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REVIEW

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Primary biliary cholangitis: Epidemiology, prognosis, and treatment

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Abstract

Primary biliary cholangitis (PBC) is a chronic cholestatic autoimmune liver disease characterized by a destructive, small duct, and lymphocytic cholangitis, and marked by the presence of antimitochondrial antibodies. The incidence and prevalence of PBC vary widely in different regions and time periods, and although disproportionally more common among White non-Hispanic females, contemporary data show a higher prevalence in males and racial minorities than previously described. Outcomes largely depend on early recognition of the disease and prompt institution of treatment, which, in turn, are directly influenced by provider bias and socioeconomic factors. Ursodeoxycholic acid remains the initial treatment of choice for PBC, with obeticholic acid and fibrates (off-label therapy) reserved as add-on therapy for the management of inadequate responders or those with ursodeoxycholic acid intolerance. Novel and repurposed drugs are currently at different stages of clinical development not only for the treatment of PBC but also for its symptomatic management. Here, we summarize the most up-to-date data regarding the epidemiology, prognosis, and treatment of PBC, providing clinically useful information for its holistic management.

INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic inflammatory hepatobiliary disease characterized by a T-cell lymphocyte–mediated destruction of the interlobular bile ducts that can lead to biliary cirrhosis and liver failure if left untreated.[1]

This autoimmune liver disease results from the combination of environmental triggers, the individual's genetic susceptibility, and epigenetic factors. Supporting

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AE2, anion exchange 2; ALP, alkaline phosphatase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; APSAL, Asian-Pacific Association for the Study of the Liver; AST, aspartate aminotransferase; BA, bile acid; BEC, biliary epithelial cell; EASL, European Association for the Study of the Liver; FDA, US Federal Drug Administration; FXR, Farsenoid X receptor; GGT, gamma-glutamyl transferase; HK1, Hexokinase 1; IBAT, ileal bile acid transporter; IPTW, inverse probability of treatment weighting; INR, international normalized ratio; KLHL12, Kelch-like 12; KORs, κ-opioid receptors; LSM, liver stiffness measurement; LT, liver transplant; MORs, μ-opioid receptors, MRCP, magnetic resonance cholangiopancreatography; NOX, nicotinamide-adenine dinucleotide phosphate oxidase; OCA, obeticholic acid; PBC, primary biliary cholangitis; pHTN, pulmonary hypertension; PPAR, peroxisome proliferator–activated receptors; SS, Sjogren syndrome; SSRI, selective serotonin receptor inhibitor; TE, transient elastography; TG, triglycerides; TSH, thyroid-stimulating hormone; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; URS, ursodeoxycholic acid response score; US, ultrasound; VCTE, vibration-controlled transient elastography.

the role of the genetic contribution to disease development, there is a 63% concordance among identical twins,[2] a relative risk of 9.13–10.5 in first-degree relatives, and a strong association with HLA and non-HLA allelic variants.[3,4] Molecular mimicry between lipoic acids, exogenous antigens, and xenobiotics accounts for the loss of tolerance to biliary epithelial cells and the T-cell cluster differentiation that characterizes the disorder.[5–7]

The serologic hallmark of PBC is the antimitochondrial antibody (AMA), an autoantibody that targets lipoic acids found in the dehydrogenase complex from the inner mitochondrial membrane, and it is positive in 90%–95% of individuals with PBC.[8,9] Given its high disease specificity, a positive AMA serology in patients with cholestasis is sufficient to ascertain the diagnosis of PBC without requiring a liver biopsy.[10,11] Approximately 30% of all patients with PBC, and up to 50% of AMA-negative patients, also have detectable titers of PBC-specific antinuclear antibodies (ANA), specifically anti-sp100 and anti-gp210. When present, these antibodies are nearly diagnostic of PBC, thus being particularly helpful in AMA-negative individuals. In addition, anti-gp210 may have prognostic significance as it has been associated with more severe PBC phenotypes.[12,13] Other PBC-specific antinuclear antibodies discovered more recently, such as anti-Kelch-like 12 (KLHL12) and anti-hexokinase 1 (HK1), are not yet commercially available, and their clinical utility needs to be validated.[14] Regardless, it is notable that AMA-negative and AMA-positive PBC exhibit similar natural history and clinical outcomes, both before and after the onset of cirrhosis.[15,16] A proposed algorithm for the diagnosis of PBC in the setting of chronic cholestasis is summarized in Figure 1.

Most patients are asymptomatic at diagnosis although nearly everyone will develop symptoms within 2 decades.

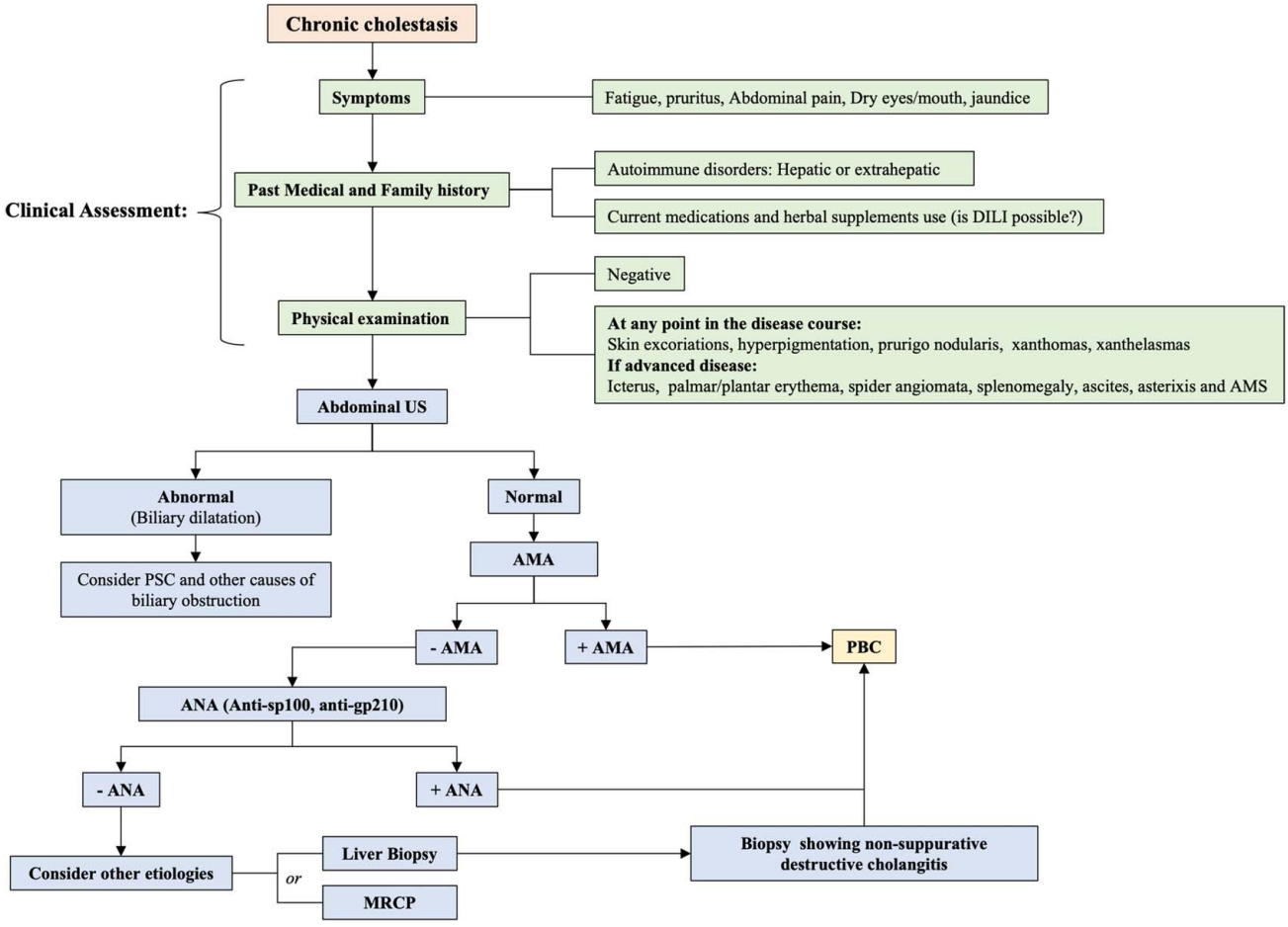

FIGURE 1 Approach to the diagnosis of PBC. The assessment of patients with cholestasis whether symptomatic or not should include a liver ultrasound and testing for the AMA in serum. A positive AMA in this setting is sufficient to make the diagnosis of PBC. PBC-specific ANAs, ie, anti-sp100 and anti-gp210, can aid in the diagnosis of PBC in individuals with cholestasis and negative AMA serology. Liver biopsy is reserved for those with unclear diagnosis after serologic workup, or when a coexisting process is suspected, including fatty liver disease and autoimmune hepatitis. Abbreviations: AMA, antimitochondrial antibody; AMS, altered mental status; ANAs, antinuclear antibodies; MRCP, magnetic resonance cholangiopancreatography; PBC, primary biliary cholangitis; US, ultrasound.

The presence or absence of symptoms at diagnosis or on follow-up does not correlate well with the stage of the disease and has shown no difference in survival outcomes[17] (Figure 2). Fatigue is the most common complaint. It is experienced by up to 80% of patients during the disease course and is often rated as the most disabling PBC symptom.[18,19] Pruritus closely follows in frequency and may be associated with sleep deprivation, worsening fatigue, depression, social isolation, and self-mutilation, thus leading to significant impairment in quality of life.[20] Patients with chronic cholestasis are at risk for developing metabolic bone disease, dyslipidemia, and lipo-soluble vitamin deficiencies (Vitamins A, D, E, and K).[21,22]

In this review, we summarize the most current data regarding the epidemiology, diagnosis, and treatment of PBC focusing on clinically useful information to assist health care providers in the integral management of these complex patients.

EPIDEMIOLOGY

PBC affects people of all sexes, races, and ethnicities. Earlier reports from case-finding studies showed a median female-to-male ratio of 10:1.[23] Modern literature has demonstrated that, although PBC remains a female-predominant disease, it is also more prevalent in males than previously thought, with a female-to-male ratio closer to 4–6:1.[24,25] PBC in males is often diagnosed at an older age, once the disease is more advanced. PBC in males has also been associated with lower biochemical response to ursodeoxycholic acid (UDCA), greater progression to cirrhosis, higher rates of liver-related death or transplantation, and increased risk for HCC.[26,27]

While non-Hispanic White patients are disproportionally diagnosed, the incidence and prevalence of PBC in racial minorities are not insignificant, with available US data showing a lower but unrelenting incidence rate and steady increases in prevalence among black and Asian-American patients. Notably, accurate racial epidemiologic estimates are hampered by health care disparities and a lack of disease recognition by providers.[24]

The incidence and prevalence of PBC increase with age, with a peak range between 60 and 79 years old. PBC is typically identified in middle-aged individuals (40–60 years of age) and is exceptionally rare under 25 years of age.[28]

The pooled global incidence and prevalence of PBC are estimated to be 1.76 and 14.60 per 100,000 persons, respectively.[29] However, these estimates vary significantly according to the search strategy utilized, the size of the study population, and the degree of scrutiny of case finding.[30] The incidence of PBC steadily rose until the year 2000 across the globe. Growth rates in North America and Europe have since plateaued, whereas the incidence of PBC in the Asian-Pacific region has continued to increase slowly, likely due to improved case reporting. The prevalence of PBC in all three regions has risen steadily over time, although at a faster pace in North America relative to

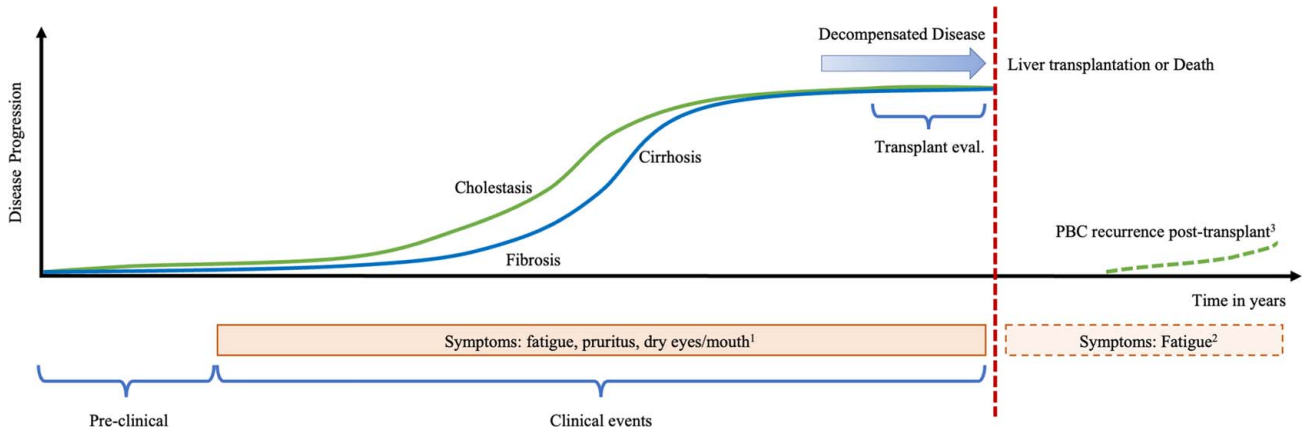

FIGURE 2 Natural history in primary biliary cholangitis (PBC). Most patients with PBC are diagnosed while asymptomatic. Liver disease progression is inevitable in most untreated individuals, with fibrosis and cirrhosis ensuing as a consequence of the inflammatory and cholestatic processes. The cumulative incidence of major non-neoplastic hepatic complications has been reported as 15% after 15 years of follow-up. Liver transplantation is the only curative treatment option for those with decompensated disease and declining liver function. PBC will recur in 20%–40% of post-transplant patients. Symptoms do not correlate with the degree of cholestasis or fibrosis although patients with more severe disease tend to experience more symptoms in general. Fatigue may not completely resolve post-transplantation even in the absence of recurrent disease. [1]Symptoms do not correlate with the disease stage and can occur at any point. [2]Fatigue may persist after liver transplant. [3]The frequency of post-transplant PBC is highly variable among studies (9%–61%).

Europe.[29] A 12-year prevalence study from the Fibrotic Liver Disease (FOLD) Consortium found that the PBC prevalence in the United States increased by over 72% among women (33.5–57.8 per 100,000 persons) and over 114% in men (7.7–15.4 per 100,000 persons) during the study period.[24] Although this change is likely multifactorial, earlier recognition of the disease and the efficacy of UDCA to prevent morbidity and mortality are likely major contributors.

Contemporary data show that the incidence of PBC is higher in North America (2.75 per 100,000 persons) relative to Europe (1.86 per 100,000 persons) and lowest in the Asian-Pacific region (0.84 per 100,000 persons) (Figure 3A). The pooled prevalence follows a similar trend, being highest in North America (21.81/1000,000), Europe (14.59/100,000), and then in the Asian-Pacific region (9.82/100,000) (Figure 3B).[29] However, a recent study suggests that the prevalence of PBC in Asia may be higher than previously reported: 11.9 per 100,000 individuals, with regional differences suggesting a higher prevalence in Japan and China (19.1 cases per 100,000), compared with 9.9 per 100,000 in New Zealand and 3.9 per 100,000 in South Korea and Australia.[31] Little is known about the incidence and prevalence of PBC in Africa, Central and South America, and Antarctica given the paucity of population-based studies in those continents.[29]

Continental and country-specific epidemiological differences have also been described within Europe and North America. For example, Eastern European countries have the lowest estimated incidence and prevalence in Europe,[29] the northern United Kingdom has a higher incidence of PBC relative to the southern United Kingdom,[32] and PBC was significantly more frequent among members of the Aboriginal First Nation's communities in British Columbia compared with reported rates in Ontario, Canada.[33] Genetic susceptibility and environmental factors partially account for these differences, with PBC being more prevalent in industrialized/polluted areas and in patients who smoke cigarettes and use nail polish and hair dye products.[34–37]

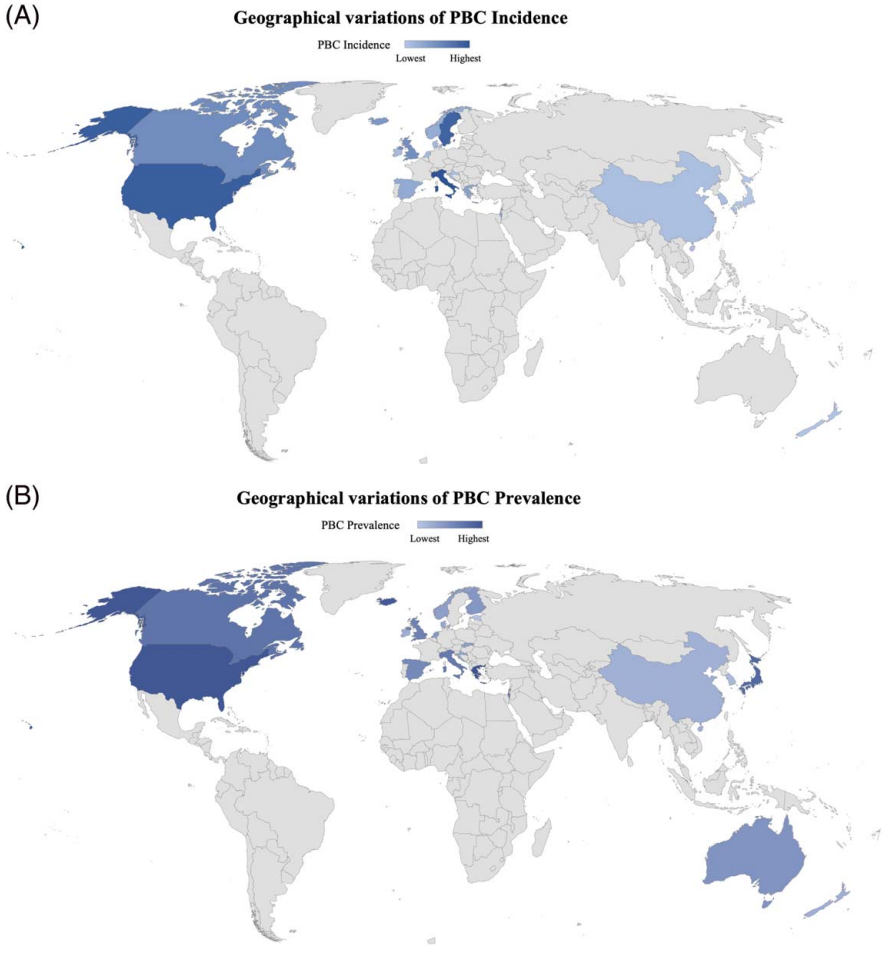

FIGURE 3 Geographical variations of PBC incidence and prevalence. (A) Global variations in PBC incidence. (B) Global variations in PBC prevalence. Lower to higher rates are qualitatively represented by lighter to darker blue, respectively. Countries with no population-based epidemiologic studies available at the time of this review are represented in gray. Abbreviation: PBC, primary biliary cholangitis.

PROGNOSIS

Transplant-free survival

The disease progression and prognosis of PBC have substantially changed in the past few decades. The mean age at PBC diagnosis has steadily increased since the 1970s by 2–3 years per decade and those who have been diagnosed more recently present with milder elevations of liver chemistries and histologic findings, and a better response to UDCA. Although the cause of these variations has not been fully elucidated, it likely reflects a combination of biological factors, changing environmental triggers, longer subclinical periods associated with increased screening in older patients, and overall increased awareness of the disease.[38]

Racial differences and health care disparities also influence survival in patients with PBC. Black and Hispanic patients have a significantly higher risk of waitlist mortality (HR: 1.26 and HR: 1.41, respectively) and removal from the transplant list due to clinical deterioration compared with Whites.[39,40] Similarly, Indigenous Canadian patients with PBC are more commonly diagnosed at advanced disease stages experiencing lower event-free survival and lower transplant-free survival compared with White patients.[41]

The introduction of UDCA has helped reshape the progression and prognosis of PBC. The transplant-free survival rate for untreated patients has been estimated at 79%, 59%, and 32% at 5, 10, and 15 years, respectively. In contrast, those treated with UDCA experience significantly higher survival rates of 90%, 78%, and 66% at 5, 10, and 15 years, respectively.[42] Similar results were obtained after pooling a large cohort of patients from the Global PBC Study Group database in which treated individuals had a 20% higher transplant-free survival rate at 10 years (79.7% among UDCA-treated patients vs. 60.7% among untreated patients) and a statistically significant reduced risk of liver transplant (LT) or death (HR: 0.46) at all histological stages of the disease.[43] Treatment with UDCA has additionally been shown to significantly delay the development of esophageal varices (16% in UDCA-treated patients vs. 58% in placebo).[44]

HCC

Patients with PBC are at a higher risk of developing HCC, but its incidence is certainly lower than that documented for other causes of chronic liver disease (4.17 per 1000 person-years). Male patients with cirrhosis are at the highest risk (9.82 per 1000 patient-years).[45,46] A Veterans Affair–based study, including 532 patients with PBC cirrhosis who were predominantly males, demonstrated a higher unadjusted rate of HCC in males (0.9 vs. 0.3, per 100-person-years) but did now show an association on multivariable analysis.[47]

Reports on the biochemical response to UDCA affecting the development of HCC are conflicting with results markedly influenced by methodologic bias.[45,48,49] Despite this, a multicenter study, including 4565 patients from the Global PBC Study Group database, showed that suboptimal response to UDCA is a significant factor predictive of future HCC in patients with early and advanced stage diseases, and remained the most significant factor predictive of future HCC risk (HR: 3.44) on multivariable analysis.[48] Periodic screening in patients with cirrhosis is recommended by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL)[10,11] whether the patient is receiving treatment or not. In addition, the AASLD recommends HCC surveillance in all males with PBC despite the absence of cost-effectiveness analyses.[10]

Risk stratification

Liver biochemistries and histology

In PBC, serum bilirubin independently and effectively predicts survival.[50] However, elevated levels are commonly seen at later stages of the disease, being less useful for initial risk stratification.[51] More recent studies indicate a differential prognostic ability of total bilirubin even when within the normal range, with values $>0.6\times$ ULN associated with worse outcomes.[52]

A log-linear association between serum alkaline phosphatase (ALP) and risk of LT and death has been described in patients with PBC, with higher levels translating into decreased transplant-free survival. In a large meta-analysis with nearly 5000 patients with PBC, an ALP level $>2\times$ ULN after 1 year of follow-up had the highest predictive ability (C statistic 0.71) although there was no statistically significant difference when compared with other cutoff values such as $1.5\times$ ULN, $1.67\times$ ULN, and $3.0\times$ ULN. The 5-, 10-, and 15-year transplant-free survival rates for patients with ALP levels $\leq 2.0\times$ ULN were 94%, 84%, and 73%, respectively, and for patients with ALP levels $>2.0\times$ ULN, these rates were 81%, 62%, and 50%, respectively ($p < 0.0001$).[42] ALP level is, therefore, considered a reliable marker of treatment response, with lower numbers associated with better prognosis, decreased mortality, and longer transplant-free survival.[53] Moreover, combining ALP with either bilirubin[42] or gamma-glutamyl transferase (GGT)[54] levels in serum further increases the prognostic capability of ALP. Although GGT has been shown to correlate with UDCA nonresponse,[54] increased the risk of liver-related death, and LT,[55] it should not be used in isolation in the assessment of biochemical response to therapy.

Untreated PBC progresses at an average rate of 1 histological stage every 1.5–2 years, with half of the cases developing cirrhosis at 4 years and only 20% remaining stable over time.[56] Histological features that significantly predict the risk of liver fibrosis progression include ductopenia and increasing severity of interface hepatitis.[57,58] Treated individuals have a 5-fold reduction in the rate of progression to cirrhosis if diagnosed at an early histologic stage.[59,60] However, the presence of advanced fibrosis (stage 3/4) at diagnosis is an independent predictor of poor transplant-free survival (HR: 2.85) even if the biochemical response has been achieved with UDCA.

Response to UDCA treatment

There is currently no consensus regarding the optimal serologic threshold to define response to UDCA. Multiple binary prognostic models have been proposed and utilized in clinical trials (Table 1). Of them, the Paris I criteria are considered the most accurate for transplant-free survival prediction.[53] In clinical practice, ALP and total bilirubin normalization or near-normalization are ideal but not always possible.[52]

The UK-PBC (https://www.uk-pbc.com/resources/tools/riskcalculator/)[61] and the GLOBE (https://www.globalpbc.com/globe)[62] scores are derived from the analysis of multicenter PBC cohorts and have been externally validated in large international studies.[63] These mathematical models are excellent at estimating outcomes: the UK-PBC score estimates the risk of LT or liver-related death at 5, 10, and 15 years, whereas the GLOBE score estimates the overall survival within 3, 5, 10, and 15 years.[61,62]

Although the Globe and the UK-PBC scores are considered excellent prognostic tools, they are not exempt from pitfalls. For instance, no specific threshold to classify high-risk or low-risk patients has been defined; therefore, they cannot be used for treatment escalation or de-escalation. Similarly, no validated data regarding their prognostic capability in patients on second-line therapy is currently available.[64] An additional limitation is that neither can identify patients who are unlikely to respond to UDCA before treatment initiation. To address this issue, the UK-PBC Research group and the Italian PBC Study Group developed the UDCA Response Score (URS). The URS, which has been externally validated, utilizes pretreatment clinical and serologic variables at the time of PBC diagnosis, ALP at the time of UDCA initiation, patient's age, and the interval from diagnosis to UDCA initiation in years to identify patients at high risk of failing UDCA monotherapy (http://www.mat.uniroma2.it/~alenardi/URS.html).[65,66] Despite having high accuracy, the model has not yet been implemented in routine clinical practice.

Not all patients benefit from UDCA treatment to the same degree, with several studies showing variable responses to the medication according to age, race, and histological stage at diagnosis.[67,68] Younger age, advanced fibrosis (stage 3/4) at the time of treatment initiation, and male sex are associated with poor biochemical response to UDCA.[59,69] Hispanic patients are more likely to exhibit features of autoimmune hepatitis and to have higher rates of biochemical nonresponse.[70] Suboptimal response to UDCA has also been described in those of Indigenous origin.[41] Black patients are more likely to respond to UDCA but are less likely to receive treatment.[71]

Liver stiffness

Liver stiffness measurement (LSM) is widely used as a surrogate marker for fibrosis in chronic liver diseases. In patients with PBC, an LSM below 6.5 kPa or above 11 kPa measured by transient elastography accurately discriminates between the absence or presence of advanced fibrosis with high sensitivity and specificity.[72]

TABLE 1 Assessment of serologic response to ursodeoxycholic acid

Serologic response to UDCA therapy in PBC	Treatment duration (mo)	Treatment failure if
Rochester	6	ALP $\geq$ 2× ULN or Mayo score $\geq$4.5
Barcelona	12	Decrease in ALP $\leq$ 40% and ALP $\geq$ 1× ULN
Paris I	12	ALP $\geq$ 3× ULN or AST $\geq$ 2× ULN or bilirubin $>$ 1 mg/dL
Rotterdam	12	Bilirubin $>$ 1 mg/dL and/or albumin $<$ 1× ULN
Toronto	24	ALP $\geq$ 1.67× ULN
Paris-II	12	ALP $\geq$ 1.5× ULN or AST $\geq$ 1.5× ULN or bilirubin $>$ 1 mg/dL
Ehime	6	Decrease in GGT $\leq$ 70% and GGT $\geq$ 1× ULN
Rochester-II	12	ALP 2× ULN
Global	12	ALP 2× ULN

Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ULN, upper limit of normal.

The utilization of LSM as a prognostic tool in PBC is an evolving field. Earlier data showed that a baseline LSM of >9.6 kPa or an increase in LSM over time of >2.1 kPa/y was associated with 5.1 and 8.4 times increased risks of adverse outcomes, respectively.[73] A recent retrospective follow-up study, including almost 4000 patients with PBC, confirmed that elevated LSM assessed by vibration-controlled transient elastography is independently associated with poor clinical outcomes, ie, liver-related complications, liver transplantation, or death. It improves the predictive value of classic biochemical criteria and validated scores. Furthermore, LSM was able to risk-stratify patients into low (LSM < 8 kPa), medium (LSM 8–15 kPa), or high risk (>15 kPa) for poor clinical outcomes with 10-year rates of clinical events among medium- and high-risk patients ranging between 20%–50% and 50%–90%, respectively.[74] Re-evaluating liver stiffness after 1 year of therapy with UDCA is likely to provide a more accurate prediction of risk.

Treatment

The management of PBC is centered on staging and treating the disease, its symptoms, and the associated extrahepatic complications (Figures 4 and 5) (Table 2). Although UDCA revolutionized the management of PBC and continues to be cardinal for its treatment, up to 40% of patients do not fully benefit.[53] This has switched the focus of clinical research toward developing new or repurposing available medications with the goal of treating inadequate responders. Important therapeutic advances have been made in the last decade, with the US Federal Drug Administration (FDA) granting approval for obeticholic acid (OCA) to be used as second-line therapy in patients without advanced liver disease. Similarly, fibrates are now endorsed as a viable off-label alternative for the management of inadequate responders by medical societies, such as the AASLD, EASL, and the Asian-Pacific Association for the Study of the Liver (APASL),[11,75,76] and bezafibrate is a *de facto* second-line treatment in Japan.[77] Unfortunately, these drugs are

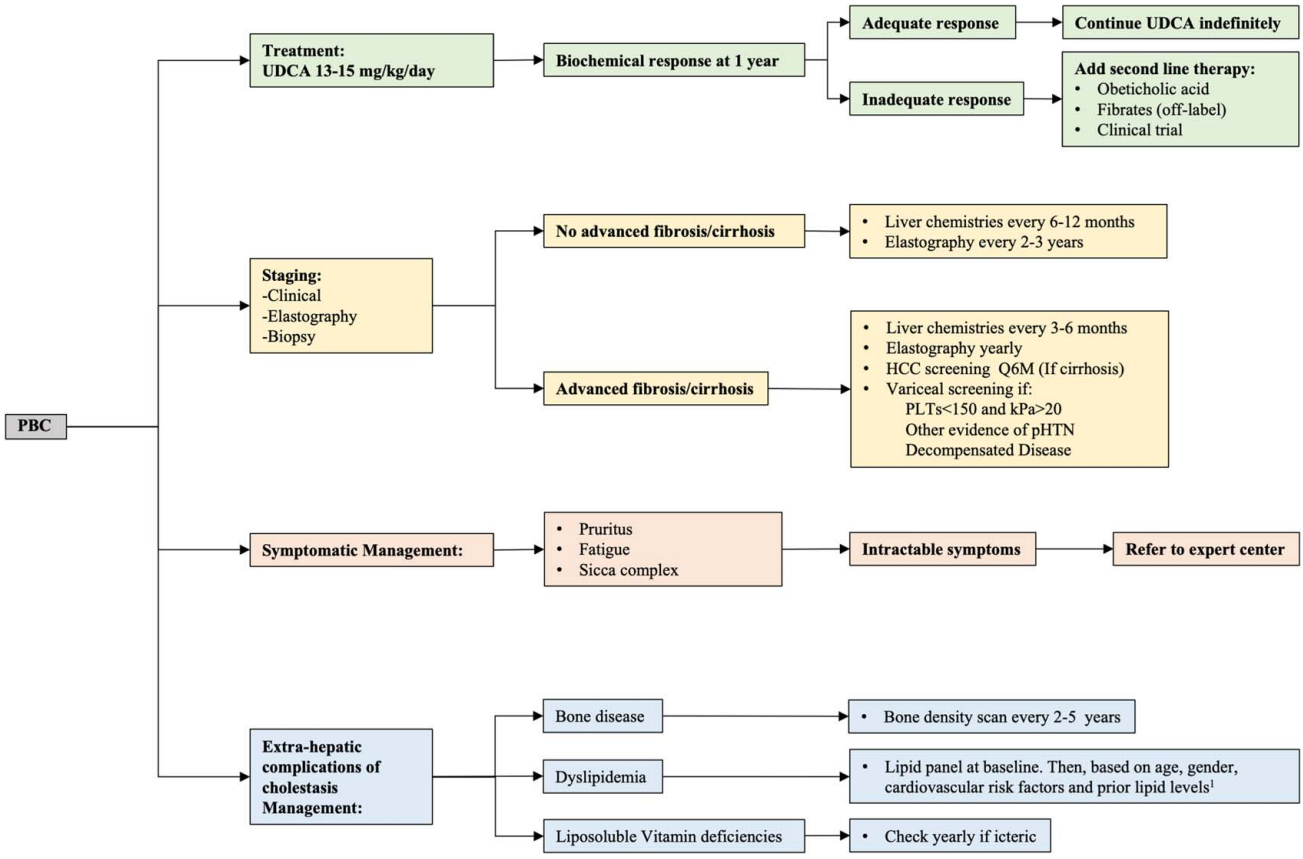

FIGURE 4 PBC management flow chart. A holistic approach for the management of patients with PBC is recommended and should be based on: (1) PBC treatment; (2) disease staging and monitoring; (3) symptomatic treatment; and (4) extrahepatic complications of cholestasis management. Currently recommended strategy supports assessing response to UDCA after 1 year of treatment although ongoing studies indicate that this may be evaluated at earlier timepoints as well. In addition, while existing guidelines still associate "response to UDCA" with achieving specific cutoff values for ALP and TB, it is likely that the field will evolve in the direction of aiming to normalize liver chemistries. [1]Per guidelines published for the general population. AHA/ACC guidelines, ACE guidelines. Abbreviations: PBC, primary biliary cholangitis; pHTN, pulmonary hypertension; PLTs, platelets; UDCA, ursodeoxycholic acid.

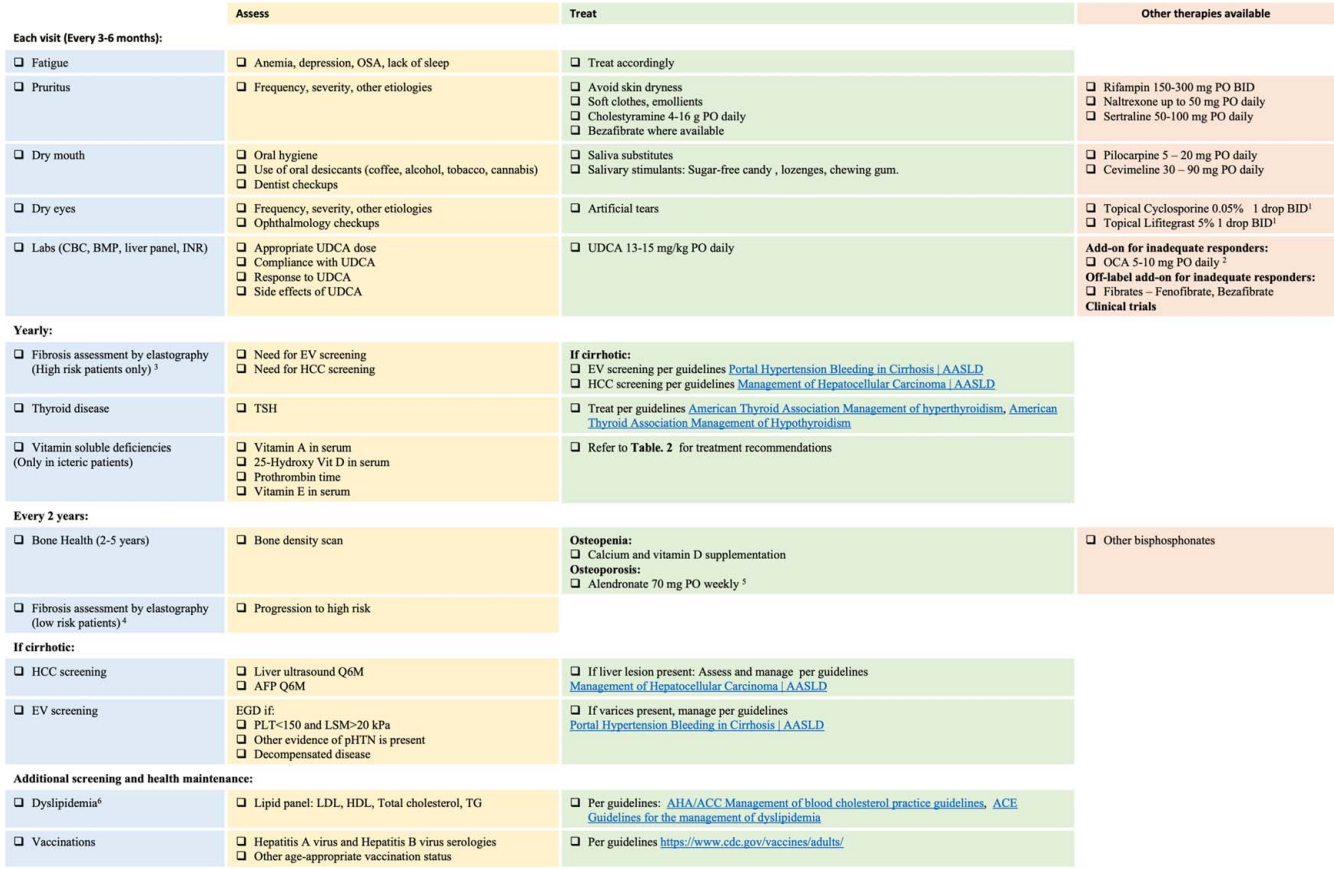

FIGURE 5 Approach to patients with primary biliary cholangitis (PBC) in the outpatient clinic. PBC is a relatively rare disease, and managing affected patients in the office can be challenging for providers not familiarized with the disorder. Although PBC treatment should be tailored to the patient's individual needs, we propose a structured approach for its management in the outpatient setting. This should include symptomatic and disease assessment and treatment during each clinic visit, periodic fibrosis staging, and screening for extrahepatic complications of cholestasis when appropriate. For those with advanced disease stages, screening for complications derived from portal hypertension is also necessary. [1]Recommend comanagment with ophthalmologist. [2]Contraindicated in cirrhosis with portal hypertension and decompensated disease. [3]Patients with LSM > 10 kPa and/or nonreponders to UDCA. [4]Patients with LSM < 10 kPa or with appropriate UDCA response. [5]Avoid in patients with esophageal varices. [6]In the absence of cardiovascular risk factors, hyperlipidemia associated with PBC does not increase the risk of cardiac events. Screening should be performed at baseline and the according to guidelines published for the general population. Abbreviations: AFP, alpha fetoprotein; BMP, basic metabolic panel; CBC, complete blood count; EV, esophageal varices; INR, international normalized ratio; LSM, liver stiffness measurement; pHTN, pulmonary hypertension; PLTs, platelets; TG, triglycerides; TSH, thyroid-stimulating hormone; UDCA, ursodeoxycholic acid.

TABLE 2 Liposoluble vitamin supplementation

Vitamin	Serum levels	Formulation names	Repletion dosage[a]	Maintenance oral dosage (daily)
Vitamin A[a]	Normal: 30–100 μg/dL	Vitamin A	Absence of symptoms: 10,000–25,000 IU (oral) daily Presence of visual symptoms: 50,000 IU (oral) daily ×1 mo If no response to oral supplementation: 100,000 IU (IM) daily × 3 days followed by 50,000 IU (IM) daily × 2 wk	15,000 IU × 2 mo
Vitamin D[a]	Normal: > 30 ng/mL	Cholecalciferol (vitamin D3) Ergocalciferol (vitamin D2)	50,000 IU vitamin D3 (oral) weekly × 8–12 wk	400–2000 IU vitamin D3
Vitamin K[a]	Normal: 0.15–1.0 μg/L	Vitamin K	2.5–10 mg (oral) twice weekly	5 mg
Vitamin E[a]	Normal: 0.5–2.0 mg/dL	Vitamin E (expressed in alpha-tocopherol equivalents)	200–2000 mg (oral) daily	15 mg

[a]Water-miscible formulas are recommended for supplementation in the setting of fat malabsorption.
Abbreviation: IM, intramuscular.

not devoid of side effects, and their use is limited to a very specific subset of patients. Furthermore, an important paradigm change in the overarching treatment of patients with PBC has been focused on managing symptoms. Multiple new drugs are currently in the pipeline showing promising results in phases II and III clinical trials.

First-line therapy: UDCA

When administered orally, only about 30%–60% of UDCA is absorbed by the bowel (80% small bowel and 20% in the colon), and once inside the hepatocytes, synthetic UDCA requires conjugation with glycine or taurine to be transported across the canalicular domain and into the bile ducts.[78] Among other beneficial effects in cholestatic diseases, UDCA increases the biliary pool of hydrophilic bile acids (BA) to 40%–50%,[79] stimulates choleresis, increases bile alkalinization through upregulation of anion exchange 2 (AE2) receptor expression, and reduces the hepatocellular and biliary expression of major histocompatibility complex class I and class II proteins, thus decreasing adaptive immune injury. UDCA also stabilizes the mitochondrial membrane preventing the activation of death receptors that ultimately signal apoptosis.[1,80]

Studies have consistently shown that the use of UDCA improves liver chemistries, delays histological progression, and delays the development of varices.[10,11] Although early meta-analyses showed no difference in liver-related mortality, all-cause mortality, and/or transplant-free survival,[81–83] a large international collaborative study from the Global PBC Study Group found an improved 10-year cumulative LT-free survival for UDCA-treated individuals (79.7% vs. 60.7%, $p < 0.001$), confirming the anecdotal experience that UDCA does influence outcomes.[43] Furthermore, improved survival with UDCA use has been shown regardless of sex or disease stage and even in those who inadequately respond to the medication.[72]

Although the use of UDCA has no effect on symptom onset or amelioration, treated patients experience a decreased incidence of non-neoplastic cirrhosis–associated hepatic complications, ie, ascites, variceal bleeding, and HE over time. In a recent retrospective study, the overall cumulative incidence of major non-neoplastic hepatic complications was 9% after 10 years and 15% after 15 years. This incidence sharply decreased to 5.8% after the year 2000, partially due to the gradual introduction of UDCA, which had just been approved to treat PBC a few years earlier.[84]

All patients with PBC should be started on UDCA at diagnosis, promptly and independently of the degree of cholestasis, fibrosis, or overall clinical status. Where available, the medication should be provided at a therapeutic dose of 13–15 mg/kg/d taken with meals, in a single oral daily dose or divided doses. Higher doses have shown no additional benefits, and dose escalation is not currently recommended.[10]

UDCA has an excellent safety profile with minimal side effects when administered at the appropriate dose. Some patients do experience weight gain, hair thinning, and gastrointestinal symptoms, such as diarrhea and/or flatulence.[85] Limited data have shown UDCA to be safe during pregnancy and breastfeeding with no teratogenic consequences.[86]

Second-line therapy

Second-line therapy should be considered for all patients with insufficient response to UDCA after 1 year of therapy. Several groups have attempted to identify those patients with an inadequate response even earlier and to allow timely initiation of second-line therapy or clinical trial participation.[87–89] However, there is no consensus on how this should be accomplished in practice.

Obeticholic acid

OCA is a synthetically modified hydrophobic BA derived from chenodeoxycholic acid that has a high affinity for Farsenoid X receptors (FXRs). FXRs are transcription factors belonging to the superfamily of nuclear receptors with high expression in the liver and intestines. FXR regulates BA synthesis, conjugation, and transport, as well as various aspects of lipids and glucose metabolism.[90] For instance, its activation upregulates the synthesis of short heterodimeric partner, a suppressive protein that inhibits the expression of cholesterol 7∝-hydroxylase. This is a rate-limiting enzyme necessary for the synthesis of BA. FXR also suppresses BA synthesis through FGF-19 and FGF-4 activation, and directly enhances the expression of several BA transporters and uptake proteins.[91] The net effect from FXR activation is, therefore, a reduction in the total BA pool by limiting their synthesis and uptake and promoting choleresis.[92]

OCA is indicated as adjunctive therapy for patients with PBC who inadequately respond to UDCA after 1 year of treatment.[10] This medication received conditional FDA approval in 2016, after a phase III randomized controlled trial showed that 47% of the patients receiving OCA 10 mg/d and 46% of those receiving OCA 5–10 mg/d achieved the primary endpoint that is now known as the POISE criteria (serum ALP reduction to $<1.67\times$ ULN, with a reduction of at least 15% from baseline and a normal total bilirubin level after 12 mo of treatment).[93] This improvement has proven to be sustained in subsequent open-label extension trials.[94] OCA can also be used as monotherapy for patients who are intolerant to UDCA.[95]

Real-world efficacy data support the beneficial effects of OCA in patients with PBC. An Italian cohort including 191 inadequate responders showed a 42.9% response rate according to POISE criteria and 11% by normal range criteria.[96] Similarly, a Canadian retrospective cohort study demonstrated a significant reduction in mean ALP and GGT regardless of their initial degree of elevation after 12 months of therapy.[97] Both studies encountered a lower response rate for those with cirrhosis, as determined by transient elastography, compared with noncirrhotic counterparts.

A recent study compared the outcomes of death or transplantation among participants in the POISE trial that continued OCA in an open-label extension for up to 6 years to propensity-matched controls from the Global PBC and UK-PBC cohorts. During the 6-year follow-up period, there were 5 composite events in 209 (2.4%) subjects in the POISE study, 135 events in 1381 (10%) patients in the Global PBC cohort, and 281 events in 2135 (13.2%) patients in the UK-PBC participants.[98] The use of OCA was associated with 71% and 70% lower hazards of death or liver transplantation compared with participants in the Global PBC and UK-PBC cohorts, respectively.[98]

The most common side effect of OCA is dose-dependent pruritus, which leads to drug discontinuation in 10%–25% of treated subjects.[93,96,97]. Therefore, OCA should be started at a low dose and up-titrated slowly to prevent its discontinuation. In addition, FXR activation by OCA causes a negative impact on the lipid panel as it decreases HDL and increases LDL-cholesterol, independently of the dose.

Multicenter case series and data from a VA cohort showing an increased risk of hepatic decompensation and death in individuals with advanced cirrhosis using OCA[99,100] led the FDA to issue a label modification in 2021 recommending against its use in patients with cirrhosis and current or prior evidence of decompensation (encephalopathy, ascites, and variceal bleed), or portal hypertension (gastroesophageal varices or persistent thrombocytopenia).[75] In summary, OCA is contraindicated in patients with cirrhosis with the Child-Pugh score of B or C, and Child A patients with any evidence of portal hypertension. The drug should be used with caution at a maximum dose of 5 mg/d in those with compensated cirrhosis without portal hypertension.

Off-label therapy: Fibrates

Fibrates are fibric acid derivatives commonly used for the management of atherogenic dyslipidemia, decreasing triglyceride and LDL levels, and increasing HDL levels.[101] Although only licensed in the United States as lipid-lowering agents, these drugs have been used off-label for the treatment of cholestatic disorders.

Fibrates are strong peroxisome proliferator–activated receptor (PPAR) agonists. PPAR are ligand-activated transcription factors that belong to the nuclear hormone receptor superfamily. They exist in 3 isoforms: PPAR-α, PPAR-δ, and PPAR-γ, with the former predominantly expressed in hepatocytes. When activated, PPAR-α induces the expression of numerous genes with a number of them involved in lipid pathways that regulate fatty acid oxidation, triglyceride degradation and BA synthesis, metabolism, and transport, reducing BA concentration inside hepatocytes, augmenting phospholipid excretion into the biliary canaliculi, and inhibiting proinflammatory agents within the liver and biliary tree.[102]

All marketed fibrates, ie, fenofibrate, bezafibrate, pemafibrate, gemfibrozil, and fenofibric acid, are predominantly PPAR-α agonists except for bezafibrate, which also has affinity for PPAR-δ and PPAR-γ. Although bezafibrate is commonly used as second-line therapy in Asia, South America, and Europe, it is not commercially available in the United States.[103,104]

The phase III randomized, placebo-controlled trial "BEZURSO" assigned 100 inadequate UDCA responders to receive bezafibrate (400-mg PO daily) or placebo in addition to UDCA for 24 months. After 2 years, 31% of patients in the treatment group normalized all liver chemistries compared with none in the placebo arm. Notably, at the end of the study, 67% of the patients in the bezafibrate group had complete ALP normalization and a mean liver stiffness reduction by vibration-controlled transient elastography of 15%. Only 2% of the controls achieved normal ALP levels, and instead, this group experienced a 22% increase in liver stiffness at the end of the study period.[105]

A recent retrospective nationwide Japanese study collecting data on PBC patients since 1980 showed that bezafibrate add-on therapy decreases all-cause mortality or LT (HR: 0.32) and liver-related mortality or LT (HR: 0.27) with a number-needed-to-treat to prevent 1 additional death or LT of 29, 14, and 8, over 5, 10, and 15 years, respectively.[77] Data on outcomes with the use of fenofibrate for inadequate responders are less robust. A few small prospective and retrospective studies have shown improved outcomes, including decompensation-free and transplant-free survival in those receiving combined UDCA and fenofibrate treatment.[106–108]

Although gastrointestinal and musculoskeletal complaints, such as myalgias and arthralgias, are more common in patients with PBC on dual UDCA-fibrate therapy,[109,110] no significant difference in the frequency of serious side effects (including elevations of aminotransferases >5 times the ULN) has been reported when compared with individuals on UDCA monotherapy.[109] In the Bezurso trial, 3 out of 50 in the bezafibrate arm, and 1 of 50 in the placebo arm developed elevated transaminases >5 times ULN.[105] In addition, serum creatinine levels increased by a median of 5% in the bezafibrate group and decreased by 3% in the placebo group compared with baseline.[105] This is a well-described effect of PPAR-α agonists that

derive from renal hemodynamic changes and/or an increased creatinine release by muscle but does not reflect renal toxicity.[111,112] Liver biochemistries and renal function should be monitored periodically in PBC patients on fibrates, and its use should be avoided in those with decompensated liver disease.

Triple therapy UDCA + OCA + fibrate

Up to half of the patients with PBC and inadequate response to UDCA will fail to achieve an appropriate biochemical response after the addition of second-line therapy. A small real-world study in which OCA or fibrates were used as third-line therapy after dual therapy failure showed an OR of ALP normalization of 3.4 and a gain in ALP reduction of 22% per first year. Fibrates as the third-line therapy had a slightly greater effect on ALP reduction than OCA.[113] Triple therapy for inadequate responders also proved to be effective in a retrospective cohort study from Spain that not only demonstrated statistically significant reductions in ALP ($p = 0.007$), GGT ($p = 0.02$), and ALT ($p = 0.04$) but also in the GLOBE score ($p = 0.04$). Confirmatory prospective clinical trials are needed to validate these results.[114]

Symptomatic management

Pruritus

Commercially available and investigational drugs used for the management of pruritus generally exert their action through different pathophysiologic targets that: (1) eliminate pruritogens from the enterohepatic circulation or alter their metabolism; (2) modulate the pruritus neural pathway, regulating central and peripheral endogenous opioid, serotonin, or non-specific nociceptive receptors; or (3) alter the itch perception.[115]

A systematic stepwise approach is currently recommended by medical societies. Skin moisturizers, emollients, and topical agents, such as camphor or menthol, are often the initial general measures recommended for mildly symptomatic patients due to their low cost and excellent safety profile although their efficacy is unproven.[11] Anion-exchange resins are considered first-line therapy for the management of cholestatic itch, with cholestyramine being the only compound FDA-approved for this indication. Cholestyramine is commonly started at a dose of 4-g PO daily and can be increased to a maximum of 16 g per day in divided doses as needed for symptomatic control. Cholestyramine should be taken at least 2–4 hours apart from other drugs—particularly UDCA—since it may prevent their absorption. Additional side effects include abdominal discomfort, bloating, and constipation.[116]

The use of fibrates to treat cholestatic itch has been proposed based on observational studies and the FITCH trial, in which 55% of bezafibrate-treated patients had more than a 50% reduction in the severity of pruritus as assessed by the visual analog scale.[117] Thus, where available, bezafibrate 400 mg/d could be used as a first-line treatment for itching. Evidence for fenofibrate in the treatment of itching is less robust.

Rifampin (150–300-mg PO BID), a pregnane X receptor agonist, enhances the rate of BA metabolism, increases the excretion of pruritogens, and decreases autotoxin levels. Small clinical trials and meta-analyses in children[118] and adults have demonstrated its efficacy at decreasing cholestatic itch,[119–121] and it is, therefore, considered a second-line treatment option in those who have failed anion-exchange resins. Although rifampin is commonly associated with minor elevation of transaminases, severe hepatitis is rare, and liver biochemistries monitoring is recommended during the first few weeks of treatment and following dose up-titration.[122] Patients should also be reminded about the benign orange-red discoloration of bodily fluids that result from the medication and its metabolites.

Endogenous opioids activate inhibitory neurons within the dorsal horn of the spinal cord that modulate the pruritic stimuli. The type of receptor activated is crucial since μ-opioid receptors (MORs) induce itch, whereas stimulation of κ-opioid receptors (KORs) inhibits it.[116] Naltrexone (25–50-mg QD) is a MORs blocker that has shown antipruritic properties in small clinical trials[123,124] and can be attempted when other treatments have failed. Although naltrexone has shown a significant reduction in cholestatic itch, the magnitude of this effect may be lower than that of rifampicin.[125] About 40% of patients on naltrexone experience adverse events with opioid-like withdrawal symptoms being the most common (32%) followed by recurrence of previous pain syndromes (4%).[126,127] Naloxone, another MORs blocker, is only available in the intravenous formulation and has been previously used as induction in selected hospitalized patients before transitioning to oral naltrexone.[128] Nalfurafine is a KORs agonist only commercially available in Asia.[129] Butorphanol is unique given its dual effect of blocking MORs while simultaneously activating KORs. A small case-series showed itch reduction in about two-thirds of the patients on this drug, and although it was safe overall, some patients experienced somnolence and sedation.[130]

Some selective serotonin receptor inhibitors (SSRI), such as sertraline (50–100-mg QD), modulate afferent itch stimuli, proving to have antipruritic properties in several patients in addition to the therapeutic antidepressant and mood stabilizer

properties that characterize this class of medications.[131] Like other SSRIs, side effects with the use of sertraline include decreased libido, restlessness, and insomnia.[132]

Other experimental (nonpharmacologic) treatments, such as plasmapheresis,[133] phototherapy,[134] nasobiliary drainage,[135] and molecular absorbent recirculating system (MARS),[136] are available as well, but their use is exclusively reserved for refractory cases.

Fatigue

Although fatigue is extremely common among patients with PBC, its pathophysiology remains largely unknown, and therefore, the development of effective treatments is hindered by the lack of specific biologic targets.[137]

Medications including antidepressants, such as fluoxetine, and stimulants, such as modafinil, have been shown to be ineffective for the treatment of fatigue in PBC[138–141] although modafinil could be considered in patients with associated increased daytime somnolence or other sleep disorders. Clinical outcomes from the BEZURSO trial showed a 28% fatigue reduction with the use of bezafibrate by a self-reported scale.[105] This finding requires further validation with prospective placebo-controlled studies utilizing standardized fatigue scales. LT has been shown to improve fatigue to a certain degree, but more than half of the patients continue to report this symptom even after years post-transplantation.[142]

In clinical practice, the management of fatigue is mainly based on evaluating and treating potential contributing causes, such as anemia, sleep apnea, hypothyroidism, depression, and medications. Since pruritus is most common during the evening and at nighttime, effectively treating it to ensure restful sleep is highly recommended. Maintenance of physical activity and lifestyle changes, such as the development of coping strategies, like introducing rest periods during the day, and avoiding social isolation are also of paramount importance.[143]

Sicca syndrome

SS is highly prevalent among PBC patients with data showing a variable prevalence of up to 66% depending on the population studied and the methodology utilized. Since Anti-Ro (SS-A) and anti-La (SS-B) antibodies preferentially affect exocrine glands, patients usually report eye and mouth dryness.[144] Artificial tears and saliva substitutes are considered the preferred initial treatment given their safety and low cost. Xylitol or sorbitol containing sugar-free mints or gum also increases salivary flow in mild cases.[10] For moderate to severe keratoconjunctivitis sicca, comanagement with an ophthalmologist is advised, and medications such as topical cyclosporine or lifitegrast have proven to be beneficial.[145] Severe xerostomia cases can be treated with oral pilocarpine or cevimeline, and patients should be reminded about receiving frequent dental checkups and optimal oral hygiene.[22]

Novel therapies

Several new drugs with diverse pharmacologic targets are currently at different stages of clinical development. These include novel PPAR agonists, nicotinamide-adenine dinucleotide phosphate oxidase (NOX) isoform 1/4 inhibitors, and ileal bile acid transporter (IBAT) inhibitors, among others.

Seladelpar is a PPARδ agonist that showed a significant dose-dependent improvement in biochemical markers of cholestasis persisting during the 52-week study period, with composite response (ALP $< 1.67\times$ULN, $\geq$ 15% ALP decrease, and normal total bilirubin) rates of 53% and 67%, and ALP normalization rates of 13% and 33% in the seladelpar 5- and 10-mg/d arms, respectively.[146] Patients on seladelpar also experienced an improvement in self-reported pruritus, sleep disturbance, and fatigue after 1 year although this was not a placebo-controlled trial.[147] Similarly, elafibranor, a dual PPARα/δ agonist, reduced ALP in patients with inadequate response to UDCA by a mean of 48.3% in those treated with 80 mg and by 40.6% in those treated with 120 mg daily. The composite endpoint was achieved by 67% of patients receiving elafibranor 80 mg/d and 79% of patients in the elafibranor 120-mg/d group.[148] Saroglitazar, a dual PPAR α/γ agonist, showed a meaningful ALP reduction of 49% and 51% at week 16 in a phase II proof-of-concept trial using 4 and 2 mg of the medication, respectively. Both seladelpar and elafibranor are being evaluated in phase III studies (NCT03301506) (NCT04526665), whereas saroglitazar is undergoing a phase IIb/III trial (NCT05133336).

Setanaxib is a selective NOX isoform 1 and 4 inhibitor. NOX has been implicated in fibrogenesis and cholestasis. PBC patients with inadequate response to UDCA and high-risk disease (LSM $>$ 9.6 kPa at baseline) had liver stiffness reduction (22%) along with improvement of GGT (32.4%) and ALP (24.3%) after 24 weeks of treatment with setanaxib 400 mg twice per day.[149,150]. A phase II/III trial is currently underway (NCT05014672).

Novel drugs for the management of cholestatic itch have also shown promising results, with IBAT inhibitors such as maralixibat and odevixibat receiving FDA approval in 2021 for the management of Alagille syndrome and progressive familial intrahepatic cholestasis–related pruritus, respectively.[151,152] Linerixibat, another IBAT inhibitor, is undergoing a phase III trial (NCT04167358) in patients with PBC after

demonstrating significant antipruritic properties in proof-of-concept and phase II studies.[153]

LIVER TRANSPLANTATION

LT is the only curative treatment for patients with PBC and associated end-stage liver disease.[154] Outcomes are excellent with 5-year post-LT mortality, retransplantation, and relisting rates of 8.2%, 14.6%, and 1.9%, respectively, in patients younger than 40 years old and 15.1%, 4.7%, and 1.5%, respectively, in older patients.[155] Fortunately, the proportion of waitlisted and transplanted patients has continued to decline steadily due to the early recognition of the disease and prompt initiation of UDCA as discussed.[156] Indications for LT in patients with PBC are analogous to LT indications for other chronic liver disorders. Patients with very severe refractory pruritus can be considered for transplantation with the caveat that no MELD exception point is granted for this particular indication due to inadequate evidence of increased risk of pretransplant mortality.

Disease recurrence after transplantation has been well documented. The frequency of post-transplant PBC is highly variable among studies (9%–61%) given their different methodologies, sample sizes, and follow-up times. In addition, no precise diagnostic criteria for recurrent disease have been validated, and clinicians rely mainly on histological findings for diagnosis. AMA remains detectable in all patients with a previous diagnosis of AMA-positive PBC, and therefore, it has no utility in diagnosing post-transplant PBC recurrence.[157,158] Prophylactic utilization of UDCA has been shown in retrospective studies to be associated with reduced disease recurrence, all-cause mortality, liver-related mortality, and graft loss.[159] The use of UDCA to prevent PBC recurrence after transplant has not been studied prospectively.

Summary and future directions

Although relatively rare, PBC is a well-known cause of chronic liver disease with devastating consequences if left unrecognized. Clinical outcomes not only depend on inherent phenotypic differences, but it is primarily the result of modifiable factors, particularly access to care and the prompt recognition of the disease with early treatment initiation. Contemporary population–based studies have shown a greater incidence and prevalence among males and racial minorities than historically documented, and these groups tend to have a more aggressive disease course than the one classically experienced by White females. Health care providers should be aware of this and appropriately screen patients with chronic cholestasis, whether symptomatic or not.

UDCA continues to be the treatment of choice for PBC. Practitioners should aim for ALP normalization or near-normalization with the understanding that this may not be possible in all cases. Inadequate responders after 1 year of treatment with UDCA should be considered for second-line therapy or clinical trial participation. OCA should be used with caution in patients with cirrhosis and avoided in patients with decompensated disease or evidence of portal hypertension. Patients at high risk for inadequate response to UDCA may also benefit from earlier initiation of adjunctive therapy. A holistic clinical approach to patients with PBC must include the periodic assessment and treatment of symptoms such as fatigue, pruritus, and sicca syndrome, given their association with impaired quality of life, the management of other comorbidities, such as bone disease and vitamin deficiencies, and appropriate health maintenance, including immunizations for HAV and HBV.

CONFLICTS OF INTEREST

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