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Review Article

Current Therapeutics in Primary Sclerosing Cholangitis

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Abstract

Primary sclerosing cholangitis (PSC) is an orphan, cholestatic liver disease that is characterized by inflammatory biliary strictures with variable progression to end-stage liver disease. Its pathophysiology is poorly understood. Chronic biliary inflammation is likely driven by immune dysregulation, gut dysbiosis, and environmental exposures resulting in gut-liver crosstalk and bile acid metabolism disturbances. There is no proven medical therapy that alters disease progression in PSC, with the commonly prescribed ursodeoxycholic acid being shown to improve liver biochemistry at low-moderate doses (15–23 mg/kg/day) but not alter transplant-free survival or liver-related outcomes. Liver transplantation is the only option for patients who develop end-stage liver disease or refractory complications of PSC. Immunosuppressive and antifibrotic agents have not proven to be effective, but there is promise for manipulation of the gut microbiome with fecal microbiota transplantation and antibiotics. Bile acid manipulation via alternate synthetic bile acids such as norursodeoxycholic acid, or interaction at a transcriptional level via nuclear receptor agonists and fibrates have shown potential in phase II trials in PSC with several leading to larger phase III trials. In view of the enhanced malignancy risk, statins, and aspirin show potential for reducing the risk of colorectal cancer and cholangiocarcinoma in PSC patients. For patients who develop clinically relevant strictures with cholestatic symptoms and worsening liver function, balloon dilatation is safer compared with biliary stent insertion with equivalent clinical efficacy.

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Keywords: Primary sclerosing cholangitis; Bile acid; Microbiome; 24-Norursodeoxycholic acid; Farnesoid X receptor agonists; Liver transplant.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALP, alkaline phosphatase; APRI, aspartate aminotransferase platelet ratio index; ASBT, apical sodium-dependent bile acid transporter; ATX, autotaxin; CCA, cholangiocarcinoma; CD, cluster of differentiation; CRC, colorectal cancer; CVC, cenicriviroc; DS, dominant strictures; EASL, European Association for the study of the Liver; ELF, enhanced liver fibrosis; ERCP, endoscopic retrograde cholangiopancreatography; FGFR4, fibroblast growth factor receptor 4; FGF19, fibroblast growth factor-19; FIB-4, Fibrosis-4; FMT, fecal microbiota transplant; FXR, farsenoid X receptor; HLA, human lymphocyte antigen; IBD, inflammatory bowel disease; IL, interleukin; LT, liver transplantation; LOXL2, Lysyl oxidase-like 2 ; LSM, liver stiffness measurement; Mdr2, multidrug resistant gene; MRCP, magnetic resonance cholangiopancreatograpy; MRS, Mayo risk score; norUDCA, 24-norursodeoxycholic acid; PPAR, peroxisome proliferator-activated receptors; PSC, primary sclerosing cholangitis; PXR, pregnane X receptor; Th, T helper; TGR5, Takeda G-protein-coupled receptor 5; UDCA, ursodeoxycholic acid; VAP1, vascular adhesion protein-1.

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Introduction

Primary sclerosing cholangitis (PSC) is an orphan, cholestatic liver disease that is characterized by multifocal areas of biliary stricturing due to chronic inflammation and fibrosis.[1,2] PSC is strongly associated with inflammatory bowel disease (IBD), colonic, and hepatobiliary cancers.[1,3,4] The majority of patients are male with a median age at diagnosis of 41 years.[1,2] The pathophysiology of PSC remains incompletely understood, however its close association with IBD[1,2,5] suggests a similar complex etiology instigated by activation of immune-mediated pathways.

In the last decade, there has been advances in our understanding of bile acid transporters. Manipulation of this system has proven beneficial to a sister cholestatic disease, primary biliary cholangitis.[6] Furthermore, genomic and metabolomic analysis of the gut microbiota via human and mouse model studies have allowed us to further understand and characterize its role in PSC and how targeting it may provide therapeutic benefit.[7] The European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD) and British Society of Gastroenterology have recently updated their Clinical Practice Guidelines on sclerosing cholangitis in accordance with the available literature in this field.[8–10] Hence, it is timely to provide a contemporary review on therapy in PSC and draw lessons from the studies done thus far.

The aim of this narrative review is to outline our existing knowledge of the genetics and immunobiology underlying the pathophysiology of PSC, consider the current and promising emerging therapeutic landscape, and highlight what is novel in this space. We also identify the challenges involved in designing clinical trials due to the small number of clinical events over feasible study periods and lack of validated surrogate endpoints. Moreover, we contemplate potential future advances in this field based on the enhanced knowledge of the gut microbiome, genomic, and metabolomic pathways to suggest potential areas for clinical trials with combinations of end points.

Pathophysiology

While the pathophysiology of PSC is not entirely understood, its strong association with other autoimmune diseases suggests an underlying immune-mediated phenomena.[2,11] In

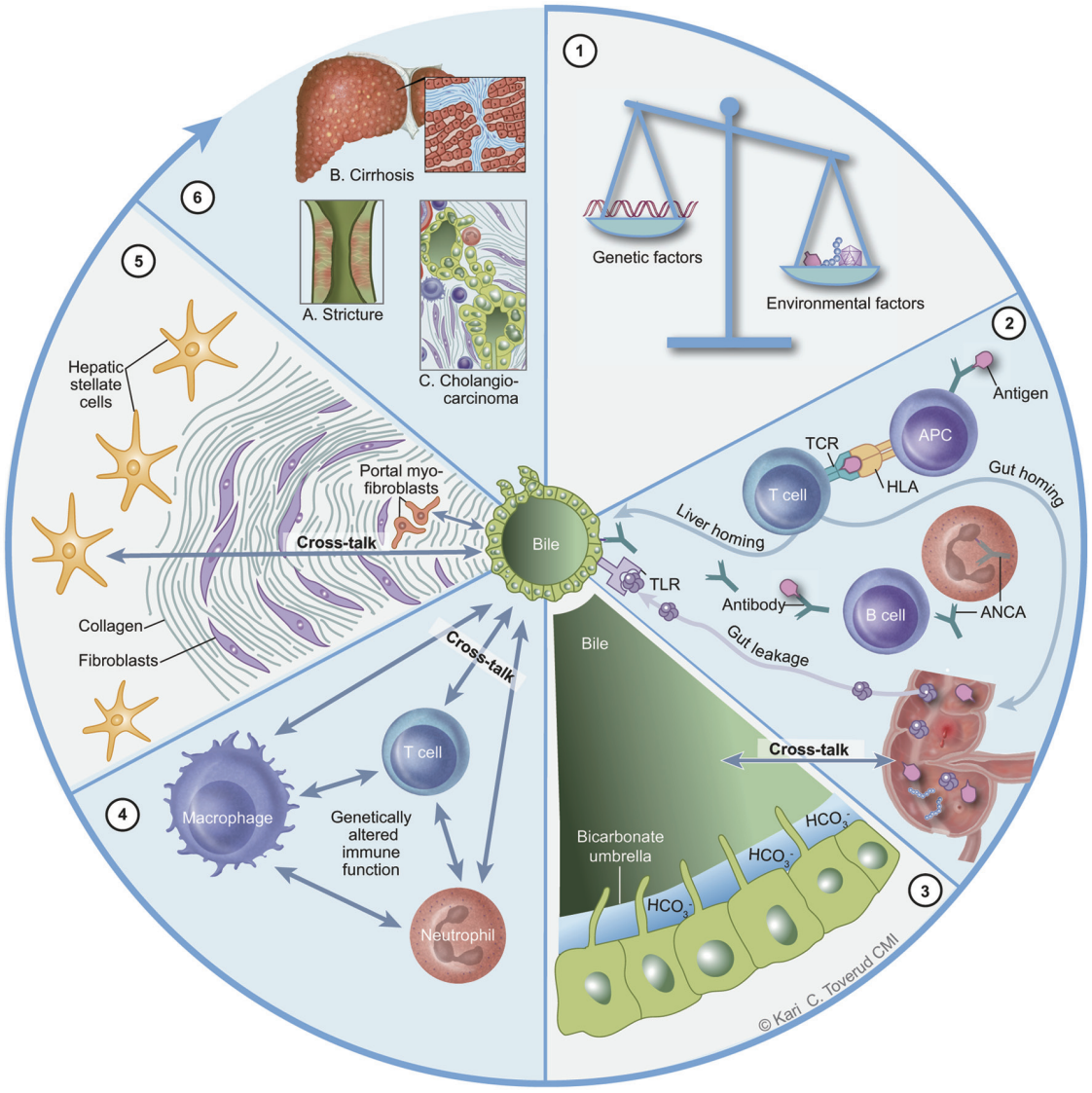

Fig. 1. Pathophysiology of primary sclerosing cholangitis. APC, antigen presenting cell; ANCA, anti-neutrophil cytoplasmic antibodies; HLA, human leukocyte antigen; TCR, T cell receptor; HCO3-, bicarbonate. Figure from Karlsen *et al*. Primary sclerosing cholangitis – a comprehensive review. J Hepatol 2017;67(6):1298–1323, https://doi.org/10.1016/j.jhep.2017.07.022. Reprinted with permission from Elsevier (Order Ref:5588).

support of this, it is thought that there is dysregulated activation of the innate and adaptive immune system by gut-derived antigens similar to IBD. Despite this, the genetic profile of PSC has greater similarities with other autoimmune diseases such as coeliac disease and multiple sclerosis than that of IBD.[2,11–13] It is likely therefore that the culmination of progressive, inflammatory biliary stricturing is due to a complex interplay of immune dysregulation, gut dysbiosis, gut-liver crosstalk with bile acid metabolism disturbance secondary to underlying genetic predispositions with environmental exposures (Fig. 1).[14]

Genetics

There is an 11-fold increased risk of first-degree relatives of PSC patients manifesting the disease phenotype, with 23 risk genes identified to date.[2,15] Genome-wide association studies identified the human lymphocyte antigen (HLA) complex on chromosome 6p21 to be responsible for homing several risk genes that may be directly or indirectly involved in the disease pathogenesis.[16,17] Several non-HLA gene associations that are involved in bile homeostasis and immune regulation affecting Interleukin (IL)-2, IL21, cluster of differentiation (CD)-28 and cytotoxic T-lymphocyte-associated protein 4 have also been identified in PSC cohorts.[17] A proposed mechanism with IL2 receptor polymorphisms is over-activation of immune responses to normal bacterial and food antigens that are suppressed under normal circumstances, secondary to decreased functional T regulatory cells.[18] A relevant fucosyltransferase-2 genotype demonstrated in some PSC patients may also influence gut microbiome composition and susceptibility to infection and development of IBD.[7]

Immunobiology

In PSC, it is suggested that pathogen-associated molecular

patterns such as lipopolysaccharides and other bacterial by-products gain access to the portal system in the presence of a permeable intestinal epithelium,[11] resulting in activation of the innate immune system via Toll-like receptors and CD-14 receptors leads. Activation of the hepatic innate immune response is thought to be the inciting factor.

The intestinal and hepatic endothelium share similar characteristics, including expressions of tight junction proteins and pattern recognition receptors. It is hypothesized that portal toxins such as aliphatic amines result in aberrant expression of intestine-specific mucosal vascular adhesion molecule 1 and chemokine C-C motif ligand 25 on the hepatic endothelium.[18,19] This results in recruitment of gut-specific lymphocytes expressing α4β7 and C-C motif chemokine receptor 9 molecules to the liver and subsequently the biliary epithelium,[18] driving persistent inflammation as supported by the predominant finding of CD4+ T cells in portal inflammatory infiltrate of PSC.[2] A recent study also demonstrated a significantly increased level of T-helper (Th)-17 and IL17/interferon-γ producing CD4+ T cell population in the colonic mucosa of patients with PSC and IBD,[20] which may tie in with homing of these lymphocytes to the liver.

Bile acid metabolism disturbance

The localization of hepatic inflammation to the biliary tree in PSC suggests that bile acid disturbance or microbial colonization might contribute to its underlying pathophysiology. This is supported by the identification of non-HLA susceptibility loci in PSC patients related to the regulation of bile acid and bicarbonate secretion.[21,22] In normal conditions, bile acids play an important role in regulating intestinal absorption, biliary secretion of metabolites, and act as signaling molecules to maintain metabolic homeostasis via activation of nuclear receptors.[23]

The biliary epithelium is protected from inherently toxic bile by a protective layer formed from the mixing of phospholipids and cholesterol to form micelles, along with biliary bicarbonate formation.[2,24] Potential disruption of the underlying sodium independent chloride-bicarbonate anion exchanger and the cystic fibrosis transmembrane conductance regulator via membrane Takeda G-protein-coupled receptor 5 (TGR5) mutations leading to downregulation in PSC may result in disruption of this protective layer and increase the vulnerability of the biliary epithelium to toxic bile.[2,24,25] This disease model has been simulated in multidrug resistant gene (Mdr2) and cystic fibrosis transmembrane conductance regulator knockout mice, in which mouse models develop biliary inflammation, fibrosis, and stricturing similar to that of PSC in humans.[26,27]

In PSC, there is interest in the manipulation of nuclear receptors involved in the regulation of bile acid production, transport and metabolism via hydroxylation and conjugation to less toxic compounds.[28,29] Potential nuclear receptors of interest include the Farnesoid X receptor (FXR), pregnane X receptor (PXR), vitamin D receptor and constitutive androstane receptor.[28] These receptors act at a transcriptional level with coactivators that may be targeted such as peroxisome proliferator-activated receptors (PPAR) which is involved in promoting transcriptional activation.[28] The FXR/fibroblast growth factor (FGF)19 pathway is a negative feedback mechanism that regulates bile acid production and uptake.[30] Activation of FXR by bile salts in the small intestine results in production of FGF19 that binds to fibroblast growth factor receptor 4 (FGFR4)/beta-Klotho complex in the liver. This leads to CYP7A1 downregulation and subsequent reduction in synthesis of bile acids. Downstream effects include reduction of expression of the apical sodium-dependent bile acid transporter (ASBT) in the ileum and other bile acid transporters in the liver, reducing hepatic bile acid levels and increasing hydroxylation and glucuronidation to form less toxic bile acid compounds for secretion back into the biliary system.[29–31] The FXR/FGF19 pathway is a promising target in animal models, demonstrating reversal of liver injury in Mdr2 knock out mice with administration of FXR agonists[32] and prevention of liver fibrosis by decreasing stellate cell activation.[31] Its therapeutic potential has already been investigated in other cholestatic liver diseases such as primary biliary cholangitis as well as in PSC. This ties together with significant upregulation of CYP7A1 expression and the FXR/FGF19 pathway in PSC-IBD patients,[20] which with its effect on the bile acid pool has been associated with Th17 cell expansion and subsequent IL17 production.[20]

Role of the microbiota

Studies of the stool and ileocolonic microbiota in PSC by RNA 16S analysis have consistently demonstrated reduced α-diversity and dominance of certain bacterial communities in PSC patients compared with healthy controls and patients with IBD alone,[20,33–38] with similar differences noted in bile and upper gastrointestinal tract microbiota studies.[39,40] Shotgun metagenomic sequencing has also demonstrated decreased bacterial production of essential nutrients such as branched-chain amino acids and vitamin B6 in patient with PSC as compared with healthy controls, and this is of relevance as the active form of vitamin B6 contributes to gut immune regulation and lymphocyte homing.[34]

Several studies have observed an increase in the genera *Escherichia, Streptococcus, Enterococcus, Clostridium*, and *Veilonella* in the stool of PSC patients, together with reduced species that contribute to the production of protective short-chain fatty acids (SCFA) in the colon.[33,34,36,38] The gut microbiota dysbiosis in PSC ties in with the hypothesis of gut-liver inflammation due to activation of vascular adhesion protein-1 (VAP1) by copper amine oxidase proteins. These proteins are produced by specific bacteria such as *Veilonella,* that are identified in the colonic tissue of patients with PSC and IBD which acts as substrates for VAP1 that mediates lymphocyte trafficking.[14,20,33] Animal models of mice inoculated with feces of patients with PSC and UC demonstrated Th17 cell priming in the liver and susceptibility to hepatobiliary injury.[41] The altered microbiome in PSC also influences bile acid metabolism via receptors like FXR and TGR5,[20,32] with Mdr2 knockout mice models demonstrating increased hepatic bile acid and injury with microbiome depletion.[32]

Surrogate endpoints in current therapeutic trials

Clinical trial design and interpretation in PSC has been challenging to date due to the heterogenous nature of the disease, and low expected number of clinically relevant events over the relatively short study periods resulting in most studies being underpowered to detect a clinically meaningful benefit.[42] Alkaline phosphatase (ALP) has been used as a surrogate endpoint in all clinical trials to date. However, a review by the International PSC Study Group in 2016 reported that there are currently no surrogate endpoints exceeding level 3 validation in PSC and novel biomarkers should be considered as exploratory endpoints in upcoming clinical trials.[43] Composite endpoints should be considered, with a combination of well-defined clinical events and surrogate markers as described below to allow for assessment of more than one element of this complex disease.[42]

Serum biomarkers

A recent systematic review on noninvasive prognostic tests included 40 studies with a total of 16,094 PSC patients. It demonstrated that normalization or reduction of ALP was associated with improved transplant-free survival and reduced risk of hepatobiliary cancers.[44] In a prospective observational study, this clinical benefit was only significant if ALP reduction was achieved below 1.5 times upper limit of normal, and not by 40% of baseline serum levels.[45] Serum ALP is currently accepted as a reasonable surrogate endpoint in clinical trials or to assess response to therapy in clinical practice,[8,9] but will likely benefit from combination with other exploratory parameters and with defined cut-off values. Moreover, there is mounting evidence that large variation of serum ALP levels exists within and between patients independent of given treatment which may hamper using ALP as a sole surrogate endpoint to demonstrate clinical efficacy in clinical trials.[46]

The enhanced liver fibrosis (ELF) score is a promising novel biomarker that is based on serum levels of hyaluronic acid, tissue inhibitor of metalloproteinase-1, and propeptide of type III procollagen. It has shown significant stability over time compared with ALP[46] and demonstrated superior predictive value for clinical events such as transplant-free survival.[47,48] As such, it has been incorporated in EASL guidelines to be used for risk stratification along with transient elastography at baseline and during follow up.[49] One retrospective cohort study reported increased ELF scores in PSC patients with cholangiocarcinoma (CCA) compared with PSC patients without, suggesting its potential as another risk stratification tool for development of CCA.

Prognostic scores

The Mayo risk score (MRS) is the most commonly used prognostic model in clinical trials. It shown superiority to the Child Pugh scoring system in predicting short-term survival, but its application is fairly limited to cirrhotic patients and only allows for prediction up to 4 years.[44] Other novel scores that have outperformed the MRS in predicting survival include the UK-PSC score, Amsterdam-Oxford model and Primary sclerosing cholangitis Risk Estimate Tool,[44] which should be considered as secondary endpoints in future clinical trials.

Magnetic resonance scores

The increasing use of magnetic resonance cholangiopancreatography (MRCP) in the diagnosis and surveillance of PSC patients allows it to be a potentially powerful tool as a surrogate endpoint in clinical trials. The Anali score (with or without gadolinium) which incorporates bile duct morphology, prestenotic dilatation and liver parenchymal changes demonstrated good predictive value for transplant-free survival and decompensated liver disease.[50,51] However, it has been reported to have poor to moderate inter-reader agreement and needs further validation in larger cohorts.[52] Despite this, MRCP prognostic scores should be considered in clinical trials with consideration of central reading and utilization of recent guidelines for reporting standards in PSC which may reduce inter-reader variability.[53] Furthermore, novel scores are in development that utilize machine learning and/or radiomics that hold promise for the availability or more accurate scoring systems in the future.[54]

Liver elastography

There is increasing confidence in the utility of noninvasive measurements of liver stiffness with transient elastography in PSC with growing evidence that it is superior to other noninvasive markers such as the aspartate aminotransferase platelet ratio index (APRI) score, Fibrosis-4 (FIB-4) score, and MRS in discriminating patients with and without advanced fibrosis.[55–57] In PSC patients, a liver stiffness measurement (LSM) of more than 9.5 kPa can be used to support the diagnosis of advanced fibrosis in compensated patients without evidence of a significant biliary obstruction.[49] It is recommended as a tool for follow up assessment of fibrosis in PSC, but optimal duration between examinations is not defined. Ongoing studies within the IPSCG aim to identify the prognostic value of transient elastography for use as a surrogate endpoint, but also how changes in LSM correlates with clinical events.[43] Magnetic resonance elastography has also been studied retrospectively in PSC patients with high specificity for detection of cirrhosis and ability to predict for decompensation based on stratified LSM values.[58]

Histology

Liver biopsy has been phased out as a method of diagnosis for PSC, unless to diagnosis small-duct disease or concomitant autoimmune hepatitis. However, it has still been used in most clinical studies to date[43] and may provide benefit in allowing for mechanistic investigation of investigational drugs, especially if presence of concomitant nonalcoholic steatohepatitis due to potential dual benefit on both pathologies. Even though sampling error is a drawback in patchy disease, histology staging does reliably correlate with transplant-free survival.[43] Despite liver biopsy being an invasive procedure, the risk of serious adverse events is low at less than 0.5% when performed under ultrasound guidance.[43] Moving forward the relationship between liver histology and available noninvasive fibrosis markers is a key priority to define as we continue to build a robust evidence base for using noninvasive methods to accurately grade fibrosis in PSC.

Patient-reported outcome

It is critically important to also focus on improving the health-related quality of life and troublesome symptoms that patients can face that may impact on mental health. A recent validated patient-reported outcome instrument[59] has shown promise as a consistent validated self-administered survey that can be utilized in trial settings for monitoring PSC-related symptoms and response to therapies.

Current and emerging therapeutics

Pharmacological therapies

Bile acid manipulation: *Ursodeoxycholic acid.* Ursodeoxycholic acid (UDCA), a hydrophilic bile acid is the most widely used therapy for PSC. Its potential therapeutic benefit is not well understood; however it may be related to increased expression of bile salt and phospholipid transporters at a cellular level,[60] leading to enhanced biliary and phospholipid excretion as part of the natural protective mechanism of the biliary tree.[61] Figure 2 summarizes the current mechanistic properties of UDCA and other upcoming therapies for PSC. UDCA has been studied at doses ranging from 10–15 mg/kg/day in several randomized clinical trials and pilot studies (Table 1).[62–68] These consistently demonstrated biochemical improvement, but variable improvement in cholestatic symptoms and no influence on transplant-free survival likely due to being underpowered.[69–71] Higher doses up to 23 mg/kg/day have previously shown a trend toward increased surviv-

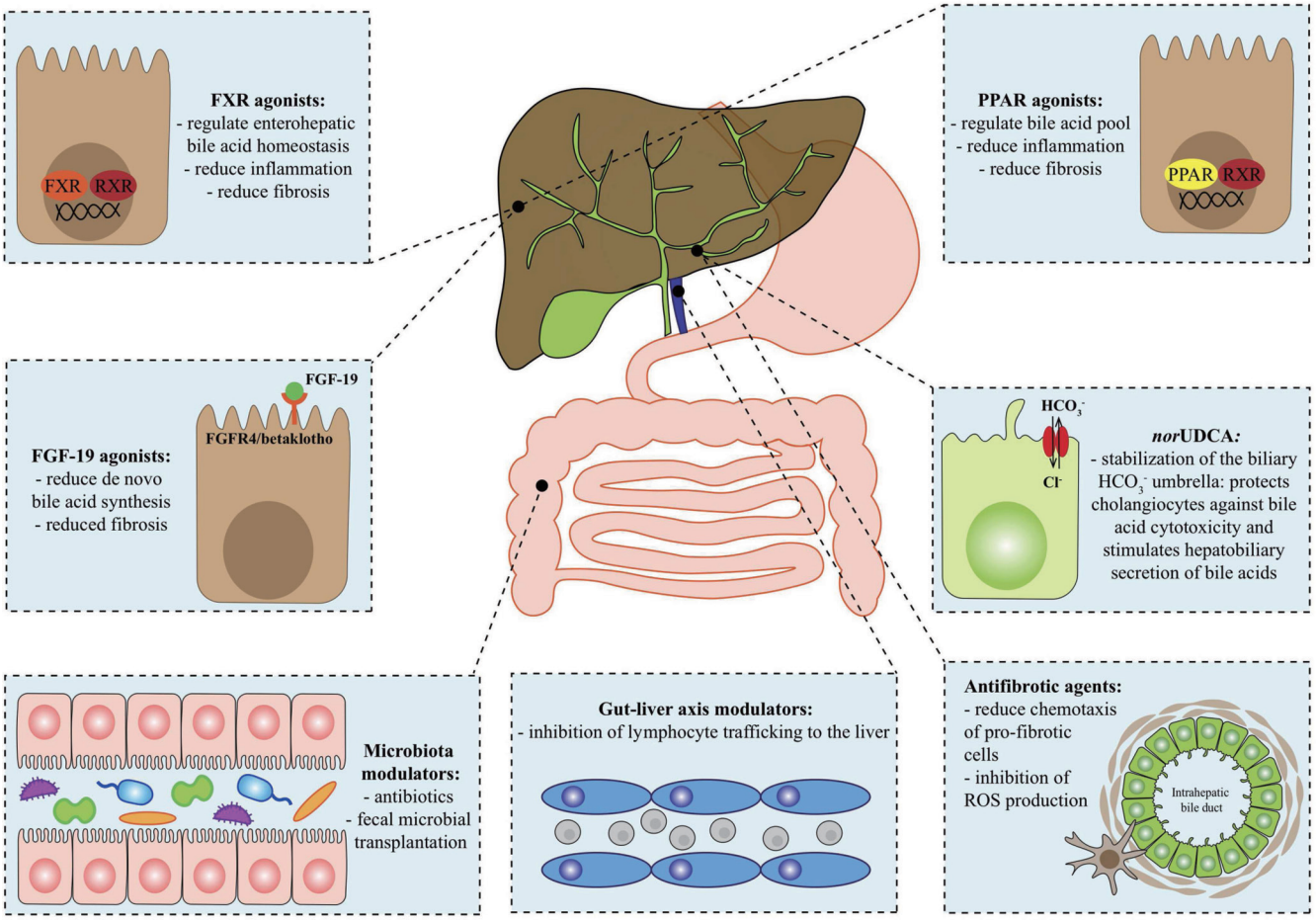

Fig. 2. Mechanisms of action of potential new PSC therapies. HCO3-, bicarbonate; FGF-19, fibroblast growth factor-19; FGFR4, fibroblast growth factor receptor 4; FXR, farsenoid X receptor; norUDCA, 24-norursodeoxycholic acid; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; RXR, retinoid X receptor. Figure from Gerussi *et al*. New therapeutic targets in autoimmune cholangiopathies. Front Med Gastro 2020;7:117, https://doi.org/10.3389/fmed.2020.00117, under the Attribution 4.0 International (CC BY 40) license creativecommons.org/licenses/by/4.

al in the UDCA treated groups.[72] However, in a randomized double-blind controlled trial of high-dose UDCA (28–30 mg/kg/day) compared with placebo,[73] patients in the UDCA arm improved their liver biochemistry but were more likely to experience adverse events of hepatic decompensation, liver transplantation (LT) or death as compared with the placebo group.[73] A proposed explanation for this unexpected finding was potential hepatotoxicity secondary to bile acids resulting from metabolism of UDCA by the gut microbiome, leading to increased liver injury, active fibrogenesis and acceleration of liver-related complications.[73] At the time of writing, there is no evidence for use of UDCA in PSC as a disease modifying agent. However, the available evidence of ALP reduction as a surrogate for improved outcomes underlies the updated recommendations by EASL, recommending UDCA at only doses of 15–20 mg/kg/day to be considered for improving liver biochemistry and surrogate markers of prognosis.[8] The previous 2011 AASLD guidelines recommended against use of UDCA for PSC, but for similar reasons have recently updated their recommendations to suggest UDCA at 13–23 mg/kg/day to be initiated and continued if well tolerated with improvements in ALP or symptoms within 1 year of treatment.[9]

UDCA as chemoprevention for colorectal cancer (CRC) development in patients with PSC-IBD has not been consistently demonstrated.[74–76] Two separate meta-analyses of UDCA for the prevention of colonic high-grade dysplasia or CRC in PSC yielded contradicting results.[77,78] In one prospective study, a high dose of 28–30 mg/kg/day UDCA was even found to be associated with increased risk of colorectal neoplasia.[79] Although, the 2011 EASL guidelines recommended UDCA be used in high-risk groups for this purpose,[80] current AASLD and EASL guidelines do not suggest it to be used as a chemopreventative agent.[8,9] Further prospective studies on this are warranted.

24-Norursodeoxycholic acid. 24-norursodeoxycholic acid (norUDCA) is a sidechain shortened C_{23} homologue of UDCA with more profound induction of bile acid detoxification, flow, and hydrophilicity as compared with UDCA.[81] At a molecular level, norUDCA was demonstrated to increase TGR5 levels in mice models which also contributed to improved biliary protection and healing.[25] It has demonstrated promising results in a randomized placebo-controlled trial in view of dose-dependent improved liver biochemistry over 12 weeks.[82] This therapeutic effect was independent of previous UDCA treatment, and interestingly response was able to be captured with increasing norUDCA doses. Further phase III studies are on their way comparing placebo to norUDCA over a 2-year time frame, with endpoints investigating improved liver bio-

chemistry and assessment of liver histology (Clinical Trials Identifier: NCT03872921).

Berberine ursodeoxycholate. An 18-week proof-of-concept study investigating berberine ursodeoxycholate (HTD1801) has recently been published.[83] This is an ionic salt of berberine and UDCA that has demonstrated pleiotropic effects including improvement in lipid and glycemic control when investigated in patients with nonalcoholic steatohepatitis.[84] Fifty-five PSC patients were randomized to placebo, HTD1801 500 mg twice daily or HTD1801 1,000 mg twice daily for 6 weeks, followed by a treatment extension period and a randomized treatment withdrawal period.[83] Significant reduction in ALP was noted at week 6 of the study and this was sustained to week 18 in patients who remained on therapy, without a dose-dependent effect. It was safe overall with no adverse events attributed to HTD1801.[83]

Bile acid metabolism manipulation via nuclear receptor agonists: *Steroidal FXR agonists.* Obeticholic acid is a selective steroidal FXR agonist that is significantly more potent than the natural primary bile acid, chenodeoxycholic acid, at activating FXR.[31] To date, promising results have been demonstrated in a phase II, randomized double-blinded placebo-controlled trial (AESOP) enrolling adult patients with noncirrhotic or compensated large-duct PSC and abnormal ALP levels.[85] During the 24-week treatment period, a 5–10 mg daily dose of obeticholic acid resulted in a significant and sustained reductions in serum ALP from baseline with pruritus being the most common side effect.[85]

Nonsteroidal FXR agonists. In similar fashion to steroidal analogs, nonsteroidal FXR agonists such as cilofexor have been demonstrated to improve serum liver biochemistry and total bile acid pool, with a trend toward improvement of markers of fibrosis in a 12-week phase II randomized-controlled, double-blinded placebo-controlled trial in noncirrhotic large-duct PSC patients.[86] A follow-on 96-week open-label extension of the above trial demonstrated safety of cilofexor, along with sustained improvement in liver biochemistry, reduction in plasma FGF19, by-products of bile acid synthesis and novel biomarkers of cell death.[87] Although there was a statistically significant increase in ELF score of 0.15, this was possibly accounted for by intrapatient variability. In this study, a nonsignificant trend toward greater increases in ELF score were observed in higher risk patients. Pruritus was a common side effect and warrants further examination in randomized-controlled trials to see if this is a true drug-related effect.[87] Unfortunately, the placebo-controlled, phase III PRIMIS study which aimed to identify the safety and efficacy of cilofexor in noncirrhotic PSC patients has been terminated early in a statement by Gilead Sciences due to futility of response as determined by interim analysis (Clinical trials identifier: NCT03890120).[88]

FGF19 analogs. Manipulation of the FXR/FGF19 pathway was also studied in a similar multicenter, 12-week phase II trial with an engineered nontumorigenic analog of FGF19, known as aldafermin (NGM282). This had previously been demonstrated to improve serum liver biochemistry in mouse models and proven safe in healthy volunteers and patients with nonalcoholic steatohepatitis.[89] However, it failed to meet the primary endpoint of reduction in serum ALP. Serum 7α-hydroxy-4-cholesten-3-one and bile acid levels were reduced which proved potent target activation along with reduction in aminotransferases and markers of fibrosis.[89] Although the primary endpoint was not met, the patient population captured was more reflective of clinical practice in view of inclusion of patients with dominant strictures, small-duct disease, autoimmune overlap, and compensated cirrhosis which were usually excluded from other studies. The reduction in other surrogate endpoints especially markers of fibrosis is promising, and further studies exploring aldafermin or other FGF19 analogs is warranted.

PPAR agonists. PPAR agonists such as fenofibrate (PPAR-alpha agonist) and bezafibrate (nonselective PPAR agonist) are co-regulators of the nuclear receptor PXR that is also involved in bile metabolism and regulation, in addition to having anti-inflammatory effects[90] A retrospective study investigating the addition benefit of fenofibrate to UDCA in cholestatic liver diseases demonstrated improved liver biochemistry, reduction in proinflammatory cytokines and reduction of total, primary, and conjugated bile acids in PSC patients.[90] Bezafibrate was prospectively studied in a small cohort of Japanese patients with demonstration of improvement in biochemistry, which shows potential albeit being a single-arm study with only 12-week follow up.[91] It has also shown effectiveness in a double-blind, randomized, placebo-controlled trial investigating fibrates for itch (FITCH study) demonstrating improvement in the degree of pruritus in PSC patients with moderate to severe itch.[92] This study demonstrated a good safety profile with short-term use and fibrates therefore show potential not only as an antipruritic agent in PSC patients but also as a disease modifier with additional anti-inflammatory and bile acid modulatory effects. Phase III trials are ongoing at time of writing (Clinical trials identifier: NCT04309773).

Apical sodium-dependent bile transporter inhibitors. Downregulation of ASBT has shown potential in animal models of sclerosing cholangitis with increased fecal bile acid excretion and associated reduction in hepatic and serum bile acids due to interruption of the enterohepatic circulation. This seemed to correlate with decreased markers of liver injury and improved liver histology.[93] In a proof-of-concept 14-week study (CAMEO) reported in abstract form at the AASLD Liver meeting 2019,[94] maralixibat, a selective inhibitor of ASBT demonstrated improvement in pruritus symptoms with only mild-moderate gastrointestinal side effects being the most common. This coincided with reduced autotaxin (ATX) and low-density lipoprotein levels, but no significant change in liver biochemistry. Further studies incorporating a combination of biomarkers, validated PSC-specific PRO, and clinical endpoints are required. Potential limitations of further use of ASBT in the therapeutic pipeline include significant bile salt acid diarrhea, worsening of fat-soluble vitamin deficiencies, and possible carcinogenic potential of increased bile acid exposure in the colon.[93]

Table 1 summarises the studies investigating the use of bile acid manipulation agents as therapy for PSC.[69–73,82,83,85–87,89–92,94–99]

Immunosuppressive and biologic agents. Most studies of immunosuppressive agents in PSC have either been case series or retrospective cohort studies.[100] Therapies such as budesonide, prednisolone, azathioprine, methotrexate, colchicine, mycophenolate mofetil, and antitumor necrosis factor-α agents have failed to demonstrate any significant impact on PSC progression.[100–104] Antitumor necrosis factor-α use has been studied in only one double-blinded, retrospective control trial investigating infliximab standard induction and dosing to 52 weeks. This study was terminated early due to an interim analysis demonstrating futility for the primary endpoint of reduction of at least 50% of serum ALP from baseline to week 18, as well as no change on paired liver biopsy.[103]

Retrospective analyses interestingly have demonstrated stronger reduction in ALP in PSC-IBD patients treated with adalimumab compared with patients on infliximab or vedolizumab[104,105] but without improvement in elastography or radiologic changes. The proposed mechanism behind this finding is unclear, and perhaps may be due to adalimumab

Table 1. Summary of studies investigating bile acid manipulation agents in PSC

Bile acid manipulation					
Study	**Type**	**Duration**	**Intervention**	**Number**	**Outcomes**
Ursodeoxycholic acid (UDCA)					
Chazouilleres, 1990[95]	Prospective cohort study	6 months	UDCA 750–1,250 mg/day	15 UDCA	Improvement in liver biochemistry and symptoms
O'Brien, 1991[71]	Open-label pilot study	30 months	UDCA 10 mg/kg	12 UDCA	Improvement in liver biochemistry and symptoms
Beuers, 1992[70]	Placebo-controlled RCT	1 year	UDCA 13–15 mg/kg	6 UDCA, 8 placebo	Improvement in liver biochemistry and liver histology features
Lindor, 1997[69]	Placebo-controlled RCT	2.2 years	UDCA 13–15 mg/kg	51 UDCA, 51 placebo	Improvement in liver biochemistry, no impact on disease progression/endpoints
Harnois, 2001[96]	Placebo-controlled RCT	1 year	UDCA 25–30 mg/kg/day, UDCA 13–15 mg/kg/day	30 UDCA higher dose, 53 UDCA lower dose, 52 placebo	Improvement in liver biochemistry most marked with high-dose UDCA, calculated expected survival with MRS significantly different between placebo and high-dose, but not between placebo and low dose
Okolicsanyi, 2003[97]	RCT	42 months UDCA group, 38 months control group	UDCA 8–13 mg/kg/day	69 UDCA, 17 controls	Improvement in liver biochemistry, fatigue, jaundice, and body weight loss
Olsson, 2005[72]	Placebo-controlled RCT	5 years	UDCA 17–23 mg/kg/day	110 UDCA, 109 placebo	Improvement in liver biochemistry, no difference in symptoms or quality of life
Lindor, 2009[73]	Placebo-controlled RCT	5-year treatment, trial ceased 6 years	UDCA 28–30 mg/kg/day	76 UDCA, 74 placebo	Improvement in liver biochemistry but increased risk of death and liver transplant in UDCA group
Norursodeoxycholic acid (norUDCA)					
Fickert, 2017[82]	Multicenter, placebo-controlled RCT	12-week therapy, 4-week follow up	norUDCA (500 mg/day, 1,000 mg/day or 1,500 mg/day)	39 500 mg/day, 41 1,000 mg/day, 39 1,500 mg/day, 40 placebo	Dose-dependent improvement in liver biochemistry, safety profile comparable to placebo
Beberine ursodeoxycholate (BUDCA)					
Kowdley, 2022[83]	18-week proof-of-concept study	6-week placebo-controlled, 6-week treatment extension, 6-week randomized treatment withdrawal	BUDCA (HTD1801) 500 mg/ twice daily or 1,000 mg/ twice daily	15 500 mg/twice daily, 24 1,000 mg/twice daily, 16 placebo	Significant reduction in ALP at week 6 without a dose-dependent response compared with placebo, sustained to week 18 but rebound increase in patients who crossed to placebo in the last 6-week phase of treatment withdrawal
Steroidal FXR agonists					
Kowdley, 2020[85]	Placebo-controlled RCT	24 weeks, 2-year safety extension	Obeticholic acid	25 1.5–3 mg/day, 26 5–10 mg/day, 25 placebo	OCA 5–10 mg reduced serum ALP, dose-related pruritus most common adverse event
Nonsteroidal FXR agonists					
Trauner, 2019[86]	Placebo-controlled RCT	12 weeks	Cilofexor	22 100 mg/day, 20 30 mg/day, 10 placebo	Cirrhotics and small-duct disease were excluded. Dose-dependent improvement in liver biochemistry (except bilirubin), reduction in bile acids in 100 mg group. No change in liver stiffness or ELF scores

(continued)

Table 1. *(continued)*

Bile acid manipulation					
Study	**Type**	**Duration**	**Intervention**	**Number**	**Outcomes**
Trauner, 2022[87]	Open-label extension of placebo-controlled RCT	96 weeks	Cilofexor	47 100 mg/day after 4-week washout period	Concurrent UDCA use in 45%. Improvement in liver biochemistry but serum ALP not significantly reduced at week 96. Reduction in C4, bile acids, CK18, M30, and M65. Pruritus in 43% which contributed to drug cessation in 11%
FGF19 analogs					
Hirschfield, 2019[89]	Multicenter, placebo-controlled RCT	12 weeks	NGM282	21 3mg/day, 21 1 mg/day, 20 placebo	No difference in ALP, reductions in C4, bile acids, ELF score, and pro C-3 in patients taking NGM282 compared with placebo
PPAR agonists					
Ghonem, 2020[90]	Retrospective cohort study	5–64 months	Fenofibrate (PPARα agonist)	11 UDCA monotherapy, 8 combination UDCA + fenofibrate	Study population included PBC and PSC patients with incomplete response to UDCA. Improved serum ALP levels with fenofibrate, reduction in proinflammatory cytokines and total bile acids
Mizuno, 2015[91]	Prospective cohort study	12 weeks	Bezafibrate (pan-PPAR agonist)	15 200 mg BD, no placebo arm	Improvement in liver biochemistry which worsened with bezafibrate cessation
De Vries, 2021[92]	Placebo-controlled RCT	3 weeks	Bezafibrate (pan-PPAR agonist)	44 PSC (27 bezafibrate, 19 placebo)	Study aimed to assess >50% reduction in pruritus (VAS score) for cholestatic liver diseases. Bezafibrate treated PSC patients had higher improvement in pruritus on post-hoc analysis
Apical sodium-dependent bile transporters					
Bowlus, 2019[94] (Abstract)	Single-arm, open-label, proof-of-concept study	14 weeks (6-week dose escalation period followed by 8-week maintenance and 4-week follow up)	Maralixibat 10 mg daily (maintenance dose)	27 patients, 6 did not receive maintenance dose	Statistically significant reductions from baseline in pruritus and serum levels of bile acid and autotaxin (more pronounced in patients who had a higher Itch Reported Outcome score at baseline)
Combination therapies					
Assis, 2017[98]	Pilot study	12-week therapy, 12-week washout	All-trans retinoic acid (ATRA) 45 mg/day + UDCA 15–23 mg/kg/day	19 ATRA + UDCA	Improvement in liver biochemistry (ALT) but did not meet primary endpoint of ALP improvement by 30%, reduction in bile acid intermediates with ATRA
Lemoinne, 2018[99]	Retrospective cohort study	6 months	Fenofibrate 200 mg/day or bezafibrate 400 mg/day + UDCA	20 fibrates + UDCA	Improvement in liver biochemistry and pruritus, however liver stiffness significantly increased

ALP, alkaline phosphatase; ALT; alanine transaminase, ATRA, all-trans retinoic acid; norUDCA, 24-norursodeoxycholic acid; OCA, obeticholic acid; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptors; PSC, primary sclerosing cholangitis; RCT, randomized-controlled trial; UDCA, ursodeoxycholic acid; VAS, visual analog score.

having a larger volume of distribution as compared with infliximab.[100] With upcoming new small molecules and subcutaneous biologics being added to the IBD therapeutic armamentarium, further studies will be warranted in investigating the effects of these medications on PSC disease course.

With the potential interaction between α4β7 and its ligand mucosal vascular adhesion molecule 1 being implicated in the pathophysiology of PSC, vedolizumab looked to be a promising therapy for both the hepatic and colonic disease in PSC. However, in a retrospective study in patients with PSC and active IBD requiring vedolizumab therapy, serum ALP levels did not significantly improve in the vedolizumab arm except in cirrhotic patients.[106] This was hypothesized to be due to reduced metabolism of vedolizumab in the cirrhotic liver resulting in enhanced serum concentrations and clinical effect.[106] Several other retrospective studies have not demonstrated an improvement in biochemistry with the use of vedolizumab,[107,108] despite its convincing mechanism of action. Although it has been hypothesized that a subgroup of patients may benefit from vedolizumab due to a proportion having reasonable ALP reductions within the retrospective studies,[100] as alluded to before intrapatient variability of ALP cannot be ignored and studies on biologics should be explored further using a combined or composite endpoints. Currently, EASL recommends considering corticosteroids or other immunosuppressive therapies in patients with concomitant autoimmune hepatitis, but not in routine treatment of PSC with or without mildly elevated serum IgG4.[8]

Lysyl oxidase-like 2 (LOXL2) is an enzyme which catalysis the cross-linkage of collagen and elastin which stabilizes the fibrotic matrix. LOXL2 inhibition demonstrated fibrosis regression and reduction of hepatic stellate cell activation in PSC mouse models.[109] However, a 96-week phase II trial with the anti-LOXL2 monoclonal antibody (mAb), simtuzumab, did not demonstrate any changes in ALP or ELF score between placebo and intervention groups.[110]

A two-stage, open-label, multicenter phase II trial investigating the safety and efficacy of timolumab,[111] an anti-VAP1 mAb, has completed enrollment with results greatly anticipated (Clinical trials identifier: NCT02239211). Other monoclonal antibodies under investigation include anti-CCL24 mAb (CM-101), which has shown promise in other fibrotic disease models such as idiopathic pulmonary fibrosis and nonalcoholic fatty liver disease in fibrosis regression[112,113] (Clinical trials identifier: NCT04595825 – The SPRING study). Investigation of an antitransforming growth factor (TGF)β mAb (PLN-74809) that allows for dual-selective inhibition of αvβ6 and αvβ1 is ongoing in a phase 2a trial with recruitment ongoing (Clinical trials identifier: NCT04480840 – INTEGRIS PSC).

Others: anti-inflammatory/antifibrotic therapies. C-C chemokine receptor types 2 and 5 are receptors for monocyte chemotactic protein-1 (MCP-1) which is a chemokine that has been found to be overexpressed in the livers of animal models of PSC and in PSC cholangiocytes.[114] Cenicriviroc (CVC), an antagonist of C-C chemokine receptor types 2 and 5, may reduce homing of activated macrophages to the liver. CVC was investigated in a proof-of-concept study that demonstrated safety of CVC and its effect on improvement in liver biochemistry over 24 weeks in PSC patients,[114] however there was lack of impact on parameters of fibrosis which may be due to the short duration of the study and the use of transient elastography and biomarkers (APRI, FIB-4 score) rather than more validated parameters like the ELF score in PSC.[47,48]

Other pharmacological therapies of interest include statins, that were found together with azathioprine to be associated with improved transplant-free survival in a large retrospective cohort study from Sweden.[115] Statins are known to have pleiotropic effects other than its lipid-lowering properties. They also have been found to have beneficial effects in other liver diseases and preventing hepatocellular carcinoma.[116,117] Phase III trials investigating the effect of simvastatin on transplant-free survival, liver decompensation and hepatobiliary cancer are currently underway (Clinical trials identifier: NCT04133792).

Aspirin is a commonly used antiplatelet and anti-inflammatory agent, with well described chemopreventative properties against gastrointestinal, CRC and even hepatocellular carcinoma.[118] It acts via inhibition of the cyclooxygenase-2 pathway resulting in reduction of carcinogenic prostaglandin E2,[118] which is of relevance to PSC-related CCA where overexpression of cyclooxygenase-2 in biliary epithelium has been described.[3,118] It also reduces platelet aggregation with a negative impact on tumor angiogenesis and metastases, and cellular inhibition of signaling pathways that promote tumor growth.[118] Evidence for aspirin use in reduction of CCA risk is growing,[118–121] however studies investigating this specifically in PSC is lacking.[122] A retrospective cohort study published in abstract form demonstrated a trend toward significant reduction in risk of PSC-related CCA with aspirin use only.[123]

Gut microbiome manipulation: *Fecal microbiota transplant.* Fecal microbiota transplant (FMT) has been studied in case reports and pilot studies in PSC-IBD, with the rationale that FMT increases gut microbial diversity, which is important in maintaining epithelial integrity, reducing gut permeability and inflammation.[124] These pilot studies have demonstrated improvement in IBD symptoms and liver biochemistry, with successful engraftment of certain operational taxonomic units correlating with increased microbiome diversity and improved serum ALP levels,[125] including bacterial species that produced SCFA. Recent mouse models have provided insight that selective donors may be necessary to improve FMT outcomes via enrichment in hepatoprotective species such as *Lachnospiraceaea* and inhibition of pathobionts (*Enterococcus faecalis and Escherichia coli)* in the gut microbiome.[126]

Antibiotics. The administration of antibiotics as a method for noninvasive manipulation of the gut microbiome has been a growing area of interest, which may manifest its therapeutic potential by way of reducing translocation of colonic bacteria and endotoxins.[124] Oral vancomycin is a minimally absorbed, glycopeptide antibiotic with immunomodulatory effects in the gut,[124,127] potentially improving both IBD and PSC.[124,128] A small case series demonstrated that oral vancomycin therapy increases T regulatory cell related cytokines (transforming growth factor beta) levels, with subsequent increase of peripheral regulatory T cells in treated pediatric patients.[127] It was also found to demonstrate the greatest reduction in serum ALP compared with other antibiotics in PSC patients,[129] including rifaximin, metronidazole, minocycline, and tetracycline.[62–65] Two pilot studies in adult PSC patients have demonstrated improvements in liver biochemistry and prognostic scores with vancomycin use compared with metronidazole or placebo, with one study demonstrating improvement in PSC-related symptoms as well.[66,67] Vancomycin is a promising antibiotic agent that warrants further investigation in large-scale, randomized-controlled trials in this population. It may also provide benefit in reducing post-transplant recurrence, as described in a patient who developed recurrent disease 4 years post-transplant with successful normalization of liver function tests with UDCA 15 mg/kg/day and vancomycin 250 mg twice daily.[128]

Another antituberculous antibiotic, rifampicin, which is recommend for use in refractory pruritus in PSC[8] may also play a beneficial role through its effects on the nuclear receptor PXR on reduction of serum ATX expression,[130] bile acid

Table 2. Summary of studies investigating gut microbiome manipulation in adult PSC

Gut microbiome manipulation					
Study	**Study type**	**Duration**	**Intervention**	**Number**	**Outcomes**
Fecal microbiota transplantation					
Allegretti, 2019[68]	Open-label pilot study	24 weeks post-FMT	FMT	10 patients (9 UC, 1 Crohn's)	30% improved ALP levels, with increased stool diversity from week 1 ($p<0.01$). Abundance of engrafted taxonomic units correlated with decreased ALP ($p=0.02$)
Vancomycin compared with metronidazole or placebo					
Tabibian, 2013[66]	RCT	12 weeks	Vancomycin or metronidazole	8 vancomycin 125 mg QID, 9 250 mg QID, 9 metronidazole 250 TDS, 9 500 mg TDS	Decrease in ALP in both vancomycin groups, MRS reduced in low dose vancomycin and metronidazole group. Pruritus decreased in high-dose metro group
Rahimpour, 2016[67]	Placebo-controlled RCT	12 weeks	Vancomycin	18 vancomycin 125 mg QID, placebo 11	Patients were on UDCA 300 mg TDS before and during study. Reduction in ALP and MRS. Secondary end point improvement in ESR, symptoms including diarrhea
Metronidazole					
Farkkila, 2004[63]	Placebo-controlled RCT	36 months	Metronidazole (600–800 mg/day) and UDCA (15 mg/kg/day)	39 metronidazole+ UDCA, 41 placebo+UDCA	Increased reduction in ALP and MRS in metronidazole + UDCA arm. Also improvement in liver histology, but no significant difference between groups
Others					
Mistilis, 1965[65]	Open-label pilot study	1.5–6 years	Tetracycline 500 mg daily	6	Increase in ALP from baseline. Two patients on prednisolone. No clinical improvement or histological change
Silveira, 2009[64]	Open-label pilot study	1 year	Minocycline 100 mg BD	16	Improvement in serum ALP and MRS
Tabibian, 2017[62]	Open-label pilot study	12 weeks	Rifaximin 550 mg BD	16	No significant change in liver biochemistry or symptoms

*Case reports and pediatric studies excluded. ALP, alkaline phosphatase; BD, twice a day; ESR, erythrocyte sedimentation rate; FMT, faecal microbiota transplantation; MRS, Mayo risk score; QID, four times a day; RCT, randomized-controlled trial; TDS, three times a day; UDCA, ursodeoxycholic acid.

metabolism, bilirubin conjugation and excretion at the cellular level as a means to exhibiting its antipruritic effect and perhaps a potential therapeutic agent worth investigating.[28] Case studies reporting the benefit of azithromycin on liver biochemistry have been described.[131,132]

Table 2 summarises the studies investigating gut microbiome manipulation as therapy in adult PSC.[62–68]

Endoscopic intervention

The use of endoscopic retrograde cholangiopancreatography (ERCP) in PSC is normally reserved for patients with symptomatic dominant strictures (DS) or if suspicion for CCA is high,[133] although in some centers is used routinely as part of surveillance programs.[134] DS are focal, high-grade strictures that may be superimposed on diffuse milder ductal narrowing.[10,101,135] The development of a DS occurs in 36–58% of patients and may incur poorer prognosis and increased risk of development of CCA.[136–140]

The best approach to surveillance or management of DS after malignancy is ruled out in PSC patients is unclear. In practice, ERCP and balloon dilatation of strictures with or without stenting is the mainstay of treatment for symptomatic patients.[101,133] Serial endoscopic intervention does seem to maintain biliary duct patency at 80% at 1 year and 60% at 3 years.[141] While improvement in transplant-free survival based on the MRS was demonstrated in some series, this may purely be a reflection of high pretherapy serum bilirubin rather than true slowing of disease progression.[142–144]

The evidence for balloon dilatation compared with stent insertion for patients with obstructive sequelae in PSC is limited with heterogenous clinical series and retrospective studies,[141,145] and only one randomized-controlled trial to date comparing the two strategies.[146] This trial was terminated prematurely due to increased safety signals in the short-term stent group; namely increased post-endoscopic complications such as pancreatitis. The primary endpoint of recurrence of DS within a 24-month follow up period was not statistically significant between the two treatment groups, although this was limited by small numbers and premature termination.[42] This is supported by a recent systematic review and meta-analysis on the optimal endoscopic therapy in management of DS in PSC, that demonstrated no difference in clinical efficacy and reduced post-ERCP adverse events with balloon dilatation compared with stent placement.[147]

For patients who fail endoscopic therapy due to difficult anatomy or other reasons, percutaneous biliary drainage has higher morbidity but offers similar efficacy to endoscopic

therapy.[101] Surgical management is used as a last resort to bypass biliary obstruction via cholangioenterostomy or resection of the extrahepatic biliary stricture and Roux en Y hepaticojejunostomy.[101] However, these surgical methods should only be reserved for noncirrhotic patients with reasonable survival outcomes, a 5-year and 10-year survival of 83% and 60%, respectively at least.[148] Cirrhotic patients derive greater survival benefit from LT, as further biliary bypass and resection is associated with increased operative morbidity and mortality in this subgroup.[149]

LT

Currently, LT is the only curative option for patients with end-stage liver disease or refractory complications such as intractable pruritus or cholangitis,[1,8,19,149] with high 5-year survival rates of 85% in patients receiving deceased donor allografts.[150] Localized cholangiocarcinoma or high-grade biliary dysplasia in highly selected patients are also considered for transplantation in selected tertiary centers.[101,149] Although PSC recurs in around 20% of grafts, this is a relatively benign disease with survival of these patients being comparable to those without evidence of recurrence.[151]

Medical therapy of PSC-related symptoms

Pruritus

A significant proportion of PSC patients (30–60%) experience pruritus as a symptom across their disease course, which significantly impacts HRQOL.[9,152] This occurs even in the absence of significant biliary obstruction, although new or worsening pruritus should prompt investigation for development of a new DS or CCA. Pruritus typically affects the limbs (especially the palms and soles) and may intensify with heat and in the evenings.[130]

As with the pathophysiology driving PSC itself, the exact cause of pruritus in this disease is not entirely known. Serum bile salts potentially activate TGR5 receptors and stimulate pruritus via gastrin-releasing peptide- and opioid-dependent mechanisms.[153] There has been increasing evidence that serum ATX and its influence on synthesis of lysophosphatidic acid plays a unique role in pruritus of cholestatic disorders.[154,155] Serum ATX activity correlates with degree of pruritus in PSC patients, as compared with other proposed pruritogens such as serum bile salts, serotonin, histamine, and endogenous opioids.[130]

Lifestyle measures for management of pruritus include topical administration of moisturizers and menthol-containing ointments, as well as avoiding heat.[9,130] Although antihistamines are commonly prescribed along with these lifestyle measures, it often does not alleviate pruritus but may lend benefits with its sedating effects.[130] Failing these, bezafibrate is recommended by EASL as first-line therapy if available due to its good safety profile, efficacy in pruritus reduction as demonstrated in the FITCH trial and complementary anticholestatic effect with UDCA.[8] Rifampicin is recommended as second line but has a risk of inducing hepatitis after 4–12 weeks of treatment. Further therapies beyond these complement the AASLD guidelines with naltrexone 50–100 mg daily and sertraline 100 mg daily being recommended as third-line treatments.[8]

Despite AASLD guidelines still recommending cholestyramine 4–16 gm daily as a first-line therapy as a bile acid sequestrant,[9] the EASL has removed it from its guidelines due to the lack of evidence in PSC, with also the concern that it may impair absorption of medications if not administered properly.[8] Further options for refractory pruritus include phenobarbital 60–100 mg daily and phototherapy. Plasmapheresis have been described in small case series[9] and recommended only in the AASLD guidelines.[9] Further novel strategies that have been discussed including ASBT inhibitors and selective PPARα or PPARδ agonists remain under investigation.[8]

Fatigue

Fatigue is another troubling symptom for PSC patients that significantly impacts HRQOL,[152] and may be related to autonomic dysregulation and concurrent active IBD.[156] Despite this, guidelines are scarce on management of fatigue in PSC. The latest AASLD guidelines recommend excluding secondary causes of fatigue such as hypothyroidism and depression. Focusing on lifestyle measures such as optimizing sleep hygiene and having a regular exercise regimen may assist in improving troublesome fatigue.[9] Although there is some data to suggest that LT significantly decreases chronic fatigue,[157,158] it is not currently an indication for LT as an isolated symptom.[8] A prospective case-control study found that female patients were less likely to have improvement in fatigue after LT compared with male patients.[158] Further large-scale studies are required to further corroborate these findings and allow us to explore the potential of treating autonomic dysregulation and LT as a management of fatigue in PSC.

Mineral bone disease

As with other cholestatic liver conditions, patients with PSC are at heightened risk of fat-soluble vitamin deficiency, malnutrition, and frailty.[9] As a result, there is also increased risk of osteopenia or osteoporosis in this cohort that persists before and after LT, with fragility fractures having a significant impact on health-related quality of life.[159,160] In a prospective study of 234 PSC patients, PSC patients had a 23-fold increased risk of osteoporosis compared with a matched population, with older age, low body mass index and long duration of IBD being risk factors for osteoporosis.[160] Assessment of bone mineral density is recommended at time of diagnosis in all PSC patients[8] and fracture risk should be calculated.

Lifestyle measures including sufficient vitamin D and calcium intake, increased weight bearing exercise, alcohol reduction, and smoking cessation should be implemented in all patients as per osteoporosis management guidelines.[161] Although there is no specific therapy for PSC-related osteoporosis, due to it being a condition largely affecting middle-aged men it is important to consider testosterone deficiency and correction of that as a therapy as per guidelines.[161] Other therapeutic agents should be used according to fracture history, osteoporosis severity, and risk of hip fracture include oral or parental bisphosphonate therapy, teriparatide, and denosumab. If patients have evidence of esophageal varices and require bisphosphonates, parental therapy is preferred due to the risk of precipitating variceal bleeding.[9] For osteopenia or osteoporotic patients their bone mineral density should be monitored every 1–2 years to assess response to therapy.[161] For patients without established mineral bone disease, 2–3 times yearly surveillance is recommended as tailored to individual risk factors.[9]

Future directions

Further placebo-controlled, randomized-controlled trials should be designed with utilization of composite endpoints to allow for the best estimation of clinical therapeutic effect. Well-defined clinical end points, a combination of serum biomarkers (investigating fibrosis and inflammation) and gut microbiota analysis (oral and fecal), radiology, and

PRO instruments should be consistently utilized. In addition to the therapeutic agents that are under investigation currently, further potential combinations should include therapies that aim to improve different aspects of the disease. Potential combinations include an UDCA analog such as norUDCA or berberine ursodeoxycholate, in addition to an antifibrotic agent or anti-inflammatory therapy. Antibiotics such as rifampicin which show potential in mediating bile acid regulation via the PXR receptor and its beneficial effects on pruritus show promise but should be investigated in pilot studies or well-designed prospective cohort studies to investigate its safety in both short- and long-term use. Prospective cohort studies also help build a biorepository to allow for further evaluation of therapies that patients are on for other indications e.g., aspirin, statins, and biologics for IBD. This may allow us to detect signals for therapeutic benefit that may have been missed in older studies, and especially with new formulations and administration routes of IBD drugs on the horizon.

Conclusion

Despite PSC being well recognized as a premalignant disease affecting younger patients with considerable risk of progression to LT or death, there are significant gaps in knowledge regarding pathophysiology and development of medical therapies. Currently, liver transplant is the only curative option for patients with end-stage disease or complications that are not amenable to endoscopic therapy. Despite UDCA being commonly prescribed, its use at this stage seems limited to improvement of liver biochemistry at moderate doses with perhaps a chemoprotective effect in patients with PSC-IBD. Advancement in our knowledge of bile acid pathway manipulation with nuclear receptor agonists, gut microbiome manipulation via fecal transplant or antibiotics paves a promising landscape especially in PSC patients with concomitant IBD and post-LT. To conclude, the therapeutic landscape of PSC has vast potential, and further research and funding in this area is absolutely critical.

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Author contributions

Authors NT, JL, WK, SR and AM contributed to the manuscript conception and design. Literature review and drafting of the manuscript was performed by NT. Authors JL, WK, SR and AM were involved in critical revision of the manuscript for important intellectual content. All authors have made a significant contribution to this manuscript and have approved the final version.

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