Received: 5 September 2024 | Accepted: 4 November 2024

DOI: 10.1097/HEP.0000000000001166

REVIEW

Primary biliary cholangitis: Personalizing second-line therapies

Cynthia Levy[1,2] | **Christopher L. Bowlus**[3]

[1]Schiff Center for Liver Diseases, University of Miami Miller School of Medicine, Miami, Florida, USA

[2]Department of Medicine, Division of Digestive Health and Liver Diseases, University of Miami Miller School of Medicine, Miami, Florida, USA

[3]Department of Medicine, Division of Gastroenterology and Hepatology, University of California Davis School of Medicine, Sacramento, California, USA

Correspondence
Cynthia Levy, Division of Digestive Health and Liver Diseases, Department of Medicine University of Miami Miller School of Medicine 1120 NW 14th Street, Suite 1284, Miami, FL 33136
Emial: clevy@med.miami.edu

Abstract

Primary biliary cholangitis (PBC) is an enigmatic, autoimmune disease targeting the small intralobular bile ducts resulting in cholestasis and potentially progression to biliary cirrhosis. Primarily affecting middle-aged women, the diagnosis of PBC is typically straightforward, with most patients presenting with cholestatic liver tests and the highly specific antimitochondrial antibody. For decades, the foundational treatment of PBC has been ursodeoxycholic acid, which delays disease progression in most patients but has no impact on PBC symptoms. Large cohort studies of patients with PBC have established the benefit of maximizing the reduction in serum alkaline phosphatase levels with ursodeoxycholic acid and the need to add second-line agents in patients who do not achieve an adequate response. Advances in the understanding of bile acid physiology have led to the development of new agents that improve cholestasis in patients with PBC and are predicted to reduce the risk of disease progression. Obeticholic acid, the first second-line therapy to be approved for PBC, significantly improves liver biochemistries and has been associated with improved long-term clinical outcomes but is limited by its propensity to induce pruritus. Elafibranor and seladelpar are peroxisome proliferator-activated receptor agonists recently approved for use in patients with PBC, whereas bezafibrate and fenofibrate are available as off-label therapies. They also have shown biochemical improvements among patients with an inadequate response to ursodeoxycholic acid but may improve symptoms of pruritus. Herein, we review the patient features to consider when deciding whether a second-line agent is indicated and which agent to consider for a truly personalized approach to PBC patient care.

Keywords: FXR, Precision Medicine, PPAR, Second-line therapies, Treatment

Abbreviations: FDA, Food and Drug Agency; FXR, farnesoid X receptor; IBAT, ileal bile acid transporter; OCA, obeticholic acid; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.hepjournal.com.

INTRODUCTION

Primary biliary cholangitis (PBC) is an immune-mediated cholestatic disease that results from a complex interaction of genetic susceptibility and environmental exposures. Loss of tolerance to mitochondrial autoantigens and marked innate, humoral, and cellular responses lead to T-cell–mediated destruction of interlobular bile ducts, with progressive cholestasis, fibrosis, and, eventually, biliary cirrhosis.[1] In the presence of chronic cholestasis, the diagnosis of PBC can be confirmed by the presence of antimitochondrial antibodies or PBC-specific antinuclear antibodies, such as anti-sp100 and anti-gp210, with a liver biopsy reserved for those who are seronegative or for whom a co-existing or alternative diagnosis is being considered.[2]

Clinically, the disease manifests primarily by fatigue and pruritus. While most patients are asymptomatic at the time of diagnosis, these symptoms will afflict up to 70% of patients at some point in their lives. Fatigue, the most disabling symptom in PBC, is often associated with cognitive impairment, in addition to social and emotional dysfunction.[3–5] Pruritus is also pervasive, causing sleep deprivation, worsening fatigue, and precipitating depression and social isolation.[6,7] Moreover, sicca symptoms are present in up to a third of patients.[8,9]

While PBC affects men and women of all races and ethnicities, it disproportionally affects middle-aged females.[10,11] A recent claims-based study in the United States revealed an estimated 105,506 individuals diagnosed with PBC, providing an adjusted prevalence of 40.9 per 100,000 adults.[12]

Globally, the prevalence of PBC has been increasing.[13] Such worldwide increase in prevalence is attributed to earlier disease diagnosis due to widespread access to a highly specific serologic marker, an increased awareness among clinicians, and the availability of a very effective first-line therapy. However, several lingering shortcomings continue to impact our capacity to properly treat people living with PBC, including a slow uptake and implementation of guideline recommendations, especially regarding the evaluation of response to therapy, limited efficacy of available second-line therapies, and poor recognition of the negative impact of symptoms on quality of life, leading to inadequate management.

Implementation of ursodeoxycholic acid (UDCA) at doses of 13–15 mg/kg/d as first-line therapy in the late 1990s has forever changed the disease course, slowing down the progression of fibrosis and development of portal hypertension, thus improving long-term survival.[14] The adjusted 10-year risk of hepatic decompensation (ascites, variceal hemorrhage, or HE), HCC, and liver-related deaths was 19%, 10%, and 35%, respectively, in the 1970s, and improved to 6%, 2%, and 6%, respectively, in the 2000s.[15] Accordingly, the number of liver transplants done for PBC has dropped worldwide.[16] Unfortunately, however, UDCA does not help control the symptoms of PBC, which remains an enormous unmet need. Furthermore, a sizeable proportion of patients fail to demonstrate a robust biochemical response to UDCA or are intolerant to UDCA and continue to progress toward cirrhosis and its complications.[17] Second-line therapy is indicated to rescue this group of patients. Until very recently, the only second-line therapy approved by the US Food and Drug Agency (FDA) was obeticholic acid (OCA), with fibrates used as off-label options. In the summer of 2024, new milestones were accomplished when the FDA granted accelerated approvals for the first peroxisome proliferator-activated receptor (PPAR) agonists, elafibranor and seladelpar, as second-line therapy in patients with PBC.

GOALS OF CARE

The 2 overarching goals in caring for people living with PBC are (1) preventing disease progression to prolong life without a liver transplant and (2) improving their quality of life (Figure 1).

It is striking that electronic health records-based studies have consistently shown critical gaps in the care of patients diagnosed with PBC. For instance, in the United States, the Fibrotic Liver Disease Consortium found that only 70% of patients with PBC were receiving the approved first-line treatment with UDCA.[11] Notably, males and African American patients were significantly less likely to receive treatment compared to females and White patients, respectively. Similarly, a national audit of the UK-wide care of people living with PBC identified several important shortfalls: although 90% of patients were receiving UDCA, nearly one-third were on suboptimal doses (<13 mg/kg/d).[18] Moreover, only half of patients with insufficient response to UDCA were receiving second-line therapy. This is very similar to data reported by Meloni and colleagues, who found that roughly 50% of Mayo Clinic patients with PBC and eligible for second-line therapy were left untreated.[19]

Another important gap evident through the above-mentioned UK national audit was the lack of proper symptom management. Nearly 40% of patients had not been assessed for fatigue in the preceding 24 months. Along the same lines, data from TARGET-PBC in the United States have shown under-reporting, under-rating, and under-treatment of pruritus in people living with PBC.[6] To improve quality of life, one must address symptoms of PBC. The most important predictor of poor PBC-related quality of life is social dysfunction, which is directly related to the presence of symptoms.[4] Fatigue, anxiety, depression, itching, and poor sleep all contribute to social isolation. Younger patients are at increased

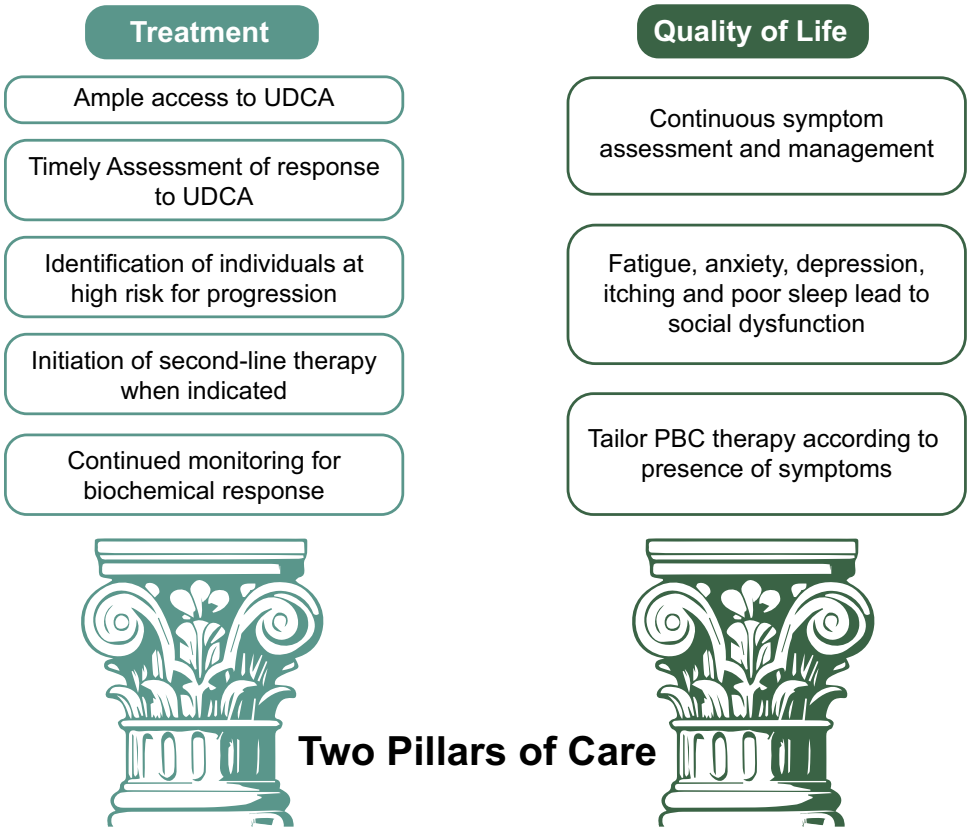

FIGURE 1 Goals of care in PBC. The 2 main pillars of PBC management are disease-specific treatment and improvement of quality of life. Implementation of existing guidelines is needed to close the gap in care. Ample access to UDCA, prescribed at the correct dose, and timely assessment of biochemical response are indispensable. Upon risk stratification, a decision can be made regarding second-line therapies, and the choice of drug will be based on individual characteristics and personal preference. Biochemical assessment must continue even after initiation of second-line drugs as a response is not universal, and some patients may require further treatment intensification. While using pharmacotherapy to modify the progression of PBC, clinicians should continuously address symptoms: fatigue and pruritus, especially, can be very pervasive and significantly impair quality of life. Additionally, the choice of second-line drug must take symptoms into consideration, as some therapies may exacerbate pruritus while others will improve it (PPAR agonists). Abbreviations: PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

risk and consistently report poorer global PBC-related quality of life. This association may be explained by insufficient coping skills and a lack of support networks in that age group. In other words, younger age at diagnosis predicts not only poorer response to UDCA and increased risk for disease progression but also more frequent debilitating symptoms and poorer quality of life.

RISK STRATIFICATION

One key development in the past decade has been the understanding that a subgroup of UDCA-treated patients are at higher risk of disease progression, and the recognition that serum alkaline phosphatase (ALP) levels while on UDCA treatment predict risk of liver transplant or death independent of serum bilirubin levels.[17] Along these lines, various response criteria have been published to date, ranging from simple binary criteria to sophisticated mathematical models, such as the GLOBE PBC and the UK-PBC risk scores.[2,20,21] Beyond utilization of ALP as a "reasonably likely to predict surrogate endpoint" in clinical trials, this allows for easy prognostication in clinical practice. Rather than identifying patients in need of a life-saving liver transplant procedure, the goal is early identification of insufficient responders to UDCA, considered at-risk for disease progression.

Timing

Practice guidance documents endorsed by the American Association for the Study of Liver Diseases and European Association for Study of the Liver recommend assessing for response to UDCA treatment after 12 months of therapy, at which point a second-line therapy should be considered.[2,22] Large real-world evidence studies indicate that response to UDCA can be estimated at an earlier timepoint, such as within 6 months of starting UDCA,[23] or even prior to treatment initiation.[24,25] Since we now have improved therapeutic options for those insufficient responders, it becomes

even more relevant to make a timely assessment. We suggest evaluation of response can be made at 6–12 months after treatment initiation and should continue throughout the course of the disease.

How to evaluate response to UDCA

While real-world evidence data are accumulating that in high-risk patients, even minimal ALP elevations can be associated with worse decompensation-free survival, these findings cannot be generalized to the entire population of people living with PBC. Among the various response criteria (Supplemental Table S1, http://links.lww.com/HEP/J631),[26–32] utilizing a combination of ALP <1.5–1.67 times the upper limit of normal (xULN) and bilirubin within normal limits, as in the modified Toronto criteria, has attracted attention due to ease of use.

Therefore, clinicians must use their judgment in combining various biochemical parameters with other nonmodifiable variables to identify individuals more likely to benefit from adding a second-line therapy. Readily available mathematical models such as the GLOBE PBC (https://www.globalpbc.com/globe) and UK PBC (https://www.uk-pbc.com/resources/tools/risk-calculator/) can estimate the risk of death or transplant after 1 year of UDCA treatment and can also assist in the decision-making process in clinical practice.

Concept of "deep response" versus "adequate response" to UDCA

Thus far, the definition of an adequate response to UDCA has been based on any of the previously published binary response criteria, with most clinical trials utilizing the POISE criteria (ALP <1.67x ULN, with at least 15% reduction from baseline, and total bilirubin $\leq$ULN) as a surrogate endpoint. However, as our knowledge about the relationship between ALP and prognosis in PBC evolves, a new concept of "deep response" has emerged.

First, the Global PBC Study Group demonstrated that patients reaching bilirubin levels ≤ 0.6x ULN had an 11% improvement in 10-year transplant-free survival compared with patients with bilirubin >0.6x ULN, and that patients with normal ALP had the highest survival rates (93% at 10 y and 84% at 15 y), significantly improved compared to those with ALP 1–1.67x ULN (86% at 10 y and 76% at 15 y) or ALP >1.67x ULN (85% at 10 y and 74% at 15 y).[33] In patients with bilirubin >0.6x ULN, normalizing ALP improved survival to rates similar to those with bilirubin ≤ 0.6x ULN.

Second, proteomics studies evaluating markers of disease activity, grouped as chemokines, chemokine modulators, cell surface and structural proteins, and metabolic factors, showed that any ongoing elevation in ALP was associated with some degree of ongoing disease activity, even in patients considered adequate responders to UDCA.[34] These findings suggest that if our goal is to completely control disease activity in PBC, the goal of therapy should be to normalize both ALP and bilirubin.

Lastly, Corpechot et al[35] compared the complication-free survival gain in patients with a normal ALP (<1.0 ULN) to those with a mildly elevated ALP (1.0–1.5 X ULN) within a group of UDCA responders according to Paris II criteria (ALP <1.5x ULN, AST <1.5x ULN and normal bilirubin). While the investigators identified a significant gain in absolute complication-free survival of 7.6 months at 10 years for the overall cohort, the greatest benefit was observed among patients with liver stiffness measurement ≥ 10 kPa and age ≤ 62 years, who had a 10-year absolute complication-free survival gain of 52.8 months.

Thus, while it appears that a high-risk group could possibly benefit from normalizing ALP, this cannot be generalized for the entire population of people living with PBC. Further research is needed to confirm that these benefits are real and outweigh the risks associated with overtreatment, including cost and adverse effects from medications.[36]

How to identify high-risk individuals

Aside from ALP and bilirubin, other variables associated with increased hazards of liver transplantation or death include the presence of advanced fibrosis at the time of diagnosis,[37] a liver stiffness measurement by vibration-controlled transient elastography >9.6–11 kPa,[38–40] enhanced liver fibrosis score (ELF) >9.8[41] and serum GGT >3.2x ULN.[42]

In most studies, younger age at the time of diagnosis is associated with an increased risk for disease progression. Specifically, in the UK-PBC cohort, younger age at diagnosis was associated with lower likelihood of meeting UDCA response criteria and higher probability of being symptomatic with pruritus and fatigue.[43] This was also shown in the Global PBC cohort, with individuals older than 65 years having a 5.5-fold increase in the odds of response to UDCA and a much lower risk of liver transplant or death compared to those younger than 45 years (HR 14.6 vs. 1.4).[44] Whether or not gender affects response to UDCA is more controversial; analysis of the Global PBC cohort did not show any significant association between gender and response to UDCA or transplant-free survival. Diagnosis of PBC is typically delayed in males, which leads to a more advanced disease at the time of diagnosis.[43] It is more likely that the fibrosis stage affects prognosis in this case, as opposed to gender alone.

Likewise, specific ethnicities such as Hispanics and First Nations in Canada have more advanced diseases at the time of diagnosis and have been linked to poor response to UDCA.[45,46] In fact, Hispanic individuals with PBC have the highest waitlist mortality and lowest rates of liver transplantation.[47]

SECOND-LINE THERAPIES

Despite the established efficacy and safety of UDCA as a first-line treatment for PBC, up to 40% of patients do not achieve an adequate biochemical response, and even fewer achieve normalization of their ALP. Treatments targeting the underlying immune mechanisms of disease have to date been unsuccessful.[48–51] In contrast, therapies that target cholestasis have demonstrated additional benefits in biochemistries predicted to improve clinical outcomes. Specifically, these include the farnesoid X receptor (FXR) agonist OCA and PPAR agonists fenofibrate, bezafibrate, elafibranor, and seladelpar; when available, a summary of their phase 3 trial findings is shown in Table 1.

Obeticholic acid

FXR is a nuclear receptor expressed in the liver, intestine, adrenal glands, and kidneys that binds to bile acids and regulates the transcription of numerous genes, including those involved in bile acid homeostasis.[56] FXR can reduce bile acid synthesis by direct action in hepatocytes or indirectly by activation in intestinal epithelial cells, where FXR induces FGF 19, which then interacts with the FGF receptor 4 on hepatocytes to reduce bile acid synthesis (Figure 2). Chenodeoxycholic acid is the most potent natural ligand for FXR; OCA is a derivative of chenodeoxycholic acid with approximately 100 times greater potency.[57] Results of 2 phase 2 studies and the phase 3 POISE study have demonstrated that OCA given to patients with an inadequate response to, or unable to tolerate, UDCA produces significant biochemical improvements that are expected to result in improved clinical outcomes (Table 1).[52,58] A major limitation of OCA has been its propensity to induce pruritus, which led to 10% of patients treated with 10 mg discontinuing treatment in the POISE study and at least similar rates in real-world studies.[18,59–61]

Based on the results of the POISE study, OCA received accelerated approval by the FDA and conditional approval by the European Medicines Agency. Due to reports of severe liver injury in patients with advanced cirrhosis, the FDA included a black box warning excluding its use in advanced cirrhosis, including those with evidence of portal hypertension.[62–64] The COBALT study, a confirmatory trial required for OCA to receive full approval, was designed to validate the efficacy of OCA to reduce clinical outcomes in patients with advanced PBC but was terminated due to futility in recruitment.[65] Despite this failure, patients from the POISE study who were treated with OCA for 5–6 years in the initial 52-week double-blind period and/or open-label long-term extension had better transplant-free and hepatic decompensation-free survival compared to matched patients from 2 large cohorts of patients with PBC treated only with UDCA (Table 2).[58]

Recently, the European Medicines Agency recommended revoking the conditional marketing authorization of OCA [https://www.ema.europa.eu/en/news/ema-recommends-revoking-conditional-marketing-authorisation-ocaliva], and the FDA is scheduled to review OCA for full approval in October 2024. In view of the challenges in conducting post-marketing confirmatory trials in PBC, stronger guidance is needed from regulatory agencies in the design of robust real-world studies that could be accepted as evidence of drug effectiveness.[68] It is anticipated that similar challenges will be faced by all new agents seeking conversion from accelerated/conditional to full approval.

PPAR agonists

PPARs are also nuclear receptors that are activated by a variety of ligands to regulate the transcription of multiple genes involved in metabolic processes, including bile acid homeostasis (Figure 2).[69] PPARs consist of 3 primary isoforms, PPARα, PPARδ, and PPARγ, which differ in tissue expression, ligand binding, and genes that are induced, but regardless of PPAR specificities, multiple PPAR agonists have demonstrated anticholestatic effects in patients with PBC. These include the PPARα-specific agonists fenofibrate[70] and pemafibrate,[71] PPARδ-specific agonist seladelpar,[55] dual PPARα/δ agonist elafibranor,[54] dual PPARα/γ agonist saroglitazar,[72] and the pan-PPAR agonist bezafibrate.[53] A particular advantage of PPAR agonists over FXR agonists is their ability to improve rather than exacerbate cholestatic pruritus.

Fibrates are hypolipidemic agents that increase phospholipid output into the bile, reduce the cytotoxicity of hydrophobic bile acids, and suppress bile acid synthesis through an FXR-independent mechanism.[73] Initial studies demonstrated that bezafibrate monotherapy and dual therapy with UDCA were effective in improving and maintaining liver biochemistries, including in patients with an incomplete response to UDCA.[74,75] Similar results have been demonstrated with fenofibrate in patients with an incomplete response to UDCA,[70] although high-quality studies are lacking. As an example, an open-label study including 48 patients randomized to either UDCA/fenofibrate or UDCA alone for 12 months found that 20% of patients on combination therapy achieved normalization of ALP,

TABLE 1 Phase 3 studies of second-line treatments for primary biliary cholangitis

Study	POISE[52]	BEZURSO[53]	ELATIVE[54]	RESPONSE[55]
Agent	Obeticholic acid	Bezafibrate	Elafibranor	Seladelpar
Arms	Placebo 5–10 mg 10 mg	Placebo 400 mg	Placebo 80 mg	Placebo 10 mg
Duration of double-blind period	12 mo	24 mo	52–104 wk	12 mo
Target	FXR	Pan-PPAR	PPARα/δ	PPARδ
Baseline ALP (active treatment groups)	326 ± 116 316 ± 104	242 (186–344)	321.9 ± 150.9	314.6 ± 123.0
Inclusion criteria	ALP > 1.67x ULN	ALP or AST > 1.5x ULN or TB > ULN (Paris 2)	ALP > 1.67x ULN	ALP > 1.67x ULN
Primary outcome	ALP < 1.67x ULN with at least 15% reduction from baseline and normal TB at 12 mo	Normal ALP, AST, ALT, total bilirubin, albumin, and INR at 24 mo	ALP < 1.67x ULN with at least 15% reduction from baseline and normal TB at 12 mo	ALP < 1.67x ULN with at least 15% reduction from baseline and normal TB at 12 mo
Response rate (%)	46 47	31	51	61.7
Response benefit over placebo (%)	36 37	31	47	41.7
ALP normalization (%)		67	15	25
ALP reduction (%)	33 39	60	40.6 ± 5.3	42.4

Abbreviations: INR, international normalized ratio; FXR, farnesoid X receptor; PPAR, peroxisome proliferator-activated receptor; TB, total bilirubin; ULN, upper limit of normal.

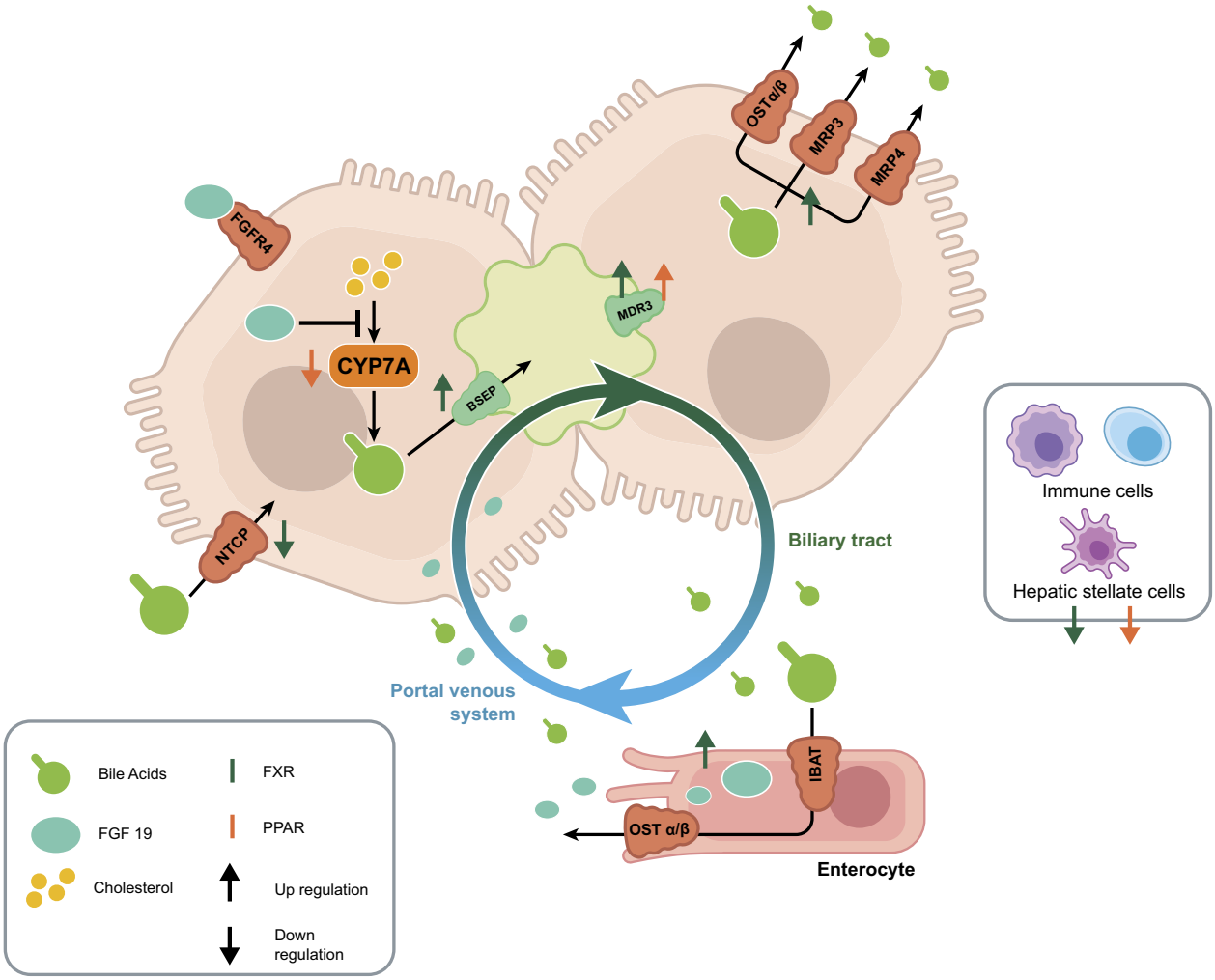

FIGURE 2 Therapeutic pathways in PBC. In hepatocytes, activation of the nuclear receptor FXR reduces BA uptake by downregulating the NTCP transporter and inhibits BA synthesis by downregulating the rate-limiting enzyme CYP7A1. Concurrently, FXR promotes the export of BA through the BSEP transporter. FXR (eg, OCA) and PPAR agonists (eg, fibrates, elafibranor, saroglitazar, and seladelpar) enhance phospholipid secretion via MDR3, thereby protecting cells from BA toxicity. Beyond their role in BA homeostasis, FXR and PPAR agonists exert anti-inflammatory effects by downregulating the NF-κB signaling pathway and modulating the activity of innate and adaptive immune cells. They also exhibit anti-fibrotic properties by reducing HSC activity. At the basolateral membrane of hepatocytes, the transporters OSTα/β, MRP3, and MRP4 facilitate the efflux of BA. MRP3 plays a crucial role in the liver's response to cholestasis, exporting retained BA and conjugated organic anions, including bilirubin, out of hepatocytes. Under cholestatic conditions, the expression of MRP3 is upregulated, enhancing protection against the accumulation of cytotoxic BA. In the intestine, BAs are absorbed through the IBAT and effluxed via OSTα/β. FXR-induced FGF19 circulates back to the liver to further suppress BA synthesis. IBAT inhibitors (eg, volixibat, linerixibat, and maralixibat) prevent BA reabsorption in the ileum, while FGF19 analogs (eg, aldafermin) offer metabolic benefits without the oncogenic risks associated with endogenous FGF19. Abbreviations: FGF, fibroblast growth factor; FXR, farnesoid X receptor; IBAT, ileal bile acid transporter; MRP, multidrug resistance protein 3 and 4; NTCP, sodium taurocholate co-transporting polypeptide; OSTα/β, organic solute transporter alpha/beta; PPAR, peroxisome proliferator-activated receptor.

GGT, and bilirubin levels compared to 0% on UDCA alone; 12.5% were intolerant and one discontinued fenofibrate due to ALT elevation > 10x ULN.[76] Further, a single-center study suggested improved rates of decompensation-free and transplant-free survival among patients using a combination of fenofibrate/UDCA as opposed to UDCA alone (Table 2).[66]

A phase 3 study (BEZURSO) investigated bezafibrate 400 mg daily in patients with PBC and incomplete biochemical response defined by Paris II criteria, with a primary endpoint that included normalization of ALP, AST, ALT, total bilirubin, albumin, and international normalized ratio at 24 months.[53] (Table 1) Thirty-one percent of patients receiving bezafibrate achieved the primary endpoint, and 67% had normalization of their ALP, while in placebo-treated patients, none achieved the primary endpoint, and only 2% normalized their ALP. Improvements in liver stiffness by vibration-controlled transient elastography, ELF score, and pruritus measured by a visual analog scale were also reported. Myalgias and increases in aminotransferases > 5x ULN occurred in 20% and 6% of bezafibrate-treated patients, respectively, compared to 10% and 2% of placebo-treated patients. While pruritus was not a key

TABLE 2 Real-world studies assessing the impact of second-line therapy on survival and the need for liver transplantation

Drug	Population	n/N	Comparisons	Follow-up	Key findings
Fenofibrate (FF)[66]	Single center, patients with PBC with inadequate response to UDCA	n = 120, of whom 46 had FF added to treatment	FF + UDCA vs. UDCA	UDCA + FF had mean follow-up of 4.9 y, vs. 3.9 in UDCA group	Combination therapy was associated with improved transplant-free and decompensation-free survival Nearly 20% discontinued FF due to adverse events, including 2 patients with a rise in bilirubin
Bezafibrate (BZF)[67]	All patients with PBC who started UDCA treatment after the year 2000	n: (UDCA): 3162 N (BZF + UDCA): 746	BZF + UDCA vs. UDCA	In the UDCA-BZF group, the mean time of exposure to BZF was 5.3 (3.8) y.	Combination therapy was associated with a significant decrease in all-cause and liver-related mortality or need for LT The NNTs with combination therapy to prevent 1 additional death or LT over 5, 10, and 15 y were 29 (95% CI: 22–46), 14 (10–22), and 8 (6–15), respectively. Discontinuation rate for BZF is 5.9% vs 0.7% for UDCA
Obeticholic acid (OCA)[58]	PBC with inadequate response to UDCA	n (Global PBC controls): 1381 n (UK-PBC controls): 2135 N (OCA): 209	OCA-treated patients from the POISE trial and its open-label extension vs. external controls from Global PBC and UK-PBC registries	6 y	OCA-treated patients had significantly greater transplant-free survival compared to both controls The risk of LT, death, or hepatic decompensation was reduced by 58% compared to the global PBC control group

Abbreviations: BZF, bezafibrate; LT, liver transplant; n, number of patients in control arm; N, number of patients in treatment arm; NNT, number needed to treat; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

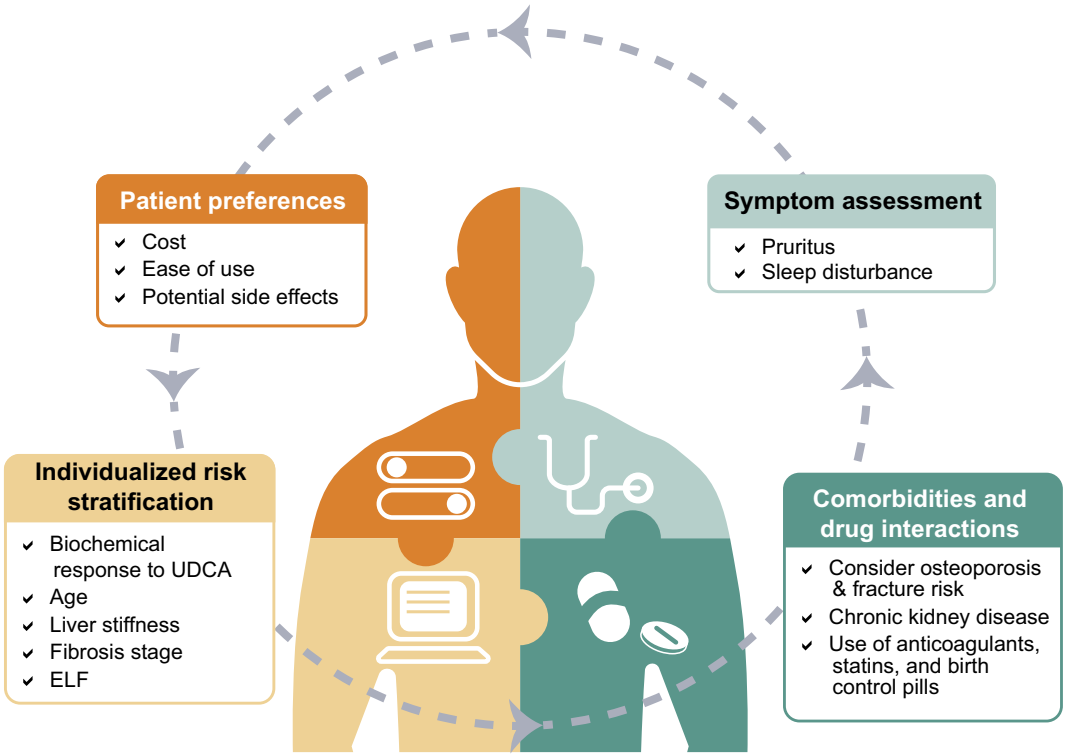

FIGURE 3 Personalizing care in primary biliary cholangitis. Framework for personalized care in primary biliary cholangitis. When choosing a second-line therapy, clinicians must consider the individual patient's risk for an adverse clinical outcome as well as presence/absence of symptoms, especially pruritus, which can be exacerbated by obeticholic acid and potentially improved by the peroxisome proliferator-activated receptor agonists. Furthermore, the decision-making process should include patient's comorbidities and life expectancy as well as the potential for drug-drug interactions. Other factors, including payer's coverage and cost-effectiveness data, will eventually emerge and affect patients' choices. Abbreviations: ELF, enhanced liver fibrosis; UDCA, ursodeoxycholic acid.

endpoint in BEZURSO, it was specifically investigated in the FITCH trial, in which bezafibrate led to a greater than 50% reduction in moderate-to-severe pruritus in 55% of included patients with PBC.[77] Furthermore, nationwide real-world study in Japan, where bezafibrate has been used for decades as a second-line agent in PBC, demonstrated a significant improvement in transplant-free survival among patients with incomplete response to UDCA receiving combination UDCA/bezafibrate as opposed to UDCA alone (Table 2).[67] Bezafibrate is currently not commercially available in the United States.

The newer, nonfibrate PPAR agonists elafibranor and seladelpar have also demonstrated efficacy in the phase 3 ELATIVE and RESPONSE trials, respectively (Table 1).[54,55] Both had similar study designs to the POISE trial, including the composite primary endpoint of an ALP <1.67 x ULN, reduction in ALP $>15\%$, and normal total bilirubin at 12 months. Although these were not head-to-head comparisons, the biochemical responses were similar in magnitude. Both studies also investigated changes in pruritus among patients with baseline moderate-to-severe pruritus defined as a patient-reported score of 4 or greater on a numeric rating scale of 0 to 10, with 0 being no itch and 10 being the worst itch imaginable. Interestingly, in both trials, approximately 40% of patients reported moderate-to-severe itch at entry, reflecting the significance of this symptom within this high-risk group of patients. Notably, seladelpar demonstrated a significant improvement in pruritus in the subpopulation of patients with numeric rating scale ≥ 4, whereas elafibranor only had a trend toward improvement. Both drugs led to improvements in the pruritus domains of PBC-40 and on 5D-itch scores. DILI and myalgias were rare in both studies.

While these studies were not specifically designed to evaluate the impact of treatment on fatigue, in an uncontrolled study with seladelpar, itching resolution was associated with improved sleep and lower PBC-40 fatigue scores.[78]

THERAPIES IN DEVELOPMENT

Novel approaches to treating PBC are in development and may offer additional avenues to treat patients in specific settings. Setanaxib is a nitrous oxide 1/4 inhibitor with antifibrotic effects in mouse models of PBC. In a phase 2a trial, it failed to demonstrate improvements in GGT (primary endpoint) but did reduce ALP (secondary endpoint) significantly.[79] Interestingly, setanaxib treatment was also associated with improvements in

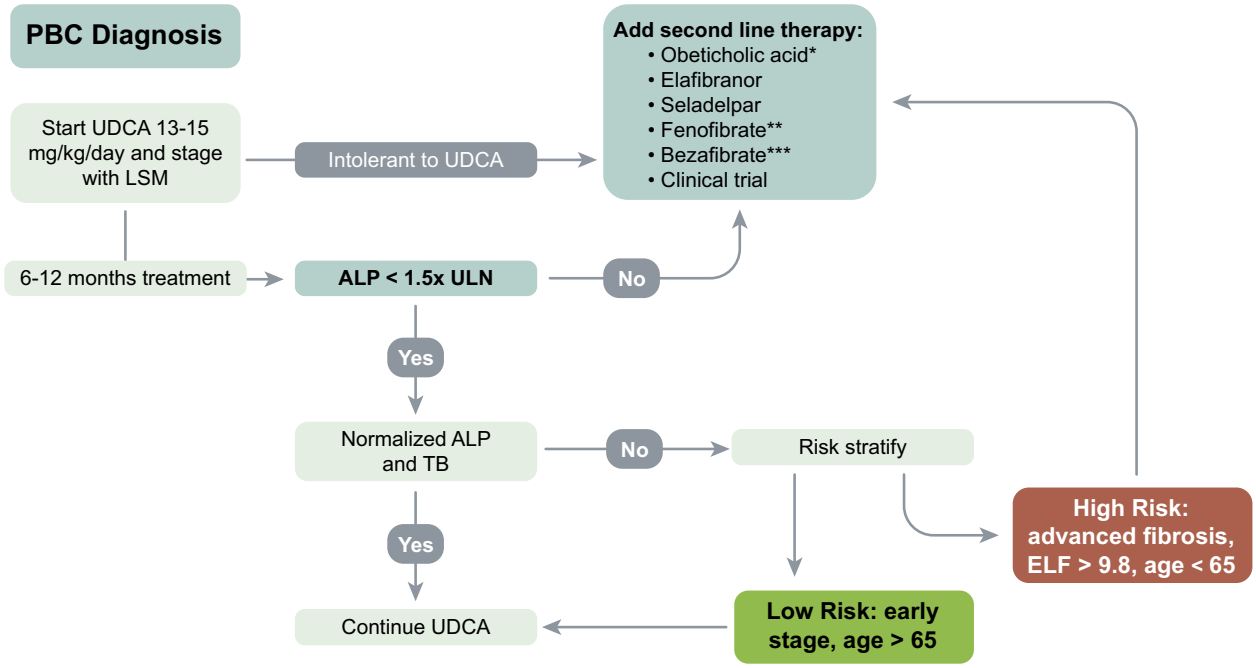

FIGURE 4 Proposed treatment algorithm in PBC. Upon diagnosis of PBC, patients should be started on treatment with ursodeoxycholic acid (UDCA) at 13–15 mg/kg/d. Response to UDCA should be evaluated after 6–12 months of therapy (and regularly during follow-up), at which point a determination is made regarding the need to add second-line therapy. We propose using an ALP threshold of 1.5x the upper limit of normal (ULN) as a reasonable goal that can be easily implemented in clinical practice. If ALP > 1.5x ULN, or if the patient is intolerant to UDCA, consider adding a second-line therapy or referring for clinical trial participation. Available second-line therapies include approved medications obeticholic acid, elafibranor, and seladelpar, and off-label use of bezafibrate and fenofibrate. ALP normalization is not necessarily beneficial for all patients, as it carries the risk of overtreatment and an increased rate of adverse effects. Normalizing ALP is more likely to benefit those individuals with advanced fibrosis (stage 3–4 disease), ELF score > 9.8, increased liver stiffness > 10 kPa, and patients younger than 65 years of age. Notably, all currently available second-line therapies are contraindicated in decompensated cirrhosis. *Obeticholic acid is also contraindicated in advanced cirrhosis (splenomegaly/thrombocytopenia/hyperbilirubinemia) or in the presence of portal hypertension. Obeticholic acid can significantly exacerbate pruritus and should be avoided in those with uncontrolled itching. **Fenofibrate is an off-label therapy, not Food and Drug Agency approved for the treatment of PBC. ***Bezafibrate is an off-label therapy, not Food and Drug Agency approved for the treatment of PBC, and not commercially available in the United States. Abbreviations: ELF, enhanced liver fibrosis; LSM, liver stiffness measurement; PBC, primary biliary cholangitis; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

fatigue.[80] A phase 2b study (NCT05014672) is currently underway for patients with advanced fibrosis based on a liver stiffness by vibration-controlled transient elastography ≥8.8 kPa, based on a post hoc analyses of the phase 2a trial, suggesting that the greatest benefits were among those with higher baseline liver stiffness. In Europe, a phase 2 trial of norucholic acid (formerly known as nor-ursodeoxycholic acid) was terminated early due to failure to meet the endpoint at interim analysis (EudraCT: EUCTR2021-001431-56-NL).

While prior therapeutic approaches targeting the underlying immunologic mechanisms of PBC have been unsuccessful, new technologies that use nanoparticles coated with specific autoantigens and specifically suppress autoreactive T cells hold immense promise. This technology has demonstrated effectiveness in animal models of PBC[81] and in patients with celiac disease.[82] A phase 2a study of CNP-104 (NCT05104853), a biodegradable nanoparticle encapsulating the PDC-E2 antigen to which the antimitochondrial antibody and autoreactive T cell of PBC react, is currently underway.

STRATEGIES TO PERSONALIZE CARE

Personalized care of patients with PBC must consider several factors, including (1) risk of clinical outcomes, (2) presence of PBC-related symptoms, (3) comorbidities and concomitant medication use, (4) drug safety profile, (5) cost-effectiveness, and (6) patient preference. For the individual patient, risk stratification should incorporate not only the biochemical response to treatment but also the patient's overall life expectancy based on age, comorbid conditions, and fibrosis stage. A more aggressive approach to treatment might be considered in a young patient with advanced fibrosis, even with near normal ALP, whereas an elderly patient with other comorbid conditions and no evidence of fibrosis might receive no benefit from adding second-line therapies (Figure 3).

At this time, given the well documented benefit in improving transplant-free survival and the excellent safety profile, UDCA remains the preferred first-line agent for individuals diagnosed with PBC.[22,62,83] After

TABLE 3 Pros and cons of currently available therapies in PBC

	Pros	Cons
Obeticholic acid	- Phase 3 data available - 40% treatment benefit over placebo using POISE criteria - Real-world evidence suggests lower rates of decompensation, liver transplantation, or death	- Can cause pruritus - Potential for hepatotoxicity in advanced cirrhosis - Cost - Unsuccessful confirmatory trial
Elafibranor	- Phase 3 data available - 47% treatment benefit over placebo using POISE criteria -15% ALP normalization rate - Possible benefit in patients with moderate to severe pruritus	- Cost - Confirmatory trials not yet complete - No real-world evidence - 4% fracture rate reported
Seladelpar	- Phase 3 data available - 42% treatment benefit over placebo using POISE criteria - 25% ALP normalization rate - Benefit in patients with moderate to severe pruritus - Durability and safety data available for up to 5 y	- Cost - Confirmatory trials not yet complete - No real-world evidence - 4% fracture rate reported
Bezafibrate	- Phase 3 data available - 30% normalized all liver chemistries vs. 0 in placebo arm - >60% ALP normalization rate - Real-world evidence suggests lower rates of liver transplant or death - Benefit in patients with moderate to severe pruritus - Inexpensive	- Not approved by FDA or EMA - Not available in the United States
Fenofibrate	- Nearly 50% reduction in ALP from baseline - May have a positive impact on pruritus - Inexpensive	- No phase 3 data - Not approved by FDA or EMA - Most data come from retrospective studies - Potential for hepatotoxicity

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Agency.

initiation of UDCA, biochemical response should be evaluated at 6–12 months using one of the well-validated criteria (Supplemental Table S1, http://links.lww.com/HEP/J631). Generally, failure to lower the ALP below 150–200 IU is considered an insufficient response and an addition of a second-line agent should be discussed at that point. Even if the ALP is below this level, the presence of variables associated with an increased risk for progression, including younger age, advanced fibrosis stage, and liver stiffness measurement >10 kPa, a second-line therapy ought to be strongly considered. Although normalization of ALP has been proposed as a new target for treatment, current phase 3 trials have not included patients with mildly elevated ALP levels (normal to 1.5–1.67 times ULN), and their efficacy in this patient population remains unknown. A proposed treatment algorithm is presented in Figure 4, and a comparison of the pros and cons of the various available drugs is shown in Table 3.

In the absence of any head-to-head trials and lack of a network meta-analysis for comparative effectiveness, the evidence to support one agent over another is limited. PPAR agonists have been suggested to have higher rates of ALP normalization compared to OCA and are clearly preferable in patients with pruritus, whereas OCA may have a more pronounced impact on transaminases.[18] However, among PPAR agonists, benefits appear largely comparable (Table 1). Studies are ongoing to determine if there is a benefit in initiating dual therapy with UDCA and OCA at diagnosis for high-risk patients (OPERA- EudraCT number 2022-000050-28). Along the same lines, early initiation of dual therapy with UDCA and a PPAR agonist is also being considered. A recent study randomized treatment-naive patients in an open-label fashion to receive UDCA alone versus UDCA with fenofibrate for 12 months.[84] More patients achieved biochemical response according to various established criteria, and rates of ALP normalization were higher, for the UDCA/fenofibrate group, with similar rates of adverse events in both groups. While early initiation of dual therapy may seem like an attractive approach, additional studies are needed to identify patients better suited for this new strategy.

The role of triple therapy (UDCA/OCA/PPAR agonist) is also under evaluation. Early results from a phase 2a trial of adding bezafibrate with or without OCA demonstrated that the reduction in ALP among patients with an incomplete response to UDCA was greatest, and the rate of deep biochemical remission highest, with the combination of bezafibrate and OCA compared to bezafibrate alone.[85] Real-world studies also support this pharmacological synergy, consistently showing improved odds of achieving biochemical response and symptom improvement after the addition of the third drug (Table 4).[86–88]

Regardless of drug selection, caution is advised in the setting of cirrhosis. OCA is contraindicated in patients with any evidence of portal hypertension and in decompensated cirrhosis. Elafibranor and seladelpar are also contraindicated in patients with decompensated cirrhosis, although early data suggest safety in Child A

TABLE 4 Real-world studies of triple therapy UDCA/OCA/PPAR in PBC

Study description	Comparisons	Follow-up	Key findings
Participants from POISE trial with inadequate response to UDCA+ OCA received add-on BZF[86] N = 11	Dual therapy (UDCA + OCA) baseline vs. Triple therapy (UDCA + OCA + BZF)	12 mo	•Significant ALP and TB reduction-ALP normalization in 7/10 patients •Change in pruritus score was not significant
Patients with inadequate response to UDCA/OCA received add-on BZF or FF[87]Dual therapy: N = 198 Triple therapy: N = 57	Dual therapy (UDCA + OCA) vs. triple therapy (UDCA + OCA + fibrates)	Median of 35.1 mo	•Significantly higher rates of ALP normalization, biochemicalremission[a] and deep response[b] among patients on triple therapy •Pruritus improvement was more pronounced in the triple therapy group, with lower pruritus scores over time •Adverse events in 41%; 18.8% had to discontinue OCA
Patients with inadequate response to dual therapy UDCA + OCA or UDCA + fibrates received add-on fibrates or OCA, respectively[88] N = 58	1. Dual therapy vs. Triple therapy 2. Order of treatment: Fibrate→OCA vs. OCA→Fibrate	Median of 11 mo	•Regardless of the order of treatment, triple therapy was associated with a greater likelihood of biochemical response and ALP normalization. •OCA→Fibrate group had a greater reduction in ALP, a higher likelihood of achieving ALP normalization, and a significant reduction in itch intensity •Fibrate→OCA group had a greater reduction gain in TB, GGT, AST, and ALT

[a]Biochemical remission was defined as deep response plus transaminase normalization.
[b]Deep response was defined as ALP normalization and TB ≤0.6x ULN.
Abbreviations: BZF, Bezafibrate; FF, Fenofibrate; N, number of patients; OCA, obeticholic acid; PBC, primary biliary cholangitis; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

cirrhosis. Interestingly, an increased rate of bone fractures was noted with both elafibranor and seladelpar when compared to placebo. Fenofibrate and bezafibrate, which are currently used off-label, are discouraged in the setting of decompensated cirrhosis.[62] Other safety concerns and potential drug-drug interactions should be reviewed prior to treatment initiation (Supplemental Table S2, http://links.lww.com/HEP/J631).

FUTURE OPTIONS

Triple therapy + ileal bile acid transporter inhibitor

The addition of an ileal bile acid transporter (IBAT) inhibitor could potentially provide benefits beyond the dual and triple therapies discussed. While IBAT inhibitors were not primarily developed as disease-modifying agents, preclinical studies suggest that certain IBAT inhibitors may protect against cholestatic injury.

In bile duct ligation mouse models, systemic IBAT inactivation lowered the total bile acid pool size, increased renal bile acid excretion, and reduced markers of cholestasis, namely ALP and bilirubin levels.[89] In a subsequent study, combination of the IBAT inhibitor linerixibat with the FXR agonist cilofexor or the FGF19 analog aldafermin led to a reduction in inflammation and fibrogenesis, which was confirmed by gene expression analysis.[90] Therefore, it is expected that the combination of IBAT inhibition with a drug that reduces bile acid synthesis will lead to improvement of pruritus and protection against cholestatic liver injury while mitigating the gastrointestinal side effects associated with interruption of the enterohepatic bile acid circulation.

CONCLUSIONS

Formulating a personalized plan of care for people living with PBC requires thorough baseline assessment and risk stratification, as well as continued monitoring of liver biochemistries and noninvasive markers of fibrosis for response to treatment. UDCA is a cornerstone of treatment and remains the first-line therapy of choice. Therefore, the first step to improve overall survival is to diagnose early and facilitate universal access to UDCA. The availability of FDA-approved OCA, elafibranor, and seladelpar, as well as off-label agents such as fenofibrate and bezafibrate, affords the clinician with the ability to intensify treatment for patients with insufficient response to UDCA who remain at significant risk for adverse outcomes, while simultaneously adjusting for and managing symptoms. At present, the lack of comparative effectiveness data precludes ranking these options, and choice will be based on the individual patient profile—disease stage, presence of symptoms

and comorbidities, potential drug-drug interactions, patient preference, and drug availability and affordability. Importantly, none of the available therapies is recommended for patients with decompensated cirrhosis nor evaluated in the population with recurrent PBC post-liver transplantation, both of which remain major unmet needs. Ongoing studies evaluating triple therapy with UDCA/OCA/PPAR agonists suggest a synergistic effect and improved safety profile. Future clinical trials should evaluate novel combination therapies to identify the most effective and well-tolerated treatment regimens capable of providing deep and durable responses in patients with PBC and to explore possible disease-modifying effects of IBAT inhibition. However, confirmation of a survival benefit with recently approved and upcoming second-line therapies is likely to require studying large real-world cohorts.

CONFLICTS OF INTEREST

Cynthia Levy advised and received grants from Calliditas, Cymabay, Gilead, GSK, Intercept, Ipsen, Kowa, and Mirum. She received grants from Target RWE and Zydus. She had other interests with Cour. All conflicts and interests were terminated over 12 months ago. Christopher Bowlus consults for and received grants from ChemoMab, Cymabay, Gilead, GSK, Ipsen, and Pliant. He consults for Alynylam and NGM Bio. He received grants from Calliditas, Cour, Hanmi, Intercept, Mirum, Novartis, Novo Nordisk, Viking, and Zydus.

ORCID

Cynthia Levy https://orcid.org/0000–0001–5498–6037
Christopher L. Bowlus https://orcid.org/0000–0002–3906–6811

REFERENCES

1. Lleo A, Wang GQ, Gershwin ME, Hirschfield GM. Primary biliary cholangitis. Lancet. 2020;396:1915–26.
2. 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.
3. Kaps L, Grambihler A, Yemane B, Nagel M, Labenz C, Ploch P, et al. Symptom Burden and Treatment Response in Patients with Primary Biliary Cholangitis (PBC). Dig Dis Sci. 2020;65:3006–13.
4. Dyson JK, Wilkinson N, Jopson L, Mells G, Bathgate A, Heneghan MA, et al. The inter-relationship of symptom severity and quality of life in 2055 patients with primary biliary cholangitis. Aliment Pharmacol Ther. 2016;44:1039–50.
5. Phaw NA, Dyson JK, Mells G, Jones D. Understanding Fatigue in Primary Biliary Cholangitis. Dig Dis Sci. 2021;66:2380–6.
6. Mayo MJ, Carey E, Smith HT, Mospan AR, McLaughlin M, Thompson A, et al. Impact of Pruritus on Quality of Life and Current Treatment Patterns in Patients with Primary Biliary Cholangitis. Dig Dis Sci. 2023;68:995–1005.
7. von Maltzahn R, Mayo MJ, Smith HT, Thompson A, Das S, de Souza AR, et al. Relationship between pruritus and sleep in participants with primary biliary cholangitis in the Phase 2b GLIMMER trial. J Patient Rep Outcomes. 2024;8:60.
8. Efe C, Torgutalp M, Henriksson I, Alalkim F, Lytvyak E, Trivedi H, et al. Extrahepatic autoimmune diseases in primary biliary cholangitis: Prevalence and significance for clinical presentation and disease outcome. J Gastroenterol Hepatol. 2021;36:936–42.
9. Muratori P, Fabbri A, Lalanne C, Lenzi M, Muratori L. Autoimmune liver disease and concomitant extrahepatic autoimmune disease. Eur J Gastroenterol Hepatol. 2015;27:1175–9.
10. Kim WR, Lindor KD, Locke GR III, Therneau TM, Homburger HA, Batts KP, et al. Epidemiology and natural history of primary biliary cirrhosis in a US community. Gastroenterology. 2000;119:1631–6.
11. Lu M, Li J, Haller IV, Romanelli RJ, VanWormer JJ, Rodriguez CV, et al. Factors Associated With Prevalence and Treatment of Primary Biliary Cholangitis in United States Health Systems. Clin Gastroenterol Hepatol. 2018;16:1333–341 e1336.
12. Buchanan-Peart KA, MacEwan JP, Levine A, Nair R, Wheeler D, Ness E, et al. United States (US) Prevalence of Diagnosed Primary Biliary Cholangitis: 41 per 100,000 Adults With Wide Regional Variability. Hepatology. 2023;78:S2088.
13. Trivella J, John BV, Levy C. Primary biliary cholangitis: Epidemiology, prognosis, and treatment. Hepatol Commun. 2023;7:e0179.
14. Harms MH, van Buuren HR, Corpechot C, Thorburn D, Janssen HLA, Lindor KD, et al. Ursodeoxycholic acid therapy and liver transplant-free survival in patients with primary biliary cholangitis. J Hepatol. 2019;71:357–65.
15. Harms MH, Lammers WJ, Thorburn D, Corpechot C, Invernizzi P, Janssen HLA, et al. Major Hepatic Complications in Ursodeoxycholic Acid-Treated Patients With Primary Biliary Cholangitis: Risk Factors and Time Trends in Incidence and Outcome. Am J Gastroenterol. 2018;113:254–64.
16. Webb GJ, Rana A, Hodson J, Akhtar MZ, Ferguson JW, Neuberger JM, et al. Twenty-Year Comparative Analysis of Patients With Autoimmune Liver Diseases on Transplant Waitlists. Clin Gastroenterol Hepatol. 2018;16:278–287 e277.
17. Lammers WJ, van Buuren HR, Hirschfield GM, Janssen HL, Invernizzi P, Mason AL, et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. Gastroenterology. 2014;147:1338–349 e1335; quiz e1315.
18. Abbas N, Smith R, Flack S, Bains V, Aspinall RJ, Jones RL, et al. Critical shortfalls in the management of PBC: Results of a UK-wide, population-based evaluation of care delivery. JHEP Rep. 2024;6:100931.
19. Meloni ST, Zein CO, Smither AR, Iyengar A, Calay ES, Wagner TE, et al. Real-world study of reasons for non-utilization of second-line treatment in patients with primary biliary cholangitis. Journal of Hepatology. 2024;80:S326.
20. Lammers WJ, Hirschfield GM, Corpechot C, Nevens F, Lindor KD, Janssen HL, et al. Development and Validation of a Scoring System to Predict Outcomes of Patients With Primary Biliary Cirrhosis Receiving Ursodeoxycholic Acid Therapy. Gastroenterology. 2015;149:1804–812 e1804.
21. Carbone M, Sharp SJ, Flack S, Paximadas D, Spiess K, Adgey C, et al. The UK-PBC risk scores: Derivation and validation of a scoring system for long-term prediction of end-stage liver disease in primary biliary cholangitis. Hepatology. 2016;63:930–50.
22. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017;67:145–72.
23. Murillo Perez CF, Ioannou S, Hassanally I, Trivedi PJ, Corpechot C, van der Meer AJ, et al. Optimizing therapy in primary biliary cholangitis: Alkaline phosphatase at six months identifies one-year non-responders and predicts survival. Liver Int. 2023;43:1497–506.

24. Carbone M, Nardi A, Flack S, Carpino G, Varvaropoulou N, Gavrila C, et al. Pretreatment prediction of response to ursodeoxycholic acid in primary biliary cholangitis: development and validation of the UDCA Response Score. Lancet Gastroenterol Hepatol. 2018;3:626–34.
25. Li J, Lu M, Zhou Y, Bowlus CL, Lindor K, Rodriguez-Watson C, et al. Dynamic Risk Prediction of Response to Ursodeoxycholic Acid Among Patients with Primary Biliary Cholangitis in the USA. Dig Dis Sci. 2022;67:4170–80.
26. Pares A, Caballeria L, Rodes J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic Acid. Gastroenterology. 2006;130:715–20.
27. Corpechot C, Abenavoli L, Rabahi N, Chretien Y, Andreani T, Johanet C, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology. 2008;48:871–7.
28. Kuiper EM, Hansen BE, de Vries RA, den Ouden-Muller JW, van Ditzhuijsen TJ, Haagsma EB, et al. Improved prognosis of patients with primary biliary cirrhosis that have a biochemical response to ursodeoxycholic acid. Gastroenterology. 2009;136:1281–7.
29. Kumagi T, Guindi M, Fischer SE, Arenovich T, Abdalian R, Coltescu C, et al. Baseline ductopenia and treatment response predict long-term histological progression in primary biliary cirrhosis. Am J Gastroenterol. 2010;105:2186–94.
30. Azemoto N, Abe M, Murata Y, Hiasa Y, Hamada M, Matsuura B, et al. Early biochemical response to ursodeoxycholic acid predicts symptom development in patients with asymptomatic primary biliary cirrhosis. J Gastroenterol. 2009;44:630–4.
31. Corpechot C, Chazouilleres O, Poupon R. Early primary biliary cirrhosis: biochemical response to treatment and prediction of long-term outcome. J Hepatol. 2011;55:1361–7.
32. Momah N, Silveira MG, Jorgensen R, Sinakos E, Lindor KD. Optimizing biochemical markers as endpoints for clinical trials in primary biliary cirrhosis. Liver Int. 2012;32:790–5.
33. Murillo Perez CF, Harms MH, Lindor KD, van Buuren HR, Hirschfield GM, Corpechot C, et al. Goals of Treatment for Improved Survival in Primary Biliary Cholangitis: Treatment Target Should Be Bilirubin Within the Normal Range and Normalization of Alkaline Phosphatase. Am J Gastroenterol. 2020;115:1066–74.
34. Jones DEJ, Wetten A, Barron-Millar B, Ogle L, Mells G, Flack S, et al. The relationship between disease activity and UDCA response criteria in primary biliary cholangitis: A cohort study. EBioMedicine. 2022;80:104068.
35. Corpechot C, Lemoinne S, Soret PA, Hansen B, Hirschfield G, Gulamhusein A, et al. Adequate versus deep response to ursodeoxycholic acid in primary biliary cholangitis: To what extent and under what conditions is normal alkaline phosphatase level associated with complication-free survival gain? Hepatology. 2024;79:39–48.
36. Bowlus CL, Levy C. Optimizing treatment of primary biliary cholangitis: Is good, good enough? Hepatology. 2024;79:3–5.
37. Murillo Perez CF, Hirschfield GM, Corpechot C, Floreani A, Mayo MJ, van der Meer A, et al. Fibrosis stage is an independent predictor of outcome in primary biliary cholangitis despite biochemical treatment response. Aliment Pharmacol Ther. 2019;50:1127–36.
38. Corpechot C, Carrat F, Poujol-Robert A, Gaouar F, Wendum D, Chazouilleres O, et al. Noninvasive elastography-based assessment of liver fibrosis progression and prognosis in primary biliary cirrhosis. Hepatology. 2012;56:198–208.
39. Corpechot C, Carrat F, Gaouar F, Chau F, Hirschfield G, Gulamhusein A, et al. Liver stiffness measurement by vibration-controlled transient elastography improves outcome prediction in primary biliary cholangitis. J Hepatol. 2022;77:1545–53.
40. Cristoferi L, Calvaruso V, Overi D, Vigano M, Rigamonti C, Degasperi E, et al. Accuracy of Transient Elastography in Assessing Fibrosis at Diagnosis in Naive Patients With Primary Biliary Cholangitis: A Dual Cut-Off Approach. Hepatology. 2021;74:1496–508.
41. Mayo MJ, Parkes J, Adams-Huet B, Combes B, Mills AS, Markin RS, et al. Prediction of clinical outcomes in primary biliary cirrhosis by serum enhanced liver fibrosis assay. Hepatology. 2008;48:1549–57.
42. Gerussi A, Bernasconi DP, O'Donnell SE, Lammers WJ, Van Buuren H, Hirschfield G, et al. Measurement of Gamma Glutamyl Transferase to Determine Risk of Liver Transplantation or Death in Patients With Primary Biliary Cholangitis. Clin Gastroenterol Hepatol. 2021;19:1688–697 e1614.
43. Carbone M, Mells GF, Pells G, Dawwas MF, Newton JL, Heneghan MA, et al. Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid. Gastroenterology. 2013;144:560–69 e567; quiz e513-564.
44. Cheung AC, Lammers WJ, Murillo Perez CF, van Buuren HR, Gulamhusein A, Trivedi PJ, et al. Effects of Age and Sex of Response to Ursodeoxycholic Acid and Transplant-free Survival in Patients With Primary Biliary Cholangitis. Clin Gastroenterol Hepatol. 2019;17:2076–84 e2072.
45. Levy C, Naik J, Giordano C, Mandalia A, O'Brien C, Bhamidimarri KR, et al. Hispanics with primary biliary cirrhosis are more likely to have features of autoimmune hepatitis and reduced response to ursodeoxycholic acid than non-Hispanics. Clin Gastroenterol Hepatol. 2014;12:1398–405.
46. Roberts SB, Hirschfield GM, Worobetz LJ, Vincent C, Flemming JA, Cheung A, et al. Ethnicity, disease severity, and survival in Canadian patients with primary biliary cholangitis. Hepatology. 2022;76:303–16.
47. Cholankeril G, Gonzalez HC, Satapathy SK, Gonzalez SA, Hu M, Khan MA, et al. Increased Waitlist Mortality and Lower Rate for Liver Transplantation in Hispanic Patients With Primary Biliary Cholangitis. Clin Gastroenterol Hepatol. 2018;16:965–973 e962.
48. Tsuda M, Moritoki Y, Lian ZX, Zhang W, Yoshida K, Wakabayashi K, et al. Biochemical and immunologic effects of rituximab in patients with primary biliary cirrhosis and an incomplete response to ursodeoxycholic acid. Hepatology. 2012;55:512–21.
49. 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;108:933–41.
50. Bowlus CL, Yang GX, Liu CH, Johnson CR, Dhaliwal SS, Frank D, et al. Therapeutic trials of biologics in primary biliary cholangitis: An open label study of abatacept and review of the literature. J Autoimmun. 2019;101:26–34.
51. Hirschfield GM, Gershwin ME, Strauss R, Mayo MJ, Levy C, Zou B, et al. Ustekinumab for patients with primary biliary cholangitis who have an inadequate response to ursodeoxycholic acid: A proof-of-concept study. Hepatology. 2016;64:189–99.
52. Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, et al. A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. N Engl J Med. 2016;375:631–43.
53. Corpechot C, Chazouilleres O, Rousseau A, Le Gruyer A, Habersetzer F, Mathurin P, et al. A Placebo-Controlled Trial of Bezafibrate in Primary Biliary Cholangitis. N Engl J Med. 2018;378:2171–81.
54. Kowdley KV, Bowlus CL, Levy C, Akarca US, Alvares-da-Silva MR, Andreone P, et al. Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis. N Engl J Med. 2024;390:795–805.
55. Hirschfield GM, Bowlus CL, Mayo MJ, Kremer AE, Vierling JM, Kowdley KV, et al. A Phase 3 Trial of Seladelpar in Primary Biliary Cholangitis. N Engl J Med. 2024;390:783–94.

56. Calkin AC, Tontonoz P. Transcriptional integration of metabolism by the nuclear sterol-activated receptors LXR and FXR. Nat Rev Mol Cell Biol. 2012;13:213–24.
57. Pellicciari R, Fiorucci S, Camaioni E, Clerici C, Costantino G, Maloney PR, et al. 6alpha-ethyl-chenodeoxycholic acid (6-ECDCA), a potent and selective FXR agonist endowed with anticholestatic activity. J Med Chem. 2002;45:3569–72.
58. Murillo Perez CF, Fisher H, Hiu S, Kareithi D, Adekunle F, Mayne T, et al. Greater Transplant-Free Survival in Patients Receiving Obeticholic Acid for Primary Biliary Cholangitis in a Clinical Trial Setting Compared to Real-World External Controls. Gastroenterology. 2022;163:1630–642 e1633.
59. D'Amato D, De Vincentis A, Malinverno F, Vigano M, Alvaro D, Pompili M, et al. Real-world experience with obeticholic acid in patients with primary biliary cholangitis. JHEP Rep. 2021;3: 100248.
60. Gomez E, Garcia Buey L, Molina E, Casado M, Conde I, Berenguer M, et al. Effectiveness and safety of obeticholic acid in a Southern European multicentre cohort of patients with primary biliary cholangitis and suboptimal response to ursodeoxycholic acid. Aliment Pharmacol Ther. 2021;53: 519–30.
61. Roberts SB, Ismail M, Kanagalingam G, Mason AL, Swain MG, Vincent C, et al. Real-World Effectiveness of Obeticholic Acid in Patients with Primary Biliary Cholangitis. Hepatol Commun. 2020;4:1332–45.
62. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2021 practice guidance update from the American Association for the Study of Liver Diseases. Hepatology. 2022; 75:1012–3.
63. Eaton JE, Vuppalanchi R, Reddy R, Sathapathy S, Ali B, Kamath PS. Liver Injury in Patients With Cholestatic Liver Disease Treated With Obeticholic Acid. Hepatology. 2020;71:1511–4.
64. John BV, Schwartz K, Levy C, Dahman B, Deng Y, Martin P, et al. Impact of Obeticholic acid Exposure on Decompensation and Mortality in Primary Biliary Cholangitis and Cirrhosis. Hepatol Commun. 2021;5:1426–36.
65. Kowdley KV, Hirschfield GM, Coombs C, Malecha ES, Bessonova L, Li J, et al. COBALT: A Confirmatory Trial of Obeticholic Acid in Primary Biliary Cholangitis With Placebo and External Controls. Am J Gastroenterol 2024.
66. Cheung AC, Lapointe-Shaw L, Kowgier M, Meza-Cardona J, Hirschfield GM, Janssen HL, et al. Combined ursodeoxycholic acid (UDCA) and fenofibrate in primary biliary cholangitis patients with incomplete UDCA response may improve outcomes. Aliment Pharmacol Ther. 2016;43:283–93.
67. Tanaka A, Hirohara J, Nakano T, Matsumoto K, Chazouilleres O, Takikawa H, et al. Association of bezafibrate with transplant-free survival in patients with primary biliary cholangitis. J Hepatol. 2021;75:565–71.
68. Jones DEJ, Beuers U, Bonder A, Carbone M, Culver E, Dyson J, et al. Primary biliary cholangitis drug evaluation and regulatory approval: Where do we go from here? Hepatology. 2024;80: 1291–300.
69. 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.
70. Grigorian AY, Mardini HE, Corpechot C, Poupon R, Levy C. Fenofibrate is effective adjunctive therapy in the treatment of primary biliary cirrhosis: A meta-analysis. Clin Res Hepatol Gastroenterol. 2015;39:296–306.
71. Joshita S, Umemura T, Yamashita Y, Sugiura A, Yamazaki T, Fujimori N, et al. Biochemical and plasma lipid responses to pemafibrate in patients with primary biliary cholangitis. Hepatol Res. 2019;49:1236–43.
72. Vuppalanchi R, Caldwell SH, Pyrsopoulos N, deLemos AS, Rossi S, Levy C, et al. Proof-of-concept study to evaluate the safety and efficacy of saroglitazar in patients with primary biliary cholangitis. J Hepatol. 2022;76:75–85.
73. Sun Y, Zhang L, Jiang Z. The role of peroxisome proliferator-activated receptors in the regulation of bile acid metabolism. Basic Clin Pharmacol Toxicol. 2024;134:315–24.
74. Rudic JS, Poropat G, Krstic MN, Bjelakovic G, Gluud C. Bezafibrate for primary biliary cirrhosis. Cochrane Database Syst Rev. 2012;1:CD009145.
75. Nakai S, Masaki T, Kurokohchi K, Deguchi A, Nishioka M. Combination therapy of bezafibrate and ursodeoxycholic acid in primary biliary cirrhosis: a preliminary study. Am J Gastroenterol. 2000;95:326–7.
76. Li C, Zheng K, Chen Y, He C, Liu S, Yang Y, et al. A randomized, controlled trial on fenofibrate in primary biliary cholangitis patients with incomplete response to ursodeoxycholic acid. Ther Adv Chronic Dis. 2022;13:20406223221114198.
77. de Vries E, Bolier R, Goet J, Pares A, Verbeek J, de Vree M, et al. Fibrates for Itch (FITCH) in Fibrosing Cholangiopathies: A Double-Blind, Randomized, Placebo-Controlled Trial. Gastroenterology. 2021;160:734–743 e736.
78. Kremer AE, Mayo MJ, Hirschfield G, Levy C, Bowlus CL, Jones DE, et al. Seladelpar improved measures of pruritus, sleep, and fatigue and decreased serum bile acids in patients with primary biliary cholangitis. Liver Int. 2022;42:112–23.
79. Invernizzi P, Carbone M, Jones D, Levy C, Little N, Wiesel P, et al. Setanaxib, a first-in-class selective NADPH oxidase 1/4 inhibitor for primary biliary cholangitis: A randomized, placebo-controlled, phase 2 trial. Liver Int. 2023;43:1507–22.
80. Jones D, Carbone M, Invernizzi P, Little N, Nevens F, Swain MG, et al. Impact of setanaxib on quality of life outcomes in primary biliary cholangitis in a phase 2 randomized controlled trial. Hepatol Commun. 2023;7:e0057.
81. Umeshappa CS, Singha S, Blanco J, Shao K, Nanjundappa RH, Yamanouchi J, et al. Suppression of a broad spectrum of liver autoimmune pathologies by single peptide-MHC-based nanomedicines. Nat Commun. 2019;10:2150.
82. Kelly CP, Murray JA, Leffler DA, Getts DR, Bledsoe AC, Smithson G, et al. TAK-101 Nanoparticles Induce Gluten-Specific Tolerance in Celiac Disease: A Randomized, Double-Blind, Placebo-Controlled Study. Gastroenterology. 2021;161: 66–80 e68.
83. You H, Ma X, Efe C, Wang G, Jeong SH, Abe K, et al. APASL clinical practice guidance: the diagnosis and management of patients with primary biliary cholangitis. Hepatol Int. 2022;16: 1–23.
84. Liu Y, Guo G, Zheng L, Sun R, Wang X, Deng J, et al. Effectiveness of Fenofibrate in Treatment-Naive Patients With Primary Biliary Cholangitis: A Randomized Clinical Trial. Am J Gastroenterol. 2023;118:1973–9.
85. Levy C, Hejda V, Louvet A, Younes Z, Mendizabal M, Bonder A, et al. Combined Effect of Obeticholic Acid and Bezafibrate in Patients with Primary Biliary Cholangitis and Inadequate Response to Or Intolerance of Ursodeoxycholic Acid: Results from Two Phase 2 Clinical Trials. Hepatology. 2023;78: S1–2154.
86. Smets L, Verbeek J, Korf H, van der Merwe S, Nevens F. Improved Markers of Cholestatic Liver Injury in Patients With Primary Biliary Cholangitis Treated With Obeticholic Acid and Bezafibrate. Hepatology. 2021;73:2598–600.
87. Gomez E, Montero JL, Molina E, Garcia-Buey L, Casado M, Fuentes J, et al. Longitudinal outcomes of obeticholic acid therapy in ursodiol-nonresponsive primary biliary cholangitis: Stratifying the impact of add-on fibrates in real-world practice. Aliment Pharmacol Ther. 2024;59:1604–15.
88. Soret PA, Lam L, Carrat F, Smets L, Berg T, Carbone M, et al. Combination of fibrates with obeticholic acid is able to normalise biochemical liver tests in patients with difficult-to-

treat primary biliary cholangitis. Aliment Pharmacol Ther. 2021; 53:1138–46.
89. Kunst RF, de Waart DR, Wolters F, Duijst S, Vogels EW, Bolt I, et al. Systemic ASBT inactivation protects against liver damage in obstructive cholestasis in mice. JHEP Rep. 2022;4: 100573.
90. Kunst RF, Bolt I, van Dasselaar RDJ, Nijmeijer BA, Beuers U, Oude Elferink RPJ, et al. Combined inhibition of bile salt synthesis and intestinal uptake reduces cholestatic liver damage and colonic bile salts in mice. JHEP Rep. 2024;6: 100917.

How to cite this article: Levy C, Bowlus CL. Primary biliary cholangitis: Personalizing second-line therapies. Hepatology. 2024;■:■■–■■. https://doi.org/10.1097/HEP.0000000000001166