Liver International

WILEY

Liver INTERNATIONAL

ORIGINAL ARTICLE OPEN ACCESS

Second-Line Treatment for Patients With Primary Biliary Cholangitis: A Systematic Review With Network Meta-Analysis

Edoardo G. Giannini[1,2,3] | Andrea Pasta[1,2] | Francesco Calabrese[1,2] | Sara Labanca[1,2] | Simona Marenco[1,2] | Giulia Pieri[1,2] | Maria Corina Plaz Torres[1,2] | Mario Strazzabosco[3]

[1]Gastroenterology Unit, Department of Internal Medicine, University of Genoa, Genoa, Italy | [2]Gastroenterology Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy | [3]Liver Center, Digestive Diseases Section, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut, USA

Correspondence: Edoardo G. Giannini (egiannini@unige.it)

Received: 27 August 2024 | **Revised:** 11 November 2024 | **Accepted:** 9 December 2024

Funding: The authors received no specific funding for this work.

Keywords: bezafibrate | elafibranor | obeticholic acid | response | seladelpar | treatment | ursodeoxycholic acid

ABSTRACT

Background & Aims: Approximately 40% of patients with Primary Biliary Cholangitis (PBC) show incomplete response to ursodeoxycholic acid, thus needing second-line treatment to prevent disease progression. As no head-to-head comparison study is available, we used a network meta-analysis (NMA) to compare efficacy and safety of available second-line therapies.

Methods: We performed a systematic literature review including randomised, placebo-controlled trials of patients with PBC and incomplete response, or intolerance, to ursodeoxycholic acid, and compared relative risks (RRs) for primary (biochemical response at 52-week) and secondary outcomes [incidence of new-onset pruritus and serious adverse events (SAEs)].

Results: The NMA included three studies, each testing obeticholic acid (OCA), seladelpar or elafibranor versus placebo (active therapy/placebo: 379/191 patients). All treatments significantly increased the RR for biochemical response with an advantage of elafibranor versus seladelpar (RR: 4.37, 95% CI: 1.01–18.87). OCA 5–10 mg/10 mg was associated with a higher risk of new-onset pruritus compared to placebo (RR: 1.43; 95% CI: 1.09–1.88/RR: 1.79; 95% CI: 1.37–2.33), while seladelpar decreased this risk (RR: 0.30; 95% CI: 0.12–0.80). Compared to placebo, OCA 5–10 mg/10 mg was associated with an increased risk of SAE (RR: 3.82; 95% CI: 1.46–10.02/RR 2.67; 95% CI: 1.00–7.08).

Conclusions: Among second line therapies for patients with PBC, elafibranor is slightly more effective in obtaining biochemical response than seladelpar that, on the other hand, is the only drug associated with a lower incidence of pruritus. While of similar efficacy, OCA was associated with increased pruritus and SAEs. These findings may help personalise second-line treatment in patients with PBC.

Abbreviations: 95% confidence interval, 95% CI; Committee for Medicinal Products for Human Use, CHMP; European Medicine Agency, EMA; Farnesoid X receptor agonists, FXR; Network meta-analysis, NMA; Obeticholic acid, OCA; Peroxisome proliferator-activated receptor, PPAR; Primary Biliary Cholangitis, PBC; Relative risk, RR; Risk difference, RD; Serious adverse events, SAEs; Upper limit of normal, ULN; Ursodeoxycholic acid, UDCA.

Edoardo G. Giannini and Andrea Pasta have contributed equally to the manuscript.

Summary

- The comparative efficacy, and safety, of second-line therapies in patients with Primary Biliary Cholangitis is unknown.
- In this systematic review and network meta-analysis including three randomised, placebo-controlled trials with 570 participants, treatment with elafibranor was associated with higher efficacy in inducing biochemical response at 52-week, while seladelpar was associated with a decreased risk of new-onset pruritus. Obeticholic acid showed similar efficacy to elafibranor and seladelpar, although was associated with an increased risk of severe adverse events.
- These findings can be used in clinical practice to personalise second-line treatment and inform decisions for patients with a rare disease such as Primary Biliary Cholangitis.

1 | Introduction

Primary Biliary Cholangitis (PBC) is an autoimmune, chronic, cholestatic liver disease that mainly affects middle-aged female patients, and whose incidence and prevalence are on the rise [1, 2]. Despite being an autoimmune disease, PBC has an unsatisfactory response to immune suppressive therapy, but responds to treatment with bile acids or to drugs that activate transcription factors relevant for bile acids metabolism [peroxisome proliferator-activated receptor (PPAR) or farnesoid X receptor agonists (FXR)] [3]. Therapy with ursodeoxycholic acid (UDCA)—a tertiary hydrophilic bile acid—prevents progression of disease and liver-related events in patients with biochemical response to treatment—a serum alkaline phosphatase level less than 1.67 times the upper limit of normal (ULN) and a reduction of ≥ 15% from baseline, with total bilirubin at or below the ULN [4–6]. Biochemical response is associated with improved liver-related prognosis, and longer liver transplantation-free period [5–7]. Unfortunately, up to 40% of patients have an incomplete biochemical response to UDCA, and a small fraction of treated patients is intolerant to the drug [8]. These patients remain at an increased risk of progression of disease, liver-related death and need for liver transplantation [3–5]. For these patients, obeticholic acid (OCA)—an FXR agonist—received conditional approval as second-line treatment, based on the results of a Phase III, 12-month, randomised, placebo-controlled trial that demonstrated its efficacy in improving biochemical endpoints [9]. In this study, OCA reached the composite primary endpoint of decrease in serum ALP and normalisation of bilirubin in approximately 47% of patients compared to 10% of placebo-treated patients, with new-onset pruritus emerging as the main adverse event [9]. In addition, real-world studies strongly suggested that second-line OCA treatment was associated with improved transplant-free survival as compared to historical cohorts [10, 11]. Later, the use of OCA was restricted to patients with compensated liver disease without portal hypertension, due to the emergence of potential toxicity in patients with more advanced disease [12, 13].

Recently, two Phase III, randomised, placebo-controlled trials showed the efficacy and safety of either seladelpar—an α-PPAR agonist—or elafibranor—a double α- and δ-PPAR agonist—on biochemical response in patients with incomplete response, or intolerant, to UDCA [14, 15]. Both trials were positive, with a response rate, as compared to placebo of 61.7% versus 20.0% and 21.0% versus 4.0% in the seladelpar and elafibranor trials, respectively, with no emerging safety signals associated with either drug, and seladelpar showing significantly improved pruritus scores among patients who had moderate-to-severe pruritus at baseline [14, 15].

As of today, no direct, head-to-head study compared the safety and efficacy of second-line treatments for patients with PBC (OCA and PPAR-agonists), and therefore there is no evidence that may potentially guide treatment decisions. Thus, with the aim to support future clinical decision-making in a potentially complex setting, we indirectly compared the efficacy and safety data of randomised, controlled second-line trials for patients with PBC using a systematic review with network meta-analysis (NMA).

2 | Materials and Methods

We conducted a systematic review with NMA to summarise and compare the available evidence on second-line therapies for the treatment of patients with PBC. The studies included in our search strategy met the following criteria: (I) Phase III, randomised, placebo-controlled trials, (II) inclusion of patients showing incomplete response, or intolerance, to UDCA and (III) evaluation of biochemical response after 1-year of treatment as the primary endpoint, defined by an ALP level less than 1.67 times the ULN and a reduction of ≥ 15% from baseline, with total bilirubin at or below the ULN. The study protocol was registered with PROSPERO (CRD42024569721). Ethical approval was not required for this evidence synthesis.

2.1 | Search Strategy

A literature review was performed using Ovid (Embase, Scopus, and Web of Science) and PubMed until 4 July 2024. Conference abstracts from leading gastrointestinal journals were also reviewed, and grey literature was searched using Google (www.google.com) and Yahoo (www.yahoo.com). The comprehensive search strategy is reported in Table S1. Two independent authors (AP and FC) screened all titles and abstracts retrieved from the databases, excluding duplicate records and studies not meeting the eligibility criteria. Full-text articles were obtained via institutional access or open-access licences and underwent further review to identify manuscripts suitable for data extraction. Discrepancies were resolved through discussion with a third author (EGG). Reviews, editorials, commentaries and other non-original studies were excluded.

2.2 | Primary and Secondary Endpoints

The main outcome measured was the biochemical response at Week 52, characterised by an ALP level less than 1.67 times the

ULN, a decrease of 15% or more from the baseline, and total bilirubin at or below the ULN. Additional secondary endpoints included the relative reduction in ALP levels, the incidence of new-onset pruritus considered as an adverse event, and the occurrence of serious adverse events (SAEs).

2.3 | Data Synthesis and Analysis

Primary data from the studies included were extracted and systematically recorded into dedicated data collection forms. We extracted the baseline characteristics of all studies, including patients' age, sex, race, disease duration and concomitant use of UDCA. Additionally, baseline levels of ALP and bilirubin, as well as liver stiffness, were recorded. To assess potential biases associated with the design, conduct, and reporting of the randomised controlled trials, we employed the Cochrane risk-of-bias assessment tool. This tool evaluates seven distinct domains of potential bias, categorising each as either 'low' or 'high' risk [16].

Continuous data were synthesised and analysed using mean and standard deviation. Standard deviations of the mean difference were obtained as previously reported [17]. Whereas the outcome measures were reported in median and interquartile range or 95% confidence interval (95% CI), mean and standard deviation values were estimated using previously described methodology [18]. The efficacy of each comparison was assessed using a pooled relative risk (RR) with 95% CIs, employing a random effects model as a conservative estimate. The risk difference (RD) with 95% CIs was also calculated to provide additional insight into the absolute effect size. Pooled least square mean difference from placebo with 95% CIs was used to represent variation in continuous parameters [19]. Heterogeneity was measured using the I^2 statistic, ranging from 0% to 100%, and the τ^2 statistic, with thresholds of approximately 0.04, 0.16 and 0.36 representing low, moderate, and high levels of heterogeneity, respectively [20]. Analyses were performed using the frequentist model in STATA BE version 18 (StataCorp. 2023, Stata Statistical Software: Release 18, Texas, USA) with the statistical package mvmeta.

3 | Results

A total of 2193 records were initially identified, with 1075 remaining after removal of duplicates. After screening, 15 articles were finally assessed for eligibility. Among them, one study was excluded as it was a Phase II study and 11 studies were excluded due to different endpoints [21]. In particular, one Phase III randomised clinical trial comparing bezafibrate to placebo (BEZURSO trial) was excluded because it considered different inclusion criteria and endpoints, while a Phase III, randomised, placebo-controlled study comparing two different seladelpar doses (ENHANCE trial) was not included as it was terminated early following an erroneous safety signal in a non-alcoholic steatohepatitis trial, and therefore efficacy data were assessed at 3- rather than 12-month as initially planned [22, 23]. Eventually, three Phase III, randomised, placebo-controlled trials were included in this NMA. Figure S1 shows the sorting process of the publications. The Phase III randomised clinical trials included in the NMA tested the safety and efficacy of OCA 5–10 mg, or 10 mg, versus placebo (POISE trial), seladelpar 10 mg versus placebo (RESPONSE trial) and elafibranor 8 mg versus placebo (ELATIVE trial) [9, 14, 15].

The network plot is provided in Figure S2. The inclusion criteria were consistent across the three trials considered, but in the RESPONSE trial, patients were also required to have aspartate and alanine aminotransferase levels greater than three times the ULN at inclusion [16]. The risk of bias was judged to be low for all three studies (Table S2), and considering the inclusion of only one study per active treatment heterogeneity remained low with both methods used (I^2 and τ^2 statistics).

Overall, 570 patients were included in the NMA, and among them 379 (66.5%) received an active therapy, while 191 (33.5%) received placebo. Table S3 reports the baseline characteristics of the populations included in the trials, showing homogeneity in the main characteristics among the intervention groups. Mean age was 56.6 ± 9.8 years, and most patients were female 477 (83.7%). The majority of patients ($n = 534$, 93.7%) were incomplete responders to UDCA, and 36 patients (6.3%) were intolerant to the drug.

3.1 | Efficacy on the Achievement of Biochemical Response and Alkaline Phosphatase Reduction

Focusing on primary endpoint, 53.0% of patients treated with an active therapy and 15.2% of patients on placebo reached the biochemical response (i.e. ALP level less than 1.67 times the ULN, a decrease of 15% or more from the baseline, and total bilirubin at or below the ULN). In detail, the RR of response was 4.85 (95% CI: 2.3–10.23) and 4.86 (95% CI: 2.3–10.24) with OCA 5–10 mg and 10 mg, respectively, 3.09 (95% CI: 95% CI, 1.86–5.11) with seladelpar, and 13.50 (95% CI: 3.42–53.22) with elafibranor (Figure 1A). Moreover, we also assessed the relative response of the single active arms as compared to placebo, and this analysis showed a RD of 0.37 (95% CI: 0.26–0.48) for both OCA 5–10 mg and OCA 10 mg, 0.42 (95% CI: 0.29–0.55) for seladelpar, and 0.47 (95% CI: 0.36–0.58) for elafibranor (Figure 1B).

Table 1 reports the direct and indirect comparisons for biochemical response at 12-month for all treatments. All active treatments were superior to placebo, while indirect comparisons showed that elafibranor was significantly more effective than seladelpar (RR 4.37, 95% CI: 1.01–18.87), while no significant differences were observed in indirect comparisons among the other treatments [seladelpar vs. OCA 5–10 mg and 10 mg: 0.64 (95% CI: 0.26–1.57) and 0.64 (95% CI: 0.26–1.56); elafibranor vs. OCA 5–10 mg and 10 mg: 2.78 (95% CI: 0.58–13.28) and 2.78 (95% CI: 0.58–13.25)].

Figure S3 shows the variations in ALP levels over 12-month of treatment, with no significant difference among the various drugs. More in detail, all drugs were associated with a decrease in ALP, with mean relative difference compared to baseline of −30.4 (95% CI: −48.4 to −12.4) and − 36.8 (95% CI: −55.9 to −17.8) for OCA 5–10 mg and 10 mg, respectively, −38.2 (95% CI: −46.3 to −30.1) for seladelpar, and − 40.6 (95% CI: −47.8 to −33.5) for elafibranor.

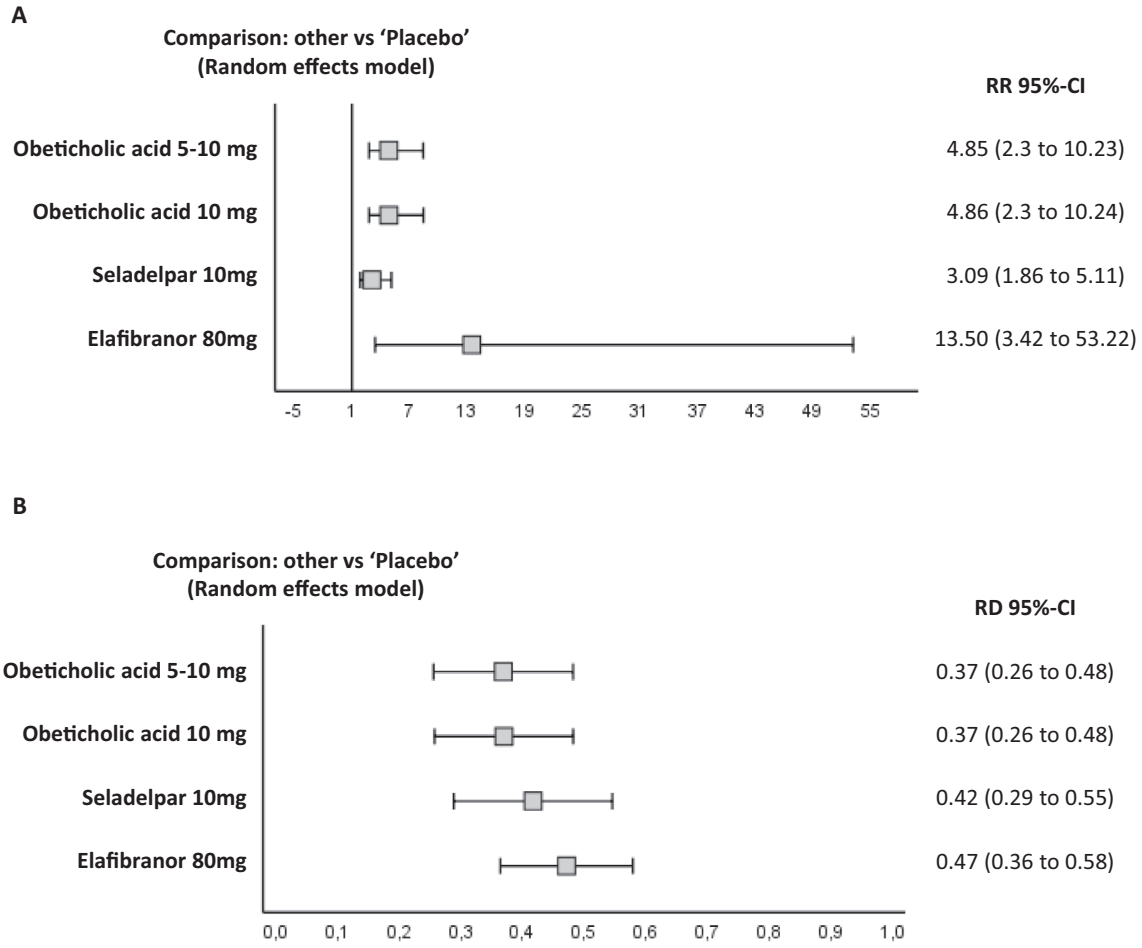

FIGURE 1 | Forest plot reporting the relative risk (A) and the risk difference (B) of biochemical response after 12-month of treatment with the various drugs.

TABLE 1 | League table for relative probability of achieving biochemical response after 12-month of treatment.

Elafibranor 80 mg				13.50 (3.42–53.22)
4.37 (1.01–18.87)	**Seladelpar 10 mg**			3.09 (1.86–5.11)
2.78 (0.58–13.28)	0.64 (0.26–1.57)	**Obeticholic acid 5–10 mg**	1.00 (0.70–1.42)	4.85 (2.3–10.23)
2.78 (0.58–13.25)	0.64 (0.26–1.56)	1.00 (0.72–1.39)	**Obeticholic acid 10 mg**	4.86 (2.3–10.24)
13.5 (3.42–53.22)	3.09 (1.86–5.11)	4.85 (2.79–8.43)	4.86 (2.3–10.24)	**Placebo**

Note: Relative risk values with 95% confidence intervals (CIs) are given in parentheses. To interpret comparisons, read from left to right across the columns relative to the rows, arranged by their overall efficacy. Direct comparisons are shown above the drug names, while indirect comparisons are below them. Grey-shaded boxes indicate statistically significant differences. Bold text identifies the drug. Data in shaded cells are those with statistically significant difference.

3.2 | Incidence of New-Onset Pruritus and Severe Adverse Events

Overall, the 12-month incidence of new-onset pruritus was 34.6%, affecting 117 patients (30.9%) receiving active treatment and 80 patients (41.9%) receiving placebo. Figure 2A shows the forest plots for the risk of new-onset pruritus (active treatments vs. placebo). OCA treatment at both 5–10 mg (RR 1.43; 95% CI: 1.09–1.88) and 10 mg (RR 1.79; 95% CI: 1.37–2.33) was associated with a significantly higher risk of new-onset pruritus, while seladelpar with a significantly lower relative risk (RR 0.30; 95% CI: 0.12–0.80), and elafibranor was not associated with either increased or decreased incidence (RR 0.77; 95% CI: 0.43–1.38). The risk difference of new-onset pruritus (Figure 2B) was significantly favourable for seladelpar [RD-0.11 (−0.20 to −0.01)] and marginally for elafibranor [RD −0.06 (−0.20 to 0.08)], while was negative for OCA at both 5–10 mg [RD 0.17 (0.04 to 0.30)] and 10 mg [RD 0.30 (0.17 to 0.43)].

Indirect comparisons (Table 2) showed a significantly decreased risk of new-onset pruritus for seladelpar compared to either OCA 5–10 mg (RR 0.21; 95% CI: 0.08–0.60) or 10 mg (RR 0.17; 95% CI: 0.06–0.47), and for elafibranor compared to OCA 10 mg

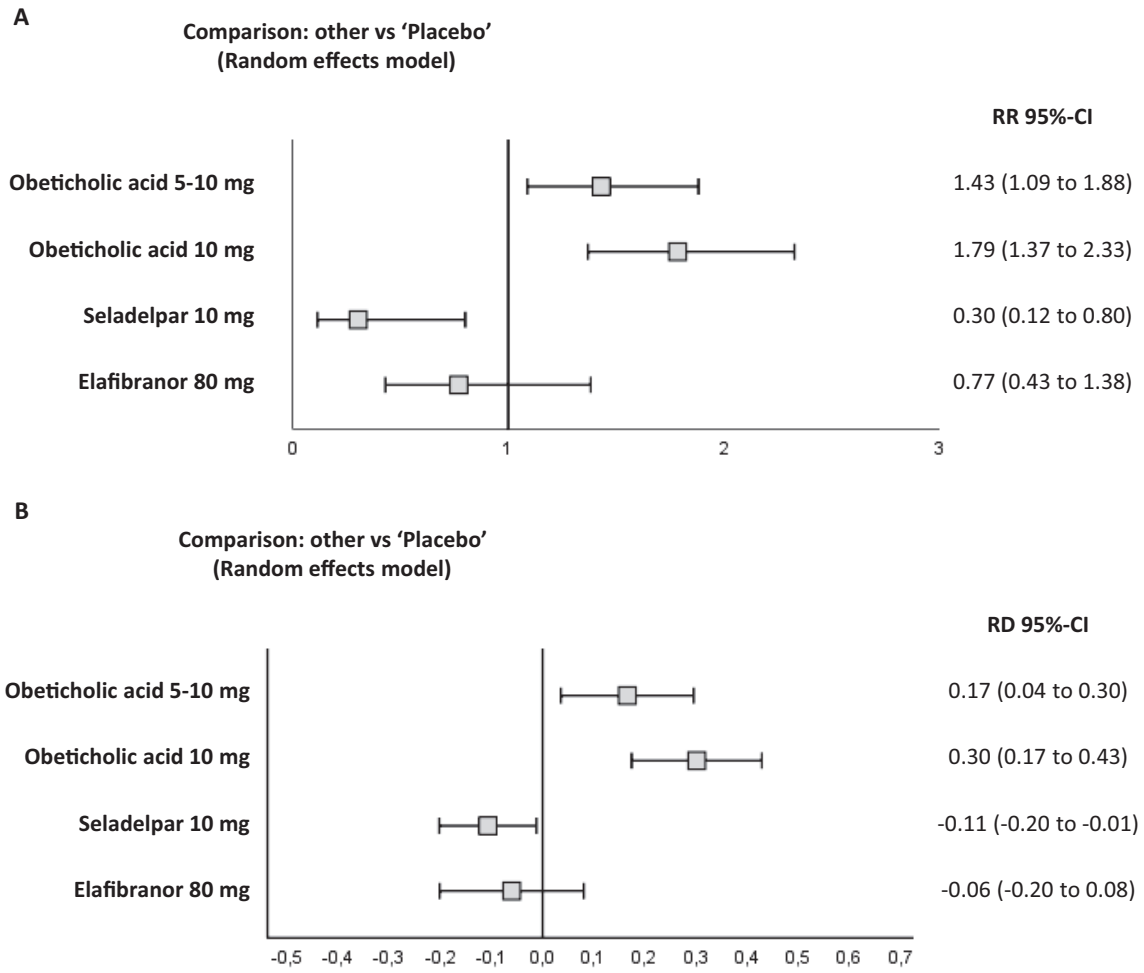

FIGURE 2 | Forest plot showing the relative risk (A) and risk difference (B) for new-onset pruritus within 12-month of treatment with the various drugs.

TABLE 2 | League table for the relative risk of experiencing pruritus within 12-month of treatment.

Elafibranor 80 mg				0.77 (0.43–1.38)
2.53 (0.82–7.83)	**Seladelpar 10 mg**			0.30 (0.12–0.80)
0.54 (0.27–1.07)	0.21 (0.08–0.6)	**Obeticholic acid 5–10 mg**	0.80 (0.62–1.04)	1.43 (1.09–1.88)
0.43 (0.22–0.84)	0.17 (0.06–0.47)	0.8 (0.64–1.01)	**Obeticholic acid 10 mg**	1.79 (1.37–2.33)
0.77 (0.43–1.38)	0.30 (0.12–0.80)	1.43 (1.09–1.88)	1.79 (1.37–2.33)	**Placebo**

Note: Relative risk values with 95% confidence intervals (CIs) are given in parentheses. To interpret comparisons, read from left to right across the columns relative to the rows, arranged by their overall efficacy. Direct comparisons are shown above the drug names, while indirect comparisons are below them. Grey-shaded boxes indicate statistically significant differences. Bold text identifies the drug. Data in shaded cells are those with statistically significant difference.

(RR 0.43; 95% CI: 0.22–0.84), while no difference was observed between elafibranor and seladelpar (RR 2.53; 95% CI: 0.82–7.83).

The overall incidence of SAEs was 9.8%, affecting 40 patients (10.6%) receiving active treatments and 16 patients (8.4%) receiving placebo. Figure S4 shows that OCA 5–10 mg (RR 3.82; 95% CI: 1.46–10.02) or 10 mg (RR 2.67; 95% CI: 1.00–7.08) was associated with an increased risk of SAE compared to placebo, while both seladelpar (RR 1.14; 95% CI: 0.37–3.57) and elafibranor (RR 0.98; 95% CI: 0.39–2.47) were not. Indirect comparisons showed no difference in the risk of SAEs across the various treatments (Table S4).

4 | Discussion

In patients with PBC, treatment with UDCA improves cholestasis, and this biochemical endpoint is associated with positive, long-term endpoints such as decrease in the risk of liver decompensation, liver-related death and transplantation [4, 5]. Therefore, in patients with PBC treated with UDCA, initial biochemical response highlighted by amelioration of ALP and bilirubin is considered a surrogate marker of future clinical benefit. Unfortunately, up to 40% of patients do not show an adequate improvement in cholestasis, and these patients are at higher risk of disease progression [3, 6, 7]. In patients not responding

to UDCA, the current second-line treatment option is represented by OCA, whose administration proved to be able to improve cholestasis in both the registration study and in various real-world cohorts [9, 10, 24]. OCA treatment for patients with PBC was conditionally approved by regulatory authorities both in the EU and US, pending the results of a Phase IV confirmatory required to confirm the efficacy of the drug, as compared to placebo, on composite clinical endpoints such as death, liver transplantation, or decompensation of liver disease. However, this study was prematurely ended due to inadequate enrolment and retention, and thus resulted underpowered for the primary composite endpoints set by the regulatory authorities. This negative result, despite positive data accrued in real-world studies since availability of the drug, led the European Medicine Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) to recommend revoking the marketing authorisation of OCA in the EU [24, 25].

In this evolving scenario, two recent studies carried out in patients who showed incomplete response, or were intolerant, to UDCA demonstrated that two PPAR agonists, seladelpar and elafibranor, may represent safe and effective treatment options for these patients [14, 15]. In both studies, the drug met the primary biochemical endpoint, with no emerging safety signals, and a significant improvement in pruritus was also demonstrated in patients with moderate-to-severe pruritus at baseline treated with seladelpar [14, 15]. As, there are no studies directly comparing second-line therapies for PBC, and we performed a systematic review and NMA to indirectly compare efficacy and safety of the available second-line therapies for patients with PBC. We set homogeneous criteria for inclusion and selected studies using well-defined and internationally accepted endpoints to assess treatment response.

We observed that, on average, the 12-month primary biochemical endpoint was met in 53.0% of patients treated with active drugs, versus an average of 15.2%, in the placebo groups, with and an average differential gain of response of 37.8%. More in detail, all treatments were associated with overlapping, higher likelihood of biochemical response compared to placebo, ranging from 3.09 with seladelpar (95% CI: 1.86–5.11), to 4.85/4.86 with the various OCA schedules (95% CI: 2.3–10.23/10.24), to 13.5 with elafibranor (95% CI: 3.42–53.22). To overcome the limitation inherent to the potential different placebo response rates among studies, we assessed and compared the relative response compared to placebo across the various studies. We observed, despite increasing numerical relative response rates from 37% with OCA (95% CI: 26%–48%), to 42% with seladelpar (95% CI: 29%–55%), and 47% with elafibranor (95% CI: 36%–58%), that the intervals were overlapping. The relative decrease in ALP, too, overlapped across the various treatments, ranging from 30% with OCA to about 40% with either seladelpar or elafibranor. Lastly and noteworthy, the NMA indirect comparison of efficacy between the various treatments showed no major differences among the various drugs in achieving biochemical response, although elafibranor was significantly superior compared to seladelpar (RR: 4.37; 95% CI: 1.01–18.87).

Another aspect of interest concerns the incidence of new-onset pruritus, a symptom that represents a major clinical issue in patients with PBC, as it worsens quality of life in patients with PBC [26, 27]. Our study showed that the average 12-month risk of developing new-onset pruritus in patients treated with placebo, is 41.9%, and that this figure is, on the average, 10% lower when patients are treated with an active drug. However, when we evaluated the effect of each single drug compared to placebo on the onset of this symptom, we observed that treatment with OCA was associated with a 12-month increased risk difference of 17%–30% of developing pruritus, while seladelpar was associated with a significant risk reduction, of about 10%, and a non-significant 6% decrease was observed with elafibranor. It must be emphasised that we limited our analysis to new-onset pruritus, identified in the various studies as an adverse event, and did not evaluate the modification in the severity of this symptom since the studies used different scores to grade pruritus, and the potential inconsistency related to the comparison of the improvement in these scores has previously been debated at length [28–30]. Noteworthy, we feel that the data reported on new-onset pruritus in patients treated with placebo may serve as a benchmark for future studies addressing this issue, and that its apparently elevated figure may be related to the fact that the symptom was consistently captured in the environment of a Phase III study, while there is evidence that pruritus is underrecorded in clinical practice [31]. Lastly, as far as overall safety is concerned, we observed that while both seladelpar and elafibranor were not associated with an increased risk of SAEs as compared to placebo, OCA at any dose was associated with a greater likelihood of SAEs.

How can the results of this NMA be put in the context of the clinical scenario of patients with PBC and incomplete response to UDCA? All treatment regimens, with variable results, showed efficacy as compared to placebo although both new drugs—seladelpar and elafibranor—showed a higher margin of efficacy as compared to OCA, and in the indirect comparison elafibranor seemed to provide some advantage over seladelpar in obtaining a biochemical response after 12 months of treatment. Therefore, considering the potential, future limitations to the use of OCA, at least in the EU, one has to balance the increased efficacy elafibranor with the lower incidence of pruritus with seladelpar, a finding that could be related to an intrinsic mechanism of action of the drug, and that might indicate its preferential use in patients at higher risk of developing this troublesome symptom [32]. Moreover, as far as safety is concerned, both seladelpar and elafibranor demonstrated an overall better safety profile as compared to OCA both in terms of new-onset pruritus and overall rate of SAEs, while seladelpar was associated with a reduced incidence of new-onset pruritus.

Given the different mechanisms of action of this class of drugs, it is hoped that future studies may help in better understanding the predictors of response and of SAEs and allow for a more precise allocation to second therapy for patients with PBC.

4.1 | Limitations

Unfortunately, because of differences in inclusion criteria and end-points, our NMA could not account for the pan-PPAR agonist bezafibrate [22, 33], that in a randomised, placebo-controlled study in patients who were incomplete responder to UDCA, normalised indexes of cholestasis and hepatic cytolysis

in 31% of patients after 24 month of treatment (0% placebo), and improved both pruritus and non-invasive tests of liver fibrosis [22]. Moreover, in a small, real-world study with paired liver biopsies performed after 5 years of treatment, bezafibrate use was associated with significant decrease in liver histological activity index, regression of liver fibrosis in 48% of patients, and reduction in the proportion of patients with cirrhosis from 19% at baseline to 3% at 5-year follow-up [34]. Lastly, the results of a large, retrospective study with a follow-up to 10 years carried out in Japan, demonstrated that the use of bezafibrate—as compared to UDCA alone—was associated with solid, long-term endpoints such as improvement in transplant-free survival (adjusted HR: 0.33, 95% CI: 0.19–0.55), and that this association was consistent across various risk groups at baseline [35]. However, in the context of this NMA, an indirect comparison of the BEZURSO study results was not feasible as the bezafibrate trial considered both different inclusion criteria and endpoints, and therefore how the efficacy and safety of this drug may compare, though indirectly, with either OCA, seladelpar and elafibranor could not be assessed due to methodological issues that would have prevented a correct analysis of data [14, 15, 22]. Since bezafibrate is currently used in clinical practice in several countries, it is likely that the results of real-world studies with direct comparison, or indirect comparison with historical cohorts, will be available in the near future and therefore help disclose the potential difference in efficacy and safety between off-label bezafibrate and the other licensed second-line therapies.

Another limitation of this study is related to the use of study-level and estimation techniques, and to the fact that the availability of a limited number of studies—and an overall relatively small number of patients—increased uncertainty around our comparative effectiveness estimates, and prevented sub-group analyses. Specifically, the absence of individual patient data restricted our ability to perform more granular analyses and might have affected the precision of our estimates. Lastly, availability of individual patient data would have allowed the inclusion of patients treated with bezafibrate. In this regard, real-world studies will likely provide more information about the efficacy and safety of the newer drugs—seladelpar and elafibranor—once they will be widely available, allowing larger scale, and possibly head-to-head, comparisons.

The inclusion of Phase III studies with a 12-month biochemical endpoint alone was a selection criterion for inclusion in the meta-analysis to increase the rigorousness of data as Phase II studies had a limited duration (i.e. 3 months), although this might have limited the sample size, and thus the robustness of the findings. To this end, we performed a sensitivity analysis of efficacy including the Phase II, randomised trial that assessed 3-month biochemical response of different elafibranor doses (80 and 120 mg) against placebo, and a Phase III, randomised, placebo-controlled study of different seladelpar doses (5 and 10 mg) that was terminated earlier than planned and whose available results in terms of biochemical response were evaluated at 3-month (21,23, network plot provided in Figure S5). This analysis, albeit limited to 3-month composite biochemical endpoint, showed that all the drugs had an overall favourable relative risk of response compared to placebo (Figure S6A), with a gradient in risk difference of 0.33 (95% CI: 0.23–0.43) for OCA 5–10 mg, 0.56 (95% CI: 0.47–0.66) for elafibranor 80 mg and 0.60 (95% CI: 0.48–0.72) for seladelpar 10 mg (Figure S6B). Direct and indirect comparisons for biochemical response at 3-month showed that all active treatments were superior to placebo (Table S5), while seladelpar 10 mg was superior to seladelpar 5 mg (RR 1.37; 95% CI: 1.05–1.79). No significant differences were observed in indirect comparisons among the other treatments. The results of this sub-analysis, though informative due to increased number of patients, need to be considered with caution due to the quite short time-horizon evaluated (3-month) and to the fact that two studies included the assessment of drug doses that were not further explored in Phase III studies [21, 23].

Lastly, due to the availability of well-detailed, registration studies, the heterogeneity across trials was quite low, and while network meta-analyses allow for the comparison of treatments not directly compared in head-to-head trials, it might inherently carry the risk of bias due to unmeasured characteristics that could affect outcomes, and therefore their results should be interpreted with caution. While this can be considered an intrinsic limitation of network meta-analyses, they are performed to overcome the limitations of direct comparisons, since they usually yield more precise estimates than a single direct or indirect estimate. Moreover, network meta-analyses allow triple comparisons, as in this case, that in real-life would be hardly performed, especially in rare diseases such as PBC.

A final consideration regards the approval status of OCA in Europe. The decision of the EMA CHMP to recommend revoking the marketing authorisation of OCA in the EU was decision was critically appraised by the scientific community and heightened the debate concerning the balance between the need to provide patients with solutions for their unmet needs, once pivotal interventional trials meet surrogate endpoints, and the requirements of regulatory authorities for long-term, placebo-controlled studies in patients with rare diseases and long natural history, [14, 15, 36]. Further discussion needs to be entertained on how to combine the challenges posed by such studies and the necessity provide patients with solutions for their unmet needs. We believe that study such this NMA might help the health authorities to analyse and compare alternatives based on available, objective data.

5 | Conclusions

On the basis of the results of this NMA, in the absence of direct comparisons between the various drugs available, selection of optimal treatment for second-line therapy of patients with PBC may be quite nuanced, and the decision should be tailored on the single patient rather than being universal. Indeed, efficacy of treatment on biochemical endpoints seems to favour the selection of elafibranor due to its better results compared to seladelpar, and to similar results compared to OCA, but with significantly better safety profile. On another note, seladelpar showed an overall efficacy similar to OCA but with a better safety profile, and was the only drug associated with a significantly lower incidence of new-onset pruritus, though indirect comparison with elafibranor showed no difference between the two drugs on this aspect. Thus, while waiting for evidence generated by real-world comparison studies, that should possibly include also bezafibrate, we feel that the results of this NMA may

inform decisions regarding second-line treatment of patients with PBC and help better tailor treatment to patients' needs.

Acknowledgements

MS and EGG wish to acknowledge the Yale Liver Center clinical and translational core (NIH P30DK034989) for helpful discussion.

Conflicts of Interest

Edoardo G. Giannini reports speaking and teaching for AbbVie, AstraZeneca, Eisai, Gilead, Roche; advising for AstraZeneca, Eisai, Gilead, Ipsen, Roche. Sara Labanca speaking and teaching for Advanz, Gilead, Ipsen. Simona Marenco speaking and teaching for Ipsen. Mario Strazzabosco advises for Engitix. Andrea Pasta, Francesco Calabrese, Giulia Pieri and Maria Corina Plaz Torres have no conflicts of interest to declare.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. F. Colapietro, A. Bertazzoni, and A. Lleo, "Contemporary Epidemiology of Primary Biliary Cholangitis," *Clinics in Liver Disease* 26, no. 4 (2022): 555–570.

2. A. Gerussi, L. Cristoferi, M. Carbone, R. Asselta, and P. Invernizzi, "The Immunobiology of Female Predominance in Primary Biliary Cholangitis," *Journal of Autoimmunity* 95 (2018): 124–132.

3. J. Trivella, B. V. John, and C. Levy, "Primary Biliary Colangitis: Epidemiology, Prognosis, and Treatment," *Hepatology Communications* 7, no. 6 (2023): e0179.

4. C. Corpechot, L. Abenavoli, N. Rabahi, et al., "Biochemical Response to Ursodeoxycholic Acid and Long-Term Prognosis in Primary Biliary Cirrhosis," *Hepatology* 48, no. 3 (2008): 871–877.

5. C. Corpechot, F. Carrat, A. M. Bonnand, R. E. Poupon, and R. Poupon, "The Effect of Ursodeoxycholic Acid Therapy on Liver Fibrosis Progression in Primary Biliary Cirrhosis," *Hepatology* 32, no. 6 (2000): 1196–1199.

6. W. J. Lammers, H. R. van Buuren, G. M. Hirschfield, et al., "Levels of Alkaline Phosphatase and Bilirubin Are Surrogate End Points of Outcomes of Patients With Primary Biliary Cirrhosis: An International Follow-Up Study," *Gastroenterology* 147, no. 6 (2014): 1338–1349.

7. R. C. de Veer, M. C. van Hooff, C. Corpechot, et al., "Ursodeoxycholic Acid Treatment-Induced GLOBE Score Changes Are Associated With Liver Transplantation-Free Survival in Patients With Primary Biliary Cholangitis," *American Journal of Gastroenterology* 118, no. 7 (2023): 1196–1203.

8. J. Gazda, S. Drazilova, M. Gazda, et al., "Treatment Response to Ursodeoxycholic Acid in Primary Biliary Cholangitis: A Systematic Review and Meta-Analysis," *Digestive and Liver Disease* 55, no. 10 (2023): 1318–1327.

9. F. Nevens, P. Andreone, G. Mazzella, et al., "A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis," *New England Journal of Medicine* 375, no. 7 (2016): 631–643.

10. C. F. Murillo Perez, H. Fisher, S. Hiu, et al., "Greater Transplant-Free Survival in Patients Receiving Obeticholic Acid for Primary Biliary Cholangitis in a Clinical Trial Setting Compared to Real-World External Controls," *Gastroenterology* 163, no. 6 (2022): 1630–1642.

11. K. V. Kowdley, G. M. Hirschfield, C. Coombs, et al., "COBALT: A Confirmatory Trial of Obeticholic Acid in Primary Biliary Cholangitis With Placebo and External Controls," *American Journal of Gastroenterology* (2024), https://doi.org/10.14309/ajg.0000000000003029.

12. U.S. Food & Drug Administration, "Due to Risk of Serious Liver Injury, FDA Restricts Use of Ocaliva (Obeticholic Acid) in Primary Biliary Cholangitis (PBC) Patients With Advanced Cirrhosis," https://www.fda.gov/drugs/drug-safety-and-availability/due-risk-serious-liver-injury-fda-restricts-use-ocaliva-obeticholic-acid-primary-biliary-cholangitis.

13. A. de Vincentis, D. D'Amato, L. Cristoferi, et al., "Predictors of Serious Adverse Events and Non-response in Cirrhotic Patients With Primary Biliary Cholangitis Treated With Obeticholic Acid," *Liver International* 42, no. 11 (2022): 2453–2465.

14. G. M. Hirschfield, C. L. Bowlus, M. J. Mayo, et al., "A Phase 3 Trial of Seladelpar in Primary Biliary Cholangitis," *New England Journal of Medicine* 390, no. 9 (2024): 783–794.

15. K. V. Kowdley, C. L. Bowlus, C. Levy, et al., "Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis," *New England Journal of Medicine* 390, no. 9 (2024): 795–805.

16. Cochrane Book Series, J. P. Higgins, S. Green *Cochrane Handbook for Systematic Reviews of Interventions* (New Jersey, USA: Wiley-Blackwell, 2019).

17. D. Follmann, P. Elliott, I. Suh, and J. Cutler, "Variance Imputation for Overviews of Clinical Trials With Continuous Response," *Journal of Clinical Epidemiology* 45, no. 7 (1992): 769–773.

18. X. Wan, W. Wang, J. Liu, and T. Tong, "Estimating the Sample Mean and Standard Deviation From the Sample Size, Median, Range and/or Interquartile Range," *BMC Medical Research Methodology* 19, no. 14 (2014): 135.

19. L. Hespanhol, C. S. Vallio, L. M. Costa, and B. T. Saragiotto, "Understanding and Interpreting Confidence and Credible Intervals Around Effect Estimates," *Brazilian Journal of Physical Therapy* 23, no. 4 (2019): 290–301.

20. B. R. da Costa and P. Juni, "Systematic Reviews and Meta-Analyses of Randomized Trials: Principles and Pitfalls," *European Heart Journal* 35, no. 47 (2014): 3336–3345.

21. J. M. Schattenberg, A. Pares, K. V. Kowdley, et al., "A Randomized Placebo-Controlled Trial of Elafibranor in Patients With Primary Biliary Cholangitis and Incomplete Response to UDCA," *Journal of Hepatology* 74, no. 6 (2021): 1344–1354.

22. C. Corpechot, O. Chazouillères, A. Rousseau, et al., "A Placebo-Controlled Trial of Bezafibrate in Primary Biliary Cholangitis," *New England Journal of Medicine* 378, no. 23 (2018): 2171–2181.

23. G. M. Hirschfield, M. L. Shiffman, A. Gulamhusein, et al., "Seladelpar Efficacy and Safety at 3 Months in Patients With Primary Biliary Cholangitis: ENHANCE, a Phase 3, Randomized, Placebo-Controlled Study," *Hepatology* 78, no. 2 (2023): 397–415.

24. D. D'Amato, A. de Vincentis, F. Malinverno, et al., "Real-World Experience With Obeticholic Acid in Patients With Primary Biliary Cholangitis," *JHEP Reports: Innovation in Hepatology* 3, no. 2 (2021): 100248.

25. "EMA Recommends Revoking Conditional Marketing Authorisation for Ocaliva," https://www.ema.europa.eu/en/news/ema-recommends-revoking-conditional-marketing-authorisation-ocaliva.

26. M. Zapata, H. Pagan-Torres, and M. J. Mayo, "Systemic Complications of Primary Biliary Cholangitis," *Clinics in Liver Disease* 28, no. 1 (2024): 115–128.

27. M. J. Mayo, E. Carey, H. T. Smith, et al., "Impact of Pruritus on Quality of Life and Current Treatment Patterns in Patients With Primary Biliary Cholangitis," *Digestive Diseases and Sciences* 68, no. 10 (2023): 4064–4065.

28. C. Arévalo-Cañas and J. Arévalo-Serrano, "Phase 3 Trials of Elafibranor and Seladelpar for Primary Biliary Cholangitis," *New England Journal of Medicine* 390, no. 20 (2024): 1933–1934.

29. G. M. Hirschfield, A. E. Kremer, and C. Levy, "Phase 3 Trials of Elafibranor and Seladelpar for Primary Biliary Cholangitis," *New England Journal of Medicine* 390, no. 20 (2024): 1934–1935.

30. K. V. Kowdley, C. Levy, and D. Jones, "Phase 3 Trials of Elafibranor and Seladelpar for Primary Biliary Cholangitis. Reply," *New England Journal of Medicine* 390, no. 20 (2024): 1935–1936.

31. U. Gungabissoon, H. T. Smith, R. von Maltzahn, et al., "Pruritus in Primary Biliary Cholangitis Is Under-Recorded in Patient Medical Records," *BMJ Open Gastroenterology* 11, no. 1 (2024): e001287.

32. A. E. Kremer, M. J. Mayo, G. M. Hirschfield, et al., "Seladelpar Treatment Reduces IL-31 and Pruritus in Patients With Primary Biliary Cholangitis," *Hepatology* 80, no. 1 (2024): 27–37.

33. A. Tanaka and C. Corpechot, "PPAR Agonists in PBC: Where Do We Go From Here? Or How to Choose Between the New and the Old," *Clinics and Research in Hepatology and Gastroenterology* 48, no. 6 (2024): 102358.

34. J. A. Sorda, E. González Ballerga, F. J. Barreyro, et al., "Bezafibrate Therapy in Primary Biliary Cholangitis Refractory to Ursodeoxycholic Acid: A Longitudinal Study of Paired Liver Biopsies at 5 Years of Follow Up," *Alimentary Pharmacology & Therapeutics* 54, no. 9 (2021): 1202–1212.

35. A. Tanaka, J. Hirohara, T. Nakano, et al., "Association of Bezafibrate With Transplant-Free Survival in Patients With Primary Biliary Cholangitis," *Journal of Hepatology* 75, no. 3 (2021): 565–571.

36. D. E. J. Jones, U. Beuers, A. Bonder, et al., "Primary Biliary Cholangitis Drug Evaluation and Regulatory Approval: Where Do We Go From Here?," *Hepatology* 80, no. 5 (2024): 1291–1300.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.