Primary Biliary Cirrhosis
Therapeutic Advances

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KEYWORDS

• Primary biliary cirrhosis • Therapeutics • Ursodeoxycholic acid • Fibrates
• 6α-Ethyl-chenodeoxycholic acid

KEY POINTS

- Ursodeoxycholic acid is the only US Food and Drug Administration–approved medical treatment for PBC, and it is associated with significant biochemical, histologic, and survival benefits.
- The only definitive treatment for end-stage primary biliary cirrhosis (PBC) is liver transplantation.
- Approximately 40% of patients with PBC respond incompletely to treatment with ursodeoxycholic acid.
- Several agents show promise in the treatment of "poorly responsive" PBC, including obeticholic acid, fibrates, tetrathiomolybdate, and rituximab.

INTRODUCTION

Primary biliary cirrhosis (PBC) is an autoimmune liver disease characterized by progressive destruction of intrahepatic bile ducts associated with cholestasis, portal inflammation, and fibrosis, which may lead to biliary cirrhosis, portal hypertension, and eventually to liver transplantation or death.[1] Histologically, focal bile duct lymphocytic infiltration and destruction with granuloma formation, termed the florid duct lesion, are considered essentially pathognomonic for PBC. Although the exact pathogenetic mechanism of PBC remains incompletely understood, PBC is thought to result from a combination of genetic predisposition and environmental triggers.[2]

The disease predominantly affects women, who are usually diagnosed in their 50s while in an asymptomatic state. Epidemiologic studies indicate annual incidence rates for PBC between 0.7 and 49 cases/1 million population and prevalence rates between

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6.7 and 402 cases/1 million population.[3] In the United States, national estimates for incidence and prevalence of PBC are ≈3500 new cases each year with 47,000 prevalent cases among the white population.[4]

Individuals with asymptomatic disease consist of 20% to 60% of all first-time diagnoses, based largely on increased use of screening liver biochemistry studies.[5] It has been suggested that symptoms develop within 5 years in most asymptomatic patients, although one third of patients may remain symptom free for many years. However, at 20 years after diagnosis, less than 5% remain asymptomatic.[6] Pruritus and fatigue are early symptoms and occur in 20% to 50% of patients.[7] Although it seems that symptomatic individuals may have poorer outcomes compared with asymptomatic patients, it is the cumulative development of complications of end-stage liver disease and portal hypertension that has been consistently associated with decreased survival.[6] PBC can be divided into 3 distinct phases (**Fig. 1**) and, as each phase advances, survival or time to transplantation diminishes.[8] Liver failure (ascites, variceal bleeding, hepatic encephalopathy, or hyperbilirubinemia >6 mg/dL) has been estimated to occur in 15% at 5 years according to a large community-based study of 770 patients in northeast England.[6]

The diagnosis of PBC is suspected based on cholestatic serum liver tests and largely confirmed by the presence of antimitochondrial antibodies (AMA), which are directed against the E2 subunit of the pyruvate dehydrogenase complex found in the inner mitochondrial membrane. Considered the serologic hallmark of PBC, AMA positivity is detected in 90% to 95% of patients with PBC and less than 1% of normal control subjects.[9,10] Several AMA subtypes have been described, with the M2 subtype being the most specific for PBC.[11,12]

In the small subset of AMA-negative patients with PBC, up to 85% will test positive for antinuclear antibodies that are frequently PBC specific, such as the anti-gp210 (rimlike pattern) and anti-sp100 (multiple nuclear dot pattern).[13–15] However, in general, patients who are AMA negative have similar clinical, biochemical, and histologic features compared with AMA-positive patients, and they have similar response rates to ursodeoxycholic acid (UDCA) therapy.[16,17] In unclear cases when both AMA and antinuclear antibodies may be negative, a liver biopsy can be used to substantiate and to assist in the diagnosis, while also providing important prognostic information.

PBC has 4 histologic stages (**Table 1**), but the liver is not affected uniformly and a single biopsy sample may demonstrate the presence of different stages of the

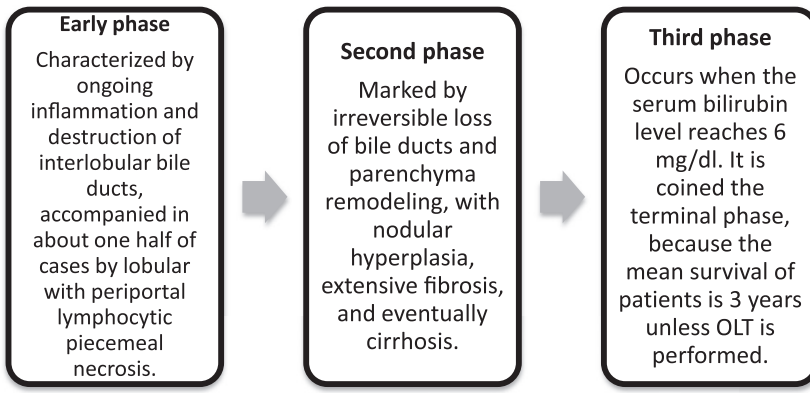

Fig. 1. Phases of PBC.