A Practical Review of Primary Biliary Cholangitis for the Gastroenterologist

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Abstract: Primary biliary cholangitis (PBC) is an autoimmune chronic cholestatic liver disease characterized by biliary destruction and progressive intrahepatic cholestasis. PBC primarily affects women in their fifth or sixth decade of life. Although many patients are asymptomatic at presentation, fatigue, pruritus, sicca syndrome, and upper abdominal discomfort are common symptom manifestations. The etiology of PBC is thought to be related to interactions between underlying genetic predisposition and microbial and xenobiotic environmental triggers. The diagnosis is established in the setting of biochemical cholestasis and antimitochondrial or disease-specific antinuclear antibodies, with histologic evidence of nonsuppurative granulomatous cholangitis being supportive, but not required, to confirm disease. Care of patients with PBC encompasses therapies to slow disease progression, manage symptoms associated with cholestasis, and treat complications of advanced liver disease. Risk stratification based on simple clinical and laboratory parameters, either as binary response criteria and/or continuous models, helps identify the patients at greatest risk of poor outcome. First-line therapy to slow disease progression is ursodeoxycholic acid (UDCA), which is the mainstay of pharmacologic therapy for all patients with PBC. The only currently approved second-line option for patients who do not achieve adequate biochemical response or are intolerant to UDCA is the novel farnesoid X receptor agonist obeticholic acid. Off-label use of peroxisome proliferator-activated receptor agonists, including the fibrate class of drugs where available, is also recognized as an option for patients.

Primary biliary cholangitis (PBC), previously known as primary biliary cirrhosis,[1] is an autoimmune cholestatic liver disease that predominantly affects middle-aged women and has variable worldwide incidence.[2,3] It is characterized by circulating antimitochondrial antibodies (AMAs) and selective destruction of intrahepatic cholangiocytes, leading to cholestasis and characteristic liver histology.[4] The disease has a chronic and often progressive

course, ultimately resulting in end-stage liver disease and its associated complications in a subset of patients.[2,5] Over the past decades, advances in the understanding of the pathophysiology of the disease, epidemiologic trends, and risk stratification have led to improved outcomes and novel treatment options for patients at highest risk of progressive disease. This article examines the current knowledge of PBC and approach to comprehensive care of patients.

Epidemiology

PBC most often affects middle-aged women with a strong female preponderance of up to 10:1, although some recent research suggests an increasing male prevalence.[6] The female predominance of PBC remains unexplained,[7] but it is presumed that there are poorly characterized epigenetic phenomena relevant to a skewed sex and age distribution of disease. Intriguingly, the disease rarely, if ever, affects children.[3] The reported annual incidence and prevalence rates vary worldwide and range from 0.3 to 5.8 and 1.9 to 40.2 per 100,000 individuals, respectively.[6] Epidemiologic shifts have been suggested with data from a large internationally representative cohort of 4805 PBC patients diagnosed between 1970 and 2014 demonstrating a trend toward older age and milder disease stage at diagnosis in recent decades.[8] These observed trends might be explained by an increase in routine testing of serum liver tests, greater physician awareness, and/or changing environmental triggers.[8]

Risk Factors and Pathogenesis

Disease is thought to arise in the background of genetic predisposition after exposure to an as-of-yet undefined environmental trigger.[9] Several large-scale epidemiologic studies have been performed that support an association with urinary tract infections (caused by *Escherichia coli*, *Mycobacterium gordonae*, or *Novosphingobium aromaticivorans*), reproductive hormone replacement, nail polish, hair dyes, past cigarette smoking, and toxic waste sites as environmental triggers associated with disease onset.[9,10] Research on induced mouse models using microbes and xenobiotics further supports environmental agents as important disease triggers.[5] Genetic susceptibility plays a key role, as emphasized by the numerous disease-associated risk loci identified by genome-wide association studies and the increased familial risk of disease. The human leukocyte antigen (HLA) locus has consistently demonstrated the strongest disease association in genetic efforts. Among the non-HLA risk loci associated with disease, the interleukin-12 axis, which plays an important role in immune regulation, has demonstrated consistent association with disease.[4]

Pathogenesis encompasses a dysregulated innate and adaptive immune insult against mitochondrial antigens within biliary epithelial cells (BECs), triggering perpetual immunologic and cholestatic injury resulting in the clinical manifestations of progressive cholestasis and fibrosis. Loss of immunologic tolerance to the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2)[11] is characteristic of the disease and triggers the activation and recruitment of autoreactive T and B cells along with production of circulating AMAs, the serologic hallmark of the disease. Despite the ubiquitous nature of the mitochondrial autoantigen, targeted biliary injury may be related to aberrant modification of PDC-E2 within apoptotic biliary epithelia, leaving the antigenic epitope immunologically preserved within an apoptotic bleb, and, thereby, recognizable by circulating AMAs. The interface between immunologic and cholestatic injury may exist at the surface of BECs through disruption of the biliary bicarbonate umbrella, critical in maintaining integrity of BECs. Anion exchanger 2 (AE2) is the primary chloride/bicarbonate exchanger on cholangiocytes and is essential for secretion and maintenance of a bicarbonate-rich layer on the cell surface of BECs, providing essential epithelial protection from toxic hydrophobic bile acids. Disruption of this protective layer via dysfunctional AE2 allows invasion of hydrophobic bile acid monomers.[12] Cholangiocytes insulted by hydrophobic bile acids are sensitized to apoptosis, and hydrophobic bile acids induce reactive oxygen species and BEC senescence, further propagating bile duct injury.[13]

Clinical Presentation and Diagnosis

Symptoms, Signs, and Disease Associations

The most common clinical symptoms associated with PBC are fatigue (present in up to 80% of patients) and pruritus (reported in 40%-80% of patients),[14,15] but many patients are asymptomatic at first presentation.[16] Fatigue may fluctuate independently of disease activity or stage,[15] is not alleviated by therapy with ursodeoxycholic acid (UDCA), and often persists after liver transplantation.[17] Pruritus can be severe and disabling, and is associated with a poor quality of life.[18] Other associated features of PBC include sicca syndrome (dry eyes/dry mouth), abdominal discomfort, depression, anxiety, and sleep disturbance.[14] Cholestasis also affects lipid metabolism, which may manifest clinically with xanthoma, xanthelasma, and high cholesterol levels. Because high-density lipoprotein cholesterol is disproportionately elevated compared with low-density lipoprotein cholesterol, patients are not thought to be at increased cardiovascular risk.[19] Low bone mass

is another extrahepatic concern, mainly in patients with advanced PBC.[20] Associated autoimmune conditions are also frequently encountered, with the most common being primary Sjogren syndrome, thyroid disease, celiac disease, and systemic sclerosis.[21]

Biochemical Abnormalities

Biochemical cholestasis measured by an abnormal serum alkaline phosphatase (ALP) level is the most typical abnormality noted, although mildly elevated serum aminotransferase levels (reflective of lobular necroinflammation) and increased immunoglobulin (Ig) concentrations (particularly IgM) are also frequently seen.[22,23] Hyperbilirubinemia is a late manifestation, and significant elevations are suggestive of advanced disease. When occurring alongside a falling platelet count, reduced albumin concentration, and elevated international normalized ratio, clinically significant cirrhosis and portal hypertension are certain.[2]

Diagnostic Criteria

The diagnosis of PBC can be established if 2 of 3 objective criteria are present: positive AMA serologic testing; persistent unexplained biochemical cholestasis, defined as an abnormal ALP level over 24 weeks; and/or compatible liver histology, specifically nonsuppurative cholangitis and interlobular bile duct injury (Figure).[2,5] Confidence in an accurate diagnosis is critical to allow prompt initiation of effective therapy and timely identification of patients at risk of progressive disease.

Antimitochondrial Antibody and Other Autoantibodies

AMA reactivity was first described in 1965[24] and is observed in more than 90% of patients with PBC.[25] AMAs are highly sensitive and specific for PBC in the context of unexplained chronic cholestasis, although they can be found in 0.1% of the general population.[26] Among patients with associated autoimmune disease, a high risk (up to 80%) of developing overt disease has been demonstrated in AMA-positive subjects without biochemical cholestasis, whereas lower rates of overt disease are seen in AMA-positive first-degree relatives.[27-29] Among the general population with positive AMAs, only 1 patient of every 6 with AMA positivity and normal ALP levels developed PBC within 5 years in a recent French study.[30] Approximately 10% to 15% of patients have AMA-negative disease.[31] When AMAs are not readily detectable, disease-specific antinuclear antibodies (ANAs) can be found in 50% of PBC patients.[32] In the correct context, a diagnosis of AMA-negative PBC can be confidently made in patients with cholestasis and specific ANAs by immunofluorescence patterns (nuclear dots or perinuclear rims) or PBC-specific ANAs, including anti-sp100 or anti-gp210.[2,33] In addition to being disease-specific, the presence of anti-gp210 has been associated with more severe disease.[34]

Imaging

There are no structural abnormalities caused by PBC that would be expected on imaging in its early stage; however, it is recommended that patients with suspected PBC should have an abdominal ultrasound to rule out extrahepatic biliary obstruction as an alternative cause of cholestasis.[2] Magnetic resonance (MR) cholangiography is not routinely needed in diagnosing PBC, as the biliary injury is targeted to small bile ducts. Abdominal and periportal lymphadenopathy is observed in up to 88% of all histologic stages, is generally reactive, and is not associated with a malignant process.[35]

Liver Biopsy

Histology is not necessary to confirm the diagnosis of PBC, although liver biopsy is indicated when PBC-specific antibodies are absent or when coexistent autoimmune hepatitis (AIH) or nonalcoholic steatohepatitis is suspected.[2] Histopathologic evaluation should be correlated with clinical and immunologic features, given the patchy nature of PBC and while acknowledging that, in early-stage disease, characteristic features may be absent.[36] Histologic features of PBC include nonsuppurative granulomatous lymphocytic cholangitis affecting interlobular and septal bile ducts (florid duct lesions) leading to progressive bile duct loss (ductopenia), chronic cholestasis, fibrosis, and cirrhosis. Other features include lymphocytic interface activity with or without parenchymal necroinflammation (although this does not necessarily imply an overlap syndrome) and nodular regenerative hyperplasia.[37] Staging systems commonly used in assessing disease severity include those described by Scheuer[38] and Ludwig and colleagues.[39] Both systems divide the histologic injury of PBC into 4 stages: florid duct lesions and portal inflammation without interface activity (stage 1); interface hepatitis, ductular proliferation, and periportal fibrosis (stage 2); bridging necrosis or bridging fibrosis (stage 3); and cirrhosis (stage 4).[37] A more recent staging system described by Nakanuma and colleagues uses fibrosis, bile duct loss, and severity of chronic cholestasis based on orcein-positive granules to assess disease progression.[40]

Noninvasive Assessment of Liver Fibrosis

Several noninvasive biomarkers have been studied to predict liver fibrosis in PBC. The Aspartate Aminotransferase (AST) to Platelet Ratio Index score, Fibrosis-4 score (which includes the AST/alanine aminotransferase [ALT] ratio, platelet count, and age), Enhanced Liver Fibrosis

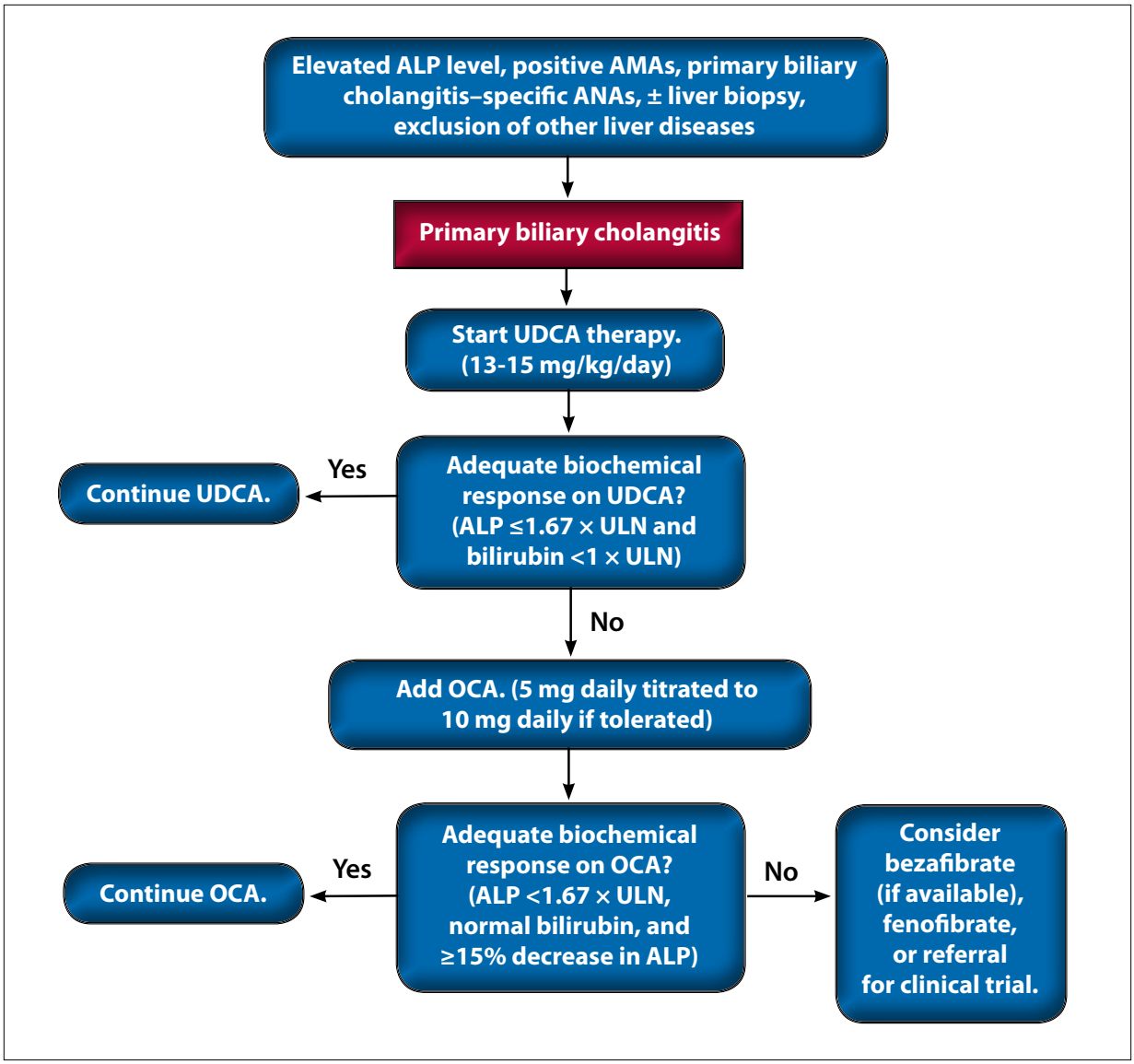

Figure. A flow chart of treatment decisions for patients with primary biliary cholangitis. UDCA is generally a lifelong therapy. Biochemical treatment response is usually determined after 6 to 12 months of UDCA. Patient stratification includes evaluation of disease stage at baseline and over follow-up. Adjunctive treatment for incomplete responders consists of OCA as the first option, with bezafibrate and clinical trials as alternatives. Fenofibrate, a distinct but related fibrate, is considered by some as an alternative to bezafibrate, although use of the fibrate class of drugs remains off-label. The stage of disease is important for safe prescribing of all therapies and the institution of appropriate surveillance in cirrhotic patients. Symptom management should parallel primary disease-modifying therapy.

ALP, alkaline phosphatase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; OCA, obeticholic acid; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

score (which includes hyaluronic acid, tissue inhibitor of metalloproteinase 1, and amino-terminal propeptide of type III procollagen), and Bilirubin-Hyaluronic index are easy to use but lack sensitivity and reproducibility in individuals with early-stage disease, although these tools can be predictors of adverse outcomes, independent of UDCA response.[41] Vibration-controlled transient elastography (VCTE), acoustic radiation force impulse, and MR elastography are additional diagnostic tools for the assessment of liver fibrosis, with VCTE having the highest

diagnostic accuracy in PBC.[42-44] Liver stiffness has been reported to correlate best with fibrosis stage; a liver stiffness of greater than 9.6 kPa is associated with a 5-fold increased risk of liver-related decompensation, transplant, or death, and increasing liver stiffness over time may be an even stronger predictor of outcome, suggesting that liver stiffness may be an important surrogate of disease progression.[42] The routine use of VCTE and serum biomarkers includes acknowledging confounding factors that may influence the results (presence of ascites, obesity, fasting time <3 hours).[44]

Risk Stratification

PBC is uncommon and slowly progressive, yet a significant proportion of patients are at risk of developing advanced disease with its associated complications. Identifying patients at highest risk of poor outcomes has historically relied largely on binary response criteria, originally developed to establish biochemical response to UDCA and consequently predict long-term transplant-free survival. These criteria, which include the Rotterdam, Barcelona, Paris I and II, and Toronto criteria, identify patients who achieve acceptable response to UDCA therapy and consequently have an expected transplant-free survival similar to an age-matched control population, as compared with patients who are suboptimal responders and are, therefore, inherently at high risk.[45] Treatment response is determined after 1 year of therapy with UDCA, although clinical outcomes may be delayed several years or even decades from this determination. Thus, identifying reliable surrogate predictors of prognosis early in the disease course is an essential step in distinguishing patients most in need of additional treatment options and to facilitate recruitment into clinical trials to expand the available therapeutic options for this at-risk cohort. Large-scale international efforts have confirmed both ALP and bilirubin values to be well-established independent surrogates of prognosis in PBC, with lower values of ALP and normal bilirubin being associated with lower risk for death or liver transplantation in patients with PBC independently of UDCA therapy and follow-up time.[46] In early-stage disease, having an ALP level less than 1.5 times the upper limit of normal (ULN) and a normal bilirubin level is associated with a prognosis equal to that of a healthy control population; furthermore, it has been recently suggested that a bilirubin level below the ULN may be associated with further improved outcomes even within the normal range of bilirubin values.[46] The GLOBE score[47] and UK-PBC risk score[48] are more recent continuous models that have demonstrated high specificity and sensitivity for predicting transplant-free survival up to 10 to 15 years and may be useful to determine the need for novel adjunctive agents.

Treatment of Primary Biliary Cholangitis

The management of patients with PBC encompasses therapies to slow disease progression (first- and second-line treatments) and therapies to control symptoms associated with chronic cholestasis (Table). Treating complications of advanced liver disease is also part of the care of these patients.

First-Line Therapy

Ursodeoxycholic Acid UDCA is a posttranscriptional secretagogue that stimulates the transfer of transport proteins and channels into their target membranes via potent posttranscriptional signalling.[49] UDCA has multiple proposed mechanisms of action, including the protection of cholangiocytes and periportal hepatocytes from the cytotoxic effects of hydrophobic bile acids, stimulation of secretion of hydrophobic bile acids, and hepatocyte protection against bile acid–induced apoptosis.[50,51] The European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) recommend oral UDCA 13 to 15 mg/kg per day for all patients with PBC either as a single daily dose or in divided doses if tolerability is an issue.[2,5] UDCA is safe with minimal side effects (weight gain in the first 12 months, hair loss, and, rarely, gastrointestinal upset), and is safe in pregnancy.[36] The clinical efficacy of UDCA is clear and characterized by improvement in biochemical parameters, slowing of histologic progression, and improvement in overall survival, particularly in patients treated in the early stages of the disease.[52] A large meta-analysis demonstrated improved 5-, 10-, and 15-year transplant-free survival in treated patients (90%, 78%, and 66%, respectively) compared with untreated patients (70%, 59%, and 32%, respectively), and transplant-free survival was significantly higher in patients with moderate to severe disease who were treated for 4 years with UDCA (relative risk, 1.9; 95% CI, 1.3-2.8).[53] However, although UDCA is clearly beneficial, approximately 40% of patients show suboptimal biochemical response to therapy and remain at risk for progression.[54]

Second-Line Therapy

Obeticholic Acid In patients intolerant of UDCA or who do not achieve an adequate biochemical response, second-line therapy is available and should be considered. Obeticholic acid (OCA; Ocaliva, Intercept) is a synthetic variant of the natural bile acid chenodeoxycholic acid and is a potent activator of the nuclear farnesoid X

Table. Disease- and Symptom-Directed Therapies in Patients With PBC

Therapy and Dose	Indication	Mechanism	Adverse Effect(s)	Consideration(s)
Disease-Directed Therapy				
First-Line Therapy				
UDCA 13-15 mg/kg/day	All PBC patients	Posttranscriptional secretagogue	Minimal weight gain in the first year, thinning of hair, abdominal discomfort	Confirm biochemical response to UDCA (eg, scoring systems such as ALP ≤1.67 × ULN ± normal bilirubin).
Approved Second-Line Therapy				
Obeticholic acid 5 mg daily titrated to 10 mg daily if tolerated	Patients with inadequate response or intolerance to UDCA	Semisynthetic FXR agonist	Pruritus	Dose adjustment required in advanced liver disease (Child-Pugh B or C)
Off-Label Second-Line Therapy				
Bezafibrate 400 mg daily	Patients with inadequate response to UDCA	Pan-PPAR agonist (alpha, gamma, and delta)	Hepatotoxicity, rhabdomyolysis, increased creatinine	RCT data available; currently off-label; not available in the United States currently
Fenofibrate variable dose 100-200 mg daily	Patients with inadequate response to UDCA	PPAR-alpha synthetic agonist	Hepatotoxicity, rhabdomyolysis, increased creatinine	RCT data unavailable
Symptom-Directed Therapy				
Cholestyramine 4-12 g daily	Pruritus	Bile acid nonabsorbable resin	Constipation, diarrhea, bloating	First-line agent; administer 2-4 hours before or after other medications
Rifampicin 150-300 mg daily	Pruritus	Pregnane X receptor agonist	Drug-induced liver injury, hemolysis, discoloration of bodily fluids	Second-line agent; monitor liver tests and CBC
Naltrexone up to 12.5-50.0 mg daily	Pruritus	Opiate antagonist	Withdrawal reactions, nausea, headache	Third-line agent; monitor long-term tolerability
Sertraline 75-100 mg daily	Pruritus	Selective serotonin reuptake inhibitor	Dizziness, loose stools, insomnia	Requires further investigation
Gabapentin 300-3600 mg daily	Pruritus	Antiepileptic drug; increases the threshold of nociception	Sedation; rarely pancitopenia, cholestasis, dyskinesia	Taper for discontinuation to avoid withdrawal reactions.

ALP, alkaline phosphatase; CBC, complete blood count; FXR, farnesoid X receptor; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; RCT, randomized, controlled trial; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

receptor.[55] In addition to its choleretic properties, OCA has anti-inflammatory and antifibrotic properties.[56] In 2016, OCA was approved by the US Food and Drug Administration for use in combination with UDCA in patients with incomplete UDCA response or as monotherapy in treatment-intolerant patients based on results from a phase 3 trial in which subjects were randomized to UDCA plus placebo, a titration arm of UDCA with OCA 5 to 10 mg, or UDCA with 10 mg of OCA daily. The prespecified primary endpoint—a reduction in ALP level to less than 1.67 times the ULN, a reduction in ALP level from baseline by at least 15%, and a normal bilirubin level after 1 year of therapy—was met in 10%, 46%, and 47% of subjects, respectively.[56] Importantly, only 20% of included patients were cirrhotic. In patients with noncirrhotic or compensated Child-Pugh A disease, the recommended starting dose of OCA is 5 mg daily, and treatment is titrated by response and tolerability at 3 to 6 months to 10 mg daily. Data for use in patients with advanced disease (Child-Pugh B or C) are limited,

and OCA should be reserved for use in clinical trials or in specialized centers. As a result of serious liver adverse events reported by the US Food and Drug Administration in patients with advanced liver disease (Child-Pugh B or C), clinicians should be cautious and dose OCA carefully and in accordance with the drug label, which specifies dose reduction in this setting. In advanced disease, the starting dose should be decreased to 5 mg weekly, with a maximum dose of 10 mg twice weekly. If decompensating events occur, the agent should be discontinued, and referral for assessment of liver transplantation should be considered. Pruritus was the most common adverse event prompting discontinuation of therapy and was dose-dependent. A decrease in serum high-density lipoprotein and triglyceride levels was also noted, although an increase in cardiovascular events has not been identified.[56,57] If pruritus develops, it can be effectively managed with a stepwise pharmacologic approach with or without including a drug holiday to allow time to escalate the initiation of antipruritogens. Initial therapy should include traditional bile acid sequestrants such as cholestyramine with alternative options including rifampicin.

Fibrates Fibrates are considered as therapeutic agents because of their potential ability to decrease bile acid synthesis and bile acid–related hepatic inflammation.[58] Their anticholestatic effects are mediated through the peroxisome proliferator-activated receptor signalling axis, which is involved in the regulation of bile acid synthesis, transport, and detoxification.[57] Small pilot studies have reported on the use of fenofibrate (100-200 mg daily) and bezafibrate (400 mg daily) off-label and have shown improvement of liver biochemistries, liver stiffness measurements, and pruritus in PBC patients.[59-62] In a recent phase 3, randomized, placebo-controlled trial, 100 PBC patients who did not meet Paris II criteria after 1 year of UDCA therapy were randomized to receive bezafibrate 400 mg daily or placebo for 2 years in addition to UDCA. The researchers found normalization of bilirubin, ALP, AST, ALT, albumin, and prothrombin time in 30% of the bezafibrate group compared with 0% of the placebo group.[63] The main concerns related to fibrates include hepatotoxicity, elevations in serum creatinine, and muscle injury, and, to date, their use remains off-label. As with OCA, few patients with cirrhosis have been included in controlled trials, and clinical benefit is reflected in improvement in surrogates of prognosis with little available data demonstrating objective improvements in liver-related death or transplant-free survival. Furthermore, while bezafibrate is accessible in most countries globally, it is currently unavailable in the United States.

Autoimmune Hepatitis–Primary Biliary Cholangitis Overlap Syndrome

Approximately 8% to 10% of PBC patients may develop so-called overlap syndrome manifesting with clinical, biochemical, serologic, and/or histologic features of AIH in addition to the cholestatic component of PBC.[64] There is no consensus on whether 2 distinct diseases coexist in one patient or whether they represent a variant form of either disease; however, the latter seems to be the most appropriate because a predominating phenotype can be identified in the majority of cases.[65] AIH-PBC overlap syndrome should be suspected when patients do not respond adequately to standard UDCA treatment or when the course of disease deviates from the expected, including a sudden increase of transaminases or deterioration of liver function.[65] According to the Paris criteria, the diagnosis of this syndrome can be considered when patients with PBC present with 2 of the following 3 features: an ALT level greater than 5 times the ULN; IgG serum levels greater than 2 times the ULN or smooth muscle autoantibody positivity; and moderate or severe interface hepatitis on histology. However, importantly, a liver biopsy is mandatory to make this diagnosis.[66] If the diagnosis can be made confidently, treatment aimed at both diseases per the current guidelines should be used, in this case with immunosuppressive therapy in addition to UDCA. Drug selection (eg, predniso[lo]ne, budesonide, or azathioprine) and monitoring should follow the guidelines for AIH.[67] It must be recognized that AIH-PBC is rare, and the distinction between inflammatory, high-risk PBC and true overlap should be carefully considered to avoid overdiagnosis and treatment. In the case of high-risk PBC, immunosuppressive therapy is unlikely to be of benefit, and second-line therapies targeting PBC should be the preferred pharmacologic approach

Management of Symptoms of Chronic Cholestasis

Pruritus

Pruritus can occur at any stage of disease[68] and can impair quality of life. Nonpharmacologic recommendations—including the use of emollients and oatmeal extract to improve dry and inflamed skin, use of cold water instead of hot baths that might trigger pruritus, exclusion of other allergens, and psychological evaluation for patients with scratching dependence—should be incorporated into guidance to patients.[2] The specific cause of pruritus remains poorly understood, although transmembrane G protein-coupled receptor 5 agonism may play a role, and inhibition of the enterocyte apical sodium-dependent bile acid transporter can improve pruritus. Stepwise pharmacologic therapy should be prescribed in symptomatic patients

starting with a bile acid nonabsorbable resin such as cholestyramine administered 2 to 4 hours before or after other medications, as it interferes with intestinal absorption.[69] Rifampicin is a second-line agent that acts as a pregnane X receptor agonist and is associated with improvement in pruritus.[70] Patients treated with rifampicin should be monitored with liver tests and complete blood counts every 2 to 4 weeks after initiation to assess for drug-induced liver injury and hemolysis.[71] Reported rates of drug injury with rifampicin vary between 5% and 13% in the literature, but given its efficacy in symptom benefit, with close monitoring it is an appropriate second-line option. Third-line agents are oral opiate antagonists such as naltrexone, which can reduce the sensation of itching.[72] The main concerns are related to withdrawal-like reactions and long-term tolerability.[73] Gabapentin and sertraline are clinically useful options based on expert opinion, although robust data supporting their efficacy are lacking. Salvage options, including ultraviolet light and plasmapheresis, can also be considered in patients with refractory symptoms.

Fatigue

Fatigue is not related to the severity of liver disease,[74] is not responsive to medical therapy, and can persist after liver transplantation.[75] Secondary causes should be ruled out, including anemia, hypothyroidism, depression, obstructive sleep apnea, and polypharmacy. Some strategies used to improve fatigue include energy management (scheduled tasks), graded exercise, physiotherapy, and occupational therapy.[76]

Sicca Syndrome

Patients with dry eyes and dry mouth can benefit from artificial tears and saliva. Pilocarpine and cevimeline (muscarinic receptor agonists) can be considered to stimulate tear production if symptoms are refractory, except in cases of glaucoma and asthma.[77] Proper oral hygiene is important to prevent the development of dental caries in patients with xerostomia.[77] Refractory cases (including vaginal dryness and severe xerostomia) should be referred for specialist management.[76] Given the high incidence of comorbid autoimmune diseases in PBC, disease-specific antibodies for Sjogren syndrome, including anti-Ro and anti-La, may be checked. If these antibodies are detected, a rheumatology review may be warranted to evaluate the multisystemic manifestations associated with primary Sjogren syndrome.

Management of Complications of Primary Biliary Cholangitis

Osteoporosis

Low bone mass and osteoporosis are common in PBC and are associated with an increased risk of fractures.[78] Age and severity of the disease, but not menopausal status, are the main risk factors for osteoporosis in women with PBC.[79] Bone mineral densitometry should be performed in all PBC patients at diagnosis along with general bone fracture risk evaluation, and monitoring should be done according to risk. Management with dietary calcium, vitamin D supplementation, and weight bearing exercise per the current guidelines is important for most patients.[2,5] Disease-specific management of bone loss in PBC patients is limited by an incomplete understanding of the pathophysiology specific to cholestatic liver disease[78]; however, antiresorptive therapy with bisphosphonates, especially weekly alendronate and monthly ibandronate, is effective in increasing bone mass in patients with PBC.[80]

Complications of Cirrhosis and Portal Hypertension

Variceal Bleeding

Portal hypertension may develop as a result of biliary cirrhosis or in early (precirrhotic) stages, including in association with nodular regenerative hyperplasia.[81] In the setting of cirrhosis, a platelet count less than 150,000/mm^3 and transient elastography values higher than 20 kPa can be used to determine the need for endoscopic surveillance.[82] The risk of variceal bleeding is significant once patients with PBC develop esophageal varices, with reports of 1- and 3-year risk of 33% and 41%, respectively.[83] Screening, prophylaxis, and management of acute variceal bleeding should follow the Baveno VI guidelines in a manner similar to other etiologies of chronic liver disease.[2]

Hepatocellular Carcinoma

The overall incidence of hepatocellular carcinoma (HCC) in patients with PBC is lower than other etiologies of liver disease at 3.4 cases per 1000 patient-years.[84,85] However, the development of HCC is a critical event, as it is associated with significantly poorer transplant-free and overall survival (hazard ratio, 22.61).[85,86] Potential risk factors for HCC include advanced age at PBC diagnosis, male sex, advanced biochemical and histologic disease, and inadequate biochemical response to UDCA.[85,87] EASL and AASLD guidelines recommend that all cirrhotic patients with PBC should undergo regular screening using ultrasound with or without alpha-fetoprotein at 6-month intervals.[2,5]

Liver Transplantation

Although PBC has declined as an indication for liver transplantation over the last several decades, the intervention remains highly effective in patients with decompensated liver disease, with 5-year survival rates greater than 80%.[88] Referral should be considered in patients with a

Model for End-Stage Liver Disease score of at least 15 and in patients whose bilirubin levels rise beyond 50 µmol/L, and can be contemplated in patients with refractory pruritus. However, the risk-benefit balance of transplantation solely for management of pruritus needs to be carefully considered.

Conclusion

The past decades have brought advances in the understanding of PBC's pathogenesis, epidemiology, and risk stratification (in particular, enhanced risk stratification for individuals), improving the ability of physicians to guide patients from diagnosis to treatment. The lifelong nature of this disease is better understood, and therapeutic options beyond UDCA have evolved to benefit patients. Unmet needs remain, particularly for patients with high-risk PBC and/or very symptomatic disease, but optimism persists that future drug therapies will ultimately tackle these components of disease with increasing efficacy.

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