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Review Article

Emerging Therapeutic Strategies in The Fight Against Primary Biliary Cholangitis

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Abstract

The liver has a vital role in many metabolic and regulatory processes in the body. Primary biliary cholangitis (PBC), previously known as primary biliary cirrhosis, is a chronic cholestatic autoimmune disease of the intrahepatic bile ducts associated with loss of tolerance to mitochondrial antigens. At this time there is no definitive cure for PBC; however, ursodeoxycholic acid (UDCA) has been shown to reduce injury when administered as the first line of treatment. Additional therapeutics can be given concurrently or as an alternative to UDCA to manage the symptoms and further curb disease progression. Currently, a liver transplant is the only potentially curative option when the patient has developed end-stage liver disease or intractable pruritus. This review aims to delineate the pathogenesis of primary biliary cholangitis and shed light on current therapeutic strategies in the treatment of PBC.

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Introduction

Primary biliary cholangitis (PBC) is a chronic, cholestatic autoimmune disease that primarily affects middle-aged women with different prevalence worldwide.[1] Although once thought of as a relatively rare disease, its prevalence has increased over time around the globe.[2] In the USA, the Fibrotic Liver Disease Consortium reported a 12-year prevalence of 29.3 per 100,000 individuals and an adjusted prevalence of 42.8 per 100,000 women.[2] A quantitative meta-analysis concluded a pooled-point prevalence rate of 22.27 cases per 100,000 individuals and a pooled annual incidence rate of 1.87 per 100,000 individuals in Europe.[3]

While the specific determinants of PBC are unknown, it is suspected to be the result of a combination of genetic predisposition, epigenetic changes, and/or environmental factors. PBC is characterized by the destruction of the intrahepatic bile ducts and hallmark serologic signature of circulating anti-mitochondrial antibodies (AMAs) that form against the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2). This disease takes a variable progressive course that may persist for several decades.

In more aggressive cases, PBC can lead to fibrosis, cirrhosis, end-stage liver disease, and death. Many patients experience early symptoms of fatigue and pruritus (itchy skin). Research suggests that symptomatic presentation of fatigue and/or pruritus in young women at disease onset appear to have an enhanced risk for a more aggressive form of the disease, are less responsive to ursodeoxycholic acid (UDCA) treatment, and are more inclined to develop cirrhosis.[4] These patients would be candidates for second-line therapies and innovative therapeutic approaches.

Late symptoms may include, but are not limited to, abdominal discomfort, sicca syndrome (dry eyes/dry mouth), trouble sleeping, weight loss, edema, jaundice, and osteoporosis.[5] Cholestasis is also known to affect lipid disposal. Thus, patients frequently develop high cholesterol serum levels, xanthomas and xanthelasma (cholesterol plaques on skin or around the eyes, respectively). Patients may also have concurrent autoimmune diseases such as Hashimoto's thyroiditis, rheumatoid arthritis, and scleroderma.

PBC is only one of three major immune disorders of the liver, the other two being autoimmune hepatitis and primary sclerosing cholangitis (PSC).[6,7] Variant forms, commonly known as overlap syndromes, of these disorders also exist. Overlap syndrome describes variant forms of AIH that present with characteristics of AIH and PBC or PSC. As these disorders are uncommon, there has been no standardization

Keywords: Cholestatic liver disease; Therapeutic approaches; Biliary epithelia ursodeoxycholic acid.

Abbreviations: AE2, anion exchanger 2; ALP, alkaline phosphatase; AMA, anti-mitochondrial antibodies; BECs, biliary epithelial cells; BSEP, bile-salt export pump; BZF, bezafibrate; CDCA, chenodeoxycholic acid; FGF19, fibroblast growth factor 19; FGF4, fibroblast growth factor receptor 4; FXR+/+, wild-type mouse; FXR, farnesoid X receptor; FXR−/−, FXR knockout mouse; HLA, human leukocyte antigen; HSC, hepatic stellate cell; IL12, interluekin-12; IL21, interluekin-21; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; norUDCA, norursodeoxycholic acid; NOX, NADPH oxidase; OCA, obeticholic acid; PDC-E2, E2 subunit of the pyruvate dehydrogenase complex; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptors; PSC, primary sclerosing cholangitis; ROS, reactive oxidative species; Sct, secretin; SR, secretin receptor; UDCA, ursodeoxycholic acid.

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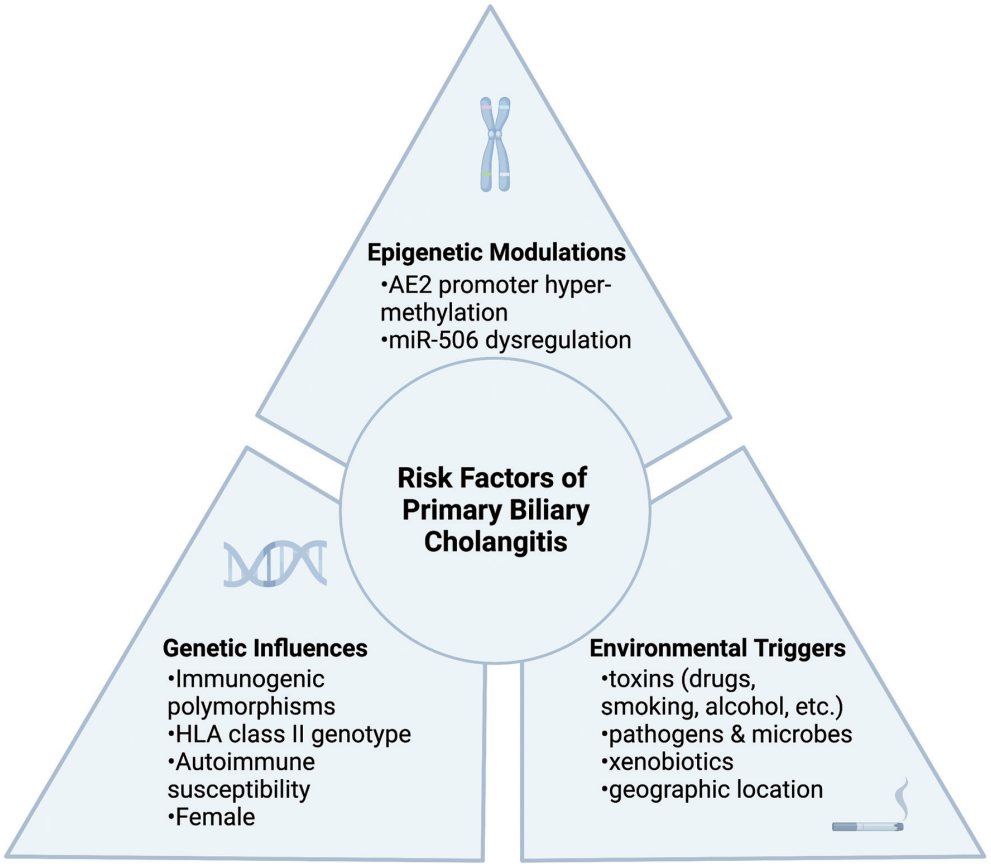

Fig. 1. Risk factors of primary biliary cholangitis. It is hypothesized that genetic factors and autoimmune susceptibility combined with certain environmental factors may trigger PBC. It is difficult to assess an individual's risk, but several factors have been correlated with an increased risk of developing PBC. Such factors include sex, age, geographic location, lifestyle choices, and inflammation.[79] PBC, primary biliary cholangitis.

of diagnostic criteria for overlap syndromes.

Pathophysiology

PBC has a multifaceted pathology in which immunologic, genetic, and environmental factors interact. It is unknown how and why PBC develops, but accumulating evidence strongly supports several concurrent factors. Current hypotheses suggest that PBC is caused when a genetically predisposed patient encounters a triggering event, such as xenobiotics (chemical compounds), pathogens and microbe exposure, or lifestyle behaviors such as alcohol or nicotine use.[8] These environmental elements can then affect patient phenotype via epigenetic modifications resulting in an altered gene expression.[8] The proposed risk factors for PBC are illustrated in Figure 1.

Immunologically, PBC is characterized by a T-lymphocyte mediated attack against the cholangiocytes that line the small intrahepatic bile ducts. Upon loss of immune tolerance to the pyruvate dehydrogenase complex (PDC-E2), disease-specific AMAs against the E2 subunit are developed. Exposure to an environmental mimic of a modified E2 subunit of PDC, may lead to an adaptive and innate immune response against mitochondrial PDC-E2.[9] Despite PDC-E2 ubiquity, it is expressed in the mitochondria of all nucleated cells, the damage seems restricted to the small biliary epithelial cells (BECs). Aside from immune-mediated injury, biliary damage is also believed to occur because of impairment of the delicate film composed of water and bicarbonate, the so-called bicarbonate umbrella, that covers and protects BECs.[10,11] The superficial alkaline microenvironment lying on the apical cholangiocyte surface buffers and prevents uncontrolled membrane permeation of protonated hydrophobic bile acids, and it is altered in PBC patients by dysregulation of the carriers involved in transepithelial Cl^-/HCO^- transport (Fig. 2). Functions of the Cl^-/HCO^- anion exchanger 2 (AE2) mainly include the maintenance of (1) appropriate intracellular pH and (2) secretin-stimulated biliary bicarbonate secretion.

Diminished AE2 expression has been consistently reported in the liver and blood mononuclear cells of PBC patients.[5,12] This AE2 dysfunction results in a rise of the cholangiocyte intracellular pH, leading to activation of soluble adenyl cyclase and bile-salt induced apoptosis.[13] Disruption of the mitophagy of (BECs) triggers oxidative stress and mitochondrial antigen presentation to immune cells.[5]

Most individuals with a PBC diagnosis are positive for specific serologic AMA, but about 5% of patients have equivalent disease and test AMA negative.[14] AMA-negative PBC has been accepted as a variant of PBC and is managed similarly. Failure to detect serologic AMA, a characteristic hallmark of PBC, can make it challenging to achieve a diagnosis. Thus, a diagnostic tool not dependent upon AMA status is needed. A study using sera from 4,371 consecutive patients identified multiple nuclear dot and rim-like/membranous antinuclear antibodies (ANA) that were highly specific to PBC and serve as a great diagnostic marker for PBC, especially in AMA-negative PBC patients.[15]

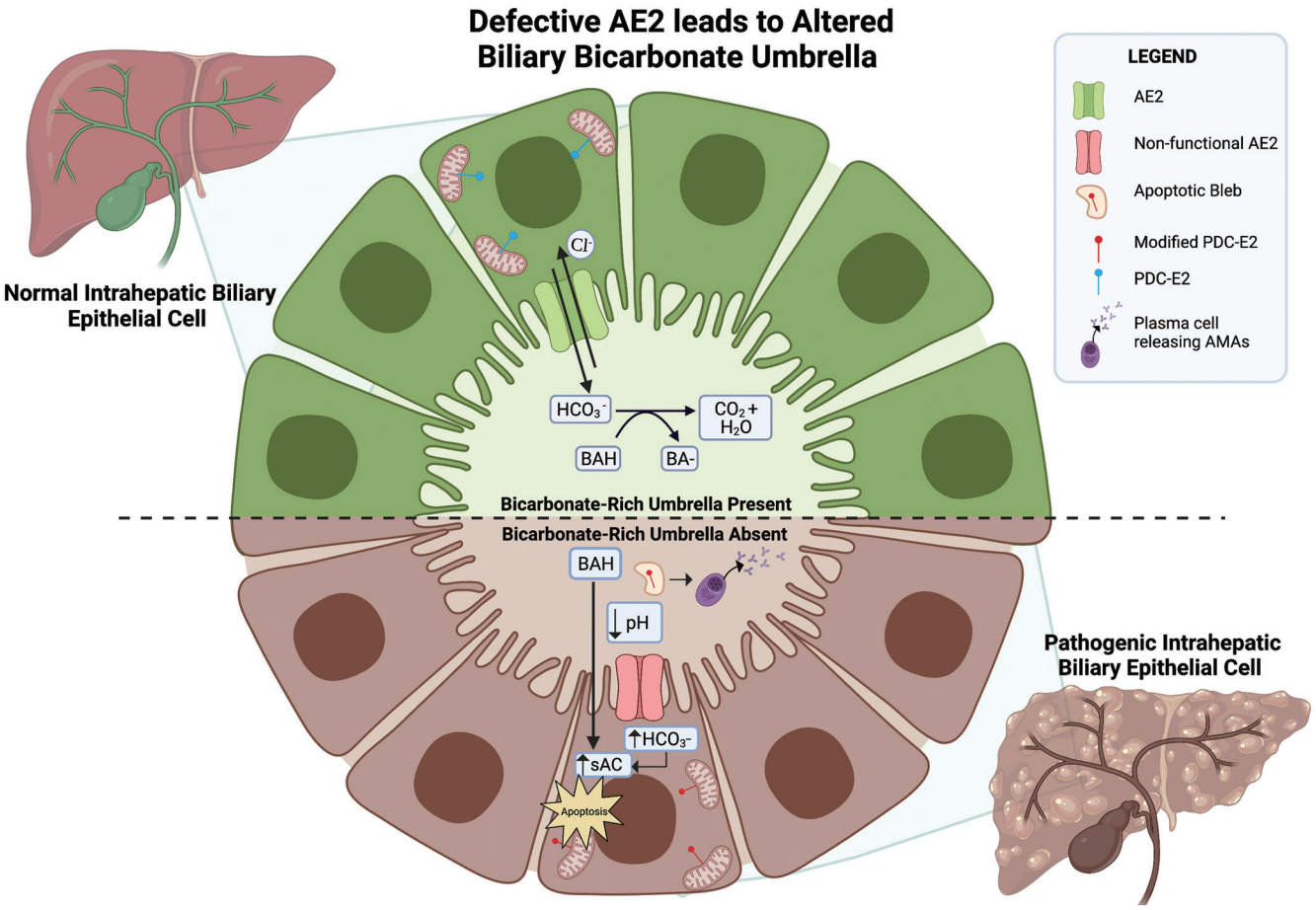

Fig. 2. Defective AE2 leads to an altered biliary bicarbonate umbrella. In a healthy intrahepatic bile duct, AE2 transmembrane transport proteins in cholangiocytes exchange chloride ions for bicarbonate ions, which can then be converted to carbon dioxide and water. In a diseased liver with PBC, the transporter is dysfunctional, resulting in a lower pH in the lumen. Apoptotic blebs then trigger plasma cells to release AMAs that can ultimately induce apoptosis in cholangiocytes. AE2, anion exchanger 2; AMA, anti-mitochondrial antibodies; PBC, primary biliary cholangitis.

Regarding genetic PBC predisposition, recent literature has implicated several genetic loci that correlate with PBC prevalence. Genome-wide association studies have confirmed that some class II human leukocyte antigen loci (HLA-DRB1*08, *11, and *13) have a strong correlation with the disease together with CTLA-4, MDR3, and others.[16] However, the identification of interluekin-21 (IL21) and IL12, including IL12A and its receptor IL12RB2, as risk loci is of particular interest because of their involvement in immunogenic signaling pathways related to PBC development and progression.[17,18] Targeting those loci may prove to be a beneficial therapeutic approach in patients with PBC.

In addition to environmental exposure and genetic risk factors, epigenetic modulation may also contribute to PBC pathogenesis. The micro-RNA, miR-506, was found to be upregulated in the cholangiocytes of PBC patients. That miRNA binds to the 3′-UTR region of AE2, silences the corresponding mRNA and prevents protein translation. That may explain the characteristic diminished AE2 activity and impaired biliary secretion observed in PBC.[5] Additionally, proinflammatory cytokines generated by environmental factors enhance miR-506 expression, contribute to AE2 downregulation, and promote an immune response.[19] Of note, the miR-506 gene is located on the X chromosome and could help explain the female predominance seen in PBC pathogenesis.[5] Furthermore, there is a significant increase in CpG-cytosine methylation at selective promoter regions of the AE2 gene, which contributes to the reduced gene transcription seen in the liver of PBC patients.[20]

Therapeutic approaches

The goal of treatment for PBC is to slow disease progression and alleviate patient symptoms. While UDCA is the first-line treatment, an emphasis has been put on combination therapies in recent years. Major pitfalls of treatment include patients who are simply indifferent to the UDCA therapy and the difficulty of achieving an early diagnosis. The disease tends to progress slowly, and it is common for a person to be unaware they have PBC. Several current and emerging treatments for PBC, including the mechanisms, clinical trials, and shortcomings in this fight against PBC are summarized below. Treatment options and major clinical trials of PBC treatments are listed in Figure 3 and Table 1.

UDCA

UDCA is the most common therapeutic in use today for PBC patients. It is a secondary bile acid produced in humans by intestinal bacteria.[21] UDCA helps improve bile flow and function by diluting toxic bile acids and curbing cirrhosis through

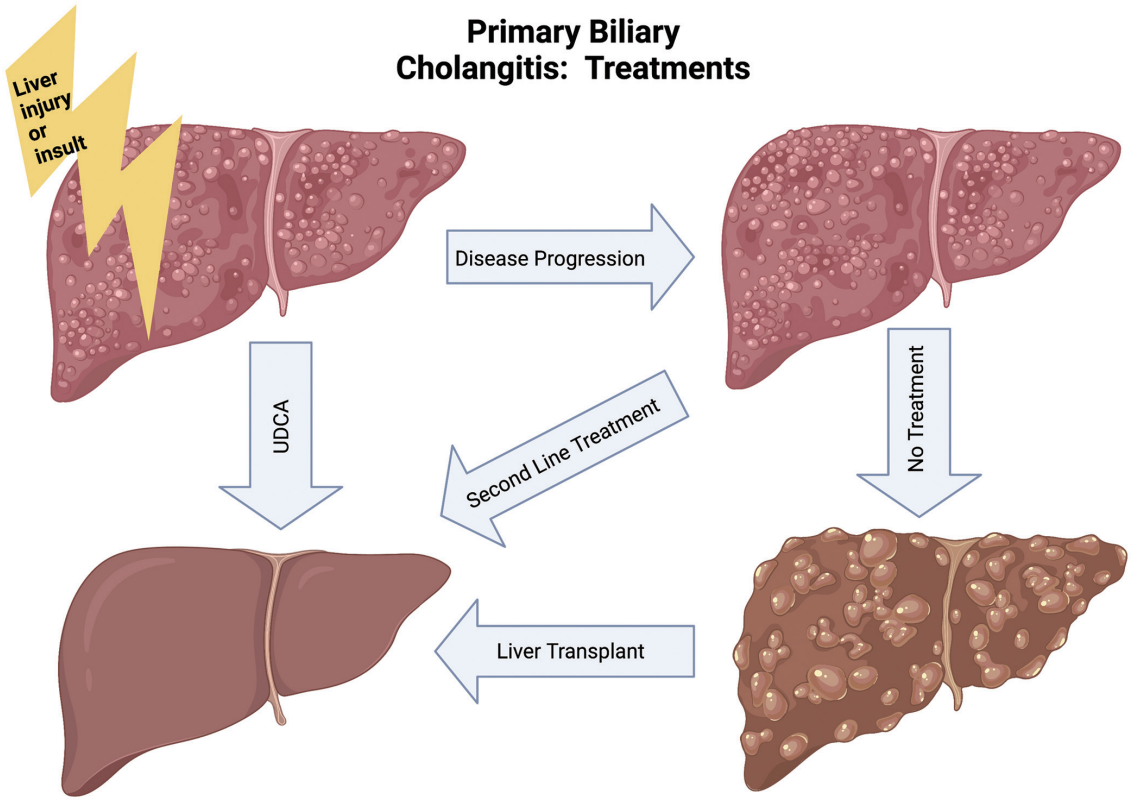

Fig. 3. Treatment of primary biliary cholangitis. Chronic liver inflammation and fibrosis is a result of immune-mediated bile duct injury and destruction. (1) Without treatment, fibrosis will progress to cirrhosis and end-stage liver disease at which point the only potentially curative therapy would be a liver transplant. (2) UDCA is the first line of defense used to treat PBC presentation. 3) If the patient has an incomplete response or intolerance to UDCA and liver fibrosis persists, UDCA would be administered concurrently with a second-line treatment such as OCA, Fibrates, PPAR agonists, Budesonide.[2,8] OCA, obeticholic acid; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptors; UDCA, ursodeoxycholic acid.

the prevention of bile duct obstructions.[22] It restores AE2 expression and promotes bicarbonate secretion to strengthen the defensive alkaline barrier that protects BECs.[5] Bile acids are known to accumulate in the liver in cases of chronic cholestatic liver diseases. They promote chronic inflammation, eventually lead to cholestasis, and are more hydrophobic than UDCA.[23] With a less toxic and more hydrophilic pool of bile acids, physicians hope to create reduced overall levels of stress in cholangiocytes. UDCA is also used to manage symptoms of PSC, intrahepatic cholestasis of pregnancy, and cystic fibrosis. Studies have also examined its efficacy in treating nonalcoholic steatohepatitis (NASH), alcoholic liver disease, and liver allograft rejection.[24] The bile acid is effective in up to 60% of patients with PBC, and the effectiveness increases if administered at earlier stages of the disease.[25,26] The survival rate of patients treated with UDCA long-term is comparable to the overall population.[27] One of the means by which UDCA succeeds in treating PBC when so many other treatments seem to fail is by acting as an intracellular signaling molecule. It activates protein kinase C, mitogen-activated protein kinases, and acts as a Ca^{2+} agonist, all of which contribute to its anticholestatic properties.[28] The optimal daily dose is approximately 13.5 mg/kg.[29] The reason for that is that UDCA epimerizes to chenodeoxycholic acid (CDCA).[24] In patients with cholestatic liver diseases, UDCA escalates the conversion of cholesterol to bile acids.[30] Thus, the overall amount of bile acid typically remains unchanged. UDCA has been the reigning first line treatment therapy for its proven efficacy in treating patient disease and symptoms alike. In a 2-year double-blind study of 73 patients who were assigned to UDCA and 73 to a placebo, 6 failed as opposed to 13 on the placebo, and pruritus was resolved for 40% of those assigned to UDCA versus 19% on the placebo.[22] However, UDCA has its limitations. Its efficacy plummets in late-stage patients, and many are simply unresponsive to the bile acid. In sum, roughly 30% of patients with PBC are unresponsive to UDCA therapy.[31] One potential explanation is increased senescence of cholangiocytes in UDCA non-responders.[31]

Senescent cells are arrested in the G1 phase of interphase and have been observed to progress to a senescence-associated secretory phenotype in which they display increased expression of inflammatory molecules and profibrotic factors.[32] However, for those who experience little to no improvement from UDCA treatment, there are other options.

Obeticholic acid[33] and farnesoid X receptor (FXR) agonists

OCA, a steroidal FXR agonist, is the most common second-line therapy used to date. It is a semi-synthetic bile acid derivative, known also as 6-ethylchenodeoxycholic acid or INT-747, and has a strong affinity for nuclear FXR.[34] FXR maintains bile acid enterohepatic circulation and homeostasis in a tissue-specific manner.[35] When FXR is activated, it regulates the synthesis, excretion, transport, absorption, and metabolism of bile acids.[36] Fibroblast growth factor 19 (FGF19) has a regulatory role in BA synthesis, as well.[37] It is a semi-synthetic bile acid derivative, also known as 6-ethylchenodeoxycholic acid or INT-747, and has a strong affinity for the nu-

Table 1. Major Clinical Trials

Clinical	Type of clinical trial		
	Results Trial	**Dose**	**Past or present**
UDCA	Completed: A 2 year randomized, double-blind, placebo-controlled trial grouped patients into four groups based on entry serum level and liver histology	10–12 mg/kg of UDCA daily	Major improvements in both the biochemical tests and histology of the liver in strata 1 and 2 (entry bilirubin <2) but had less effect on patients with entry serum bilirubin of > or +2 (strata 3 and 4).[26]
OCA	(1) Completed: Phase 3 double-blind, placebo-controlled, parallel group clinical trial + 5-year long-term safety extension. (2) Ongoing: Phase 2 double-blind, randomized, active controlled, parallel group study.	(1) Ocaliva:5–10 mg daily. (2) Four treatment arms consisting of either 100 mg or 400 mg BZF paired with either a placebo or 5 mg OCA	(1) Reduce ALP and bilirubin levels. (2) None to date.
Budesonide	Completed: A 3-year placebo-controlled, randomized clinical trial.	9 mg of budesonide daily along with the patient's ongoing 12–16 mg/kg of UDCA for 3 years.	No improvement in liver histology but secondary analyses displayed improvement in biochemical markers of disease.[50]
PPAR agonists	Completed: A 2-year placebo-controlled, double-blind, phase 3 trial.	400 mg of BZF daily along with continued UDCA.	Normal levels of total bilirubin, and ALP, aminotransferases, and albumin observed in 31% of patients assigned to BZF versus 0 in the placebo group.[53]
NOX-1,4 Inhibitor	(1) Completed: Phase 2 double-blind, randomized, placebo-controlled clinical trial. (2) Ongoing: TRANSFORM phase 2b/3 randomized, placebo-controlled, double-blind clinical trial.	(1) Setanaxib 400mg twice daily. (2) Setanaxib 1,200 mg or 1,600 mg daily.	(1) The treatment group saw a significant reduction in ALP, liver stiffness, and levels of fatigue.[72] (2) None to date.

ALP, alkaline phosphatase; BZF, bezafibrate; NOX, NADPH oxidase; OCA, obeticholic acid; PPAR, peroxisome proliferator-activated receptors; UDCA, ursodeoxycholic acid.

clear FXR.[34] FXR maintains bile acid enterohepatic circulation and homeostasis in a tissue-specific manner.[35] When FXR is activated, it regulates the synthesis, excretion, transport, absorption, and metabolism of bile acids.[36] FGF19 regulates bile acid synthesis, and after being activated by FXR in the ileum, it travels to the liver where it suppresses bile acid synthesis.[37] β-klotho complexes with the fibroblast growth factor receptor 4 (FGF4) on the hepatocyte surface and is activated by binding FGF19.[37] OCA works by increasing levels of FGF19, thereby decreasing bile acid synthesis.[38] Aside from regulating the synthesis and secretion of bile acids, FXR is an intuitive target for an agonist for a variety of other cellular functions. FXR protects the liver from the toxic buildup of bile acids through the expression of the bile-salt export pump (BSEP). In one study, BSEP expression was maintained in common bile duct-ligated $FXR^{+/+}$ wild-type mice and was undetectable when the same procedure was performed in $FXR^{-/-}$ knockout mice.[39] One caveat with OCA is its use in patients with Child-Pugh class B or C cirrhosis, in whom a Federal USA Food and Drug Administration (FDA) precaution includes a strict ceiling of 5 mg a week.[8] In short, OCA activates FXR, which in turn helps control bile acid circulation in the liver and increases FGF19 to keep the concentration of bile acids in check to prevent a toxic overaccumulation.

OCA is just one of many FXR modulators. As previously discussed, FXR is a promising target for the treatment of PBC because of its ability to sense the intracellular presence of bile acids by compelling changes in gene expression.[40,41] It is responsible for maintaining enterohepatic bile acid circulation. FXR agonists are known to regulate the expression of FGF19, which in turn hinders the expression of cholesterol 7 alpha-hydroxylase in human hepatocytes through a c-Jun N-terminal kinase-dependent pathway.[42] Decreasing that cholesterol is known to be associated with liver regeneration.[43,44] FXR agonists are derived from CDCA, an endogenous bile acid, which is the backbone. Addition of functional groups have proved pivotal in the quest for an efficacious FXR agonist. For example, OCA is a 6α-ethyl derivative of the natural human BA and has nearly 100-fold more FXR agonist activity.[45] FXR agonists are a powerful class of drugs for patients with PBC, but more research is needed on longer-term clinical trials involving patients with chronic liver diseases.

A recent clinical trial shed light on the efficacy of OCA for treatment of PBC for patients who cannot tolerate or have an inadequate response to UDCA. In the phase three double-blind, placebo-controlled, parallel-group phase, 217 participants received either a placebo (73 patients) or one of two ocaliva treatments, 5 mg (71 patients) or 10 mg (73 patients) of OCA daily.[46] Primary endpoints included a reduction of serum alkaline phosphatase (ALP) levels to <1.67 times the upper limit of normal and a ≥15% reduction from baseline ALP levels and normal bilirubin levels at the conclusion of the 12-month study.[46] 47% of patients in the 10 mg OCA group and 46% in the 5–10 mg OCA group met the primary endpoint compared with 10% in the placebo group.[46] Although the drug increased the chance of adverse events and pruritus, the study found that using OCA in conjunction with UCDA or as its own independent therapy in PBC patients for 12 months resulted in a significant reduction in ALP and total bilirubin levels compared with the placebo group.[46] However, the same trial found no notable decrease in noninvasive measures of liver fibrosis.[46] Following the conclusion of the 12-month double-blind phase, a long-term safety extension of the trial was started in which participants were offered the opportunity to

continue to use OCA for up to 5 years.[47] The 209 patients were started on a 5 mg dose and could be titrated up to a maximum dose of 10 mg.[47] Intercept Pharmaceuticals has claimed that receiving the OCA treatment improved transplant-free survival compared with external control groups, lowering the risk of death or liver transplant by 72% to 80% for the study group compared with control groups.[48]

Combination therapy is another promising area of research. A phase 2 study conducted by Intercept Pharmaceuticals is currently underway to explore the possible synergy of a fixed-dose combination of OCA and bezafibrate (BZF). Sixty patients were assigned to four treatment arms, either 100 mg or 400 mg BZF tablets paired with either a placebo or 5 mg of OCA. OCA therapy to treat PBC has been a rewarding area of research and will hopefully continue to provide more options to individuals suffering from PBC. ALP levels will be tracked over a 12-week period to determine the effectiveness of treatment.[48]

Budesonide

Budesonide is a synthetic corticosteroid that is used to treat Crohn's disease, asthma, ulcerative colitis, among other diseases. It is a member of a class of corticosteroids intended to mitigate the familiar systemic effects of steroids on conditions such as osteoporosis and hypertension. This nonhalogenated glucocorticoid is designed to have a greater ratio of local to systemic effect, with one study finding the human liver to degrade budesonide three times faster than triamcinolone acetonide.[49] The efficacy of steroids in the treatment of PBC is moot. One clinical study showed that budesonide given in addition to UDCA did not improve liver histology in patients with PBC disease progression. However, improvement of biochemical markers of disease activity were seen.[49,50] Another clinical trial of the glucocorticoid budesonide reported improvement of both biochemical and histological markers, such as a decrease in liver enzymes and immunoglobulin M and G levels, but adverse effects typically associated with steroids, such as decrease in bone mineral density were observed.[51] The same trial did not observe changes in the titer of AMAs.[51] Nevertheless, another clinical trial did report improvement of the liver histology of PBC patients, with a 25% decrease in fibrosis in biopsies of patients with combination therapy of budesonide and UDCA.[52] The efficacy of budesonide in treating PBC is controversial. Additional studies are needed.

Peroxisome proliferator-activated receptor (PPAR) agonists

Nuclear receptors are important in the regulation of cholesterol and bile acid formation and secretion in the liver. PPARs are a class of these receptor proteins that have shown promising therapeutic benefits. PPAR-α, an isoform receptor of PPAR, is involved in fatty acid and triglyceride metabolism, and has anti-inflammatory activity via suppression of nuclear factor kappa B (NFκB) signaling. In disease states, PPAR-α expression is low, resulting in toxic accumulation of bile acids. Fibrates are PPAR ligands. A synthetic PPAR-α drug, BZF, has shown to be beneficial in treating patients with an incomplete response to UDCA and at risk for disease progression. When used in combination with UDCA, BZF reduced PBC symptoms and resulted in a complete biochemical response, decreasing the markers representative of cholestasis.[53]

PPAR-δ is ubiquitously expressed and significantly influences bile acid and lipid metabolism, in addition to inflammation and fibrosis. Seladelpar demonstrated its anti-cholestatic activity in a year-long, uncontrolled phase II study at both 5 mg and 10 mg.[54] Seladelpar is currently under evaluation in a 52-week, placebo-controlled, randomized, phase III study.

A dual PPARα/δ agonist, elafibranor, has also shown promising results by decreasing the activity of disease markers seen in PBC.[55] A randomized placebo-controlled phase II trial found elafibranor to be safe and effective when administered at 80 mg or 120 mg per day for 12 weeks.[55] The efficacy of 80 mg elafibranor is now being evaluated in the ELATIVE phase III clinical trial, (NCT04526665), for a longer duration of time.[56]

Immunosuppressive medications

Immunosuppressive medications are, in theory, attractive agents to treat PBC, an autoimmune disease. However, these medications have proven to be ineffective in slowing the progression of PBC and prolonging survival.[57] The destruction of bile ducts is not the sole cause of cholestasis in early PBC because cholestatic serum markers are elevated before the onset and significant injury to bile ducts. This phenomenon is thought to be explained by the biliary bicarbonate umbrella hypothesis.[10,57] Cholangiocytes become more susceptible to autoimmune responses because of impaired AE2 function and aberrant PDC-E2 expression.[57] B-cell and T-cell mediated immune responses are activated by bile acid-mediated cellular damage. Immunosuppressants and immunomodulators typically will no longer be effective in reversing the effects of chronic inflammation and progression of liver fibrosis or cirrhosis.

Liver transplantation

Liver transplantation is the only known effective treatment for patients who did not fully respond to first- or second-line defense therapies, resulting in liver failure or decompensated cirrhosis. Liver transplantation has proven to be beneficial. However, in about 20% of patients, PBC recurs post-transplant.[58] Although recurrence is of limited clinical significance in many cases. The exact incidence and factors causing the recurrence of PBC is unknown. Some theories involve age, HLA patterns, and the rapid weaning of immunosuppressive medication post-transplant, but the data remains unclear and ill-defined.[59]

New therapies and alternative targets

Norursodeoxycholic acid (norUDCA)

norUDCA is a derivative of UDCA with a shortened side chain that grants it increased resistance to amidation in addition to cholehepatic shunting properties.[60] In cholehepatic shunting, norUDCA is first absorbed by cholangiocytes before being resecreted by hepatocytes, something not possible for UDCA because of the presence of an additional methylene group.[29] The result is the production of bicarbonate ions, which facilitates production of a more hydrophilic environment that favors hepatocytes and cholangiocytes and is less conducive to the toxic accumulation of bile acids.[61] One study found that in common bile duct-ligated mice, liver injury in the group treated with norUDCA was significantly lower than the UDCA group.[62]

While its efficacy is better documented in PSC, the drug still has potential in PBC patients. SIRT1 is a NAD-dependent deacetylase that has a complex role in many different biological activities. It is highly expressed in liver tumors, and its presence is believed to have a negative correlation with a patient prognosis.[63]

NOX-1,4 inhibitor GKT831 (GenKyoTex)

Hepatic stellate cells (HSCs) and portal fibroblasts are precur-

sors of terminally differentiated myofibroblasts.[64–66] Myofibroblasts are responsible for the production of extracellular matrix material that promotes a profibrotic environment.[64,67,68] While activation and differentiation of myofibroblasts are important to promote wound healing and connective tissue repair following liver injury, fibrosis occurs when this activity is sustained.

NADPH oxidases (NOXs) are being studied as potential targets to reduce reactive oxidative species (ROS) in the liver and to treat hepatic fibrosis.[68] NOX proteins are responsible for transferring electrons from NADPH across biological membranes to form superoxide and hydrogen peroxide in a transmembrane electron transport chain.[64,69] NOX1 and NOX4 have been extensively studied because of the essential role they play in HSC proliferation and activation.[70] However, NOX dysregulation in these genes can cause disrupted ROS homeostasis which promotes a more profibrotic phenotype.[64,71]

GenKyoTex (Geneva, Switzerland) has developed a specific NOX1/NOX4 inhibitor, setanaxib (GKT831). In a 24-week double-blind, randomized, placebo-controlled phase 2 clinical trial, 111 participants were assigned to either a placebo group (37 patients) or to treatment with setanaxib 400 mg twice a day in 36 patients or 400 mg once a day in 38 patients.[72,73] The treatment group that received 400 mg setanaxib twice daily saw a 12.9% reduction in ALP.[72] Liver stiffness puts patients at elevated risk for disease, and setanaxib reduced stiffness by 22% in a predefined patient population, compared with a 4% reduction in placebo control.[72] This patient population also saw a 24% decline in ALP levels with that treatment.[72] Setanaxib 400 mg BID significantly reduced fatigue levels in patients who received the therapy.[72] Calliditas is currently recruiting for a 52-week randomized, placebo-controlled phase 2b/3 TRANSFORM study. The double-blind study will recruit 318 patients with PBC, liver stiffness, and poor response to UDCA, to measure reduction in ALP levels with secondary consideration given to changes in liver stiffness, pruritis, and fatigue.[72] Patients are assigned to either a placebo group, or one of two treatment groups receiving 1,200 mg daily or 1,600 mg daily.[74] At the conclusion of the 24th week of study, data analysis will be performed to determine the optimal dosage to continue with in phase 3 of the trial.[72] The FDA approved Calliditas for Fast Track Designation for use of setanaxib in PBC treatment in August 2021.

Gut microbiome

The balance and functions of gut bacteria might play a key role in the pathogenesis of cholangiopathies. Changes in the gut microbiome have been associated with the etiology and progression of other forms of liver disease, such as nonalcoholic fatty liver disease (NAFLD) and NASH.[75] Current evidence indicates that PBC patients present a different microbiota composition than healthy controls.[75,76] In a 2018 study of 60 PBC patients who had not previously received UDCA treatment, there was a significant reduction in the diversity of the microbiome compared with 80 healthy controls.[77] The PBC patients experienced an increase in eight genera associated with PBC and a decrease in four associated with a healthy microbiome. After UDCA treatment, the abundance of six of the PBC-related genera decreased.[77] While the understanding of the relationship between gut microbiome and progression of PBC is limited, this could be a potential therapeutic target for the disease.[78]

Hormones

Another area of emerging interest is the influence of hormones on the progression of PBC. The secretin (Sct)/secretin receptor (SR) axis is being investigated as a potential therapeutic option for early-stage PBC patients. Secretin is a hormone released by the duodenum to stimulate cholangiocytes and the pancreas to release bicarbonate ions. Cholangiocytes express the Sct/SR axis, that when activated, increases proliferation of cholangiocytes and liver fibrosis.[79] It is believed that overexpression of the Sct/SR axis signaling down-regulates miR-125b, expression. That enhances TGF-β/R1/VEGF-A expression and promotes HSC activation leading to liver fibrosis.[79] In human early-stage PBC patients, there was increased expression of Sct and SR, as well as serum Sct levels.[79] Mouse models of early-stage PBC reported increased Sct/SR axis expression accompanied by several other markers of liver damage like ductular reaction, HSC activation, and fibrosis.[79] When the mice received an SR antagonist (Sec 5–27) treatment led to lower levels of Sct/SR expression and reduced signs of liver injury, which provides a novel avenue for potential therapies for PBC patients.[79]

Conclusion

Several perplexing occurrences of PBC and its pathogenesis remain unanswered and may be necessary to develop more effective therapeutic approaches. A few of these fundamental questions are as follows. (1) If PDC-E2 is ubiquitously expressed, why is the damage restricted to BECs? (2) What contributes to the disease predominance seen in women? 3) What key biomarkers could serve as a sign for early disease detection and prevention?

Many potential targets have been identified, but it is difficult to find an effective treatment that does not completely block bile acid metabolism or secretion, as both are necessary for normal hepatic function. Furthermore, developing a stronger alternative to UDCA that can strengthen the biliary bicarbonate umbrella in fibrosing cholangiopathies should remain an important consideration.

PBC has a heterogeneous presentation, yet it is treated homogenously. Future therapeutic strategies should consider incorporating stage-dependent therapies concurrently with previously identified, first- and second-line combination therapies. Efforts to uncover factors responsible for the varying UDCA efficacy and drug intolerance seen in PBC patients as well as efforts to identify high-risk patients early in the disease course could be important in enabling stratified intervention and developing proactive measures. Lastly, further research should focus on the connection between specific genetic factors and their corresponding clinical presentation and outcome.

In summary, this review highlights some perplexing characteristics of PBC that remain unanswered and identifies recent discoveries in the field that are paving the way for new, promising therapeutics.

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Conflict of interest

GA has been an associate editor of *Journal of Clinical and Translational Hepatology* since 2023 and SC has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2021. The other authors have no conflict of interests related to this publication.

Author contributions

Review concept and design (SG, AM, JC), literature review (AM, JC, AL), drafting of the manuscript (AM, JC, AL), critical revision of the manuscript for important intellectual content (LB, SG), administrative, technical, or material support (SG, SC, GA). All authors have made a significant contribution to this study and have approved the final manuscript.

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