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New Treatment Paradigms in Primary Biliary Cholangitis

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Primary biliary cholangitis (PBC) is an archetypal autoimmune disease. Chronic lymphocytic cholangitis is associated with interface hepatitis, ductopenia, cholestasis, and progressive biliary fibrosis. People living with PBC are frequently symptomatic, experiencing a quality-of-life burden dominated by fatigue, itch, abdominal pain, and sicca complex. Although the female predominance, specific serum autoantibodies, immune-mediated cellular injury, as well as genetic (HLA and non-HLA) risk factors, identify PBC as autoimmune, to date treatment has focused on cholestatic consequences. Biliary epithelial homeostasis is abnormal and contributes to disease. The impact of cholangiocyte senescence, apoptosis, and impaired bicarbonate secretion enhances chronic inflammation and bile acid retention. First-line therapy is a non-specific anti-cholestatic agent, ursodeoxycholic acid. For those with residual cholestasis biochemically, obeticholic acid is introduced, and this semisynthetic farnesoid X receptor agonist adds choleretic, anti-fibrotic, and anti-inflammatory activity. Future PBC licensed therapy will likely include peroxisome proliferator activated receptor (PPAR) pathway agonists, including specific PPAR-delta agonism (seladelpar), as well as elafibrinor and saroglitazar (both with broader PPAR agonism). These agents dovetail the clinical and trial experience for off-label bezafibrate and fenofibrate use. Symptom management is essential, and encouragingly, PPAR agonists reduce itch; IBAT inhibition (eg, linerixibat) also appears promising for pruritus. For those where liver fibrosis is the target, NOX inhibition is being evaluated. Earlier stage therapies in development include therapy to impact immunoregulation in patients, as well other approaches to treating pruritus (eg, antagonists of MrgprX4). Collectively the PBC therapeutic landscape is exciting. Therapy goals are increasingly proactive and individualized and aspire to rapidly achieve normal serum tests and quality of life with prevention of end-stage liver disease.

Keywords: Primary Biliary Cholangitis; Treatment; Pruritus; Risk Stratification.

Primary biliary cholangitis (PBC) is an autoimmune liver disease in which immune-mediated injury is focused on small bile ducts. The granulomatous lymphocytic cholangitis drives a progressive cholestatic liver disease that when untreated can lead to liver cirrhosis, hepatocellular carcinoma, liver failure, and death. As in most autoimmune diseases there is a female predominance, but unlike other autoimmune liver diseases, children are virtually never diagnosed with PBC.[1–3]

Laboratory hallmarks of disease include characteristic biochemical markers of cholestasis, including elevation of serum alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), and bilirubin, frequently accompanied by an elevation in immunoglobulin M concentration. The archetypical liver histology is described as a chronic non-suppurative cholangitis with granuloma formation alongside progressive destruction of small intrahepatic bile ducts. Antimitochondrial antibodies (AMA) targeting the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2) of the inner mitochondrial membrane are highly specific for PBC and are present in more than 90% of patients. The diagnostic accuracy of cholestasis as evidenced biochemically, alongside positive serum AMA testing, has resulted in the majority of patients not needing a liver biopsy to reach a secure diagnosis of PBC.[4,5] Among patients with normal serum liver tests but positive AMA, 16% will develop features of PBC within 5 years.[6] In addition to AMA, PBC-specific antinuclear autoantibodies, namely anti-glycoprotein 210 (anti-gp 210) and/or anti-sp100, reflect the autoimmune nature of this disease. Anti-glycoprotein 210 and/or anti-sp100 occur in up to 50% of PBC patients negative for AMA. PBC-specific antinuclear antibodies can be used to diagnose PBC in the absence of AMA and may offer prognostic information (Table 1).[7,8]

The etiology of PBC remains unknown. Conceptually it is recognized that environmental factors likely trigger an autoimmune process toward bile duct epithelia in genetically predisposed individuals.[9] Pathogenic mechanisms leading to chronic non-suppurative cholangitis are incompletely understood, although persistent cholestatic

Abbreviations used in this paper: **ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibodies; AST, aspartate aminotransferase; FXR, farnesoid X receptor; GGT, gamma glutamyl transferase; LSM, liver stiffness measurement; NOX, nicotinamide adenine dinucleotide phosphate oxidases; OCA, obeticholic acid; PBC, primary biliary cholangitis; PDC-E2, E2 subunit of the pyruvate dehydrogenase complex; PPAR, peroxisome proliferator activated receptor; ROS, reactive oxygen species; UDCA, ursodeoxycholic acid; ULN, upper limits of normal.**

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Table 1. Frequency and Significance of PBC-Associated Antinuclear Antibodies in AMA Positive and Negative PBC Patients

Antibody	Frequency		Clinical significance
	AMA (+)	AMA (–)	
Anti-gp210, rim-like pattern	16%–18%	15%–45%	60%–100% specific, commercially available Poorer transplant-free survival
Anti-sp100, multiple nuclear dots pattern	2%–31%	13%–54%	60%–100% specific, commercially available
Anti-hexokinase 1	39%–56%	12%–40%	95% specific, not commercially available Poorer transplant-free survival
Anti-kelch	19%–26%	10%–29%	95% specific, not commercially available

AMA, antimitochondrial antibody; PBC, primary biliary cholangitis.
Adapted from Leung and Hirschfield.[7]

injury is a hallmark for progressive disease. The (auto) immune attack may relate to incomplete proteolysis of PDC-E2 and other mitochondrial factors during apoptosis of biliary epithelial cells.[10] In addition to the humoral loss of tolerance, there is also a clustering of autoreactive CD4+CD8+ pyruvate dehydrogenase complex (PDC-E2) specific T cells in the liver.[11,12] Changes in biliary epithelial cell physiology, in particular a loss of the protective bicarbonate extracellular environment, is predicted to equally be relevant to disease, because accumulation of hydrophobic bile acids further sensitize the cholangiocytes to apoptosis. Supporting the role of cytotoxic bile acids on disease pathogenesis is the fact that over the years, therapies proven to be most efficacious in PBC are those involving modulation of bile acid homeostasis as opposed to immunomodulation. Candidate environmental triggers include urinary tract infections, reproductive hormone replacement, nail polish, cigarette smoking, and xenobiotics.[5,13]

Clinicians and patients are concerned about liver disease progression and also about quality of life. Important prevalent clinical symptoms that contribute to substantial morbidity for people living with PBC include fatigue, itching, right upper abdominal quadrant discomfort, as well as sicca complex.[5,14]

The Historic Standard of Care: Ursodeoxycholic Acid

As a result of ursodeoxycholic acid (UDCA) becoming the standard of care in PBC management,[15–18] the clinical course and prognosis for people living with PBC have improved significantly over recent decades. Untreated, this chronic cholestatic disease runs a progressive course leading to liver cirrhosis and all its complications including death and/or transplantation. Baseline risk factors for disease progression associated with mortality and/or need for liver transplantation are ALP and bilirubin values,[19] male sex,[20] diagnosis at an early age (<45 years),[21] advanced fibrosis stage,[22] and anti-gp 210 and anti-centromere antibodies.[23–27] Because male sex is also associated with later diagnosis, it remains unclear whether it can be used as independent prognostic factor for PBC outcome.[21] Although in the 1980s PBC was one of the major indications for liver transplantation, there is nowadays a decline for this indication.[28] Diagnosis is now made at earlier stages, and UDCA is accepted and widely used.

Where available, UDCA is given as standard of care to all patients with PBC and abnormal biochemical parameters irrespective of the fibrosis stage, and treatment is lifelong, including post-transplant. Treatment is generally well-tolerated, and the optimal dose is 13–15 mg/kg/day.[5] The proposed mechanisms of action are multiple, including choleretic, cytoprotective (bile alkalinization through anion exchange induction), anti-inflammatory, and immunomodulatory properties. The Global PBC study group has shown in a large analysis of 4845 patients that UDCA-treated individuals had significantly improved transplant-free survival at 5, 10, and 15 years compared with untreated individuals (90%, 78%, and 66% versus 79%, 59%, and 32%, respectively).[29]

Monitoring Response to Therapy and Prognosis

Serum liver tests provide not only baseline diagnostic and prognostic information but also offer insights to ongoing risk of disease progression on treatment. The biochemical treatment response is currently assessed after 12 months, focusing on ALP and bilirubin values. Several published criteria can define response to UDCA and offer prognostic information. Fundamentally they classify the same message, either through a dichotomous or continuous approach, namely that best outcomes are seen in patients with the best serum liver tests. Classifiers include Rochester I & II,[30,31] Barcelona,[32] Paris I[33] & II,[34] Rotterdam,[35] and Toronto[36] (Table 1), UK PBC,[37]

Table 2. Various Classifiers Used to Determine Response to Treatment With Ursodeoxycholic Acid

Criteria	Months after starting UDCA	Criteria for incomplete response
Binary		
Rochester-I[26]	6	ALP > 2 × ULN
Rochester-II[27]	12	ALP ≥ 2 × ULN or TB > 1 mg/dL
Barcelona[28]	12	≤40% reduction from baseline in ALP, and ALP > ULN
Paris-I[29]	12	ALP > 3 × ULN, AST > 2 × ULN, or TB >1 mg/dL
Paris-II[30]	12 (for early disease stages: Stage 1-2 according to Ludwig or normal TB and albumin levels)	ALP > 1.5 × ULN, AST >1.5 × ULN, or TB > 1 mg/dL
Rotterdam[31]	12	TB > ULN and/or albumin < LLN
Toronto[32]	24	ALP > 1.67 × ULN
Continuous		
GLOBAL PBC[25]	12	12 months: TB, ALP, albumin, and platelet count; Baseline: age
UK-PBC[33]	12	12 months: TB, ALP, and AST (or ALT); Baseline: albumin and platelets

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LLN, lower limit of normal; TB, total bilirubin; UDCA, ursodeoxycholic acid.

and Globe Score[29,38] (Table 2). Patients with an insufficient response to UDCA fulfilling these criteria, roughly 20%–40% of all patients with PBC, have poorer survival free of liver transplantation and increased rates of hepatocellular carcinoma.[29,38,39] In general, these patients are thus candidates for second-line therapy (Figure 1).

In addition, important nuances should be recognized. A recent analysis from the Global PBC study group showed that normalization of ALP and a total bilirubin <0.6 × upper limits of normal (ULN) are independently associated with lower rates of liver transplantation and liver-related death compared with previously published and used criteria (Table 2).[40] In addition, patients with PBC fulfilling remission criteria (ALP <1.5 ULN, Paris II criteria) but showing at the same time elevated GGT levels of >3.2 ULN had higher risk for liver transplantation and liver-related mortality.[41]

Furthermore, liver fibrosis at start of therapy is a risk factor for progression independent of treatment response.[22] Patients with advanced fibrosis/cirrhosis

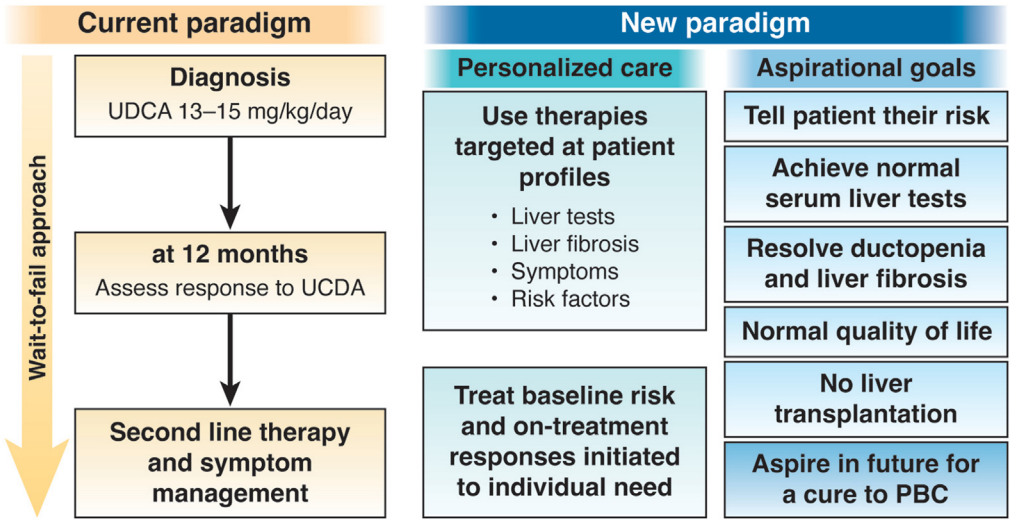

Figure 1. Current treatment paradigm in PBC involves early diagnosis and initiation of ursodeoxycholic acid (UDCA), with reassessment after 1 year of therapy. A decision is made to initiate second-line therapy in case of insufficient response to UDCA based on one of many sets of available response criteria. The choice of second-line therapy depends on several variables including existing symptoms, comorbidities, and drug availability. In other words, one waits for treatment to fail to add a second-line drug. The new paradigm is based on a more personalized approach, where individual risk is assessed at baseline, and consideration is given to earlier initiation of second-line drugs for high-risk individuals. We should aspire to normalize liver chemistries and make it a priority to address patients' quality of life.

and complete response to UDCA have a reduced transplant-free survival compared with those patients in early stages with incomplete response. Therefore, fibrosis staging at start of therapy is important to consider. Ultrasound-based noninvasive technologies of transient elastography are of increasing importance for liver stiffness measurement (LSM) at start of therapy and also to monitor response to treatment in longitudinal studies.[42,43] LSM at baseline can independently predict prognosis in PBC, with a LSM cutoff value of 15 kPa identifying a high-risk subgroup with 10-year rate of clinical events in the 50%–90% range, whereas patients with LSM <8 kPa are at low risk for events (<20%).[44]

Second-Line Therapy

People living with PBC, as well as clinicians managing their care in 2023, should therefore not believe that therapy stops at UDCA. Although for a long time the only treatment option with widespread adoption was UDCA and then liver transplantation, that is not reflective of current practice, which has grown in confidence around risk-stratified individualized care. This aligns with enhanced goals of care, and second-line therapies are now firmly established and growing in adoption. Additional anti-cholestatic therapy remains the main approach for added therapy in PBC (Figure 1) and focuses at present on the licensed use of obeticholic acid (OCA), the first approved semisynthetic farnesoid X receptor (FXR) agonist, as well as on the off-label use of the peroxisome proliferator-activated receptor (PPAR) agonists bezafibrate (strongest evidence) and fenofibrate (uncontrolled evidence). It is important to recognize that availability and use of these drugs vary worldwide, with fibrates being more liberally used as second-line therapy in Asia, certain European countries, and South America. Corticosteroids have not been widely adopted as second-line therapy because of concern over long-term use and thus side effects, but there is some evidence for budesonide in patient care.

Obeticholic acid. OCA is a semisynthetic hydrophobic bile acid analogue that is highly selective for FXR, a nuclear bile acid receptor. The natural ligand is chenodeoxycholic acid, and OCA has exponential potency relative to this. FXR is a nuclear receptor that functions as a central transcriptional sensor of bile acids and is found in the liver and bowel. The main FXR target gene in the bowel is fibroblast growth factor-19. This enterokine activates the duo fibroblast growth factor receptor 4/beta KLOTHO on hepatocyte basolateral membranes, triggering intracellular pathways that inhibit cholesterol 7-α-hydroxylase, a rate limiting enzyme in bile acid synthesis.

OCA is currently approved for second-line therapy in patients with PBC who have incomplete response to UDCA or who are intolerant of UDCA. The labelled indication excludes patients with decompensated cirrhosis, but OCA can be used in patients with cirrhosis so long as no features of significant portal hypertension are evident. This change in label occurred because of concerns that in patients with very advanced liver disease treatment benefit was unlikely, and potentially there might be FXR agonist-driven hepatotoxicity.[45] Judging the severity of advanced liver disease is not always easy, and it is equally likely that once the bilirubin is >2 × ULN that benefit from any add-on therapy is unlikely, even if there is no apparent portal hypertension. Therapy is usually add-on to existing UDCA, in keeping with a current paradigm of enhancing anti-cholestatic pathways for patient benefit. The scientific rationale for a FXR agonist in cholestatic liver disease is therefore strong because of the need for a therapy that is anti-cholestatic, anti-inflammatory, and anti-fibrotic. The clinical evidence supporting ongoing use in people living with PBC spans phase 2 dose-finding trials,[46,47] a phase 3 placebo-controlled study,[48] a follow-up long-term safety extension study,[49] as well as real-world efficacy data from international cohorts.[50–52] Finally, there are now efficacy data based on real-world control cohort data, comparing OCA use from the trial setting with clinical outcomes from large PBC registries.[53] Placebo-controlled data looking at clinical endpoints are in analysis. As was the case for UDCA when it first launched, proving a new therapy in PBC changes clinical outcomes is extremely hard for a variety of disease and real-world reasons, most notably the rare nature of disease, the reluctance of patients to stay on placebo as part of long-term outcome trials, and the relatively infrequent nature of clinical events.

In the registration phase 3 clinical trial (PBC OCA International Study of Efficacy) patients with high-risk PBC (prior biochemical non-response according to modified Toronto criterion; ALP >1.67 × ULN and/or elevated total bilirubin <2 × ULN) were evaluated in a randomized placebo-controlled trial.[48] The primary endpoint during the 12-month double-blind period was reaching both an ALP value <1.67 × ULN (with ≥15% reduction from baseline) and a normal serum bilirubin. Biochemical response was met in 10% of the placebo group relative to 47% and 46% in the 10 mg and 5–10 mg dose-titrated OCA arms, respectively. The average decrease in serum ALP from baseline was 39% and 33% in the 10 mg and titrated OCA groups, respectively, versus 5% for patients in receipt of placebo ($P < .0001$ for both). Both OCA groups met predefined secondary endpoints including reduction in serum aspartate aminotransferase (AST) and total serum bilirubin (both OCA groups $P < .001$ vs placebo). Treatment with OCA is associated with a dose-dependent increase in pruritus, which is reported in roughly 40% of treated patients and is the leading cause for drug discontinuation. The mechanism is not clear, but for a related synthetic FXR agonist, specific cytokine (interleukin 31) changes have been associated with FXR-induced pruritus. OCA-treated patients may also exhibit (reversible) alterations in serum lipid levels, most notably a small decrease in high-density lipoprotein.

Real-world data continue to emerge that mirror treatment efficacy from clinical trials, and that now seek to look at clinical outcomes and not solely biochemistry. This array of studies has shown persistent improvements in ALP in addition to stabilization of bilirubin.[54] In addition, there is now evidence that OCA-treated patients from the long-term safety clinical trial have better clinical outcomes than carefully matched synthetic real-world controls.[53]

Bezafibrate and similar agents. PPAR activation is associated mechanistically with regulation of bile acid synthesis, metabolism, and transport; crosstalk with FXR and PXR potentiates this anti-cholestatic effect. In addition, down-regulation of nuclear factor kappa B contributes to anti-inflammatory properties. For some time, there have been reports of using fenofibrate (a synthetic PPAR-alpha agonist) and bezafibrate (a pan-PPAR agonist) for the adjunctive treatment of PBC. Those reports comprise a variety of open label experience and more lately also include randomized controlled data for bezafibrate.[55,56] This has been aligned with robust observational data from Japan suggesting the widespread use of fibrates in PBC patients when indicated may be associated with improved transplant-free survival.[57] For this reason, there is significant interest in use of agents such as this in current PBC care, as well as developing these agents, and related ones, more formally as PBC therapies. Widespread adoption in non-specialist practice in the United States has been hampered by a lack of an approved PBC indication for these agents.

In the BEZURSO trial, 100 patients with PBC and incomplete response to UDCA (according to the Paris-II criteria) were included in a randomized placebo-controlled study of add-on bezafibrate.[58] Patients were randomized to a 2-year treatment period with either bezafibrate 400 mg/day or placebo in addition to UDCA. The primary endpoint was complete normalization of ALP, AST, alanine aminotransferase (ALT), total bilirubin, albumin, and prothrombin time by month 24; this was achieved by 30% of patients on bezafibrate and none on the placebo group. Two-thirds of patients on bezafibrate normalized ALP. Liver stiffness was noted to improve, and pruritus burden fell. Bezafibrate is being developed as a combination therapy with OCA (NCT04594694, NCT05239468) and presently is not available in routine U.S. practice. In the United States, some clinicians therefore use fenofibrate, which equally has been associated with anti-cholestatic effects. Real-world data are emerging on combination use of UDCA, OCA and fibrates, so-called triple therapy, suggesting substantial improvement in markers of cholestasis and inflammation in difficult-to-treat patients who were incomplete responders to second-line therapy.[59,60]

Fibrates at high dose inhibit some CYP enzymes, in particular CYP2C9. At therapeutic doses fibric acid derivatives may increase serum ALT and AST activity, which may relate to known transcriptional effects on liver transaminase synthesis. Reversible creatinine elevations can also occur, likely because of hyperproduction from muscle, and concern over nephrotoxicity requires ongoing investigation and caution. Other adverse effects are recognized; 5%–10% of patients, mostly with bezafibrate, get muscle-skeletal pain,[61] and caution is needed when co-prescribed with statins.

Budesonide. The role of immunosuppression has always been controversial in PBC, which, despite being classically autoimmune in nature, has had treatment focused on anti-cholestatic therapies. In patients with PBC exhibiting "florid" interface hepatitis on biopsy, there are reports demonstrating the efficacy of budesonide in improving liver histology and biochemistry when used in combination with UDCA.[62] Budesonide add-on therapy was not associated with improved liver histology in patients with PBC and incomplete response to UDCA in a clinical trial setting, despite prior studies; however, of note, improvements in biochemical markers of disease activity were demonstrated in secondary analyses.[63] The proportion of patients with ALP $<1.67 \times$ ULN, $\geq$15% decrease in ALP, and normal bilirubin was higher in the budesonide group than in the placebo group at 12, 24, and 36 months ($P < .05$, each). In contrast to placebo, budesonide reduced mean ALP, and 35% of budesonide-treated patients achieved normalization of ALP (placebo 9%; $P = .023$). Serious adverse events occurred in 10 patients receiving budesonide and 7 patients receiving placebo. Therefore, budesonide use has been hard to define for guidelines, but clinicians may consider it for patients with significant interface hepatitis independent of its use in PBC/AIH overlap syndrome.[64]

Treatment of Extrahepatic Symptoms

Pruritus. UDCA is not used as a symptom therapy. Although responders to UDCA have fewer symptoms, UDCA per se does not tackle the prevalent PBC symptom complex and indeed in rare patients can exacerbate itch. Pruritus occurs in 20%–70% of patients[5,43] and negatively impacts quality of life because it is associated with sleep deprivation, depression, social isolation, and worse fatigue.[65–67] It may occur in very early stages and may be present even after liver biochemistries have normalized with UDCA treatment. Pruritus has a circadian rhythm, with worsening in the evening.[68] Severe pruritus may also be notably challenging in the more ductopenic variant of PBC generally seen in younger patients.[69]

Currently, the first choice for treatment of pruritus is cholestyramine (4–16 g/day), a non-absorbable anion-exchange resin, which is given 20 minutes before meals and 2–4 hours before or after other medications because it interferes with their intestinal absorption[70,71] (Figure 2). The beneficial effect of the PPAR agonist bezafibrate on cholestatic pruritus was previously suggested in observational studies[72] and was recently demonstrated in prospective, randomized placebo-controlled trials.[58,73] Although not currently included in

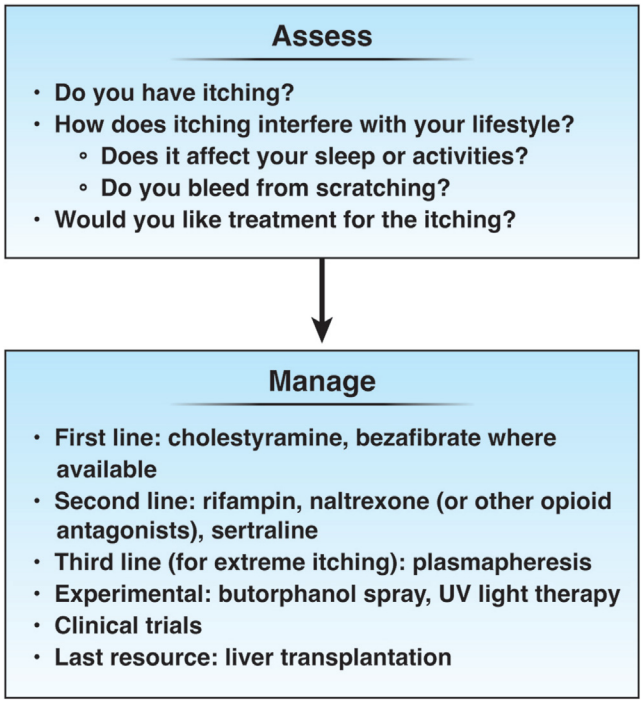

Figure 2. A large proportion of patients with clinically significant pruritus remain untreated. An important part of the overall management of patients living with PBC lies on assessing the presence and significance of extrahepatic symptoms, especially pruritus, and determining the need to initiate therapy. Available guidelines suggest a stepwise approach. As is the case with the treatment of PBC itself, a variety of clinical trials are now under way for difficult-to-treat pruritus: NCT04167358, NCT04950127, NCT 05525520, NCT05050136, and NCT03995212.

existing societal guidelines, it is anticipated that bezafibrate may be used as first-line therapy for itching where available.

Rifampicin (150–300 mg twice daily) is an efficient second-line agent for the treatment of pruritus refractory to cholestyramine.[74,75] However, drug-induced liver injury and renal impairment can occur among other side effects with rifampicin.[76] As an enzyme-inducing agent, interactions with other medications have to be considered. Opiate antagonists such as naltrexone (titrated up to 50 mg daily) interfere with increased levels of endogenous opioids and are effective for treatment of cholestatic pruritus.[75] However, opiate withdrawal reactions should be considered, and gradual increase in dosage is therefore recommended. There is also some evidence that the selective serotonin reuptake inhibitor sertraline (given at a dose of 75–100 mg per day) may improve pruritus independently from the improvement of depression.[77,78]

Because cholestatic pruritus is not histamine-related, antihistamines should be avoided for its treatment. These agents may deteriorate fatigue because of their sedative properties and worsen dry mouth as a typical side effect.

Despite these multiple therapeutic options, observational studies from the United Kingdom and United States suggest that up to 40% of patients with PBC and itching remain untreated.[66,67] These findings highlight both the need for increased awareness and utilization of existing treatment guidelines and the unmet need for safe and more effective therapies.

Fatigue. Fatigue, which has a significant negative impact on the patients' quality of life, occurs in up to 78% of PBC patients.[65,79–81] It is characterized by inability to perform activities of daily living as well as diminished mental and physical capacity. It is often stable but may progress with time.

Other causes of fatigue including depression, hypothyroidism, anemia, and sleep disorders (eg, caused by itching) have to be considered. So far, there is no specific drug approved for the treatment of fatigue. Therefore, education and counseling for patients in how to cope with the symptoms and implementation of a structured exercise program remain the only potentially useful options,[82,83] and the impact of mindfulness is under evaluation (NCT03684187, NCT05374200). Whereas pruritus improves with liver transplantation, fatigue usually persists after liver transplantation.[84]

Sicca syndrome. Sicca syndrome with dry eyes and mouth is frequently observed in patients with PBC and can reduce the quality of life.[85] Dry eyes can be managed with artificial tears. In refractory cases pilocarpine or cevilemine can be used.[86,87] For patients with xerostomia, improved oral hygiene and use of sugar-free gum or candy to stimulate saliva production or saliva substitutes can be recommended. Pilocarpine or cevilemine can be used in cases of xerostomia symptoms despite saliva-inducing or -substituting agents. Women with PBC may also notice vaginal dryness, and in post-menopausal women vaginal estrogens may be helpful.

The Pipeline for Future PBC Therapies

There is substantial interest in developing more licensed therapies to be used as add-on to UDCA for patients with PBC (Table 3). Furthermore, early start of combination therapy is also under investigation for patients with clear high-risk disease. Most therapy has focused on nonimmune pathways of action, and although interest still exists for immunotherapy, those approaches remain at an earlier stage of development.

Disease-modifying Therapies

PPAR agonists, beyond fibrates. As members of the nuclear receptors' superfamily, PPARs are key transcriptional regulators functioning as metabolic sensors that modulate transcriptional activation depending on the metabolic status of the cell. PPAR activation leads to variable effects based on which isoform is targeted. Whereas PPAR-alpha is predominantly expressed in the liver, PPAR-delta and -gamma are more ubiquitously expressed in metabolic active tissues.[88] A variety of anticholestatic, anti-inflammatory, and anti-fibrotic properties are attributed to PPAR agonists, making them

Table 3. Drugs Advancing to Phase 3 Trials for the Treatment of Primary Biliary Cholangitis or Cholestatic Pruritus

Drug, NCT	Mechanism of action	No. of patients in phase 2 trial, study duration	Summary of findings to date
Seladelpar NCT04620733	PPAR-delta agonist	N = 112, 1 year; Long-term extension in progress	69% met POISE with 10 mg/day at 1 year, 79% at 2 years 33% normalized ALP at 1 year Improvement in pruritus Improvement in sleep
Elafibranor NCT04526665	PPAR-alpha/delta agonist	N = 45, 12 weeks	79% met POISE with 120 mg/day 21% normalized ALP Improvement in pruritus
Saroglitazar NCT05133336	PPAR-alpha/gamma agonist	N = 37, 16 weeks	71% met POISE
Setanaxib NCT05014672	NOX 1/4 inhibitor	N = 111, 24 weeks	24% reduction in ALP among patients with liver stiffness >9.6 kPa treated with 400 mg twice a day; post hoc analyses with improvement in fatigue scores
Linerixibat NCT04950127	ASBT inhibitor	N = 147, 12 weeks; Long-term extension in progress	Improvement in itching; Improvement in sleep

NOTE. Based on last access to clinicaltrials.gov database on December 5, 2022.
ALP, alkaline phosphatase; ASBT, apical sodium-bile acid transporter (same as IBAT, ileal bile acid transporter); NCT, National Clinical Trial; NOX, NADPH oxidase; PBC, primary biliary cholangitis; POISE, composite score for response to treatment indicating ALP <1.67 × ULN, with reduction >15% from baseline and total bilirubin (TB) < ULN; PPAR, peroxisome proliferator-activated receptor.

attractive targets in the management of cholestatic liver diseases.[89,90] Besides the fibrates, which are currently used as off-label therapy in patients with PBC, other agents with specific PPAR activity are gaining support and are undergoing phase 3 evaluation (Table 3). As a class, these drugs consistently lead to improvement in markers of cholestasis, without a detrimental effect on the cholesterol profile and often with the added benefit of improvement in itching.

Seladelpar. Seladelpar is a selective PPAR-delta agonist. Expressed in hepatocytes, Kupffer cells, and hepatic stellate cells, PPAR-delta activation is associated with reduced bile acid synthesis, suppression of inflammatory cytokines, and inhibition of hepatic stellate cell proliferation and activation, among other important metabolic effects.

In an international, open-label phase 2 trial, 121 patients with PBC and incomplete response or intolerance to UDCA were randomized to seladelpar 5 mg/day or 10 mg/day for 52 weeks.[91] The study showed dose-dependent reductions in serum ALP. Remarkably, 31% of patients in the 10 mg/day cohort showed normalization of ALP levels, an effect observed as early as week 12, with a mean reduction from baseline of 43%. The POISE criteria (reaching ALP <1.67 × ULN, ≥15% decrease in ALP, and normal bilirubin) were met by 67% of patients on 10 mg/day. Total bilirubin levels remained stable, and transaminase activity declined.[91] As expected for PPAR agonists, median levels of bile acid precursor C4 were decreased from baseline, as were mean low-density lipoprotein cholesterol and triglyceride levels. There were no serious safety signals; reversible elevations in transaminases were observed in 2 patients.

Treatment duration has now been extended to 2 years for 103 patients, with sustained improvement in biochemical profile and without evidence of treatment-related serious adverse events. The POISE composite endpoint was met by 79% of patients treated with 10 mg/day at 2 years.[92] In fact, because of improvements in serum ALP and bilirubin, the calculated GLOBE PBC score was significantly reduced at 2 years, leading many patients to drop from high-risk to low-risk category.[93] Notably, this effect was observed both in patients with cirrhosis and in those without. These data suggest that use of seladelpar for 2 years could lead to improvement in transplant-free survival.

The impact of seladelpar on symptoms of PBC was specifically evaluated using well-validated questionnaires. Among patients with moderate-to-severe itching at baseline, 93% showed statistically and clinically significant improvement after 1 year of treatment.[94] Furthermore, roughly 80% had improvement in itch-related sleep disturbance.

The original phase 3 trial, ENHANCE, was terminated early because of subsequently unconfirmed concerns for a drug-induced liver injury in an unrelated nonalcoholic steatohepatitis trial. With an amended primary endpoint at 12 weeks, significantly more patients receiving seladelpar met the primary endpoint (seladelpar 5 mg, 57.1%; 10 mg, 78.2%) versus placebo (12.5%) ($P < .0001$). ALP normalization occurred in 5.4% ($P = .08$) and 27.3% ($P < .0001$) of patients receiving 5 mg and 10 mg seladelpar, respectively, versus 0% receiving placebo. Seladelpar 10 mg significantly reduced mean pruritus numeric rating scale versus placebo (10 mg, −3.14 [$P = .02$]; placebo, −1.55).[95]

Elafibranor. Elafibranor is a dual PPAR-alpha/delta agonist. Thus, in addition to above-mentioned effects of PPAR-delta agonists, PPAR-alpha activation also simulates phospholipid secretion through up-regulation of MDR3, stimulates bile acid detoxification by phase 1 and 2 enzymes, down-regulates CYP7A1 and NTCP expression, reduces inflammation through suppression of nuclear factor kappa B, and reduces expression of several profibrogenic genes in hepatic stellate cells.[96]

In a proof-of-concept phase 2 trial, 45 patients with PBC and incomplete response or intolerance to UDCA were randomized to placebo, elafibranor 80 mg/day, or elafibranor 120 mg/day and treated for 12 weeks. Mean ALP change relative to placebo was –52% for the 80 mg arm and –43.9% for the 120 mg arm.[97] The proportion of patients normalizing ALP and that of patients meeting the POISE composite endpoint at week 12 were significantly greater for patients on active treatment with elafibranor in comparison with placebo. The composite endpoint was met by 66.7% in the elafibranor 80 mg/day group, 78.6% in elafibranor 120 mg/day group, and 6.7% in the placebo group. The study also demonstrated a favorable trend on pruritus but not on other domains of the quality-of-life surveys.

Other observed effects were reductions in total and low-density lipoprotein cholesterol and in serum triglyceride levels and decreased circulating levels of the bile acid precursor C4. Severe treatment-related side effects occurred at similar rates in all treatment groups. The most common side effects were nausea, diarrhea, fatigue, and headache. There was a slight increase in serum creatinine, but not in cystatin C, in the elafibranor 120 mg/day group. One patient on elafibranor 80 mg/day and one on 120 mg/day had elevations in transaminases, which in one case was considered by the investigator as a suspected flare of autoimmune hepatitis presumably as part of an overlap syndrome.

Saroglitazar. Saroglitazar is a dual PPAR-alpha/gamma agonist, thus adding beneficial metabolic effects associated with improved hepatic sensitivity to insulin and fatty acid oxidation. The drug was examined in a proof-of-concept phase 2 trial including 37 patients with incomplete response or intolerance to UDCA who were randomized to saroglitazar 4 mg/day, saroglitazar 2 mg/day, or placebo. As with other PPAR agonists, greater reduction in biochemical markers of cholestasis was seen among treated patients as early as week 4, approaching 50% reduction in serum ALP with the 4 mg dose, with 71% meeting the composite endpoint.[98] Four patients had significant elevations in both ALT and AST, leading to permanent discontinuation of the study drug. It is possible that lower doses will bring similar benefits, with a better safety profile. This is currently under investigation in the phase 3 trial (NCT05133336).

NOX 1/4 inhibitors. The nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOX) encompass a family of enzymes involved in the physiological response to stress and represent the greatest source of reactive oxygen species (ROS).[99] In low/moderate levels, ROS play a significant role regulating cell growth, immune responses, cell signaling, and autophagy. However, in high levels, ROS lead to oxidative stress-induced damage to lipids, proteins, and DNA, contributing to cell death. Seven NOX isoforms have been identified; NOX 1 and 4 are highly expressed in endothelial cells, and NOX 4 in particular is also preferentially expressed in hepatocytes, fibroblasts, and smooth muscle cells. These enzymes play a role in stellate cell–mediated fibrogenesis,[100] and inhibition of NOX in mice models reversed cholestatic fibrosis.[101]

Setanaxib is a selective NOX1/4 inhibitor. A proof-of-concept phase 2 trial including 111 patients with PBC showed modest improvements in serum ALP and GGT especially among subjects with increased liver stiffness ($\geq$9.6 kPa) at baseline who were treated with setanaxib 400 mg twice daily.[102] Post hoc analysis also suggested improvement in fatigue scores, a finding that deserves more in-depth investigation.[103]

Novel Therapies Targeting Pruritus

Apical sodium-dependent bile acid transporter inhibitors. By inhibiting apical sodium-dependent bile acid transporter, linerixibat interrupts the enterohepatic circulation of bile acids and minimizes bile acid accumulation and toxicity. Bile acids are among the many pruritogenic substances implicated in the pathogenesis of cholestatic itch.[104] The efficacy and tolerability of linerixibat were evaluated in a large international phase 2 trial including 147 patients with PBC and moderate itching. After a 4-week period of single-blinded placebo treatment, patients were treated with 1 of 5 different doses of linerixibat or placebo for 12 weeks, followed by another 4-week single-blinded placebo treatment. Combined, linerixibat groups were not significantly different versus placebo in the primary intent-to-treat analysis ($\geq$2-point mean reductions in mean worst daily itch). However, in comparison with placebo, the change from baseline in the monthly itch score was significant for the 40 mg twice daily, 90 mg twice daily, and 180 mg daily groups, and patients on the 40 mg twice daily dosing also had statistically significant improvements in social and emotional domains in quality of life. The safety profile appears acceptable, with 10% of patients withdrawing because of diarrhea or abdominal pain.[105]

Other ileal bile acid transporter inhibitors (volixibat, NCT05050136), a kappa-opioid receptor agonist (difelikefalin, NCT03995212), and inhibition of the MRGPRX4 receptor on small nerve fibers (EP547, NCT05525520) are also being studied in patients with PBC and cholestatic pruritus. Ileal bile acid transporter inhibitors are successfully used in other cholestatic liver diseases associated with pruritus such as maralixibat in Alagille syndrome[106] and odevixibat in progressive familial intrahepatic cholestasis.[107]

The Future

Treatments for PBC continue to progress positively, and realistically it is possible to aspire for normal liver biochemistry, low symptom burden, and avoidance of liver transplantation. Where available, UDCA remains the first-line therapy for now, but with better choices patients will have access to a variety of mechanistically driven interventions. Close monitoring using routine laboratory tests, elastography, and/or validated risk models will lead to early identification of a high-risk subgroup of incomplete responders who will now benefit from add-on second-line therapy. The pipeline of additional second-line drugs is clearly rapidly expanding, with various PPAR agonists and a first in class NOX inhibitor entering phase 3 trials.[108] Norucholic acid, a side chain-shortened UDCA homologue with promising phase 2 results in primary sclerosing cholangitis, is currently undergoing phase 2 trial for PBC in Europe (EudraCT number: 2021-001431-56). In addition, a paradigm change using top-down approach for treatment-naive high-risk patients with PBC is currently being initiated.

Beyond maximizing anti-cholestatic and anti-fibrotic therapies, attempts at inducing tolerance to an encapsulated PDC-E2 antigen and reprograming the immune system are in progress (NCT05104853). Furthermore, renewed understanding of the role of cholangiocytes senescence and its correlation with disease progression is likely to inspire new therapeutic approaches for cholestatic diseases.[109]

Alongside disease control, one major concept change in recent years has been a determined focus on symptoms including itching and fatigue. Clinicians should regularly assess the impact of PBC on their patients' quality of life,[67] evaluate the need for pharmacologic therapy, and consider available options to manage refractory itching (Figure 2).[5,43,110] Fatigue remains a difficult-to-treat symptom, where there is room to improve the current management strategy that includes non-pharmacologic approaches such as exercise intervention and mindfulness techniques.[83,111] For this complex symptom arena, it is reassuring to see a willingness from industry to consider novel approaches designed to improve patient quality as well as quantity of life.

In conclusion, the future of therapy for PBC is as bright and dynamic as it ever has been.

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