Annals of Gastroenterology (2025) **38,** 121-132

Primary biliary cholangitis: a summary of pathogenesis and therapies

Imen Jallouli[a]*, Michael Doulberis[a,b,c]*, Jannis Kountouras[b]

Medical University Department, Kantonsspital Aarau, Switzerland; Ippokration Hospital, Aristotle University of Thessaloniki, Macedonia, Greece; Gastroklinik, private Gastroenterological Practice, Horgen, Switzerland

Abstract

Primary biliary cholangitis (PBC) is a progressive autoimmune liver disease characterized by chronic inflammation and destruction of interlobular bile ducts. Its pathogenesis involves a complex interplay of genetic predisposition, environmental triggers, and immune-mediated mechanisms, particularly T-helper cell activity, leading to bile duct damage. First-line therapy includes ursodeoxycholic acid (UDCA), which improves liver biochemistry and slows disease progression, with obeticholic acid (OCA) as an option for non-responders. Double and/or triple therapy, including UDCA, OCA, and fibrates, appears to be superior in achieving therapeutic benefits in UDCA-nonresponsive PBC patients. Emerging therapies, such as peroxisome proliferator-activated receptor-α agonists, biologics such as dacetuzumab and rituximab, and experimental approaches such as stem-cell therapy, offer promising advances in managing PBC. Liver transplantation remains a final treatment option for advanced cases.

Keywords Primary biliary cholangitis, pathogenesis, therapy, peroxisome proliferator-activated receptor agonists, ileal bile acid transporter inhibitors

Ann Gastroenterol 2025; 38 (2): 121-132

Introduction

Primary biliary cholangitis (PBC), although generally considered a rare pathology, represents one of the most common progressive autoimmune liver diseases. It predominantly affects middle-aged women and involves chronic, persistent inflammation of the interlobular bile ducts [1], which can ultimately lead to liver damage through retention of bile acids (BAs) in the liver [2]. If left untreated, PBC can lead to liver fibrosis, cirrhosis, liver decompensation and even death, necessitating novel therapies and/or liver transplantation [3,4]. Early diagnosis and timely treatment are crucial to prevent progression to end-stage liver disease [2].

The prevalence of PBC varies widely across different regions, from 1.9-40.2 cases per 100,000 [5]. In the US, although its incidence initially remained steady at 4-5.8 per 100,000 people, the prevalence has risen to 39-40.2 per 100,000 as a result of earlier detection and reduced mortality from treatment.

The etiology of PBC remains unclear, and its pathogenesis is complex. It is a multifactorial disease involving immune-mediated destruction of small and medium intrahepatic bile ducts, influenced by genetic factors, epigenetics, the gut–liver axis and environmental exposures. Pathogenetic mechanisms include the roles of genetic risk, and how the environment and gut dysbiosis cause immune cell dysfunction and aberrant BA signaling. Gut dysbiosis is increasingly recognized as a significant contributing factor. Cholangiocytes, the epithelial cells lining the bile ducts, are the primary target of the dysregulated immune response, with cholangiocyte senescence documented as a driving mechanism that compromises bile duct function and accelerates disease progression. Additionally, BAs play a pivotal role in the development and treatment of PBC.

While BAs-based therapies, particularly ursodeoxycholic acid (UDCA) and obeticholic acid (OCA), remain the

[a]Division of Gastroenterology and Hepatology, Medical University Department, Kantonsspital Aarau, Switzerland (Imen Jallouli, Michael Doulberis); [b]Department of Internal Medicine, Second Medical Clinic, Ippokration Hospital, Aristotle University of Thessaloniki, Thessaloniki, Macedonia, Greece (Michael Doulberis, Jannis Kountouras); [c]Gastroklinik, Private Gastroenterological Practice, Horgen, Switzerland (Michael Doulberis)

Conflict of Interest: None

*Equal contribution

Correspondence to: Prof. Jannis Kountouras, Second Medical Clinic, School of Medicine, Ippokration Hospital, Aristotle University of Thessaloniki, 8 Fanariou St, Byzantio, Thessaloniki, Macedonia 551 33, Greece, e-mail: jannis@auth.gr; ancoratus2010@gmail.com

Received 28 October 2024; accepted 17 February 2025; published online 28 February 2025

DOI: https://doi.org/10.20524/aog.2025.0953

cornerstone of PBC treatment, several novel therapeutic strategies have been introduced in recent years [4,5]. The aim of this narrative review is to briefly discuss the pathogenesis of PBC and provide an updated overview of both established and emerging treatment options.

Pathogenesis

Understanding the pathogenesis of PBC (Fig. 1) is crucial for identifying effective therapies. The disease is characterized by autoimmune-mediated destruction of intrahepatic bile ducts, driven by genetic predisposition and environmental triggers such as infections, toxic chemicals, or drugs [6]. Although there is substantiated pathogenesis of PBC, the most widely accepted theory is that a genetically predisposed patient meets an autoimmune triggering event. This trigger may be an environmental factor, a virus, an allergen, a chemical molecule or a drug [6].

The key serological finding in PBC is the presence of disease-specific antimitochondrial antibodies (AMA) that can be detected in more than 95% of patients [7,8]. These autoantibodies are specific to the antigenic determinant E2, located within different subunits of the complex of dehydrogenase enzyme in the mitochondrial membrane. These subunits are: 2-oxo-acid (2OADC-E2), pyruvate (PDC-E2), branched-chain 2-oxo-acid (BCOADC-E2), and 2-oxo-glutarate (OGDC-E2). The immunodominant autoantigen in PBC is PDC-E2. Loss of tolerance to PDC-E2 is accompanied by the development of cholangiocyte damage, chronic cholestasis and eventual liver fibrosis [9]. In addition to disease-specific AMA, anti-sp100 and anti-gp210 antibodies are highly specific markers for PBC. Both are found in approximately 20-30% of PBC patients and are particularly relevant in AMA-negative cases. Anti-gp210 is additionally associated with more severe disease progression and a worse prognosis [7,8]. Genetic predisposition involved in PBC includes major histocompatibility complex (MHC) class II (*DR8, 1*0102*) and MHC class III (C4 null) variants, as well as non-MHC genes such as CTLA-4 [10-12]. Genetic predisposition—associations with human lymphocyte antigen (HLA) and non-HLA haplotypes involved in bile homeostasis and associated with inflammatory regulatory pathways—are the main mechanisms that trigger and maintain inflammation in PBC. Genome-wide association studies identified the HLA complex on chromosome 6p21 to be responsible for harboring several risk genes that may be directly or indirectly involved in the pathogenesis of PBC. Familial links, such as higher prevalence in first-degree relatives and identical twins, and associations with other autoimmune diseases, suggest a strong genetic basis [13-15]. There is an 11-fold greater risk of first-degree relatives of PBC patients manifesting the disease phenotype, with at least 23 risk genes identified.

Environmental factors (infections, selenium or vitamin D deficiency, toxic bile) also trigger and maintain inflammation in PBC. Specifically, recurrent urinary tract infections, exposure to chemicals and smoking, may initiate the autoimmune cascade in predisposed individuals [16-18].

In the immunological response, autoreactive T cells play a central role. CD8+ T cells directly attack biliary epithelial cells (BECs). CD4+ T cells, including T-helper (Th) 1 and Th17 cells, contribute to an inflammatory microenvironment via cytokines such as interleukin-12, interferon-γ and tumor necrosis factor-α [2]. Th17 cells drive fibrosis in later stages, while regulatory T cells (Tregs), which maintain immune tolerance, are impaired in number and function [19,20]. PBC pathogenesis is also influenced by dysregulated cellular processes, such as autophagy, apoptosis and senescence. Overexpression of microRNA-506 in BECs downregulates bicarbonate transporters, leading to intracellular alkalization and enhanced apoptotic activity [21].

Impaired bile bicarbonate secretion increases vulnerability to BAs toxicity, further exacerbating bile duct damage [21]. Additionally, gut dysbiosis compromises intestinal permeability,

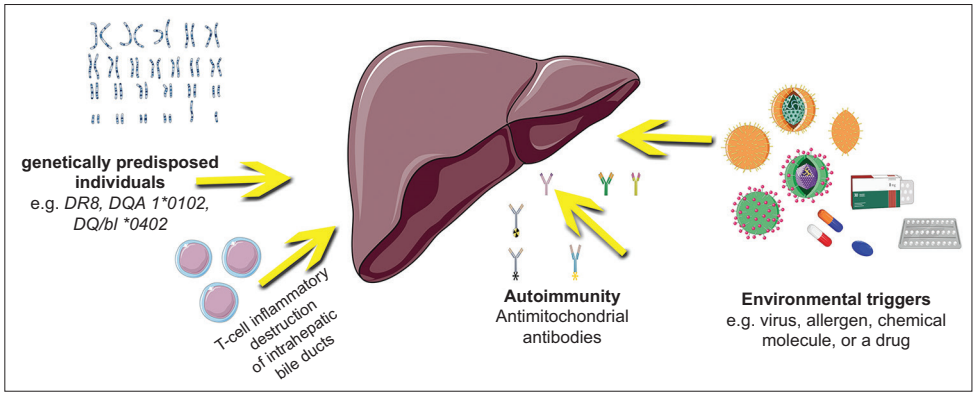

Figure 1 Simplified pathogenesis of primary biliary cholangitis, which develops through a combination of genetic predisposition and autoimmune triggers, often initiated by environmental factors (e.g., infections or toxins). T lymphocytes, particularly T-helper (Th) 1 and Th17 cells, infiltrate and attack the intrahepatic bile ducts, leading to chronic inflammation and damage. This immune response, driven by molecules like interferon-γ, is enhanced by genetic factors such as major histocompatibility complex variants and impaired T-cell regulation. Cellular damage is also worsened by dysregulation of autophagy and miR-506-induced downregulation of key cellular transporters, resulting in biliary epithelial cell apoptosis

allowing inflammatory metabolites to enter the liver and worsen disease progression [22]. Recent research highlights the intricate connection between PBC, gut microbiota, and BAs. PBC patients exhibit gut dysbiosis and altered BAs profiles. Gut microbes convert primary BAs into secondary BAs, influencing the BAs pool. BAs affect the abundance and composition of gut microbiota via their antibacterial activity, and also impact the intestinal barrier function through related receptors. UDCA treatment partially restores gut microbiota balance in PBC patients, suggesting new avenues for therapeutic approaches in PBC.

Histologically, PBC is characterized by intrahepatic bile duct destruction, lymphocytic infiltrates in portal areas, and granuloma formation in early stages, progressing to fibrosis and cirrhosis [7,8].

Recent evidence also highlights the impact of metabolic dysfunction-associated steatotic liver disease, which exacerbates liver injury and worsens outcomes in PBC [23].

While the exact sequence of events in PBC remains unclear, the interplay of genetic susceptibility, environmental factors and immune dysfunction provides a framework for understanding its pathogenesis and guiding therapeutic advancement.

Treatment

Established therapies (Fig. 2)

UDCA

Despite the emergence of several novel treatments, UDCA remains the first-line treatment (Table 1). UDCA consists of the 7-β epimer of the primary human BA chenodeoxycholic acid. The absorption of UDCA as a hydrophilic BA occurs in the small intestine, then its transport to the liver is mediated through the portal circulation (with an approximately 50% first pass extraction rate). Subsequently, UDCA is conjugated with glycine and taurine and actively secreted into bile. There is a competition between UDCA and endogenous BAs for active transport into the portal bloodstream and enterohepatic recirculation. On the other side, non-absorbed UDCA molecules can be de-conjugated, and finally eliminated in stools after their conversion to lithocholic acid by intestinal bacteria [24].

UDCA exerts its effect through the following several mechanisms of action:

(a) choleretic and anti-cholestatic effects, due to intracellular molecular signaling pathways that stimulate cellular secretions by promoting vesicular exocytosis and insertion of transmembrane carriers [25].

(b) cytoprotection against toxic effects of BAs and cytokine-induced injury, by stabilization of cell membranes, enhancement of the defenses against oxidative stress and inhibition of apoptosis [26]. Moreover, UDCA contributes to the biliary bicarbonate (HCO^{3-}) umbrella, enhancing biliary HCO^{3-} secretion against the acidification of the apical surface of cholangiocytes and hepatocytes due to BAs [27], and upregulates liver glutathione synthesis [28].

(c) immunomodulation and anti-inflammatory effects, by inhibiting prostaglandin E2, thus blocking the propagation of autoimmune liver injury. In addition, UDCA strongly lessens the hepatocellular expression of MHC class I and the biliary expression of MHC class II, therefore interfering with the autoimmune basic mechanism [29]. It also diminishes

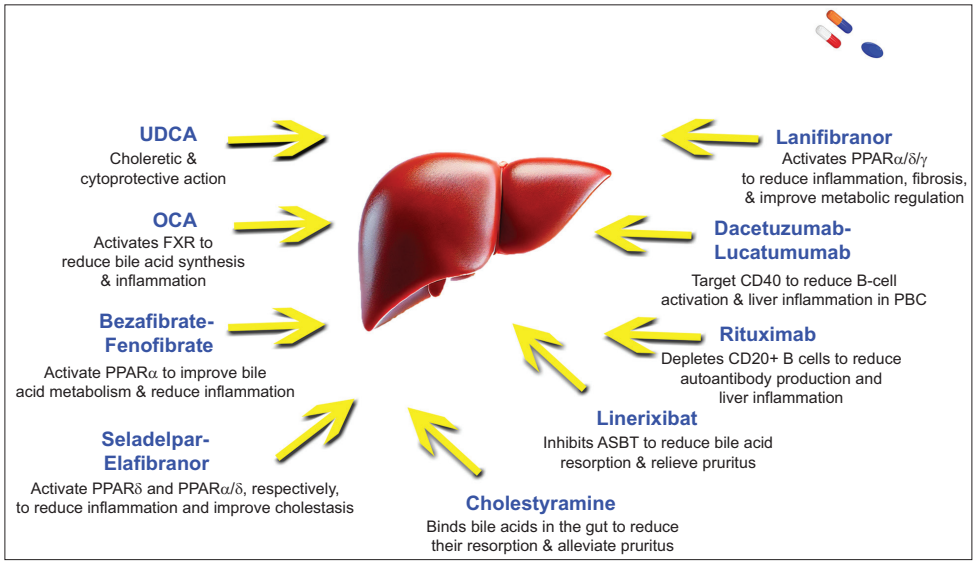

Figure 2 The figure illustrates current treatments for primary biliary cholangitis, with UDCA as the first-line therapy to enhance bile flow and reduce toxicity. OCA, a selective FXR agonist, reduces bile acid synthesis in UDCA non-responders. Fibrates (bezafibrate, fenofibrate) improve bile metabolism via PPAR-α activation. Seladelpar (PPAR-δ) and elafibranor (PPAR-α/δ) target bile acid homeostasis, while lanifibranor (pan-PPAR) offers metabolic and anti-inflammatory benefits. Dacetuzumab, lucatumumab, and rituximab modulate B-cell activity, while linerixibat and cholestyramine reduce bile acid resorption to relieve pruritus

UDCA, ursodeoxycholic acid; OCA, obeticholic acid; FXR, farnesoid x receptor; PPAR, peroxisome proliferator-activated receptor; PBC, primary biliary cholangitis

Table 1 Overview of therapies for PBC

Treatment	Mechanism of Action	Status
Ursodeoxycholic acid	Improves bile flow, reduces bile acid toxicity (UDCA); reduces bile acid production (OCA)	FDA-approved
Obeticholic acid (OCA)	Activates FXR to reduce bile acid production and inflammation	FDA-approved for second-line therapy
PPAR agonists	Regulates lipid metabolism, reduces inflammation, and improves cholestasis	Phase 3 trials completed
Dacetuzumab/lucatumumab (anti-CD40)	Modulates CD40 to reduce immune activation and liver inflammation	Phase 2 trials completed
Rituximab (anti-CD20)	Targets CD20 to reduce B cell-mediated immune response	Phase 2 trials ongoing
ASBT inhibitors	Inhibits bile acid resorption to alleviate pruritus	Phase 3 completed
Liver transplantation	Replaces the diseased liver with a healthy donor liver	Standard treatment for end-stage PBC
Microbiota	Restores gut microbiota to modulate immune response	Early-phase trials ongoing
Stem cell transplantation	Modulates immune response and promotes tissue repair	Early-phase trials ongoing

ASBT, apical sodium-dependent bile acid transporter; CD, cluster of differentiation; FDA, Food and Drug Administration; FXR, farnesoid X receptor; OCA, obeticholic acid; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; UDCA, ursodeoxycholic acid

eosinophil levels in the bloodstream, and suppresses the immune reaction against PAMPs such as LPS [28,30].

(d) increasing the hydrophilicity of the circulating endogenous BAs pool [28].

Clinical practice guidelines from the European Association for the Study of the Liver, the American Association for the Study of Liver Diseases, and the Asian-Pacific Association for the Study of the Liver, recommend UDCA treatment with a dosage of 13-15 mg/kg per day, as the gold standard in the first-line treatment of PBC, for all patients with PBC and elevated cholestatic enzymes [31-33]. It can be administered in 2 divided doses, or as a single dose [34]. Despite the existence of numerous studies investigating higher and lower dosages, no added benefit has been demonstrated [35]. Those patients with positive AMA and normal alkaline phosphatase (ALP) may have PBC by histology, but rapid UDCA therapy for this population might be unnecessary, because related data revealed that patients positive for AMA and with normal ALP concentrations did not progress to cirrhosis after 17.8 years [36], and only 16% of them progressed to obvious PBC after 5 years [37]. The use of UDCA is associated with improved survival without liver transplantation, even among patients with an incomplete biochemical response. UDCA is usually well tolerated by patients: most adverse effects are mild and include weight gain, gastrointestinal symptoms, as well as hair thinning [2].

According to Lindor *et al* there is scientific evidence regarding survival benefit in UDCA-treated patients with PBC compared to placebo-treated counterparts [30] Apart from the survival benefit, there is a lessened risk of death and need for liver transplantation, as was demonstrated by Harms *et al* in a cohort study including patients from the Global PBC Study Group. The 10-year cumulative liver transplant-free survival was 79.7% (95% confidence interval [CI] 79.1-81.2) in patients treated with UDCA compared to 60.7% (95%CI 58.2-63.4) for the placebo arm [38] When given in the early stages of PBC, UDCA normalizes survival rates, but unfortunately, if it is administered when the liver disease has been established, UDCA displays much lower efficacy [39].

The first clinical assessment to evaluate the biochemical response to UDCA should be performed 1 year after the initiation of therapy (Rotterdam criteria). The liver parameters ALP and bilirubin are of particular interest, as elevated bilirubin and albumin-bilirubin (ALBI) score are indicative of a poor outcome in PBC. Moreover, noninvasive monitoring of the fibrosis should be performed by means of elastography, since the biochemical response does not always predict the underlying histological changes. About 20-40% of patients with PBC do not respond adequately to UDCA treatment, and another third have an incomplete response [3,33,40]; the treatment response to UDCA is incomplete in about 20-40% of patients with PBC after 1 year, as judged by various biochemical criteria, either binary or continuously [33]. In these patients, UDCA should be continued and supplemented with a second-line treatment. The GLOBE score and the UK-PBC score are best suited for the selection of patients requiring second-line therapy [41].

Unfortunately, up to 40% of patients have an incomplete biochemical response to UDCA, and a small fraction of treated patients are intolerant to the drug. These patients remain at increased risk of progression of PBC, liver-related death, and the need for liver transplantation.

Criteria for non-response and progressive disease

The criteria for non-response to UDCA are typically defined by biochemical markers after 1 year of treatment, including:

- ALP levels: persistently elevated ALP >1.67× the upper limit of normal (ULN) [42,43]
- Bilirubin levels: elevated serum bilirubin >1 mg/dL, or showing a progressive increase over time [44]

- Other markers: in some cases, additional biochemical parameters, such as γ-glutamyl transferase (GGT) and immunoglobulin M (IgM) levels, as well as histological progression, can indicate non-response [42]

Patients meeting 1 or more these criteria are at risk for progressive disease, which may lead to cirrhosis, liver failure, or the need for liver transplantation. Early identification of non-response is therefore critical.

Risk factors for non-response

(1) Clinical factors:
- Advanced age at diagnosis, which correlates with more severe disease [42]
- Male sex, linked to a more aggressive disease course [42]

(2) Baseline biochemical indicators:
- Higher baseline ALP and bilirubin levels [43]
- Presence of significant fibrosis or ductopenia at diagnosis [43]

(3) Genetic factors:
- Variants in genes such as IL-12A and IL-12RB2, associated with a Th1-driven inflammatory response [42]

(4) Microbiota dysregulation:
- A Clostridia^{low} microbiota subtype has been associated with a higher rate of UDCA non-response compared to the Clostridia^{high} subtype [43]

Alternative or escalation therapy should be considered in patients who show an inadequate biochemical response, or who are intolerant to UDCA after 1 year has elapsed.

In refractory PBC, triple treatment, including UDCA, prednisolone and an immunosuppressant, may be associated with a noticeable decrease and normalization of ALP and other parameters [45]. Likewise, triple therapy, including UDCA, obetocholic acid (OCA), and fibrates appears to be superior in achieving therapeutic benefits in UDCA-nonresponsive PBC (Paris-II criteria) with PBC decompensation primarily connected to pre-existing portal hypertension. However, OCA is contraindicated in decompensated PBC, as its administration has been associated with further hepatic decompensation and hepatic failure. These adverse effects can be severe, and may require liver transplantation or even be fatal. In clinical trials, regarding treatment-naive patients with PBC, the combination of fenofibrate and UDCA also results in a significantly higher biochemical response rate, and fenofibrate appears to be well tolerated. Treatment with UDCA and bezafibrate led to a significant decrease in ALP and GGT, but not in bilirubin and IgM, compared to UDCA monotherapy; it thus needs further evaluation.

OCA (a selective farnesoid X receptor agonist)

Second-line treatment for PBC typically includes the following medications: OCA, bezafibrate and potentially other fibrates, as well as budesonide.

Farnesoid X receptor (FXR) is mainly expressed in the gastrointestinal tract and the liver. It is a key receptor that ensures the homeostasis of BAs via a complex signaling pathway; it is a major regulator of BA homeostasis through transcriptional regulation of genes involved in BAs synthesis and cellular membrane transport. Impairment of BAs efflux due to cholangiopathies leads to chronic cholestasis, ultimately resulting in a rise of intrahepatic and systemic BAs levels. By modulating FXR activation, OCA regulates the synthesis and secretion of BAs and changes their composition [46] (Table 1). OCA exhibits anti-inflammatory and antifibrotic effects by activating the sinusoidal cells of the liver endothelium and Kupffer cells [47]. The activation of these cells and the decrease in the production of proinflammatory cytokines reduce the activation of stellate cells, which are responsible for fibrogenesis [46]. OCA modulates fibroblast growth factor 19 (FGF-19) activity, leading to a hepatoprotective effect of OCA that is superior to that of UDCA [48]. The activation of FGF-19 also contributes to the anticholestatic effect of OCA [46].

Specifically, OCA is a potent and selective FXR agonist that is 100-fold more potent than the endogenous ligand chenodeoxycholic acid [49]. FXRs are transcription factors belonging to the superfamily of nuclear receptors. FXR orchestrates hepatic BA homeostasis along the induction of small heterodimer partner in the liver and induction of FGF in the intestine; both inhibit the rate-limiting enzyme cholesterol 7a-hydroxylase, resulting in reduced hepatic BAs synthesis. FXR also regulates BAs uptake NTCP and efflux (bile salt export pump) systems, thereby restricting hepatic BAs overload [50]. Additionally, FXR exhibits anti-inflammatory properties by decreasing the activation of nuclear factor kappa-light-chain-enhancer (NF)-mediated inflammation in active B cells, and potentially possesses immunomodulatory properties [51]. In parallel, FXR promotion may boost gut inflammation and barrier activity under cholestatic conditions [52]. These immunometabolic effects of FXR could have major implications for the therapy of immune-mediated cholestatic disturbances such as PBC.

OCA is indicated as an add-on treatment for patients with PBC who inadequately respond to UDCA after 1 year of treatment [53]. It is notable that 47% of the patients with intake of OCA 10 mg/d and 46% of those receiving OCA 5-10 mg/d achieved the primary endpoint of the so-called POISE criteria (serum ALP reduction to <1.67 × ULN, with a reduction of at least 15% from baseline and a normal total bilirubin level after 12 months of treatment) [54]. The most common adverse effect of OCA is dose-dependent and includes pruritus, which leads to drug discontinuation in 10-25% of patients under treatment [54]. Therefore, OCA should be initiated at a low dose and up-titrated slowly to prevent its discontinuation. In addition, FXR activation by OCA gives rise to a negative impact on the lipid panel, as it reduces high-density lipoprotein (HDL) cholesterol and elevates low-density lipoprotein (LDL) cholesterol, independently of the dose.

Real-world data strongly suggest that second-line OCA treatment in PBC is associated with better transplant-free survival compared to historical cohorts. Later, the use of OCA was restricted to patients with compensated liver disease

without portal hypertension, in view of the emergence of potential toxicity in patients with more advanced disease.

In June 2024, the European Medicines Agency recommended revoking the conditional marketing authorization for OCA in Europe. This decision was based on results from the COBALT trial, which failed to demonstrate significant clinical benefits of OCA in reducing disease progression or mortality in patients with PBC. Additional supportive data were deemed insufficient to justify its continued use. Despite a temporary suspension of this decision, the General Court of the European Union later upheld the revocation, leading to the drug's withdrawal from the European market in November 2024 [55,56].

Therapies under evaluation (Fig. 2)

Peroxisome proliferator-activated receptor (PPAR)-α

PPARs are nuclear receptors, first identified and cloned in 1990, that play a key role in the regulation of transcription of genes involved in inflammation, carcinogenesis and metabolic pathways. This makes them crucial molecular targets in cholestatic liver diseases, including PBC. Potential mechanisms of action encompass the upregulation of multidrug resistance protein 3, leading to enhanced biliary phospholipid concentration protecting cholangiocytes from potentially toxic BAs, repression of BAs synthesis, and direct anti-inflammatory effects [57].

A 2024 meta-analysis published in *Frontiers in Pharmacology* evaluated the efficacy and safety of PPAR agonists in treating PBC. The study analyzed randomized controlled trials comparing PPAR agonists to placebo or standard treatment. The findings indicated that PPAR agonists significantly improved biochemical markers, including ALP, in patients with an inadequate response to UDCA. Additionally, the analysis reported improvements in pruritus and other clinical symptoms associated with PBC [58].

PPAR-α agonists: bezafibrate and fenofibrate (Table 1)

PPAR-α is predominantly expressed in tissues with high fatty acid oxidation rates, including the liver, kidney, skeletal muscle, heart and brown adipose tissue. In hepatocytes, PPAR-α functions as a transcriptional regulator of genes involved in glucose production, β-oxidation, BA homeostasis and lipid transport, including the fasting/feeding transition. Hepatic activation of PPAR-α triggers an enhancement of fatty-acid oxidation and elimination of triglycerides from plasma, resulting in increased levels of HDL. In murine models of atherosclerosis and nonalcoholic steatohepatitis (currently renamed to metabolic dysfunction-associated steatohepatitis [MASH]), PPAR-α inhibits the expression and duration of action of proinflammatory cytokines and chemokines by transrepression of the AP1 and NF-κB signaling pathway, thus reducing both acute and chronic inflammatory processes.

PPAR agonists, including fibrates traditionally known as hypolipidemic agents, have emerged as potential alternatives for treating PBC patients who have an incomplete response to UDCA. PPAR agonists such as fenofibrate (PPAR-α agonist) and bezafibrate (nonselective PPAR agonist) are co-regulators of the nuclear receptor PXR, which is also involved in BAs metabolism and regulation, in addition to having anti-inflammatory effects. Fenofibrate acts only on PPAR-α. Its major role is to regulate cholesterol and BA homeostasis: it inhibits the enzymatic activity of cholesterol 7α-hydroxylase, leading to decreased synthesis of BAs, regulates the detoxification of BAs, and facilitates the export of phospholipids. Fenofibrate decreases the proinflammatory response through nuclear factor κB. Bezafibrate acts on PPAR-α, PPAR-β/δ, and PPAR-γ, thereby exhibiting further possible effects. Activation of PPAR-γ affects lipoprotein metabolism and provides the anti-inflammatory and antifibrotic effects of bezafibrate.

In clinical settings, bezafibrate has been more extensively studied than fenofibrate. As mentioned before, bezafibrate, when combined with UDCA, has demonstrated improvements in biochemical markers such as ALP, bilirubin and IgM levels.

In 2018, Carpechot *et al* conducted the BEZURSO trial (Table 2), which evaluated the efficacy of bezafibrate in combination with UDCA for patients with PBC. The study's primary outcome—complete biochemical response, defined as normalization of total bilirubin, alkaline phosphatase, aminotransferases, albumin and prothrombin index at 24 months—was achieved in 31% of patients, highlighting the potential of bezafibrate as an effective adjunctive therapy in PBC management. Additionally, bezafibrate has been associated with significant reductions in pruritus and improved quality of life in PBC patients [59]. Fenofibrate, while less commonly used, has also shown efficacy in improving cholestatic markers and may be a suitable alternative in specific cases However, head-to-head comparisons between bezafibrate and fenofibrate in PBC remain limited.

A 2019 review further confirmed the efficacy of fibrates in reducing ALP levels and improving other biochemical markers in PBC patients who are incomplete responders to UDCA [60]. This analysis emphasized the significant potential of fibrates, particularly bezafibrate, in achieving therapeutic goals when used in combination with UDCA.

Additionally, studies have provided insights into the safety profile of fibrates. While these agents are generally well-tolerated, there have been reports of adverse effects, underscoring the need for regular liver function monitoring during treatment. Additionally, fenofibrate has been associated with an increase in serum creatinine, particularly in patients with renal impairment. However, this does not indicate necessarily impaired renal function or altered tubular creatinine secretion. The increase is not dose-dependent and is believed to result from an elevated metabolic production rate of creatinine rather than muscular cell lysis.

Clinical guidelines have not yet universally recommended fibrates for PBC, given the potential safety concerns, including elevations in creatinine levels and the risk of hepatotoxicity [43].

Table 2 Summary of phase 3 clinical trials for therapies in PBC

Treatment	Mechanism of action	Trial Name	Date of publication	Key findings
Obeticholic Acid	Farnesoid X receptor (FXR) agonist	POISE	2016	47% of patients on OCA 10 mg/d and 46% on OCA 5-10 mg/d achieved the POISE criteria (ALP reduction to <1.67 × ULN, ≥15% baseline reduction, and normal bilirubin) at 12 months Noninvasive liver fibrosis measures showed no significant differences between treatment and placebo groups at 12 months. Pruritus was more frequent with obeticholic acid
Bezafibrate	PPAR-α agonist	BEZURSO	2018	31% of patients achieved complete biochemical response (normal levels of the main biochemical markers of the disease at 24 months. Reduction in pruritus and fatigue. Amelioration of noninvasive liver fibrosis measures such as liver stiffness and the Enhanced Liver Fibrosis (ELF) score
Elafibranor	Dual PPAR-α/δ agonist	ELATIVE	2023	15% of patients achieved complete biochemical response (normal levels of the main biochemical markers of the disease at 52 weeks. Pruritus: no significant difference using WI-NRS, but improvement with elafibranor on the 5-D Itch scale. 51% achieved the secondary end points (ALP reduction to <1.67 × ULN, ≥15% baseline reduction, and normal bilirubin) at 52 weeks.
Seladelpar	PPAR-δ agonist	RESPONSE	2024	25% of patients achieved complete biochemical response at 12 months. 61.7% achieved the secondary endpoints (ALP reduction to <1.67 × ULN, ≥15% baseline reduction, and normal bilirubin) at 12 months A significant reduction of pruritus.
Linerixibat	ASBT inhibitor	GLISTEN	2024	Statistically significant improvement in itch over 24 weeks. Linerixibat has the potential to be the first global therapy indicated to treat itch in PBC

ALP, alkaline phosphatase; ASBT, apical sodium-dependent bile acid transporter; ELF, enhanced liver fibrosis; FXR, farnesoid X receptor; OCA, obeticholic acid; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; ULN, upper limit of normal; WI-NRS, worst itch numerical rating scale

PPAR-δ agonists (seladelpar) and dual PPAR-α/δ agonists (elafibranor) (Table 3)

Elafibranor, the first FDA-approved PPAR agonist for second-line treatment of PBC (Table 3), has shown promise in improving biochemical responses, reducing mortality, and alleviating pruritus [61]. Moreover, synthetic PPAR-α agonists have demonstrated antifibrotic activity in cirrhotic rats, with effects extending to reducing portal hypertension [62].

In 2023, the ELATIVE Phase 3 trial evaluated elafibranor, a dual PPAR-α/δ agonist, for the treatment of PBC. The trial reported that 15% of patients achieved a complete biochemical response, defined as the normalization of key biochemical markers of the disease at 52 weeks. Regarding pruritus, no significant difference was observed using the worst itch numerical rating scale (WI-NRS) score; however, improvement was noted with elafibranor on the 5-D Itch Scale, suggesting a potential benefit for patients experiencing itching. Additionally, 51% of participants met the secondary endpoints, which included a reduction in ALP levels to <1.67 × ULN, a ≥15% decrease from baseline, and normal bilirubin levels at 52 weeks, demonstrating the efficacy of elafibranor in achieving these critical treatment goals [63].

Seladelpar, a selective PPAR-δ agonist, is another potential second-line therapy for PBC. In patients with an inadequate response to UDCA, seladelpar 10 mg significantly improved biochemical markers of cholestasis, reduced moderate-to-severe pruritus, and alleviated sleep disturbances and fatigue, as evaluated using the 5-D Itch and PBC-40 questionnaires [64-66].

In 2024, the RESPONSE Phase 3 trial, evaluated the efficacy of seladelpar in the treatment of PBC. The trial demonstrated that 25% of patients achieved a complete biochemical response at 12 months, defined by normalization of key biochemical markers. Additionally, 61.7% of participants met the secondary endpoints, including a reduction in ALP levels to <1.67 × ULN, a ≥15% decrease from baseline, and normal bilirubin levels. Importantly, the trial also reported a significant reduction in pruritus, a challenging and common symptom in PBC, underscoring the potential of PPAR agonists to address both disease progression and patients' quality of life [67]. Seladelpar, as a second-line therapy for PBC, appears to be the only drug associated with a lower incidence of pruritus. It displays significantly improved pruritus scores among PBC patients who had moderate-to-severe pruritus at baseline, while elafibranor is slightly more effective in achieving a biochemical response than seladelpar.

Table 3 Overview of PPAR agonists in the treatment of PBC

Type of PPAR-agonist	Mechanism of action	Summary of side effects
PPAR-α agonists: bezafibrate and fenofibrate	PPAR-α is predominantly expressed in tissues with high fatty acid oxidation rates (e.g., liver, heart, kidney). Activates genes involved in glucose production, β-oxidation and BA homeostasis, reduces triglycerides, and increases HDL levels. Anti-inflammatory effects through inhibition of AP1 and NF-κB signaling pathways	Generally well-tolerated but may cause dyspepsia, increased creatinine levels, hepatotoxicity, and rare cases of rhabdomyolysis Regular liver function monitoring is required
PPAR-δ agonists: seladelpar	Selective PPAR-δ agonist that improves biochemical markers of cholestasis, reduces moderate-to-severe pruritus, and alleviates fatigue and sleep disturbances	Mild gastrointestinal symptoms, headaches, and transient ALT/AST elevations
Dual PPAR-α/δ agonists: elafibranor	Dual activation of PPAR-α and δ reduces inflammation, improves bile acid metabolism, and enhances lipid metabolism	Transient ALT/AST elevations, fatigue, and gastrointestinal symptoms
Pan-PPAR agonists: lanifibranor	Targets all 3 PPAR isoforms (PPAR-α, PPAR-γ, PPAR-δ), combining metabolic, anti-inflammatory, and antifibrotic effects	Weight gain, edema, and potential cardiovascular risks. Lanifibranor has potential for future exploration in PBC, though no trials have yet been conducted for this indication

ALT, alanine aminotransferase; AP1, activator protein 1; AST, aspartate aminotransferase; BA, bile acid; HDL, high-density lipoprotein; NF-κB, nuclear factor kappa B; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor

Pan-PPAR agonists (lanifibranor) (Table 3)

Pan-PPAR agonists, such as lanifibranor, target all 3 PPAR isoforms (PPAR-α, PPAR-γ and PPAR-δ) to combine metabolic, anti-inflammatory and antifibrotic effects. While primarily studied for metabolic and inflammatory diseases like MASH, their potential in PBC remains unexplored. By addressing multiple pathways simultaneously, pan-PPAR agonists could offer a promising avenue for comprehensive disease management in cholestatic liver diseases, pending future research.

Dacetuzumab/lucatumumab (anti-CD40)

In PBC, B cells express CD40, a receptor that enhances antigen presentation to T-helper (Th) cells and promotes antibody class switching. Many PBC patients exhibit sex chromosome abnormalities overlapping with the CD40 gene, while elevated IgM levels are linked to epigenetic silencing of the CD40L promoter, rather than genetic mutations, suggesting environmental influence [68]. Apart from B cells, CD40 is expressed on dendritic cells and macrophages, where its interaction with CD40L induces interleukin-12 production and promotes a Th1 immune response. In cholangiocytes, CD40 signaling contributes to Fas-dependent cell death, exacerbating bile duct injury in PBC [69]. Dacetuzumab modulates CD40 to reduce immune activation and liver inflammation (Table 1).

Rituximab (anti-CD20)

B cell depletion has been explored as a therapeutic approach in PBC, given the high prevalence of AMA and the suppressive effects of B cells on Tregs (Table 1). Rituximab (anti-CD20) depletes B cells while sparing plasma cells, reducing autoantibody production [70,71]. Clinical trials in UDCA-refractory patients have shown mixed results. Rituximab lowers ALP, IgM and AMA levels, though AMA titers do not correlate with disease severity. One study reported a 16% median ALP reduction at 6 months [72]. The treatment also transiently modulates immune responses, increasing Tregs and shifting cytokine expression [73].

Apical sodium-dependent bile acid transporter (ASBT) inhibitors (Table 1)

The hepatocellular BAs reuptake and subsequently biliary BAs concentrations are determined by ileal ASBT; the ileal bile acid transporter (IBAT) protein expressed in the distal ileum plays a key role in the enterohepatic circulation of BAs. Thus, the liver toxicity driven by BAs can be counteracted by the inhibition of ASBT, leading in turn to reduced cholestatic liver disease and fibrosis. This mechanism is enhanced by increasing fecal BA elimination, reducing total and especially hydrophobic biliary BAs concentrations, while preserving biliary bicarbonate and phospholipid secretion in Mdr22/2 mice (as a model of sclerosing cholangitis [74]). Intestine-restricted ASBT inhibitors effectively lower serum-conjugated BAs concentrations and improve itching scores in patients with PBC [75,76]. Another relevant clinical trial for ASBT inhibitors in phase I demonstrated a dose-dependent reduction of serum BAs and FGF19 levels. However, several adverse events, including abdominal discomfort with nausea and diarrhea, have to be acknowledged [77].

Building on this, a selective small-molecule inhibitor of the ileal bile acid transporter (ASBT) blocks resorption of BAs in the gastrointestinal tract, thereby lowering BAs in the

systemic circulation and reducing itch. In this regard, the recent GLISTEN trial (2024) evaluated the ASBT inhibitor linerixibat and reported a statistically significant improvement in itch over 24 weeks of administration, further reinforcing its potential as a therapeutic option. If approved, linerixibat could become the first globally indicated therapy for treating itch in PBC, addressing a significant unmet need for symptom relief [78].

Despite these advances, cholestyramine remains the first-line treatment option for pruritus in PBC. As an oral anion exchange resin, it binds BAs and promotes their fecal excretion. The recommended starting dose is 4 g daily, with gradual increases up to 16 g in cases of therapeutic failure, administered before meals. While effective, its tolerability is often limited by gastrointestinal side effects and drug interactions.

The effectiveness of ASBT inhibition is encouraging, but it is limited by the currently available data. Larger clinical studies with long-term records on efficacy, safety and tolerability are necessary to confirm the use of IBAT inhibitors in clinical practice and their place on the itch treatment ladder. Further focus should also be directed to investigating their PBC-modifying potential [79].

Microbiota (Table 1)

With the development of studies targeting the gut microbiome, the role of the gut microbiome in both intestinal and extraintestinal pathologies, including PBC, is now increasingly recognized [80]. Gut dysbiosis, imbalance of BAs, and immune-mediated bile duct damage comprise the triad of the pathogenesis in PBC [3]. In the murine medulla, a decrease in *S24-7, Ruminococcaceae, Rikenellaceae*, and *Porphyromonadaceae* has been observed, with a parallel increase in *Lachnospiraceae* and *Bacteroidaceae* [81]. Further studies have investigated the salivary microbiome to investigate a linkage between the oral microbiome and PBC [82,83]. Most of these studies reported a lower level of microbiome diversity in patients with PBC compared to healthy individuals [84-87]. An elevation in the levels of certain pathogenic bacteria has been observed, with a concomitant decrease in the levels of beneficial bacteria. Additionally, various beneficial types of clostridia were reduced [81]. Bilirubin levels, the abovementioned prognostic marker for late stage PBC, correlate well with the microbiome profile, demonstrating the contribution of intestinal dysbiosis to disease progression. Recent evidence also indicates that gut dysbiosis and myeloid-derived suppressor cells (MDSCs) are involved in the pathogenesis of PBC [88]. In this regard, butyrate plays a crucial role in the modulation of MDSC homeostasis by arranging epigenetic and metabolic crosstalk, thereby suggesting a novel therapeutic approach for treating PBC [88]. Moreover, given the correlation between PBC pathology and the gut microbiota, prospective treatments targeting gut dysbiosis may include probiotics and fecal microbiota transplantation; thus, further investigation is needed [89].

Stem cell transplantation (Table 1)

Transplantation of hematopoietic stem cells (HSCs) represents a new therapeutic approach, given their immunomodulatory properties and low immunogenicity. Currently, HSC transfer is used mainly for hematological disorders, peripheral neurological lesions and Covid-19 [90]. The mode of action of this new approach is based on several actions, including hepatocyte differentiation potential and immunomodulatory action.

Transplantation of HSCs has been shown to reduce hepatic cytolysis and alleviate cholestasis in PBC. Two studies have reported the safety and efficacy of the clinical use of mesenchymal stem cells (MSCs) for treating PBC patients [91,92]. However, both studies had only a small sample size, which was their main limitation. Randomized larger-scale studies and intensive mechanistic exploration of the therapeutic effect of MSCs in PBC are necessary for future clinical trials.

In this regard, owing to their immunomodulatory properties, MSCs are considered as promising therapeutic agents for the therapy of PBC. Intravenous transplantation of bone marrow-derived (BM) or umbilical cord (UC)-MSCs appears to be a safe and beneficial therapeutic strategy for the management of UDCA-resistant patients with PBC [93]. Another recent study showed that autologous BM-MNC transplantation in patients with PBC leads to modifications in immune cells and liver function. Thus, the results of this study signify possible therapeutic approaches using BM-MNC transplantation in the control of PBC. Moreover, they propose concepts relating to the dynamics of immune cells linked to this management of BBC [94].

Since for patients with end-stage PBC liver transplantation remains the only effective therapeutic approach, increasing efforts have been made to improve the effectiveness of MSC treatment, which may enhance the future use of MSC in the treatment of PBC [95].

Liver transplantation (Table 1)

Liver transplantation remains a treatment option for selected PBC patients with progressive disease despite medical therapy. It offers the highest survival rates among all liver transplant indications, though its absolute numbers have declined as a result of earlier diagnosis and treatment. Indications include liver decompensation, a model for end-stage liver disease score above 15, and PBC-specific cases such as refractory pruritus [96,97]. "Recent evidence suggests that living-donor liver transplantation (LDLT) can be a safe and effective option for PBC patients with MELD scores below 20, demonstrating zero mortality in a recent study [98]."

Concluding remarks

The treatment landscape for PBC encompasses a range of therapeutic options, from well-established medications to

experimental approaches. UDCA remains the cornerstone of PBC management, effectively improving liver biochemistry and slowing disease progression. OCA provides a complementary or alternative treatment option for patients with an inadequate response to UDCA. Additionally, PPAR agonists have gained significant attention, with the recent FDA approvals of elafibranor and seladelpar. Double and/or triple therapy, including UDCA, OCA and fibrates, appears to be superior in achieving therapeutic benefits in UDCA-nonresponsive PBC patients. These advances mark a major step forward in the therapeutic landscape for PBC, providing novel options to address disease progression and improve patient outcomes. Emerging treatments such as dacetuzumab and rituximab target specific immune pathways, offering potential benefits in reducing liver inflammation. Apart from seladelpar, ASBT inhibitors, such as linerixibat, have demonstrated significant improvements in pruritus, addressing one of the most debilitating symptoms of PBC, though their long-term efficacy and safety require further investigation. Innovations such as microbiota modulation are under investigation, aiming to address underlying metabolic and inflammatory processes. For advanced disease, liver transplantation remains the definitive treatment, providing a life-saving intervention. Experimental therapies, including stem cell transplantation, hold promise for future advancement in alleviating symptoms, regenerating liver tissue, and modulating immune responses. Collectively, these treatments reflect a multifaceted approach to managing PBC, with ongoing research continuing to expand the therapeutic possibilities.

References

1. Donato F, Pigozzi MG, Colarieti G, Festa M, Tabaglio E. Why are rare diseases underdiagnosed? A clinical management study on detection of primary biliary cholangitis in primary care. *Ann Ig* 2024;**36**:614-618.
2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: the diagnosis and management of patients with primary biliary cholangitis. *J Hepatol* 2017;**67**:145-172.
3. Guo Z, He K, Pang K, et al. Exploring advanced therapies for primary biliary cholangitis: insights from the gut microbiota-bile acid-immunity network. *Int J Mol Sci* 2024;**25**:4321.
4. Fiorucci S, Urbani G, Di Giorgio C, Biagioli M, Distrutti E. Current landscape and evolving therapies for primary biliary cholangitis. *Cells* 2024;**13**:1580.
5. Faisal MS, Gonzalez HC, Gordon SC. Primary biliary cholangitis: epidemiology, diagnosis, and presentation. *Clin Liver Dis* 2024;**28**:63-77.
6. Younossi ZM, Bernstein D, Shiffman ML, et al. Diagnosis and management of primary biliary cholangitis. *Am J Gastroenterol* 2019;**114**:48-63.
7. Li X, Li Y, Xiao J, et al. Unique DUOX2+ACE2+ small cholangiocytes are pathogenic targets for primary biliary cholangitis. *Nat Commun* 2023;**14**:29.
8. Younossi ZM, Bernstein D, Shiffman ML, et al. Diagnosis and management of primary biliary cholangitis. *Am J Gastroenterol* 2019;**114**:48-63.
9. Cornillet M, Geanon D, Bergquist A, Björkström NK. Immunobiology of primary sclerosing cholangitis. *Hepatology* 2024 Sep 2 (Online ahead of print). doi: 10.1097/HEP.0000000000001080.
10. Agarwal K, Jones DE, Bassendine MF. Genetic susceptibility to primary biliary cirrhosis. *Eur J Gastroenterol Hepatol* 1999;**11**:603-606.
11. Akimoto S, Abe M, Ishikawa O, Takagi H, Mori M. HLA-DRB1 and DQB1 genes in anticentromere antibody positive patients with SSc and primary biliary cirrhosis. *Ann Rheum Dis* 2001;**60**:639-640.
12. Tanaka A, Nezu S, Uegaki S, et al. The clinical significance of IgA antimitochondrial antibodies in sera and saliva in primary biliary cirrhosis. *Ann N Y Acad Sci* 2007;**1107**:259-270.
13. Mantaka A, Koulentaki M, Chlouverakis G, et al. Primary biliary cirrhosis in a genetically homogeneous population: disease associations and familial occurrence rates. *BMC Gastroenterol* 2012;**12**:110.
14. Selmi C, Mayo MJ, Bach N, et al. Primary biliary cirrhosis in monozygotic and dizygotic twins: genetics, epigenetics, and environment. *Gastroenterology* 2004;**127**:485-492.
15. Oertelt S, Rieger R, Selmi C, et al. A sensitive bead assay for antimitochondrial antibodies: Chipping away at AMA-negative primary biliary cirrhosis. *Hepatology* 2007;**45**:659-665.
16. Corpechot C, Chrétien Y, Chazouillères O, Poupon R. Demographic, lifestyle, medical and familial factors associated with primary biliary cirrhosis. *J Hepatol* 2010;**53**:162-169.
17. Parikh-Patel A, Gold EB, Worman H, Krivy KE, Gershwin ME. Risk factors for primary biliary cirrhosis in a cohort of patients from the United States. *Hepatology* 2001;**33**:16-21.
18. Howel D, Fischbacher CM, Bhopal RS, Gray J, Metcalf JV, James OF. An exploratory population-based case-control study of primary biliary cirrhosis. *Hepatology* 2000;**31**:1055-1060.
19. Schrumpf E, Tan C, Karlsen TH, et al. The biliary epithelium presents antigens to and activates natural killer T cells. *Hepatology* 2015;**62**:1249-1259.
20. Chen Z, Liu S, He C, et al. CXCL12-CXCR4-mediated chemotaxis supports accumulation of mucosal-associated invariant T cells into the liver of patients with PBC. *Front Immunol* 2021;**12**:578548.
21. Sasaki M, Nakanuma Y. Bile acids and deregulated cholangiocyte autophagy in primary biliary cholangitis. *Dig Dis* 2017;**35**:210-216.
22. Hernández-Pérez M, Riado D, Pena E, et al. The overlap with metabolic dysfunction-associated steatotic liver disease negatively affects outcomes of primary biliary cholangitis. *Aliment Pharmacol Ther* 2024;**60**:613-619.
23. Alam N, Jia L, Cheng A, et al. Global research trends on gut microbiota and metabolic dysfunction-associated steatohepatitis: Insights from bibliometric and scientometric analysis. *Front Pharmacol* 2024;**15**:1390483.
24. Floreani A, Mangini C. Primary biliary cholangitis: old and novel therapy. *Eur J Intern Med* 2018;**47**:1-5.
25. Beuers U, Trauner M, Jansen P, Poupon R. New paradigms in the treatment of hepatic cholestasis: from UDCA to FXR, PXR and beyond. *J Hepatol* 2015;**62**:S25-S37.
26. Beuers U. Drug insight: mechanisms and sites of action of ursodeoxycholic acid in cholestasis. *Nat Clin Pract Gastroenterol Hepatol* 2006;**3**:318-328.
27. Beuers U, Hohenester S, de Buy Wenniger LJ, Kremer AE, Jansen PL, Elferink RP. The biliary HCO(3)(-) umbrella: a unifying hypothesis on pathogenetic and therapeutic aspects of fibrosing cholangiopathies. *Hepatology* 2010;**52**:1489-1496.
28. Poupon R. Ursodeoxycholic acid and bile-acid mimetics as therapeutic agents for cholestatic liver diseases: an overview of their mechanisms of action. *Clin Res Hepatol Gastroenterol* 2012;**36** Suppl 1:S3-S12.
29. Calmus Y, Gane P, Rouger P, Poupon R. Hepatic expression of class I and class II major histocompatibility complex molecules in primary biliary cirrhosis: effect of ursodeoxycholic acid. *Hepatology* 1990;**11**:12-15.

30. Lindor KD, Therneau TM, Jorgensen RA, Malinchoc M, Dickson ER. Effects of ursodeoxycholic acid on survival in patients with primary biliary cirrhosis. *Gastroenterology* 1996;**110**:1515-1518.
31. You H, Ma X, Efe C, et al. APASL clinical practice guidance: the diagnosis and management of patients with primary biliary cholangitis. *Hepatol Int* 2022;**16**:1-23.
32. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2018 practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2019;**69**:394-419.
33. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. *J Hepatol* 2017;**67**:145-172.
34. Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ; American Association for Study of Liver Diseases. Primary biliary cirrhosis. *Hepatology* 2009;**50**:291-308.
35. Angulo P, Jorgensen RA, Lindor KD. Incomplete response to ursodeoxycholic acid in primary biliary cirrhosis: is a double dosage worthwhile? *Am J Gastroenterol* 2001;**96**:3152-3157.
36. Metcalf JV, Mitchison HC, Palmer JM, Jones DE, Bassendine MF, James OF. Natural history of early primary biliary cirrhosis. *Lancet* 1996;**348**:1399-1402.
37. Dahlqvist G, Gaouar F, Carrat F, et al; French network of Immunology Laboratories. Large-scale characterization study of patients with antimitochondrial antibodies but nonestablished primary biliary cholangitis. *Hepatology* 2017;**65**:152-163.
38. Harms MH, van Buuren HR, Corpechot C, et al. Ursodeoxycholic acid therapy and liver transplant-free survival in patients with primary biliary cholangitis. *J Hepatol* 2019;**71**:357-365.
39. Corpechot C, Carrat F, Bahr A, Chrétien Y, Poupon RE, Poupon R. The effect of ursodeoxycholic acid therapy on the natural course of primary biliary cirrhosis. *Gastroenterology* 2005;**128**:297-303.
40. Drazilova S, Babinska I, Gazda J, et al; Eastern Slovakia PBC Group. Epidemiology and clinical course of primary biliary cholangitis in Eastern Slovakia. *Int J Public Health* 2020;**65**:683-691.
41. Gazda J, Drazilova S, Gazda M, et al. Treatment response to ursodeoxycholic acid in primary biliary cholangitis: A systematic review and meta-analysis. *Dig Liver Dis* 2023;**55**:1318-1327.
42. Guo Z, He K, Pang K, et al. Exploring advanced therapies for primary biliary cholangitis: insights from the gut microbiota-bile acid-immunity network. *Int J Mol Sci* 2024;**25**:4321.
43. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: the diagnosis and management of patients with primary biliary cholangitis. *J Hepatol* 2017;**67**:145-172.
44. Drazilova S, Babinska I, Gazda J, et al; Eastern Slovakia PBC Group. Epidemiology and clinical course of primary biliary cholangitis in Eastern Slovakia. *Int J Public Health* 2020;**65**:683-691.
45. Yao TT, Qian JD, Wang GQ. Efficacy of ursodeoxycholic acid combined with prednisolone and immunosuppressant triple therapy in the treatment of refractory primary biliary cholangitis. *Med Clin (Barc)* 2020;**155**:165-170.
46. Floreani A, Gabbia D, De Martin S. Obeticholic acid for primary biliary cholangitis. *Biomedicines* 2022;**10**:2464.
47. Verbeke L, Mannaerts I, Schierwagen R, et al. FXR agonist obeticholic acid reduces hepatic inflammation and fibrosis in a rat model of toxic cirrhosis. *Sci Rep* 2016;**6**:33453.
48. Chapman RW, Lynch KD. Obeticholic acid-a new therapy in PBC and NASH. *Br Med Bull* 2020;**133**:95-104.
49. Pellicciari R, Costantino G, Camaioni E, et al. Bile acid derivatives as ligands of the farnesoid X receptor. Synthesis, evaluation, and structure-activity relationship of a series of body and side chain modified analogues of chenodeoxycholic acid. *J Med Chem* 2004;**47**:4559-4569.
50. Halilbasic E, Baghdasaryan A, Trauner M. Nuclear receptors as drug targets in cholestatic liver diseases. *Clin Liver Dis* 2013;**17**:161-189.
51. Zhu C, Fuchs CD, Halilbasic E, Trauner M. Bile acids in regulation of inflammation and immunity: friend or foe? *Clin Exp Rheumatol* 2016;**34**(4 Suppl 98):25-31.
52. Verbeke L, Farre R, Verbinnen B, et al. The FXR agonist obeticholic acid prevents gut barrier dysfunction and bacterial translocation in cholestatic rats. *Am J Pathol* 2015;**185**:409-419.
53. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2018 practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2019;**69**:394-419.
54. Nevens F, Andreone P, Mazzella G, et al; POISE Study Group. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. *N Engl J Med* 2016;**375**:631-643.
55. Dyson JK, Hirschfield GM, Adams DH, Beuers U, Mann DA, Lindor KD, et al. Novel therapeutic targets in primary biliary cirrhosis. *Nat Rev Gastroenterol Hepatol*. 2015;**12**:147-58.
56. European Medicines Agency. EMA recommends revoking conditional marketing authorisation for Ocaliva. Available from: https://www.ema.europa.eu/en/news/ema-recommends-revoking-conditional-marketing-authorisation-ocaliva [Accessed 26 February 2025].
57. Ghonem NS, Assis DN, Boyer JL. Fibrates and cholestasis. *Hepatology* 2015;**62**:635-643.
58. Tang G, Zhang J, Zhang L, et al. Efficacy and safety of peroxisome proliferator-activated receptor agonists for the treatment of primary biliary cholangitis: a meta-analysis of randomized controlled trials. *Front Pharmacol* 2024;**15**:1432814.
59. Corpechot C, Chazouillères O, Rousseau A, et al. A placebo-controlled trial of bezafibrate in primary biliary cholangitis. *N Engl J Med* 2018;**378**:2171-2181.
60. Corpechot C. The role of fibrates in primary biliary cholangitis. *Curr Hepatol Rep* 2019;**18**:107-114.
61. Chen Y, Zheng K, Da G, et al. Revisiting PPAR agonists: novel perspectives in the treatment of primary biliary cholangitis. *Expert Opin Pharmacother* 2024;**25**:1825-1834.
62. Colapietro F, Gershwin ME, Lleo A. PPAR agonists for the treatment of primary biliary cholangitis: Old and new tales. *J Transl Autoimmun* 2023;**6**:100188.
63. Kowdley KV, Bowlus CL, Levy C, et al; ELATIVE Study Investigators' Group. Efficacy and safety of elafibranor in primary biliary cholangitis. *N Engl J Med* 2024;**390**:795-805.
64. Hirschfield GM, Shiffman ML, Gulamhusein A, et al; ENHANCE Study Group*. Seladelpar efficacy and safety at 3 months in patients with primary biliary cholangitis: ENHANCE, a phase 3, randomized, placebo-controlled study. *Hepatology* 2023;**78**:397-415.
65. Bowlus CL, Galambos MR, Aspinall RJ, et al. A phase II, randomized, open-label, 52-week study of seladelpar in patients with primary biliary cholangitis. *J Hepatol* 2022;**77**:353-364.
66. Kremer AE, Mayo MJ, Hirschfield G, et al. Seladelpar improved measures of pruritus, sleep, and fatigue and decreased serum bile acids in patients with primary biliary cholangitis. *Liver Int* 2022;**42**:112-123.
67. Hirschfield GM, Bowlus CL, Mayo MJ, et al; RESPONSE Study Group. A phase 3 trial of seladelpar in primary biliary cholangitis. *N Engl J Med* 2024;**390**:783-794.
68. Lleo A, Liao J, Invernizzi P, et al. Immunoglobulin M levels inversely correlate with CD40 ligand promoter methylation in patients with primary biliary cirrhosis. *Hepatology* 2012;**55**:153-160.
69. Carbone M, Invernizzi P. Novel treatments targeting immune-related mechanisms in primary biliary cholangitis. *Clin Liver Dis (Hoboken)* 2016;**8**:127-131.
70. Dhirapong A, Lleo A, Yang GX, et al. B cell depletion therapy exacerbates murine primary biliary cirrhosis. *Hepatology* 2011;**53**:527-535.
71. Tsuda M, Moritoki Y, Lian ZX, et al. Biochemical and immunologic effects of rituximab in patients with primary biliary cirrhosis and an incomplete response to ursodeoxycholic acid. *Hepatology* 2012;**55**:512-521.

72. Myers RP, Swain MG, Lee SS, Shaheen AA, Burak KW. B-cell depletion with rituximab in patients with primary biliary cirrhosis refractory to ursodeoxycholic acid. *Am J Gastroenterol* 2013;**108**:933-941.
73. Khanna A, Jopson L, Howel D, et al. Rituximab is ineffective for treatment of fatigue in primary biliary cholangitis: a phase 2 randomized controlled trial. *Hepatology* 2019;**70**:1646-1657.
74. Baghdasaryan A, Fuchs CD, Österreicher CH, et al. Inhibition of intestinal bile acid absorption improves cholestatic liver and bile duct injury in a mouse model of sclerosing cholangitis. *J Hepatol* 2016;**64**:674-681.
75. Hegade VS, Kendrick SF, Dobbins RL, et al. BAT117213: Ileal bile acid transporter (IBAT) inhibition as a treatment for pruritus in primary biliary cirrhosis: study protocol for a randomised controlled trial. *BMC Gastroenterol* 2016;**16**:71.
76. Hegade VS, Kendrick SF, Dobbins RL, et al. Effect of ileal bile acid transporter inhibitor GSK2330672 on pruritus in primary biliary cholangitis: a double-blind, randomised, placebo-controlled, crossover, phase 2a study. *Lancet* 2017;**389**:1114-1123.
77. Graffner H, Gillberg PG, Rikner L, Marschall HU. The ileal bile acid transporter inhibitor A4250 decreases serum bile acids by interrupting the enterohepatic circulation. *Aliment Pharmacol Ther* 2016;**43**:303-310.
78. Karatza E, Swift B, Carreño F, et al. Serum bile acid change correlates with improvement in pruritus in patients with primary biliary cholangitis receiving linerixibat. *Liver Int*. 2024;**44**:2293-2302
79. Gairola A, Wetten A, Dyson J. Sodium/bile acid co-transporter inhibitors currently in preclinical or early clinical development for the treatment of primary biliary cholangitis. *Expert Opin Investig Drugs* 2024;**33**:485-495.
80. Marchesi JR, Adams DH, Fava F, et al. The gut microbiota and host health: a new clinical frontier. *Gut* 2016;**65**:330-339.
81. Ma HD, Zhao ZB, Ma WT, et al. Gut microbiota translocation promotes autoimmune cholangitis. *J Autoimmun* 2018;**95**:47-57.
82. Abe K, Takahashi A, Fujita M, et al. Dysbiosis of oral microbiota and its association with salivary immunological biomarkers in autoimmune liver disease. *PLoS One* 2018;**13**:e0198757.
83. Lv L, Jiang H, Chen X, et al. The salivary microbiota of patients with primary biliary cholangitis is distinctive and pathogenic. *Front Immunol* 2021;**12**:713647.
84. Tang R, Wei Y, Li Y, et al. Gut microbial profile is altered in primary biliary cholangitis and partially restored after UDCA therapy. *Gut* 2018;**67**:534-541.
85. Furukawa M, Moriya K, Nakayama J, et al. Gut dysbiosis associated with clinical prognosis of patients with primary biliary cholangitis. *Hepatol Res* 2020;**50**:840-852.
86. Zhou YJ, Ying GX, Dong SL, Xiang B, Jin QF. Gut microbial profile of treatment-naive patients with primary biliary cholangitis. *Front Immunol* 2023;**14**:1126117
87. Kitahata S, Yamamoto Y, Yoshida O, et al. Ileal mucosa-associated microbiota overgrowth associated with pathogenesis of primary biliary cholangitis. *Sci Rep* 2021;**11**:19705
88. Wang R, Li B, Huang B, et al. Gut microbiota-derived butyrate induces epigenetic and metabolic reprogramming in myeloid-derived suppressor cells to alleviate primary biliary cholangitis. *Gastroenterology* 2024;**167**:733-749
89. Zhang L, Yang L, Chu H. Targeting gut microbiota for the treatment of primary biliary cholangitis: from bench to bedside. *J Clin Transl Hepatol* 2023;**11**:958-966.
90. Yamagiwa S, Ichida T. Recurrence of primary biliary cirrhosis and primary sclerosing cholangitis after liver transplantation in Japan. *Hepatol Res* 2007;**37** Suppl 3:S449-S454
91. Wang L, Li J, Liu H, et al. Pilot study of umbilical cord-derived mesenchymal stem cell transfusion in patients with primary biliary cirrhosis. *J Gastroenterol Hepatol* 2013;**28** (Suppl 1):85-92.
92. Wang L, Han Q, Chen H, et al. Allogeneic bone marrow mesenchymal stem cell transplantation in patients with UDCA-resistant primary biliary cirrhosis. *Stem Cells Dev* 2014;**23**:2482-2489.
93. Arsenijevic A, Harrell CR, Fellabaum C, Volarevic v. mesenchymal stem cells as new therapeutic agents for the treatment of primary biliary cholangitis. *Anal Cell Pathol (Amst)* 2017;**2017**:7492836Wang L, Li J, Liu H, et al. Pilot study of umbilical cord-derived mesenchymal stem cell transfusion in patients with primary biliary cirrhosis. *J Gastroenterol Hepatol* 2013;**28** (Suppl 1):85-92.
94. Saipiyeva D, Askarov M, Jafari N, et al. Bone marrow and peripheral blood mononuclear cell phenotype changes after cultivation and autologous infusion in patients with primary biliary cholangitis. *Iran J Med Sci* 2024;**49**:559-572.
95. Yang Y, Zhao RC, Zhang F. Potential mesenchymal stem cell therapeutics for treating primary biliary cholangitis: advances, challenges, and perspectives. *Front Cell Dev Biol* 2022;**10**:933565.
96. Martin EF. Liver transplantation for primary biliary cholangitis. *Clin Liver Dis* 2022;**26**:765-781
97. Yang Y, Zhao RC, Zhang F. Potential mesenchymal stem cell therapeutics for treating primary biliary cholangitis: advances, challenges, and perspectives. *Front Cell Dev Biol* 2022;**10**:933565.
98. Yanagaki M, Onda S, Furukawa K, et al. Zero mortality in living-donor liver transplantation for primary biliary cholangitis in patients with a MELD score of <20. *Transplant Proc* 2023;**55**:898-900.