Primary Biliary Cholangitis

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Primary biliary cholangitis (PBC) is the most common chronic cholestatic liver disease in adults in the United States and disproportionately affects middle-age women (9:1 female-to-male ratio). Since its initial description in 1851, there have been countless debates about the appropriate nomenclature for this disease and great disapproval of the time-honored terminology “primary biliary cirrhosis”, particularly because cirrhosis is absent in most patients with this disease. Disputes about appropriate nomenclature appear to have settled down, at least until now, following agreement by major international hepatology and gastroenterology societies and patient advocacy groups, and the subsequent publication of a multi-societal position paper on September of 2015 that established the change in nomenclature for this disease while maintaining the commonly used acronym “PBC” [1].

PBC is characterized by progressive immune-mediated inflammatory destruction of septal and interlobular bile ductules. Similar to other autoimmune diseases, the fundamental pathophysiological mechanism for PBC is likely related to a complex interaction between unidentified environmental triggers and genetically susceptible individuals. Molecular mimicry, loss of tolerance, and dysregulated immune attack directed against the E2 subunit of pyruvate dehydrogenase complex (PDC-E2) appear to be cornerstone in the pathogenesis of PBC [2]. The end-result, at least microscopically, reflects the new terminology and is characterized by non-suppurative cholangitis, which manifests biochemically as cholestasis. In the absence of pharmacological treatment, progressive fibrosis characterizes the natural history of PBC. Clinical features are non-specific and include fatigue, pruritus, right upper quadrant abdominal pain, dyslipidemia, bone mineral density loss, and in rare cases xanthoma and xanthelasma. The diagnosis of PBC may be established in the presence of two of the following three criteria in the absence of a cholestatic drug reaction or biliary obstruction: a) biochemical evidence of cholestasis (elevation of serum alkaline phosphatase), b) presence of autoantibodies, typically anti-mitochondrial antibody (AMA); and, c) histological findings of non-suppurative destructive cholangitis [3]. Characteristic histological features, once thought to be necessary for establishing the diagnosis of PBC, are not mandatory if the other two diagnostic criteria are present. Furthermore, the pathognomonic “florid duct lesion” is only present in a minority of patients with PBC, particularly during early stages [4]. It is also important to recognize that AMA, the hallmark autoantibody of PBC, may not be detectable in approximately 5 to 10% of patients with the disease (the so-called AMA-negative PBC), in which case histology is mandatory to establish the diagnosis and complementary PBC-specific autoantibodies such as Sp100 and/or gp210 may be obtained [5].

Ursodeoxycholic acid (UDCA) was the first pharmacological agent licensed for treatment of PBC and has proven to significantly alter the natural history of the disease when administered orally at a dose of 13 - 15 mg/kg/day [6]. Important outcomes associated with UDCA therapy in PBC include reduced fibrosis progression, diminished need for liver transplantation (LT), and improve LT-free survival. Nevertheless, up to 40% of individuals with PBC treated with UDCA for at least 12 months have an inadequate biochemical response and experience lesser benefits on long-term outcomes [7]. Response to pharmacologic therapy is assessed by reductions in serum alkaline phosphatase and bilirubin levels, two biochemical markers that accurately predict long-term outcomes in PBC [8]. Nevertheless, criteria used for determining response versus no-response vary widely and needs to be standardized in the future.
Obeticholic acid (OCA) was recently licensed on May 27, 2016 by the Food and Drug Administration and is currently indicated for treatment of PBC in combination with UDCA in adults with an inadequate biochemical response to UDCA for at least 12 months, or as monotherapy in adults unable to tolerate UDCA. OCA is a selective farnesoid X receptor (FXR) agonist derived from the naturally occurring bile acid chenodeoxycholic acid, an endogenous FXR ligand. FXR is a member of the nuclear bile acid receptor superfamily expressed in high levels in hepatocytes and enterocytes in the terminal ileum and its activation results in suppression of cholesterol 7 alpha-hydroxylase (CYP7A1) and transcription of fibroblast growth factor (FGF) 19. CYP7A1 is the rate-limiting enzyme in bile acid synthesis from cholesterol, thus FXR activation markedly reduces the bile acid pool. Similarly, increased levels of FGF19 inhibit de novo synthesis of bile acids; nevertheless, this hormone also regulates several metabolic pathways, including insulin sensitivity and lipid metabolism. Furthermore, in animal models, FXR activation has proven to result in regression of fibrosis [9]. The recommended dosing of OCA for individuals without cirrhosis and compensated cirrhosis (Child Pugh class A) is 5 mg orally daily with the goal of titrating to 10 mg orally daily after three months if the drug is well tolerated (particularly pruritus). Importantly, dose reduction is required in patients with severe hepatic dysfunction because OCA is predominantly excreted by the liver (87%) and the recommended dose for individuals with decompensated cirrhosis (Child Pugh classes B and C) is 5 mg orally once weekly for three months and titration to 5 mg orally every third day and subsequently 10 mg every third day in the absence of severe pruritus and elevation of aminotransferases. Results from a recently published randomized, placebo-controlled trial demonstrate that OCA administered with UDCA or as monotherapy for 12 months’ results in marked improvement in biochemical markers (reduction of alkaline phosphatase and bilirubin) in 47% of individuals treated with this agent compared to 10% of those that received placebo [10].

Fibrates activate peroxisome proliferator-activated receptor (PPAR) alpha and may prove to be useful for treatment of individuals with PBC and incomplete biochemical response to UDCA. Data from several retrospective studies show that addition of fenofibrate to UDCA markedly increases the proportion of individuals achieving biochemical response compared to UDCA monotherapy [11,12]. Nevertheless, use of fibrates in PBC is off-label and should be restricted to patients with no significant impairment of hepatic function, as their use is contraindicated in hepatic dysfunction. The role of fibrates as adjunct therapy for patients taking OCA has not been evaluated.

PBC is the sixth leading indication for LT in the United States and pharmacological therapy has resulted in a steady decline in the number of individuals requiring LT since approval of UDCA [13]. Outcomes following LT for PBC are excellent and have been considered the benchmark for patient and allograft survival to which other indications for LT are compared. Nevertheless, recurrence post-LT occurs relatively commonly but has no significant impact on survival. Data from a retrospective study suggest that preventive administration of UDCA may markedly diminish recurrence of PBC 10 years post-LT: 21% of LT recipients treated with preventive UDCA versus 53% of those not taking this agent [14]. These data need to be corroborated by prospective studies and there are currently no data on the role of OCA and prevention of recurrent PBC post-LT.

In conclusion, PBC is a cholestatic liver disease characterized by autoimmune non-suppurative cholangitis that if left untreated typically progresses to cirrhosis and end-stage liver disease. Pharmacologic therapy has proven to markedly alter the natural history of the disease. UDCA remains the first line of therapy for PBC; however, individuals with inadequate biochemical response to this agent are at significant risk for disease progression. OCA was recently approved for treatment of patients with inadequate response or intolerance to UDCA and improves biochemical parameters that are accurate surrogate markers for patient-important outcomes.

**Bibliography**


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