

# Natural history and management of primary biliary cirrhosis

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**Abstract:** Primary biliary cirrhosis (PBC) is a chronic inflammatory autoimmune disease that mainly targets the cholangiocytes of the interlobular bile ducts in the liver. It is a rare disease with prevalence of less than one in 2000. Its prevalence in developing countries is increasing presumably because of growth in recognition and knowledge of the disease. PBC is thought to result from a combination of multiple genetic factors and superimposed environmental triggers. The contribution of the genetic predisposition is evidenced by familial clustering. Several risk factors, including exposure to infectious agents and chemical xenobiotics, have been suggested. Common symptoms of the disease are fatigue and pruritus, but most patients are asymptomatic at first presentation. The prognosis of PBC has improved because of early diagnosis and use of ursodeoxycholic acid, the only established medical treatment for this disorder. When administered at adequate doses of 13–15 mg/kg/day, up to two out of three patients with PBC may have a normal life expectancy without additional therapeutic measures. However, some patients do not respond adequately to ursodeoxycholic acid and might need alternative therapeutic approaches.

**Keywords:** primary biliary cirrhosis, natural history, long-term outcome, ursodeoxycholic acid, biochemical response, target therapy

## Introduction

Primary biliary cirrhosis (PBC) is a chronic slowly progressive cholestatic liver disease, characterized by nonsuppurative destruction of the interlobular and septal bile ducts that may lead to cirrhosis. PBC is a rare autoimmune disease affecting predominantly middle-aged women. Typical patients used to have symptoms of fatigue and pruritus and biochemical evidence of cholestasis.<sup>1,2</sup> Ursodeoxycholic acid (UDCA) is currently the only recommended therapy for PBC. Patients with a good response to UDCA survive as long as age- and sex-matched healthy subjects.<sup>2</sup> This review provides an overview of the clinical characteristics and natural history of PBC. Furthermore, the current knowledge on the role of UDCA will be summarized and the directions for future management of the disease will be discussed.

## Pathogenesis

The exact pathogenesis of PBC remains largely unknown. It is thought to be due to a combination of genetic predisposition and environmental triggers. Evidence of genetic predisposition is shown by a high concordance rate among monozygotic twins,<sup>3</sup> familial clustering,<sup>4–6</sup> and a genome-wide association study.<sup>7</sup> The contribution of environmental factors includes increased prevalence in relation to specific

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geographical areas,<sup>8,9</sup> and clinical or experimental findings supporting infectious agents or chemical compounds as possible triggering factors.<sup>4-6,10-12</sup>

## Epidemiology

Several demographic studies indicate that all racial groups may be affected and that the disease predominately affects middle-aged women worldwide. PBC also appears in young premenopausal fertile women, and does affect men.<sup>13</sup> The youngest case is a 15-year-old woman diagnosed with the disease.<sup>14</sup> Present estimates place the prevalence of the disease at around one in 1000 women over the age of 40 years. Since antimitochondrial antibodies (AMA) have been introduced into the diagnosis of PBC, patients are increasingly being detected in the early stages of the disease; hence the reported prevalence of PBC has increased. A systematic review of the frequency of PBC highlights an increased incidence throughout the developed countries,<sup>8</sup> particularly in the United Kingdom, United States, Japan, and also Australia, where population studies estimate a prevalence of between 19 per million among natives and 183 per million among those who have migrated to the continent from Europe.<sup>15,16</sup> Incidence of PBC ranged from 0.7–49 cases per million per year in most recent studies. The point prevalence was estimated to range from 19–402 cases per million.<sup>15</sup>

## Diagnosis of PBC

The diagnosis of PBC is suspected in the case of chronic cholestasis after exclusion of other causes of liver disease. The differential diagnosis includes a cholestatic drug reaction, biliary obstruction, sarcoidosis, autoimmune hepatitis, and primary sclerosing cholangitis. Currently the diagnosis is made with confidence when two of the following three criteria are met: (1) biochemical evidence of cholestasis with elevation of alkaline phosphatase (ALP) activity for more than 6 months; (2) presence of AMA, which is present in 90%–95% of patients and is often detectable years before clinical signs appear; and (3) histopathologic evidence of chronic nonsuppurative destructive cholangitis of small- or medium-sized bile ducts if a biopsy is performed.<sup>2</sup> It has also been identified that some patients may have the clinical, biochemical, and histological features of PBC but remain consistently AMA-negative, even when the most common immunoblotting techniques are used.<sup>17</sup> One-half of patients with PBC are also antinuclear antibody positive, and unlike the nonspecific antinuclear antibodies in autoimmune hepatitis, highly PBC-specific antinuclear antibody target antigens have been identified.<sup>18</sup> The most relevant

immunofluorescence are perinuclear/rim-like membranous patterns formed by antiglycoprotein-210 and lamin B receptor (constituents of the nuclear envelope) – giving the appearance of a thin ring confined to the nuclear membrane – and multiple nuclear dot-like pattern formed by anti-Sp100 and promyelocytic leukemia protein. The antigenic targets of antimultiple nuclear dot are discrete nuclear dots – different from nucleoli by being larger, fewer in number, and not seen in mitotic cells or on metaphase chromosome spreads. Another antinuclear antibody pattern commonly seen in PBC, but not disease-specific, is anticentromere antibody staining. The anticentromere antibody reactivity is directed against discrete granules in interphase cells and is evident particularly in mitotic cells. The target antigen of anticentromere antibodies in patients who have PBC is centromere protein B. Multiple nuclear dots and perinuclear/rim-like membranous patterns are extremely specific for PBC irrespective of AMA status, and may provide supportive evidence for PBC especially in those who test AMA negative.<sup>13</sup> In addition, the significance of autoantibodies has been proposed by several groups. Antiglycoprotein-210 is associated with aggressive disease and progression to liver failure in individuals with PBC, and therefore is a marker of poor prognosis.<sup>19</sup> In addition, the anticentromere antinuclear antibody pattern has been associated with the development of portal hypertension but not hepatic failure.<sup>19</sup>

Histological examination of the liver is not required for clinical diagnosis in PBC.<sup>20</sup> However, it is valuable for prognostic evaluation and provides a baseline for evaluating the response to treatment. It allows the stage of the disease to be determined and identification of features that predict the clinical course such as interface hepatitis and ductopenia. It may also help in guiding management (eg, screening for hepatocellular carcinoma).

More recently, a large number of putative serum markers have been evaluated for the assessment of hepatic fibrosis. Simple approaches including the aspartate aminotransferase-to-alanine aminotransferase ratio, the aspartate aminotransferase-to-platelet ratio index, and Forns indices do not always have sufficient accuracy to detect advanced fibrosis, and thus remain unstudied in PBC.<sup>21,22</sup> The investigation of biological markers of fibrosis including the European Liver Fibrosis score (an algorithm comprised of age, serum hyaluronic acid – a tissue inhibitor of metalloproteinase-1, and an N-terminal propeptide of type III procollagen) showed acceptable diagnostic accuracy for significant fibrosis or cirrhosis.<sup>23</sup> There are currently no strongly established and routinely recommended serum surrogate markers of liver fibrosis in PBC.

A number of noninvasive imaging techniques have been evaluated for possible use in diagnosing hepatic fibrosis. Transient elastography has been introduced as a new, simple, and reliable technique that easily and noninvasively measures the mean liver stiffness.<sup>24</sup> Corpechot et al compared liver stiffness as determined by transient elastography (FibroScan®; Echosens, Paris, France) to histological findings obtained by liver biopsy in patients with PBC or primary sclerosing cholangitis, and showed a highly significant correlation of liver stiffness with both degree of fibrosis and histological stage.<sup>25</sup> Recently the same group did a prospective performance analysis of transient elastography for the diagnosis of METAVIR fibrosis stages in a cohort of 103 PBC-specific patients as compared to the previous one.<sup>26</sup> Their study confirms the diagnostic performance and accuracy of transient elastography in the noninvasive quantification of liver fibrosis in PBC.

Additional autoimmune diseases are commonly observed in patients with PBC. More than 84% of PBC patients have been reported to exhibit features of at least one nonhepatic autoimmune disease sometime during the clinical course, and evidence of two or more nonhepatic autoimmune diseases can be found in about 40% of PBC cases.<sup>27</sup> Thyroid dysfunction is frequently associated (25%) with PBC, often predating its diagnosis.<sup>28</sup> Sicca syndrome is seen in up to 70% of patients.<sup>29</sup> The risk of Sjogren syndrome and Raynaud's phenomenon was about four-fold higher than unaffected controls. Scleroderma was prevalent at 8%.<sup>30</sup> Celiac disease has been reported in up to 6% of patients and is by far more commonly associated with PBC than inflammatory bowel diseases.<sup>31,32</sup> Other less common autoimmune disorders include systemic lupus erythematosus, renal tubular acidosis, glomerulonephritis, and various pulmonary syndromes (Table 1).<sup>33</sup>

Patients with PBC have been reported to be at increased risk of osteoporosis in some studies.<sup>34</sup> Risk factors for osteoporosis in PBC are older age, lower body mass index, severity of cholestasis, and advanced histological stage. Patients who have advanced stage PBC have a five-fold increase in risk for developing osteoporosis compared with those who have early-stage (Ludwig stage I or II) disease.<sup>35</sup> Osteoporosis is generally silent but is easily detected using bone mineral density scans and should be part of the routine workup of all chronic cholestatic patients at diagnosis and during the follow-up period.

## Patterns of clinical disease and natural history in the pre-UDCA era

The patterns of clinical disease and natural history have changed significantly in the last two decades. The diagnosis

**Table 1** Diseases associated with primary biliary cirrhosis

Common (up to 80%)
• Sicca syndrome
Less common (about 20%)
• Thyroid disease
• Arthralgia
• Raynaud's syndrome
• Sclerodactyly
• Fibrosing alveolitis
Uncommon (less than 5%)
• CREST (calcinosis, Raynaud's phenomenon, esophageal involvement, sclerodactyly, telangiectasia) syndrome
• Addison's disease
• Celiac disease
• Glomerulonephritis
• Vitiligo
• Renal tubular acidosis
• Myasthenia gravis
• Hypertrophic pulmonary osteoarthropathy

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of PBC is now made more often and earlier in the course of the disease than it used to be.<sup>8</sup> Earlier, PBC was believed to be a rare autoimmune disease and nearly all patients were diagnosed in an advanced stage with classical signs and symptoms (pruritus, jaundice, and xanthomatosis) of the disease. The prognosis of these cases was often poor with a life expectancy of only few years.<sup>8</sup> It is now recognized that such cases represent only the most severe part of a wider clinical spectrum. In the present era, however, PBC is diagnosed in a growing number of asymptomatic patients with early histological stages, and these patients receive treatment at earlier stages. As a result, the prognosis is much better now than it formerly was.<sup>36</sup> As such, the natural history of PBC appears to have changed. Nevertheless, these data are mainly from developed countries. The clinical picture in developing countries is quite different, where the majority of patients are symptomatic and still diagnosed at cirrhotic stage.<sup>37</sup> The main reasons are presumably due to the difference in access to health care including health checkup and recognition of the disease among health care providers.

The natural history of untreated PBC is one of the gradual progressions through four phases. First, it now seems likely that there is a long preclinical course of this disease when AMA alone is present in the serum. In this respect, a 10-year longitudinal follow-up study on 29 untreated pre-clinical patients whose initial liver biopsy was diagnostic or compatible with PBC has shown that the majority of the patients developed biochemical cholestasis (83%) and became symptomatic (76%).<sup>38</sup> Repeat liver biopsy was done

for ten patients during a median follow-up of 11.4 years (range 1–14 years), and progression of the histological stage was found in four patients but none of the patients developed cirrhosis. The median follow-up period from the first positive AMA test to persistently abnormal liver tests in this series was 6 years (range 1–19 years). Based on these data, individuals positive for AMA without any clinical and biochemical indices should be considered as having slowly progressing PBC; as such, periodical follow-up is required.

The next phase is characterized by gradual elevation of the serum ALP levels. Currently the vast majority of newly diagnosed patients with PBC are asymptomatic. The course of the disease in asymptomatic patients is, however, unpredictable and patients may later develop symptoms and signs of progressive disease.<sup>39</sup> No predictors were found as to which of the untreated patients would develop symptoms. Asymptomatic disease does not always equate with an early stage of the disease. The long-term survival of asymptomatic patients who develop symptoms is shorter than that of age- and sex-matched healthy subjects. It is important to consider that there may be a subgroup of asymptomatic PBC patients who do not develop symptoms. This group will probably have a survival rate similar to that of the general population.<sup>40</sup>

Symptomatic patients typically have symptoms such as pruritus, fatigue, and abdominal pain. Fatigue is reported in up to 80% of PBC patients overall, impairing quality of life and interfering with daily life activities.<sup>41,42</sup> However, no correlation with the severity of the liver disease, histologic stage, or duration could be demonstrated.<sup>42</sup> The exact pathophysiological mechanisms leading to chronic fatigue in PBC remain poorly understood. Several studies indicated heterogeneous mechanisms ranging from both the central nervous system and the peripheral motor system to autonomic dysfunction and excessive daytime somnolence.<sup>43–46</sup> On the other hand, a study on fatigue suggests that there are extrahepatic conditions that exist (ie, body mass index, medication) that may cause symptoms of fatigue in patients with PBC.<sup>47</sup> Another common symptom experienced by patients with PBC is pruritus.<sup>48</sup> This appears to be a more specific symptom for PBC and it is the second most common symptom (after fatigue) in patients who do not have jaundice. It was reported to occur in 20%–70% of patients. However, its frequency has been decreasing because the disease is increasingly recognized in its asymptomatic stage. The onset of pruritus generally precedes the onset of jaundice by months to years. It is usually worse at night, and may initially occur during the third trimester of pregnancy and persist after delivery. Like fatigue, it does not correlate with progression of liver

disease, and may even improve or disappear as the disease gets more advanced.<sup>13</sup> However, pruritus is correlated with fatigue.

The mechanism of itch in cholestasis remains largely unknown. Some hypotheses include derangements in bile salt production and excretion, alterations in progesterone metabolites, histamine imbalance, substance P dysregulation, and alterations of endogenous opioids.<sup>48</sup> Recent experimental evidence implicated the lysophospholipase autotaxin and its product, lysophosphatidic acid, as potential mediators of cholestatic pruritus.<sup>50</sup>

The median duration of survival for symptomatic patients ranges from 5–8 years from the onset of symptoms.<sup>39,50</sup> Symptoms related to portal hypertension usually appear later but occasionally in precirrhotic stage.<sup>51</sup> The 10-year cumulative incident rates for developing complications of portal hypertension are higher (10%–20%) compared to asymptomatic individuals at diagnosis. In addition, nearly 25% of symptomatic patients at diagnosis progress to liver failure within 10 years. Once progressive jaundice develops, patients enter a terminal phase defined by the condition where serum bilirubin reaches 100  $\mu\text{mol/L}$  (6 mg/dL) with or without gastrointestinal bleeding, ascites, or encephalopathy. This terminal phase can last up to 2 years.<sup>50</sup>

Concerning the histological stage of asymptomatic and symptomatic patients, contemporary series have shown that with earlier diagnosis, 42%–66% of asymptomatic patients are at an earlier stage, whereas 82% of symptomatic patients are at a later histological stage of the disease.<sup>52</sup> In several natural history models, histological stages have been found to predict survival.<sup>53</sup> These historic data showed that the natural history of histological changes in PBC (without treatment) is a progression to cirrhosis.<sup>53–55</sup> The majority of patients will progress to their histological stages within 2 years. Over 4 years, cirrhosis developed in 31% of patients going through stage I at diagnosis and in 50% of patients going through stage II, and the probability of remaining in the early stage was 29%. The presence of frank cirrhosis predicted a shorter survival in PBC patients.<sup>53</sup> Overall the histological stage progressed by one stage every 1.5 years.

## Natural history in the UDCA era

A variety of immunosuppressive medications have been used in PBC (Table 2). Several drugs such as corticosteroids,<sup>56,57</sup> azathioprine,<sup>58–60</sup> cyclosporine,<sup>61,62</sup> methotrexate,<sup>63–65</sup> penicillamine,<sup>66</sup> colchicines,<sup>67,68</sup> and other agents such as malotilate,<sup>69</sup> chlorambucil,<sup>70</sup> and thalidomide<sup>71</sup> have been evaluated. However, a clear benefit from immunosuppressive

**Table 2** Drugs used to treat primary biliary cirrhosis

Drug	Efficacy	Toxicity
Glucocorticoids <sup>56,57,101–104</sup>	Limited efficacy	Worsen osteoporosis
Azathioprine <sup>58–60,102</sup>	Limited efficacy	+/-
Cyclosporine <sup>61,62</sup>	Limited efficacy	Many side effects
Methotrexate <sup>63–65,107–110</sup>	Efficacy not proven in double-blind trials	+
D-penicillamine <sup>66</sup>	No efficacy	Serious toxic effects
Colchicine <sup>67,68,105,106</sup>	Efficacy not proven in double-blind trials	-
Mycophenolate mofetil <sup>111,112</sup>	Limited efficacy	
Silymarin <sup>113</sup>	No efficacy in pilot study	

agents has not been demonstrated to date. Many of them are ineffective and their use is limited by side effects.

UDCA is currently the only therapy for PBC recommended by the American Association for the Study of Liver Disease and is approved for this purpose by the United States Food and Drug Administration.<sup>2</sup> The rationale for the use of UDCA in the treatment of PBC depends on its many therapeutic actions. UDCA is a hydrophilic naturally occurring bile acid that has several interrelated functions, including expansion of the hydrophilic bile acid pool as well as direct choleric, anti-inflammatory, and antiapoptotic effects on hepatic epithelia.<sup>72</sup> Overall, the data suggest that the optimal (safest and most cost-effective) dosage for UDCA is 13–15 mg/kg/day, commonly as a single dose.<sup>73,74</sup>

Randomized trials show that UDCA improved biochemical evidence of cholestasis.<sup>75–77</sup> Serum concentrations of bilirubin, the most important prognostic marker of the disease, were reduced by administration of UDCA. None of the studies showed any significant effects on fatigue, autoimmune conditions, or on bone disease in PBC.<sup>78,79</sup> Only one study reported a significant reduction of pruritus in the UDCA-treated group.<sup>80</sup> UDCA has also been shown to delay histological progression in PBC.<sup>53,81,82</sup> In an early study, the rate of histological progression to cirrhosis was significantly less in the UDCA group than in the control group (13% versus 49%).<sup>81</sup> Current available data indicate that UDCA slows disease progression in patients with early-stage histological involvement. UDCA therapy was associated with a five-fold lower progression rate from early-stage disease to extensive fibrosis or cirrhosis (7% per year under UDCA versus 34% per year under placebo,  $P < 0.002$ ). At 4 years the probability of remaining in early-stage disease was 76%. Combined results of four large randomized UDCA trials (N = 367) also showed that significantly less histological progression occurred from stages I and II to stages III and IV

in patients treated with UDCA compared to those treated with the placebo.<sup>82</sup> No effect was measurable in patients already in stage III and IV. Likewise, patients in the liver insufficiency phase do not experience benefit from UDCA and should be considered for liver transplantation. Studies have also shown that the incidence of cirrhosis is only 4%, 12%, and 59%, respectively, after 5 years of UDCA treatment among follow-up patients for Ludwig stages I–III.<sup>83</sup> Predictive factors for development of cirrhosis included serum bilirubin higher than 1 mg/dL, and moderate to severe lymphocytic piecemeal necrosis on the liver biopsy.<sup>83</sup> UDCA has also been shown to prolong survival time without liver transplantation.<sup>53,84–87</sup> The long-term effect of UDCA has recently been reported in a study of 262 PBC patients who had received 13–15 mg/kg daily for a mean of 8 years (range 1–22 years). The results of this study showed that treatment with UDCA normalized the survival rate (for death or transplantation) for patients with stage I or II disease who were treated, whereas those patients with more advanced stages had significantly worse survival.<sup>84</sup>

The number of patients who have hepatocellular carcinoma in PBC is increasing, perhaps because patients with PBC may survive much longer even with cirrhosis and/or portal hypertension than they used to. The overall incidence of hepatocellular carcinoma among PBC patients varies from 0.7%–3.8%, whereas an incidence of up to 14% has been reported for those with cirrhotic disease.<sup>88,89</sup> Several risk factors for hepatocellular carcinoma have been reported, including histological stage, sex, age, presence of portal hypertension, and history of blood transfusion.<sup>89–91</sup> These data indicate that PBC patients who have risk factors should be systemically screened for hepatocellular carcinoma.

## Biochemical response to UDCA

Observational studies in PBC have shown that the degree of the biochemical response to UDCA between 6 months and 2 years identifies patients with an excellent long-term prognosis (Table 3).<sup>85,92–97</sup> Indeed, patients with PBC who have achieved a biochemical response to UDCA have longer liver transplantation-free survival and longer overall survival comparable to that observed in a control population.<sup>87</sup> Different definitions of the biochemical response as a surrogate marker of survival without transplantation have been proposed: the Paris I criteria (ALP less than three times the upper limit of normal, aspartate aminotransferase less than two times the upper limit of normal, and bilirubin less than 1.0 mg/dL),<sup>92</sup> Paris II criteria for early-stage disease (ALP and aspartate aminotransferase up to 1.5 times the upper limit of

**Table 3** Criteria of “biochemical response to ursodeoxycholic acid” in primary biliary cirrhosis

Criteria	“Biochemical response to ursodeoxycholic acid”	Definition of adverse outcome
Barcelona Pares et al <sup>85</sup>	Decrease of serum ALP by >40% or ALP normalization (after 1 year)	Death or liver transplantation
Paris I Corpechot et al <sup>92</sup>	ALP $\leq 3 \times$ ULN, AST $\leq 2 \times$ ULN, and serum bilirubin $\leq 1$ mg/dL (after 1 year)	Death or liver transplantation
Paris II Corpechot et al <sup>93</sup>	ALP and AST $\leq 1.5 \times$ ULN, and normal bilirubin level (after 1 year)	Death or liver transplantation
Rotterdam Kuiper et al <sup>94</sup>	Normalization of abnormal serum bilirubin and/or albumin (after 1 year)	Death or liver transplantation
Toronto Kumagi et al <sup>95</sup>	ALP $< 1.67 \times$ ULN (after 2 years) ALP $< 1.76 \times$ ULN (after 2 years)	Progression by $\geq 1$ histological stage Progression by $\geq 2$ histological stage
Ehime Azemoto et al <sup>96,97</sup>	Normalization of GGT level or reduction rate of GGT above the ULN $> 70\%$ (after 6 months)	Development of symptoms Death or liver transplantation

**Abbreviations:** ALP, alkaline phosphatase; AST, aspartate aminotransferase; GGT,  $\gamma$ -glutamyl transpeptidase; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

normal with normal bilirubin level),<sup>93</sup> the Barcelona criteria (decline in ALP of more than 40% of baseline or to a normal value),<sup>85</sup> or the Rotterdam criteria (normalization of bilirubin and/or albumin after treatment if one or both were abnormal at baseline).<sup>94</sup> Recently, Kumagi et al from Toronto studied a cohort of 69 patients with PBC with a follow-up liver biopsy about 10 years after first biopsy and start of UDCA treatment.<sup>95</sup> They found that an ALP greater than 1.67 times the upper limit of normal after 2 years of UDCA treatment (Toronto criteria), along with ductopenia (bile duct loss  $> 50\%$ ) at the first biopsy, predicted the progression of disease by at least one stage after 10 years. The most recent report from a Japanese group defined the UDCA responder as the normalization of the  $\gamma$ -glutamyl transpeptidase level or a  $\gamma$ -glutamyl transpeptidase reduction rate that exceeded the upper limit of normal by more than 70% after 6 months of treatment (Ehime criteria). They showed that the biochemical response to UDCA predicts symptom development in asymptomatic PBC and also predicts long-term outcome.<sup>96,97</sup> Although differently proposed, these criteria appear beneficial in predicting long-term outcomes in patients with PBC and allow identification of nonresponders who may benefit from further trials.

## Incomplete response to UDCA

A complete response, which is a normalization of biochemical tests without histological progression, occurs in at least 25%–30% of patients with PBC on UDCA.<sup>98</sup> Unfortunately, some patients have an incomplete response. Approximately 40% of patients with PBC respond incompletely to long-term UDCA monotherapy.<sup>98</sup> Biochemical response to UDCA is an essential predictor of long-term outcome (death or liver transplantation), even in patients lacking poor prognostic factors at baseline (advanced histological stage or hyperbilirubinemia).<sup>92</sup> Various factors could be

associated with poor response to UDCA. High concentrations of serum ALP as well as presence of histological interface hepatitis, ductopenia, and cirrhosis pretreatment predict incomplete response compared with complete responders.<sup>95,98</sup> In patients with a suboptimal response to UDCA, several potential causes must be excluded: (1) noncompliance and inappropriate dosage regimen, (2) coexisting fatty liver, autoimmune thyroid dysfunction, and celiac disease, and (3) postbiopsy arterioportal fistula. An incomplete response might also arise if an overlap syndrome with autoimmune hepatitis is present.<sup>99</sup> The suboptimal response to UDCA has elicited interest in regard to further treatment. An increase in the dose was not found to be of any benefit in patients who did not respond to standard doses of treatment and adjuvant therapy is recommended.<sup>100</sup>

## Adjuvant treatment

Combinations of UDCA with other agents have been studied in patients with an incomplete response to UDCA alone in an effort to enhance the efficacy of treatment (Table 2). The use of glucocorticoids along with UDCA treatment may help in improving liver biochemistry and histology.<sup>101–104</sup> Budesonide in particular has been used in this setting at 6–9 mg/day. The combination of UDCA and budesonide therapy has been shown to improve biochemical and histological response in terms of inflammation and fibrosis, but it may worsen osteopenia. However, studies were of too short treatment duration to show convincingly whether or not budesonide will improve survival. The addition of azathioprine,<sup>102</sup> colchicines,<sup>105,106</sup> methotrexate,<sup>107–110</sup> mycophenolate mofetil,<sup>111,112</sup> and silymarin<sup>113</sup> had no additional benefits compared with UDCA alone. There are insufficient data at present to support the use of immunosuppressive therapy for PBC.<sup>114</sup>

## New approaches for PBC

Many novel therapeutic approaches are proposed to target patients with no or incomplete biochemical response to UDCA.<sup>115</sup> Among them, peroxisome proliferator-activated receptor  $\alpha$  agonists,<sup>116–121</sup> farnesoid X receptor agonists,<sup>122,123</sup> and biotherapies such as anticluster of differentiation-20,<sup>124,125</sup> glucagon-like peptide-1 receptor agonists,<sup>126,127</sup> and estrogen- $\alpha$  receptor agonists<sup>128</sup> could be promising.

A number of agents are worthy of comment. The effect of fibrate on the biochemical indices of patients with PBC has been described in several cohorts of Japanese patients. A number of studies report response to both bezafibrate<sup>118,119</sup> and fenofibrate<sup>120,121</sup> over 12–26 weeks in those who have previously failed to respond to UDCA. Given that such biochemical indices are shown to be important in predicting long-term outcome in PBC, more randomized clinical trials of combination fibrate and UDCA therapy with sufficient numbers and follow-up to demonstrate changes in clinical outcome should be performed in patients who fail to respond to UDCA monotherapy. Farnesoid X receptor is a bile acid-activated nuclear receptor highly expressed in both the liver and gastrointestinal tract. It has a role in regulating bile and cholesterol metabolism. The use of potent farnesoid X receptor ligands such as obeticholic acid has recently been shown to offer potentially important therapeutic benefits in UDCA-refractory PBC. A recent report of an international double-blind, placebo controlled trial in patients with PBC showed substantial improvement in various liver enzymes including ALP,  $\gamma$ -glutamyl transpeptidase, and alanine aminotransferase with different doses of the drug (10, 25, or 50 mg or placebo) given in addition to UDCA therapy. This recent finding has now opened the door for future therapeutic trials to make use of farnesoid X receptor agonists such as obeticholic acid for the treatment of chronic cholestatic liver diseases.<sup>122,123</sup> Rituximab, an immunosuppressant and chimeric monoclonal antibody that works against cluster of differentiation-20, was administered in the form of two infusions at days one and 15 in patients who had PBC and an incomplete response to UDCA. It still may be controversial but shows considerable promise as a therapy for PBC.<sup>124,125</sup>

## Liver transplantation

Liver transplantation has greatly improved survival in patients with PBC, and it is the only effective treatment for those with liver failure. The 5-year survival rate after orthotopic liver transplantation in PBC may be as high as 85%, one of the best outcomes of any liver disease. Recurrence rate

of the disease postorthotopic liver transplantation is about 20%, usually between 3–7 years postorthotopic liver transplantation. Disease progression after recurrence is slow and retransplantation is rarely necessary.<sup>129,130</sup>

## Treatment of symptoms and complications

Fatigue may be multifactorial; causes other than PBC should be considered. Medications such as modafinil, a stimulant used in conditions such as narcolepsy, have been shown to be effective.<sup>131</sup> Many treatments are available to counteract the morbidity from pruritus, which results in significant improvement in the quality of life in these patients. Table 4 lists drugs used to treat pruritus in patients with PBC. Cholestyramine (a bile acid sequestrant) at a dose of 8–24 g/day is effective in alleviating symptoms in nearly 90% of patients.<sup>48</sup> The antibiotic rifampin, at a dose of 150 mg twice daily, is another medication that can be used in those patients who cannot tolerate cholestyramine or do not respond to it.<sup>132</sup> Sertraline (75–100 mg/day), a serotonin reuptake inhibitor, seems to be an effective and well-tolerated treatment for pruritus caused by chronic cholestasis.<sup>133</sup> The opioid antagonists naloxone and naltrexone may be effective in patients who do not respond to ammonium resins or rifampin.<sup>48</sup> Plasmapheresis should be considered when treatment of pruritus is urgently required, especially when the patient is suicidal due to severe and uncontrollable pruritus.<sup>134</sup>

UDCA induces an average decrease of 15%–20% in total and low-density lipoprotein cholesterol after 1 year of therapy.<sup>135</sup> In patients who continue to have increased serum cholesterol, other conditions leading to hypercholesterolemia mainly due to metabolic syndrome and their therapeutic

**Table 4** Treatment of the symptoms of primary biliary cirrhosis

Pruritus	
1st line	Cholestyramine 4 g/day (before and after breakfast)
2nd line	Rifampin 150 mg twice daily
3rd line	Sertraline (antidepressant)
4th line	Naloxone/naltrexone by an experienced physician
5th line	Liver transplantation
Supportive	Ultraviolet light, sunlight
Emergency	Plasmapheresis
Raynaud's	
1st line	Calcium channel blockers
2nd line	Alternative: prostacyclin and its derivatives, endothelin receptor antagonists, and phosphodiesterase inhibitors
Sicca syndrome	
Dry eyes	Artificial tears
Dry mouth	Dental hygiene, dental visit every 3–6 months
Dry vagina	Vaginal lubricants

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measures may be considered.<sup>2</sup> Current treatments for osteoporosis include physical activity, calcium and vitamin D supplementation to achieve at least 30 ng/mL of serum 25-hydroxyvitamin D3, and bisphosphonates or estrogen supplementation.<sup>2</sup>

## Future directions and conclusion

The clinical picture of PBC has changed in two decades mainly due to the introduction of UDCA, improvement of testing AMA profiles, increased knowledge of the disease among health care providers, and closer access to health checkup. Although becoming much clearer, the exact pathogenesis of the disease and difference in the patterns of disease progression remain unclear.<sup>136</sup> In this regard, newly developed animal models as well as currently undergoing genome-wide association studies worldwide may provide us with a better understanding of PBC.<sup>7,137,138</sup>

## Disclosure

The authors report no conflicts of interest in this work.

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