Primary biliary cirrhosis is a chronic cholestatic liver disease of adults. This disorder is characterised histologically by chronic non-suppurative destruction of interlobular bile ducts leading to advanced fibrosis, cirrhosis, and liver failure. The precise aetiological basis of primary biliary cirrhosis remains unknown, although dysregulation of the immune system and genetic susceptibility both seem to be important. Affected patients are typically middle-aged women with abnormal serum concentrations of alkaline phosphatase. Presence of antimitochondrial antibody in serum is almost diagnostic of the disorder. Identification of primary biliary cirrhosis is important, because effective treatment with ursodeoxycholic acid has been shown to halt disease progression and improve survival without need for liver transplantation. However, therapeutic options for disease-related complications—including fatigue and metabolic bone disease—remain unavailable. Mathematical models have been developed that accurately predict the natural history of primary biliary cirrhosis in individuals. Despite advances in understanding of the disease, it remains one of the major indications for liver transplantation worldwide.

Primary biliary cirrhosis affects all races, yet seems to cluster within specific geographical areas. Women are mainly affected, with a female/male ratio of 9:1. The median age of disease onset is 50 years, but varies between 20 and 90 years. Estimates of annual incidence and prevalence range from 2 to 24 cases per million and 19 to 240 cases per million population, respectively. Data from Olmsted County, Minnesota, USA, suggest a stable incidence rate over the past 25 years but a higher prevalence than described in Canada. Differences in methodology and case definitions have impeded comparisons between series.

The worldwide variation in disease prevalence suggests that environmental factors are needed for phenotypic expression of primary biliary cirrhosis. From a population-based study in northern England, affected individuals are typically middle-aged women with asymptomatic rises of serum hepatic biochemical variables. Fatigue, pruritus, or unexplained hyperlipidaemia at initial presentation might also suggest a diagnosis of primary biliary cirrhosis. Serum antimitochondrial antibody positivity is nearly diagnostic of the disease. Disease identification is important because effective medical treatment with ursodeoxycholic acid can halt disease progression and extend survival free of liver transplantation. Mathematical models that accurately characterise the natural history of primary biliary cirrhosis may also assist in determining the optimum timing for liver transplantation when indicated.

Epidemiology
Primary biliary cirrhosis affects all races, yet seems to cluster within specific geographical areas. Women are mainly affected, with a female/male ratio of 9:1. The median age of disease onset is 50 years, but varies between 20 and 90 years. Estimates of annual incidence and prevalence range from 2 to 24 cases per million and 19 to 240 cases per million population, respectively. Data from Olmsted County, Minnesota, USA, suggest a stable incidence rate over the past 25 years but a higher prevalence than described in Canada. Differences in methodology and case definitions have impeded comparisons between series.

The worldwide variation in disease prevalence suggests that environmental factors are needed for phenotypic expression of primary biliary cirrhosis. From a population-based study in northern England, a large case-control US investigation, presence of tobacco use and extrahepatic autoimmune disorders have been associated with the disease when compared with controls. First-degree relatives of people with primary biliary cirrhosis are also known to have at least a two-fold increased risk of autoimmune diseases. A high rate of urinary-tract infections in smokers with the disease has raised the possibility of an infectious cause. Data of the association between gravidity and primary biliary cirrhosis are conflicting.

Genetics
Genetic predisposition to autoimmunity in primary biliary cirrhosis has been associated with alleles from MHC loci. However, class 2 MHC loci, including DR8, DQA1*0102, and DQB1*0402, have only been reported in selected patients with the disorder. The haplotypes DR3, DR8, and DR4 are more frequent in white populations by contrast with DR2 and DR8 haplotypes in Japanese patients. Conflicting results, however, are noted for the observation between the DQA1*0102 haplotype and disease resistance.

Presence of a raised familial risk for primary biliary cirrhosis could be an indirect link to a genetic component for disease susceptibility. Results of studies have estimated frequency of the disease among first-degree relatives of index cases to be between 1·3% and 6%, in. A positive family history of primary biliary cirrhosis, using population-based epidemiological methods, was identified in 6·4% of instances. The overall prevalence in offspring of patients with the disease was 1·2%, with a 2·3% rate in

Search strategy and selection criteria
Sources including published reports and abstracts, reference books, and selected references from affiliated bibliographies provided the material for this Seminar. Peer-reviewed publications were identified by computerised search of the MEDLINE database (1966–present) with the terms “primary biliary cirrhosis” and “biliary cirrhosis”. Clinical trials were included if they had been published as peer-reviewed manuscripts or in abstract form. Randomised controlled trials examining survival, treatment failure, or both were specifically identified.
females. An increased rate in first-degree relatives is based on a predominance of mother/daughter relationships. With a population-based prevalence of 0·05% in women older than age 40 years, the relative risk for primary biliary cirrhosis among their daughters was 15.16

Pathogenesis

Immune-mediated mechanisms

Present evidence lends support to the notion of primary biliary cirrhosis as an immune-mediated disease. Cellular and humoral abnormalities have both been noted. Immunohistochemical staining of T lymphocytes in portal and periportal areas shows CD4-positive and CD8-positive T cells.27 Furthermore, abnormal suppressor T-cell activity has been reported in asymptomatic first-degree relatives of people with the disease.30 Intraepithelial adhesion molecules (eg, ICAM-1), which are expressed in areas of epithelial-cell damage, can also participate in pathogenesis of primary biliary cirrhosis.19 The importance of raised concentrations of tumour necrosis factor α, interleukin 8, and interleukin 12 in patients with advanced-stage versus early-histological-stage disease remains unknown.28

The major finding associated with humoral immunity in primary biliary cirrhosis resides with recognition of the antimitochondrial antibody.21 Formation of this antibody is directed against the E2 subunit of the pyruvate dehydrogenase complex in more than 95% of patients.22 Advances in understanding of the mechanisms associated with development of this antibody have also emerged.23 These include recognition of apoptotic biliary-cell phagocytosis,24 and in-vivo25 and in-vitro26 expression of the E2 subunit of the pyruvate dehydrogenase complex on biliary epithelial cells. Arguments against direct cytotoxic activity from antimitochondrial antibody include: persistence of antibody after liver transplantation without immediate disease recurrence; absence of correlation between serum antibody titre and hepatic involvement; absence of antibody in some patients with histological confirmation of primary biliary cirrhosis; and induction of the antibody in response to the recombinant E2 subunit of the pyruvate dehydrogenase complex in animals, without resulting primary biliary cirrhosis.27

Non-immune mediated mechanisms

The idea of molecular mimicry by microbial antigens has been proposed as an underlying mechanism for primary biliary cirrhosis, in which crossreactivity with self-antigens happens via the immune system.20 Induction of phenotypic disease after coculture of normal biliary epithelial cells and lymph nodes from affected patients also lends support to the hypothesis of a transmissible agent.29 Abnormal involvement; absence of antibody in some patients with histological confirmation of primary biliary cirrhosis; and induction of the antibody in response to the recombinant E2 subunit of the pyruvate dehydrogenase complex on biliary epithelial cells. Arguments against direct cytotoxic activity from antimitochondrial antibody include: persistence of antibody after liver transplantation without immediate disease recurrence; absence of correlation between serum antibody titre and hepatic involvement; absence of antibody in some patients with histological confirmation of primary biliary cirrhosis; and induction of the antibody in response to the recombinant E2 subunit of the pyruvate dehydrogenase complex in animals, without resulting primary biliary cirrhosis.27

Clinical features

Asymptomatic primary biliary cirrhosis

Individuals with asymptomatic disease consist of 20–60% of all first-time diagnoses, based largely on increased use of screening liver-biochemistry profiles.31 Asymptomatic patients tend to be older than symptomatic counterparts at diagnosis.1 However, most asymptomatic patients, over time, will develop symptoms and hepatic disease will progress.2 No specific features to predict development of symptomatic disease have been identified.36

Symptomatic primary biliary cirrhosis

The most common symptoms reported in this disorder include fatigue and pruritus, especially in female compared with male patients.27 Cutaneous hyperpigmentation, hepatosplenomegaly, and xanthelasmas (excessive subcutaneous deposition of cholesterol) have been described on physical examination. Jaundice is usually a late symptom that heralds onset of advanced histological disease, but which was seen in 20% of patients from an early series.38 Complications of cirrhosis and portal hypertension—such as ascites, variceal bleeding, and hepatic encephalopathy—are similar to other primary hepatic disorders. Table 1 summarises the clinical features originally reported in patients with primary biliary cirrhosis; with advances in diagnosis, a growing proportion of patients are being identified with asymptomatic early-stage disease.

Diagnosis

Biochemical features

Rises in serum alkaline phosphatase (2–10 times upper limit of normal) are frequently seen at diagnosis of primary biliary cirrhosis; normal values (41–133 IU/L) are rarely noted.34 No association exists between the amount of the rise in serum alkaline phosphatase and outlook in untreated patients. Modestly raised values for alanine aminotransferase and aspartate aminotransferase are typical. Serum total bilirubin concentrations are generally normal at diagnosis yet rise with histological disease progression. Values reaching 342 μmol/L are unusual, but may arise without extrahepatic biliary obstruction. Amplified serum prothrombin time might indicate vitamin K malabsorption or advanced primary biliary cirrhosis. Hypercholesterolaemia in up to 85% of patients could arise at diagnosis. Increased concentrations of serum IgM and bile acid (cholic acid, chenodeoxycholic acid)40 are typical in patients with primary biliary cirrhosis.

Serological features

Between 90% and 95% of people with antimitochondrial antibody in serum, at titres of 1/40 or greater, have primary biliary cirrhosis.41 Seropositivity for this antibody is not specific to the disease, but remains highly sensitive (98%). Antinuclear antibody and smooth muscle antibody arise in 35% and 66% of patients with primary biliary cirrhosis, respectively.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>25</td>
</tr>
<tr>
<td>Fatigue</td>
<td>65</td>
</tr>
<tr>
<td>Pruritus</td>
<td>55</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>25</td>
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<tr>
<td>Hyperpigmentation</td>
<td>25</td>
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<tr>
<td>Splenomegaly</td>
<td>15</td>
</tr>
<tr>
<td>Jaundice</td>
<td>10</td>
</tr>
<tr>
<td>Xanthelasma</td>
<td>10</td>
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</tbody>
</table>

Table 1: Symptoms and signs at initial presentation of primary biliary cirrhosis
respectively. Serum anticentromere antibodies in patients affected by the CREST syndrome (calcinosis, Raynaud’s phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasias) are noted in 10–15% of instances. Other autoantibodies in association with the disease include rheumatoid factor (70%) and antithyroid (antimicrosomal, antithyroglobulin) antibodies (40%).

Absence of seropositivity for antimitochondrial antibody in patients with clinical features suggestive of primary biliary cirrhosis has been termed autoimmune cholangitis. Serum autoantibodies, including antinuclear antibody, smooth muscle antibody, and anticarbonic anhydrase, are usually present. Of note, no difference seems to be present in natural history or responsiveness to ursodeoxycholic acid treatment in patients with autoimmune cholangitis compared with those with antimitochondrial antibody-positive primary biliary cirrhosis. An overlap syndrome between primary biliary cirrhosis and autoimmune hepatitis, which remains poorly understood, arises in fewer than 10% of patients.

Radiological features

Ultrasonography is most frequently used to exclude extrahepatic biliary obstruction. Other cross-sectional imaging techniques, such as CT or MRI, could provide additional information, such as features of portal hypertension (splenomegaly, intra-abdominal varices, and reversal of portal vein flow), which might be present in occult advanced disease. Non-progressive portal adenopathy in 15% of patients with primary biliary cirrhosis is not associated with disease progression. Large or bulky adenopathy, if present, warrants exclusion of malignancy.

Histological features

A liver biopsy specimen is useful for staging of the disease, although its value in diagnosis is questionable. However, a diagnosis of antimitochondrial antibody-negative primary biliary cirrhosis cannot be made without a liver biopsy specimen. Histological classification schemes have categorised the disease into four stages (figure 1). Stage 1 is associated with portal-tract inflammation from predominantly lymphoplasmacytic infiltrates, resulting in destruction of septal and interlobular bile ducts up to 100 µm in diameter. Focal-duct obliteration with granuloma formation has been termed the florid duct lesion, and is judged almost pathognomonic for primary biliary cirrhosis when present (figure 2). Stage 2 entails periportal extension of inflammation. Cholangitis, granulomas, and ductular proliferation are most typically seen. Stage 3 is dominated by septal or bridging fibrosis. Ductopenia (defined as loss of >50% of interlobular bile ducts) becomes more frequent, resulting in cholestasis and raised hepatic copper deposition within periportal and paraseptal hepatocytes. Stage 4 accords with biliary cirrhosis. Because of increased sampling variability from liver biopsy specimens in the disease, the highest recognised stage should be used to establish extent of involvement.

Differential diagnosis

The patient who is diagnosed with primary biliary cirrhosis is typically a woman in the fifth or sixth decade of life with complaints of fatigue, pruritus, or both. A growing number of asymptomatic patients are diagnosed with the disease after systematic assessment of abnormal serum liver enzymes. Several other disorders however, need further investigation to be excluded. Primary alternate diagnoses include extrahepatic biliary obstruction, primary sclerosing cholangitis (especially the small-duct variant), cholestatic hepatitis from drug-induced hepatotoxic effects, overlap syndrome with autoimmune hepatitis, hepatic sarcoidosis, and idiopathic adulthood ductopenia.

Associated disorders

Coexistent extrahepatic autoimmune disease-states arise in 70% of individuals with primary biliary cirrhosis (table 2). Keratoconjunctivitis sicca (Sjögren’s syndrome) is the

Figure 1: Schematic representation of staging system for primary biliary cirrhosis (Ludwig’s classification)

Stage 1 is inflammation within the portal space, focused on the bile duct. Stage 2 is inflammation extending into the hepatic parenchyma (interface hepatitis or piecemeal necrosis). Stage 3 is fibrosis, and stage 4 is cirrhosis with regenerative nodules. Reprinted from Sleisenger MH, Fordtran JS. Gastrointestinal and liver disease, 6th edn. Philadelphia: WB Saunders, 1998. With permission from Elsevier Inc.

Figure 2: Florid duct lesion in stage 1 primary biliary cirrhosis
most frequent disorder, occurring in about 75% of patients. Scleroderma or any component of the CREST syndrome can be noted in up to 10% of patients. Presence of detectable antithyroid antibodies (antimicrosomal, antithyroglobulin) with lymphocytic (Hashimoto’s) thyroiditis might not be associated with clinical disease. Graves’ disease and hyperthyroidism are uncommon. Proximal or distal renal tubular acidosis is usually without clinical significance but is described in 50% of reported patients. Idiopathic pulmonary fibrosis and inflammatory bowel disease each arise in fewer than 5% of individuals with primary biliary cirrhosis.

### Symptoms and disease complications

#### Fatigue

Frequency of fatigue in people with primary biliary cirrhosis is reported to be between 65% and 85%. Alterations in central neurotransmission and impaired corticotropin-releasing hormone response have been postulated as putative causes. Results of investigations with validated methods that measure fatigue severity show it to be independent of severity of hepatic disease, sleep disturbance, or depression. However, a lower than expected frequency of reported fatigue in cases versus controls, using population-based methods, has been reported. No effective medical treatment has been recognised to alleviate this symptom.

#### Pruritus

Pruritus is reported in 25–70% of patients affected by primary biliary cirrhosis. Hypotheses to explain this symptom have included serum bile-acid retention with cholestasis and amplified release of endogenous opioids. Whereas symptom severity is independent of histological stage, rises in serum alkaline phosphatase concentration and Mayo risk score are independent adjusted predictors for pruritus at diagnosis. In most patients, pruritus gradually resolves with progression of hepatic disease. Treatment with antihistamines or phenobarbital have been largely ineffective. Cholestyramine (4 g before and after breakfast) usually reduces pruritus intensity. In refractory cases, rifampicin (150–600 mg daily) is associated with rapid onset of action and symptom relief. Although well tolerated, this drug is associated with hepatoxic and bone-marrow aplasia on rare occasions. Parenteral naloxone and oral nalmefene have also led to symptomatic improvement in pilot and controlled trial settings. Flumecicol and stanozolol could benefit selected individuals with primary biliary cirrhosis. In patients with pruritus refractory to medical treatment, liver transplantation is the most effective option.

#### Hyperlipidaemia

Hyperlipidaemia arises in up to 85% of patients, and could be the initial serum abnormality in primary biliary cirrhosis. Concentrations of both serum cholesterol and triglyceride are raised. In early-stage disease, lipoprotein abnormalities are typically reported, including reduced lipoprotein a. Initial rises in HDL rather than LDL are seen but they reverse with progression of histological disease. No clear correlation exists between xanthelasma formation and serum cholesterol concentrations in primary biliary cirrhosis. Reduction in amount of serum cholesterol (specifically LDL) and improvement in xanthelasma formation are associated with unoxoehydroxyacid treatment. In patients unresponsive to this therapy, empirical use of cholestyramine and inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase have anecdottely been effective. Despite strikingly altered serum lipid values, no evidence exists for a raised prevalence of atherosclerotic disease and cardiovascular-related mortality in primary biliary cirrhosis.

#### Metabolic bone disease

Reduced bone formation is considered the primary explanation for osteoporosis in at-risk individuals with primary biliary cirrhosis. Metabolism of calcium and vitamin D is almost always normal in anicteric patients. Discovery of polymorphisms of the vitamin D receptor, and their potential association with osteoporosis in patients with primary biliary cirrhosis, has been described. Cigarette smoking and subsequent reductions in serum vitamin D concentrations might also be important. About a third of patients with the disease have osteopenia, whereas 11% have osteoporosis. Risk factors for metabolic bone disease in people with primary biliary cirrhosis include age, body-mass index, and stage 3 or 4 histological disease. In patients undergoing liver transplantation, a transient decline in bone density by 20% might happen for up to 6 months after surgery, which greatly increases fracture risk.

Oral calcium (1000–1200 mg daily) with weight-bearing activity is recommended. Vitamin D deficiency, when present, arises on the basis of fat-soluble vitamin malabsorption. Oral replacement treatment is indicated when measured serum concentrations are reduced compared with normal values. The 25-hydroxylation of vitamin D is intact in patients with primary biliary cirrhosis, thus obviating the need for 1,25-dihydroxyvitamin D or 25-hydroxyvitamin D compounds. Dosing is generally between 25 000 and 50 000 IU two to three times per week. Despite controversy, hormone replacement therapy is safe and effective in postmenopausal women with primary biliary cirrhosis. The potential risk of worsening jaundice and liver failure, however, needs close surveillance, with repeated biochemical assessment at 2-week intervals for 2 months. Calcitriol, sodium fluoride, and etidronate have not been conclusively shown to improve bone density. Results from a randomised, placebo-controlled trial of alendronate are awaited.

#### Steatorrhoea

Steatorrhoea is a typical finding in patients with advanced primary biliary cirrhosis. Impairment of bile-acid delivery to the small intestine, untreated coeliac disease, and exocrine pancreatic insufficiency are the most usual causes. Bacterial overgrowth syndrome causing steatorrhoea in primary biliary cirrhosis might arise in the presence of scleroderma and its variant forms. In patients with decreased bile-acid concentrations, oral replacement of median-chain triglycerides for long-chain compounds, coupled with an overall reduced fat intake, is usually of benefit. Adherence to a gluten-free diet in coeliac disease should improve symptoms. Pancreatic enzyme replacement therapy and rotating empirical antibiotic use are also of benefit with pancreatic insufficiency and bacterial overgrowth, respectively.

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**Table 2: Extrahepatic autoimmune disorders associated with primary biliary cirrhosis**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratoconjunctivitis sicca</td>
<td>75</td>
</tr>
<tr>
<td>Renal tubular acidosis</td>
<td>50</td>
</tr>
<tr>
<td>Gallstones</td>
<td>30</td>
</tr>
<tr>
<td>Arthritis</td>
<td>20</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>15</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>15</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>10</td>
</tr>
<tr>
<td>CREST syndrome</td>
<td>5</td>
</tr>
</tbody>
</table>

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Fat-soluble vitamin deficiency
Malabsorption of fat-soluble vitamins is typical in patients with advanced primary biliary cirrhosis. Vitamin A deficiency, seen in 20% of cases, is often clinically asymptomatic. Oral replacement therapy with 25,000–50,000 IU two to three times a week is recommended. Serum concentrations should be reassessed after 6–12 months to avoid excessive replacement and potential vitamin A hepatotoxic effects. Vitamin D deficiency (as discussed previously) is the next most common fat-soluble vitamin deficiency. Symptomatic vitamin E deficiency is rarely seen but could present as ataxia from abnormalities of the posterior vertebral columns of the spinal cord. Parenteral vitamin E replacement is not universally effective in reversal of neurological dysfunction. However, oral replacement therapy with 400 IU daily is indicated for asymptomatic patients. Vitamin K deficiency can be treated at doses of 5–10 mg daily.

Cancer
In primary biliary cirrhosis, occurrence of hepatocellular carcinoma is amplified, which is usually recognisable in late-stage disease. Increased risk of extrahepatic malignancy including breast cancer is controversial.

Disease-modifying therapies
Ursodeoxycholic acid is the only medical treatment for primary biliary cirrhosis that has received US Food and Drug Administration approval.

Immunosuppressive drugs
Corticosteroids, azathioprine, ciclosporin, and methotrexate have not been shown to be effective treatments for primary biliary cirrhosis.

Antifibrotic agents
Penicillamine, a potential antifibrotic drug studied in 312 patients, was ineffective and associated with drug-related toxic effects in primary biliary cirrhosis. Although a rise in liver-related survival from colchicine treatment was reported in one investigation after all placebo-treated patients were crossed over to colchicine, no effect was seen in a meta-analysis of three studies combining results of all placebo-treated patients. A fall in cytokine concentrations and potential vitamin A hepatotoxic effects. Vitamin D deficiency (as discussed previously) is the next most common fat-soluble vitamin deficiency. Symptomatic vitamin E deficiency is rarely seen but could present as ataxia from abnormalities of the posterior vertebral columns of the spinal cord. Parenteral vitamin E replacement is not universally effective in reversal of neurological dysfunction. However, oral replacement therapy with 400 IU daily is indicated for asymptomatic patients. Vitamin K deficiency can be treated at doses of 5–10 mg daily.

Incomplete responders to treatment
An estimated 66% of patients with primary biliary cirrhosis are described as incomplete responders to long-term ursodeoxycholic acid monotherapy. Incomplete response is defined as failure to return serum concentrations of hepatic enzymes to normal, development of cirrhosis, or both. High concentrations of serum alkaline phosphatase at treatment onset seem predictive of incomplete response compared with complete responders. Histological disease progression by one to three stages arises in 11% of incomplete responders versus 4% of complete responders. Presence of histological cirrhosis before treatment with ursodeoxycholic acid also reduces the chance for a successful response. Of patients with a suboptimum response to the drug, several potential extrahepatic causes must be excluded. In addition to non-adherence or inappropriate dosing, the diagnoses of autoimmune hypothyroidism and coeliac disease must be eliminated as causes of raised serum hepatic enzymes. An incomplete response might also arise if an overlap syndrome with autoimmune hepatitis is present.

Combination treatments
Adjuvant treatments have also been studied in patients with primary biliary cirrhosis with an incomplete response to ursodeoxycholic acid alone. Corticosteroids, azathioprine, ciclosporin, and methotrexate have all been used with this drug. No significant histological or survival benefit has been reported. In an investigation of ursodeoxycholic acid with colchicine (compared with monotherapy), however, reductions in the number of treatment failures, slow progression of Mayo risk score, and improvement in hepatic histology, were reported. Results of a long-term, multicentre North American trial involving ursodeoxycholic acid and methotrexate are awaited.

Novel agents
Malotilate, chlorambucil, thalidomide, and silymarin have not been associated with significant biochemical or histological improvements. Bezafibrate is a hypolipidaemic agent, which stimulates the canicular
phospholipid pump MDR3 by activation of the transcription factor peroxisome-proliferator-activated receptor α. Bezafibrate alone125 or in combination with ursodeoxycholic acid126 has been associated with similar improvements in serum concentrations of hepatic enzymes. Long-term studies, however, are required. Results from pilot investigations of mycophenolate mofetil127 are awaited.

Natural history and prognosis

Asymptomatic primary biliary cirrhosis

The natural history of asymptomatic disease has not been extensively reported. In a study, 29 patients with antimitochondrial antibody titres of 1/40 or greater and normal serum hepatic enzyme concentrations were followed up for a median of 17·8 years.128 Initial liver histological findings at study entry were diagnostic for or accorded with primary biliary cirrhosis in 24 patients (83%). 22 (76%) developed symptoms associated with the disorder, including fatigue, pruritus, and right upper abdominal pain. Of ten patients who underwent repeat liver biopsy, histological disease progression was noted in 40% of patients during median follow-up of 11·4 years. Despite a cohort mortality rate of 15%, no deaths from liver-related causes were reported. From time of diagnosis, asymptomatic patients have a greater overall median survival than do symptomatic individuals. Those remaining asymptomatic have equivalent survival rates compared with an age-matched and sex-matched healthy population.129

Symptomatic primary biliary cirrhosis

Estimates of overall median survival range between 10 and 15 years from time of diagnosis, whereas advanced histological disease (stage 3 or 4) imparts a median survival approaching 8 years.130 Risks in total bilirubin above 136–6–171·0 μmol/L have been associated with median life expectancy of 2 years.131 Prognostic indicators of poor outcome include old age, raised serum total bilirubin concentrations, reduced hepatic synthetic function, and advanced histological stage. Development of complications from portal hypertension happens in symptomatic individuals with primary biliary cirrhosis as well. An increased risk for oesophageal varices and resultant haemorrhage over 3 years (40% and 20%, respectively) has been noted.132 Identification of oesophageal varices in patients with precirrhotic primary biliary cirrhosis results from presinusoidal hepatic fibrosis caused by granulomatous bile-duct inflammation and portal oedema.

Prognostic survival models

To account for known clinical variables as determinants of survival, several mathematical models simulating the natural history of primary biliary cirrhosis have been developed. The Mayo Clinic model133 is most frequently used for prediction of long-term survival based on extensive validation in independent populations. Patient’s age, serum total bilirubin, albumin, prothrombin time, and presence or absence of oedema and ascites are the model’s independent predictor variables. Because the model does not need histological stage to predict survival, invasive procedures such as liver biopsy can be avoided. Subsequent model refinement with time-dependent methods has improved accuracy of prediction of short-term survival within 2 years of clinical assessment.134

Initial concerns about the potential discrepancy between improvements in serum bilirubin and accuracy of survival prediction were raised after approval of ursodeoxycholic acid as medical treatment for primary biliary cirrhosis. The Mayo risk score, however, retains its ability to predict survival in patients treated with this drug.135

Liver transplantation

Primary biliary cirrhosis remains one of the top five indications for liver transplantation in the USA. Survival rates of patients and grafts after liver transplantation are reported to approach 92% and 85% at 1-year and 5-year intervals, respectively.136 Fatigue and pruritus usually resolve, with metabolic bone disease improving after transient worsening in the first 6–12 months after liver transplantation. Data show an association between improved clinical and economic outcomes with a pretransplant Mayo risk score less than 7·8.137 Hepatic retransplantation happens in fewer than 10% of patients with primary biliary cirrhosis.

Previously considered a controversial topic, recurrence of primary biliary cirrhosis after liver transplantation has now been shown. Initial reports of allograft histological features consistent with stage 1 primary biliary cirrhosis were limited by absence of explicit criteria. The cumulative risk for recurrent disease has now been estimated at 15% at 3 years and 30% at 10 years with prospective follow-up. Serum antimitochondrial antibody status seems to be independent of recurrence risk. This antibody could disappear soon after liver transplantation only to return later with or without recurrent disease. Tapering of systemic corticosteroids, use of tacrolimus for immunosuppression after liver transplantation, or both have been suggested to be potential risk factors for recurrent primary biliary cirrhosis. No information is available about the efficacy of ursodeoxycholic acid treatment in halting disease progression from recurrent primary biliary cirrhosis.138

Conflict of interest statement

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References


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