Efficacy and safety of pharmacological interventions for pruritus in primary biliary cholangitis: A systematic review and meta-analysis

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Background and objective: Pruritus is a common complication in patients with primary biliary cholangitis (PBC). The pathogenesis is not clear, and also the precise therapeutic measures remain alluring. In order to systematically evaluate the efficacy and safety of drug interventions in the treatment of pruritus associated with PBC, this systematic review and meta-analysis was conducted.

Methods: The randomized controlled trials (RCTs) on drug interventions in the treatment of pruritus associated with primary cholangitis were searched in the electronic databases of PubMed, EMBASE, Cochrane Library, Web of Science, and ClinicalTrials.gov. Two researchers independently screened the literature, extracted and integrated the data, and assessed the bias risk of the selected literature, according to the Cochrane handbook. Finally, the STATA 15.0 software was used for the meta-analysis.

Results: A total of 23 RCTs involving 2,194 patients were studied, that included 12 pharmacological interventions. In terms of itching relief, compared with placebo, UDCA, methotrexate and GSK2330672 had a definite effect in improving pruritus (pruritus remission rate before and after treatment, p < 0.05). In terms of serum indexes, compared with placebo group, UDCA, OCA, rifampicin, cyclosporine, NGM282, seladelpar and colchicine may improve blood alkaline phosphatase (ALP) (p < 0.05), but only rifampicin showed low heterogeneity. UDCA, bezafibrate, OCA, rifampicin, NGM282 and others may improve blood γ-glutamyl transpeptidase (γ-GGT) (p < 0.05), but due to the high heterogeneity and the limitation of research samples, a clear conclusion cannot be drawn. In terms of adverse events, except high (>15 mg/kg/day) and low doses (<13 mg/kg/day) of UDCA increased the incidence of adverse events, there were no risk of increasing the incidence of adverse events compared with placebo (p > 0.05), and a moderate dose of UDCA (13–15 mg/kg/day) and malotilate (1,500 mg/day) may also help in reducing the incidence of adverse events (p < 0.05).
Conclusion: UDCA, methotrexate and GSK2330672 may relieve itching in patients with PBC, but there is a lack of robust evidence to support their effect on ALP or γ-GGT. Due to the heterogeneity in the published studies, based on the present review, we cannot explicitly recommend any specific drug for the treatment of PBC-related pruritus.

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KEYWORDS
primary biliary cholangitis, pruritus, pharmacological interventions, alkaline phosphatase, γ-glutamyl transpeptidase

Introduction

Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is an autoimmune liver disease, which is predominantly seen in women. The interaction of specific anti-mitochondrial antibodies with specific autoantigens, accompanied by pathophysiological processes such as bile duct injury, cholestasis, liver fibrosis and even liver cirrhosis, are the main features of the pathological progress of PBC (Lee et al., 2019; Gulamhusein and Hirschfield, 2020). At present, the incidence of PBC is geographically varied, and the number is on the rise too. According to a survey, there are 118.75 cases of prostate cancer per million people in the Asia-Pacific region (Zeng et al., 2019), 218.1 cases per million people in North America, 145.9 cases per million people in Europe, and 189.0 cases per million in Victoria, Australia (J et al., 2020). It was reported to be 346.0 cases per million in Sweden (Hu et al., 2019), 149.0 cases per million in Slovakia (Drazilova et al., 2020), and 279.0 cases per million in Italy (Rajaobelina et al., 2019). Environmental and genetic factors play an important role in the occurrence of the disease (Carey et al., 2015). The levels of serum alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (γ-GGT) are generally increased in patients with PBC.

Fatigue and pruritus are the most common symptoms in patients with PBC. Scratching, sleep deprivation, depression and, even suicidal thoughts caused by itching affect 20%–70% of patients (Beuers et al., 2014; Carey et al., 2015), seriously affecting their quality of life. The accumulation and deposition of bile acid and bile salt, the regulation of lysophosphatidic acid, the abnormality of endogenous opioid receptors and the effects of serotonin and substance P are considered to be the main pathophysiological mechanisms of cholangitis pruritus (Bray et al., 2018). Even so, the pathogenesis of cholestatic pruritus has not been well described because of its diversity and complexity (Tajiri and Shimizu, 2017; SP et al., 2019).

A cross-sectional study of 2194 PBC pruritus patients in the United Kingdom shows that there is a lack of adequate understanding, management and guidelines for the disease, and there is insufficient evidence on the recommended treatment (Hegade et al., 2019). There exist few evidence-based guidelines for treating PBC pruritus, but the limitation is that there are specific clinical conditions where these guidelines cannot be applied. Ursodeoxycholic acid (UDCA) and OCA are drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of PBC, which can improve the liver biochemical indexes, prolong survival time and delay the development of esophageal varices. However, UDCA cannot completely cure this disease, and its effectiveness in the treatment of cholangitis pruritus is still controversial (IS et al., 2012). Interestingly, another potential anti-PBC drug, OCA, was reported to increase the risk of itching (Trauner et al., 2019). The search for an effective treatment for PBC-related pruritus interventions has never stopped. Newer pharmacological interventions have been reported such as cholestyramine (TB et al., 1961), rifampicin (CN and SG, 1988), sertraline (MJ et al., 2007), ondansetron (JW et al., 2005), maralixibat (Mayo et al., 2019), ileal apical sodium bile acid transporter (ASBT) inhibitors such as GSK2330672 (Hegade et al., 2017). In order to determine the efficacy and safety of the available drugs for the treatment of PBC-associated pruritus, we conducted a systematic review and meta-analysis of pharmacological interventions in PBC-related pruritus.

Materials and methods

We followed a predetermined protocol and the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for this systemic review and meta-analysis (DG et al., 2009).

Search strategy

To systematically evaluate the efficacy of interventions, we searched PubMed, EMBASE, Cochrane Library, Web of Science, and ClinicalTrials.gov from inception up to June 2021. The search strategy was implemented by an experienced medical librarian.
Strategies were selected using a combination of medical subject headings (MeSH) and text words, and search terms included “primary biliary cholangitis (cirrhosis),” “pruritus” or “pruritis” or “itching,” and “randomized controlled trial.” The language was limited to English, and the publication status was not restricted.

Selection criteria

The inclusion criteria were as follows

1. The study was a randomized controlled trial (RCT).
2. The diagnosis of PBC was based on at least two of the following: the presence of anti-mitochondrial antibody (AMA), cholestasis with an elevation of ALP activity, histopathologic evidence of nonsuppurative cholangitis and destruction of small or medium-sized bile ducts (KD et al., 2019), and patients of primary biliary cholangitis with persistent pruritus (course of disease ≥ 3 months).
3. All pharmacological interventions related to the treatment of pruritus in PBC.
4. Outcomes related to the efficacy and safety of pruritus in PBC.

Exclusion criteria

1. The interventions are not suitable (more than three interventions or the study interventions beyond our study).
2. PBC associated with other underlying diseases.
3. Unavailable data (there is no data we need in the study).
4. Absence of a clear basic information about the study subjects.
5. Duplicate publications.
6. Studies with ambiguous diagnostic criteria.

Study selection and data extraction

Two reviewers (Chenyi Xu and Xuelian Lv) independently extracted basic information about the articles (article title, first author, year of publication, sample size, country or region), trial design (participants, interventions, time span of the trial, follow-up time), clinical efficacy and adverse events.

Clinical efficacy measures included pruritus scores; 0–10 numerical rating scale (NRS), quality of life scale for primary biliary cirrhosis (cholangitis) (PBC-40), and 5-D itch scale (or the pruritus relief rate before and after treatment). Secondary outcomes were laboratory parameters such as the changes in serum alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (γ-GGT). We considered both iatrogenic and non-iatrogenic adverse events, and carried out a quantitative analysis of these events.

Risk of bias assessment

Two investigators evaluated each of the included RCTs and recorded the following six items, as per the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2008): the methods of blinding, the generation of information, data, distribution of randomized control sequences, selective reports and other possible problems. The risk of bias was marked as high, uncertain, or low.

Statistical analysis

STATA15.0 (STATA statistical software: Release 15.0 College Station, TX: Stata Corp LP) was used to analyze the data. Successive mean differences in pruritus scores were reported as standardized mean differences (SMD), and binary variables used risk ratios (RR) or odds ratio (OR), providing a 95% confidence interval (CI) for each effect. Heterogeneity was evaluated by I², p < 0.05 was considered to be statistically significant. The studies with high heterogeneity (p ≤ 0.10 and I² ≥ 50%) were analyzed by random effect model, the studies with low heterogeneity (p > 0.10 and I² < 50%) were analyzed by fixed effect model. The stability of the results was evaluated by subgroup analysis and sensitivity analysis. If enough studies were included in meta-analysis (n ≥ 10), funnel chart analysis was used for evaluate publication bias.
| Study and year | Design | Population | Sample size | Intervention | Outcomes | Follow-up | Concomitant treatment |
|----------------|--------|------------|-------------|--------------|----------|-----------|-----------------------|
| **UDCA**       |        |            |             |              |          |           |                       |
| Hiroshi OKA 1990 | RCT    | PBC. Mean age 59 years, 89% female | 22 UDCA 23 Placebo | UDCA 8–12 mg/kg/day | (1) (2) (3) (4) 2 years | None detailed |
| Poupon RE 1991  | RCT    | PBC. Mean age 56 years, 92% female | 73 UDCA 73 Placebo | UDCA 13–15 mg/kg/day | (1) (2) (3) (4) 2 years | None detailed |
| Matti 1995      | RCT    | PBC. Mean age 54.5 years, 92% female | 30 UDCA 31 Placebo | UDCA 12–15 mg/kg/day | (1) (2) (3) (4) 2 years | None detailed |
| Albert Parés 2000 | RCT    | PBC. Mean age 54.1 years, 93% female | 99 UDCA 93 Placebo | UDCA 14–16 mg/kg/day | (1) (2) (4) 2 years | Cholestyramine at least 2 h after the intake of UDCA or Placebo |
| E. Jenny heathcote 1994 | RCT    | PBC. Mean age 56.4 years, 93% female | 111 UDCA 111 Placebo | UDCA 14 mg/kg/day | (1) (3) (4) 2 years | Cholestyramine, in the morning or at least 4 h before the trial capsules |
| P.M. Battezzati1993 | RCT    | PBC. Mean age 54.5 years, 89% female | 44 UDCA 44 Placebo | UDCA 8.7 mg/kg/day | (1) (3) (4) 1 year | Cholestyramine take at least 4 h before or after the study drug |
| Poupon RE 1990  | RCT    | PBC. Mean age 56.5 years, 91% female | 70 UDCA 68 Placebo | UDCA 13–15 mg/kg/day | (1) (2) (3) (4) 2 years | None detailed |
| K. D. Lindor1994 | RCT    | PBC. Mean age 53 years, 89% female | 89 UDCA 91 Placebo | UDCA 13–15 mg/kg/day | (1) (3) (4) 2 years | Cholestyramine were asked to take drug 2 h after their study drug |
| **Rifampicin** |        |            |             |              |          |           |                       |
| Laura Bachs 1989 | RCT    | PBC. Mean age 49.7 years, 100% female | 21 Rifampicin 18 Phenobarbitone | Rifampicin 10 mg/kg/day, Phenobarbitone 3 mg/kg | (1) (2) (3) (4) 14 days | None detailed |
| Ana Podesta 1991 | RCT    | PBC. Mean age 43 years, 93% female | 14 Rifampicin 14 Placebo | Rifampicin 300 mg twice a day | (1) (3) (4) 3 months | None detailed |
| **GSK2330672** |        |            |             |              |          |           |                       |
| Vinod S Hegade 2017 | RCT    | PBC. Mean age 52.9 years, 90% female | 22 Placebo run-in 21 GSK2330672 | GSK2330672 45 mg twice per day on days 1–3, and 90 mg twice daily on days4–14 | (1) (2) (3) (4) 28 days | 19 patients taking UDCA (14 mg/kg/day) during study period |
| **Maralixibat** |        |            |             |              |          |           |                       |
| M. J. Mayo 2019  | RCT    | PBC. Mean age 53.4 years, 91% female | 21 Maralixibat 10 mg 21 Maralixibat 20 mg | Maralixibat 10 mg,10 mg/day Maralixibat 20 mg, 20 mg/day | (1) (2) (3) (4) 13 weeks | None detailed |
| **Obeticholic Acid** |        |            |             |              |          |           |                       |
| F. Nevens 2016  | RCT    | PBC. Mean age 56 years, 91% female | 70 OCA5–10 mg 73 OCA 10 mg 73 Placebo | OCA 5–10 mg/day or 10 mg/day | (1) (3) 1 year | standard-of-care UDCA (13–15 mg/kg/day) or not |
| Kris V. Kowdley 2018 | RCT    | PBC. Mean age 54 years, 85% female | 20 OCA 10 mg 16 OCA 50 mg 23 Placebo | OCA10 mg/day or 50 mg/day | (1) (3) (4) 3 months | None detailed |
Results

Study selection

A total of 468 records were retrieved from the electronic database (PubMed n = 90, EMBASE n = 80, Cochrane Library n = 151, Web of Science n = 106, ClinicalTrials.gov n = 41), and 332 records were excluded after duplicates removed. After browsing the titles and abstracts, 41 articles were excluded based on article type (review n = 28, meta-analysis n = 12, protocol n = 1). After that, 54 articles were assessed as full text and 31 were excluded for the following reasons: not RCTs (n = 9), improper intervention (n = 7), data duplication (n = 1), unavailable data (n = 11), non-English literature (n = 1), absence of a clear basic information about the study subjects (n = 2). Finally, 23 studies were obtained. The details are shown in the flowchart (Figure 1). Of the 23 studies included, eight were RCTs studies of UDCA (Poupon et al., 1990; Oka et al., 1991; Poupon et al., 1991; Battezzati et al., 1993; Lindor et al., 1994; Heathcote et al., 1995; Vuoristo et al., 1995; Parés et al., 2000).

| Study and year | Design | Population | Sample size | Intervention | Outcomes | Follow-up | Concomitant treatment |
|---------------|--------|------------|-------------|--------------|----------|-----------|-----------------------|
| G. M Hirschfield 2014 | RCT | PBC. Mean age 55.1 years, 95% female | 38 OCA 10 mg 48 OCA 25 mg 41 OCA 50 mg 38 Placebo | OCA10 mg/day or 25 mg/day or 50 mg/day | (2) (3) (4) | 3 months | UDCA (15.6–16.3 mg/kg/day) |
| Bezaﬁbrate | C. Corpechot 2018 | RCT | PBC. Mean age 53 years, 95% female | 50 Bezaﬁbrate 50 Placebo | Bezaﬁbrate 400 mg/day | (1) (2) (3) (4) | 2 years | UDCA (13–15 mg/kg/day) |
| Tatsuo Kanda 2003 | RCT | PBC. Mean age 56 years, 86% female | 11 UDCA with Bezaﬁbrate 11 UDCA | Bezaﬁbrate 400 mg/day | (1) (2) (3) (4) | 0.5 years | UDCA (600 mg/day) |
| Study and year | Design | Population | Sample size | Intervention | Outcomes | Follow-up | Concomitant treatment |
| NGM282 | M. J. mayo 2018 | RCT | PBC. Mean age 56.3 years, 91% female | 14 NGM282 0.3 mg NGM282 0.3mg/day NGM282 3 mg NGM282 3 mg/day 15 Placebo | NGM282 0.3mg, 0.3 mg/day NGM282 3mg, 3 mg/day | (1) (2) (3) (4) | 28 days | None detailed |
| Seladelpar (MBX-8025) | David Jones 2017 | RCT | PBC. Mean age 56 years, 95% female | 13 Seladelpar50 mg 13Seladelpar200 mg 12 Placebo | Seladelpar50 mg,50 mg/day Seladelpar200 mg,200 mg/day | (1) (2) (3) (4) | 12 weeks | Continue UDCA at the same dose |
| Malotilate | A European Multi−centre Study Group 1993 | RCT | PBC. Mean age 54.4 years, 96% female | 52 Malotilate 49 Placebo | Malotilate:500 mg, three times a day | (1) (2) (3) (4) | 1.5 years | None detailed |
| Cyclosporine | R.H. Wiesner 1990 | RCT | PBC. Mean age 46.8 years, 97% female | 19 Cyclosporine 10 Placebo | cyclosporine 4 mg/kg/day | (1) (2) (3) (4) | 2 years | None detailed |
| Study and year | Design | Population | Sample size | Intervention | Outcomes | Follow-up | Concomitant treatment |
| Colchicine | P. L. Almasio 2000 | RCT | PBC. Mean age 54.4 years, 90% female | 46 Colchicine plus UDCA 44 UDCA | Colchicine, 1 mg/daily | (1) (2) (3) (4) | 3 years | Cholestyramine, no more than 8 g/day |
| Methotrexate | M.T. Hendrickse1999 | RCT | PBC. Mean age 57 years, 92% female | 30 MTX 30 Placebo | MTX, 7.5 mg/wk (on Friday, Saturday, and Sunday of each week, 2.5 mg/day) | (1) (2) (3) (4) | 6 years | None detailed |

Abbreviations: PBC, Primary biliary cholangitis; MTX, Methotrexate; OCA, Obeticholic Acid; UDCA, Ursodeoxycholic acid; (1) ALP, Alkaline phosphatase; (2) γ-GGT, Gamma-glutamyltranspeptidase; (3)Number with pruritus, grade of pruritus; (4)Adverse event rate(%).
The remaining 15 RCTs contained three studies of obeticholic acid in PBC (Hirschfield et al., 2015; Nevens et al., 2016; Kowdley et al., 2018), two studies of bezafibrate in PBC (Kanda et al., 2003; Corpechot et al., 2018), and two studies of rifampicin (Bachs et al., 1989; Podesta et al., 1991), and one RCT each evaluating the ileal bile acid transporter inhibitor GSK2330672 (Hegade et al., 2017), FGF19 analog NGM282 (Mayo et al., 2018), selective PPAR-δ agonist seladelpar (MBX-8025) (Jones et al., 2017), cyclosporine (Wiesner et al., 1990), colchicine (Almasio et al., 2000), methotrexate (Hendrickse et al., 1999), maralixibat (Mayo et al., 2019) and malotilate (Listed, 1993).

The 23 RCTs included 2,194 patients, 92% of the study population was women, and the average age was 54.9 years. The studies included in our systematic review are shown in Table 1.

**Study quality**

Of all the 23, 11 studies mentioned the randomization techniques (including random sampling with computer (Battezzati et al., 1993; Hendrickse et al., 1999; Hirschfield et al., 2015; Hegade et al., 2017; Jones et al., 2017; Corpechot et al., 2018; Kowdley et al., 2018; Mayo et al., 2019), or interactive voice/web response system (Mayo et al., 2018), or random numbers (Listed, 1993; Heathcote et al., 1995)), while two studies were considered "high risk" because the random methods were inappropriate (Podesta et al., 1991; Vuoristo et al., 1995). Twelve studies followed allocation concealment (including third-party random allocation (Poupon et al., 1990; Battezzati et al., 1993; Lindor et al., 1994; Jones et al., 2017; Corpechot et al., 2018; Mayo et al., 2018; Mayo et al., 2019), sequence number (Listed, 1993; Heathcote et al., 1995; Hendrickse et al., 1999; Hegade et al., 2017), or envelope (Parés et al., 2000)). Of all the included studies, two followed single-blind (Oka et al., 1991; Heathcote et al., 1995), and the rest followed double-blind designs. The data evaluator was blinded in five studies. All the 23 studies reported complete data and there was no risk of other biases. The Cochrane deviation risk assessment tool was used for risk assessment, and the results are shown in Figures 2A,B.

### Pruritus (relief rate)

Most trials reported only the number of patients with pruritus pre-treatment and post-treatment, so we considered the relief rate as the primary outcome. Among the eight studies (Poupon et al., 1990; Oka et al., 1991; Poupon et al., 1991; Battezzati et al., 1993; Lindor et al., 1994; Heathcote et al., 1995; Vuoristo et al., 1995; Parés et al., 2000), of UDCA seven documented itching. The results showed that UDCA combined with or without cholestyramine, compared to placebo (RR = 1.85, 95%CI (1.40, 2.45), $p < 0.001$, $I^2 = 0.0\%$), had a significant difference in relieving pruritus (Figure 3A). Among these, two studies recorded the itching score in detail (Battezzati et al., 1993; Parés et al., 2000). Compared with placebo, UDCA combined
FIGURE 3

(A) The effect of UDCA on pruritus relief compared with placebo. (B) Two studies of UDCA in pruritus scores compared with placebo. (C) OCA increases the risk of pruritus compared with placebo. (D) The effect of Rifampicin on the rate of pruritus relief compared with placebo.
with cholestyramine significantly reduced the itching score (SMD = −1.78, 95% CI (−2.26, −1.29), p < 0.001, I² = 64%), but had a high heterogeneity (p = 0.095, I² = 64.0%) (Figure 3B).

Three studies (Hirschfield et al., 2015; Nevens et al., 2016; Kindley et al., 2018) compared the relief of pruritus after OCA treatment, and the heterogeneity among studies was low (p = 0.311, I² = 14.4%). Meta-analysis showed that OCA increased the incidence of pruritus, compared with placebo (RR = 1.511, 95% CI (1.07, 2.12), p = 0.018) (Figure 3C).

Two studies (Borch et al., 1989; Podesta et al., 1991) compared the relief of pruritus after rifampicin treatment, and the heterogeneity between the studies was low (p = 0.882, I² = 0.0%). The results of meta-analysis showed that rifampicin had no significant effect on itching compared with placebo or control drugs [RR = 1.595, 95%CI (0.97, 2.63), p = 0.067] (Figure 3D).

One study (Wiesner et al., 1990) reported the incidence of pruritus in patients with PBC, before and after treatment, with cyclosporine and placebo. The results showed that cyclosporine did not significantly reduce the incidence of pruritus compared with placebo [RR = 0.726, 95%CI (0.51, 1.03), p = 0.072].

One study (Mayo et al., 2018) reported a comparison between NGM282 and placebo. The results suggested that NGM282 had no significant effect on 5-D itch score [SMD = −0.429, 95%CI (−1.06, 0.20), p = 0.179] and VAS score [SMD = 0.335, 95%CI (−0.29, 0.96), p = 0.293] in patients with PBC.

One study (Listed, 1993) reported a comparison between malodlrate and placebo, which suggested that malodlrate did not significantly reduce the incidence of pruritus [RR = 1.083, 95%CI (0.43, 2.73), p = 0.865].

One study (Jones et al., 2017) reported the comparison of seladelpar and placebo after treatment. The results suggested that seladelpar did not significantly reduce pruritus in patients with PBC. The 5-D itch score [SMD = 0.000, 95%CI (−0.79, 0.79), p = 1.000] and VAS score [SMD = 0.138, 95%CI (−0.65, 0.92), p = 0.731] showed no significant alteration.

One study (Mayo et al., 2019) reported a comparison between maralixibat and placebo. The results suggested that maralixibat did not significantly reduce the pruritus 5-D itch score in patients with PBC [SMD = −0.09, 95%CI (−0.59, 0.41), p = 0.725].

A study (Hendrickse et al., 1999) on methotrexate showed that, compared with placebo, it significantly reduced pruritus scores [SMD = 1.000, 95%CI (−1.54, −0.46), p = 0.000].

In a comparative study (Vuoristo et al., 1995) between colchicine plus UDCA and UDCA, it was found that colchicine had no significant effect on reducing the incidence of pruritus [RR = 0.964, 95%CI (0.42, 2.24), p = 0.931].

Another study (Hegade et al., 2017) on GSK2330672 used different scoring systems to evaluate the change in pruritus score before and after treatment. The percentage changes from baseline itch scores were -57% [95% CI (−73, −42), p < 0.0001] in NRS, −31% (−42−20, p < 0.0001) in PBC-40 itching, and −35% (−45−25, p < 0.0001) in 5-D itch score.

One study (Pariès et al., 2000) of UDCA could not be analyzed because of the lack of data. Indicators changes before and after treatment for all included studies are listed in Table 2.

### Alkaline phosphatase

Compared with placebo, UDCA, OCA and rifampicin could reduce serum ALP levels, UDCA [SMD = −2.91, 95%CI (−4.37, −1.44), p = 0.000], OCA [SMD = −5.56, 95%CI (−9.82, −1.30), p = 0.011], rifampicin [SMD = −0.53, 95%CI (−1.02, −0.04), p = 0.033]. However, the change brought about by bezafibrate [SMD = −4.98, 95%CI (−12.09, 2.16), p = 0.172] was not statistically significant. But the ALP results showed a high degree of heterogeneity in UDCA (p = 0.000, I² = 98.7%), OCA (p < 0.01, I² = 97.5%), and bezafibrate (p < 0.01, I² = 98.8%) (Figures 4A–C). However, the heterogeneity of the results of rifampicin was low (p = 0.704, I² = 0.0%) (Figure 4D). We conducted sensitivity analysis (Supplementary Material S1) and subgroup analysis (according to UDCA dose, medium: 13–15 mg/kg/d, low: <13 mg/kg/d, high: >15 mg/kg/d) (Supplementary Material S2), study area (Asia, Europe, America) (Supplementary Material S3), and if cholestyramine was used as a combination (Supplementary Material S4).

A study (Wiesner et al., 1990) comparing cyclosporine with placebo found that, cyclosporine was superior to placebo in reducing ALP [SMD = −5.36, 95%CI (−6.98, −3.74), p = 0.000].

One study (Mayo et al., 2018) reported a comparison between NGM282 and placebo. The results suggested that NGM282 could significantly reduce the level of ALP in patients with PBC [SMD = −1.205, 95%CI (−1.98, −0.44), p = 0.002].

One study (Listed, 1993) reported a comparison between malodlrate and placebo. The results showed no significant difference in the reduction of ALP between the two [SMD = −0.236, 95%CI (−0.63, 0.16), p = 0.238].

One study (Jones et al., 2017) reported a comparison between seladelpar and placebo, which suggested that seladelpar significantly reduced ALP [SMD = −2.224, 95%CI (−3.24, −1.21), p = 0.000].

One study (Mayo et al., 2019) on comparison between maralixibat and placebo concluded that maralixibat did not significantly reduce serum ALP [SMD = −0.183, 95%CI (−0.77, 0.40), p = 0.540].

A study (Vuoristo et al., 1995) on colchicine plus UDCA against UDCA alone showed that, compared with UDCA, colchicine plus UDCA significantly reduced ALP [SMD = −0.183, 95%CI (−0.77, 0.40), p = 0.540]. The other studies on methotrexate (Listed, 1993), colchicine (Almasio et al.,
| Study ID            | Intervention                        | Change in pruritus (event/noevent) | Change in ALP (U/L) (MD ± SD) | Change in γ-GGT (U/L) (MD ± SD) | Chang in adverse events (event/noevent) |
|---------------------|-------------------------------------|------------------------------------|-------------------------------|---------------------------------|------------------------------------------|
| F. Nevens 2016      | OCA 10 mg                           | 6/50                               | −130 ± 15                     | Not reported                    | Not reported                             |
|                     | Placebo                             |                                    | −14 ± 15                      | Not reported                    |                                          |
| K.V. Kowdley 2018   | OCA 10 mg                           | Not reported                       | −159 ± 67                     | Not reported                    | 33/3                                     |
|                     | Placebo                             |                                    | 1 ± 17                        |                                 | 21/2                                    |
| Hirschfield 2014    | OCA 10 mg                           | Not reported                       | Not reported                  | −92 ± 31                        | 34/4                                     |
|                     | Placebo                             |                                    | −1 ± 31                       |                                 | 32/6                                    |
| C. Corpechot 2018   | Bezafibrate                         | Not reported                       | −60 ± 4                       | −38 ± 9                         | 43/7                                     |
|                     | Placebo                             |                                    | 0 ± 9                         | 7 ± 16                          | 45/5                                    |
| Tatsuo Kanda 2003   | Bezafibrate + UDCA                  | 1/6                                | −310 ± 234                    | −31 ± 20                        | 1/10                                     |
|                     | UDCA                                | 0/5                                | −5 ± 219                      | −1 ± 14                         | 0/11                                    |
| Poupon RE 1990      | UDCA                                | 18/20                              | −417 ± 403                    | −413 ± 394                      | Not reported                             |
|                     | Placebo                             | 10/20                              | 20 ± 328                      | −32 ± 512                       |                                          |
| Albert Paris 2000   | UDCA                                | Not reported                       | −466 ± 56                     | −256 ± 33                       | 9/90                                     |
|                     | Placebo                             | −97 ± 64                           | −17 ± 30                      |                                 | 6/87                                     |
| P.M. Battezzati 1993| UDCA                                | 11/29                              | Not reported                  | Not reported                    | 4/40                                     |
|                     | Placebo                             | 5/34                               |                                |                                 | 1/43                                     |
| E.J. Heathcote 1994 | UDCA                                | 24/63                              | −42 ± 99                      | Not reported                    | 12/99                                    |
|                     | Placebo                             | 16/63                              | 3 ± 98                        |                                 | 19/92                                    |
| K. D. Lindor 1994   | UDCA                                | 27/21                              | −711 ± 811                    | Not reported                    | 21/68                                    |
|                     | Placebo                             | 12/39                              | −300 ± 633                    |                                 | 43/48                                    |
| Laura Bachs 1989    | Rifampicin                          | 19/2                               | −316 ± 647                    | −99 ± 187                       | 1/20                                     |
|                     | Phenobarbitone                      | 8/10                               | 125 ± 795                     | 173 ± 294                       | 3/15                                     |
| Study ID            | Intervenion Change in pruritus (event/noevent) Change in ALP (U/L) (MD ± SD) Change in γ-GGT (U/L) (MD ± SD) Change in Adverse events (event/noevent) |
| Ana Podesta 1991    | Rifampicin                          | 14/0                               | −383 ± 683                    | Not reported                    | 0/14                                     |
|                     | Placebo                             | 6/8                                | −92 ± 697                     |                                 | 0/14                                     |
| M. J. mayo 2018     | NGM282 3 mg                         | 5-D itch.:−2.1 ± 4.7, VAS:−6.2 ± 15.6 | −66 ± 57.7                   | −50.8 ± 71.9                   | 22/8                                     |
|                     | Placebo                             | 5-D itch.:−0.2 ± 3.8, VAS:−12.6 ± 24.9 | 3.3 ± 57.3                   | −5.6 ± 47.3                    | 12/3                                     |
| R. H. Wiesner 1990  | Cyclosporine                        | 16/1                               | −143 ± 623                    | Not reported                    | 15/4                                     |
|                     | Placebo                             | 3/6                                | 273 ± 345                     |                                 | 5/5                                      |
| A European Multi-centre study group | Malotilate                        | 8/16                               | −61 ± 111                     | Not reported                    | 13/39                                    |
|                     | Placebo                             | 6/20                               | −30 ± 150                     |                                 | 2/47                                     |
| David Jones 2017    | Seladelpar 200 mg (continue UDCA)   | 4/1                                | −156 ± 100                    | Not reported                    | 12/12                                    |
|                     | Placebo (continue UDCA)             | 3/1                                | 4.7 ± 3.5                     |                                 | 6/7                                      |

(Continued on following page)
and GSK2330672 (Hegade et al., 2017) did not report any change of ALP level after drug treatment.

**Gamma-glutamyl transpeptidase**

Blood γ-GGT levels were reported in 5 RCTs of UDCA (Poupon et al., 1990; Oka et al., 1991; Poupon et al., 1991; Vuoristo et al., 1995; Parés et al., 2000) and two of bezafibrate (Kanda et al., 2003; Corpechot et al., 2018). The results showed that UDCA and bezafibrate could reduce serum γ-GGT levels (UDCA [SMD = −2.18, 95%CI (−2.43, −1.93), p = 0.000], bezafibrate [SMD = −2.65, 95%CI (−4.34, 0.96), p = 0.002]) (Figures 5A,B). However, there was obvious heterogeneity for UDCA (p < 0.01, I² = 98.9%) and bezafibrate (p < 0.01, I² = 88.8%). Therefore, we conducted a subgroup analysis based on the dose of UDCA (Supplementary Material S5), study area (Supplementary Material S6) and whether cholestyramine was combined with UDCA (Supplementary Material S7), to evaluate its effect on serum γ-GGT. Sensitivity analysis showed that the results were consistent (Supplementary Material S8).

A study (Hirschfield et al., 2015) on the effect of OCA in serum γ-GGT showed that OCA reduced serum γ-GGT than placebo [SMD = −2.935, 95%CI (−3.59, −2.28), p = 0.000].

One study (Bachs et al., 1989) reported a comparison between rifampicin and placebo. The results suggested that the former could significantly reduce the level of serum γ-GGT [SMD = −1.123, 95%CI (−1.80, −0.44), p = 0.001].

One study (Mayo et al., 2018) reported a comparison between NGM282 and placebo. The results suggested that NGM282 can reduce the level of γ-GGT [SMD = −0.738, 95% CI (−1.47, −0.01), p = 0.047] in patients with PBC.

A study (Mayo et al., 2019) on the effect of maralixibat on serum γ-GGT, compared with placebo, showed no significant difference between the two drugs [SMD = −0.068, 95% CI (−0.65, 0.52), p = 0.819].

The other two studies of OCA (Nevens et al., 2016; Kowdley et al., 2018), three of UDCA (Battezzati et al., 1993; Lindor et al., 1994; Heathcote et al., 1995), one of rifampicin (Podesta et al., 1991), one of cyclosporine (Wiesner et al., 1990), one of malotilate (Listed, 1993), one of seladelpar (Jones et al., 2017), one of methotrexate (Hendrickse et al., 1999), one of colchicine (Almasio et al., 2000) and one of GSK2330672 (Hegade et al., 2017) did not report any change of serum γ-GGT level after treatment.

**Adverse events**

Compared with placebo, the incidences of adverse events with UDCA were lower [OR = 0.61, 95%CI (0.42, 0.89), p = 0.011], and there was no significant difference in OCA (OR = 1.03, 95%CI (0.61, 1.75), p = 0.901) and bezafibrate (OR = 0.99, 0.52).
FIGURE 4
(A) The effect of UDCA in serum ALP. (B) The effect of OCA on serum ALP. (C) The effect of Bezafibrate on serum ALP. (D) The effect of Rifampicin on serum ALP.
The results showed that the heterogeneity was low, (for UDCA: $p = 0.195$ and $I^2 = 32.0\%$, for OCA: $p = 0.892$ and $I^2 = 0.0\%$, and for bezafibrate: $p = 0.504$, $I^2 = 0.0\%$) (Figures 6A–C).

Sensitivity analysis of UDCA indicated that the results were consistent (Supplementary Material S9). Subgroup analysis based on UDCA dose (Supplementary Material S10), study area (Supplementary Material S11), year of publication (Supplementary Material S12) and whether UDCA was combined with cholestyramine (Supplementary Material S13), showed that the occurrence of adverse events was dose-dependent. Both high (>15 mg/kg/day) and low doses (<13 mg/kg/day) of UDCA increased the incidence of adverse events, while the middle dose (13–15 mg/kg/day) of UDCA did not increase the incidence of adverse events.

A study (Mayo et al., 2018) on the comparison of adverse reactions between NGM282 and placebo showed no significant difference [OR = 0.917, 95%CI (0.36, 2.34), $p = 0.856$].

One study (Wiesner et al., 1990) reported no significant difference in the incidence of adverse events when cyclosporine and placebo were compared [OR = 1.579, 95%CI (0.44, 5.62), $p = 0.481$].

A study (Listed, 1993) compared malolitale with placebo, showed that malolitale was superior than placebo in reducing adverse events [OR = 6.125, 95%CI (1.31, 28.52), $p = 0.021$].

Two separate studies (Jones et al., 2017; Mayo et al., 2019) reported no significant difference in the reduction of adverse events between seladelpar (MBX-8025) and placebo groups [OR = 1.820, 95%CI (0.59, 5.62), $p = 0.298$], and between Maralixibat and placebo [OR = 1.558, 95%CI (0.59, 4.13), $p = 0.372$].

Similarly, studies (Hendrickse et al., 1999; Almasio et al., 2000; Hegade et al., 2017) reported no significant differences for the adverse events between methotrexate and placebo [OR = 1.105, 95%CI (0.50, 2.46), $p = 0.806$], colchicine and placebo [OR = 0.522, 95%CI (0.18, 1.53), $p = 0.236$], and GSK2330672 and placebo [OR = 1.000, 95%CI (0.41, 2.47), $p = 1.000$].

Two studies (Bachs et al., 1989; Podesta et al., 1991) reported no significant difference in the reduction of adverse events between rifampicin and placebo [OR = 0.286, 95%CI (0.03, 2.99), $p = 0.296$].
FIGURE 6
(A) The adverse events for UDCA. (B) The adverse events for OCA. (C) The adverse events for Bezafibrate. (D) The adverse events for NGM282.
Discussion

The rising incidence of pruritus in PBC and the lack of effective treatment methods were serious concerns. One study found that the incidence of pruritus can growing from 19% at the beginning to 80% in 10 years later (Prince et al., 2002). Pruritus in PBC was belong to cholestatic pruritus. Unlike histamine-related pruritus, cholestatic pruritus had no evidence-based guidelines because the underlying pathogenesis was unclear. Some studies had shown that itching symptoms often occurred in female patients with PBC, accompanied by increasing levels of ALP and γ-GGT, but the mechanism behind it was still unknown. Existing studies had found that PBC-related pruritus was mainly related to bile acids, lysophosphatidic acid A (LPA), G-protein coupled bile acid receptor1 (GPBAR1), endogenous opioids, 5-hydroxytryptamine (5-HT), nitric oxide and substance P. But since the circulation level of these substances was not well correlated with the severity of pruritus, there may be complex interactions among multiple pruritus substances (Quarneti et al., 2015). Firstly, for the treatment of PBC-related pruritus, we need to rule out renal failure, psoriasis, idiopathic dermatitis and other diseases that can cause pruritus. Secondly, drugs treatment and non-drugs treatment measures should be adopted according to the severity of the disease. The first-line treatment drugs were mainly bile acid-binding resin (Gideon et al., 2017), such as colesvelam hydrochloride, which has better therapeutic effect than cholestyramine. Second-line therapeutic drugs such as rifampicin, opioid antagonists (naltrexone) and modulators of 5-HT receptor pathway (sertraline) can be used as supplements to first-line drugs. In addition, most of the non-drug treatments belong to invasive treatment strategies, and liver transplantation was the last choice for patients with intractable pruritus when all treatment strategies were ineffective. Unfortunately, due to lack of evidence-based evidence, the role of many drug interventions in the treatment of cholestatic pruritus, including PBC was uncertain. This result has also been confirmed in a recent related study (Dervout et al., 2022).

Moreover, drugs for PBC were indispensable in the treatment of pruritus. In recent years, newer target drugs were introduced, which mainly focus on reducing cholestasis and reduced bile acid toxicity, and are immunomodulatory in action and antiinbriotic in nature (Shah and Kowdle, 2020). However, the efficacy of these drugs remains to be further evaluated. For example, OCA was a semisynthetic chenodeoxycholic acid analogue, which can inhibit bile acid synthesis and stimulate bile secretion to protect hepatocytes by activating farnesol X receptor. Amazingly, it was found that pruritus increased dose-dependently with OCA treatment (Gong et al., 2008; Trauner et al., 2019), and so it using in patients with PBC associated pruritus was limited. Systematic reviews and meta-analyses on UDCA showed that it improved the levels of serum ALP and γ-GGT, but there were no significant effects on pruritus, fatigue, or reduction in adverse events in PBC (Gong and Gluud, 2005). Similar results were obtained for methotrexate (Guo et al., 2015), fenofibrate (Zhang et al., 2015), and bezafibrate (Gong et al., 2007). Cyclosporin A may significantly improving pruritus, but it had significant side effects compared with placebo (Gerussi et al., 2021). However, we found that these studies did not consider pruritus as a primary outcome measure, and we need an effective and safe pharmacological intervention for pruritus associated with PBC was yet unmet.

Therefore, we conduct this systematic review and meta-analysis to find the effective and safety pharmacological intervention for managing pruritus in PBC.

Pruritus (relief rate)

This meta-analysis of 23 RCTs found that UDCA, methotrexate and GS2330672 improved pruritus (comparing the pruritus relief rate before and after treatment). OCA may increase the risk of pruritus, hence it was not recommended for patients suffering from PBC pruritus. However, due to the limited number of studies, it was suggested that more RCTs be conducted to understand their role in improving the symptom of itching (Specific data are summarized in Table 2).

Serum alkaline phosphatase and γ-glutamyl transpeptidase

Serum ALP and γ-GGT were two important indicators for the diagnosis and prognosis of PBC[57], while these also serve as important markers to diagnose the existence of cholestasis. We analyzed the effects of drug intervention on ALP and γ-GGT. All the included studies reported that UDCA, OCA, rifampicin, cyclosporine, NGM282, seladelpar and colchicine may improve blood ALP. Further, UDCA, bezafibrate, OCA, rifampicin and NGM282 may improve blood γ-GGT. We found that rifampicin can significantly reduce the blood ALP level with low heterogeneity, while UDCA and OCA have high heterogeneity in reducing the level of ALP. Although UDCA and bezafibrate reduce the level of blood γ-GGT, they have high heterogeneity. Rifampicin and NGM282 were equally efficacious in reducing blood ALP and γ-GGT, which was an area worthy of further study.

Adverse events

The existing evidence showed that a medium dose of UDCA (13–15 mg/kg/day) and malotilate may have the benefit of reducing the incidence of adverse events (p < 0.05), and these studies showed low heterogeneity. It was also found that the other drugs that inculded did not significantly raising the incidence of adverse events compared with placebo (p > 0.05).
Conclusion

In this study, we attempted to evaluate the efficacy and safety of drug interventions in the treatment of PBC-associated pruritus. It was found that UDCA, methotrexate, and GSK2330672 may improve pruritus, but due to the existence of literature quality and heterogeneity of the included drugs, we cannot recommend some therapeutic drugs in line with clinical practice. Notably, with the continuous accumulation of high-quality clinical trial evidence of some emerging drugs such as bezafibrate and ileal apical bile acid transporter inhibitors (GSK2330672), perhaps in the near future, PBC-related pruritus will get more high-quality evidence and standardized treatment, and the rate of utilization of liver transplantation will become lower.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

Conceptualization: CX and RY. Date extracted: CX and XL. Assessed evidence: XL and CX. Date analyzed: CX and XL. Writing-review and editing: CX and MD. Interpreted the results: SW.

References

Almasio, P., Floreani, A., Chiaravalloti, M., Provenzano, G., Battezzati, P., Crossian, A., et al. (2008). Multicentre randomized placebo-controlled trial of ursodeoxycholic acid with or without colchicine in symptomatic primary biliary cirrhosis. Aliment. Pharmacol. Ther. 14 (12), 1645–1652. doi:10.1046/j.1365-2036.2008.00869.x

Bachs, L., Parés, A., Elena, M., Pares, A., and Rodes, J. (1989). Comparison of rifampicin with phenobarbitone for treatment of pruritus in biliary cirrhosis. Lancet 1 (8638), 574–576. doi:10.1016/s0140-6736(89)91608-5

Battezzati, P. M., Poddà, M., Bianchi, F. B., Naccarato, R., Orlandi-Surrenti, C., et al. (1993). Ursodeoxycholic acid for symptomatic primary biliary cirrhosis. Preliminary analysis of a double-blind multicenter trial. Italian Multicenter Group for the Study of UDCA in PBC. J. Hepatol. 17 (3), 332–338. doi:10.1016/S0168-8278(03)80214-4

Beuers, U., Kremer, A., Bolier, R., and Elferink, R. P. J. O. (2014). Pruritus in cholestasis: Facts and fiction. Hepatology 60 (1), 399–407. doi:10.1002/hep.26909

Bray, G., Hessel, W., Afsahn, A., Jensen, M. D., Dietz, W. H., Long, M., et al. (2018). The science of obesity management: An endocrine society scientific statement. Endocr. Rev. 39 (2), 79–132. doi:10.1210/er.2017-00253

Carey, E. J., Ali, A. H., and Lindor, K. D. (2015). Primary biliary cirrhosis. Lancet 386 (10003), 1565–1575. doi:10.1016/S0140-6736(15)00543-3

Ca, G., and Sg, C. (1988). Treatment of pruritus in primary biliary cirrhosis with rifampin. Results of a double-blind, crossover, randomized trial. Gastroenterology 94 (2), 488–493. doi:10.1016/S0016-5085(88)90442-8

Corpechot, C., Chazouillères, O., Rousseau, A., le Gruyer, A., Habersetzer, F., Mathurin, P., et al. (2018). A placebo-controlled trial of bezafibrate in primary biliary cholangitis. N. Engl. J. Med. 378 (23), 2171–2181. doi:10.1056/NEJMoa1714519

Dervout, C., Boulais, N., Barretche, T., Noubaba, J. B., Brenaut, E., and Misery, L. (2022). Efficacy of treatments for cholestatic pruritus: A systemic review and meta-analysis. Acta Derm. Venereol. 102, adv00653. doi:10.2340/actadermv102.310

Dg, A., J. T., Tetzlaff, J., Mulrow, C., Gotschke, P. C., Ioannidis, J. P. A., et al. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. BMJ Clin. Res. ed.) 339, b2700. doi:10.1136/bmj.b2700

Drezner, S., Babinska, I., Gazda, J., Halanowa, M., Janicko, M., Kucinska, B., et al. (2020). Epidemiology and clinical course of primary biliary cholangitis in Eastern Slovakia. Int. J. Public Health 65 (5), 683–691. doi:10.1007/s00038-020-01391-6

Gerussi, A., Bernasconi, D., D’Oonnell, S., Lammers, W. J., Van Buuren, H., Hirschfeld, G., et al. (2021). Measurement of gamma glutamyl transferase to determine risk of liver transplantation or death in patients with primary biliary cholangitis. Clin. Gastroenterol. Hepatol. 19 (8), 1688–1697. e1614. doi:10.1016/j.cgh.2020.08.006

Gideon, H., Ulrich, B., Christophe, C., Pietro, I., David, J., Marco, M., et al. (2017). EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J. Hepatol. 67 (1), 145–172. doi:10.1016/j.jhep.2017.03.022

Gong, Y., Christensen, E., and Gluud, C. (2007). Cyclosporin A for primary biliary cirrhosis. Cochrane Database Syst. Rev. 3, CD000552. doi:10.1002/14651858.CD000552.pub2

Gong, Y., and Gluud, C. (2005). Methotrexate for primary biliary cirrhosis. Cochrane Database Syst. Rev. 3 (3), CD004385. doi:10.1002/14651858.CD004385.pub2

Gong, Y., Zhi, B. H., Christensen, E., and Gluud, C. (2008). Ursodeoxycholic acid for primary biliary cirrhosis. Cochrane Database Syst. Rev. 3 (3), CD000551. doi:10.1002/14651858.CD000551.pub2

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Mayo, M. J., Wigg, A. J., Leggett, B. A., Arnold, H., Thompson, A. J., Weltman, M., et al. (2018). NGM282 for treatment of patients with primary biliary cholangitis: a multicenter, randomized, double-blind, placebo-controlled trial. Hepatol Commun. 2 (9), 1037–1050. doi:10.1002/hep4.1209

Mj, M., I., H., S., S., Jacob, H., Getachew, Y., and Rush, A. J. (2007). Sertraline as a first-line treatment for cholestatic pruritus. Hepatology 45 (3), 666–674. doi:10.1002/hep.21553

Nevens, F., Andreone, P., Mazzella, G., Strasser, S. I., Bowls, C., Invernizzi, P., et al. (2016). A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. Nat. Engl. J. Med. 375 (7), 631–643. doi:10.1056/NEJMoa1509480

Oka, H., Toda, G., Itoka, Y., Hashimoto, N., Kamamura, T., et al. (1991). A multicenter, double-blind controlled trial of ursodeoxycholic acid for primary biliary cirrhosis. Gastroenterol. Jpn. 26 (5), 774–780. doi:10.1002/9782779919

Parés, A., Caballéria, L., Rodés, J., Bruguera, M., Rodríguez, L., García-Plaza, A., et al. (2008). Long-term efficacy of rifampin in primary biliary cirrhosis. Results of a double-blind controlled multicentric trial. UDCA-cooperative group from the Spanish association for the study of the liver. J. Hepatol. 23 (4), 561–566. doi:10.1016/j.jhep.2008.03.0216–0

Podaesta, A., Lpez, T., Teg, R., Villamil, F., Flores, D., Mastai, R., et al. (1991). Treatment of pruritus of primary biliary cirrhosis with rifampin. Dig. Dis. Sci. 36 (2), 216–220. doi:10.1002/fodp.10397

Poupon, R. E., Balkau, B., Eschwege, E., and Poupon, R. (1991). A multicenter, controlled trial of ursodeoxycholic acid for the treatment of primary biliary cirrhosis. UDCA-PBC Study Group. N. Engl. J. Med. 324 (22), 1548–1554. doi:10.1056/NEJM19911032422204

Poupon, R. E., Eschwege, E., and Poupon, R. (1990). Ursodeoxycholic acid for the treatment of primary biliary cirrhosis: Interim analysis of a double-blind multicenter randomized trial. J. Hepatol. 11 (1), 16–21. doi:10.1016/0168-8979(89)90265-8

Prince, M., Chetwynd, A., Newman, W., Metcalf, J. V., and James, O. F. W. (2002). Survival and symptom progression in a geographically based cohort of patients with primary biliary cirrhosis: Follow-up for up to 28 years. Gastroenterology 123 (4), 1044–1051. doi:10.1053/gast.2002.302672

Quarneti, C., Muratori, P., Lalanne, C., Fabbi, A., Menichella, R., Granito, et al. (2015). Fatigue and pruritus at onset identify a more aggressive subset of primary biliary cirrhosis. Liver Int. 35 (2), 636–641. doi:10.1111/liv.12560

Rajabellina, K., Dow, C., Romana Mancino, F., Louis, B., Bontourn-Russel, M. C., Balkau, B., et al. (2019). Population attributable fractions of the main type 2 diabetes mellitus risk factors in women: Fatigue and ursodeoxycholic acid in primary biliary cirrhosis. J. Diabetes 11 (3), 242–253. doi:10.1007/s13461-017-02839

Shah, R. A., and Kowdley, K. V. (2020). Current and potential treatments for primary biliary cholangitis. Lancet. Gastroenterol. Hepatol. 5 (3), 306–315. doi:10.1016/s2468-1253(19)30343-7

Sp, P., C., B. H., Meijzos, J., Dong, X., and Kwatra, S. G. (2019). Cholestatic pruritus: Emerging mechanisms and therapeutics. J. Am. Acad. Dermatol. 81 (6), 1371–1378. doi:10.1016/j.jaad.2019.04.035

Tajiri, K., and Shimizu, Y. (2017). Recent advances in the management of pruritus in chronic liver diseases. World J. Gastroenterol. 23 (19), 4318–4326. doi:10.3748/wjg.v13.i19.4318

Th, B. V. S., Ha, R. S., and Tennent, D. M. (1961). The treatment of pruritus and hypercholesterolemia of primary biliary cirrhosis with cholestyramine. N. Engl. J. Med. 265, 469–474. doi:10.1056/nejm19610926256004

Trauner, M., Nevens, F., Shnfinn, M., Drentt, J. P. H., Bowls, C. L., Vargt, V., et al. (2019). Long-term efficacy and safety of obeticholic acid for patients with primary biliary cholangitis: 3-year results of an international open-label extension study. Lancet. Gastroenterol. Hepatol. 4 (6), 445–453. doi:10.1016/s2468-1253(19)30049-9

Vuoristo, M., Farkikl, M., Karvonen, A. E., Leino, R., Hehtola, J., Makinen, J., et al. (1995). A placebo-controlled trial of primary biliary cirrhosis treatment with colchicine and ursodeoxycholic acid. Gastroenterology 108 (5), 1470–1478. doi:10.1016/s0016-5085(95)90066-7

Wiesner, R. H., Lindor, K. D., Jorgensen, R. A., Balduin, W. P., Homburger, H. A., et al. (1990). A controlled trial of cyclosporine in the treatment of primary biliary cirrhosis. N. Engl. J. Med. 322 (20), 1419–1424. doi:10.1056/nejm199010173222003

Zeng, N., Duan, W., Chen, S., Wu, S., Ma, H., Ou, X., et al. (2019). Epidemiology and clinical course of primary biliary cholangitis in the asia-pacific region: A systematic review and meta-analysis. Hepatol Int. 13 (133–1341), 788–799. doi:10.1002/hep4.2019.09894.x

Zhang, Y., Chen, K., Dai, W., Xia, Y., Wang, F., Shen, M., et al. (2015). Combination therapy of bevacizumab and ursodeoxycholic acid for primary biliary cirrhosis: A meta-analysis. Hepatol Res. 45 (1), 48–58. doi:10.1111/hepr.12373