/liter. Thirteen studies administered UDCA or allowed its continuation for both groups. [25–29,31–38] In addition, ten studies included patients with unresponsive or inadequate biochemical responses to UCDA. [25–31,33,34,36] Finally, there was a significant variability of follow-up duration between the studies. (Table 1)

3.2 Pooled analysis of all studies

In those patients receiving PPAR agonists, the ALP (MD -130.93, 95% CI -156.44 to -105.42, $p<0.01$, $I^2=84\%$, Figure 2), GGT (MD -39.83, 95% CI -78.44 to -1.22, $p=0.04$, $I^2=94\%$, Figure 3) and total bilirubin levels (SMD -0.03, 95% CI -0.06 to -0.01, $p<0.01$, $I^2=69\%$, Figure 4) were significantly lower when compared to control group. There was no statistically significant difference in terms of direct bilirubin (SMD 0, 95% CI -0.05 to 0.04, $p=0.91$, $I^2=60\%$, Figure 5), AST (MD -1.85, 95% CI -5.72 to 2.02, $p=0.35$, $I^2=64\%$, Supplementary Figure 2) and ALT levels (MD -5.15, 95% CI -12.48 to 2.19, $p=0.17$, $I^2=85\%$, Supplementary Figure 3).

PPAR agonists significantly reduced the incidence of pruritus (RR 0.63, 95% CI 0.41 to 0.96, $p=0.031$, $I^2=9\%$, Figure 6) when compared to the control group. The normalization of ALP levels (RR 10.65, 95% CI 2.18 to 52.01, $p=0.003$, $I^2=83\%$, Supplementary Figure 4) was significantly higher when compared to the control group. However, the incidence of abdominal pain (RR 1.91, 95% CI 1.04 to 3.53, $p=0.038$, $I^2=0\%$, Supplementary Figure 5) and laboratory abnormalities (RR 2.15, 95% CI 1.37 to 3.37, $p<0.001$, $I^2=0\%$, Supplementary Figure 6) were significantly higher in the PPAR agonists group.

There was no statistically significant difference in terms of nausea (RR 1.65, 95% CI 0.89 to 3.05, $p=0.112$, $I^2=0\%$, Supplementary Figure 7), headache (RR 1.78, 95% CI 0.67 to 4.72, $p=0.244$, $I^2=37\%$, Supplementary Figure 8).
Supplementary Figure 8), fatigue (RR 0.85, 95% CI 0.56 to 1.28, p=0.436, $I^2=19\%$, Supplementary Figure 9), myalgia (RR 1.59, 95% CI 0.68 to 3.72, p=0.282, $I^2=0\%$, Supplementary Figure 10), and diarrhea (RR 0.68, 95% CI 0.32 to 1.48, p=0.337, $I^2=5\%$, Supplementary Figure 11).

3.3 Subgroup analyses in selected populations

In a subanalysis restricted to studies with 12 to 35 weeks (MD -152.67, 95% CI -164.99 to -140.35, p<0.01, $I^2=36\%$, Supplementary Figure 12) and 52 to 104 weeks (MD -111.20, 95% CI -139.91 to -82.49, p<0.01, $I^2=86\%$, Supplementary Figure 12) of follow-up, the change in ALP levels was significantly reduced in the PPAR agonists group compared to the control group. In addition, in a subanalysis restricted to type of PPAR agonist, ALP levels were significantly reduced in the intervention group compared to the control group: seladelpar (MD -104.05, 95% CI -122.63 to -85.47, p<0.01, $I^2=0\%$, Supplementary Figure 13), elafibrinor (MD -128.78, 95% CI -161.09 to -96.47, p<0.01, $I^2=68\%$, Supplementary Figure 13), bezafibrate (MD -169.11, 95% CI -191.59 to -146.62, p<0.01, $I^2=31\%$, Supplementary Figure 13), and fenofibrate (MD -95.34, 95% CI -150.38 to -40.31, p<0.01, $I^2=83\%$, Supplementary Figure 13).

3.4 Sensitivity analyses

The leave-one-out analysis showed the robustness of the pooled results for the levels of ALP, direct and total bilirubin. Leave-one-out analysis for the normalization of ALP levels was also consistent with the pooled results. For those outcomes, there was no significant variability in effect size with the removal of each study. For the continuous outcomes, it was not possible to identify one single study responsible for the high heterogeneity, so we identified the study that rendered the lowest heterogeneity possible for each outcome.

Meta-regression analysis for the outcome of ALP levels showed that the heterogeneity remained high ($I^2$) and the p-value for the test of significance of the model (QMp) was not significant, independently of the chosen predictor. For the outcome of GGT levels, the heterogeneity remained high independently of the chosen predictor. However, the value of ALP at baseline was a statistically significant predictor of GGT levels (QMp = 0.049) and explained 23.8% of the outcome's variance. For the outcome of total bilirubin levels, the heterogeneity was reduced below the 25% threshold independently of the chosen predictor. The remaining heterogeneity ranged from 17.94% to 0.05%. The time of follow up and the PPAR dosage were statistically significant predictors of total bilirubin levels (QMp = 0.029 and 0.009, respectively) (Supplementary Table 1).

3.5 Quality assessment

Individual bias assessment is reported in Supplementary Figure 1. RCTs were evaluated using Rob2. Seven studies lost points in domains related to deviation from intended interventions or outcome measurement. [29–35] A crossover study was assessed using Rob2 for crossover, considered at high risk of bias due to insufficient time for carryover effects to dissipate before outcome assessment in the
second period and lack of blinding of participants and assessors. [38] The remaining studies were considered at low risk.

Publication bias was investigated for the outcomes of ALP, GGT, and total bilirubin levels, as at least 10 studies were available. Overall, some outcomes showed asymmetry of the funnel plots, but the possibility of small study effect was contradicted by a more profound analysis with the help of the enhanced contour and Egger’s Test (Supplementary Table 2) in most cases.

4. Discussion

In this systematic review and meta-analysis of 13 RCTs, including 1,198 patients, the safety and efficacy of PPAR analogs were compared with placebo plus UDCA or UDCA monotherapy in patients with PBC. The main findings from the combined analysis were: (1) reduction in ALP and GGT levels in patients that received PPAR analogs; (2) PPAR analogs were associated with a lower incidence of pruritus; and (3) there was no difference between the intervention and control groups in fatigue incidence.

PBC is a progressive autoimmune disease that primarily affects middle-aged women. [39] The pathophysiology of the disease is related to injury to the bile ducts by the immune system’s attack. Due to epithelium inflammation, bile excretion is impaired, causing bile accumulation in the gallbladder and reflux of substances to the liver. [40] Among the main substances are bile salts with hepatotoxic potential, which, when returning to the liver, stimulate the synthesis of ALP, reflecting hepatocyte and ductal cell distress. Recent studies demonstrated the benefits of PPAR analogs in laboratory markers by reducing bile acid toxicity and associated lesions. [41] As observed in a recent RCT, 400 mg of benzafibrate per day for 104 days resulted in a reduction of 20 U/L in ALP levels. [27] These data corroborate the findings of our meta-analysis, in which the medication was associated with a reduction in ALP.

Furthermore, liver damage resulting from the action of bile secretion also leads to increased levels of GGT, a hepatic enzyme marking oxidative stress. Although some findings lacked sufficient statistical power to demonstrate a difference in GGT levels, [35, 38] the pooled analysis points to the benefits of PPAR analogs compared to placebo or standard treatment. Benzafibrate, seladelpar, saroglitazar, and elafibrinor act on reducing the production of interleukins and bile acid toxicity in patients with PBC, reducing liver injury and improving the biochemical profile. [42] Among the studies included in our meta-analysis, a recent RCT showed the greatest change from baseline, with a reduction of 113.64 U/L. In this study, patients received a daily dose of 2 and 4 milligrams of saroglitazar or placebo, with the continued use of UCDA in both groups, for 16 weeks. It is important to note that these results reveal that the change from baseline is not directly dependent on the medication dosage, as 2 milligrams of saroglitazar are associated with a greater reduction in GGT than the dosage of 4 milligrams. [37]

Although the data are promising, it is essential to address potential side effects before considering these medications as adjunctive treatment to UCDA in PBC patients. Overall, PPAR analogs were considered safe. Regarding pruritus, this meta-analysis revealed an incidence in 8.9% of PPAR analog users,
whereas among those who received placebo or standard treatment, the incidence was 12.9%. In this sense, it is important to highlight that recent studies reveal the potential of PPAR signaling in improving pruritus, an important symptom of PBC, due to the control of cytokine release and consequently immunological balance. This data reveals the potential of PPAR analogs not only in improving the biochemical and clinical profile of patients but also as an alternative to reducing medication side effects. Regarding fatigue, no significant differences were found between the two groups. [27]

This study has some limitations. First, the follow-up period of the included studies ranged between 3 to 478 weeks. To explore this heterogeneity, subgroup analysis was performed, stratifying studies by periods of 12 to 35 weeks and 52 to 104 weeks. Meta-regression analyses also showed no relation between the follow-up period and the observed results for ALP, GGT and direct bilirubin. Second, we utilized data only from the first part of Itakura et al. trial since there was not a washout period. This could introduce a potential unit-of-analysis error to this meta-analysis. This type of error results in losses of the information collected. In addition, if the data are available, they are likely to represent a biased subset of trials. [43] Third, patients with different baseline characteristics were pooled together. Therefore, we performed meta-regressions addressing the influence of PPAR agonists’ dosage, ALP and GGT levels on the primary endpoints that had at least 10 trials. [24]

5. Conclusion

In summary, the use of PPAR analogs plus UDCA was associated with a greater reduction in serum levels of ALP, GGT, and total bilirubin in patients with PBC. Additionally, there was a greater normalization of ALP levels, as well as a lower incidence of pruritus as an adverse event. These findings suggest that PPAR analogs should be considered as an adjuvant therapy to UDCA for the PBC treatment.

Abbreviations

PBC
Primary Biliary Cholangitis
UDCA
Ursodeoxycholic Acid
ALP
alkaline phosphatase
GGT
gamma-glutamyltransferase
AST
aspartate aminotransferase
ALT
alanine aminotransferase

Declarations
Disclosures: All authors report no relationships that could be construed as a conflict of interest. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Author Contribution

HSF conceived and designed the study. TTC and BN independently assessed the studies for possible inclusion and collected the data. RCP extracted the baseline characteristics. HSF, APS, TTC, BN, MVS and VGS extracted the data. HSF and VGS were responsible for data interpretation. MVS and ORG analyzed the quality assessment of included studies. All authors were responsible for writing the final version. DGC and EBS made general supervision. All authors approved the final version of the manuscript.

Data Availability

Data is provided within the manuscript or supplementary information files.

References


34. C. Li et al., ‘A randomized, controlled trial on fenofibrate in primary biliary cholangitis patients with incomplete response to ursodeoxycholic acid’, *Ther Adv Chronic Dis*, vol. 13, p. 204062232211141,


### Tables

Table 1 is available in the Supplementary Files section.

### Figures
Figure 1

PRISMA flow of included studies.
Figure 2

PPAR agonists significantly reduced the levels of ALP compared with the control group.

![Image](image1.png)

Figure 3

PPAR agonists significantly reduced the levels of GGT compared with the control group.

![Image](image2.png)
Figure 4

PPAR agonists significantly reduced the levels of total bilirubin compared with the control group.

Figure 5

There was no statistically significant difference in terms of direct bilirubin levels.
Figure 6

PPAR agonists significantly reduced the incidence of pruritus compared with the control group.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TABLE1.docx
- SUPPLEMENTARYMATERIAL.docx