Primary biliary cholangitis

Ana Lleo, Giu-Qiang Wang, Merrill Eric Gershwin, Gideon M Hirschfield

Primary biliary cholangitis is an autoimmune liver disease that predominantly affects women. It is characterised by a chronic and destructive, small bile duct, granulomatous lymphocytic cholangitis, with typical seroreactivity for antimitochondrial antibodies. Patients have variable risks of progressive ductopenia, cholestasis, and biliary fibrosis. Considerations for the cause of this disease emphasise an interaction of chronic immune damage with biliary epithelial cell responses and encompass complex, poorly understood genetic risks and environmental triggers. Licensed disease-modifying treatment focuses on amelioration of cholestasis, with weight-dosed oral ursodeoxycholic acid. For patients who do not respond sufficiently, or patients with ursodeoxycholic acid intolerance, conditionally licensed add-on therapy is with the FXR (NR1H4) agonist, obeticholic acid. Off-label therapy is recognised as an alternative, notably with the pan-PPAR agonist bezafibrate; clinical trial agents are also under development. Baseline characteristics, such as young age, male sex, and advanced disease, and serum markers of liver injury, particularly bilirubin and ALP, are used to stratify risk and assess treatment responsiveness. Parallel attention to the burden of patient symptoms is paramount, including pruritus and fatigue.

Lancet 2020; 396: 1915–26

Department of Biomedical Sciences, Humanitas University, Milan, Italy (A Lleo MD); **Division of Internal Medicine and Hepatology, Department of Gastroenterology, Humanitas Clinical and Research Center IRCCS, Rozzano, Italy** (A Lleo); **Department of Infectious Diseases and Center for Liver Diseases, Peking University First Hospital, Beijing, China** (G-Q Wang MD); **Department of Infectious Diseases and Liver Diseases, Peking University International Hospital, Beijing, China** (G-Q Wang); **Division of Rheumatology, Allergy and Clinical Immunology, The University of California, Davis, CA, USA** (M E Gershwin MD); **Toronto Centre for Liver Disease, Division of Gastroenterology and Hepatology, University of Toronto, Toronto, ON, Canada** (Prof G M Hirschfield PhD)

Correspondence to:
Prof Gideon M Hirschfield, Toronto Centre for Liver Disease, Division of Gastroenterology and Hepatology, University of Toronto, Toronto, ON M5G 2C4, Canada
gideon.hirschfield@uhn.ca

Introduction

Primary biliary cholangitis (formerly known as primary biliary cirrhosis) is the most common autoimmune liver disease;[1] as a lifelong illness, it is reflected histopathologically by a chronic immune-driven injury to the small bile duct (figure 1).[2] Understanding autoimmune diseases such as primary biliary cholangitis includes an appreciation of the burden of disease to patients,[3] alongside the science explaining the role of genetics, lymphoid subsets as regulators, effector pathways of immune damage, and tissue responses to injury. Primary biliary cholangitis is usually identified (table 1) at an early stage in a patient with a cholestatic pattern of serum liver tests—elevated serum activities of ALP, GGT, or both—and the presence of circulating antimitochondrial antibodies. Symptom burden, although variable, can be marked regardless of underlying disease severity, and sicca complex, abdominal discomfort, pruritus, fatigue, and bone pain are frequently reported by patients. Disease-modifying therapy has a substantial effect when tackling the inflammatory and profibrotic consequences of cholestasis, and the two licensed agents, ursodeoxycholic acid[4] and obeticholic acid,[5] are bile acid-based therapies ameliorating the consequences of cholestasis; alternative anticholestatic therapies include off-label bezafibrate[6] and other emerging clinical trial agents that also target the PPAR pathway.

Patient care focuses on confirming a clear diagnosis; appreciating the severity of liver disease at presentation and over the course of follow-up; identifying the patients at greatest risk for disease progression on the basis of baseline presenting features and on-treatment disease markers; and addressing accompanying symptom burden to mitigate against reduced patient quality of life.

Primary biliary cholangitis: a global perspective

Every year, at least 100 000 individuals worldwide receive a diagnosis of primary biliary cholangitis, with studies suggesting that at least one in 1000 women over the age of 40 years have primary biliary cholangitis.[7] The first descriptions of primary biliary cholangitis were of women with dermatological features of end-stage icteric liver disease, with profound xanthelasma or xanthoma (figure 1A). As non-invasive immune serology became commonplace and was validated for primary biliary cholangitis, most notably, the ability of primary-care and secondary-care physicians to access immunofluorescence for antimitochondrial antibodies, and the opportunities to diagnose disease earlier, increased.[8] This early identification contrasts with descriptions of advanced disease,[9] and patients will now most likely be identified at a time in their disease course when often the only manifestation is biochemical cholestasis in association with seropositivity for antimitochondrial antibodies.

The presumption that primary biliary cholangitis is globally homogeneous in its presentation and outcome is challenged by the description of an aggressive clinical course of primary biliary cholangitis in First Nation Canadians, for example.[10] In the Asia-Pacific region, the prevalence and incidence of primary biliary cholangitis appears higher than previously thought, with a pattern of disease diagnosis at a slightly older age (ie, approximately aged around 60 years). A systematic review identified 18 studies from seven Asia-Pacific countries or regions (including Japan, China, New Zealand, South Korea, Australia, India, and Singapore).[11] The overall prevalence of primary biliary cholangitis was 118·75 cases

Search strategy and selection criteria

Data for this Seminar were identified by searches of MEDLINE, Current Contents, PubMed, and references from relevant articles by use of search terms, including "primary biliary cholangitis", "autoimmune liver diseases", and "cholangiocyte biology". Only articles published in English were included. We largely selected publications that were published between Jan 1, 2010, and Jan 1, 2020, but we did not exclude commonly referenced and highly regarded older publications.

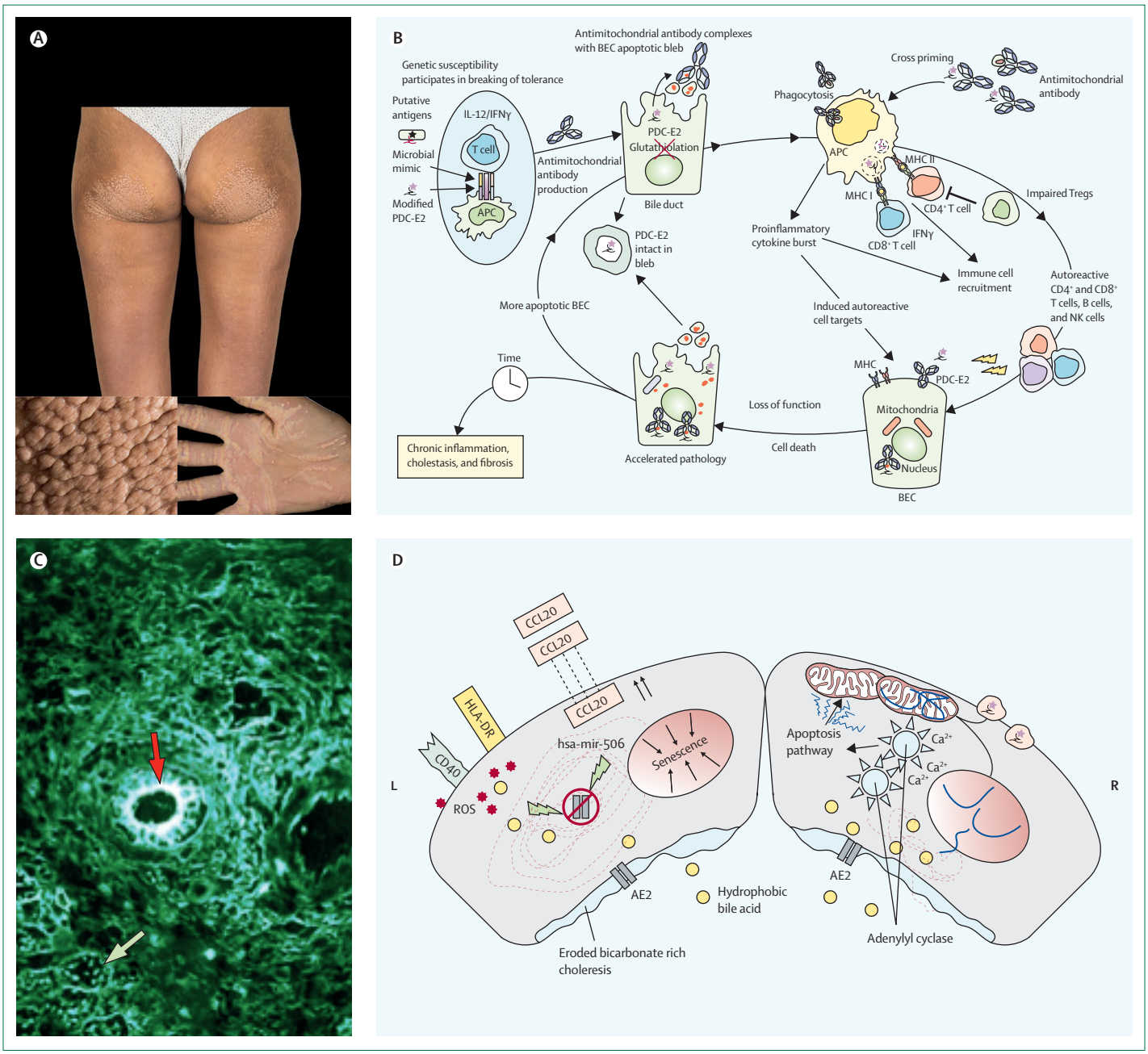

Figure 1: **Biological and histopathological understanding of disease pathophysiology**
(A) Dermatological manifestations associated with cholestasis and hyperlipidaemia (xanthoma and xanthelasma) are characteristic in patients with primary biliary cholangitis. (B) Autoimmune susceptibility participates in breaking of tolerance, eventually producing antimitochondrial antibodies and a cycle of immune-mediated injury. (C) Autoantibodies against the components of mitochondria are densely localised to the apical surface of biliary epithelial cells and are associated with apoptosis. Confocal microscopy of bile duct apical localisation of PDC-E2 stained with mouse anti-PDC-E2 antibody (red arrow) and typical mitochondrial staining in hepatocytes (green arrow).(D) An active BEC bicarbonate rich choleresis (which is membrane protective) is eroded because of low expression of AE2 solute transporter. Without the bicarbonate umbrella, hydrophobic bile acids permeate BEC membranes in an uncontrolled manner. APC=antigen presenting cell. BEC=biliary epithelial cell. IL-12=interleukin-12. NK cells=natural killer cells. PDC-E2=E2 component of the pyruvate dehydrogenase complex. ROS=reactive oxygen species. Tregs=T-regulatory cells.

per million (95% CI 49·96–187·55), with variation from high prevalence in Japan and China (191·18 cases per million) to low prevalence in South Korea and Australia (39·09 cases per million). When symptom profiles from a large cohort of Japanese patients were evaluated, added distinctions were reported. Yagi and colleagues[12] described a Japanese-based multicentre, observational, cross-sectional study, in which female sex, a younger age at diagnosis (ie, <50 years), and a lower concentration of serum albumin were independently associated with

measures of fatigue, whereas a longer follow-up period and lower concentrations of serum albumin were associated with the burden of itch.

Observational epidemiological risks for disease development include smoking, a previous history of cholestasis in pregnancy, and recurrent urinary tract infections.[13,14] The global nature of primary biliary cholangitis raises questions as to disease triggers and, speculatively, whether more burdensome environmental risks might exist in different parts of the world, including classical risks (eg, smoking rates) and exposure to environmental toxins (eg, from toxic waste, coal-mining heritage, concentrations of environmental cadmium). These potential risk factors might additionally affect the distribution of disease among the sexes. Data from China have added to the discussion that the distinct ratio of disease between men and women might not be a steadfast facet of primary biliary cholangitis. In one large Chinese cohort, the ratio of women to men was 6·1:1·0,[15] and this mirrors a large study from Beijing, in which 168 of 1255 Chinese patients with primary biliary cholangitis were men, and 1087 were women.[16] Although these studies suggest that the proportion of women with primary biliary cholangitis is lower than classically expected, and similar, more recent reports exist from European populations, further study is required.[17] Therapy approaches have, at times, also been distinct internationally. In Japan, for example, fibrates as second-line therapies have been used for some time, with much interest in attempts to see whether survival benefit can now be identified as a result.[18] Such analyses presume that tools for risk stratification are applicable globally—Asia-Pacific data supports this, and a study with a substantial cohort of patients, predominantly from Turkey, also suggested that biochemical surrogates of the disease appear to have broad applicability[19]—but nation-specific work is needed to compare outcomes in patients with primary biliary cholangitis with outcomes in healthy comparator individuals.

Pathogenesis

Primary biliary cholangitis predominantly affects women and rarely affects children.[20] The disease is characterised by an *HLA-DR*-associated loss of immune tolerance to a crucial enzyme of oxidative phosphorylation, the E2 component of the pyruvate dehydrogenase complex (PDC-E2).[21,22] An interleukin-12 (IL-12) and IFNγ driven immune-mediated lymphocytic cholangitis with consequent destructive chronic injury to the biliary epithelial cells (BECs), senescence, and apoptosis define disease, although effector mechanisms might vary and change during the evolution, treatment, and stages of primary biliary cholangitis.[23,24] A predisposition necessitates an underlying immunogenetic risk[25,26] and has a requirement for an environmental trigger; the concordance rate of primary biliary cholangitis in identical twins is approximately 60%,[27] and repeated studies show geo-epidemiological clustering.[28,29]

	Result	Suspicion	Diagnosis	Prognosis
Serum liver tests				
ALP	Increased	Y	Y	Y
GGT	Increased	Y	N	Y
AST (AspAT) or ALT	Increased	Y	N	Y
Serum autoantibody profile				
Antimitochondrial antibodies (>1 in 40)	Positive	Y	Y	N
IgM	Increased	Y	N	N
Anti-gp210	Positive	N	Y	Y
Anti-sp100	Positive	N	Y	N
Anti-centromere	Positive	Y	N	Y
Liver function				
Bilirubin	Increased	N	N	Y
Albumin	Decreased	N	N	Y
International normalised ratio	Increased	N	N	Y
Platelets	Decreased	N	N	Y
Imaging				
Ultrasound	NA	N	N	Y
Transient elastography	NA	N	N	Y
Histology				
Liver biopsy	Descriptive	Y	Y	Y

Y=yes. N=no. NA=not applicable.

Table 1: **Broad clinical usefulness of diagnostic and prognostic testing**

Immunobiology

Primary biliary cholangitis has features of systemic autoimmunity but equally is a hepatobiliary disease, with progressive lymphocytic cholangitis, centred on small intrahepatic bile ducts, often associated with portal and parenchymal granulomata. Autoantibodies against mitochondria are densely localised to the apical surface of BECs and associated with apoptosis.[30,31] A similar staining pattern can be seen on salivary epithelium in patients with primary biliary cholangitis who have co-incident sicca complex.[32] Several murine models of primary biliary cholangitis have been developed, including spontaneous models, models induced by chemical xenobiotic immunisation, and models of so-called bioengineered mice with altered interferon or cytokine pathways, or both.[33] Collectively, these models indicate a loss of tolerance to PDC-E2, the major mitochondrial autoantigen, as the earliest immunological event that occurs before clinical disease manifests. A mouse model with a female predominance of biliary injury has been generated through a focus on chronic type 1 IFN expression, suggesting this expression to be a potential axis for disease genesis.[34] Experimentally, the triad of primary biliary cholangitis monocytes, biliary apotopes, and antimitochondrial antibodies generates an intense proinflammatory cytokine burst in vitro.[35] Further, the frequent recurrence of primary biliary cholangitis after liver transplantation indicates that disease activity includes both adaptive and innate immune mechanisms (figure 1B).[36]

The current models of immunoregulatory pathways in primary biliary cholangitis focus on T-helper-1 (Th1) cells and Th17 cells.[37] As is consistent with involvement of the adaptive immune system, the immune infiltrate is predominantly comprised of $CD4^+$ T cells, with fewer increases in cytotoxic ($CD8^+$) T cells. Numbers of $CD4^+$ T cells are substantially increased in the hilar lymph nodes and the liver compared with in the blood. $CD4^+$ and $CD8^+$ T cells that are specific to mitochondrial autoantigens are not detected in either healthy controls or patients with other liver diseases. Both MHC class I and II proteins are also expressed on BECs from patients with primary biliary cholangitis, and class I proteins are thought to present antigens to cytotoxic $CD8^+$ T cells whereas class II proteins are thought to present antigens to $CD4^+$ Th cells. $CD4^+$ T cells are particularly implicated by the cytokine signature of primary biliary cholangitis, the presence of $CD4^+$ T cells specific to mitochondrial autoantigens, and the expression of MHC class II on injured BECs.[38] The lessons learned from careful immunophenotyping of the liver lymphoid are mirrored by immunogenetic risks, with multiple HLA and non-HLA gene associations;[39] non-HLA gene associations carry low individual hazard, but are presumed to collectively interact with an ill-defined, triggering environmental burden.

Environment and genetics

Environmental factors are either chemical or infectious and most likely act through molecular mimicry. A priming event, involving antigen presentation by dendritic cells, and co-stimulatory regulatory signalling are necessary, and indeed non-HLA genetic risk markers in primary biliary cholangitis emphasise co-stimulation as an important event (eg, *CD80* and *CTLA-4* gene loci disease associations). The European ancestry genome-wide association studies showed novel non-HLA associations with a particular characteristic signal emphasising immune-regulatory pathways, and most notably IL-12/IL-23 signalling.[25,26] These findings align with results from animal models and with immunophenotypic and immunohistochemical evaluation of peripheral blood mononuclear cells and liver tissue. However, a Japanese genome-wide association study did not report IL-12/IL-23 associations, supporting the concept of multiple pathways to liver injury.[40] An immunogenetic risk was also emphasised, with association for the immune loci *TNFSF15* and *POU2AF1*. Studies from a Han Chinese population have provided support for previously identified susceptibility loci for primary biliary cholangitis in European and Japanese populations and identified additional immunogenetic risk variants (eg, in *IL21, IL21R, CD28–CTLA4–ICOS, CD58, ARID3A,* and *IL16*).[41]

As with other autoimmune diseases, loci that are specific to primary biliary cholangitis risk are relevant to the development of other autoimmune diseases. This shared relevance supports a pleiotropic effect of genetic risk that predisposes an individual to autoimmunity, with shared mechanisms and an opportunity to develop novel pathway-specific interventions. Epigenetic (ie, tissue-specific and cell-specific) effects modulating immune responses are likely to be equally relevant, as they are thought to be relevant in biliary epithelial responses.

Biliary epithelial cell factors

Epigenomic effects are additively important, presumably to modulate the sex selectivity and biliary selectivity of disease and disease expression: one example being the role of microRNAs in pathogenesis.[2,42] Many biliary transporters have adjusted expression in cholestasis, including those regulating bile acid entry or exit into the hepatocyte (eg, SLCO, SLC10A1, OSTa/OSTb complex) and those affecting biliary canalicular function (eg, ABCB11 and ABCB4).[43] Normal biliary epithelial cell function includes an active bicarbonate rich choleresis that is membrane protective and includes an important role for the AE2 solute transporter, in conjunction with the CFTR chloride channel (figure 1D). The bicarbonate umbrella deprotonates apolar hydrophobic bile acids, rendering them unable to permeate membranes in an uncontrolled manner.[44] In patients with primary biliary cholangitis, reduced AE2 expression in BECs has been shown, supporting evidence for toxicity from bile acids entering the BECs.[44,45] Hydrophobic bile acids suppress expression of AE2 by induction of reactive oxidative stress and, in culture with biliary epithelium, the hydrophobic bile acid glycochenodeoxycholic acid increases the expression of the immunologically relevant cell surface markers HLA-DR and CD40 on BECs.[46] Further apoptosis induced by bile salts is regulated by soluble adenylyl cyclase, which depends on intracellular Ca^{2+} stores and is mediated by the intrinsic apoptotic pathway; down-regulation of AE2 sensitises cholangiocytes to apoptotic insults by activating soluble adenylyl cyclase.[47] The expression of hsa-mir-506 (encoded on the X-chromosome) is increased in patients with primary biliary cholangitis, and hsa-mir-506 might have a role in negatively regulating expression of AE2 and ITPR3.[24] The oxidative stress that is driven by hydrophobic bile acids and the related secretory phenotype that is associated with senenscence also include chemokine (eg, CCL20) production, with resultant portal accumulation of Th17 cells that are presumed to be injurious. A meta-analysis of genome-wide association studies identified the *CCL20* gene as a novel risk locus in primary biliary cholangitis,[26] re-enforcing the concept of chemokine-directed inflammation in the context of biliary injury (figure 1D).

The cycle of injury that is shown (ie, immunological damage, cholestasis, and fibrosis) defines the opportunities for new intervention, beyond the general established post-transcriptional secretagogue properties of ursodeoxycholic acid. Clinical trials of specific and non-specific immune-regulating therapies have not, to date,

shown meaningful clinical benefit for patients,[48–51] and general antifibrotic therapies for liver disease have not yet been readily translated into clinical practice. With the biological dominance of cholestasis in patients with primary biliary cholangitis, increasingly specific anticholestatic therapies (eg, FXR [NR1H4] agonists, PPAR agonists, and FGF19 analogues)[52] are being evaluated in early and late-stage clinical trials.[53,54] Such efforts thus extend beyond the current use of obeticholic acid (ie, a semisynthetic bile acid FXR agonist)[5] and the data on off-label use of bezafibrate (ie, a pan-PPAR agonist).[6]

Diagnosis

Reaching a diagnosis

Immunoserology, which must always be interpreted in the context of a patient's overall clinical presentation, is key to diagnosing a patient with primary biliary cholangitis. Over 90% of patients will be positive for antimitochondrial antibodies. This result is most often accompanied by a non-specific rise in serum IgM concentration. When a patient is negative for antimitochondrial antibodies, immunofluorescence patterns of ANAs might help to diagnose patients; notably multinuclear dot, perinuclear rim, and centromere reactivity. Specific immunoassays related to antinuclear reactivities might show anti-glycoprotein-210 or anti-sp100 antibodies, which are both specific for primary biliary cholangitis; in some series, anti-glycoprotein-210 reactivity has been associated with disease severity.[55,56]

Guidelines provide recommendations that the presence of antimitochondrial antibodies (eg, a greater titre than 1/40, identified by immunofluorescence) or ANAs that are highly specific to primary biliary cholangitis, in the appropriate context of cholestatic liver biochemistry, without alternate explanation, is generally sufficient for the diagnosis of primary biliary cholangitis (table 1).[21,22] Liver biopsy is now an infrequent investigation in the diagnostic pathway, although a role for this procedure persists in the absence of characteristic serological reactivity, where features of autoimmune hepatitis are also present, or in cases where it is unclear if there could be an added liver injury, as is increasingly seen with non-alcoholic fatty liver disease. Liver biopsy can also be a relevant component of some clinical trial designs. Although usefulness can be considered for fibrosis staging by use of liver biopsy, most clinical practice nowadays focuses on the use of non-invasive testing strategies to address the assessment of disease stage.

The necessity of arranging a baseline ultrasound is not to visualise disease per se, since the biliary injury is restricted to the small bile ducts; however, ultrasound is used predominantly to exclude biliary obstruction as a cause for cholestatic serum liver test results. Ultrasound can also simply and safely identify features of cirrhosis and portal hypertension (eg, splenomegaly), the presence of which provides baseline information for the degree of risk of future poor outcomes (ie, the risks of developing complications of liver failure). Finally, elastography has been shown to be a reliable non-invasive means for assessing biliary fibrosis and can contribute to disease staging in patients with primary biliary cholangitis, recognising that elastography is a measure of liver stiffness, which itself is the cumulative consequence of inflammation, cholestasis, and fibrosis.[57]

Serum liver test abnormalities

The predominant pattern that is recognised by serum liver tests in patients with primary biliary cholangitis reflects the clinically dominant cholestatic injury, with a rise in ALP activity. A concomitant rise in GGT activity is consistent with a biliary origin for the ALP, but although GGT activity is largely related to biliary injury, it also reflects broader inflammatory and oxidative stress. Elevated serum ALP activity appears as a surrogate marker of bile acid retention, and the increased serum activity associated with cholestasis reflects heightened hepatic synthesis and subsequent release of the liver isoform of ALP in the sinusoidal blood flow. Data before therapy with ursodeoxycholic acid suggested that serum bile acid concentrations and ALP activities were linearly related, consistent with decreased canalicular secretion and hepatocellular retention of bile acids increasing liver ALP synthesis and release into the bloodstream (as opposed to bile). Bile acids, notably cholic acid and chenodeoxycholic acid (but by contrast, not ursodeoxycholic acid), both FXR activators of differing potency, are the major regulators of synthesis, doing so through activating transcription pathways. Lipopolysaccharides can also potently activate liver ALP synthesis.[58] When studied in health, genome-wide association studies have reported parallel insights, with association between serum ALP activity and allelic variations spanning multiple gene loci that are involved in bile acid transport (eg, *ABCB11* and *ATP8B1*) and glycoprotein synthesis or glycobiology (eg, *ABO*, *ASGR1*, *FUT2*, *GPLD1*, and *ST3GAL4*).[59]

Patients might also have elevations in serum aminotransferase activity but these are usually not as marked; values above five times the upper limit of normal are uncommon in classically presenting primary biliary cholangitis. Although elevations in serum aminotransferase activity are consistent with hepatocyte injury, they might not mechanistically be a consequence of immune injury, since bile acid toxicity of hepatocytes will also raise serum aminotransferase activity.

Disease and risk stratification

Transplant rates for primary biliary cholangitis have fallen over time, consistent with the concept that improving the cholestatic consequence of disease through therapy is effective. Nevertheless, the development of progressive biliary disease is associated with portal hypertension, liver failure, and risk for hepatocellular carcinoma. Survival in primary biliary cholangitis is

associated with identifiable baseline and on-treatment risk factors.

To stage liver disease in primary biliary cholangitis, attention is given to markers of disease severity—bilirubin values and platelet count in particular—and usually imaging findings; these findings encompass evidence of cirrhotic liver morphology or presence of splenomegaly on ultrasound, or both, and interpretation of serial transient elastography or magnetic resonance elastography. Serum markers of fibrosis, such as the enhanced liver fibrosis score, can also be used. Staging is important as patients with advanced liver disease have a higher risk of future disease progression and a need for appropriate surveillance strategies; additionally, effective interventions are most beneficial if offered before the disease reaches a late stage.

Ongoing risk stratification should account for baseline risk factors (eg, young age at diagnosis [<45 years], male sex, specific ANAs, and advanced stage at presentation—particularly cirrhosis and elevated bilirubin)[60] and on-treatment laboratory markers of disease activity that indicate increased risk of developing complications of end-stage liver disease. Multiple studies show a high risk of adverse events for patients with insufficient response to ursodeoxycholic acid treatment—usually judged 1 year after initiation, either by dichotomous or continuous scoring systems (eg, GLOBE score[61] or UK-PBC risk score.[62,63,64] Individualised follow-up is advised according to baseline risk factors, symptom burden, and the patient's stage of disease.

Treatment response criteria are defined differently in the literature. In the registration trial of obeticholic acid,[5] the inclusion criteria (ALP activity >1·67×the upper limit of normal or elevated bilirubin concentration <2·00×the upper limit of normal, or both) identified a population of patients with an average age at diagnosis of younger than 50 years, reflective of patients who are at high risk of poor outcomes with primary biliary cholangitis. The definitions of inadequate biochemical response to ursodeoxycholic acid, however, vary but all encompass an evaluation of serum liver tests, in particular bilirubin and ALP activity. Interface hepatitis is a histological marker of poor prognosis and persistent aminotransferase elevations in the serum are also identifiable as risk markers. No single approach for classifying treatment response has been adopted uniformly and a low risk of poor outcomes (ie, least clinical events) has proved easier to have consensus on. A common definition of treatment response is an ALP value of less than 1·50×the upper limit of normal, as well as a normal bilirubin value.

Managing the patient

Inflammation, cholestasis, and fibrosis define the persistent cycle of injury in patients. Targeting immune injury with biologically based therapies has been unhelpful to date,[48–51] and treatment is focused on bile acid-based drugs, which modify cholestasis, associated inflammation, and subsequent fibrogenesis (table 2). In managing patients, care usually spans primary-care and secondary-care settings, with tertiary programmes focusing on patients at the greatest risk of complications or with the greatest symptom burden. Furthermore, specialist care by a physician assistant or nurse is valuable and a means for not only attending to the need for patient education but also giving timely input and guidance for symptom control, as well as safe monitoring of advanced therapies, such as rifampicin for pruritus or second-line therapy with obeticholic acid.

Ursodeoxycholic acid is a naturally occurring tertiary bile acid (resulting from β-epimerisation of the secondary bile acid chenodeoxycholic acid by microbiota) that is choleretic and anti-inflammatory, via post-transcriptional and post-translational effects.[52] Once a patient has been diagnosed with primary biliary cholangitis, guidelines suggest that all patients should be offered treatment with weight-based oral ursodeoxycholic acid (ie, 13–15 mg/kg per day) with the intention that treatment will be for the duration of life (figure 2);[21,22] therapy even after liver transplantation has benefit.[65] For most patients, ursodeoxycholic acid (safely taken once, twice, or three times per day, as per the patient choice) is well tolerated, side-effects being limited to bloating, weight gain, and sometimes self-reported thinning of hair. Biochemical response to treatment with ursodeoxycholic acid is an

	Suitability	Dose	Mechanism	Comments
Ursodeoxycholic acid	Offer to all patients	13–15 mg/kg per day	Post-translational secretagogue	Established therapy
Obeticholic acid	Patients with inadequate response or intolerance to ursodeoxycholic acid	5 mg daily titrated to 10 mg daily if tolerated; dose adjustment in advanced liver disease (Child-Pugh score B or C)	Semisynthetic bile acid FXR (NR1H4) agonist	Licensed add-on therapy or alternative to ursodeoxycholic acid; associated with exacerbation of pruritus; use with caution for advanced liver disease
Bezafibrate	Patients with inadequate response to ursodeoxycholic acid	400 mg daily; unlicensed; not available in the USA; warning over use for liver disease	Pan-PPAR agonist	Randomised controlled data; concern over hepatotoxicity, rhabdomyolysis, and creatinine changes
Fenofibrate	Patients with inadequate response to ursodeoxycholic acid	Variable; unlicensed; warning over use for liver disease	PPARα synthetic agonist	No randomised controlled data; concern over hepatotoxicity, rhabdomyolysis, and creatinine changes

Table 2: **Treatment choices included in guidelines for patients**

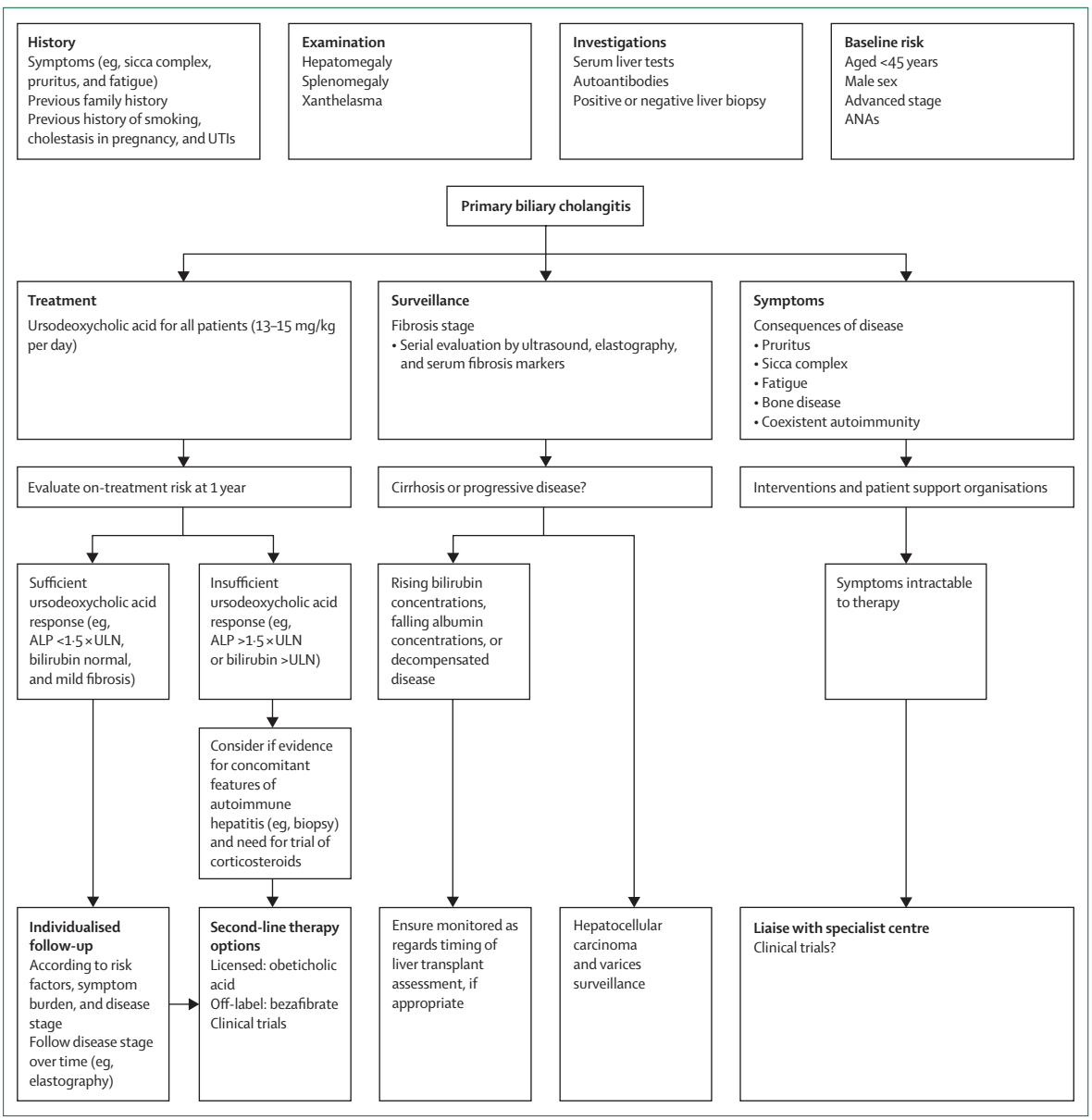

Figure 2: **Diagnostic, treatment, and management pathway**
A simplified care pathway that emphasises the key approaches to, and suggestions for, effective care of patients. ULN=upper limits of normal. UTIs=urinary tract infections.

important marker of treatment effectiveness, and is associated with prolonged survival (table 1).[62] Treatment effectiveness is evaluated by follow-up serum liver tests, with the therapeutic goal of improving markers of liver injury—namely a decrease in ALP activity and, particulary, normalisation or stabilisation of bilirubin values. For patients with non-cirrhotic liver disease who have a complete response to therapy biochemically, survival is excellent and, in some series, no different to an age-matched healthy control population.[66,67]

If patients are intolerant to ursodeoxycholic acid therapy, or biochemically do not have a sufficient response, then accounting for their baseline risk, a second-line therapy in the form of added obeticholic acid can be considered. Obeticholic acid is a semisynthetic bile acid (6α-ethyl-chenodeoxycholic acid) that, in milligram quantities, is a selective FXR agonist, with anti-inflammatory, antifibrotic, and choleretic properties; pharmacological effect is a result of engagement with the FXR receptor in the bowel and liver, and the consequences of FGF19 production (an enterokine).[52] The optimal dose of obeticholic acid appears to be 10 mg daily; obeticholic acid is started at 5 mg daily and can be titrated at 3 months, if tolerated, to 10 mg daily in

the USA according to the drug label approved by the US Food and Drug Administration (FDA; outside of the USA, titration occurs at 6 months because the drug label approved by the European Medicines Agency reflects the titration point in the original phase 3 trial[5]). In a phase 3, 12 month, clinical trial of obeticholic acid, nearly half of patients at high risk of disease progression were deemed to be biochemical responders to therapy, by use of a dichotomous response criteria.[5] In the use of obeticholic acid, it is important to assess the likelihood of benefit and whether a dose adjustment is needed in patients with advanced disease. As per the drug label, obeticholic acid is dose-adjusted to 5 mg per week initially (with a maximum dose of 10 mg twice per week) in patients with liver disease classified as Child-Pugh score B or C. However, it is not likely that any therapy would help a patient with liver disease classified as Child-Pugh score C and use of any therapy in patients with cirrhosis classified as Child-Pugh score B equally needs careful thought. Patients with cirrhosis should have intensified early safety evaluation and, in the context of the development of decompensation for a patient on obeticholic acid, dose adjustment or treatment cessation might be indicated. Pruritus is a clear, and not infrequent, side-effect of obeticholic acid treatment; however, in clinical trial settings, treatment discontinuation overall is less than 10% at labelled doses of obeticholic acid. The pruritus associated with obeticholic acid frequently appears to resolve over time and can be treated with colestyramine or rifampicin, as well as by adjusting the dose of obeticholic acid; in patients who have pruritus before treatment with obeticholic acid, optimisation of pruritus management before initiating obeticholic acid is logical, as could be dose adjustment at treatment initiation.

In the absence of readily available licensed therapies, and given the rare nature of primary biliary cholangitis, interest has been longstanding into repurposed therapies (ie, drugs that are not licensed for primary biliary cholangitis but in which there is use by experts because of evidence of benefit). In some countries, such as Japan, such therapeutic approaches in patients with primary biliary cholangitis are well established. Thus, other agents used to treat primary biliary cholangitis, although not approved by the FDA or EMA, are still used by specialist clinicians and, in particular, include fibrates. In this regard, it is notable that some of the molecules that are in late-stage development for treatment of patients with primary biliary cholangitis are similar therapies that also target the PPAR pathway, but are being clinically developed specifically for patients with primary biliary cholangitis. The use of fenofibrate and bezafibrate off label has been reported for some time, and observational data have reported biochemical effectiveness, as well as efforts to support long-term benefit.[68] Concern has been raised for hepatotoxicity or possible drug-induced autoimmunity and elevations in serum creatinine. However, effective use of fibrates has been supported by the report of a 24 month, randomised, placebo-controlled trial of bezafibrate (a pan-PPAR agonist)[6] that showed biochemical treatment efficacy, along with reported improvements in transient electrography and pruritus (n=50 in the active treatment group). As with obeticholic acid, more information on how to use the therapy in a population with more advanced disease is needed (although the bezafibrate trial did include patients with advanced disease on the basis of histology, liver stiffness, or bilirubin–albumin status), and understanding the implications, as well as the management of, increases in creatinine and liver enzymes in some patients needs ongoing evaluation. The data from the randomised study showed that creatinine concentrations increased by 5% in the bezafibrate group and decreased by 3% in the placebo group from baseline; this difference was noticeable at month 3 and remained mostly stable during the rest of the trial. Four patients had increases in aminotransferase values that were more than five times the upper limit of the normal range (ie, three patients in the bezafibrate group and one in the placebo group). Myalgia was reported in 20% (10 of 50) of the patients in the bezafibrate group and in 10% (5 of 50) of patients in the placebo group. Moderate, asymptomatic rhabdomyolysis developed at 3 months in one patient in the bezafibrate group, who concomitantly had statin therapy; the rhabdomyolysis resolved after discontinuation of bezafibrate. Substantial caution is relevant to the co-prescription of statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) with bezafibrate. There is no accepted definition of non-responsiveness to treatment for either obeticholic acid or bezafibrate, and largely practice reflects continuation so long as there is some biochemical effectiveness and treatment is tolerated without adverse effect.

Symptom burden can be high in patients with primary biliary cholangitis and proactive recognition and holistic interventions are recommended.[69] In this regard, patient support groups or apps can help (eg, PBCers Organization and PBC Foundation). Medical treatments for pruritus (table 3) can be effective, albeit precise insights into the cause of pruritus are scarce. Patients are usually started on the bile acid resin, colestyramine. Rifampicin is often used second line and necessitates monitoring, as there is a small but definable risk of hepatotoxicity in particular.[70] Other agents often trialled for itch include gabapentin, naltrexone, and sertraline. Clinical trials for pruritus are at an important juncture with early positive data for the use of inhibitors of the SLC10A2.[71] Off-label use of bezafibrate in the management of cholestatic itch has also been reported.[72] Patients with sicca complex can benefit from appropriate interventions to improve dry eyes and dry mouth (eg, artificial saliva, pilocarpine, or newer therapies for sicca complex).

Fatigue is a frequent observation across many chronic inflammatory diseases. Attention to the exclusion of

For more on **PBCers Organization** see https://www.pbcers.org

For more on **PBC Foundation** see https://www.pbcfoundation.org.uk

alternate causes (eg, medication, depression, anaemia, thyroid disorder, sleep disturbance, or social isolation) are important; practically, physical exercise can sometimes help patients to cope with a heightened fatigue burden. Although pruritus is very occasionally managed by liver transplantation, fatigue is not an indication for a liver graft. A practical approach to fatigue has been coined the TrACE algorithm:[73] treat the treatable, ameliorate the amelioratable, cope, and empathise.

A small proportion of patients with primary biliary cholangitis also show some, or all, of the clinical features of autoimmune hepatitis. Features that should raise concern for overlap usually relate to elevated ALT activity and IgG concentrations, and finding at least moderate interface hepatitis on biopsy. The frequency of overlap is hard to establish, since a diagnosis of autoimmune hepatitis requires a liver biopsy. However, triggers for biopsy are inconsistent in practice and a true consensus on objective thresholds, particularly of serum aminotransferase activities, to offer immunosuppression to patients is absent. The concept that high-risk progressive primary biliary cholangitis might reflect itself as being more hepatitic is also relevant, and existing data identifies the presence of interface hepatitis as one risk factor for disease progression.[74,75] One testable postulate for the future is that increasing access to effective therapies for primary biliary cholangitis, beyond ursodeoxycholic acid, will result in fewer patients for whom overlap with autoimmune hepatitis is considered. In the absence of true consensus, considering immunosuppression with autoimmune hepatitis therapies (eg, corticosteroids or azathioprine) is reasonable (figure 2) in a few patients. To diagnose an overlap syndrome, two of three criteria are proposed to be required: an ALT activity more than five times the upper limit of normal, IgG more than twice the upper limit of normal or positive anti-smooth muscle antibodies, and liver biopsy with moderate or severe periportal or periseptal lymphocytic piecemeal necrosis (ie, interface hepatitis), all in the context of a primary biliary cholangitis diagnosis; a refinement to this has been the requirement that patients should have liver biopsy features as one of the findings. By use of such criteria, primary biliary cholangitis and autoimmune hepatitis overlap is uncommon (ie, under 2% of patients with primary biliary cholangitis), although there might be differences based on patient heritage, in keeping with variable global risks for autoimmune liver diseases.

Managing the complications of primary biliary cholangitis

The management of cirrhosis in patients with primary biliary cholangitis includes a priority to diagnose hepatocellular carcinoma early, preventing variceal haemorrhage, and reducing the risk of osteoporotic fracture. Nuances include a rare potential for non-cirrhotic portal hypertension in patients with primary biliary cholangitis and a recognition that the risk of hepatocellular carcinoma is skewed in patients with primary biliary cholangitis to those with advanced liver disease, patients who do not respond to treatment, and men.[76]

	Dose	Mechanism	Comments
Colestyramine	4–12 g per day	Bile acid sequestrant	Ensure pharmacy advice to avoid interactions with concomitant medications; gastrointestinal symptoms (eg, constipation)
Rifampicin	150–600 mg daily	PXR (NR1I2) agonist	Caution in advanced liver disease; consider vitamin K supplementation if icteric; monitor haematology and serum liver tests; consider local prevalence of tuberculosis
Gabapentin	Variable	Structural analogue of the inhibitory neurotransmitter gamma-aminobutyric acid	Some patients find helpful; used in other pruritus settings
Bezafibrate	Up to 400 mg daily	Pan-PPAR agonist	Multiple reports and series showing effect on itch; monitor serum liver tests and creatinine
Naltrexone	Usually up to 50 mg daily	Partial opioid antagonist	Occasionally helpful; risk of paradoxical pain syndrome
Sertraline	Up to 100 mg daily	Selective serotonin reuptake inhibitor	Dry mouth as side-effect; effectiveness can be low
SLC10A2 inhibitors	Trials only	Inhibit reabsorption of bile acids	Multiple agents in development with positive early phase data

Table 3: **Pharmacological treatment choices for pruritus**

As liver disease progresses, patients are followed up with repeated serum liver tests, imaging, and elastography, all of which help to define the pattern of disease progression and surveillance needs, including timing of endoscopy for varices. In patients who develop persistent marked jaundice, decompensated liver disease, or intractable pruritus, liver transplantation should be considered, as it is a highly effective intervention.[77] Listing a patient for transplantation usually requires a disease severity score that is consistent with accepting the risk of surgery alongside an overt indication, albeit accounting for the well described trajectory that patients with primary biliary cholangitis developing persistent jaundice usually take. Given the time that it can take between referral, assessment, and ultimately listing, practice varies as to when to refer a patient if relying soley on bilirubin values. A reasonable approach is to be very cautious in patients with a bilirubin concentration more than 3 mg/dL, but to clearly document discussion about suitability of transplantation in those with a bilirubin concentration over 5 mg/dL.

Other features that are associated with primary biliary cholangitis are low bone mass from osteoporosis and hyperlipidaemia associated with cholestasis. Patients are usually recommended to take calcium and vitamin D supplements, have a bone-density evaluation, and have a general evaluation for the risk of bone fracture. The cholestasis of primary biliary cholangitis is associated with a lipogenic, non-atherogenic profile—characterised by high concentrations of cholesterol and HDLs—and tissue

deposits of lipids (ie, xanthelasma). The hyperlipidaemia of primary biliary cholangitis is usually not a concern, requiring intervention only if there are added metabolic or cardiac risks.[78] However, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors can be used safely if indicated. Routine screening for associated autoimmune diseases in patients with primary biliary cholangitis is not evidence based, but consideration should be made to the high rate of thyroid and coeliac disease.

Conclusion

Primary biliary cholangitis is an autoimmune liver disease with therapeutic options and treatment goals that are increasingly ambitious and aimed at full disease control.[79] Registry studies, alongside clinical trial data, have helped to inform patient care and focus attention on opportunities for patients with primary biliary cholangitis to prolong their life and improve their quality of life. Future therapeutic approaches might ultimately transition from a present model of escalating therapy on the basis of non-responsiveness to treatment, to a model of top-down pre-emptive therapy in appropriately stratified patients.

Contributors

AL and GMH were responsible for the literature search and analysis. All authors were responsible for the study concept and design, manuscript preparation, revision, and final approval.

Declaration of interests

MEG received grant support from National Institutes of Health (DK090019). MEG has been an investigator for primary biliary cholangitis trials sponsored by Arena Pharmaceuticals, Bristol-Myers Squibb, Cymabay Pharmaceuticals, Genentech, and Johnson and Johnson. GMH is supported by the Lily and Terry Horner Chair in Autoimmune Liver Disease Research. GMH has been a study investigator for primary biliary cholangitis and primary sclerosing cholangitis trials within the last five years sponsored by Cymabay, Falk Pharma, FF Pharma, Genfit, Genkyotek, Gilead, GlaxoSmithKline, Intercept Pharma, Johnson and Johnson, NGM Biopharmaceuticals, Novartis, and Shire. Within the last five years GMH has consulted ad hoc for Blade, Pliant, Cymabay, Genfit, Falk Pharma, GlaxoSmithKline, Intercept Pharma, Mirum Pharmaceuticals, and Novartis. AL has been an investigator for primary biliary cholangitis trials sponsored by Intercept Pharma and Lilly. AL has consulted for Intercept Pharma, Abbvie, Gilead, and Merck Sharp and Dohme. G-QW has consulted for Gilead, AbbVie, GlaxoSmithKline, and Merck Sharp and Dohme.

Acknowledgments

We acknowledge the ongoing support of patients with primary biliary cholangitis for the conduct of multiple observational and interventional studies that have informed the content of this Seminar. GMH is the recipient of the Lily and Terry Horner Chair in Autoimmune Liver Disease Research.

References

1 Gulamhusein AF, Hirschfield GM. Primary biliary cholangitis: pathogenesis and therapeutic opportunities. *Nat Rev Gastroenterol Hepatol* 2020; **17:** 93–110.

2 Rodrigues PM, Perugorria MJ, Santos-Laso A, Bujanda L, Beuers U, Banales JM. Primary biliary cholangitis: a tale of epigenetically-induced secretory failure? *J Hepatol* 2018; **69:** 1371–83.

3 Rice S, Albani V, Minos D, et al. Effects of primary biliary cholangitis on quality of life and health care costs in the United Kingdom. *Clin Gastroenterol Hepatol* 2020; published online June 17. https://doi.org/10.1016/j.cgh.2020.06.025.

4 Poupon RE, Lindor KD, Cauch-Dudek K, Dickson ER, Poupon R, Heathcote EJ. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. *Gastroenterology* 1997; **113:** 884–90.

5 Nevens F, Andreone P, Mazzella G, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. *N Engl J Med* 2016; **375:** 631–43.

6 Corpechot C, Chazouillères O, Rousseau A, et al. A placebo-controlled trial of bezafibrate in primary biliary cholangitis. *N Engl J Med* 2018; **378:** 2171–81.

7 Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. *J Hepatol* 2012; **56:** 1181–88.

8 Murillo Perez CF, Goet JC, Lammers WJ, et al. Milder disease stage in patients with primary biliary cholangitis over a 44-year period: a changing natural history. *Hepatology* 2018; **67:** 1920–30.

9 Sherlock S, Scheuer PJ. The presentation and diagnosis of 100 patients with primary biliary cirrhosis. *N Engl J Med* 1973; **289:** 674–78.

10 Asuri S, McIntosh S, Taylor V, et al. Primary biliary cholangitis in British Columbia First Nations: clinical features and discovery of novel genetic susceptibility loci. *Liver Int* 2018; **38:** 940–48.

11 Zeng N, Duan W, Chen S, et al. Epidemiology and clinical course of primary biliary cholangitis in the Asia-Pacific region: a systematic review and meta-analysis. *Hepatol Int* 2019; **13:** 788–99.

12 Yagi M, Tanaka A, Abe M, et al. Symptoms and health-related quality of life in Japanese patients with primary biliary cholangitis. *Sci Rep* 2018; **8:** 12542.

13 Prince MI, Ducker SJ, James OFW. Case-control studies of risk factors for primary biliary cirrhosis in two United Kingdom populations. *Gut* 2010; **59:** 508–12.

14 Corpechot C, Chrétien Y, Chazouillères O, Poupon R. Demographic, lifestyle, medical and familial factors associated with primary biliary cirrhosis. *J Hepatol* 2010; **53:** 162–69.

15 Fan X, Wang T, Shen Y, Xi X, Yang L. Underestimated male prevalence of primary biliary cholangitis in China: results of a 16-yr cohort study involving 769 patients. *Sci Rep* 2017; **7:** 6560.

16 Zhang XX, Wang LF, Jin L, et al. Primary biliary cirrhosis-associated hepatocellular carcinoma in Chinese patients: incidence and risk factors. *World J Gastroenterol* 2015; **21:** 3554–63.

17 Lleo A, Jepsen P, Morenghi E, et al. Evolving trends in female to male incidence and male mortality of primary biliary cholangitis. *Sci Rep* 2016; **6:** 25906.

18 Honda A, Tanaka A, Kaneko T, et al. Bezafibrate improves GLOBE and UK-PBC scores and long-term outcomes in patients with primary biliary cholangitis. *Hepatology* 2019; **70:** 2035–46.

19 Efe C, Taşçilar K, Henriksson I, et al. Validation of risk scoring systems in ursodeoxycholic acid-treated patients with primary biliary cholangitis. *Am J Gastroenterol* 2019; **114:** 1101–08.

20 Dahlan Y, Smith L, Simmonds D, et al. Pediatric-onset primary biliary cirrhosis. *Gastroenterology* 2003; **125:** 1476–79.

21 Hirschfield GM, Beuers U, Corpechot C, et al. EASL clinical practice guidelines: the diagnosis and management of patients with primary biliary cholangitis. *J Hepatol* 2017; **67:** 145–72.

22 Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2018 practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2019; **69:** 394–419.

23 Bae HR, Hodge DL, Yang G-X, et al. The interplay of type I and type II interferons in murine autoimmune cholangitis as a basis for sex-biased autoimmunity. *Hepatology* 2018; **67:** 1408–19.

24 Erice O, Munoz-Garrido P, Vaquero J, et al. MicroRNA-506 promotes primary biliary cholangitis-like features in cholangiocytes and immune activation. *Hepatology* 2018; **67:** 1420–40.

25 Hirschfield GM, Liu X, Xu C, et al. Primary biliary cirrhosis associated with HLA, IL12A, and IL12RB2 variants. *N Engl J Med* 2009; **360:** 2544–55.

26 Cordell HJ, Han Y, Mells GF, et al. International genome-wide meta-analysis identifies new primary biliary cirrhosis risk loci and targetable pathogenic pathways. *Nat Commun* 2015; **6:** 8019.

27 Selmi C, Mayo MJ, Bach N, et al. Primary biliary cirrhosis in monozygotic and dizygotic twins: genetics, epigenetics, and environment. *Gastroenterology* 2004; **127:** 485–92.

28 Triger DR. Primary biliary cirrhosis: an epidemiological study. *BMJ* 1980; **281:** 772–75.

29 Ala A, Stanca CM, Bu-Ghanim M, et al. Increased prevalence of primary biliary cirrhosis near Superfund toxic waste sites. *Hepatology* 2006; **43:** 525–31.

30 Matsumura S, Van De Water J, Leung P, et al. Caspase induction by IgA antimitochondrial antibody: IgA-mediated biliary injury in primary biliary cirrhosis. *Hepatology* 2004; **39:** 1415–22.

31 Lleo A, Selmi C, Invernizzi P, et al. Apotopes and the biliary specificity of primary biliary cirrhosis. *Hepatology* 2009; **49:** 871–79.

32 Tsuneyama K, Van De Water J, Yamazaki K, et al. Primary biliary cirrhosis an epithelitis: evidence of abnormal salivary gland immunohistochemistry. *Autoimmunity* 1997; **26:** 23–31.

33 Katsumi T, Tomita K, Leung PSC, Yang GX, Gershwin ME, Ueno Y. Animal models of primary biliary cirrhosis. *Clin Rev Allergy Immunol* 2015; **48:** 142–53.

34 Bae HR, Leung PSC, Tsuneyama K, et al. Chronic expression of interferon-gamma leads to murine autoimmune cholangitis with a female predominance. *Hepatology* 2016; **64:** 1189–201.

35 Lleo A, Bowlus CL, Yang G-X, et al. Biliary apotopes and anti-mitochondrial antibodies activate innate immune responses in primary biliary cirrhosis. *Hepatology* 2010; **52:** 987–98.

36 Montano-Loza AJ, Hansen BE, Corpechot C, et al. Factors associated with recurrence of primary biliary cholangitis after liver transplantation and effects on graft and patient survival. *Gastroenterology* 2019; **156:** 96–107.

37 Yang C-Y, Ma X, Tsuneyama K, et al. IL-12/Th1 and IL-23/Th17 biliary microenvironment in primary biliary cirrhosis: implications for therapy. *Hepatology* 2014; **59:** 1944–53.

38 Shimoda S, Miyakawa H, Nakamura M, et al. CD4 T-cell autoreactivity to the mitochondrial autoantigen PDC-E2 in AMA-negative primary biliary cirrhosis. *J Autoimmun* 2008; **31:** 110–15.

39 Liaskou E, Hirschfield GM. Genetic association studies and the risk factors for developing the "immuno-bile-logic" disease primary biliary cholangitis. *Hepatology* 2018; **67:** 1620–22.

40 Nakamura M, Nishida N, Kawashima M, et al. Genome-wide association study identifies TNFSF15 and POU2AF1 as susceptibility loci for primary biliary cirrhosis in the Japanese population. *Am J Hum Genet* 2012; **91:** 721–28.

41 Qiu F, Tang R, Zuo X, et al. A genome-wide association study identifies six novel risk loci for primary biliary cholangitis. *Nat Commun* 2017; **8:** 14828.

42 Banales JM, Sáez E, Úriz M, et al. Up-regulation of microRNA 506 leads to decreased Cl-/HCO3- anion exchanger 2 expression in biliary epithelium of patients with primary biliary cirrhosis. *Hepatology* 2012; **56:** 687–97.

43 Trauner M, Fuchs CD, Halilbasic E, Paumgartner G. New therapeutic concepts in bile acid transport and signaling for management of cholestasis. *Hepatology* 2017; **65:** 1393–404.

44 Hohenester S, Wenniger LM, Paulusma CC, et al. A biliary HCO_3^- umbrella constitutes a protective mechanism against bile acid-induced injury in human cholangiocytes. *Hepatology* 2012; **55:** 173–83.

45 Melero S, Spirlì C, Zsembery A, et al. Defective regulation of cholangiocyte Cl-/HCO3(-) and Na+/H+ exchanger activities in primary biliary cirrhosis. *Hepatology* 2002; **35:** 1513–21.

46 Hisamoto S, Shimoda S, Harada K, et al. Hydrophobic bile acids suppress expression of AE2 in biliary epithelial cells and induce bile duct inflammation in primary biliary cholangitis. *J Autoimmun* 2016; **75:** 150–60.

47 Chang J-C, Go S, de Waart DR, et al. Soluble adenylyl cyclase regulates bile salt-induced apoptosis in human cholangiocytes. *Hepatology* 2016; **64:** 522–34.

48 Combes B, Emerson SS, Flye NL, et al. Methotrexate (MTX) plus ursodeoxycholic acid (UDCA) in the treatment of primary biliary cirrhosis. *Hepatology* 2005; **42:** 1184–93.

49 Myers RP, Swain MG, Lee SS, Shaheen AAM, Burak KW. B-cell depletion with rituximab in patients with primary biliary cirrhosis refractory to ursodeoxycholic acid. *Am J Gastroenterol* 2013; **108:** 933–41.

50 Hirschfield GM, Gershwin ME, Strauss R, et al. Ustekinumab for patients with primary biliary cholangitis who have an inadequate response to ursodeoxycholic acid: a proof-of-concept study. *Hepatology* 2016; **64:** 189–99.

51 de Graaf KL, Lapeyre G, Guilhot F, et al. NI-0801, an anti-chemokine (C-X-C motif) ligand 10 antibody, in patients with primary biliary cholangitis and an incomplete response to ursodeoxycholic acid. *Hepatol Commun* 2018; **2:** 492–503.

52 Beuers U, Trauner M, Jansen P, Poupon R. New paradigms in the treatment of hepatic cholestasis: from UDCA to FXR, PXR and beyond. *J Hepatol* 2015; **62** (suppl): S25–37.

53 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.

54 Mayo MJ, Wigg AJ, Leggett BA, et al. NGM282 for treatment of patients with primary biliary cholangitis: a multicenter, randomized, double-blind, placebo-controlled trial. *Hepatol Commun* 2018; **2:** 1037–50.

55 Oertelt S, Rieger R, Selmi C, et al. A sensitive bead assay for antimitochondrial antibodies: chipping away at AMA-negative primary biliary cirrhosis. *Hepatology* 2007; **45:** 659–65.

56 Nakamura M, Kondo H, Mori T, et al. Anti-gp210 and anti-centromere antibodies are different risk factors for the progression of primary biliary cirrhosis. *Hepatology* 2007; **45:** 118–27.

57 Corpechot C, El Naggar A, Poujol-Robert A, et al. Assessment of biliary fibrosis by transient elastography in patients with PBC and PSC. *Hepatology* 2006; **43:** 1118–24.

58 Poupon R. Liver alkaline phosphatase: a missing link between choleresis and biliary inflammation. *Hepatology* 2015; **61:** 2080–90.

59 Chambers JC, Zhang W, Sehmi J, et al. Genome-wide association study identifies loci influencing concentrations of liver enzymes in plasma. *Nat Genet* 2011; **43:** 1131–38.

60 Carbone M, Mells GF, Pells G, et al. Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid. *Gastroenterology* 2013; **144:** 560–69.

61 The Global PBC Study Group. The GLOBE score for patients with primary biliary cholangitis (PBC). https://www.globalpbc.com/globe (accessed Sept 28, 2020).

62 Lammers WJ, van Buuren HR, Hirschfield GM, et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. *Gastroenterology* 2014; **147:** 1338–49.

63 Lammers WJ, Hirschfield GM, Corpechot C, et al. Development and validation of a scoring system to predict outcomes of patients with primary biliary cirrhosis receiving ursodeoxycholic acid therapy. *Gastroenterology* 2015; **149:** 1804–12.

64 UK-PBC. UK-PBC risk score calculator. https://www.uk-pbc.com/resources/tools/riskcalculator (accessed Sept 28, 2020).

65 Corpechot C, Chazouillères O, Belnou P, et al. Long-term impact of preventive UDCA therapy after transplantation for primary biliary cholangitis. *J Hepatol* 2020; **73:** 559–65.

66 Kuiper EMM, Hansen BE, de Vries RA, et al. Improved prognosis of patients with primary biliary cirrhosis that have a biochemical response to ursodeoxycholic acid. *Gastroenterology* 2009; **136:** 1281–87.

67 Parés A, Caballería L, Rodés J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic acid. *Gastroenterology* 2006; **130:** 715–20.

68 Honda A, Ikegami T, Nakamuta M, et al. Anticholestatic effects of bezafibrate in patients with primary biliary cirrhosis treated with ursodeoxycholic acid. *Hepatology* 2013; **57:** 1931–41.

69 Dyson JK, Wilkinson N, Jopson L, et al. The inter-relationship of symptom severity and quality of life in 2055 patients with primary biliary cholangitis. *Aliment Pharmacol Ther* 2016; **44:** 1039–50.

70 Webb GJ, Rahman SR, Levy C, Hirschfield GM. Low risk of hepatotoxicity from rifampicin when used for cholestatic pruritus: a cross-disease cohort study. *Aliment Pharmacol Ther* 2018; **47:** 1213–19.

71 Hegade VS, Kendrick SFW, Dobbins RL, et al. Effect of ileal bile acid transporter inhibitor GSK2330672 on pruritus in primary biliary cholangitis: a double-blind, randomised, placebo-controlled, crossover, phase 2a study. *Lancet* 2017; **389:** 1114–23.

72 Reig A, Sese P, Pares A. Effects of bezafibrate on outcome and pruritus in primary biliary cholangitis with suboptimal ursodeoxycholic acid response. *Am J Gastroenterol* 2018; **113:** 49–55.

73 Swain MG, Jones DEJ. Fatigue in chronic liver disease: new insights and therapeutic approaches. *Liver Int* 2019; **39:** 6–19.

74 Corpechot C, Carrat F, Poupon R, Poupon RE. Primary biliary cirrhosis: incidence and predictive factors of cirrhosis development in ursodiol-treated patients. *Gastroenterology* 2002; **122:** 652–58.

75 Corpechot C, Abenavoli L, Rabahi N, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. *Hepatology* 2008; **48:** 871–77.

76 Trivedi PJ, Lammers WJ, van Buuren HR, et al. Stratification of hepatocellular carcinoma risk in primary biliary cirrhosis: a multicentre international study. *Gut* 2016; **65:** 321–29.

77 Aguilar MT, Carey EJ. Current status of liver transplantation for primary biliary cholangitis. *Clin Liver Dis* 2018; **22:** 613–24.

78 Allocca M, Crosignani A, Gritti A, et al. Hypercholesterolaemia is not associated with early atherosclerotic lesions in primary biliary cirrhosis. *Gut* 2006; **55:** 1795–800.

79 Murillo Perez CF, Harms MH, Lindor KD, et al. Goals of treatment for improved survival in primary biliary cholangitis: treatment target should be bilirubin within the normal range and normalization of alkaline phosphatase. *Am J Gastroenterol* 2020; published online Feb 20. https://doi.org/10.14309/ajg.0000000000000557.