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Review Article

Primary Biliary Cholangitis: A Review

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Abstract

Primary biliary cholangitis (PBC), which is formally known as primary biliary cirrhosis, is a progressive chronic cholestatic liver disease. Previous epidemiologic studies have demonstrated female predominance. Furthermore, the pathophysiology of PBC is multifactorial, and involves loss of immune tolerance to biliary epithelial cells, with interdependent biliary injury, cholestasis, and progressive liver fibrosis. Moreover, its progression to liver fibrosis highly varies among individuals, but most cases are indolent and slowly progressive. Over the past decade, research has provided great insight into personalized care for patients with PBC. Individualized care and early utilization of second- and third-line therapies have improved the outcomes, and decreased the progression of this disease. The present mini-review focus on providing an overview of PBC, including its pathophysiology, clinical presentation, treatment, treatment goals, recommended follow-up, and future research.

Introduction

Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic liver disease that predominantly affects the biliary system, leading to progressive liver injury and fibrosis. Chronic injury to biliary epithelial cells, with dysregulated and interacting immune and cholestatic pathobiology, would likely lead to fibrotic changes in the bile ducts and liver. Furthermore, it has been presumed that essential environmental triggers contribute to the disease pathophysiology and progression, which include infections that can cause immunogenetic risk, epigenetic regulation of the biliary epithelia, adaptive and innate immunity activation, and bile acid physiology across the gut-liver axis.[1] PBC remains as a great public health concern. The present review provides an overview of PBC, including its pathophysiology, clinical presentation, treatment, treatment goals, recommended follow-up, and future research.

Pathophysiology

The pathophysiology of PBC remains complex, and its development is considered to be affected by a number of genetic and environmental factors. The antimitochondrial antibody (AMA) is an antibody highly specific for PBC that targets the E2 component of the pyruvate dehydrogenase complex on mitochondrial membranes.[1] Researchers have proposed various explanations on why AMA specifically targets the mitochondria of biliary cells, when compared to other targets. One explanation highlights the unique mechanism of apoptosis in biliary epithelial cells.[2] Furthermore, the disruption of anion transporters and the bile acid synthesis pathway have been implicated in its disease progression. The targeting of the biliary epithelial cell mitochondria and loss of immune tolerance of biliary epithelial cells can lead to biliary duct injury, resultant cholestasis, and eventually, liver fibrosis. A strong genetic component in PBC has been suggested, in which studies have identified HLA allele associations and the higher concordance of the disease in monozygotic twins.[3] In addition, environmental factors, such as molecules that interact with lipoic acid (2-octynoic acid [in cosmetics and foods] and 2-nonyamide), have been associated with the PBC-like disease state in animal models.[4,5] Furthermore, repeated infections, such as *Escherichia coli* urinary tract infections, as well as smoking and physical environmental exposures to toxins, have also been associated with the development of PBC, and linked to both molecular mimicry and loss of immunologic tolerance.[6,7] The gut-liver axis is an area of active investigation, and pathogenesis of PBC, due to the close relationship between antigens and bio-flora from the gut, and the pathway to the liver, and resultant immune and cytotoxic interactions.[8]

Clinical presentation and diagnosis

PBC presents as a cholestatic liver disease that is typically progressive. Patients may present at any stage of the disease. However, features suggestive of PBC, including cholestatic elevations

Keywords: Primary biliary cholangitis; Cholestatic liver disease; Chronic liver disease.

Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; CP, child-pugh score; FDA, Federal Drug Administration; FXR, farnesoid x receptor; norUDCA, norusodeoxycholic acid; OCA, obeticholic acid; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator activator receptor; SSRI, selective serotonin reuptake inhibitor; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

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in liver tests, primarily alkaline phosphatase (ALP), for patients without alternatives, are likely etiologies of abnormal liver tests. Furthermore, transaminases, bilirubin and immunoglobulins may also be elevated.[9] Symptoms, such as pruritus and jaundice, would raise the suspicion for cholestasis, and fatigue is a common symptom that is more specific to PBC, and possibly correlated to the autoimmune action against mitochondria.[10] General symptoms of liver disease, such as hepatosplenomegaly, right upper quadrant discomfort, and the sequelae of cirrhosis, can also present as symptoms of PBC, particularly in the late stage of the disease. Present studies have estimated a 9:1 prevalence ratio for females-to-males with AMA positivity, and the average age at diagnosis is approximately 50 years old.[11] Overall, this data suggests that a typical epidemiologic patient with PBC would be a middle-aged woman, although this is certainly not exclusive. Other autoimmune disorders may also more frequently co-occur in patients with PBC, such as Sjogren's syndrome and Raynaud's phenomenon, which should be assessed based on history and laboratory tests.[12] Baseline testing at the time of diagnosis for hyperlipidemia, celiac disease, and thyroid studies may also be helpful. It is noteworthy that some studies have revealed that fatigue and pruritus at diagnosis may be associated with worse outcomes. In a cohort of 216 patients, Quarneti C *et al*. reported that symptomatic patients were significantly more often female (98.6% *vs.* 87.2%, $p = 0.004$) and younger in age (mean age: 49 ± 12 *vs.* 55 ± 12 years old, $p = 0.003$), and had more severe biochemical profiles, as indicated by the high ALP (mean: 2.93 ± 2.00 *vs.* 2.12, $p = 0.002$) and aminotransferase (mean: 1.92 ± 1.00 *vs.* 1.47 ± 1.27, $p = 0.014$) levels.[13] Furthermore, symptomatic patients were less likely to respond to ursodeoxycholic acid therapy (63% *vs.* 81%, $p = 0.006$), but more often developed cirrhosis and subsequent complications (31% *vs.* 13%, $p = 0.004$).[13]

The diagnosis hinges on the autoimmune elements of PBC that lead to biliary injury. A positive AMA test with a typical pattern of liver tests can often confirm the diagnosis, since AMA is positive in 90–95% of PBC cases.[14,15] In rare cases of AMA-negative PBC, other antibodies may be positive, such as anti-nuclear antibody (ANA), anti-gp210, anti-sp100, or antibodies against other mitochondrial components.[16] In the study conducted by Granito *et al*., the presence of anti-gp210 was proposed to be associated with worse prognosis and decreased response to ursodiol. However, multicenter studies are still needed.[17] In the same study, antigenic targets for PBC-specific ANA, including nuclear pore complex proteins (gp210 and nucleoporin p62), a nuclear membrane protein (lamin B receptor), and nuclear body components (Sp100, PML, Sp140 and SUMO), were also reported, and it was noted that these were sensitive and specific to the diagnosis of PBC.[17] Furthermore, the authors of that study proposed that this should be the next step in the diagnostic approach for PBC in patients with an unclear diagnosis.[17] There is also a variant overlap syndrome between PBC and autoimmune hepatitis (AIH), in which there may be histologic evidence of parenchymal hepatitis and necrosis, as well as a positive anti-smooth muscle antibody. Notably, biopsy is no longer necessary to make a diagnosis, although histologic findings suggestive of PBC include chronic nonsuppurative cholestasis with severe duct inflammation and necrosis. Imaging, such as magnetic resonance cholangiopancreatography, may be indicated when the diagnosis is uncertain in cholestatic patients. Elastography can be helpful to ascertain the stage of the fibrosis and disease. However, this is not necessary for making the diagnosis.

The prevalence of this disease is increasing worldwide, suggesting the likely earlier detection and diagnosis of this disease.[18] A number of patients positive for AMA may remain asymptomatic for a period of time, or even indefinitely. Studies have estimated that 36–89% of these patients would develop the disease within a 5–20-year timespan, with a median time-to-disease interval of six years.[19–21] From the time of diagnosis, PBC progresses both histologically and clinically, with an average progression of one stage of fibrosis every 1.5 years, although this progression highly varies.[22] Furthermore, the development of decompensated cirrhosis in a 5-year time span from diagnosis was estimated to be 15–25%.[20]

For subgroups of patients with AMA-negative PBC, further molecular tests may be useful. Results, such as serum antinuclear antibodies with "multiple nuclear dots" or "rim-like/membranous" patterns, in highly sensitive and specific tests are often detected by indirect immunofluorescence in patients with primary biliary cirrhosis.[23] A. Granito *et al*. reported that the specificity of these two antibody patterns for PBC was 99%. That is, the positive predictive value and likelihood ratio for a positive test was 86% (95% CI: 72.7–94) and 221 (95% CI: 91.7–544) for the multiple nuclear dot pattern, respectively, and 79% (95% CI: 62.2–90.1) and 132 (95% CI: 56.8–312.7) for the rim-like/membranous pattern, respectively, suggesting this test may be very helpful for patients without AMA positivity, but seeks a diagnosis.[23]

Management and goal of treatment

Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) remains as the first-line therapy for PBC. The mechanism of action for this medication is multifold, and includes anti-inflammatory, immune-modulatory, choleretic, and cytoprotective mechanisms.[1,2,7] The benefit of UDCA has been demonstrated in numerous studies, with improved liver biochemistry outcomes.[1–10] Studies with longer follow-up periods have also demonstrated improved survival.[1–7] UDCA is used at a dose of 13 mg/kg, and this can reach up to 15 mg/kg. Furthermore, UDCA may be split into a twice-daily dose (Table 1). Small studies and previous clinical experience have suggested better compliance when taking the entire dose at once prior to bedtime. Furthermore, multiple studies have revealed improved outcomes in symptoms, transplant free survival, and liver failure. In a large international meta-analysis conducted by Lammers *et al*., patients who were treated with UDCA had significantly improved transplant-free survival, when compared to non-treated patients (90% at 5-years, 78% at 10-years, and 66% at 15-years *vs.* 79%, 59% and 32%, respectively). That study included 4,845 patients. For patients treated with UDCA, it may take up to one year to determine the optimal therapeutic response that would manifest through the biochemical improvement in ALP and bilirubin.[1,2]

Obeticholic acid

Obeticholic acid (OCA) was approved by the US Food and Drug Administration (FDA) in 2016, and is used in conjunction with UDCA for patients who do not respond to UDCA therapy alone. The monotherapy with OCA was approved by the FDA for individuals who could not tolerate UDCA. OCA is a Farnesoid X receptor (FXR) agonist that is much stronger than its endogenous counterpart, chenodeoxycholic acid.[1] OCA activates FXR, which modulates bile acid synthesis, absorption, transport, secretion and metabolism. Collectively, this leads to choleresis (increased secretion of bile from the liver).[1,24] In animal models, FXR activation has demonstrated anti-fibrotic and anti-inflammatory properties.[1] The dose escalation approach has been utilized to determine the best response in patients with PBC, and the available doses are 5,

Table 1. Drug therapies for primary biliary cholangitis

Drug name	Dosing (optimal timing)	Side effects/ Contraindications	Benefits/Goal of treatment	Contraindications
UCDA	13 mg/kg to 15 mg/kg; May be split to twice-daily dose; Better compliance with once-daily QHS dose	Weight gain; Hair loss; Diarrhea	Multiple studies revealed biochemical improvement and improved transplant free survival; May take up to one year for optimal biochemical response	Hypersensitivity to UDCA; Complete bile duct obstruction
OCA	Available in 5–25 mg dose escalation; Daily to BID dose	Pruritus; Worsening decompensation in patients with CP-B, CP-C	Biochemical normalization; Animal studies revealed improvement in fibrosis	Decompensated cirrhosis CP-B or higher
Fibrates (Not FDA approved for PBC)	Bezafibrate 400 mg daily; Fenofibrate 160 mg daily	Elevated transaminases; Worsening decompensation in patients with CP-B, CP-C	Biochemical normalization	Decompensated cirrhosis

ALP, alkaline phosphatase; BID, twice a day; CP, child-pugh score; OCA, obeticholic acid; FDA, federal drug administration; PBC, primary biliary cholangitis; QHS, every night at bedtime; UDCA, ursodeoxycholic acid.

10, 25 and 50 mg. Most patients respond to the 10 mg dose (Table 1).[24] The limiting side effect to OCA is pruritis, and this may have contributed to the discontinuation rate of 10–12% for the 10 mg dose.[1,24] Biochemical improvement has been documented in large clinical trials and real-world data. However, the long-term survival data is not fully available at this time. Furthermore, OCA use is contraindicated for patients with decompensated cirrhosis (Child-Pugh B and C).

Fibrates

Fibrates are lipid lowering agents that activate the peroxisome proliferator activator receptor (PPAR), which is a nuclear receptor involved in a variety of metabolic processes, including bile acid homeostasis. PPAR exists in three isoforms: α, δ and γ. In particular, PPAR-α regulates bile acid synthesis and detoxification, phospholipid secretion, and inflammatory pathways.[1,3,7] The activation of PPAR-δ and -γ have exhibited profound effects on lipid and glucose metabolism, and anti-inflammatory and anti-fibrotic properties.[1] Two fibrates have been studied in patients with PBC: fenofibrate 160 mg daily and bezafibrate 400 mg daily (Table 1). An open-label trial revealed the improvement of ALP by 50% after 48 weeks of treatment for patients who had two times the upper limit of normal (ULN) ALP after one year treatment with UDCA.[1] In other studies, bezafibrate was initially studied in 48 patients with incomplete response to UDCA, who received additional treatment with bezafibrate at 400 mg/day for a median of 38 months.[1,25] One of those studies reported that the ALP levels of 54% of patients decreased to normal within the first four months of treatment.[1,25] Furthermore, older patients and patients with less fibrosis at baseline were more likely to respond. In addition, patients who were treated with bezafibrate, and had pruritus at baseline, noted a significant improvement for this symptom.[26] Multiple studies have replicated these findings.[1,25] However, fibrates are not FDA approved for PBC, and are used off label. An informed consent is recommended prior to starting fibrates. Fibrates may cause elevated transaminases. Thus, careful monitoring is indicated. Furthermore, fibrates are contraindicated for patients with decompensated liver cirrhosis.

Other previously studied medications

The other medications that have been studied revealed no clear benefits on mortality for transplant free survival, including chlorambucil, penicillamine, cyclosporine, corticosteroids, budesonide, azathioprine, mycophenolate mofetil, thalidomide, methotrexate, malotilate, vancomycin, and colchicine.[1,9,10]

Management of symptoms

Fatigue is one of the most common symptoms, and various medications have been utilized for its treatment, including modafinil, selective serotonin reuptake inhibitors (SSRIs), and ondansetron, although there is no first-line agent.[26] Alternative etiologies for fatigue should be appropriately ruled out, such as hypothyroidism and depression.

For pruritus, patients can have symptoms that range from mild to debilitating. The first-line therapy is cholestyramine. Other agents, such naltrexone or naloxone, rifampin, SSRIs and antihistamines, have also demonstrated variable efficacy. Interestingly, pruritus has been associated with increased opioidergic tone, and this is the reason why opioid antagonists, such as naltrexone, are preferred when medicating with opioid agonists for pain management in PBC.[27,28]

Other symptoms that have been reported include right upper quadrant abdominal pain, dry eyes, and dry mouth, and these may be treated on a case-by-case basis. The management of dry eyes should start with artificial tears, and pilocarpine or cevimeline can be used for patients with refractory symptoms. Cyclosporine or lifitegrast ophthalmic emulsion can be used for patients whose disease is refractory to other agents, preferably under the supervision of an ophthalmologist, according to AASLD guidelines.[9] Xerostomia and dysphagia may be managed via saliva substitute, with pilocarpine or cevimeline as the second-line therapy.[9]

Other complications from cholestasis

Osteopenia, osteoporosis, dental infections, fat soluble vitamin deficiency, and hyperlipidemia may occur due to chronic cholestasis. A multidisciplinary approach in the management of these issues, combined with endocrinology, primary care physicians, and dentists, is recommended for these complications.

Recommended monitoring and follow-up

Given the importance of biochemical markers in predicting disease progression and response, laboratory studies have become the cornerstone in disease monitoring. The monitoring of serum studies (ALP, bilirubin, transaminases and platelet count) at 3- to 6-month intervals is recommended.[9] Thyroid studies should be annually re-

peated, due to the association with hypothyroidism, and DEXA should be obtained every two years, due to the association with osteopenia and osteoporosis.[1,9] In addition, regular monitoring of fat-soluble vitamin levels (Vitamins A, D, E and K) should be considered for patients with jaundice. For patients with cirrhosis, the screening for esophageal varices, and monitoring for hepatocellular carcinoma with 6-month interval imaging should be ensured.[9]

The screening of genetically related family members may be reasonable for first-degree female relatives over the age of 30 with elevated ALP,[9] although there is no consensus on this recommendation.

Treatment response has been defined based on the biochemical improvement. Various criteria have been developed and studied for the recommendations of lab goals:

Rochester I[29]ALP below 2×ULN;

- Barcelona[30] reduction in ALP of 40% from baseline or normalization of ALP;
- Paris I[31] ALP below 3× ULN, AST 2×ULN, and total bilirubin (TB) under 1 mg/dL;
- Rotterdam[32] TB 1×LLN;
- Toronto[33] ALP 1.67×ULN;
- Paris II[32] ALP 1.5×ULN, AST 1.5×ULN, and TB under 1 mg/dL;
- Rochester II[34] ALP 2×ULN;

Global[35] ALP 2×ULN.Most prognostic scores agree that decreasing the ALP level to lower than two times the upper limit of normal improves the transplant free survival. In addition, bilirubin is a strong predictor of survival in PBC, and this has been utilized in most predictive models. The recent study conducted by Murillo Perez *et al*. noted that the optimization of treatment goals and biochemical improvements remain under investigation, and they suggested that for patients with PBC, bilirubin level of <0.6 ULN or ALP in the normal range are associated with the lowest risk for transplant or death.[35]

Elastography is emerging as another important modality of monitoring due to the benefit of non-invasive testing. A fibrosis score of 9.7 KPa predicts the progression of the disease, and the requirement for a transplant.[1,36,37]

Ultimately, patients who develop decompensated disease or intractable symptoms should be referred for liver transplant evaluation, based on the MELD or Mayo models. Survival data is promising for post-transplant PBC patients, and is superior to the outcomes of a transplant for most of the other indications. However, there is a high rate of recurrent PBC in these patients (30% at 10 years and 40% at 15 years).[1,9,36–38]

Future research

The gut-microbiome and gut-liver axis continues to be an area of active investigation. Recent studies have suggested that the gut flora is less diverse in patients with PBC, when compared to the average population, and the loss of certain protective bacteria is possibly predictive of a poor prognosis.[39] In mice models, the application of quadruple-antibiotics to kill the gut flora in PBC-diseased mice has led to improvements in splenomegaly and hepatic fibrosis, suggesting some modulation of pathophysiology through the gut flora.[40]

In addition, a number of new targets for therapeutics are being actively investigated in PBC. A recent phase 2a clinical trial for the ileal bile acid transporter inhibitor, GSK2330672, demonstrated its efficacy in reducing pruritus for patients with PBC.[41] In a phase 2 trial, elafibranor, a PPAR-δ and -γ agonist, reduced ALP by 48.3%, when compared to the placebo, and the patients presented with decreased pruritus after treatment.[42] Another recent study on the fibroblast growth factor analogue, which acts on the bile acid synthesis pathway, NGM282, revealed that 50% of patients in the treatment group responded with a >15% decrease in ALP from baseline, when compared to merely 6.7% of patients in placebo.[43] The 24-norusodeoxycholic acid (norUDCA) is a derivative of UDCA that bypasses normal enterohepatic absorption, instead of undergoing cholehepatic shunting, theoretically leading to less toxicity at the non-biliary sites. NorUDCA has been shown to have efficacy in reducing ALP levels in PSC, and in animal models, although its effects in PBC remains under investigation.[44] Another PPAR-δ agonist that is presently being studied and shows promise is seladelpar, and it has been demonstrated in a clinical study that this has potent anti-cholestatic effects.[45] Furthermore, the open-label study conducted by Kremer *et al*. revealed a substantial improvement in pruritus in 58% and 93% of patients in the 5 mg and 10 mg treatment groups, respectively.[45] In addition, seladelpar-treated patients also presented with significant reductions of 46% (5 mg daily dose recipients) and 31% (10 mg daily dose recipients) in serum bile acid precursor C4, and reductions reaching up to 38% in serum bile acids.[45] Seladelpar is presently undergoing clinical trials.

Conclusions

PBC is a complex disease that predominantly affects the biliary system and liver. The disease presentation and clinical features of PBC have been well-described in the literature. Its effective diagnosis requires clinical assessments, and laboratory tests for autoimmune markers and evidence of biliary and/or liver damage. Its treatment has been revolutionized by UDCA, which remains as the first-line therapy. Alternative and adjunctive therapies are an area of active investigation, since novel drug targets are based on complex pathophysiology. Future studies may elucidate additional pathophysiologic features, drug targets, and the involvement of the gut-liver axis.

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Conflict of interest

The authors have no financial disclosures to declare.

Author contributions

Study concept and design: BY; acquisition of data: BY and HX; analysis and interpretation of data: BY and HX; drafting of the manuscript: BY and HX; critical revision of the manuscript for important intellectual content: BY and HX; administrative, technical and material support, and study supervision: BY and HX.

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