Primary Biliary Cholangitis: Novel and Emerging Therapies

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Abstract: Primary biliary cholangitis (PBC) is a slowly progressive autoimmune liver disease that, if not promptly and appropriately treated, can lead to significant morbidity, mortality, and a substantial decline in patients' quality of life. Ursodeoxycholic acid is the first-line therapy; however, up to 40% of patients exhibit an inadequate response. For these individuals, 2 US Food and Drug Administration–approved second-line therapies are currently available, which not only demonstrate biochemical efficacy but may also alleviate pruritus as well as fatigue, thereby potentially enhancing quality of life. Ongoing research is focused on developing additional therapeutic options for patients with PBC. This article aims to provide a comprehensive review of existing and emerging PBC treatments that may mitigate disease progression and improve patient outcomes.

Keywords
Primary biliary cholangitis, therapy, ursodeoxycholic acid, peroxisome proliferator-activated receptor agonist, farnesoid X receptor, pruritus

Primary biliary cholangitis (PBC) is an autoimmune liver disease characterized by chronic lymphoplasmacytic portal infiltration and progressive immune-mediated destruction of small intrahepatic bile ducts.[1,2] This leads to impaired bile flow, hepatocyte injury, and fibrosis, possibly leading to biliary cirrhosis and end-stage liver disease.

PBC can affect adult males and females of all races and ethnicities. Incidence and prevalence increase with age, with a typical presentation in middle-aged individuals (40-60 years), while the overall mean age at diagnosis has risen since the 1970s.[3] Although PBC remains a female-predominant disease, studies suggest a higher prevalence in males than previously thought, with a female-to-male ratio varying from 4:1 to 10:1.[4-7] Possibly owing to a low index of suspicion, males are often diagnosed later in life, at an advanced disease stage, which is associated with poorer response to treatment and increased rates of progression to cirrhosis.[8] Of note, the prevalence of PBC among Black and Asian-American individuals also appears to be rising.[7,9]

Diagnosis is based on 2 of the following 3 criteria: (1) biochemical evidence of cholestasis with alkaline phosphatase (ALP) elevation, (2) antimitochondrial antibody (AMA) positivity or other PBC-specific antinuclear autoantibody (anti-gp210 or anti-sp100) positivity if AMA-negative, and

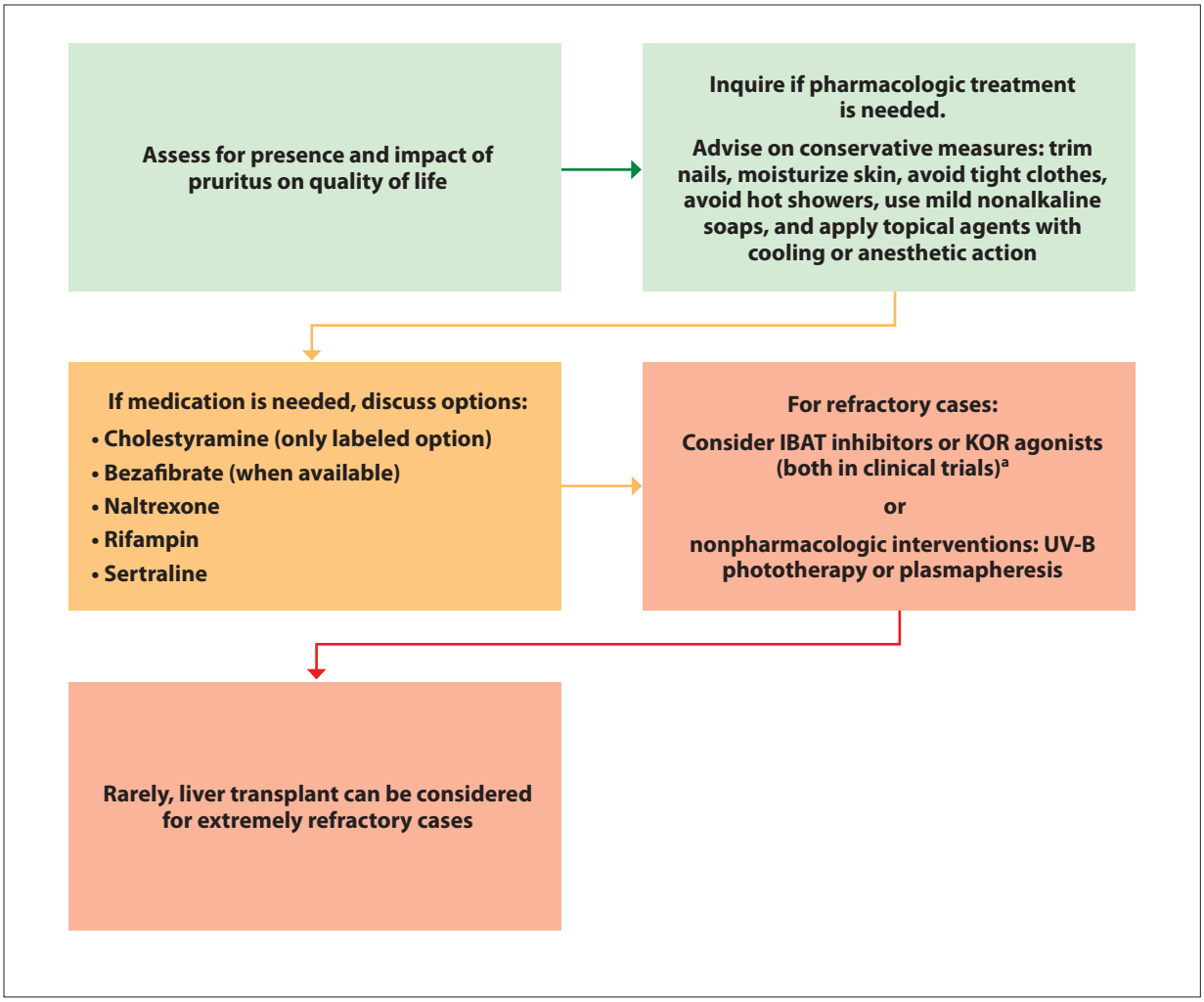

Figure 1. Proposed algorithm for evaluation and management of pruritus in people living with primary biliary cholangitis.

[a]The IBAT inhibitors linerixibat and volixibat are currently under evaluation. Linerixibat completed phase 3 trials and may receive regulatory approval in the near future. In that case, it will become a first-line option for moderate-to-severe itching.

IBAT, ileal bile acid transporter; KOR, kappa opioid receptor.

(3) histopathologic evidence of nonsuppurative cholangitis with small or medium-sized bile duct destruction.[2,10] Ursodeoxycholic acid (UDCA) at a dose of 13 to 15 mg/kg/day is well established as a first-line therapy and should be initiated at the time of diagnosis.[10] The rate of PBC progression may extend over decades and varies according to individual risk factors and responses to treatment. Compared with untreated patients, those receiving UDCA have a significant increase in transplant-free survival at 5 years (90% vs 79%), 10 years (78% vs 59%), and 15 years (66% and 32%).[11]

Although most patients are asymptomatic at the time of diagnosis, clinicians should remain vigilant for the presence of symptoms and their potential impact on patients' overall health. When present, the most common symptoms are fatigue, pruritus, and sicca syndrome. Fatigue has been reported in 50% to 78% of patients and is the most debilitating of PBC symptoms.[12,13] Pruritus, which can follow a circadian rhythm pattern (worse in the evenings) and has periods of flare-ups or quiescence, is reported by up to 80% of patients.[14-19] Fatigue and pruritus significantly impair the quality of life of people living with PBC, as these symptoms are associated with sleep and mood disturbances, emotional distress, and impaired social interactions.[13,20] These symptoms should be addressed regardless of disease-modifying strategies, including in patients with normalized liver chemistries. Although no therapy has been shown to improve fatigue, a few pharmacologic options exist for management of pruritus, with additional, improved therapies

Table 1. Effect of First- and Second-Line Drug Therapies on Biochemistries, Pruritus, and Survival in Patients With Primary Biliary Cholangitis

Drug	Improvement in biochemistries	Improvement in pruritus	Survival data from real-world studies	Survival data from randomized controlled trials
Ursodeoxycholic acid	✓	None	✓	✓
Fenofibrate	✓	Probable	Unclear	NA
Bezafibrate	✓	✓	✓	NA
Seladelpar	✓	✓	NA	NA
Elafibranor	✓	Probable	NA	NA

NA, not available.

currently in development. Figure 1 shows a proposed management algorithm for cholestatic pruritus.

This article provides an overview of the goals of care for people living with PBC as well as a thorough discussion of existing and emerging PBC treatments, aimed at both slowing disease progression and improving quality of life.

Treatment Goals and Monitoring

The overall management of PBC focuses on 3 goals: treating the underlying disease process, monitoring for and treating extrahepatic complications, and improving quality of life by managing the associated symptoms. Based on current data, the impact of currently available first- and second-line therapies in patients with PBC is outlined in Table 1. Treatment with UDCA has been shown to improve liver chemistries, delay histologic progression, and improve survival without liver transplant,[21-23] and should be started at the time of diagnosis (Figure 2). Potential side effects of UDCA include weight gain, hair thinning, diarrhea, and flatulence.[10]

Treatment response to UDCA can be assessed using several published biochemical response monitoring criteria.[24-29] Improvement in liver chemistries can begin within a few weeks of UDCA initiation, and up to 90% of UDCA benefit is seen within 6 to 9 months while on therapy. Guidelines recommend evaluating for a biochemical response after 1 year of treatment with UDCA.[10] ALP and total bilirubin are the 2 most essential markers that should be used in day-to-day practice.[10,30] Overall, the degree of ALP elevation has been strongly associated with the severity of ductopenia and inflammation, and lower ALP levels after 1 year of UDCA treatment are associated with lower hazard ratios of transplant or death.[28,31]

However, inadequate treatment response is observed in up to 40% of patients, and these patients are at increased risk for disease progression.[10,30] Therefore, efforts should be placed on improving access to UDCA for all patients diagnosed with PBC and identifying inadequate UDCA responders, even as early as 6 months, to optimize treatment strategies for these patients.[32] It is generally accepted that an ALP level greater than 1.67 × upper limit of normal (ULN) after 12 months of treatment with UDCA represents an insufficient response. Furthermore, based on data from the Global PBC Study Group, an ALP level greater than 1.9 × ULN after 6 months of therapy has been associated with lack of response to UDCA at 1 year. Thus, this simple laboratory parameter could be utilized for early identification of individuals in need of second-line therapy.

In addition to monitoring biochemical markers, use of liver stiffness measurement (LSM) by transient elastography can help assess disease progression and predict clinical outcomes, including risk of death and transplant. LSM scores greater than 10 to 11 kilopascals (kPa) have been associated with an increased risk of developing an adverse clinical outcome.[33-35] More recently, a large international study also demonstrated that any relative change in LSM over time can affect the risk of a serious clinical event.[36] For example, a 20% increase in LSM over a yearlong period was associated with a greater than 2-fold increase in the adjusted hazard ratio for an event. Importantly, LSM improvement correlated with a reduced risk of events.[36]

Other variables associated with incomplete response to UDCA and worse clinical progression include younger age, presence of advanced fibrosis at the time of diagnosis, male sex, and certain ethnicities, such as Hispanics and Native Indigenous populations in Canada.[2,9,11] All of these factors should be taken into consideration alongside biochemical response and LSM when deciding whether to

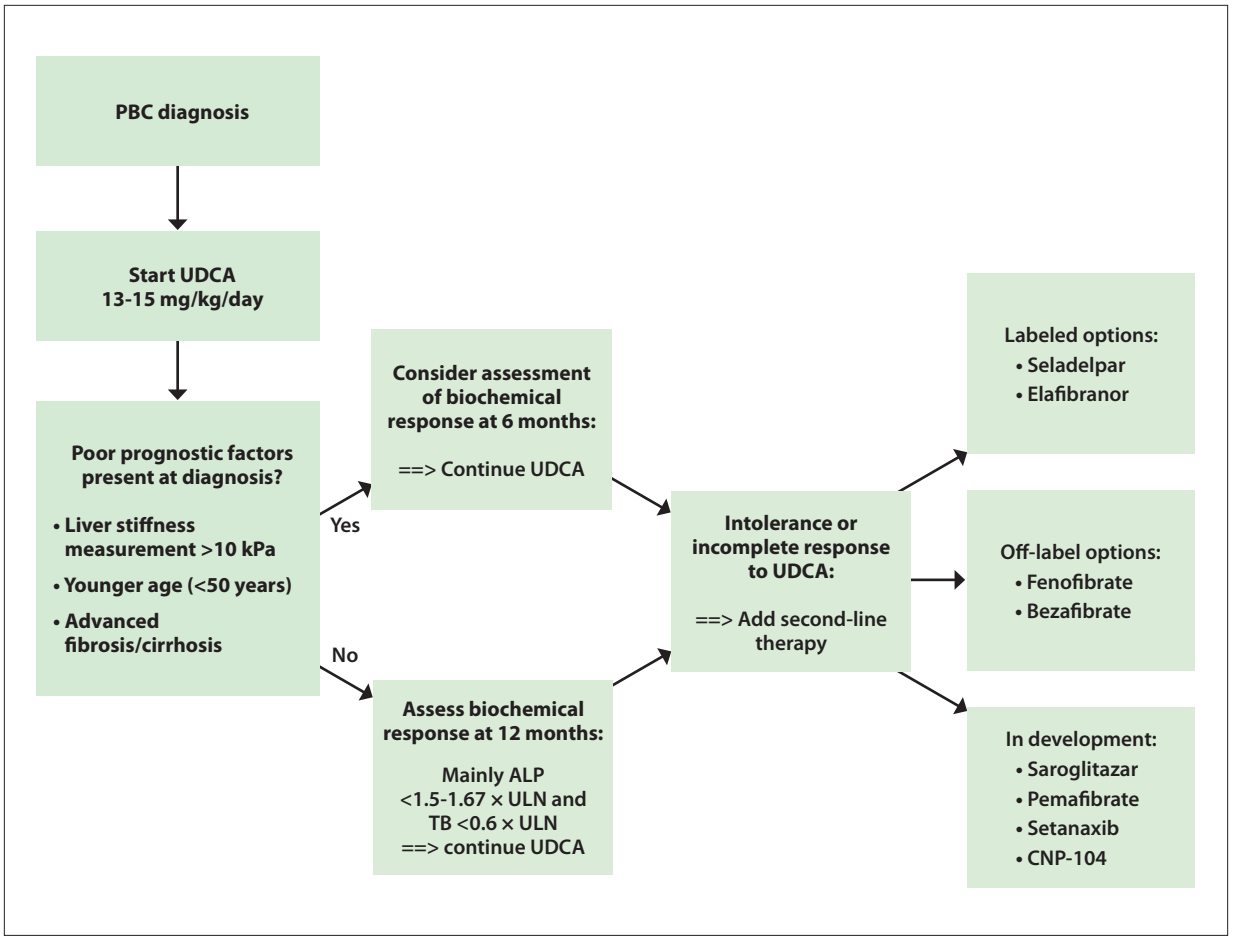

Figure 2. Flowchart illustrating a suggested management approach for PBC, including first-line therapy and currently available second-line treatment options, based on biochemical response and prognostic factors. Additionally, 4 investigational drug therapies are in development for use in PBC.

ALP, alkaline phosphatase; kPa, kilopascals; PBC, primary biliary cholangitis; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

add a second-line drug. Accelerated US Food and Drug Administration (FDA) approval was granted to obeticholic acid (OCA; Ocaliva, Intercept) in 2016, followed by elafibranor (Iqirvo, Ipsen) and seladelpar (Livdelzi, Gilead) in 2024, for use as second-line therapy, whereas fibrates (such as fenofibrate and bezafibrate) are utilized as off-label alternatives. Although OCA was withdrawn from the US market in September 2025, the drug remains available to currently prescribed patients until mid-November 2025 to facilitate transition to alternative therapies.

Second-Line Therapies

Obeticholic Acid

Activation of the farnesoid X receptor by OCA leads to decreased synthesis and uptake of bile acids and improved conjugation and transport, ultimately reducing cholestasis and cytotoxicity.[37,38] The drug also has other anti-inflammatory and antifibrotic properties.[39]

POISE was a phase 3, double-blind, placebo-controlled trial that evaluated patients with an inadequate response to or intolerance of UDCA.[19] The primary endpoint, a composite of ALP level less than 1.67 × ULN with a reduction of at least 15% from baseline and a normal total bilirubin level, came to be known as the POISE criteria and was achieved in approximately half of treated patients compared with 10% in the placebo group. Subsequent real-world studies across multiple countries confirmed similar reductions in ALP, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin, including in patients with PBC/autoimmune hepatitis overlap syndrome.[40-43] Long-term follow-up of POISE participants compared with propensity-matched, OCA-naive controls from the real world (Global PBC and UK PBC cohorts)

Table 2. Completed Phase 3 Trials of PPAR Agonists in PBC[a]

Drug name (dose); study name	Number of pts; study duration	% of pts meeting POISE endpoint vs placebo	Median ALP at baseline (U/L)	% of ALP normalization vs placebo	Impact on lipids	Impact on pruritus vs placebo (point reduction from baseline NRS score)	Other quality-of-life measures	Adverse events
Bezafibrate (400 mg); BEZURSO	100; 24 months	b	Bezafibrate: 244 (range, 211-308) Placebo: 242 (range, 186-344)	67%	↓ Total cholesterol, LDL, and HDL	c	No change in quality of life based on Nottingham Health Profile	Myalgia Abdominal pain Nasopharyngitis, bronchitis, flu-like syndrome Transient aminotransferase and creatine kinase elevation
Seladelpar (5 mg/10 mg); ENHANCE	265; 3 months	5 mg: 57.1% 10 mg: 78.2% Placebo: 12.5%	5 mg: 290.5 ± 104.2 10 mg: 290.8 ± 109.1 Placebo: 293.4 ± 106.2	5 mg: 5.4% 10 mg: 27.3% Placebo: 0%	Total cholesterol: 5 mg: ↓ 3.7% 10 mg: ↓ 4.4% Placebo: ↓ 1.8% LDL: 5 mg: ↓ 5.6% 10 mg: ↓ 8.2% Placebo: ↓ 0.6% Triglycerides: 5 mg: ↓ 5.9% 10 mg: ↓ 13.1% Placebo: ↓ 0.6% HDL: 5 mg: ↑ 1% 10 mg: ↑ 6.7% Placebo: ↓ 3%	5 mg: -2.01 (*P*=.48) 10 mg: -3.14 Placebo: -1.55 Improvement in PBC-40 itch domain score	No improvement in PBC-40 total score	Upper abdominal pain Nausea
Seladelpar (10 mg); RESPONSE	193; 12 months	Seladelpar: 61.7% Placebo: 20%	Seladelpar: 314.6 ± 123.0 Placebo: 313.8 ± 117.7	Seladelpar: 25% Placebo: 0%	Total cholesterol: 10 mg: ↓ 4.4% LDL: 10 mg: ↓ 9% Triglycerides: 10 mg: ↓ 15.1% HDL: 10 mg: ↑ 4.4%	Seladelpar: -3.2 Placebo: -1.7 Reduction in the 5-D itch total score from baseline	Improvements in PBC-40 total score and in sleep with seladelpar	Headache Abdominal pain Nausea Abdominal distension
Elafibranor (80 mg); ELATIVE	161; 52 weeks	Elafibranor: 51% Placebo: 4%	Elafibranor: 321.3 ± 121.9 Placebo: 323.1 ± 198.6	Elafibranor: 15% Placebo: 0%	Greater ↓ in total cholesterol, LDL, and VLDL in elafibranor groups vs placebo No significant change in HDL levels	No significant difference in NRS between groups (-1.93 vs -1.15) Improvement in PBC-40 itch domain and total 5-D itch score	PBC-40 total score with similar changes in both groups	Abdominal pain Diarrhea Nausea Vomiting

[a]All reported results were statistically significant unless otherwise stated.
[b]In BEZURSO, the proportion of patients with a complete biochemical response (normal serum levels of ALP, AST, ALT, total bilirubin, and albumin) was used as the primary endpoint.
[c]Pruritus was not a key secondary endpoint in this trial.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NRS, numerical rating scale; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; pts, patients; VLDL, very low-density lipoprotein.

showed that only 2.4% of OCA-treated patients required liver transplant or died, compared with 10% to 13.2% in the matched external controls.[44] Although the COBALT confirmatory trial failed to replicate these benefits owing to functional unblinding and crossover to commercially available OCA, analyses incorporating real-world propensity-matched controls suggested a 60% to 63% reduction in the risk of hepatic decompensation, transplant, or death among OCA-treated patients.[45,46] The most common side effect of OCA was dose-dependent pruritus, which led to treatment discontinuation in approximately 10% of individuals.[19,41-43,47,48] Furthermore, OCA was contraindicated in advanced cirrhosis or in patients with portal hypertension or hepatic decompensation, as the drug may increase the risk of hepatotoxicity and liver failure.[49]

Despite these results, the US FDA Advisory Committee issued a negative review of the proposed benefits of OCA and its safety profile, informing that it would continue to evaluate postmarketing data for the safety and efficacy of the drug in PBC.[50-52] On September 11, 2025, Intercept Pharmaceuticals voluntarily withdrew OCA from the US market at the FDA's request owing to ongoing concerns about severe liver injury. All clinical trials involving OCA were placed on hold. Additionally, on November 26, 2024, the General Court of the European Union had decided to uphold the European Commission's decision to revoke the license for OCA, which remains authorized only in Canada, Switzerland, Australia, and the United Kingdom.

Peroxisome Proliferator-Activated Receptor Agonists

Generally, peroxisome proliferator-activated receptor (PPAR) agonists have anti-inflammatory properties and affect bile acid homeostasis by decreasing bile acid synthesis and regulating its transport and detoxification.[53-55] The completed phase 3 trials for PPAR drug therapies are shown in Table 2.

Elafibranor

Elafibranor is a dual PPAR-α/-δ agonist first studied in a phase 2 trial in noncirrhotic PBC patients. Patients were randomized to receive either elafibranor 80 mg, elafibranor 120 mg, or placebo once daily for 12 weeks with continued UDCA use. The study showed significant ALP reductions in the elafibranor 80-mg and 120-mg groups, achieving the primary endpoint (POISE criteria) in 67% and 79% of patients, respectively, compared with only 6.7% in the placebo group. Additionally, based on changes in the visual analog scale, a dose-dependent improvement in pruritus was observed in elafibranor-treated patients (7% in the placebo-treated group vs 24% and 49% in the elafibranor 80-mg and 120-mg groups, respectively).[56]

A large, phase 3, double-blind, placebo-controlled trial (ELATIVE) was then conducted in which 161 patients were randomized to receive once-daily elafibranor at a dose of 80 mg or placebo for 52 weeks. The primary endpoint was the proportion of patients meeting POISE criteria at week 52, which was met in 51% of elafibranor-treated patients vs 4% of placebo-treated patients. Additionally, 15% of the patients in the elafibranor group vs 0% in the placebo group achieved ALP normalization.[57] Among patients with moderate-to-severe pruritus, no significant change from baseline was observed between treatment groups. Elafibranor was well tolerated, with few adverse effects reported. In response to the successful phase 3 trial and good safety profile, elafibranor was granted FDA accelerated approval on June 10, 2024 for use in PBC patients in combination with UDCA in those with inadequate response to UDCA or as monotherapy in patients intolerant to UDCA.[58]

Seladelpar

Seladelpar is a selective PPAR-δ agonist with anti-inflammatory, anticholestatic, and antipruritic properties. In the dose-finding, open-label, phase 2 study, patients received either 5 mg or 10 mg of seladelpar for 52 weeks. A sustained dose-dependent reduction in ALP was observed, with 55% and 69% of patients in the 5-mg and 10-mg groups achieving the POISE composite endpoint after 1 year of treatment, respectively.[59] Additionally, patients had improvement in pruritus, especially in the 10-mg treatment arm.[59,60] These results showing the dual therapeutic benefit of using seladelpar in treating PBC patients prompted the phase 3 ENHANCE trial, which was initially designed to assess the efficacy and tolerability of seladelpar over 12 months. The study, however, was terminated prematurely at 3 months owing to safety concerns surrounding seladelpar use in a concurrent metabolic dysfunction-associated steatohepatitis trial.[61] These concerns proved to be unfounded, and the RESPONSE trial then followed.

In the RESPONSE trial, a 12-month placebo-controlled trial, patients with PBC and intolerance of or inadequate response to UDCA were treated with 10 mg of seladelpar or placebo. At the end of the study, 61.7% of seladelpar-treated patients achieved the primary outcome (POISE criteria) vs 20% on placebo, and 25% in the seladelpar group achieved ALP normalization.[62] Similarly, the seladelpar group experienced reductions in ALT and gamma-glutamyl transferase (GGT) that were more than 3 times greater than those in the placebo group. Among patients with moderate-to-severe pruritus (numerical rating scale ≥4) at baseline, substantial and sustained improvement was observed, with a 3.2-point reduction in

seladelpar vs a 1.7-point reduction for placebo. No serious adverse events were reported. The long-term safety and tolerability of seladelpar were evaluated in an open-label trial, which showed sustained and markedly improved biochemical markers of cholestasis and liver injury throughout the 2-year follow-up period.[59] On August 14, 2024, seladelpar was granted accelerated FDA approval for treating PBC in combination with UDCA in adults who have had an inadequate response to UDCA or as monotherapy in patients unable to tolerate UDCA. As is the case for all PPAR agonists, seladelpar is not recommended for people with decompensated cirrhosis.

Seladelpar continues to demonstrate promising results. Interim findings from the ongoing open-label phase 3 ASSURE trial, which serves as a rollover of the phase 3 RESPONSE trial and legacy studies, revealed that 61.8% and 72.4% of patients met the composite endpoint at 6 and 12 months, respectively, along with 75% and 93.8% of placebo crossover patients at the same intervals. Key endpoints included the composite ALP response; notably, 33.3% of patients achieved ALP normalization at 6 months (17.2% at 12 months) with ongoing treatment. In the ASSURE legacy patients, endpoints were reached by 73.2% (at 12 months) and 69.7% (at 24 months), with 42.1% and 42.4% achieving ALP normalization. Improvement in pruritus was consistent across both trials, and no serious adverse events related to the treatment were observed.[63]

Off-Label Therapies: Fibrates

The 2 fibrates most often studied in PBC are fenofibrate (a PPAR-α agonist available in the United States) and bezafibrate (a pan-PPAR agonist not commercially available in the United States). Their observed benefits in several smaller pilot studies led to the pivotal BEZURSO trial in which bezafibrate was used as an add-on therapy in patients with inadequate UDCA response based on Paris II criteria.[29] The primary endpoint was a complete normalization of all liver chemistries (ALP, total bilirubin, AST, ALT, albumin, and prothrombin time index) at 24 months. The study showed impressive biochemical improvement, with 67% of patients on bezafibrate normalizing ALP and one-third normalizing all liver chemistries.[64] Although the study did not stratify for itching, a significant improvement in pruritus was observed. Later, the FITCH trial was designed specifically to assess the impact of fibrates on cholestatic itching. Greater than 50% reduction in moderate-to-severe pruritus occurred in 45% of bezafibrate-treated patients (41% primary sclerosing cholangitis, 55% PBC) vs 11% of placebo-treated patients.[65]

Bezafibrate's demonstrated efficacy in biochemical response and symptomatology may slow disease progression while improving these patients' quality of life.[64,66,67] The most common adverse event reported with fibrate use was myalgia (20% in the bezafibrate group vs 10% in the placebo group), and elevated creatinine was observed in a smaller percentage of patients (5% increase from baseline in the bezafibrate group and 3% decrease in the placebo group). Comparatively, a recently concluded phase 3 trial using fenofibrate as add-on therapy in UDCA treatment–naive patients with PBC showed improved biochemical response rates based on Barcelona criteria. In the UDCA-fenofibrate group, 81.4% (69.9%-92.9%) of patients achieved the primary endpoint compared with 64.3% (51.9%-76.8%) in the UDCA-only group (P=.048).[68] Pruritus was not evaluated as an endpoint in this study, and, in fact, 1 patient in the UDCA-fenofibrate group discontinued the study owing to pruritus compared with none in the UDCA-alone group.[68]

Real-world studies with varying levels of statistical power have been conducted to evaluate the efficacy of fibrate add-on therapy in patients with PBC who exhibit a suboptimal response to UDCA.[66,69-76] These studies generally demonstrated improvements in biochemical response rates and various PBC risk scores. However, the impact of fenofibrate on GLOBE scores yielded mixed results.[77,78] Notably, a Japanese study investigated the effect of combination therapy on transplant-free survival, revealing that use of UDCA-bezafibrate combination therapy was associated with a significant reduction in both all-cause and liver-related mortality, as well as the need for liver transplant.[79]

Triple Therapy

Real-world studies were carried out on patients with difficult-to-treat PBC, employing a combination of UDCA, OCA, and fibrates (also called triple therapy). Further ALP reduction and higher normalization rates were reported with the addition of the third drug to the existing regimens of UDCA-fibrate or UDCA-OCA.[43,80,81] Improvement in GLOBE score was also observed with triple therapy.[81] Although a phase 2a randomized clinical trial to provide a better understanding of the risks and benefits of this treatment strategy was completed on September 1, 2025 (NCT05239468), plans for a phase 3 trial were aborted.

Bone Health and Peroxisome Proliferator-Activated Receptor Agonist Use

The impact of PPAR agonists on bone mineral density (BMD) has not been properly examined in humans; in rats, this effect is dependent on the specific PPAR isoform. The PPAR-α agonist fenofibrate has been shown to increase femoral BMD while PPAR-α/-δ agonists can upregulate osteoblast differentiation and induce periosteal bone formation.[82] On the contrary, PPAR-γ

agonists demonstrated increased bone loss and elevated fracture risk.

In the RESPONSE trial, 4% of patients treated with seladelpar developed fractures vs none in the placebo group.[61] Cirrhosis was identified as a potential additional risk factor for fracture in seladelpar-treated patients. Similarly, 6% of elafibranor-treated patients in the ELATIVE study had fractures compared with none in the placebo group.[56] Notably, these studies were not designed to address risk of fracture. Therefore, treatment groups were unbalanced at baseline as far as fracture risk, and dual-energy x-ray absorptiometry scans were not regularly obtained at baseline and the end of study. At this time, the recommendation for bone health monitoring in patients on PPAR agonists is per current standards of care.[10]

Therapies in Development

Saroglitazar

Saroglitazar has a higher PPAR-α/-γ affinity and has been studied in people with metabolic dysfunction-associated steatotic liver disease. In a phase 2 trial in steatotic liver disease, saroglitazar improved ALT levels, liver fat content, markers of insulin resistance, and dyslipidemia.[83] The use of saroglitazar in PBC patients was studied in a double-blind, phase 2, proof-of-concept trial in which 37 PBC patients were randomized to receive saroglitazar 4 mg (n=13), saroglitazar 2 mg (n=14), or placebo (n=10). ALP declined by 49% (P<.001) and 51% (P<.001) in the saroglitazar 4-mg and 2-mg groups compared with 3% in the placebo group.[84] A phase 3 randomized controlled trial is ongoing to assess the safety and efficacy of saroglitazar at lower treatment doses (NCT05133336).

Setanaxib (GKT137831)

This potentially antifibrotic drug is a selective nicotinamide adenine dinucleotide phosphate oxidase (NOX) isoform 1 and 4 inhibitor. Earlier in vivo and animal model studies have suggested that NOX inhibition can reverse cholestasis-associated fibrosis.[85-87] This was supported by the post hoc analysis of the phase 2 trial of setanaxib, which hypothesized that the drug could be beneficial for PBC patients with advanced liver disease (LSM >9.6 kPa at baseline) as it reduced liver stiffness by 22% when administered twice daily over 24 weeks.[87] Additionally, the phase 2a trial 6-week interim analysis reported a dose-dependent reduction in the biochemical markers GGT (7%, 12%, and 23%) and ALP (2%, 8%, and 17%) in the placebo, 400-mg once-daily, and 400-mg twice-daily groups, respectively (P<.001 for 400 mg twice daily vs placebo).[87] Furthermore, based on the PBC-40, setanaxib improved quality of life in individuals with moderate-to-severe fatigue at baseline, with a higher reduction in mean fatigue score reported in a post hoc analysis.[88] The phase 2b/3 TRANSFORM trial is underway to evaluate the effect of setanaxib on biochemical response in participants with PBC and with elevated LSM over 52 weeks (NCT05014672).

CNP-104

CNP-104 is a biodegradable, tolerogenic nanoparticle that encapsulates the E2 subunit of the mitochondrial pyruvate dehydrogenase complex (PDC-E2). This dominant autoantigen in PBC is thought to promote loss of tolerance and induce biliary disease.[89] A phase 2a first-in-human randomized controlled trial in patients with PBC and ALP level greater than 1.5 × ULN after treatment with UDCA and/or OCA was conducted with 41 patients, who were randomized to receive either CNP-104 or placebo. At day 120, the proportion of antigen-specific Th17 T cells in patients treated with CNP-104 was lower than that of those treated with placebo. Additionally, vibration-controlled transient elastography showed stabilization of liver stiffness in the CNP-104 treatment arm vs an increase in the placebo arm. There was no difference in ALP level between the groups. CNP-104 was safe and well tolerated.[89]

Novel Therapies for Pruritus Management

Ileal Bile Acid Transporter Inhibitors

Ileal bile acid transporter (IBAT) inhibitors reduce bile acid buildup and toxicity by interrupting the enterohepatic circulation and bile acid absorption.[90,91] Drugs in this class that are currently under evaluation for the treatment of pruritus in PBC include linerixibat and volixibat (Figure 1).

Linerixibat demonstrated efficacy in reducing pruritus severity in a smaller phase 2a trial, with reductions in serum total and conjugated bile acids also being reported.[92] The larger multicenter, randomized, phase 2b GLIMMER trial that followed was conducted in patients with PBC and moderate-to-severe pruritus. Patients received varying doses of linerixibat to investigate a primary endpoint of dose-related change in mean worst daily itch. In the primary intent-to-treat analysis, the impact of linerixibat on itch did not vary substantially from placebo; however, in the per-protocol population, linerixibat was linked to a significant dose-dependent decrease in itch.[93] GLISTEN, a 2-part, randomized, placebo-controlled, double-blind, multicenter, phase 3 study, evaluated the efficacy and safety of linerixibat for the treatment of cholestatic pruritus in participants with PBC. Preliminary analysis showed that the endpoint of the study was met with a significant reduction from baseline in monthly itch score over 24 weeks vs placebo.[94] There is ongoing analysis of these data.

The most common side effect of linerixibat, as expected for IBAT inhibitors, was diarrhea, but drug discontinuation owing to this adverse event was not common.

The interim analyses of a phase 2a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of volixibat in treating cholestatic pruritus in patients with PBC (VANTAGE) were released in June 2024. Patients were randomized to receive volixibat 20 mg, volixibat 80 mg, or placebo. A 3.8-point reduction from baseline and a 2.3-point placebo-adjusted (P=.0026) reduction in the primary endpoint of pruritus were observed.[95] A notable improvement in fatigue was seen in the volixibat treatment arms in comparison with placebo. Diarrhea was the most common adverse event. Phase 2b studies are underway.

Kappa Opioid Receptor Agonist

By stimulating kappa opioid receptors on peripheral neurons and immune cells, difelikefalin (CR845), a long-acting, selective peripheral kappa opioid receptor agonist, demonstrates antipruritic effects.[96] It is currently approved by the FDA for use in hemodialysis patients with moderate-to-severe pruritus. A phase 2 multicenter, randomized, double-blind, placebo-controlled study was initiated to evaluate the safety and efficacy of oral CR845 in patients with PBC with moderate-to-severe pruritus. However, the study was terminated owing to slow enrollment attributed to COVID-19. The results have not been published yet.

Mas-Related G Protein–Coupled Receptor X4 Antagonist

Mas-related G protein–coupled receptor X4 (MRGPRX4) is a neuronally expressed receptor stimulated by various metabolites that cause itching, such as bile acids, bilirubin, and associated heme metabolites.[97,98] EP547 is a highly selective antagonist of MRGPRX4 that was studied in a phase 1 trial evaluating the treatment of pruritus associated with cholestasis and uremia. According to the study, EP547 was safe and well tolerated in healthy volunteers and patients with chronic cholestatic or kidney disease at all tested doses.[99] Enrollment is complete for the phase 2 proof-of-concept study (PACIFIC, NCT05525520) evaluating the effects of EP547 in patients with cholestatic pruritus owing to PBC or primary sclerosing cholangitis, and results are awaited.

Conclusion

PBC is an indolent autoimmune liver disease that can be refractory to conventional therapies in approximately 40% of cases. Recent advances in treatment aim to slow disease progression, enhance transplant-free survival, and improve quality of life. PPAR agonists demonstrated significant improvement in biochemical markers, leading to accelerated FDA approval; the positive impact on pruritus is an added benefit. Fibrates have shown promise as off-label therapies that are widely available at lower cost. Emerging therapies include other PPAR agonists, such as saroglitazar, as well as novel therapeutics using nanoparticles to improve immune tolerance (CNP-104). Finally, clinicians should remain mindful of symptom management, especially as novel therapies with IBAT inhibition for the treatment of cholestatic pruritus are likely to become available in the near future.

Disclosures

Dr Buchanan-Peart and Dr Dasani have no relevant conflicts of interest to disclose. Dr Levy has received research grants from Calliditas, CymaBay, Escient, Gilead, Genfit, Intercept, Ipsen, Kowa, GSK, Mirum, Target RWE, and Zydus.

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