Review Article

Primary sclerosing cholangitis

Anahita Rabiee, Marina G. Silveira

Section of Digestive Diseases, Yale University School of Medicine, New Haven, CT, USA

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Correspondence to: Marina G. Silveira, MD. Section of Digestive Diseases, Yale University School of Medicine, 333 Cedar Street; LMP 1080, New Haven, CT 06520, USA. Email: marina.silveira@yale.edu.

Abstract: Primary sclerosing cholangitis (PSC) is a rare chronic cholestatic liver disease characterized by inflammatory destruction of the intrahepatic and/or extrahepatic bile ducts, leading to bile stasis, fibrosis, and ultimately to cirrhosis, and often requires liver transplantation (LT). PSC occurs more commonly in men, and is typically diagnosed between the ages of 30 and 40. Most cases occur in association with inflammatory bowel disease (IBD), which often precedes the development of PSC. PSC is usually diagnosed after detection of cholestasis during health evaluation or screening of patients with IBD. When symptomatic, the most common presenting symptoms are abdominal pain, pruritus, jaundice or fatigue. The etiology of PSC is poorly understood, but an increasing body of evidence supports the concept of cholangiocyte injury as a result of environmental exposure and an abnormal immune response in genetically susceptible individuals. PSC is a progressive disease, yet no effective medical therapy for halting disease progression has been identified. Management of PSC is mainly focused on treatment of symptoms and addressing complications. PSC can be complicated by bacterial cholangitis, dominant strictures (DSs), gallbladder polyps and adenocarcinoma, cholangiocarcinoma (CCA) and, in patients with IBD, colorectal malignancy. CCA is the most common malignancy in PSC with a cumulative lifetime risk of 10–20%, and accounts for a large proportion of mortality in PSC. LT is currently the only life-extending therapeutic approach for eligible patients with end-stage PSC, ultimately required in approximately 40% of patients. LT secondary to PSC has an excellent outcome compared to other LT indications, although the disease can recur and result in morbidity post-transplant.

Keywords: Cholangiopathy; autoimmune liver disease; treatment; management

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Clinical features and diagnosis

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease that is characterized by intra- and/or extrahepatic bile duct injury (1). The clinical presentation of PSC correlates with the sequence of inflammatory bile duct destruction and fibrosis, which results in bile duct stricturing, cholestasis, and eventually biliary cirrhosis with end-stage liver disease and hepatic dysfunction (2). PSC is increasingly diagnosed early in the stage of the disease course, and, as a result, the majority of patients do not have any clinical symptoms at the time of diagnosis (3). In the majority of cases, the diagnosis of PSC is prompted by the finding of cholestasis at the time of routine health evaluation or screening of high-risk patients such as those with inflammatory bowel disease (IBD). In patients who present with symptoms, abdominal pain is the most frequent symptom (20%) followed by pruritus (10%), jaundice (6%), and fatigue (6%) (3), but the presentation may differ widely among patients. Hepatomegaly and splenomegaly can be present in 44% and 39% of patients, respectively (4,5). Acute pruritus and/or cholangitis, presenting with jaundice,

fever, and abdominal pain, may be a result of benign or malignant biliary tract obstruction. Indeed, worsening cholestatic signs and symptoms should raise concern about cholangiocarcinoma (CCA), the most feared and not uncommon complication of PSC. Presentation with variceal bleeding, ascites, or hepatic encephalopathy may occur once a patient has progression to end-stage liver disease. In patients with associated IBD, abdominal pain, diarrhea, and gastrointestinal bleeding may be the only presenting symptoms along with abnormal liver biochemistries.

Elevations in serum alkaline phosphatase (ALP) and gamma-glutamyl transferase values in a cholestatic pattern are the biochemical hallmark of PSC, though up to 30% to 40% of patients have normal ALP at diagnosis or during the course of their disease (6,7). Increases of serum aspartate and alanine aminotransferase levels are usually less pronounced and typically less than 5 times the upper limits of normal (ULN). The serum total bilirubin level is normal in the majority of cases at diagnosis. Elevation in transaminases might suggest a more inflammatory disease with features of autoimmune hepatitis (AIH), which is present in approximately 5–14% of cases (8). Elevation in bilirubin concentrations suggest presence of dominant stricture (DS) or advanced liver disease.

Currently, no autoimmune antibodies are sufficiently specific in the diagnosis of PSC. The most commonly positive autoantibodies are the perinuclear antineutrophilic autoantibodies (pANCA), which are found in approximately 80% of patients but lack diagnostic specificity (9-12). Other autoantibodies such as antinuclear antibodies and anti-smooth muscle antibodies have been reported in 20% to 50% of individuals, and their presence, especially along with elevations of total immunoglobulins, or subsets, may warrant evaluation for AIH and PSC with features of AIH. Antimitochondrial antibodies are seldom positive in PSC. Serum immunoglobulin 4 (IgG4) levels are observed in approximately 10% of patients with PSC (13,14) in the absence of IgG4-related disease (IgG4-RD) and may be associated with poorer outcomes. The specificity of IgG4 for IgG4-related disease increases when levels of more than 4 times the ULN or IgG4:IgG1 ratio is greater than 0.24 (15).

Cholangiographic evaluation in patients with PSC typically reveals a beaded appearance of the intrahepatic and/or extrahepatic bile ducts, caused by multifocal strictures with intervening segments of normal or dilated bile ducts. The diagnostic modality of choice for the diagnosis of PSC is magnetic resonance cholangiopancreatography (MRCP), which has been shown in a meta-analysis to have a sensitivity of 86% and specificity of 94% when compared to endoscopic retrograde cholangiopancreatography (ERCP) (16). ERCP was once the gold standard for diagnosis, but it is invasive, associated with complications, and less cost effective in comparison to MRCP (17), thus is currently reserved for therapeutic interventions or diagnostic assessments of bile duct strictures. Invasive cholangiography might be more sensitive in detecting early disease compared to MRCP (97% overall diagnostic accuracy versus 90, respectively) (18) and thus might be considered in cases in which MRCP (and potentially liver biopsy) is negative but a high degree of clinical suspicion remain.

The histological hallmark of PSC is the finding of concentric periductal fibrosis, also known as "onion-skin fibrosis", but it is only detected in less than 15% of liver biopsies of patients with PSC. Furthermore, it is not specific, having been described occasionally in bile duct obstruction, primary biliary cholangitis, ductopenic rejection post-liver transplant and intra-arterial chemotherapy (19). Liver biopsy is not necessary to diagnose PSC (20), unless there is suspicion for small duct PSC or PSC with features of AIH. In patients with clinical and biochemical features of PSC but with normal cholangiography, a liver biopsy should be considered for evaluation of small duct PSC (21). In those with a disproportionate elevation in aminotransferases, biopsy is also recommended to exclude overlap syndrome (22). Liver biopsy might be of value to assess the degree of interface hepatitis consistent with PSC-AIH overlap syndrome and might help decide if immunosuppressive therapy is indicated. Though liver biopsy has been historically performed for staging purposes, prognostic models and non-invasive fibrosis markers have obviated the need for liver biopsy for staging of the disease.

The diagnosis of PSC is typically established in patients with chronic cholestasis when cholangiographic studies (MRCP, ERCP, or percutaneous transhepatic cholangiogram) show characteristic features of PSC, and secondary forms of sclerosing cholangitis (23), as summarized in *Table 1*, are excluded (22).

IgG4-associated cholangitis (IAC), the biliary manifestation of IgG4-RD, is a distinct entity which might mimic PSC. This condition is responsive to steroids and is not a pre-malignant condition, which makes it clinically significant to distinguish from PSC. Guidelines recommend measuring IgG4 in all patients with PSC to exclude IAC. In particular, IAC is frequently found to be associated with pancreatic involvement in IgG4-RD and is termed AIP-

Table 1 Causes of secondary sclerosing cholangitis

Cholangiocarcinoma (CCA)
Diffuse intrahepatic metastasis
Ischemic cholangitis
IgG4-associated cholangitis (IAC)
Recurrent pyogenic cholangitis
Sclerosing cholangitis in critical illness
Choledocolithiasis
AIDS cholangiopathy
Sarcoidosis
Portal hypertensive biliopathy (choledochal varices)
Congenital (choledochal cysts, biliary atresia)
Chronic biliary infestation (liver fluke or ascaris)
Surgical biliary trauma
Cystic fibrosis
Eosinophilic cholangitis
Histiocytosis X
Mast cell cholangiopathy
Sclerosing cholangitis in critically ill patients

SC. However, IAC can also be seen without concurrent pancreatitis and can be difficult to distinguish between PSC using cholangiography alone. Diagnosis is usually established based on two or more main manifestations: elevated serum IgG4, suggestive pancreatic imaging findings, other organ involvement and bile duct/ampullary biopsy (with >10 IgG4 positive cells/high power field) along with a significant response to steroid therapy (24).

Small duct PSC

Though the large bile ducts are affected in the majority of patients PSC, up to 9% of cases have disease that affects bile ducts that are too small to be identified by cholangiogram, referred to as small duct PSC (25). Small duct PSC is characterized by consistent liver biopsy findings and cholangiographically normal bile ducts (26,27) and appears to have a less aggressive course and to be less likely to lead to CCA compared to large duct PSC (28,29). Approximately 5–15% of patients with small duct PSC ultimately progress to large duct disease over the course of the disease (28,30), but the frequency of progression and its predictors are poorly defined.

PSC with features of AIH or PSC-AIH overlap syndrome

A subset of patients with PSC have additional biochemical, serological, and histological features typical for AIH, including markedly elevated transaminases and IgG, characteristic autoantibodies and moderate to severe interface hepatitis. Though there is no consensus on the nomenclature, or diagnosis, of this presentation and whether it is a distinct entity, it is commonly referred to as PSC-AIH overlap syndrome or PSC with features of AIH. Adequate recognition of such features is clinically relevant as the component of AIH may be responsive to steroids and patients may benefit from therapy with immunosuppressants (31,32). In children, due to the high prevalence of such syndrome, MRCP is recommended for patients with a diagnosis of AIH, especially if there is failure to respond to first-line steroid therapy (33,34). In adults, the reported prevalence varies between 7–14% depending on the diagnostic criteria used (8), and the described long-term outcomes are worse than classic AIH but better than PSC (35).

Demographics and epidemiology

PSC is diagnosed more commonly in men (65–70%) between the ages of 30 and 40 years, though it can occur at any age.

The prevalence of PSC is highest among patients with underlying IBD. Indeed, up to 70% of patients have concurrent IBD (36), most often characterized as ulcerative colitis (UC). One study found that approximately 8% of patients with IBD who were screened with MRCP had cholangraphic features consistent with PSC (37). In general, IBD is diagnosed several years earlier than PSC (38), but it can be diagnosed at any time during the course of PSC, including after liver transplantation (LT). Likewise, PSC can occur at any time during the course of IBD (38), including many years after proctocolectomy for colitis (39). PSC is more common in those with pancolitis compared to those with isolated left-sided colitis or proctitis (40).

Though there is geographical variability, the prevalence of PSC is estimated at up to 16.2 per 100,000 population (41) and annual incidence up to 1 case per 100,000 population (42), being the highest in northern Europe and the United States and markedly lower in Asia. True population-based studies, however, are scarce and limit the understanding of

the prevalence and incidence of PSC. A large population-based epidemiological study from the Netherlands reported an annual incidence of 0.5 per 100,000, with a point prevalence of 6 per 100,000 in 2008, with prevalence rates increasing significantly over time (25), as described in other studies (43,44). In the US, the incidence of PSC in a large, ethnically diverse cohort revealed lower incidence rates compared to studies including predominantly Caucasian populations (43,45). With estimated less than 200,000 cases in the US and less than 5 per 10,000 persons in Europe, PSC meets the criteria for a rare or "orphan" disease.

Pathogenesis

The pathogenesis of PSC is not fully understood but appears to be multifactorial and several mechanistic theories have been proposed. Cholangiocyte injury appears to result from environmental exposure and an abnormal cholangiocyte immune response leading to clinical disease in genetically susceptible individuals. Little is known about the role of the environmental risks including the influence of colonic toxins, gut microbiota, portal bacteria, or viral infections (46).

The role of genetic factors in the etiology of PSC is underscored by the finding that first-degree relatives of patients with PSC have an increased risk of PSC (up to 11-fold) (47). Genetic susceptibility factors for PSC may overlap with UC as first-degree relatives of patients with PSC without IBD are also at an increased risk of UC (8-fold) (47). Through the application of genome-wide association studies, greater than 20 susceptibility genes for PSC have been established, with the human leukocyte antigen (HLA) complex on chromosome six representing the strongest finding by several orders of magnitude (48). The overall genetic architecture of PSC appears to share features with both autoimmune diseases and IBD. Strong HLA gene associations, along with several susceptibility genes that are critically involved in T-cell function, support the involvement of adaptive immune responses in development of disease, and support the long-standing notion of PSC as an autoimmune disease (49). Nonetheless, genetic findings in PSC so far explain less than 10% of disease liability, and environmental risk factors are estimated to account for greater than 50% of the unexplained fraction (48).

Several factors support the involvement of the gut microbiota in the pathogenesis of PSC, including the long described association of PSC with IBD, genome-wide association study data identifying genetic variants in PSC that are associated with UC (such as those encoding GPR35) or influence biliary bacterial composition (such as those encoding FUT2) (50), the presence of bacterial products in the liver explants of patients with PSC (51), growth of bacteria and fungi from bile cultures acquired at time of first ERCP and increased T-cell response to microbial agents (52). Conversely, *in vitro* data have shown that biliary epithelial cells isolated from patients with PSC have aberrant TLR-nuclear factor-κB (NF-κB) immune responses to intestinal endotoxins with increased production of pro-inflammatory cytokines, such as IL-8 and TNF-α (53), suggesting that pro-inflammatory cytokines and endotoxins induce inappropriate innate immune responses in activated cholangiocytes in patients with PSC. Additionally, an overall reduction in bacterial diversity and altered abundance of certain bacteria in gut microbiota is observed in patients with PSC compared with the healthy state (54), but the mechanisms by which this alteration in gut microbial community results in disease remain unclear.

The strong HLA associations found in genetic studies suggest that adaptive immune responses are involved (54). The HLA class I and class II molecules present potentially antigenic peptides, derived from intracellular and extracellular sources, respectively, to the T cell receptor on CD8 and CD4 positive T cells. Gut derived antigens presented by PSC-associated HLA variants to the T cell receptor are potential triggers of these responses, and activated T cells may migrate to both the liver and gut following clonal expansion because of the overlapping expression in the gut and the liver of relevant lymphocyte homing components including mucosal vascular address in cell adhesion molecule 1 (MadCAM-1) and vascular cell adhesion molecule 1 (VCAM-1), α4β7 integrin, along with Chemokine C-C motif ligand 25 (CCL25) secretion, and contribute to the pathogenesis of PSC (55). In the liver, these recruited lymphocytes have been implicated in biliary inflammation leading to apoptosis and necrosis of cholangiocytes, and eventually fibrosis (56).

Inflammation and fibrosis lead to cholestasis and parenchymal injury. A distinct bile acid profile has been noted in IBD-PSC patients with a direct toxic effect of bile acids on cholangiocytes believed to contribute to disease progression (57,58). Primary or secondary disturbances in bile homeostasis as part of disease processes in the bile ducts or the colon (59-61), or deficiencies in protective or compensatory mechanisms, such as the so-called "bicarbonate umbrella" (62) have been implicated in the pathogenesis of PSC. The cholangiocytes show an activated

phenotype in PSC, which may further trigger an immune response through interactions with hepatic stellate cells and/or portal myofibroblasts, promoting development of peribiliary fibrosis and eventually cirrhosis (63,64).

Natural history and prognosis

PSC is a progressive disease, with evolution to biliary cirrhosis and malignancy in the majority of patients (65). The estimated 10-year survival for patients with PSC is approximately 65% (43). In a large population-based study, in which 92% of patients were treated with UDCA, the estimated survival time from diagnosis until PSC-related death or LT was 21 years, compared to median 13 years transplant-free survival in a cohort from three liver transplant centers (37). Though patients who are asymptomatic have a better prognosis than those with symptoms at diagnosis, symptoms often develop over time (3). However, there is significant variation among individuals and between different subtypes. For example, patients with small duct PSC disease generally have better outcomes than those with classic disease and do not seem to develop CCA, unless the disease has progressed to large-duct PSC (21). Other favorable prognostic factors include younger age at diagnosis, and female sex (36). On the other hand, poor prognostic factors include extensive intrahepatic or extrahepatic biliary strictures (66), DSs (67), recurrent cholangitis (68), UC [compared to Crohn's disease (CD) or no IBD] (36), evidence of liver synthetic dysfunction and cirrhosis with portal hypertension.

Biomarkers to predict the pace of progression of any form of PSC have been described. One or 2 years after diagnosis, a serum ALP level of less than 1.5 times the ULN has been associated with better outcomes, regardless of treatment (6,7). Worsening cholestasis predicts poorer outcomes, including increased risk of LT, hepatobiliary cancer, and death (69,70). However, ALP has a naturally unpredictable fluctuating nature in PSC which limits the value of single measurements at any point in time for follow-up or clinical trials. The Enhanced Liver Fibrosis (ELF) Panel, a panel of three serum markers of fibrosis (hyaluronic acid, procollagen III aminoterminal peptide, and tissue inhibitor of metalloproteinase 1) has been shown to predict transplant-free survival in PSC (71). Interestingly, ELF can also be elevated when there is acute inflammation and biliary obstruction. Parenchymal changes on MRI (72), relative enhancement with hepatocyte-specific agents (73) and arterial peribiliary hyperenhancement (74,75) have been shown to correlate with clinical outcomes in several small studies. A recent retrospective study including an internal cohort and an external validation cohort of 238 patients showed that two MR risk scores, referred to as Anali with and without gadolinium, which combine cholangiographic changes and parenchymal features such as dysmorphy, portal hypertension and enhancement heterogeneity, were associated with the occurrence of clinically significant outcomes (cirrhosis decompensation and transplant-free survival) and may be useful to predict radiographic progression in patients with PSC (76). Liver stiffness as measured by transient elastography or by magnetic resonance elastography (MRE), both at baseline or its variation over time, has been shown to predict the clinical outcome of patients with PSC (77,78). Spleen size has also been shown to predict outcomes in those with PSC (79), probably as a reflection of progression of portal hypertension. The prognostic value of histological scores such as the Ludwig and Nakanuma staging systems have been confirmed to be independent predictors of long-term outcome is PSC (80). However, the routine applicability of liver biopsy in PSC is limited due to its invasive nature, high rate of sampling error, and slow rates of histological progression, particularly fibrosis.

Multiple prognostic scoring systems that incorporate various clinical factors have been proposed. The most commonly used scoring system is the Mayo risk score (MRS), which is calculated based on measurements of serum bilirubin, AST, and albumin; the age of the patient and the presence of variceal bleeding (81). It was developed to predict short-term mortality in PSC, but has not been validated to predict long-term outcomes or other clinically relevant events such as LT. The Amsterdam Cholangiographic Scoring System (66), in which cholangiographic classification of intra- and extrahepatic biliary lesions using ERCP estimate medium- and long-term prognosis in PSC, has been validated as a prognostic model in PSC. The need for an invasive procedure to evaluate biliary changes reduces applicability in clinical practice. Other prognostic scores have been recently proposed, including the Amsterdam-Oxford model (AOM) (82), the UK-PSC risk score (83) and the Primary Sclerosing Cholangitis Risk Estimate Tool (PREsTo) (78). The AOM, which predicts PSC-related death or LT, was developed and internationally validated with recent work highlighting an incremental improvement in the model's performance over time (such as at 5 years after diagnosis) (84). Nonetheless, the C statistic of 0.68 at the time of diagnosis was relatively

modest, and its overall predictive ability was inferior compared with the MRS (C statistic 0.75). The UK-PSC risk score, which predicts LT and all-cause mortality, was derived from approximately 1,000 patients enrolled in the UK-PSC research cohort and independently validated. It includes a short-term (2-year) and a long-term (10-year) risk score, both of which outperformed the MRS (C statistics 0.81 and 0.80, respectively). The PREsTo is one of the newest prognostic models to accurately predict liver decompensation patients with PSC at 5 years. The PREsTo was derived from approximately 500 patients from a referral center and validated in about 300 patients in an international cohort, using a machine-based learning technique, and consists of nine variables: bilirubin, albumin, serum ALP times the ULN, platelets, aspartate aminotransferase (AST), hemoglobin, sodium, patient age, and number of years since PSC was diagnosed. It significantly outperforms current prediction scoring systems with a C statistic of at least 0.90.

Although they can be of benefit in research settings, the role of prognostic models in clinical practice and their use for individual patients is still evolving.

Medical management

No medical therapy has been shown to alter the course of PSC. Current treatments focus on symptom management (such as fatigue and pruritus), therapy of complications such as bacterial cholangitis and DSs, and management of coexisting conditions such as IBD, coexisting autoimmune diseases, and metabolic bone disease.

Ursodeoxycholic acid (UDCA) is the most extensively studied and most commonly used medication for PSC, but studies have not corroborated its effectiveness. In one randomized double blind controlled trial, UDCA at doses of 13–15 mg/kg/day was associated with a reduction in liver enzymes compared to placebo, but it failed to demonstrate any significant difference in clinically significant endpoints such as time to LT, progression to cirrhosis or mortality (85). A study evaluating moderate doses of UDCA (17–23 mg/kg/day) revealed reduction in ALP, but not clinically relevant endpoints of symptoms, need for LT or death (86). A large multi-center study comparing high dose UDCA (28–30 mg/kg/day) with placebo unexpectedly found the risk of primary endpoint of development of cirrhosis, CCA, liver transplant or death was 2.3 times higher in the treatment group, despite improvement in serum ALP levels, leading to early termination of the trial (87). Meta-analyses of published data report no benefit from UDCA in the treatment of PSC (88,89). Although guidelines advise against the use of high doses of UDCA, the use of lower and moderate doses (13–20 mg/kg/day) remains controversial, in part due to post-hoc analyses from clinical trial data that reveal normalization of the ALP level is associated with a better long-term prognosis (6,7). Current guidelines differ in terms of recommendation regarding the use of low to moderate doses of UDCA: the American Association for the Study of Liver Diseases recommends against its use for PSC (22), whereas the American College of Gastroenterology and the European Association for the Study of the Liver do not make any specific recommendations (90,91). Many centers prescribe low to moderate doses of UDCA for 6 months, to be continued only if normalization (or near normalization) of serum ALP levels is observed (92).

Many other medications are being assessed in ongoing clinical trials, as summarized in *Table 2*. The majority of the clinical trials focus on cholestatic and fibrotic targets [e.g., 24-nor-UDCA, obeticholic acid (OCA) and other farnesoid X receptor (FXR) agonists, anti- lysyl oxidase-like 2 (LOXL2)]. There is an ongoing phase 3 study of nor-UDCA, a synthetic bile acid that produces a bile acid-dependent bicarbonate-rich choleresis, based on promising results of a phase 2 randomized study including 161 patients that demonstrated a significant dose-dependent improvement in ALP in those receiving 500–1,500 mg nor-UDCA compared to placebo (93). OCA, a semisynthetic analogue of chenodeoxycholic acid and potent FXR agonist, was recently evaluated in a phase 2 randomized trial, which showed a significant reduction in the serum ALP at week 24 with OCA 5–10 mg compared to placebo, but not with OCA 1–3 mg (94). As seen in studies in primary biliary cholangitis, the most common adverse event was dose-dependent mild to moderate dose-related pruritus (94). Similarly, a phase 2 study including 52 patients demonstrated that treatment with cilofexor, a non-steroidal FXR agonist, resulted in a dose-dependent reduction in ALP and markers of cholestasis after 12 weeks of treatment, with lower observed rates of moderate to severe pruritus compared to placebo (95). A phase 3 study of cilofexor in patients with non-cirrhotic PSC is underway. Results of a small study of oral vancomycin, which may target the gut microbiota and may act as an immunomodulator, by increasing regulatory T-cells, appear promising, with reduction in ALP and bilirubin (96) and further randomized trials are ongoing.

Notable recent negative studies include a phase 3 study

Table 2 Ongoing clinical trials in PSC*

Treatment	Study title	Registry identifier	Status	Size	End date
Bezafibrate	Efficacy of 24 months of bezafibrate in PSC with persistent cholestasis despite UDCA therapy	NCT04309773	Not yet recruiting	104	–
Cilofexor	Safety, tolerability, and efficacy of cilofexor in non-cirrhotic adults with PSC	NCT03890120	Recruiting	400	–
HTD1801	A POC and dose-ranging study of HTD1801 in PSC patients	NCT03333928	Active	59	–
Mitomycin	Mitomycin C therapy for patients with PSC	NCT01688024	Unknown	130	–
nor-UDCA	nor-UDCA acid *vs*. placebo in PSC	NCT03872921	Recruiting	300	–
Selected mesenchymal stromal cells derived from human umbilical cord	A single-arm, Phase IIa, safety and efficacy trial of selected MSCs in the treatment of patients with PSC and AIH	NCT02997878	Recruiting	56	–
Simvastatin	Effect of simvastatin on the prognosis of PSC	NCT04133792	Recruiting	700	–
Sulfasalazine	Sulfasalazine for the treatment of PSC	NCT03561584	Recruiting	42	–
Vancomycin	Vancomycin for PSC	NCT03710122	Recruiting	102	–
Vancomycin	Effect and safety of oral vancomycin in PSC patients	NCT02605213	Unknown	30	–
Vancomycin	Treating PSC and biliary atresia with vancomycin	NCT02137668	Recruiting	200	–
Vidofludimus calcium	Vidofludimus calcium for PSC	NCT03722576	Recruiting	30	–

*, Includes only trials including ≥30 adult patients registered on clinicaltrials.gov. PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid; AIH, autoimmune hepatitis.

of simtuzumab, a monoclonal antibody against LOXL2 with anti-fibrotic properties, which did not provide any clinical or histological benefit over placebo after 96 weeks in a randomized controlled trial including 234 patients with compensated PSC (97). A phase 2 study of NGM282, a non-tumorigenic FGF19 analogue, showed that after 12 weeks of treatment there were no significant changes in serum ALP levels from baseline between the NGM282 and placebo groups, despite significant reduction in markers of cholestasis and fibrosis in the treatment group (98). A retrospective analysis of 102 patients with PSC from a large international cohort who as part of their treatment for IBD received vedolizumab, which blocks the integrin α4β7 and thus targets T lymphocyte homing, reported a small increase in liver biochemistries including bilirubin at the end of the study; only one-fifth of patients had a significant reduction in level of serum ALP (99).

Clinical trial design and execution in PSC are hampered by multiple factors, including rarity of the disease, heterogeneity of presentation, protracted natural history course, variable rates of disease progression, competing risk events, and relatively low event rate of clinically relevant endpoints that are hard to predict. Regulatory agencies recognize that to promote drug development in serious and life-threatening rare diseases lacking effective medical therapy, accelerated pathways for approval are needed. Surrogate endpoints that are reasonably likely to predict clinical benefit or a clinical endpoint that can be measured earlier than irreversible morbidity (that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit) may be used as a basis for accelerated approval. So far, no biomarkers have been validated for use as surrogate endpoints in clinical trials for PSC, but many potential candidate surrogate biomarkers have been proposed (100,101) and are listed in *Table 3* (further described in the "Natural history and prognosis" section). Combinations of biomarkers and/or clinical outcomes, such serum ALP levels and progression of fibrosis (using histology or noninvasive methods such as elastography), may increase content validity and be acceptable surrogate endpoints, recognizing that different endpoints may need to be individualized to patient phenotypes, drug mechanisms, and aspects of the disease targeted (i.e., inflammation, biliary stricturing, parenchymal fibrosis). Clinical trials that

Table 3 Potential candidate surrogate biomarkers for clinical trials in PSC

Biochemical markers
Alkaline phosphatase (ALP)
ELF Score
Non-invasive imaging
MRI/MRCP
Spleen size
Transient elastography
MRI elastography
Invasive
ERCP
Histology

PSC, primary sclerosing cholangitis; ALP, alkaline phosphatase; ELF, Enhanced Liver Fibrosis; MRCP, magnetic resonance cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography.

target symptoms associated with PSC may benefit from the use of a recently developed and preliminarily validated PSC-specific patient-reported outcome instrument (PSC PRO) as a surrogate endpoint (102).

Management of complications and associated conditions

Bacterial cholangitis

As a result of biliary strictures and bile stasis, patients with PSC are at increased risk for bacterial cholangitis, which may occur spontaneously, particularly in the setting of a DS, or after biliary tract instrumentation. Due to increased risk of post-ERCP cholangitis (103), prophylactic antibiotics should be administered prior to and following biliary interventions (91). Bacterial cholangitis may contribute to disease progression (104). Empirical antibiotics are typically effective. Urgent endoscopic biliary decompression is recommended for patients who have acute cholangitis in the setting of a dominant biliary stricture.

Dominant stricture

DSs, defined as stenoses with a diameter of up to 1.5 mm in the common bile duct (CBD) or up to 1 mm in the hepatic ducts on ERCP (105), are a frequent finding in patients with PSC and occur in 45% to 65% of patients during follow-up. Patients can present with an increase in serum bilirubin, worsening symptoms of jaundice and pruritus, cholangitis, or progressive bile duct dilation on imaging. Though the majority of these strictures prove to be benign (105,106), a DS might harbor malignancy. One retrospective study including 128 patients showed one-fourth of patients with DS developed CCA during 10-year follow-up (67). DS portend a poor prognosis with markedly reduced survival rates (18-year survival of 25% in those with DSs compared to 75% in those without) (68), predominantly due to strong association with CCA. These patients should be evaluated by ERCP; brushings for cytology or biopsy for pathology to exclude CCA should be performed concomitantly with endoscopic treatment (22). A meta-analysis including 11 studies with 747 patients revealed that even though the specificity of endoscopic brushings for cytologic analysis in detecting CCA is very high (97%), their sensitivity is low (43%), and thus bile duct brushing is reliable in establishing a diagnosis CCA but not in excluding malignant strictures (107). Fluorescence in situ hybridization (FISH) increases sensitivity for detecting neoplasia to 68% (specificity 70%) from one cytology specimen, with more modest improvement if polysomy is considered diagnostic (sensitivity 51% and sensitivity 93%) (107). In patients with equivocal cytology results, the sensitivity increases to 74% but specificity is only 57% (107). The presence of FISH polysomy on two sequential specimens may denote a higher risk of development of CCA compared to those in patients in whom initial polysomy reverts to non-polysomy on subsequent specimen (108). Cholangioscopy allows for direct visualization of the bile duct with targeted biopsies of suspicious lesions, which has been reported to increase sensitivity to 65% and specificity to 97%, with a diagnostic accuracy of 96% (109). However, one of the disadvantages of this technique is that the passage of the cholangioscope may be difficult in the narrow, strictured bile ducts in PSC. Interestingly, a recent study suggests that while cholangioscopy-guided and transpapillary biopsies improve the sensitivity for the detection of CCA in combination with other ERCP-based techniques compared to brush cytology alone, these modalities in addition to FISH did not significantly improve the sensitivity for the detection of malignancy in patients with PSC. Further investigation is needed to determine the added benefit of endoscopic ultrasound including intraductal ultrasound and confocal endomicroscopy in the diagnosis of CCA in patients with PSC.

Endoscopic treatment of dominant stenoses relieves obstruction and improves cholestasis in the short-term (110). Radiographic improvement is often noted on follow-up cholangiography. Long-term benefits are less clear—model-based comparisons suggest endoscopic therapy prolongs survival in comparison to predicted survival (105,111,112). In an intriguing large retrospective study including 268 patients with DS who were offered either scheduled ERCP and dilatation, or procedures based on clinical symptoms, transplant-free survival at 5 years was significantly higher in those with scheduled procedures compared to those in the clinically indicated ERCP group (51% *vs*. 29%) (113), but these findings have not yet been confirmed and surveillance ERCP is not recommended in the management of PSC. Balloon dilatation and plastic stents are the main modalities for endoscopic therapy of DS. Due to an apparent increased risk of procedure-related cholangitis with placement of biliary stents, short-term stenting is likely preferable to long-term (110). While both balloon dilatation and stents have been shown to be effective, a recent randomized trial was halted early due to significantly higher occurrence of treatment-related adverse events, particularly pancreatitis and cholangitis, in patients who were treated with short-term stent placement (114), suggesting balloon dilatation should be the initial treatment of choice for DS in patients with PSC and stenting should be reserved for strictures that are refractory to dilation. Antibiotic prophylaxis is recommended to reduce cholangitis for all patients with PSC undergoing ERCP (115).

For patients with severe or recurrent obstruction, surgical management might be an option. In highly selected patients without cirrhosis and with predominantly extrahepatic biliary strictures, resection of the extrahepatic biliary tree may improve jaundice and delay LT (116), and long-term survival rates may be comparable between noncirrhotic patients with PSC status post resection compared to that of cirrhotic patients undergoing LT (117).

Cholangiocarcinoma

CCA is the most common malignancy in PSC. Compared to the general population, patients with PSC have an almost 400-fold increased risk of developing CCA, with the annual incidence estimated at 0.6% per year and a cumulative lifetime risk of 10–20% (25). Patients with DSs are at higher risk of CCA, whereas patients with small-duct PSC are at low risk (2). Duration of PSC does not appear to be a risk factor for development of CCA, and up to half of the patients are diagnosed with CCA within a year of diagnosis of PSC (118). Although symptoms such as weight loss, fever, jaundice and elevation in ALP and bilirubin may suggest superimposed CCA, in early stages CCA can be asymptomatic thus early diagnosis can be quite challenging despite the availability of a variety of diagnostic modalities. CCA accounts for a large proportion of mortality in patients with PSC, with reported mortality rates as high as 80% at median of 1 year of follow-up (25). Timely identification of malignancy may have a significant impact on management, including therapeutic options and long-term outcomes. Though guidelines do not universally recommend surveillance for CCA (22,91,115), a retrospective study including 79 patients with PSC who developed hepatobiliary cancer revealed that patients who underwent surveillance had a significantly improved 5-year survival compared to the no-surveillance group (68% *vs*. 20%) (119). MRCP, combined with contrast-enhanced MRI of the liver, is the imaging modality most widely used for annual assessment, often combined with annual CA19-9 (91), yet the optimal method for surveillance for CCA is unknown. Though meta-analysis suggests elevated CA19-9 might be a useful tumor marker for the diagnosis of CCA, with an overall sensitivity and specificity of 72% and 84%, respectively (120), CA19-9 levels are influenced by complicated cholangitis and biliary strictures, and should not be used alone for screening or diagnosis of CCA. The diagnosis of CCA in PSC typically is established based on a combination of tumor markers (CA19-9), multiple imaging modalities, and ERCP-based brush cytology, biopsy and FISH, as discussed in the previous section.

Early or locally-advanced stage CCA may be associated with a better prognosis and a higher chance of survival (121). Surgery with complete resection or LT are the only treatments with curative intent for CCA. In carefully selected patients with unresectable, perihilar early-stage CCA, LT following neoadjuvant therapy, including external beam radiotherapy combined with radio-sensitizing chemotherapy, endoluminal brachytherapy and maintenance chemotherapy can be considered (121). However, in the majority patients CCA is diagnosed at an advanced stage when surgery and LT are not appropriate options (122). For those who are ineligible for surgery or LT, systemic chemotherapy is recommended as the mainstay palliative treatment modality; a combination of gemcitabine with cisplatin is typically used as first-line treatment (123). Other palliative treatment strategies include endoscopic stenting and photodynamic therapy. For unresectable CCA, the

median survival time is only 5–12 months after diagnosis with or without chemotherapy (124).

Gallbladder polyps and adenocarcinoma

Gallbladder lesions or polyps are observed in 4% to 6% of patients with PSC (125,126), many of which are malignant. Studies looking at these lesions have shown that greater than 50% are adenocarcinoma (126,127). At minimum, annual ultrasound examinations are recommended for screening (22,91). Though small lesions may harbor neoplasia, a cut-off of 0.8 cm for cholecystectomy has been proposed (128,129) given the low prevalence of malignancy in small polyps and high early post-operative morbidity associated with cholecystectomy in patients with PSC, particularly when advanced liver disease is present (128).

IBD and colorectal malignancy

The estimated prevalence of IBD in patients with PSC is approximately 60–80% (22). The majority of these patients have UC, while a minority have CD with colonic involvement and many patients may have "indeterminate colitis" (not easily classified as having UC or colonic CD). Interestingly, the IBD pattern in patients with PSC appears to differ from that of patients without PSC. The disease presents earlier in life, is often quiescent and may be asymptomatic. Involvement of the entire colon is very common (either UC or CD) (41), with a right-side predominance, and features such as backwash ileitis and rectal sparing are more common in this population compared with patients with IBD without PSC (40). Patients may be more likely to develop pouchitis after ileo-anal anastomosis. Pancolectomy with ileostomy is associated with a risk of peristomal varices. Patients with IBD-PSC also tend to have a more quiescent course compared with regular IBD patients (130). In most cases, diagnosis of IBD precedes PSC; however, IBD can also present at any point after diagnosis of PSC (40), even after LT. Nonetheless, treatment of IBD in patients with PSC is based on general IBD guidelines.

The risk of colorectal dysplasia and cancer in patients with IBD-PSC compared to patients with IBD alone is approximately 4- to 5-fold higher (131), and patients with PSC-IBD should undergo annual surveillance colonoscopy with segmental mucosal biopsies (91,115). The role of UDCA as chemoprophylaxis against colorectal cancer in PSC-IBD remains unclear (132).

In newly diagnosed patients without known diagnosis of IBD, evaluation for concurrent IBD with colonoscopy with biopsies is recommended, regardless of the presence of symptoms (91,115). The frequency of surveillance colonoscopy is still unclear for patients who are not diagnosed with IBD on initial colonoscopy (22,54), but many clinicians repeat colonoscopy with biopsies in 3–5 years.

Cirrhosis and LT

Once patients with PSC develop cirrhosis as a result of the natural history of the disease, the management and surveillance strategies used are similar to those used for other causes of cirrhosis and are beyond the scope of this review.

Because of the progressive nature of PSC, approximately 40% of patients with this disease will ultimately require LT (4). The main indication for LT in PSC is decompensated cirrhosis caused by the disease, but those with refractory cholangitis may benefit and LT is also recommended for highly selected patients with unresectable early-stage hilar CCA (133). PSC has become the dominant autoimmune indication for LT in the US (134), accounting for 5% of LTs performed in the US from 1988 through 2015 (5).

Outcomes after LT are excellent compared to other indications, yet it is estimated that approximately 20% of patients have recurrent PSC after LT (91), which is associated with significant morbidity and mortality, often requiring retransplantation (135). Though no single risk factor has consistently been reported to impact the risk of recurrent PSC, several studies investigating post-transplant outcomes have found that active IBD after LT is a risk factor for recurrent PSC, whereas colectomy appears to be protective (135-138).

Conclusions

PSC remains a poorly understood disease for which medical therapy is lacking, despite numerous scientific advances over the recent years. Combination medical treatment targeting various aspects of pathogenesis in parallel might offer new opportunities. Clinical trial design to study drugs to improve prognosis is hampered by rarity of the disease, heterogeneity of presentation and relatively low event rate of clinically relevant endpoints that are hard to predict. To address this, biomarkers are necessary to serve as surrogate endpoints in clinical trials, but none have been established for use in clinical trials. Research is needed in many areas,

including pathogenesis, medical and endoscopic treatment, comorbidities, risk of malignancy, complications after liver transplant. A collaborative approach is crucial for undertaking large studies to meaningfully advance the knowledge in the field of PSC and benefit the individuals afflicted by it.

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Footnote

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