Primary biliary cirrhosis

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Primary biliary cirrhosis is a chronic cholestatic liver disease characterised by destruction of small intrahepatic bile ducts, leading to fibrosis and potential cirrhosis through resulting complications. The serological hallmark of primary biliary cirrhosis is the antimitochondrial antibody, a highly disease-specific antibody identified in about 95% of patients with primary biliary cirrhosis. These patients usually have fatigue and pruritus, both of which occur independently of disease severity. The typical course of primary biliary cirrhosis has changed substantially with the introduöction of ursodeoxycholic acid (UDCA). Several randomised placebo-controlled studies have shown that UDCA improves transplant-free survival in primary biliary cirrhosis. However, about 40% of patients do not have a biochemical response to UDCA and would benefit from new therapies. Liver transplantation is a life-saving surgery with excellent outcomes for those with decompensated cirrhosis. Meanwhile, research on nuclear receptor hormones has led to the development of exciting new potential treatments. This Seminar will review the current understanding of the epidemiology, pathogenesis, and natural history of primary biliary cirrhosis, discuss management of the disease and its sequelae, and introduce research on new therapeutic options.

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Introduction

In 1950, Ahrens and colleagues[1] defined primary biliary cirrhosis in a compilation of 25 cases of diagnosed chronic intrahepatic biliary obstruction with xanthomatosis, reported between 1851 and 1950. The first case of primary biliary cirrhosis had been described almost 100 years earlier by Addison and Gull.[2] Ahrens and colleagues noted the female preponderance, hyperpigmentation, jaundice, pruritus, hepatomegaly, hyperlipidaemia, and xanthomatosis that are now known to be characteristic of the disease. In 1959, Sherlock[3] reported an exhaustive description of 42 patients followed up for up to 15 years. It is now known that primary biliary cirrhosis is a progressive disease characterised by the destruction of small intrahepatic bile ducts, leading to periportal inflammation, fibrosis, and potential cirrhosis. However, many patients with primary biliary cirrhosis do not have cirrhosis and this misnomer has led to concern that patients are unfairly stigmatised for a disorder that they do not have. Patient advocacy groups are working with the medical community to choose a new name that more accurately describes the disease.

Primary biliary cirrhosis is deemed a model autoimmune disease because of the serological findings, detection of antimitochondrial antibody (AMA), and specific bile duct pathological changes that occur in the disorder.[4] Primary biliary cirrhosis is most often diagnosed when routine laboratory studies reveal an increase in alkaline phosphatase. AMA, the serological hallmark of primary biliary cirrhosis, is present in about 95% of patients with the disorder, but in less than 1% of healthy adults.[5–7] High alkaline phosphatase in conjunction with presence of AMA is sufficient to diagnose the disorder. Liver biopsy is not necessary for diagnosis but can be useful in the absence of AMA or in the presence of overlap syndromes. Primary biliary cirrhosis predominantly affects women, and usually presents in the fifth or sixth decade of life.

Fatigue and pruritus are the most common symptoms of primary biliary cirrhosis, and both can be debilitating in some patients. The only accepted therapy is ursodeoxycholic acid (UDCA), which has been shown to extend transplant-free survival, especially when started early in the course of disease. However, UDCA does not cure the disease and about 40% of patients with primary biliary cirrhosis do not have a biochemical response to UDCA. Recent years have brought exciting new insights into the mechanisms that contribute to the disorder, including advances that are leading to novel treatments.

Epidemiology

Primary biliary cirrhosis is mainly diagnosed in women, with a female to male ratio of about 10 to 1.[4,8] A systematic review[9] of population-based epidemiological studies across Europe, North America, Asia, and Australia revealed an incidence of 0·9 to 5·8 per 100 000 people, with 92% of patients women. Although some groups have reported increased incidence over the past 40 years,[10–13] others have not substantiated this finding.[14,15] Whether these incidence trends indicate a true increase or are confounded by advances in diagnosis and treatment is unclear.

The prevalence of primary biliary cirrhosis ranges from 1·91 to 40·20 per 100 000 people and has increased over time.[9] The increased prevalence is probably attributable to a combination of increased disease recognition, better data capture by electronic medical records, and increased survival after the introduction of UDCA. Substantial geographical disparity is a feature of

Search strategy and selection criteria

A MEDLINE search was done with the terms "primary biliary cirrhosis", "cholestatic liver disease", and "PBC" for articles published between Jan 1, 2000, and Feb 28, 2015. Preference was given to more recent articles, but highly relevant older articles were not excluded. Results in all languages were reviewed. The reference lists of these publications provided additional relevant information. Review articles and book chapters are included to provide more details and references than can be cited here.

the prevalence of primary biliary cirrhosis, suggesting a possible role of environmental triggers in the development of disease.

Pathogenesis

Primary biliary cirrhosis is thought to be related to complex interactions between genetic predisposition and environmental triggers. Geographical clustering of cases has been described around Superfund sites (areas of toxic waste disposal) in the USA and in low-income areas (associated with increased pollution, cigarette smoking, and toxin exposure) in the UK, suggesting a role of environmental toxins.[14,16] Primary biliary cirrhosis has been associated with infectious agents (*Escherichia coli, Mycobacterium gordonae, Novosphingobium aromaticivorans*), hair dyes, nail polish, and cigarette smoking, although a causative role has not been established.

The prevalence of primary biliary cirrhosis is higher in families with an affected member, and 1·2% of children of patients develop the disease.[17] The odds ratio in a first-degree relative of a patient is 11 (95% CI 4·23–27·27) and daughters of women with primary biliary cirrhosis have the highest relative risk.[17] Several North American and European studies[18–20] have reported a strong link between HLA alleles and primary biliary cirrhosis. In particular, DRB1*08, DR3, DPB1*0301, DRB1*08-DQA1*0401-DQB1*04 are associated with susceptibility to the disorder, whereas DRB1*11 and DRB1*13 have been reported to confer protection.[21] The advent of genome-wide association studies is beginning to unravel the complex relation between genetics and disease, but full understanding remains elusive. Risk alleles in primary biliary cirrhosis tend to occur in genes associated with immune function, and cross many different immune pathways. These risk alleles are frequently identified in other autoimmune diseases, but it is not yet known by what mechanisms they affect phenotype. Immune pathways identified in primary biliary cirrhosis genome-wide association studies involve myeloid cell differentiation, antigen presentation, T-cell differentiation, and B-cell function.[22] A high concentration of natural-killer T cells, which secrete pro-inflammatory cytokines, is recorded in patients with primary biliary cirrhosis. Biliary epithelial cells are targeted in primary biliary cirrhosis, and express T-cell ligands that are thought to be essential for the induction of biliary epithelial autolysis. Biliary epithelial cells might act as antigen-presenting cells, amplifying the immune response.[23]

Bile acids are steroid compounds synthesised by the liver and secreted into the small intestine during digestion. They return to the liver through the portal vein, a process known as enterohepatic circulation. The enterohepatic circulation of bile acids is regulated at several sites. Farnesoid X receptors are nuclear hormone receptors that play a key part in bile acid metabolism. Bile acids are natural ligands for farnesoid X receptors. When bound to bile acids, the receptors downregulate bile acid biosynthesis through the suppression of the gene coding for cholesterol 7α-hydroxylase, the rate-limiting enzyme in bile acid biosynthesis.[24] Fibroblast growth factor-19 (FGF-19), a regulatory protein secreted by the ileal enterocytes, downregulates the biosynthesis of bile acids by suppressing the expression of cholesterol 7α-hydroxylase through a c-Jun N-terminal kinase-dependent pathway. Finally, bile acid uptake across the ileal enterocytes is mediated by a sodium dependent bile acid transporter (apical sodium dependent bile acid transporter). The discovery of these key regulatory elements in bile acid metabolism led to the development of new therapeutic strategies in cholestatic liver diseases that are being investigated.

Diagnosis

AMA in a patient with raised alkaline phosphatase is diagnostic of primary biliary cirrhosis, assuming other intrahepatic and extrahepatic causes of cholestasis have been excluded.[4]

Most patients are diagnosed when routine laboratory studies reveal abnormal serum biochemistry and trigger an in-depth assessment.[25] This often occurs before the onset of clinical symptoms. Higher than normal alkaline phosphatase is necessary for diagnosis; serum amino-transferases might be high but this is not the predominant feature. Fractionation of alkaline phosphatase might be necessary in patient groups at risk for increase of bone alkaline phosphatase. Total bilirubin is usually normal in early-stage disease and an abnormal value should raise concern for advanced disease. IgM is often high, and hyperlipidaemia is common.[4]

AMA is present in about 95% of patients with primary biliary cirrhosis[7,26] and is unusual in those without the disease.[5,6] AMA targets a family of mitochondrial enzymes, the 2-oxo-acid dehydrogenase complexes, which include pyruvate dehydrogenase (PDC-E2), branched chain 2-oxo-acid dehydrogenase (BCOADC-E2), and 2-oxo-glutaric acid dehydrogenase (OADC-E2). An AMA titre of 1:40 or more is regarded as positive. Magnitude of AMA positivity does not correlate with severity of disease; in fact AMA often continues to be present after liver transplantation in the absence of disease.[27,28]

Other autoantibodies, such as antinuclear antibody, are often identified in patients with primary biliary cirrhosis. Anti-Sp100 and anti-gp210 have a high specificity for primary biliary cirrhosis and could be helpful when AMA is negative.[27] Presence of anti-Sp100 or anti-gp210 is associated with more clinically aggressive disease.[29] In the presence of a cholestatic liver profile and AMA, liver biopsy is not necessary to establish the diagnosis. However, biopsy could be helpful when AMA is absent, if the biochemical profile shows a mixed cholestatic and hepatocellular pattern, or in the setting of other comorbidities such as non-alcoholic steatohepatitis. The florid duct lesion, an intense inflammatory infiltrate centred around the bile ducts, is the characteristic histological finding in primary biliary cirrhosis but seen

in only about 10% of biopsy specimens (figure). This infiltrate could consist of lymphocytes, plasma cells, macrophages, and polymorphonuclear cells coalesced to form a granuloma. These granulomas can resemble those resulting from infectious or other inflammatory aetiologies, and an expert hepatopathologist is essential to distinguish between the disease states. The inflammatory activity of primary biliary cirrhosis affects the small interlobular and septal bile ducts with sparing of the large and extrahepatic ducts. Many histological staging systems have been developed, but Ludwig's is the most widely used: Stage 1=portal inflammation, stage 2=extension to the periportal areas, stage 3=septal fibrosis or inflammatory bridging, and stage 4=cirrhosis.[30] In patients with portal hypertension, a reticulin stain can exclude the presence of nodular regenerative hyperplasia, a known complication of non-cirrhotic primary biliary cirrhosis.[31]

Abdominal imaging should be done at the onset of abnormal liver biochemistries to exclude biliary obstruction and to assess for signs of advanced fibrosis or portal hypertension. The extrahepatic bile ducts should be healthy in primary biliary cirrhosis. Imaging is otherwise not routinely necessary in the management of primary biliary cirrhosis except in the cirrhotic patient when hepatocellular carcinoma surveillance is likely.

Liver biopsy remains the gold standard for assessment of hepatic fibrosis, but is limited by sampling error and risk for serious adverse event. Non-invasive methods to assess hepatic fibrosis are gaining attention, as they assess the entirety of the hepatic parenchyma, are associated with lower risk, and are often less expensive than liver biopsy. Transient elastography has more than 90% sensitivity and specificity for detecting advanced fibrosis in patients with primary biliary cirrhosis, and is more accurate than previously established risk scores.[32,33] Transient elastography might not be universally applicable, because factors such as obesity, ascites, and extrahepatic cholestasis could lead to invalid results. However, transient elastography will probably play an increasing part in the longitudinal management of primary biliary cirrhosis patients.

Results of physical examination, especially in early stages of primary biliary cirrhosis, are usually healthy. Fewer than 10% of patients will have xanthomas or xanthelasmas from underlying hyperlipidaemia. Patients with pruritus might have excoriations or bleeding as a result of chronic scratching. Hyperpigmentation of the skin could be present in up to 50% of patients, a result of melanin deposition and unrelated to hyperbilirubinaemia. In late-stage disease, typical signs of cirrhosis and portal hypertension (spider nevi, palmar erythema, ascites, splenomegaly, muscle wasting) might be present.

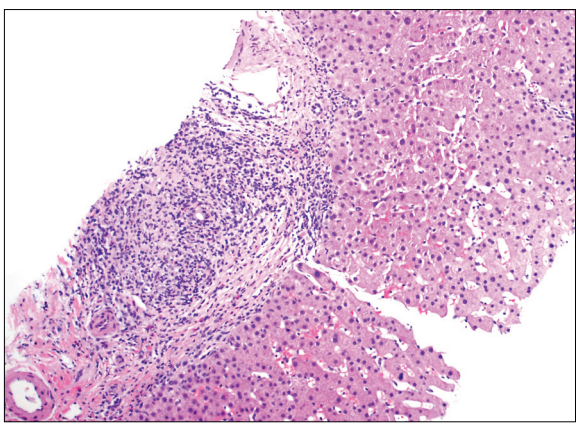

Figure: **Florid duct lesion in a patient with early-stage primary biliary cirrhosis**
Figure supplied by Dr Dora Lam-Himlin, Mayo Clinic, with permission.

Treatment

UDCA remains the only approved drug for the treatment of primary biliary cirrhosis. UDCA has been shown to improve serum hepatic biochemistries, delay histological progression, and delay the development of oesophageal varices.[34–46] UDCA improves transplant-free survival, and when UDCA is started in early-stage disease, overall survival is similar to that of the general population. A combined analysis[44] of three randomised placebo-controlled trials suggests that patients with moderate to severe disease probably derive the most benefit from UDCA. UDCA is the only drug approved by the US Food and Drug Administration for the treatment of primary biliary cirrhosis and is the only drug recommended for primary biliary cirrhosis by the European Association for the Study of the Liver.[25]

UDCA is a naturally-occurring hydrophilic bile acid, the 7-β-epimer of the primary bile acid chenodeoxycholic acid. UDCA inhibits intestinal absorption of bile acids, increases biliary secretion of bile acids, and increases the elimination of toxic substances from hepatocytes. Bile acid accumulation in hepatocytes creates an inflammatory state resulting in cell necrosis and apoptosis in late-stage disease. UDCA acts as an anti-inflammatory and stimulates secretion of a bicarbonate-rich fluid from cholangiocytes, decreasing cholestasis. Finally, UDCA augments micelle formation, decreasing the toxic effect of bile acids to cell membranes.[47]

UDCA 13–15 mg/kg per day is recommended for all patients with primary biliary cirrhosis, usually for life unless intolerance occurs. The most frequently reported adverse effects of the drug include loose stool (2–9%), headache, and mild weight gain; these rarely lead to discontinuation.[4] UDCA does not affect the symptoms of fatigue and pruritus.

Several other drugs and herbal supplements have been tested in primary biliary cirrhosis but none have shown therapeutic efficacy with an acceptable safety profile. Corticosteroids improved serum biochemistries and histology but with substantial deterioration of bone mineral density, precluding use as a long-term agent in patients already at risk for osteopenia.[25] Budesonide, in combination with UDCA, has shown biochemical and

histological improvement in small trials without the large side-effect profile usually seen with corticosteroids.[48] The use of budesonide is not recommended for patients with cirrhosis, because of impaired and unpredictable hepatic metabolism.

Bezafibrate, a ligand of the peroxisome proliferator-activated receptor, has shown safety and tolerability in several small trials in primary biliary cirrhosis.[49] Almost half of women who did not respond to UDCA had normalisation of alkaline phosphatase with the addition of bezafibrate. Long-term combination therapy of UDCA and bezafibrate resulted in improved alkaline phosphatase and Mayo risk score without a difference in survival.[50] Various agents have been tried with little or no efficacy, including methotrexate, azathioprine, ciclosporin A, mycophenolate mofetil, colchicine, d-penicillamine, silymarin, atorvastatin, thalidomide, lamivudine, and sulindac.

Discovery of the interaction between bile acids and nuclear hormone and membrane receptors has led to new targets for drug development in cholestatic liver disease (table 1). Obeticholic acid (INT-747) is a farnesoid X receptor agonist tested in primary biliary cirrhosis patients with inadequate response to UDCA. In a large, multicentre, randomised placebo-controlled trial,[51] almost half of primary biliary cirrhosis patients who did not respond to UDCA showed improved serum biochemistries on obeticholic acid. NGM282 is a novel FGF-19 analogue under investigation in phase 2 trials for primary biliary cirrhosis (NCT02135536).

	Potential therapeutic agents
Nuclear receptor target	
Farnesoid X receptor	Obeticholic acid
Peroxisome proliferator-activated receptor α	Bezafibrate, fenofibrate
Vitamin D receptor	Vitamin D
Membrane receptor target	
Fibroblast growth factor 4	Fibroblast growth factor 19, fibroblast growth factor 19 analogue NGM 282
G-protein-coupled BA receptor TGR5	TGR5 agonist Int-777
Apical sodium bile salt transporter	Apical sodium bile salt transporter inhibitors

NGM 282 is a novel FGF-19 analogue. Data from Beuers and colleagues.[24]

Table 1: **Potential therapeutic agents**

	Duration of response	Origin
Decrease in alkaline phosphatase to <2 times ULN	6 months	Mayo Clinic[59,60]
Decrease in alkaline phosphatase 40% from baseline or to normal value	1 year	Spanish[40]
Decrease in alkaline phosphatase to <3 times ULN, decrease in aspartate aminotrasferase to <2 times ULN, and normal bilirubin	1 year	Paris I[61]
Normalisation of bilirubin or albumin	1 year	Dutch[62]
Decrease in alkaline phosphatase to <1·67 times ULN	2 years	Toronto[63]
Decrease in alkaline phosphatase to <1·5 times ULN or aspartate aminotrasferase <1·5 times ULN, and normal bilirubin	1 year	Paris II[64]

ULN=upper limit of normal.

Table 2: **Criteria to define biochemical response to ursodeoxycholic acid.**

Natural history, prognosis, and survival

Before the widespread use of screening liver chemistries and the availability of UDCA, primary biliary cirrhosis was not usually diagnosed until the disease had reached an advanced stage, with subsequent median survival of 6–10 years.[52,53] Most patients who were asymptomatic at diagnosis developed symptoms after about 5 years.[54,55] However, the introduction of UDCA has led to a substantial change in patient outcomes. Survival of those who respond to UDCA is similar to that of age-matched and sex-matched healthy people.[45,56] UDCA delays histological progression, development of oesophageal varices, and need for liver transplantation in patients with primary biliary cirrhosis.[34–43,57] A retrospective review of almost 550 patients with primary biliary cirrhosis who had been enrolled in placebo-controlled trials with UDCA revealed significantly worse transplant-free survival in the placebo group, with relative risk 1·9 (95% CI 1·3–2·8).[44] A meta-analysis[58] of 4845 patients enrolled in long-term cohort studies revealed an overall transplant-free survival of 88% at 5 years, 77% at 10 years, and 63% at 15 years. Patients given UDCA had transplant-free survival of 90% at 5 years, 78% at 10 years, and 66% at 15 years, compared with 79% at 5 years, 59% at 10 years, and 32% at 15 years in untreated patients.

The biochemical response to UDCA is an important predictor of prognosis. About 40% of patients will not have an adequate biochemical response to UDCA, and these patients have a more rapid progression of disease than those with normalisation of alkaline phosphatase.[40] The exact definition of biochemical response has been the subject of debate (table 2).[40,59–64] Despite the absence of consensus on what constitutes a biochemical response, it is clear that normalisation or near-normalisation of alkaline phosphatase with UDCA is a marker of favourable outcomes. Patients without biochemical response had relative risk of 5·51 (95% CI 1·70–15·99) of death or liver transplantation compared with those with a response.[40] In a meta-analysis[58] of over 4800 patients with primary biliary cirrhosis, the strongest predictor of death or liver transplantation was alkaline phosphatase more than 2 times the upper limit of normal, 1 year after study enrolment (C statistic 0·71, 95% CI 0·69–0·73). These markers are therefore useful surrogate endpoints for clinical trials or other assessment of response to therapy. Male sex and young age at presentation are predictors of non-response to UDCA.[65]

Management of symptoms

Fatigue and pruritus are the most common symptoms in primary biliary cirrhosis patients, and often have a more negative effect on quality of life than the disease itself.[66,67]

Fatigue

Fatigue is the most common and debilitating symptom of primary biliary cirrhosis, affecting up to 80% of patients. Fatigue is unrelated to disease activity or stage, and tends to wax and wane throughout the course of illness. The fatigue of primary biliary cirrhosis is associated with inability to work, depression, decreased quality of life, and increased mortality.[68–74] Objective assessment of fatigue can be obtained via the Fatigue Impact Scale or the PBC-40 questionnaire.[75]

The cause of fatigue in primary biliary cirrhosis is not well understood, but centrally-mediated mechanisms are implicated. Chronic cholestasis results in accumulation of substances which cross the blood–brain barrier and cause degenerative changes in the brain. Neurological abnormalities in primary biliary cirrhosis include impaired concentration and memory, disturbed sleep pattern, and autonomic dysfunction leading to hypotension and muscle dysfunction.[76,77] Over half of patients with primary biliary cirrhosis show impaired concentration and memory on neuropsychiatric testing,[78] and the reported fatigue is associated with pronounced impairment in functional status.[79]

Treatment with UDCA does not change the frequency or the severity of fatigue. Other agents, including ondansetron and fluoxetine, have not shown benefit.[80,81] Modafinil, approved by the US Food and Drug Administration for wakefulness disorders, seemed to help in open-label trials but the benefit did not continue in the long term.[82–84] Other contributors to fatigue, such as hormonal imbalance, polypharmacy, or obstructive sleep apnoea, should be sought and treated when present. In the absence of effective medical therapy, patients and their providers should develop lifestyle modifications to accommodate the burden of fatigue. A supportive environment can improve the sense of wellbeing, and primary biliary cirrhosis support groups exist internationally.

Pruritus

Pruritus is the second most common symptom in primary biliary cirrhosis, affecting 20–70% of patients. Pruritus can range in severity from mild to severe and is sometimes debilitating.[85] Similar to fatigue, the presence and severity of pruritus tend to fluctuate throughout the course of disease and are not necessarily related to primary biliary cirrhosis stage or activity. The pruritus of cholestasis causes intense, sometimes intolerable, itch leading to scratching, excoriation, sleep deprivation, depression, and even suicidal ideation.[85,86] The 5-D itch scale is a useful instrument for objective assessment of pruritus severity. Patients with primary biliary cirrhosis with early-onset pruritus have more aggressive disease and substantially worse survival than those with later onset of pruritus.[87] The cause of cholestatic pruritus is unknown. Proposed mechanisms include the accumulation and deposition of bile acids in tissues, and excesses of histamine, substance P, lysophosphatidic acid, and autotoxin.[85,88–90]

Many treatment options exist for managing pruritus in primary biliary cirrhosis, with varying benefit. UDCA does not relieve pruritus and patients with pruritus should be offered a trial of drugs other than UDCA for symptom relief.

Cholestyramine, a bile acid sequestrant that increases faecal excretion of bile acids, is the first-line agent for management of cholestatic pruritus.[91] Because of sequestrant properties, cholestyramine can bind drugs, and therefore should be given separately from other drugs. Cholestyramine improves pruritus in most patients with primary biliary cirrhosis, with only minor adverse effects such as bloating or diarrhoea. The recommended dose for primary biliary cirrhosis-related pruritus is 4 g up to four times per day. Dosing with the first meal of the day is recommended, to bind the pruritogens that accumulate in the gallbladder overnight which are then secreted into the small intestine with eating.

The antibiotic, rifampin at 150–600 mg/day is a very effective agent for relief of pruritus in primary biliary cirrhosis.[92] Cholestatic hepatitis, nephrotoxic effects, and haemolytic anaemia have been reported.[91,93] Opioid antagonists such as naloxone and naltrexone result in a slight reduction of pruritus. To avoid the risk of an opiate withdrawal-like reaction, initiating a low dose with gradual upward titration is recommended. In a small trial,[94] 75–100 mg of sertraline per day improved pruritus in patients with cholestatic liver disease. Bezafibrate at 400 mg daily has shown improvement in small pilot studies.[95] Ondansetron, a serotonin receptor 3 antagonist, has been associated with relief of pruritus in case reports but two small placebo-controlled trials were inconclusive.[96,97] Antihistamines are often used although there is little evidence for their effectiveness.

More invasive methods to manage pruritus exist. Plasmapheresis can be considered when pruritus is refractory to medical therapy. Cholestatic pruritus should always respond to plasmapheresis, with duration of benefit ranging from weeks to years.[98] The expense, invasiveness, and inconvenience of plasmapheresis make this procedure a last resort. Nasobiliary drainage is another effective but inconvenient method. The molecular absorbance recirculating system is an extracorporeal liver dialysis system capable of removing albumin-bound substances such as bile acids and bilirubin with a positive effect against medically-refractory pruritus.[86]

Disorders associated with primary biliary cirrhosis

Patients with primary biliary cirrhosis, particularly women, have a higher likelihood of concomitant autoimmune disease (table 3). Up to 55% of patients with primary biliary cirrhosis could have an additional autoimmune process.[99–101] The presence of these disorders might impair quality of life but does not reduce survival in primary biliary cirrhosis.

	Frequency (%)
Sjögren's syndrome	7–34
Raynaud's syndrome	9–13
Hashimoto's thyroiditis	11–13
Rheumatoid arthritis	3–8
Psoriasis	6
Scleroderma or CREST	1–2
Inflammatory bowel disease	1
Any autoimmune disease	33–55

CREST (calcinosis, raynaud phenomenon, oesophogeal dysmotility, sclerodactyly, and telangiectasia syndrome) is a limited type of scleroderma.

Table 3: **Concomitant autoimmune diseases in women with primary biliary cirrhosis**

Sjögren's syndrome

Sjögren's syndrome is a common chronic autoimmune disorder of the exocrine glands characterised serologically by the presence of anti-Sjögren's syndrome-related antigen A, anti-Sjögren's syndrome-related antigen B, or antinuclear antibody, and histologically by lymphocytic infiltrates of the affected glands. The most common symptoms of Sjögren's syndrome are dry eyes and dry mouth (known as the sicca complex), and these symptoms are likewise common in patients with primary biliary cirrhosis. Several studies have shown association between primary biliary cirrhosis and Sjögren's syndrome, with reported prevalence of about 34% in primary biliary cirrhosis patients.[102] The Schirmer's test provides an objective measurement of tear production and is highly sensitive for the diagnosis of Sjögren's syndrome. Patients with Sjögren's syndrome or sicca symptoms might benefit from topical therapies to keep the mucus membranes moist and from specialised dental care to prevent complications related to decreased saliva production.

Complications of chronic cholestasis

Osteopenia and osteoporosis

Osteopenic bone disease is a common complication of primary biliary cirrhosis. Most patients with primary biliary cirrhosis have osteopenia and 20–44% have osteoporosis,[103] with associated risk of fragility fracture. The osteopenia of primary biliary cirrhosis is multifactorial. Risk factors for osteopenia include female sex, low body-mass index, advanced age, history of fragility fracture, and advanced disease with cholestasis.[104,105] Chronic cholestasis can result in fat-soluble vitamin deficiency, including vitamin D which is essential to bone metabolism. However, vitamin D deficiency does not fully explain the osteopenia of primary biliary cirrhosis, and these patients are noted to have more markers of bone resorption (urinary hydroxyproline) and fewer bone formation markers (osteocalcin).[104]

Patients with primary biliary cirrhosis need bone mineral density testing at the time of diagnosis; the timing of subsequent testing depends on the baseline values. Dual-energy x-ray absorptiometry remains the gold standard for measurement of bone mineral density, because it is inexpensive, has negligible radiation exposure, and is readily available. Primary biliary cirrhosis patients should be counselled on lifestyle interventions for bone health, including smoking cessation and avoidance, minimisation of alcohol use, regular weight-bearing activity, and muscle-strengthening exercise. When osteopenia is present, calcium and vitamin D supplementation is recommended. Patients with osteoporosis should be considered for additional therapy. Bisphosphonate therapy improves bone mass in patients with primary biliary cirrhosis and has an excellent safety profile, although oral bisphosphonates should be avoided in patients with oesophageal or gastric varices.[105–107] In general, hormone replacement therapy is not recommended, as it has been associated with an increased risk of adverse events without an improvement in bone density or fracture rate.[108]

Hyperlipidaemia

Hyperlipidaemia affects around 75–95% of patients with primary biliary cirrhosis,[109] and is a result of many complex processes related to biliary cholestasis. Despite a sometimes striking increase in cholesterol, the hyperlipidaemia seen in primary biliary cirrhosis is generally not associated with increased atherosclerotic-related risk.[110] The presence of metabolic syndrome, however, does increase the risk for cardiovascular events in patients with primary biliary cirrhosis.[111] If indicated for other reasons such as family history, diabetes mellitus, or hypertension, lipid-lowering agents including statins can be safely used.[112] UDCA, fibrates, and obeticholic acid are associated with slight reductions in serum lipids.[49,51,113]

Vitamin deficiencies

Patients with primary biliary cirrhosis might have decreased bile acid secretion, leading to an increased risk for malabsorption of lipids, including fat-soluble vitamins. Vitamin A, important in night vision, is low in about a third of patients with advanced disease. Deficiency of vitamin D occurs in 13–33% of patients with primary biliary cirrhosis and can be associated with osteopenic bone disease.[114] Vitamin D deficiency is more common in advanced-stage primary biliary cirrhosis than in early-stage disease. Vitamin E deficiency, which can cause peripheral neuropathy, myopathy, and immune derangement, is reported in few patients. Deficiency of vitamin K occurs in 8–23% of patients with primary biliary cirrhosis and can cause disruption of the vitamin K-dependent clotting factors.[115]

Complications related to cirrhosis

Although most patients with primary biliary cirrhosis are not cirrhotic, cirrhosis is the end stage of the disease and patients are at risk for all of the results of cirrhosis.

Portal hypertension

A unique feature of primary biliary cirrhosis is the development of varices before the onset of cirrhosis; about 6% of patients with early-stage disease have varices.[116,117] Oesophageal varices develop in about a third of patients with stage 3–4 disease over a median of 5·6 years; roughly half of these patients will have a bleeding event. The 3 year survival after initial variceal bleed is about 50%.[4]

Screening for varices is initiated when clinical or histological evidence of cirrhosis is reported. Whether screening for varices should begin before the diagnosis of cirrhosis remains uncertain. Platelet counts of less than 140 000 or less than 200 000 have been suggested as a threshold for the initiation of variceal screening, as has a Mayo risk score greater than 4·1.[4] Transient elastography might be a useful method to help guide this process in the future.

Primary prophylaxis for large varices includes either non-selective β blockers or variceal band ligation. Small varices in compensated cirrhosis need no treatment and should be followed up at 2 years. Patients with decompensated cirrhosis and small varices can be considered for primary prophylaxis with a β blocker or can be followed up at 1 year. The management of oesophageal varices in patients with primary biliary cirrhosis follows established guidelines for portal hypertension and cirrhosis of any cause.

Hepatocellular carcinoma

Hepatocellular carcinoma occurs in 1–6% of patients with primary biliary cirrhosis per year. Hepatocellular carcinoma surveillance with abdominal imaging and α-fetoprotein is recommended every 6–12 months for patients. Risk factors for the development of hepatocellular carcinoma in patients with primary biliary cirrhosis include older age, male sex, presence of portal hypertension, advanced histological stage, and inadequate response to UDCA.[118–122] Liver transplantation is the standard of care for those with decompensated cirrhosis and patients who are candidates for liver transplantation should be referred to a transplant centre.[118] Patients who are not candidates for liver transplantation are given locoregional therapies such as ablation or chemoembolisation. Sorafenib improves survival by about 3 months for advanced metastatic hepatocellular carcinoma or disease that is not amenable to locoregional therapies.[123]

Liver transplantation

Liver transplantation is an excellent treatment for patients with decompensated disease. 1 year graft survival is 88%, and 5 year graft survival is 78%, with 90–95% 1 year patient survival.[124] Liver transplantation is usually indicated for the life-threatening disorders of decompensated cirrhosis or hepatocellular carcinoma; on rare occasions, intractable pruritus might justify transplantation. Referral to a transplant centre should occur at the onset of decompensated disease or when total bilirubin approaches 6 mg/dL, or the Model for End-stage Liver Disease score is 12 or more.[25]

Recurrent primary biliary cirrhosis after liver transplantation occurs in up to 25% of patients.[4] AMA might persist after liver transplantation and is therefore not a reliable marker in liver transplantation recipients.[28] Liver biopsy is necessary for diagnosis of post-liver transplantation primary biliary cirrhosis. Pruritus resolves after liver transplantation, but fatigue can persist.[125] Preliminary data suggest that prophylactic UDCA after liver transplantation might reduce the risk of recurrent primary biliary cirrhosis but this is not yet standard of care.[126]

Variant syndromes

AMA-negative primary biliary cirrhosis

5% of patients with primary biliary cirrhosis do not have detectable AMA.[127] Patients with AMA-negative primary biliary cirrhosis have high alkaline phosphatase concentration and characteristic features on liver biopsy. In the absence of a positive AMA, liver biopsy is necessary to establish the diagnosis. Antinuclear antibody, particularly anti-gp210 and anti-Sp100 antibodies, are helpful in establishing the diagnosis of primary biliary cirrhosis when the AMA is undetectable. The clinical features, natural history, and response to UDCA are the same for AMA-positive and AMA-negative primary biliary cirrhosis.[128]

Primary biliary cirrhosis and autoimmune hepatitis overlap syndrome

Most patients with primary biliary cirrhosis have classic features of the disease, but some present with features of both primary biliary cirrhosis and autoimmune hepatitis. This can include a non-cholestatic pattern of liver injury tests, positive antinuclear antibody (with or without positive AMA), and histological features of both primary biliary cirrhosis and autoimmune hepatitis. Overlap between primary biliary cirrhosis and autoimmune hepatitis might be more common in people of Hispanic heritage.[129]

The most widely used criteria (the Paris criteria) need two features each of both primary biliary cirrhosis and autoimmune hepatitis to diagnose the overlap syndrome (panel).[130] The natural history of primary biliary cirrhosis

Panel: **Paris Study Group Criteria for primary biliary cirrhosis–autoimmune hepatitis overlap syndrome**

Primary biliary cirrhosis

- Alkaline phosphatase >2 times ULN
- Positive antimitochondrial antibody
- Liver biopsy showing biliary features of primary biliary cirrhosis

Autoimmune hepatitis

- Alanine transaminase >5 times ULN
- IgG >2 times ULN or smooth muscle antibody >1:80
- Liver biopsy showing periportal or periseptal lymphocytic piecemeal necrosis

Primary biliary cirrhosis–autoimmune hepatitis overlap syndrome requires at least two of three diagnostic criteria for each disease. ULN=upper limit of normal.

with autoimmune hepatitis seems to take a more aggressive course than primary biliary cirrhosis alone, with earlier onset of portal hypertension and need for liver transplantation.[129,131] Treatment for primary biliary cirrhosis–autoimmune hepatitis overlap syndrome might include UDCA and immunosuppression. Rarely, classic primary biliary cirrhosis transforms to autoimmune hepatitis over time.[132,133]

Isolated AMA positivity

The presence of isolated AMA is not uncommon, as up to 0·64% of healthy individuals have AMA in the absence of clinically apparent liver disease or abnormal liver biochemistries.[5,6] AMA can be a hallmark of preclinical disease, and up to 19% will develop primary biliary cirrhosis over 5 years.[5,134] There is no consensus on appropriate follow-up for these individuals, but periodic monitoring of alkaline phosphatase is reasonable.

General management

General precautions

Patients with primary biliary cirrhosis who are not immune to hepatitis A and B should receive appropriate vaccination. Regular alcohol consumption is not recommended for patients with chronic liver disease, and raw or undercooked seafood should be avoided to prevent *Vibrio vulnificus* infection. Cigarette smoking accelerates fibrosis in primary biliary cirrhosis and therefore smoking cessation is recommended.[135,136] Patients with cirrhotic primary biliary cirrhosis will need routine variceal screening (every 1–3 years, depending on findings) and hepatocellular carcinoma surveillance (every 6–12 months). Although first-degree relatives of index patients have a 4–6% risk of developing primary biliary cirrhosis, the clinical usefulness of routine screening is unclear.[137]

Pregnancy and hormone replacement

Most women with primary biliary cirrhosis are perimenopausal, but up to 25% present with the disease in childbearing years.[138] Oral contraceptives are not contraindicated in women with primary biliary cirrhosis but could induce or worsen pruritus.[4] Women with primary biliary cirrhosis seem to have healthy pregnancy outcomes without increased risk to the mother or fetus.[139] UDCA has an excellent safety profile in pregnancy and can be continued in all trimesters.[140] Half of pregnant women will develop new-onset pruritus, most of whom will need symptom-specific therapy. A post-partum rise in liver function tests occurs in 72% of patients without evidence of clinical significance.[139] In pregnant women with cirrhosis, screening for varices should occur early in the second trimester.

Conclusions and future directions

Primary biliary cirrhosis is a chronic cholestatic disease resulting in progressive hepatic fibrosis. The most common symptoms of primary biliary cirrhosis are fatigue and pruritus, although all the symptoms of decompensated cirrhosis and portal hypertension can occur in late stages of the disease. UDCA is the only drug approved for the treatment of primary biliary cirrhosis, and the availability of UDCA has greatly changed the clinical course of primary biliary cirrhosis, because most patients will not progress to cirrhosis or need for liver transplantation. Advances in the understanding of the interactions between bile acids and nuclear hormone receptors have led to the promise of targeted therapy for primary biliary cirrhosis. Future research will focus on continued development of targeted therapy for primary biliary cirrhosis, better treatments for the symptoms of fatigue and pruritus, and use of non-invasive markers to monitor disease progression.

Contributors

EJC wrote the first draft and coordinated revisions, and coordinated the table and figure development. AHA contributed to editing and approval of the final submitted version. KDL contributed to formulating the manuscript and the editing and approval of the final submitted version.

Declaration of interests

EJC receives research funding from Intercept Pharmaceuticals and NGM Biopharmaceuticals. KDL serves as a consultant in clinical trials of experimental drugs for cholestatic liver disease and is an unpaid advisor for Lumena Pharmaceuticals and Intercept Pharmaceuticals. AHA declares no competing interests.

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