Primary Biliary Cholangitis in 2025: A New Frontier

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ABBREVIATIONS: AASLD, American Association for the Study of Liver Diseases; ALP, alkaline phosphatase; PBC, primary biliary cholangitis; OCA, obeticholic acid; QoL, quality of life; PPAR, peroxisome proliferator-activated receptors; TFS, transplant-free survival; UDCA, ursodeoxycholic acid

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INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic, progressive autoimmune liver disease characterized by destruction of intrahepatic bile ducts. Over time, patients can develop cholestasis, fibrosis, cirrhosis, and portal hypertension. These physiologic changes are associated with a myriad of extrahepatic manifestations, which can be debilitating (Figure 1) (1). Fatigue is the most prevalent symptom, reported in up to 80% of patients, and has the greatest reported impact on quality of life (QoL). It is also commonly associated with cognitive dysfunction or "brain fog." Pruritus, which is reported in 20%–70% of patients, is the second most common symptom and similarly has a major effect on reported QoL (2). These symptoms are difficult to manage and often dissociated from biochemical improvements (2).

Treatment options for PBC were historically limited to those targeting histologic progression of disease. Recently, clinical management has undergone a paradigm shift toward earlier initiation of second-line therapy and holistic assessment of the patient experience. New therapeutic options have emerged, with several more in late-stage development, which may offer disease-modifying and QoL benefits. Recent reviews have summarized established therapies, such as ursodeoxycholic acid (UDCA) (3). We aim to explore the current PBC therapeutic landscape, highlight potential novel therapies under investigation, and suggest areas for future exploration.

INITIAL THERAPY AND TREATMENT TARGETS IN PBC

UDCA was the first drug approved for treatment of PBC in the United States. It has been studied extensively, with data showing that UDCA improves biochemical markers, decreases histologic progression of disease, and increases rates of transplant-free survival (TFS) (4). Both the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases (AASLD) recommend initiating UDCA at diagnosis and reassessing response to treatment at 1 year (4,5).

Although there is some uncertainty regarding the definition of an adequate biochemical response, the PBC Obeticholic Acid International Study of Efficacy (POISE) criteria (alkaline phosphatase [ALP] $<$ 1.67 times the upper limit of normal and normal total bilirubin at 1 year) are commonly used in clinical trials (4–6). Despite its excellent safety profile, 30%–40% of patients do not achieve an adequate biochemical response or cannot tolerate UDCA. Common adverse effects include gastrointestinal upset, hair loss, headaches, and fatigue. Patients with an incomplete response to UDCA have worse TFS, highlighting the need for early identification of this subgroup of patients (7).

Liver biopsy may be considered if there is concern for an overlap syndrome or other liver disease, such as autoimmune hepatitis or metabolic dysfunction-associated liver disease, which may lead to an incomplete response. However, data to guide this practice are limited (4).

The goal of PBC treatment was to delay fibrosis progression, prevent portal hypertension, and avoid liver transplantation. Various factors, such as incomplete response to UDCA, have been studied for their association with disease progression. Although symptom burden and QoL are important when considering adjuvant therapy, current data do not demonstrate a clear association between symptom severity and disease progression. Some evidence, however, suggests that autoantibodies to gp210 are associated with disease progression and worse patient outcomes (8). Although these antibodies are not recommended for routine use in the AASLD practice guidelines, they may be considered in patients without anti-mitochondrial antibody positivity or during the diagnostic workup for cholestasis (4,5).

Emerging evidence indicates that transient elastography and ALP levels at 6 months can predict an incomplete response to first-line therapy, prompting consideration of earlier treatment with adjuvant options in some scenarios (9). Assessing biochemical response to UDCA earlier and aiming for ALP normalization is associated with better TFS (7,10).

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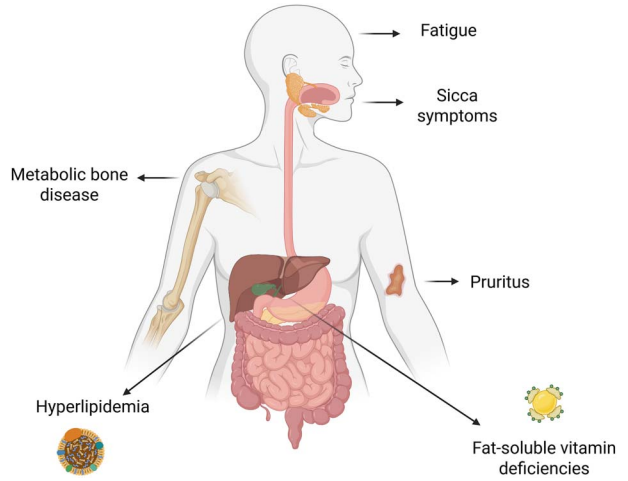

Figure 1. Extrahepatic manifestations of PBC. Created in *BioRender*. PBC, primary biliary cholangitis.

SECOND-LINE THERAPIES: AN EXPANDING ARMAMENTARIUM

Obeticholic acid

In 2016, obeticholic acid (OCA), a farnesoid X receptor, received accelerated (conditional) approval in the United States and Europe as a second-line treatment of PBC, after initial results demonstrating biochemical response with OCA compared with placebo (6). However, further study revealed adverse effects of OCA in patients with portal hypertension and decompensated cirrhosis, while also highlighting insufficient evidence to support long-term mortality benefits or decreased liver-related events between patients receiving OCA vs placebo (11). As a result, full approval in the United States and Europe was recently denied, and its viability as a recommended second-line agent remains uncertain. In addition, OCA has been linked to increases in low-density lipoprotein and decreases in high-density lipoprotein, raising concerns about potential cardiovascular risk, although strong evidence for this association is limited (12).

Fibrates

Fibrates, which bind peroxisome proliferator-activated receptors (PPAR), target nuclear receptors that regulate bile acid metabolism. Bezafibrate, a pan-PPAR agonist currently approved in Europe, has the strongest body of evidence for use in PBC. In the Fibrates for Itch in Fibrosing Cholangiopathies trial, bezafibrate reduced ALP by 35% from baseline compared with a 6% increase in the placebo group; there was also significant reduction in pruritus (13).

Fenofibrate, a United States Food and Drug Administration-approved treatment of dyslipidemia in the United States, is a PPARα agonist that has demonstrated off-label benefits in PBC (4). When combined with UDCA, fenofibrate significantly improved ALP levels, with approximately 86% of patients showing improvements or stability of fibrosis compared with those receiving UDCA monotherapy (14). Pemafibrate, another PPARα agonist available in Japan, has some data to suggest off-label benefit in PBC, though further research is needed (4).

Although promising, fibrate use in PBC has drawbacks. First, these agents may cause elevations in transaminases. Second, their utility and safety in patients with decompensated liver disease is unknown and thus not recommended by the current AASLD practice guidance (4). In addition, there is a lack of long-term studies to understand their impact on disease progression (13,14).

Newer generation PPAR agonists

In 2024, 2 newer PPAR agonists were granted accelerated approval as second-line options for PBC. Elafibranor, a dual PPAR α/δ agonist, is indicated as an adjuvant therapy for patients with inadequate response to UDCA or as monotherapy for those unable to tolerate UDCA. The Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis trial showed that 51% of patients who received elafibranor met POISE criteria for biochemical improvement compared with 4% in the placebo group (15). In addition, ALP levels fully normalized in 15% of the treatment group compared with 0% in the placebo group (15). Although reductions in pruritus intensity were observed in individuals receiving the drug, statistical significance was not achieved, highlighting the need for further research (15).

Seladelpar, a δ selective PPAR agonist, also demonstrated positive results in the RESPONSE trial. Approximately 62% of patients receiving seladelpar met POISE criteria for biochemical response compared with 20% receiving placebo, and ALP normalization occurred in 25% in the treatment group compared with 0% in the placebo group (16). Statistically significant reductions in moderate-to-severe pruritus symptoms were achieved in patients who received seladelpar compared with those who did not (16).

Both elafibranor and seladelpar work quickly, showing ALP reduction within 4 weeks of initiation. They have similar side effect profiles, which are generally favorable, though neither has been studied in patients with decompensated liver disease (15,16). The most common side effects are gastrointestinal, including nausea, vomiting, diarrhea, and abdominal pain. Muscle-related issues leading to discontinuation of therapy were more frequent in elafibranor compared with placebo, potentially indicating the need for monitoring (15,16).

Further clinical experience is necessary to confirm trial data and assess whether these agents can provide meaningful QoL benefits. If confirmed, indications for use could expand beyond just inadequate responders to UDCA. Like OCA, full approval of elafibranor and seladelpar will be dependent on longitudinal studies demonstrating their ability to reduce adverse liver-related events. Current recommendations for PBC diagnosis and treatment are summarized in Figure 2.

PBC THERAPIES IN DEVELOPMENT

In addition to these newer PPAR agonists, there remains a robust channel of investigational therapies. The aim of traditional disease modification was at slowing fibrosis progression and improving TFS remains a priority, particularly for UDCA nonresponders. Two agents currently under investigation are saroglitazar, a dual PPAR α/γ agonist, and setanaxib, a NOX1/4 inhibitor, both aiming to reduce cholestasis and fibrosis (10,17). Preliminary results suggest setanaxib may also reduce fatigue, though this requires confirmation (10).

A novel agent, COUR Pharmaceutical Nanoparticle Platform (CNP)-104, is a nanoparticle encapsulating the E2 component of the mitochondrial pyruvate dehydrogenase complex, an autoantigen linked to PBC. By targeting the autoimmune response that drives chronic inflammation and fibrosis, CNP-104 addresses the disease

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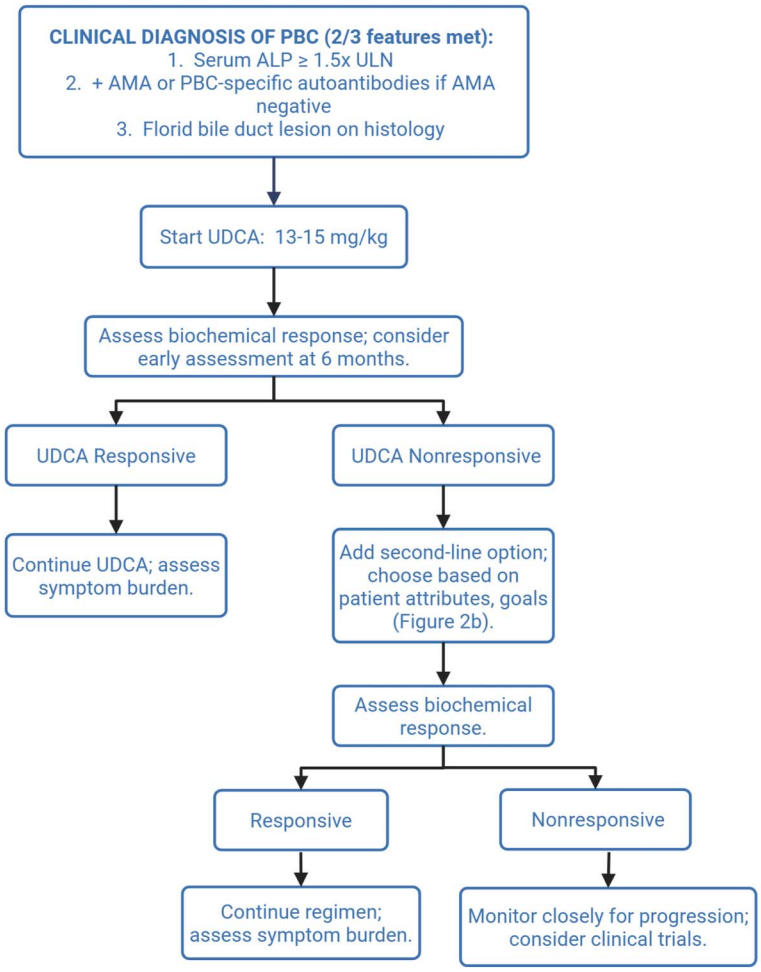

Second-line Options

Sample text	Supporting	Opposing
Fibrates	• Improves pruritus severity • May improve lipid profile • Generally well-tolerated	• Off-label • May cause elevated liver tests • Limited long-term data • Risk of renal side effects
Elafibranor, Seladelpar	• Quick onset of action • FDA-approved • Seladelpar potentially improves pruritus • Generally well-tolerated	• Not studied in decompensated liver disease • Limited long-term data • Unclear association with osteoporotic fractures

Figure 2. Current diagnosis and management options for PBC. (**a**) Initial diagnostic and treatment algorithm for patients with PBC. (**b**) Second-line treatment options for patients with PBC. *Created in BioRender.* ALP, alkaline phosphatase; AMA, anti-mitochondrial antibody; FDA, United States Food and Drug Administration; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid, ULN, upper limit of normal.

upstream of current therapies (ClinicalTrials.gov, NCT05104853). Public dissemination of results from phase 2a study is forthcoming.

Improving QoL and extrahepatic symptoms of PBC also remain a focus. Linerixibat, a selective ileal bile acid transporter inhibitor, is being investigated for its role in alleviating pruritus by lowering systemic bile acid levels; with early studies showing promising results (18). Volixibat, another ileal bile acid transporter inhibitor, recently received breakthrough therapy

Table 1. Evolving therapies for the treatment of PBC

Drug name	Mechanism of action	Phase of development	Reported outcomes	Next steps
Saroglitazar	PPARα/γ agonist	Completed phase 2b/3 trial (EPICS-III)	Significant reduction in ALP compared with placebo	Open-label phase 3 trial ongoing to evaluate safety and efficacy
Setanaxib	NOX1 and NOX4 enzyme inhibition	Completed phase 2b trial (TRANSFORM)	Decreased serum ALP from baseline	Phase 2b/3 trial (TRANSFORM) recently completed, awaiting results
CNP-104	PDC-E2 autoantigen	Phase 2a trial ongoing	Improvement in liver stiffness and reduction in pathogenic T-cell populations at 120 d	Phase 2a trial ongoing, awaiting results
Linerixibat	IBAT inhibitor	Completed phase 3 trial (GLISTEN)	Significant reduction in pruritus	Open-label phase 3 trial ongoing to evaluate safety and efficacy
Volixibat	IBAT inhibitor	Phase 2b trial ongoing (VANTAGE)	Reduction in pruritus and serum bile acids	Phase 2b trial ongoing, awaiting results

ALP, alkaline phosphatase; CNP, COUR Pharmaceutical Nanoparticle Platform; IBAT, ileal bile acid transporter; PBC, primary biliary cholangitis; PDC, pyruvate dehydrogenase complex; PPAR, peroxisome proliferator-activated receptors.

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designation from the United States Food and Drug Administration following published data demonstrating significant improvement in pruritus and reduction in bile acids compared to placebo (ClinicalTrials.gov, NCT05050136). A summary of evolving therapies for the treatment of PBC is provided in Table 1.

UNMET NEEDS AND FUTURE DIRECTIONS

Future developments in PBC treatment are incredibly promising, fueled by recent approval of new second-line therapies and ongoing drug development. These innovations offer the potential to more effectively address the underlying disease process, renewing hope for patients who have not responded to or tolerated traditional treatment options. Therapies that target pruritus, a symptom with profound effects on QoL, demonstrate a major step forward in management.

Although progress has been made, there remains an ongoing need for continued exploration into combination therapies and options for extrahepatic manifestations of PBC. Though previous evidence demonstrated efficacy in triple therapy with UDCA, OCA, and a fibrate for improved biomarkers and pruritus scores, further research is needed to re-explore this regimen or alternative triple-therapy options given recent recommendations regarding OCA use in clinical practice (19). In addition, fatigue and brain fog have a profound impact on QoL but currently have a paucity of evidence-based therapeutic options. As we look to the future, priorities include confirming long-term benefits of novel second-line therapies and their safety profile in patients with decompensated disease, updating societal practice guidance to support earlier assessment of UDCA response and initiation of second-line therapies, and placing a renewed focus on improving patient QoL.

CONFLICTS OF INTEREST

Guarantor of the article: Brian J. Wentworth, MD, MSc.

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