

An update on the management of cholestatic liver diseases

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ABSTRACT

Cholestatic liver diseases are a challenging spectrum of conditions arising from damage to bile ducts, leading to build-up of bile acids and inflammatory processes that cause injury to cholangiocytes and hepatocytes. Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are the two most common cholestatic disorders. In this review we detail the latest guidelines for the diagnosis and management of patients with these two conditions.

Primary biliary cholangitis

Primary biliary cholangitis (PBC) is a chronic autoimmune liver disorder characterised by immune-mediated destruction of epithelial cells lining the intrahepatic bile ducts, resulting in persistent cholestasis and, in some patients, a progression to cirrhosis if left untreated. The exact mechanisms remain unclear but are most likely a result of exposure to environmental factors in a genetically susceptible individual.¹ The majority of patients are asymptomatic at diagnosis, though symptoms including fatigue and pruritis (which can be severe and disabling) may occur at presentation or can develop later in the disease course. PBC has an estimated prevalence of 35/100,000, with an incidence of 2–3/100,000,² and most commonly affects middle-aged women with a clear female preponderance of 10:1. The nomenclature for PBC changed in 2015 from primary biliary cirrhosis to primary biliary cholangitis, reflecting the fact that many patients do not present with cirrhosis at diagnosis or develop it in their lifetime.³

The most common blood test abnormality is an elevation in alkaline phosphatase (ALP) and immunoglobulin M (IgM), which may be associated with elevated transaminase levels (alanine aminotransferase (ALT) and aspartate transaminase (AST)). An abnormal bilirubin is typically only seen in advanced disease. Serum antimitochondrial antibody (AMA) positivity greater than 1:40 is observed in 95% of patients and is directed towards the PDC-E2 or M2 subunit antigens. Patients who are AMA-negative but have cholestatic liver biochemistry and a strong clinical suspicion of PBC should be evaluated further with specific antinuclear antibodies (ANA), including sp100 and gp210. An index ultrasound should be performed to exclude an alternative biliary pathology or focal liver lesions. Liver biopsy is rarely needed in current practice due the high sensitivity and specificity of

autoantibodies though may be performed in cases of diagnostic doubt, suspected overlap syndrome or co-existent liver pathology such as fatty liver.

Key points

Ursodeoxycholic acid can favourably alter the natural history of primary biliary cholangitis in a majority of patients, given at the appropriate dose of 13–15 mg/kg/day.

Risk stratification is of paramount importance in the management of primary biliary cholangitis to identify patients with suboptimal response to ursodeoxycholic acid and poorer long-term prognosis. Alkaline phosphatase >1.67 times the upper limit of normal and a bilirubin above the normal range indicate high-risk disease and suboptimal treatment response.

Recent trial data support the use of obeticholic acid or bezafibrate as second-line therapy in addition to ursodeoxycholic acid in primary biliary cholangitis patients with a suboptimal treatment response.

Primary sclerosing cholangitis requires a low threshold for magnetic resonance cholangiopancreatography in a patient with cholestatic liver function tests, recognition of overt or covert inflammatory bowel disease and exclusion of secondary cholangitis.

Patients with primary sclerosing cholangitis face the dual risk of progression to end-stage liver disease and of the development of malignancy (of the bile duct, gallbladder, pancreas and colon). When this is suspected, urgent cross-sectional imaging or colonic assessment should be undertaken and referral to hepato-pancreato-biliary or colorectal multidisciplinary team is essential.

Effective therapies to alter the natural history of primary sclerosing cholangitis and to improve disease prognosis are currently lacking but are the focus of ongoing clinical trials.

KEYWORDS: Primary biliary cholangitis, primary sclerosing cholangitis, risk stratification, ursodeoxycholic acid, cholangiocarcinoma

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Box 1. Autoimmune conditions associated with primary biliary cholangitis

Sjogren's syndrome
 Autoimmune thyroid disease, eg Hashimoto's
 Rheumatoid arthritis
 Coeliac disease
 Systemic sclerosis
 Pernicious anaemia
 Vitiligo
 Addison's disease

Other autoimmune conditions can be seen in patients with PBC and should be screened for (see Box 1). Bone mineral density loss is also common, and all patients with PBC should be offered calcium/vitamin D supplementation, and bisphosphonate therapy if osteoporotic.⁴

Treatment and risk stratification

At present, no cure exists for PBC; however, therapy has been shown to be effective at preventing disease progression.⁵ Pharmacotherapy with ursodeoxycholic acid (UDCA) at an optimal dose of 13–15mg/kg/day promotes liver bile acid secretion from damaged biliary epithelial cells, thereby reducing further injury and preventing further toxic bile acid injury. It is well tolerated with few side effects, and numerous trials have demonstrated that it can prevent progression to cirrhosis or the need for liver transplantation in PBC.^{6,7} Biochemical and clinical parameters can help healthcare professionals to stratify individual risk of long-term adverse outcome. Baseline and post-treatment ALP and bilirubin are simple biomarkers that can be used to predict prognosis. Normalisation of bilirubin and a reduction of ALP to less than 1.67 times the upper limit of normal after 1 year of UDCA therapy is used to gauge efficacy, as recommended by current guidelines.⁸ Important clinical characteristics including age (<40), ductopenia and liver fibrosis stage can signal a more aggressive disease course. UDCA treatment response is important to identify suboptimal responders who will have worse outcomes and who warrant second-line therapy.

Obeticholic acid (OCA) is a farnesoid X receptor (FXR) agonist that has been shown to have anti-inflammatory and antifibrotic properties in addition to its choleric properties. It has been approved by the National Institute for Health and Care Excellence (NICE) as adjunctive second line therapy in patients who do not

achieve an adequate biochemical response or have intolerance to UDCA.⁹ Pruritis and dyslipidaemia are common side effects but are usually manageable, and dose adjustments are required in patients with advanced cirrhosis (Child–Pugh B and C). While unlicensed, fibrates are an alternative therapy option with good recent data from randomised controlled trials to support their use.¹⁰ Other agents, such as peroxisome proliferator-activated receptor agonists, are currently being evaluated in phase II and III trials.

Staging and surveillance

Patients should undergo disease staging through non-invasive tests such as transient elastography. Patients with features of cirrhosis should be enrolled into hepatocellular carcinoma and varices screening programmes. Early referral for liver transplantation should be considered, particularly in patients with a rising bilirubin as this is a late feature of advanced PBC.

Managing symptoms

Fatigue is the most common complaint in patients with PBC and is likely to be multifactorial. It responds poorly to attempts at pharmacotherapy and psychological approaches to strengthen coping strategies as well as promoting regular physical activity may be beneficial. Other causes of tiredness should be sought and treated, including anaemia, hypothyroidism and sleep disturbance.

Pruritis is commonly reported and often undertreated by clinicians. Table 1 highlights the current best practice in pruritis therapy. Cholestyramine and rifampicin are the most widely used in clinical practice and are the most effective. Antihistamines have limited efficacy and may exacerbate fatigue. UDCA improves cholestasis but does not treat pruritis. Second line therapies have variable effects; OCA can exacerbate itch and should be initiated with dose titration, bezafibrate may help ameliorate pruritis.

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic immune mediated disease of the larger intra- and extrahepatic bile ducts leading to multifocal strictures and progressive liver disease. Studies report an estimated incidence rate of 0.9–1.3 per 100,000 person-years.¹¹ Men are more commonly affected than women (2:1) with a mean age of diagnosis between 30 and 40 years. Box 2 gives examples of how PSC may present to the general physician.

Typically, PSC causes a chronically abnormal and fluctuant liver function tests (LFTs) with a cholestatic pattern (raised ALP and GGT). No reliable autoantibodies have been identified and the diagnosis of PSC is usually made on cholestatic liver biochemistry

Table 1. Options for the medical management of cholestatic pruritis

| Pharmacotherapy | Dose | Notes |
|-----------------|--|---|
| Cholestyramine | 4 g/day to a maximum of 16 g/day as required | Administration requires adequate spacing to avoid affecting the absorption of other medications |
| Rifampicin | 300–600 mg/day | Needs careful monitoring of LFTs; small risk of hepatotoxicity |
| Naltrexone | 50 mg/day | Careful dosing required to avoid opioid withdrawal side effects |
| Sertraline | 100 mg/day | |
| Gabapentin | 300 mg/day, dose titrate as normal | |

LFTs = liver function tests.

Box 2. Ways in which a patient with primary sclerosing cholangitis may present to the general physician

Incidental findings of abnormal liver biochemistry in an asymptomatic individual
 Persistent abnormal liver biochemistry in patients followed up for inflammatory bowel disease
 Jaundice or pruritis secondary to cholestasis
 Bacterial cholangitis
 Jaundice secondary to liver decompensation
 Complications of portal hypertension (variceal bleeding or ascites)
 Cholangiocarcinoma or gallbladder carcinoma

and typical magnetic resonance cholangiopancreatography appearances of intra-/extrahepatic strictures. Liver biopsy may help in cases of diagnostic doubt but is prone to marked sampling variability. There is a strong association between inflammatory bowel disease (IBD) and PSC, which is both genetically and clinically different from IBD alone. As symptoms of IBD may be overt or covert, an index colonoscopy should be performed in all newly diagnosed patients with PSC. Jaundice is more common than in PBC, and may reflect an episode of cholangitis, a new dominant biliary stricture, the development of a cholangiocarcinoma (CCA) or progression of liver dysfunction. Box 3 highlights important other causes of a sclerosing cholangiopathy, which should be considered in patients with cholestatic liver enzymes.

Small studies have suggested that UDCA may improve liver biochemistry but improvement in survival, avoidance of liver transplantation or prevention of PSC-associated cancers have not been shown. Its use is not currently recommended.¹² The only treatment with long-term efficacy is liver transplantation and currently there are no established tools that can reliably estimate prognosis for the individual patient.

The cholestatic course of PSC can be much more unpredictable than it is in PBC and this makes the design of clinical trials for PSC therapies difficult. Bilirubin and ALP are less reliable prognostic markers than in PBC. Nonetheless, phase II and phase III trials assessing changes and biochemical parameters and liver histology are currently being conducted. *nor*UDCA (a synthetic side chain-shortened UDCA derivative), seladelpar (a selective PPAR- δ agonist) and cilofexor (an FXR agonist) are being evaluated with encouraging early results.^{13–15} Numerous microbiota alterations

Box 3. Alternative causes of sclerosing cholangiopathy

Chronic choledocholithiasis (bile duct stones)
 Chronic pancreatitis
 Immunoglobulin G4-related disease
 Traumatic bile duct injury (iatrogenic, penetrating/blunt trauma)
 Ischaemic bile duct injury
 HIV cholangiopathy
 Parasitic infections of the biliary tract
 Helminth (ascaris)
 Trematoda (flukes)

are reproducible in PSC patients across geographical regions, pointing towards a microbiota composition that is shaped by the disease itself and not by environmental factors.¹⁶ As a result, altering the microbiome through faecal transplantation¹⁷ and antibiotic therapy are two other emerging areas of interest.^{18,19}

Cholangitis

Cholangitis is a common complication of PSC, with bacterobilia reported in 55% of patients with advanced disease. Risk factors for developing cholangitis include biliary strictures, previous instrumentation (endoscopic retrograde cholangiopancreatography (ERCP)) and active colitis. Patients with severe cholangitis and dominant bile duct strictures require urgent biliary decompression, as the mortality rate if untreated is high. Long-term rotating antibiotics can be considered in patients with recurrent cholangitis but may lead to antibiotic resistance.

Malignancy

The risk of CCA in PSC is increased approximately 160-fold with a higher incidence in those who have dominant biliary strictures.²⁰ It is the most common cause of death for patients who have not undergone liver transplantation. CCA may present as a new mass lesion associated with the bile duct or within the liver parenchyma but may also just present as a new biliary stricture. The differential diagnosis between an inflammatory and a malignant stricture can be difficult, and CA19-9 has a low positive predictive value as elevations are also frequently seen in cholestasis and cholangitis. Advances in cholangioscopy at ERCP have led to an improved tissue diagnosis of indeterminate strictures.^{20,21} At present a validated screening modality or strategy for CCA in PSC is lacking.

Patients with IBD–PSC have 20–30% lifetime incidence of colorectal cancer, with a 10 times greater risk than the general population and four times greater risk than those with IBD alone²² and should undergo annual colonoscopy surveillance. Compared with the general population, gall bladder polyps in patients with PSC are associated with an increased risk of gall bladder cancer, which is estimated to be 3–14%. Annual ultrasound gallbladder surveillance can be considered, and cholecystectomy is recommended when polyps are present.^{23,24}

Conclusion

The progression of PBC can be abated with long-term UDCA treatment. Patients who are suboptimal responders or have high-risk disease should be identified and require second-line therapy with agents such as obeticholic acid or bezafibrate. PSC remains a more difficult and unpredictable disease for which current treatment options are limited. PSC patients also face the dual risk of progression to end-stage liver disease and of developing malignancy. Acceptable, cost-effective cancer screening strategies still need to be defined.

Cholangiopathies may present with limited fibrosis but significant portal hypertension. Therefore, referral to hepatology services is essential so that variceal assessment can be undertaken with timely referral to a liver transplant centre if indicated. ■

References

- 1 Tanakaa A, Leung PS, Young HA, Gershwin ME. Toward solving the etiological mystery of primary biliary cholangitis. *Hepatol Commun* 2017;1:275–87.

- 2 James OF, Bhopal R, Howel D *et al*. Primary biliary cirrhosis once rare, now common in the United Kingdom? *Hepatology* 1999;30:390–4.
- 3 Beuers U, Gershwin ME, Gish RG *et al*. Changing nomenclature for PBC: From ‘cirrhosis’ to ‘cholangitis’. *Hepatology* 2015;62:1620–2.
- 4 Chalifoux SL, Konyn PG, Choi G, Saab S. Extrahepatic manifestations of primary biliary cholangitis. *Gut Liver* 2017;11:771–80.
- 5 Lindor K. Ursodeoxycholic acid for the treatment of primary biliary cirrhosis. *N Engl J Med* 2007;357:1524–9.
- 6 Poupon RE, Balkau B, Eschwège E, Poupon R. A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. UDCA-PBC Study Group. *N Engl J Med* 1991;324:1548–54.
- 7 Poupon RE, Bonnand AM, Chrétien Y, Poupon R. Ten-year survival in ursodeoxycholic acid-treated patients with primary biliary cirrhosis. The UDCA-PBC Study Group. *Hepatology* 1999;29:1668–71.
- 8 Hirschfield GM, Dyson JK, Alexander GJM *et al*. The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. *Gut* 2018;67:1568–94.
- 9 Hirschfield GM, Mason A, Luketic V *et al*. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. *Gastroenterology* 2015;148:751–61.
- 10 Corpechot C, Chazouilleres O, Rousseau A *et al*. A placebo-controlled trial of bezafibrate in primary biliary cholangitis. *N Engl J Med* 2018;378:2171–81.
- 11 Liang H, Manne S, Shick J, Lissos T, Dolin P. Incidence, prevalence, and natural history of primary sclerosing cholangitis in the United Kingdom. *Medicine (Baltimore)* 2017;96:e7116.
- 12 Chapman MH, Thorburn D, Hirschfield GM *et al*. British Society of Gastroenterology and UK-PSC guidelines for the diagnosis and management of primary sclerosing cholangitis. *Gut* 2019;68:1356–78.
- 13 Fickert P, Hirschfield GM, Denk G *et al*. norUrsodeoxycholic acid improves cholestasis in primary sclerosing cholangitis. *J Hepatol* 2017;67:549–58.
- 14 Jones D, Boudes PF, Swain MG *et al*. Seladelpar (MBX-8025), a selective PPAR- δ agonist, in patients with primary biliary cholangitis with an inadequate response to ursodeoxycholic acid: a double-blind, randomised, placebo-controlled, phase 2, proof-of-concept study. *Lancet Gastroenterol Hepatol* 2017;2:716–26.
- 15 Trauner M, Gulamhusein A, Hameed B *et al*. The nonsteroidal farnesoid X receptor agonist cilofexor (GS-9674) improves markers of cholestasis and liver injury in patients with primary sclerosing cholangitis. *Hepatology* 2019;70:788–801.
- 16 Rühlmann M, Liwinski T, Heinsen FA *et al*. Consistent alterations in faecal microbiomes of patients with primary sclerosing cholangitis independent of associated colitis. *Aliment Pharmacol Ther* 2019;50:580–9.
- 17 Allegretti JR, Kassam Z, Carrellas M *et al*. Fecal microbiota transplantation in patients with primary sclerosing cholangitis: a pilot clinical trial. *Am J Gastroenterol* 2019;114:1071–9.
- 18 Rahimpour S, Nasiri-Toosi M, Khalili H *et al*. A triple blinded, randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of oral vancomycin in primary sclerosing cholangitis: a pilot study. *J Gastrointest Liver Dis* 2016;25:457–64.
- 19 Tabibian JH, Weeding E, Jorgensen RA *et al*. Randomised clinical trial: vancomycin or metronidazole in patients with primary sclerosing cholangitis – a pilot study. *Aliment Pharmacol Ther* 2013;37:604–12.
- 20 Yan S, Tejaswi S. Clinical impact of digital cholangioscopy in management of indeterminate biliary strictures and complex biliary stones: a single-center study. *Ther Adv Gastrointest Endosc* 2019;12:2631774519853160.
- 21 Montano-Loza AJ, Ebadi M, Sandha G. The role of cholangioscopy in the management of primary sclerosing cholangitis. *Curr Hepatol Reports* 2020;19:78–85.
- 22 Lazaridis KN, LaRusso NF. Primary sclerosing cholangitis. *N Engl J Med* 2016;375:1161–70.
- 23 Fung BM, Lindor KD, Tabibian JH. Cancer risk in primary sclerosing cholangitis: Epidemiology, prevention, and surveillance strategies. *World J Gastroenterol* 2019;25:659–71.
- 24 Razumilava N, Gores GJ, Lindor KD. Cancer surveillance in patients with primary sclerosing cholangitis. *Hepatology* 2011;54:1842–52.

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