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News & Views

Primary biliary cholangitis: personalized medicine for optimal therapeutic opportunities

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Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease that is characterized by inflammation of the interlobular bile ducts. Although PBC is a slowly progressive disease, with a natural history of 10–15 years leading to end-stage liver disease, high-risk cases may rapidly progress to decompensated cirrhosis or even death. As the most common autoimmune liver disease, the prevalence of PBC has been increasing globally, largely due to increased disease awareness, improved diagnosis, and treatment with ursodeoxycholic acid (UDCA). PBC is more likely to occur in middle-aged women, with a female-to-male ratio ranging from 1.6 to 10; however, men have a higher disease severity [1,2].

The question of whether PBC is induced by the dysregulation of autoimmunity or bile acid metabolism is prompted by the following: (1) anti-mitochondrial autoantibodies (AMAs) are the signature of PBC, (2) immunosuppressive therapy alone fails to delay the disease course [1,2], and (3) UDCA, the only first-line therapeutic agent that targets bile acid metabolism, can significantly ameliorate cholestasis and improve liver transplantation (LT)-free survival independent of sex, age, disease stage, and biochemical response [1,2].

Recent studies have notable findings. First, mice exposed to an environmental mimic of a modified E2 subunit of the mitochondrial pyruvate dehydrogenase complex (PDC-E2) recapitulate autoimmune cholangitis. Second, the activation of innate and adaptive immunity leads to sensitization and apoptosis of biliary epithelial cells (BECs), subsequent AMA recognition of PDC-E2 of BECs and further immune-mediated biliary injury. Third, BEC damage is driven by aberrant immune responses characterized by an imbalance of pro-inflammatory effector and regulatory T cells, ultimately leading to sustained inflammation, cholestasis, and fibrosis [1,2]. Finally, the interferon signaling pathway plays an important role in sex-biased autoimmune cholangitis and can modulate the gut microbiome and metabolite homeostasis, with robust sex differences in mitochondrial proteins and bile acid composition in ARE-Del mice. The downregulation of the interferon signaling pathway with a Janus kinase inhibitor effectively inhibits the development of autoimmune cholangitis [3]. Moreover, the combination of anti-BAFF and anti-CD20 monoclonal antibodies reduces portal inflammation and biliary damage in these mice [4]. These preclinical data highlight their therapeutic potential in PBC. Currently, UDCA and obeticholic acid (OCA; second-line therapeutic agent) have been approved for the treatment of PBC, and the off-label use of fibrates is beneficial in patients with an inadequate response to UDCA. Owing to the limited drugs available for PBC treatment, precise timing of treatment initiation, add-on therapy, and dynamic monitoring are critical to achieving the effective clinical management of PBC.

Identification of patients with definite PBC from potential cases. While all patients with PBC should receive UDCA at a dose of 13–15 mg kg^{-1} d^{-1} for life, it remains challenging to decide whether those with atypical or asymptomatic presentations should receive UDCA. In most cases, a "wait-to-treat" strategy is usually adopted, and UDCA therapy is immediately initiated once a diagnosis of PBC is confirmed during follow-ups. The underlying reasoning is based on the low prevalence of definite PBC in the general population, even in those who are AMA-positive but do not fulfill the PBC diagnostic criteria. However, if patients' genetic background, demographic characteristics, and histological features are considered, therapeutic decision-making may be quite different. Our group analyzed the diagnosis and treatment conditions of 115 AMA-positive patients with completely normal alkaline phosphatase (ALP) levels. As most of these patients were first-degree relatives of patients with definite PBC, all of them agreed to undergo a liver biopsy. The final results showed that 77 (67%) patients had histological PBC features [5]. Immunoglobulin M > 0.773 × upper limit of normal (ULN) and age >42 years were found to be associated with PBC, providing criteria distinguishing high-risk ones from patients with potential PBC [5]. Liver biopsy should not be universally recommended in such patients, and the precise classification of these patients according to risk factors is important to maximize the benefits of this invasive test. In fact, the consistency of PBC in monozygotic twins was 0.63, and a family history was also frequently reported under different conditions [1]. This elucidates the need for a detailed inquiry into the genetic background of patients to allow for risk stratification. Large-scale genome-wide association studies (GWAS) have demonstrated a strong association between variants at the human leukocyte antigen locus and PBC, but this correlation depends on ethnic backgrounds [1]. The

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latest GWAS data from multiple European and Asian cohorts identified 56 genome-wide significant loci and candidate genes, including *FCRL3*, *INAVA*, *PRDM1*, *IRF7*, *CCR6*, *CD226*, and *IL12RB1*, at the newly identified loci. These genes are involved in inflammation-associated signaling and differentiation of T helper (Th) 1 and Th17 cells [6]. Detecting these susceptible gene loci may provide new insights into the risk stratification of patients with potential PBC. However, efforts are still needed to optimize the combination of ethnically specific candidate genes, and more clinical specimens are required to validate these new genes in the diagnosis of PBC. In addition, epigenetic abnormalities are characteristics of patients with PBC, and these epigenetic modifications may significantly contribute to disease pathogenesis [1,2]. For example, differential expression of multiple hepatic microRNAs has been repeatedly reported in PBC, and miR-506 was most extensively evaluated because of its critical roles in regulating the maintenance of the protective bicarbonate-rich umbrella and sensitization to toxic hydrophobic bile acids of BECs [1]. Considering that miR-506 is an X-linked microRNA, its function in PBC highlights the possibility that aberrant epigenetic X-inactivation may contribute to the female predominance of disease, but this hypothesis needs to be demonstrated in human PBCs [1].

In summary, distinguishing patients with definite PBC from potential cases is critical for effective drug therapy. For atypical or asymptomatic cases, the comprehensive evaluation of genetic, epigenetic, and other high-risk factors may provide important information regarding the need for liver biopsy or aid in a definite diagnosis.

Optimization of therapeutic strategy for patients with PBC and inadequate responses to UDCA. OCA is a highly selective ligand for the farnesoid X receptor (FXR), and its administration leads to a decrease in bile salt synthesis, uptake, and absorption, a reduction in inflammatory cytokines, and hepatic fibrogenesis. The approval of OCA for the treatment of PBC in North America and Europe was based on the results of a trial of patients with PBC and inadequate response to UDCA [2], and the latest data show lower incidence of LTs and deaths in patients treated with OCA in the POISE double-blind, placebo-controlled trial and open-label extension than in controls from the Global PBC and UK-PBC cohorts [7]. Fibrates, the agonists of peroxisome proliferator-activated receptor (PPAR), have been approved only as lipid-lowering agents, despite their ALP and γ-glutamyl transpeptidase (GGT)-lowering effects that have been reported for decades. A recent UK nationwide observational cohort study showed that fibrates promoted ALP normalization and pruritus reduction, whereas OCA resulted in more alanine transferase (ALT) normalization. However, the overall rates of biochemical response and drug discontinuation were similar with both treatments [8]. These findings have promoted enthusiasm for the selective FXR and PPAR agonists in development (Table 1). Despite the definite effects and drug tolerance in patients with early-stage PBC, little is known about the efficacy and safety of second-line therapeutic agents in patients with cirrhosis because this population was underrepresented in clinical trials and cohorts. An Italian study evaluated the safety and efficacy of OCA in a cohort of consecutive patients with PBC and cirrhosis and found that male sex, coagulation function, Child–Pugh score, Model for End-Stage Liver Disease, and bilirubin were independent factors associated with non-response to OCA [9]. The most important contribution of this study was its evaluation of the development of liver-related serious adverse events, with the authors suggesting that a bilirubin level >1.4 mg/dL was the most accurate predictor [9]. Findings from this study indicated that an accurate assessment before OCA initiation is crucial to identify patients with cirrhosis who may benefit from OCA. According to our clinical experience, the administration of fenofibrate in patients with PBC and cirrhosis results in a higher ALP normalization and lower UK-PBC scores and does not cause additional increases in bilirubin and creatinine levels and the estimated glomerular filtration rate [10]. Further validation in other cohorts is necessary to update clinical practice guidelines, and more patients with PBC, cirrhosis and limited therapeutic options could benefit from OCA and fibrates. The development of selective FXR and PPAR agonists holds promise as new therapeutic agents, but the attempts to expand the application of OCA and fibrates in patients with cirrhosis will be of great clinical significance in managing PBC.

Table 1
Targets and drugs investigated for the treatment of primary biliary cholangitis.

Drug	Mechanism	Clinical trial status	NCT No.
PPAR			
Bezafibrate	PPARα, δ, and γ agonists	Phase 3 trial completed (BEZURSO)	NCT01654731
Fenofibrate	PPARα agonist	Phase 2 trial completed	NCT02823353
Saroglitazar Magnesium	PPARα and γ agonists	Phase 2/3 trial underway	NCT05133336
		Phase 2 trial completed (EPICS)	NCT03112681
Seladelpar	PPARα and δ agonists	Phase 2 trial completed	NCT02955602
		Phase 3 trial underway (RESPONSE)	NCT04620733
		Phase 3 trial completed (ENHANCE)	NCT03602560
Elafibranor	PPARα and δ agonists	Phase 2 trial completed	NCT03124108
		Phase 3 trial underway (ELATIVE)	NCT04526665
FXR			
ASC42	FXR agonist	Phase 2 trial underway	NCT05190523
EDP-305	FXR agonist	Phase 2 trial completed	NCT03394924
Cilofexor	FXR agonist	Phase 2 trial terminated	NCT02943447
Tropifexor	FXR agonist	Phase 2 trial completed	NCT02516605
FGF19			
NGM282	FGF 19 analog	Phase 2 trial completed	NCT02026401
Other targets			
CNP-104	PLGA particles with PDC-E2 peptide	Phase 2a trial underway	NCT05104853
E6011	Anti-CX3CL1 antibody	Phase 2 trial terminated (sponsor's decision)	NCT03092765
Etrasimod	S1PR1 and S1PR4 agonists	Pilot, open-label, proof-of-principle study terminated (sponsor's decision)	NCT03155932
Setanaxib (GKT137831)	NOX1 and NOX4 inhibitors	Phase 2 trial completedPhase 2b/3 trial underway (TRANSFORM)	NCT03226067 NCT05014672
Baricitinib	JAK1 and JAK2 inhibitors	Phase 2 trial terminated (enrolment futility)	NCT03742973
PRI-724	CBP/β-catenin inhibitor	Phase 1 trial completed	NCT04047160

For more details, refer to Supplementary materials (online). FGF 19: fibroblast growth factor 19; PLGA: poly(lactic-*co*-glycolic acid); S1PR: sphingosine 1-phosphate receptor; NOX: NADPH oxidase; JAK: Janus kinase.

The role of environmental factors in the development of autoimmunity has been extensively studied. In addition to the disease-specific alterations of gut microbiota in PBC, a recent study showed that exposure to *Escherichia coli*, which elicits antibodies specific to ePDC-E2, could result in the production of classic autoantibody to hPDC-E2LD, suggesting that this is the first step in PBC development [11]. Therefore, targeting specific microbes (e.g., infection elimination and fecal microbiota transplants) could be a treatment option for refractory PBC. To date, two small proof-of-concept studies of mesenchymal stem cell transplantation for refractory PBC, which were performed in China, reported a reduction in ALP levels and improvements in clinical symptoms [2]. A larger, randomized, placebo-controlled study is still ongoing (NCT03668145).

Dynamic monitoring for better prognosis prediction. The evaluation of UDCA responses typically takes 6 (Rochester and Ehim), 12 (Barcelona, Paris-I, Paris-II, Rotterdam, UK-PBC, and GLOBE), or 24 (Toronto) months, depending on the different criteria and scoring models. Our observation from a cohort of 569 patients with an average follow-up period of 59 months showed that 41% (29/71) of adverse outcomes, defined as liver-related death, LTs, and decompensated events, occurred within 2 years after diagnosis, suggesting the need for an earlier evaluation [12]. In addition, the serum levels of ALP, GGT, aspartate aminotransferase (AST), ALT, and bilirubin dropped sharply 1 month after UDCA treatment and remained stable thereafter [12]. Therefore, we developed a 1-month early criterion (named the Xi'an criterion: ALP $\leq 2.5 \times$ ULN, AST $\leq 2 \times$ ULN, and TBIL $\leq 1 \times$ ULN) that could efficiently screen high-risk cases with rapid progression and more likely to benefit from earlier add-on therapy [12]. This concept is in accordance with the shift in clinical opinion from a "wait-to-fail" concept to early individualized and highly effective targeted therapy [1]. An ongoing attempt to explore an early combination of UDCA and fenofibrate for a rapid and sustained reduction in ALP may provide new insights into this topic (NCT02823353).

Advanced fibrosis and cirrhosis have a relevant prognostic relevance to PBC because they are risk factors for disease progression and inadequate UDCA responses. Recent studies have focused on liver stiffness measurement (LSM) using vibration-controlled transient elastography as an accurate and noninvasive means of measurement. In an Italian multicenter study of patients with treatment-naïve PBC, LSM $\leq$ 6.5 and > 11.0 kPa were reported to discriminate the absence or presence of advanced fibrosis in patients with PBC at diagnosis [13]. In an international multicenter study of 3985 patients with PBC recruited from 12 countries, the predictive capacity of baseline LSM for poor clinical outcomes remained stable over the years, and an add-on effect of LSM on the performance of reported criteria and predictors at baseline was further confirmed. If patients were optimally divided into low-, medium-, and high-risk groups according to the thresholds set for the LSM (8 and 15 kPa) and Globe scores (0.5 and 1.8) at baseline, this combination could enable a more precise stratification of patients with different poor clinical outcome-free survival and, therefore, appropriately timed interventions [14].

Screening and validation of serum biomarkers also shed light on the precise prognostic prediction of PBC. A preliminary serum proteomic analysis of the UK-PBC cohort revealed an inflammatory proteome characteristic that was partially resolved by UDCA, whereas those with inadequate responses had increased levels of serum chemokines released by BECs, which was potentially related to cellular senescence [15]. This study confirms that searching for diagnostic and prognostic biomarkers using omics analysis of blood samples is feasible. More systemic metabolite analyses should be performed. As discussed above, enhanced monitoring of liver biochemical markers could facilitate an earlier prediction of disease progression, and the construction and validation of multifactorial criteria, including LSM and new biomarkers, are worth attempting.

In conclusion, precise timing for clinical decision-making is the key to the clinical management of PBC. Joint efforts from research groups worldwide focusing on multi-omics studies with large prospective cohort studies will greatly enhance our knowledge of the natural history of PBC and provide new perspectives for optimizing therapeutic strategies.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary materials

Supplementary materials to this news & views can be found online at https://doi.org/10.1016/j.scib.2022.11.029.

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