Primary biliary cirrhosis is a chronic liver disease characterised by intrahepatic bile-duct destruction, cholestasis, and, in some cases, cirrhosis. Evidence supporting the autoimmune nature of this disorder includes the appearance of highly specific antimitochondrial antibodies (AMAs) and autoreactive T cells. Concordance rates in monozygotic twins, familial prevalence, and genetic associations underscore the importance of genetic factors, whereas findings of epidemiological studies and murine models suggest a possible role for exogenous chemicals and infectious agents through molecular mimicry. The incidence of primary biliary cirrhosis has increased over recent decades, possibly attributable to augmented testing of liver biochemistry rather than a rise in disease incidence. AMAs remain the hallmark of diagnosis in most cases and allow detection of asymptomatic patients. Symptomatic individuals usually present with either pruritus or fatigue and, more rarely, with either jaundice or complications of cirrhosis. The prognosis of primary biliary cirrhosis has improved because of early diagnosis and use of ursodeoxycholic acid, the only established medical treatment for this disorder. Although not a cure, treatment can slow disease progression and delay the need for liver transplantation. However, some patients do not respond adequately to ursodeoxycholic acid and might need alternative therapeutic approaches.

Introduction

Primary biliary cirrhosis is an autoimmune liver disease characterised by the presence in serum of highly specific antimitochondrial antibodies (AMAs) and progressive destruction of intrahepatic bile ducts, resulting in chronic cholestasis, portal inflammation, and fibrosis that can lead to cirrhosis and, ultimately, liver failure. The disease is characterized by the presence in serum of highly specific antimitochondrial antibodies (AMAs) and autoreactive T cells. Concordance rates in monozygotic twins, familial prevalence, and genetic associations underscore the importance of genetic factors, whereas findings of epidemiological studies and murine models suggest a possible role for exogenous chemicals and infectious agents through molecular mimicry. The incidence of primary biliary cirrhosis has increased over recent decades, possibly attributable to augmented testing of liver biochemistry rather than a rise in disease incidence. AMAs remain the hallmark of diagnosis in most cases and allow detection of asymptomatic patients. Symptomatic individuals usually present with either pruritus or fatigue and, more rarely, with either jaundice or complications of cirrhosis. The prognosis of primary biliary cirrhosis has improved because of early diagnosis and use of ursodeoxycholic acid, the only established medical treatment for this disorder. Although not a cure, treatment can slow disease progression and delay the need for liver transplantation. However, some patients do not respond adequately to ursodeoxycholic acid and might need alternative therapeutic approaches.

Epidemiology

Data about incidence and prevalence of primary biliary cirrhosis have generally been obtained passively and might not indicate true rates in the general population; regional differences could vary on the basis of medical awareness and expertise. Indeed, a population-based approach to case detection has little feasibility for primary biliary cirrhosis because of its rarity. As a result, reported prevalence ranges between 19 and 402 cases per million. Differences in estimates of incidence and prevalence of primary biliary cirrhosis are probably secondary to variable diagnostic criteria, case-finding methods, doctors' awareness, and quality levels of health-care systems. On the basis of data from case-finding studies, however, a latitudinal geographical pattern of occurrence of primary biliary cirrhosis has been proposed, with the disease being most frequent in northern Europe and North America. Indeed, the highest prevalence and incidence rates have been reported in Scandinavia, Great Britain, and the northern midwest region of the USA. Exceptions to this pattern are the high rates noted in the Spanish area of Sabadell. Some researchers suggest that incidence of primary biliary cirrhosis is also growing. Indeed, rates rose from 5·8 to
20·5 cases per million population of Sheffield, UK, per year between 1980 and 1999,12,13 and from 11 to 32 cases per million population per year in Newcastle-upon-Tyne, UK, between 1976 and 1994.14,15 This increase was paralleled by prevalence reaching more than 200 cases per million in the middle to late 1990s. Whether these changes are due to rising disease incidence or are secondary to augmented detection of mild asymptomatic cases or slowly progressing disease remains to be established. However, age at diagnosis of mid-to-late 50s has remained consistent across different periods of study.

Most autoimmune diseases are predominant in female patients, and in primary biliary cirrhosis, this preponderance is especially striking—the ratio of affected females to males is as high as 10:1.16 The observation that, in the general population, detection of AMAs in serum is not skewed to females16 suggests either that the diagnosis of primary biliary cirrhosis might be suspected more frequently in women than men or that progression from loss of tolerance to the autoantigen to clinical liver disease is more common in female patients.

Risk factors associated with an uncommon disease such as primary biliary cirrhosis are difficult to ascertain because of obstacles in undertaking studies of sufficient size; however, some associations have been found frequently enough to suggest validity of associations. Cumulatively, risk of development of primary biliary cirrhosis is raised with a positive family history of the disease, a history of urinary or vaginal infections,17 comorbidity with other autoimmune diseases, past or present smoking, and previous pregnancies. Frequent use of nail polish or hair dye has a weak association with disease risk.18,19

Cause and pathogenesis

Three important observations must be taken into account for us to understand the pathogenic basis of primary biliary cirrhosis (figure 1). First, appearance of AMAs before liver disease suggests that loss of tolerance to the mitochondrial autoantigen is an early event and could be independent of the development of liver disease. Second, although the autoantigen is present ubiquitously in all nucleated cells, the immune response is restricted to epithelial cells of intrahepatic bile ducts and, to a lesser degree, to cells of salivary and lacrimal glands. Finally, recurrence of primary biliary cirrhosis after liver transplantation supports the idea that the bile duct epithelial cell is a generic target and is not unique to the patient with primary biliary cirrhosis.20 Similar to other complex diseases, the combination of a susceptible genetic background and exposure to environmental triggers is needed to initiate and promote the disorder.

Observations that 1–6% of individuals with primary biliary cirrhosis have at least one family member manifesting disease,9 and a 63% concordance rate in monozygotic twins (vs null concordance in dizygotic sets),21 show the substantial genetic effect on disease susceptibility, one of the strongest for any autoimmune disorder. Many candidate genes have been investigated for a role in susceptibility to primary biliary cirrhosis, disease progression, or both in case-control cross-sectional studies. Findings of a genome-wide association study undertaken in a northern American set of patients and controls22 indicated a significant association between primary biliary cirrhosis and polymorphisms of HLA-DQB1, IL12A, IL12RB2, and to a minor extent, STAT4, and these associations have been confirmed in an independent cohort of Italian patients and controls with a combined analysis.23

Several environmental factors—mainly infectious and chemical—are also thought to contribute to the onset of primary biliary cirrhosis, largely through molecular mimicry or modification of autoantigens. Geographic clustering of cases near toxic waste sites in New York City24 and space-time clustering in northeast England25 provide epidemiological evidence for a role of chemicals, infectious agents, or both. Additional data that lend support to a role for infections in disease development include the significantly higher prevalence than usual of recurrent urinary-tract infections in patients with primary biliary cirrhosis,26 and experimental findings of sequence similarity between the E2 enzyme of the pyruvate dehydrogenase complex recognised by autoantibodies and bacterial proteins.27 Several bacterial strains—including the non-pathogenic gram-negative bacterium Novosphingobium aromaticivorans—have the highest known homology to the immunodominant autoepitope of the E2 enzyme.28,29 Several other infectious agents have been proposed, including Escherichia coli, Helicobacter spp.,29 organisms of the genus Mycoplasma,30 and a human β retrovirus,31 although support for the retrovirus has not been substantiated.32

Other environmental factors proposed to trigger disease onset are foreign chemicals (ie, xenobiotics) that can either alter or form a complex with a defined self or non-self protein, causing a change in the protein’s molecular structure that induces an immune response. Lipoic acid is attached to only a few proteins, yet it is a vital component of the E2 epitope.33 The structure of the E2 enzyme exposes lipoic acid at the exterior of the protein complex, making this compound accessible to chemical modification.34 The role of xenobiotics in

![Figure 1: Factors possibly entailed in onset and perpetuation of bile-duct injury in primary biliary cirrhosis](image-url)
primary biliary cirrhosis is supported by serum reactivity against specific organic compounds with structures similar to lipoic acid;\textsuperscript{46} furthermore, two of these compounds (6-bromohexanoate and 2-octynoic acid) can induce AMAs and liver lesions similar to those of primary biliary cirrhosis in guinea pigs\textsuperscript{45} and mouse models.\textsuperscript{46,47}

Primary biliary cirrhosis has been regarded as an autoimmune disease from the time of the first seminal reports\textsuperscript{38} because of the predominance of female patients, frequent autoimmune comorbidities, and, most importantly, by loss of immune tolerance to self-mitochondrial proteins.\textsuperscript{39} Panel 1 summarises Witebsky’s criteria both for and against the autoimmune basis of primary biliary cirrhosis.\textsuperscript{40} Although most evidence argues that primary biliary cirrhosis is a disease of autoimmunity directed against antimitochondrial antigens on biliary epithelial cells, proof of a direct pathogenic role for serum autoantibodies is scarce: seronegative patients manifest similar disease features to those of their AMA-positive counterparts,\textsuperscript{41} changes in AMA titres do not correlate with severity of primary biliary cirrhosis, disease stage, or both; and immunosuppressive treatment has been fairly ineffective in patients with primary biliary cirrhosis.

AMAs in serum are highly sensitive and specific for primary biliary cirrhosis: they are detected in nearly 95% of patients, with specificity close to 100% when tested with recombinant antigens.\textsuperscript{42} Indirect immunofluorescence remains the test used for screening, but it can be associated with a substantial number of false-positive results.\textsuperscript{43} Follow-up data from AMA-positive individuals without signs of liver disease suggest that autoantibodies arise several years before onset of primary biliary cirrhosis and have a high predictive value.\textsuperscript{44} Epitopes recognised by AMAs include lipoylated domains (via the Asx-Lys-Ala motif) within subunits of the mitochondrial respiratory chain,\textsuperscript{45} in particular, E2 subunit and E3 binding-protein components of the pyruvate dehydrogenase complex and E2 components of the 2-oxoglutarate dehydrogenase and branched-chain 2-oxo acid dehydrogenase complexes (table).\textsuperscript{46,47}

In addition to AMAs, autoreactive CD4+ and CD4+ T cells to the E2 component of the pyruvate dehydrogenase complex have been identified both in peripheral blood and within the liver of patients with primary biliary cirrhosis, and the immunodominant epitope of these T cells maps in close proximity to the epitope recognised by AMAs in serum. Autoreactive CD4+ cell clones specific for the E2 enzyme have been isolated in intrahepatic and peripheral lymphocytes, not only in AMA-positive individuals but also in patients without antibodies, thus corroborating the notion that primary biliary cirrhosis either positive or negative for AMAs is one nosological entity.\textsuperscript{48}

CD4+ CD25\textsuperscript{high} regulatory T cells act to prevent autoreactivity, as shown in several autoimmune diseases, including autoimmune hepatitis.\textsuperscript{49} Patients with primary biliary cirrhosis are characterised by substantially lower frequencies of CD4+ CD25\textsuperscript{high} regulatory T cells as proportions of total T-cell receptor-αβ+/CD4+ cells, and this factor could be important in the breakdown of tolerance.\textsuperscript{50} Moreover, raised amounts of polyclonal IgM and hyper-responsiveness to CpG (cytosine-phosphate-guanine dinucleotide motif),\textsuperscript{51} and enhanced natural killer cell\textsuperscript{52} and monocyte responses,\textsuperscript{53} which are all features found in primary biliary cirrhosis, also lend support to a role for innate immunity.

### Panel 1: Features of primary biliary cirrhosis for and against autoimmune pathogenesis

**In support of autoimmunity**

- Specific serum autoantibodies\textsuperscript{41,42}
- Autoreactive T cells\textsuperscript{43}
- Adaptive transfer of cholangitis using CD8+ T cells (in murine models)\textsuperscript{44}
- Functional T regulatory defects\textsuperscript{45}
- Female predominance\textsuperscript{46}
- Autoimmune comorbidity\textsuperscript{46,47}
- MHC association\textsuperscript{48}

**Against autoimmunity**

- Absence of disease after autoantibody transfer (in mice)
- Absence of correlation between titre of antimitochondrial antibodies and disease severity\textsuperscript{48}
- Failure to respond to immunosuppressive agents (based on limited data)\textsuperscript{46,47}

Features shown according to Witebsky’s criteria, as modified by Rosa and Bona.\textsuperscript{40}

### Table: Sensitivity of serum autoantibodies in primary biliary cirrhosis

<table>
<thead>
<tr>
<th>Antigen/Monitor</th>
<th>Indirect immunofluorescence</th>
<th>ELISA</th>
<th>Immunoblotting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AMAs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General\textsuperscript{50}</td>
<td>70–90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDC-E2\textsuperscript{51}</td>
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<td>79.6%</td>
<td>81.7%</td>
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<tr>
<td>OGD-C-E2\textsuperscript{54}</td>
<td>…</td>
<td>NA</td>
<td>27.4%</td>
</tr>
<tr>
<td>BCOMC-E2\textsuperscript{53}</td>
<td>…</td>
<td>56.7%</td>
<td>59.1%</td>
</tr>
<tr>
<td>pMIT3\textsuperscript{55}</td>
<td>…</td>
<td>94%</td>
<td>92%</td>
</tr>
<tr>
<td><strong>ANAs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rim-like pattern\textsuperscript{51,52}</td>
<td>10–52%</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Gp210\textsuperscript{53}</td>
<td>…</td>
<td>16–32%</td>
<td>10–42%</td>
</tr>
<tr>
<td>Nup62\textsuperscript{51,54}</td>
<td>…</td>
<td>NA</td>
<td>22–32%</td>
</tr>
<tr>
<td>Multiple nuclear dots\textsuperscript{51}</td>
<td>13–25%</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Sp100\textsuperscript{51}</td>
<td>…</td>
<td>21–39%</td>
<td>NA</td>
</tr>
<tr>
<td>PML</td>
<td>…</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Centromere</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General\textsuperscript{51}</td>
<td>9–20%</td>
<td>…</td>
<td></td>
</tr>
<tr>
<td>CENPA, B, C\textsuperscript{51}</td>
<td>26%</td>
<td>…</td>
<td>21%</td>
</tr>
</tbody>
</table>

AMAs=antimitochondrial antibodies. E2=E2 component. PDC=pyruvate dehydrogenase complex. OGD=2-oxoglutarate dehydrogenase. BCOMC=branched-chain 2-oxo acid dehydrogenase. ANAs=antinuclear antibodies. Gp210=glycoprotein 210. Nup62=nucleoporin 62. PML=promyelocytic leukaemia. CENP=centromere protein. NA=data not available. For ELISA and immunoblotting, only data obtained with recombinant antigens are shown, and references are for the largest studies.
Once tolerance to AMAs is lost, additional mechanisms entailed in the immune response to a ubiquitous autoantigen begin to be unravelled. These lead to specific injury of biliary epithelial cells and seem to be linked to unique processes of apoptosis.\textsuperscript{78,79} Unlike other cell types, the E2 component of the pyruvate dehydrogenase complex remains intact in bile-duct cells after apoptosis, thus probably retaining its immunogenicity.\textsuperscript{74} Furthermore, this enzyme is found within apoptotic blebs and is accessible to AMAs\textsuperscript{75} and local antigen-presenting cells. Moreover, findings of in-vitro experiments have shown an intense and specific immune response when macrophages of patients with primary biliary cirrhosis are combined with apoptotic blebs of biliary epithelial cells and AMAs.\textsuperscript{76} However, recurrence of primary biliary cirrhosis after liver transplantation suggests that this occurrence is not an intrinsic defect of bile-duct cells of affected individuals but is a feature of biliary epithelia in general, not seen in other epithelial cells.

**Clinical features**

The clinical features and natural history of primary biliary cirrhosis vary greatly between patients, ranging from asymptomatic and slowly progressive to rapidly evolving. The frequency of asymptomatic disease seems to be increasing, probably because of raised awareness of the disease together with broad use of routine testing of liver biochemistry. Many asymptomatic patients will, however, develop symptomatic liver disease within 5 years of diagnosis, although a third could remain symptom-free for many years.\textsuperscript{77}

Although non-specific, fatigue is the most common symptom of primary biliary cirrhosis; it is present in nearly 80\% of patients and more than 40\% report moderate-to-severe symptoms.\textsuperscript{72,73} The mechanism of fatigue associated with this disease remains unknown despite many proposals, including autonomic dysfunction,\textsuperscript{80} muscle impairment,\textsuperscript{81} excessive daytime somnolence,\textsuperscript{82} changes in cortical excitability,\textsuperscript{83} and altered manganese homoeostasis within the CNS.\textsuperscript{84} Fatigue in patients with primary biliary cirrhosis is typically characterised as excessive daytime somnolence and can impair quality of life. Despite sparse correlation between fatigue and severity of liver disease, fatigue can be associated with decreased overall survival.\textsuperscript{85,86}

Of symptoms related to longstanding cholestasis, pruritus seems to be the most typical complaint and is reported by 20–70\% of patients in studies, usually preceding jaundice. Widespread use of ursodeoxycholic acid has led to a substantial reduction in the frequency of this distressing symptom despite the absence of a direct effect. Many factors contribute to pruritus onset and intensity. First, cholestasis itself impairs biliary excretion of several compounds leading to an increased systemic concentration of putative so-called pruritogenic compounds. Of these substances, bile acids could be important, as suggested by the ability of bile-acid binding resins—ie, colestyramine—to ameliorate pruritus.\textsuperscript{87} Second, on the basis of both augmented opioidergic activity reported in individuals with cholestasis and experimental neuroendocrinology data obtained in cultured cholangiocytes,\textsuperscript{88} a central origin of pruritus has been suggested.\textsuperscript{89} Accordingly, opioid antagonists are currently used to treat this symptom, although these agents are sometimes tolerated poorly by patients.\textsuperscript{89} An important association has been reported between severity of pruritus and circulating concentrations of the extracellular lysophospholipase autotaxin, a protein already implicated in neoplasia and immunity regulation.\textsuperscript{90} A reduction in bone density is common in patients with primary biliary cirrhosis, with features of osteopenia (33\%) and, less frequently, osteoporosis (11\%).\textsuperscript{91} By contrast with previous reports,\textsuperscript{91} researchers have suggested that primary biliary cirrhosis might not represent an additional risk factor for bone demineralisation in women with compensated disease supplemented with calcium and vitamin D.\textsuperscript{92} Therefore, in clinical practice, such supplementation—along with monitoring of bone density and vitamin D concentrations in serum—is highly recommended, even in individuals with early disease.\textsuperscript{93,94} With more advanced disease, deficiencies of other fat-soluble vitamins and steatorrhoea are common and must be monitored and supplemented.

Hypercholesterolaemia, typically caused by a rise in HDL cholesterol, is common in patients with primary biliary cirrhosis but does not increase cardiovascular risk\textsuperscript{95} or cause early signs of atherosclerosis.\textsuperscript{86} Use of statins is, therefore, not usually necessary, but these drugs are tolerated safely in people with other cardiovascular risk factors.\textsuperscript{96}

Several autoimmune diseases could coexist with primary biliary cirrhosis. In our experience, as many as a third of patients are diagnosed with another autoimmune disease,\textsuperscript{97} most frequently Sjögren’s syndrome and autoimmune thyroid disease. Whether coexisting autoimmune diseases indicate a common genetic background or represent similar pathogenetic mechanisms is unclear.\textsuperscript{98} Autoimmune comorbidities do not modify the natural history or clinical presentation of primary biliary cirrhosis, with the exception of a reported slower progression of liver fibrosis in patients with scleroderma.\textsuperscript{99}

Once primary biliary cirrhosis has progressed to frank cirrhosis, liver complications do not differ much from those seen in cases of cirrhosis due to other causes, with the exception of oesophageal varices, which can arise early in the disease course, sometimes before other signs of cirrhosis. This outcome is probably attributable to the presence of presinusoidal inflammation and consequent fibrosis induced by granulomas. Other complications of portal hypertension (ie, ascites and hepatic encephalopathy) happen typically in end-stage primary biliary cirrhosis. The occurrence of hepatocellular carcinoma in individuals with primary biliary cirrhosis is similar to
other forms of cirrhosis and warrants surveillance in patients at advanced disease stages.102

**Diagnosis and liver histology**

The diagnosis of primary biliary cirrhosis should be suspected in anyone with findings of chronic cholestasis after liver tests, particularly with raised concentrations of alkaline phosphatase. Furthermore, patients with primary biliary cirrhosis generally have increased amounts of aminotransferases and immunoglobulins (mainly IgM).

Diagnosis can be established if two of three objective criteria are present: a concentration in serum of AMAs at titres of 1:40 or higher; an unexplained rise in the amount of alkaline phosphatase of at least 1-5 times the upper limit of normal for more than 24 weeks; and compatible liver histological findings, specifically non-suppurative cholangitis and interlobular bile duct injury.6 Whether AMA-positive individuals without biochemical abnormalities will eventually develop primary biliary cirrhosis is still debatable, but expectant follow-up with annual liver biochemical analysis is reasonable.4 By contrast, individuals with AMA-negative primary biliary cirrhosis (currently synonymous with autoimmune cholangitis) diagnosed on the basis of abnormal concentrations of alkaline phosphatase and liver histological findings manifest a similar course to their seropositive counterparts.4 In these cases, MRI or endoscopic retrograde cholangiography are recommended to rule out primary sclerosing cholangitis or other disorders that might lead to chronic cholestasis.

In addition to AMAs, antinuclear antibodies (ANAs) are detected by indirect immunofluorescence in about 50% of serum samples from patients with primary biliary cirrhosis (table). Two nuclear fluorescence patterns are found in primary biliary cirrhosis. A rim-like pattern results from autoantibody reaction with glycoprotein 210 and nuleoporin 62 (within the nuclear pore complex), and a pattern of multiple nuclear dots results from reaction with Sp100 and the promyelocytic leukaemia antigen (possibly also cross-reacting with small ubiquitin-like modifiers).101 The pathogenic role of ANAs in primary biliary cirrhosis remains to be established, as is the case with AMAs, although cross-sectional and longitudinal data suggest an association between ANA positivity specific to primary biliary cirrhosis and severe disease.101-103

The need to undergo liver biopsy in primary biliary cirrhosis is controversial, although most clinicians agree that this procedure is valuable for disease staging, particularly in clinical trials.104 From a diagnostic point of view, liver biopsy specimens are not required when the other two less invasive diagnostic criteria are fulfilled. Thus, routine liver biopsy should be done only when considering a differential diagnosis from other disorders, including small-duct primary sclerosing cholangitis, sarcoidosis, or drug-induced cholestasis. Histological staging is based on Ludwig’s105 and Scheuer’s106 classifications, ranging from portal-tract inflammation with predominantly lymphoplasmacytoid infiltrates and septal and interlobular bile-duct loss (stage I) to frank cirrhosis (stage IV). Eosinophils and granulomas are also characteristic but not diagnostic of primary biliary cirrhosis. When two or more stages manifest within the same liver sample, the patient is classified as belonging to the more severe stage. However, because of the heterogeneous nature of biliary involvement, liver biopsy findings could include sampling error on the basis of histological variability in different areas,107 but this factor does not warrant taking of several biopsy specimens.

Although many patients with primary biliary cirrhosis will have mildly raised concentrations of aminotransferases, and findings of liver biopsy might even show some degree of piecemeal necrosis, a poorly characterised subgroup exists in which features of so-called hepatitis are relevant.107 This finding has led to the designation of primary biliary cirrhosis–autoimmune hepatitis overlap, but specific diagnostic criteria for this disorder remain to be established. In addition to histological findings, primary biliary cirrhosis–autoimmune hepatitis overlap should be considered when the ratio of alkaline phosphatase to aspartate aminotransferase is less than 1.5, serum concentration of IgG is increased, and antibodies against smooth muscle are present at greater than 1:80 titre. A suspected diagnosis of primary biliary cirrhosis–autoimmune hepatitis overlap could be clinically relevant because this disorder seems to have a more severe prognosis than primary biliary cirrhosis alone, and other treatments could be considered, including immunosuppressive agents.108

**Treatment and natural history**

The natural history and prognosis of primary biliary cirrhosis has become notably more benign, with substantial improvements in disease outcome reported in studies. Although these observations could be secondary to early diagnosis and a consequent lead-time bias,109 falling rates of liver transplantation for primary biliary cirrhosis in Europe and North America since widespread use of ursodeoxycholic acid was introduced suggest a true change in natural history.110,111 Figure 2 presents a schematic and somewhat arbitrary view of the natural history of primary biliary cirrhosis. Before the introduction of ursodeoxycholic acid, time from diagnosis to symptom-onset was about 2.0–4.2 years, and survival was compromised relative to a healthy population.112,113 Classically, presence of symptoms at diagnosis was an important determinant of disease progression and survival.110 However, in a study from the UK of a large cohort of patients followed up for 24 years, although mortality due to liver disease was greatest in symptomatic patients, overall survival was similar in individuals with and without symptoms at time of presentation. Prediction of patients’ survival in primary biliary cirrhosis has been attempted, and the Mayo model is the most well regarded,100 which includes five
independent prognostic variables (age, total concentrations in serum of bilirubin and albumin, prothrombin time, and severity of ascites), with amount of bilirubin in serum as the most heavily weighted. Use of an enhanced liver fibrosis algorithm (based on fibrosis markers in serum)\textsuperscript{106} or presence of ANA in serum specific to primary biliary cirrhosis\textsuperscript{107} might predict the occurrence of major events and survival of patients with primary biliary cirrhosis, especially in early-stage disease, but independent verification is awaited.

Many therapeutic agents have been proposed for primary biliary cirrhosis on the basis of different views of disease pathogenesis. Rarity of the disorder, its variable natural history, and slow progression necessitate large, multicentre, and long-term studies. The only currently established treatment for primary biliary cirrhosis is ursodeoxycholic acid 13–15 mg/kg a day, which can be subdivided into two or three doses.\textsuperscript{108} The treatment is well tolerated and, with the exception of moderate weight gain, does not lead to substantial adverse effects over time.

Methods of action of ursodeoxycholic acid in primary biliary cirrhosis remain unclear, yet the hydrophilic nature of this agent could lead to a reduction in amounts of primary bile acids, and the substance might also regulate cellular signalling and protect against apoptosis.\textsuperscript{109,110} Several randomised controlled trials have been undertaken to assess the efficacy of ursodeoxycholic acid, and in all series, this agent resulted in a substantial improvement in serum markers of cholestasis. Results of randomised placebo-controlled studies of ursodeoxycholic acid, which were of sufficient duration to assess the effects on histology and survival, have been reviewed.\textsuperscript{111} Although some consistency was recorded across studies in terms of biochemical, clinical, and histological response,\textsuperscript{112,113} an effect on general survival was noted in only one study.\textsuperscript{114} About 20% of patients treated with ursodeoxycholic acid will have no histological progression over 4 years, and some will have no progression over a decade or longer.\textsuperscript{115} This agent has the potential to prevent portal hypertension and the appearance of oesophageal varices and to delay time to liver transplantation.\textsuperscript{116} Survival rates of patients with stage I or II disease treated with ursodeoxycholic acid are similar to those of age-matched healthy controls.\textsuperscript{117} A combined analysis of three studies\textsuperscript{120} and three meta-analyses\textsuperscript{121,122} has been done to achieve sufficient statistical power to investigate the effects of ursodeoxycholic acid on survival. A significant survival improvement was only seen in patients with amounts of bilirubin in serum higher than 24 μmol/L at baseline.\textsuperscript{123}

Despite the effectiveness of ursodeoxycholic acid, a subgroup of patients with primary biliary cirrhosis will have an incomplete response to treatment and are at greatest risk of progression. Criteria have been proposed to define the group of complete responders, including: a decrease in the amount of alkaline phosphatase greater than 40% of the baseline or to a normal level;\textsuperscript{124} concentrations of alkaline phosphatase less than three times the upper limit of normal, aspartate aminotransferase less than twice the upper limit of normal, and bilirubin less than 17 μmol/L.\textsuperscript{125} and normalisation of abnormal concentrations of bilirubin, albumin, or both.\textsuperscript{126} In a prospective assessment of these criteria, response—as defined by the latter two criteria—was associated with better survival in patients with moderately advanced disease, compared with the group of patients who did not have these features.\textsuperscript{127}

For patients who do not have a complete response to ursodeoxycholic acid, a need for new treatments remains. Future trials should focus specifically on this subpopulation with primary biliary cirrhosis, and most data on use of a farnesoid X receptor agonist have been promising.\textsuperscript{128} The benefit of steroids remains to be established in primary biliary cirrhosis.\textsuperscript{129} However, in view of the many adverse effects, short-term steroid use should be considered only in individuals with primary biliary cirrhosis–autoimmune hepatitis overlap or with other autoimmune comorbidities. Use of other immunosuppressive or antifibrotic agents, alone or in combination with ursodeoxycholic acid, is not recommended, either because toxic effects outweigh any potential benefits or owing to absence of effectiveness.

In addition to prevention of liver disease progression, management of primary biliary cirrhosis includes treatment of symptoms and comorbidities associated with the disorder, which constitute a clinical challenge. Proposed treatments are sometimes unsatisfactory, particularly for symptoms that substantially reduce quality of life, such as pruritus. In general terms, the oral anion exchange resin colestyramine remains the treatment of choice for pruritus, whereas rifampicin can be used in the short term for unresponsive cases (panel 2). Of note,
colestyramine can inhibit absorption of ursodeoxycholic acid, requiring a break of 2 h between drugs. Unless another underlying cause—such as hypothyroidism or anaemia—can be identified, fatigue is poorly responsive to treatment. Antidepressants have not been effective, and in small trials of modafinil, only a few patients have been able to tolerate the drug. Sjögren’s syndrome, which can be seen in up to 75% of patients, should initially be managed with liberal use of artificial tears and saliva. Pilocarpine or cevimeline can be used in refractory cases.

Because of the high rate of osteopenia and osteoporosis in patients with primary biliary cirrhosis, bone density measurements should be done every 2–3 years. Daily supplementation of vitamin D (1000 IU) and calcium (1500 mg) is advisable, with alendronate 70 mg per week given to individuals with osteopenia (panel 2).

Primary biliary cirrhosis is a common indication for liver transplantation; this procedure is the only effective treatment in patients with end-stage disease. Indications for liver transplantation in individuals with primary biliary cirrhosis do not differ from those in other liver diseases, namely decompensated cirrhosis with diuretic-resistant ascites and spontaneous bacterial peritonitis, recurrent variceal bleeding, encephalopathy, or hepatocellular carcinoma. Severe pruritus that is refractory to treatment could be judged an indication in special cases. Post-transplant survival rates are 92% at 1 year and 85% at 5 years, and the recurrence rate is 30% at 10 years. Fortunately, recurrence of primary biliary cirrhosis affects survival rarely, and retransplantation is uncommon. Although ursodeoxycholic acid has not been shown to enhance post-transplant outcomes, it does lead to biochemical improvements post transplant and should be considered in view of its good safety profile. Use of high-dose steroids immediately after transplantation can lead to severe bone loss and should be monitored and treated aggressively.

Management guidelines
On the basis of guidelines from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver for management of primary biliary cirrhosis, we propose a pragmatic approach to patients with this disorder. Irrespective of the presence of symptoms or signs of liver cirrhosis, individuals with primary biliary cirrhosis should be treated with ursodeoxycholic acid (13–15 mg/kg per day). Monitoring of biochemical response is helpful for prediction of those at greatest risk of progressive liver disease. If no response to ursodeoxycholic acid arises, or if features of autoimmune hepatitis are present, alternative treatment strategies should be considered. In all patients, the concentration of bilirubin in serum and platelet count should be measured regularly to detect early signs of disease progression or portal hypertension. As with other chronic liver diseases, we recommend that individuals with primary biliary cirrhosis should undergo ultrasonography and be measured for amount of α-fetoprotein every 6 months, to screen for hepatocellular carcinoma. Liver transplantation is to be considered in patients with advanced disease, as shown by appropriate staging methods.

Future perspectives
Several important steps towards better understanding of the causes and pathogenesis of primary biliary cirrhosis have been taken in recent years, yet important knowledge gaps remain with respect to genetic and immunological aberrancies that lead to the disorder. Data for epigenetic changes in primary biliary cirrhosis are sparse, which is perhaps surprising in view of the regularity with which such studies are reported for other complex conditions. Despite improvements in outcomes with ursodeoxycholic acid, additional treatments are needed for patients who have an incomplete response or have features of autoimmune hepatitis. As our understanding of underlying immune effector mechanisms grows, we are optimistic that new biological agents targeted at specific immune response mechanisms will prove beneficial for this subgroup of patients.

Contributors
All authors contributed to the literature search and writing of the Seminar.

Conflicts of interest
We declare that we have no conflicts of interest.
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