New Therapeutic Strategies for Primary Sclerosing Cholangitis

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Primary sclerosing cholangitis (PSC) is an uncommon chronic cholestatic liver disease, which in the majority of patients progresses to liver transplantation or death. To date, no medical treatment has been proven to be of benefit, although ursodeoxycholic acid is widely used. The etiopathogenesis of PSC is unclear, although it is associated with inflammatory bowel disease. Various hypotheses have been suggested, which have led to different therapeutic strategies. Recent studies have suggested that the microbiome may play a role in PSC, raising the possibility of efficacy of antibiotics and fecal microbiota transplantation. Gut-homing T cells may be important in the pathogenesis of PSC, and several agents are in development, targeting various receptors, integrins, and ligands on this pathway, including VAP-1, MadCAM-1, α4β7, and CCR9. Nuclear receptor agonists such as obeticholic acid and fibrate hold promise, as do other therapies that alter bile acid composition such as norUDCA. Antifibrotic agents such as Loxl2 inhibitors are also being assessed. In conclusion, it is likely that an effective drug therapy for PSC will become available over the next decade.
whether it may exert a chemoprotective effect on the bowel to prevent colonic dysplasia and colon cancer in patients with coexisting IBD.\textsuperscript{13–18} It has no effect on symptoms such as pruritus, abdominal pain, and fatigue.

In this review we will (1) examine the potential pathogenesis of PSC that can direct potential therapies, (2) discuss the difficulties in designing and conducting interventional studies in PSC, (3) briefly describe the drugs that have already been unsuccessfully trialed in PSC, and (4) evaluate the possible therapeutic benefits and mechanisms of the novel agents currently being developed and trialed for the future management of this potentially devastating condition. A summary of the various agents mentioned in this article according to pathogenic target is provided in Fig. 1.

Pathogenesis

As mentioned earlier, the etiology of PSC is not clear. Genetic factors appear to play an important role, as initially demonstrated by candidate gene studies up to 30 years ago, and subsequently confirmed by recent GWASs and Immunochip studies.\textsuperscript{19–21} These studies confirm a strong association with risk loci on chromosome 6 that pertain to the MHC, especially HLA-B8 and HLA-DR3. A further 15 non-HLA risk loci have been identified, including FUT-2 involved in regulating bacteria in the intestine and interleukin-2 loci and other genes found in other autoimmune diseases. These genetic studies have emphasized the importance of the acquired and innate immune responses and interaction with the biome, in the pathogenesis of PSC.

Other factors are believed to play a role in the etiology, such as a toxic effect of bile on damaged biliary epithelium; the so-called leaky gut theory, where preexisting IBD predisposes to increased bowel wall permeability and therefore increased exposure of the bile ducts to bacteria and other pathogens and toxins; and also an increase in homing T cells and other cytokines from the bowel to the liver, involving upregulation of VAP-1, CCR9, and various other chemokines.\textsuperscript{22,23} The pathogenesis of PSC is discussed in more detail in a recent review.\textsuperscript{24}

Challenges of Designing Trials in Primary Sclerosing Cholangitis

There are many barriers to designing and carrying out a successful clinical trial in PSC, which may be one of the factors that an effective medical therapy remains elusive. First, PSC is a rare disease, with a prevalence varying from 0.22 per 100,000 population to 16.2 per 100,000 population and an incidence of 0.04 to 1.31 per 100,000 person-years.\textsuperscript{25,26} This makes recruitment of sufficient patients for an adequately powered trial challenging; national and often international multicenter trials are usually required.

Second, the median time in the natural history of PSC to clinically meaningful endpoints, such as liver transplantation or death, is 10 to 21 years, which is not feasible for a clinical

![Fig. 1](image-url) A schematic representation of the various elements contributing to pathophysiology of primary sclerosing cholangitis PSC (colored boxes), and the therapeutic agents, listed above, which may be directed against this particular element. Agents in italics are still in development and are not licensed. PAMP, pathogen-associated molecular patterns; MΦ, monocyte; TLR, toll-like receptors; BE, biliary epithelium; Th1, T-helper 1; LOXL2, lysyl oxidase-like 2; BA, bile acid; PL, phospholipid; MDR3, multidrug resistance 3 gene; CFTR, cystic fibrosis transmembrane conductance; TGR5, G-protein coupled receptor; UDCA, ursodeoxycholic acid; atRA, all-trans retinoic acid; PSC, primary sclerosing cholangitis. (Adapted from a figure courtesy of Chris Bowlus, University of California, Davis, CA.)
trial. Therefore, surrogate markers are used as clinical endpoints, such as reduction in ALP and/or Mayo Risk Score. A reduction in ALP is currently the favored primary endpoint of most interventional trials in PSC, as there have been four moderate-to-large studies from different cohorts around the world, demonstrating an association of reduction of ALP (whether it be <1.5 times the upper limit of normal, a >40% drop or normalization) with a favorable clinical outcome. However, it is unclear whether a reduction in ALP caused by a novel therapy is a reliable predictor of a favorable long-term outcome.

There is an urgent need for proven surrogate markers in PSC. It is to be hoped that serum markers of fibrosis such as ELF and new imaging modalities such as transient elastography and new magnetic resonance (MR) techniques such as MR elastography and multiparametric MR scanning will provide the solution. However, there is a challenge in the future to convince regulatory bodies that these surrogate markers will translate to hard clinical endpoints for the licensing of any potential therapies.

Lastly, recent large cohort studies have demonstrated that PSC is a heterogeneous disease, with some patients having a poor prognosis, whereas others have a normal life span. This is probably related to different underlying genotypes and phenotypes. It is clear that some patients previously misdiagnosed as PSC have IgG4-associated sclerosing cholangitis with an entirely separate etiology and natural history. IgG4-related hepatobiliary diseases including sclerosing cholangitis will be reviewed in detail in the November 2016 issue of Seminars in Liver Disease. Primary sclerosing cholangitis associated with IBD (PSC/IBD) makes up the majority of cases, but approximately 20% of Northern European patients do not have IBD and may have a more favorable clinical course.

Within the diagnostic category of PSC PSC/IBD, patients with small-duct PSC (a variant where patients have cholestatic liver enzymes and biliary changes on liver histology, but a normal cholangiogram), constitute approximately 10 to 15% of patients. Such patients have a very good prognosis.

Large cohorts of up to 7,000 PSC patients are currently being investigated studying the phenotype of a patient with their genotype and the relationship to prognosis. This will help to stratify their clinical care (e.g., more aggressive management for those with a poor prognosis, such as early inclusion in clinical trials of novel agents); in addition, it will also help direct specific therapies for specific phenotypes. In the context of designing a clinical trial of new therapeutic agents in PSC, the differing phenotypes among the study population can lead to an underpowered trial and the possibility of a type II error of what may potentially have been a beneficial agent.

Previous Trials in Primary Sclerosing Cholangitis

Ursodeoxycholic Acid

Ursodeoxycholic acid is a hydrophilic dihydroxy bile acid that makes up 3% of endogenous human bile acids, but as a drug is used to good effect in various cholestatic liver conditions, particularly primary biliary cholangitis (PBC; formerly known as primary biliary cirrhosis). As mentioned above, UDCA has been shown to reduce ALP in PSC. Between 1991 and 2009, there have been 11 clinical trials evaluating varying doses of UDCA in PSC (from 8 mg/kg/d up to 30 mg/kg/d), 9 of which have been placebo controlled and the majority double blinded. In 10 of the 11 trials, an improvement in liver biochemistry was shown, but none has shown a survival benefit or symptomatic improvement. The duration of these trials varies from 1 to 5 years, and the number of patients enrolled range from 12 to 219. The most recent large trial of 150 patients looked at high-dose UDCA (28–30 mg/kg) versus placebo, and in fact showed an adverse outcome in PSC, with increased mortality in the UDCA group. This surprising result, which was in conflict with the previous smaller studies of UDCA in lower doses, has caused increased caution over the use of UDCA in PSC, particularly in high doses, and has brought a halt to further studies of UDCA in PSC. It is worth noting that, compared with other studies of UDCA in PSC, there was not as significant a biochemical response to UDCA as compared with placebo. Whether this reflects a problem with compliance is not clear, and it is also unclear whether the results truly reflect an adverse effect of the UDCA.

Recently, it was shown that withdrawal of UDCA in patients with PSC causes a rebound rise in ALP (76% increase), which supports a potential benefit of UDCA. A treatment algorithm for judicious use of UDCA in PSC has been proposed, although it is not validated.

There is also under way a trial of UDCA in children and adolescents, given that this disease behaves in a slightly different and more aggressive manner than adult-onset disease and there has been a lack of prior trials of UDCA in the pediatric population.
Other Agents TRIaled in PSC

Given the potential immunomediated pathogenesis, multiple pilot studies and case series have been published of various immunosuppressants in PSC, all with negative results. These include azathioprine, cyclosporine, methotrexate, tacrolimus, penicillamine, and colchicine, and infliximab. Corticosteroids such as prednisolone are only recommended in the minority of PSC patients with overlap with autoimmune hepatitis.

Antifibrotic Strategies

The diagnosis of PSC is dependent upon the demonstration of either strictures of the large bile ducts as seen on a cholangiogram (classical PSC), or in the absence of this, a characteristic liver biopsy with periductular scarring (so-called onion skinning; small duct PSC), along with cholestatic liver function tests. Thus, at diagnosis, patients already have established fibrosis within their liver, targeted around the bile ducts, eventually progressing to cirrhosis. Although it is likely that an inflammatory, immunomediated process leads to this fibrosis, there are no diagnostic techniques currently available to detect this nonfibrotic inflammatory process at an early enough phase to implement anti-inflammatory medications to halt the progression of disease. Hence, in the presence of established fibrosis, fibrotic pathways in PSC are being targeted to either stem the fibrosis, or potentially reverse it.

Lysyl Oxidase-Like 2 Inhibitors

Although there is no ideal animal model for PSC, the Abcb4 (−/−) mouse, formally called Mdr2 (−/−), is frequently used to characterize chronic cholangitis, with onion-skin lesions resembling those of PSC. A Norwegian study analyzing gene transcription in this mouse model found upregulation of the enzyme lysyl oxidase-like-2 (Loxl2), indicating its potential role as a profibrotic protein in PSC. Loxl2 plays an important role in extracellular matrix synthesis and repair by promoting the cross linking of collagen fibers (particularly collagen I). Furthermore, Loxl2 has been identified in both human fibrotic liver diseases (hepatitis C and nonalcoholic steatohepatitis [NASH]), and also in animal fibrotic liver models. It has been shown in animal models to play a central role in the development of fibrotic stroma in fibrotic diseases by activating and recruiting fibroblasts to the pathologic site. A monoclonal antibody against Loxl2, simtuzumab, has been developed and is currently in phase II trials, with preliminary results expected within the next 2 years. It is also being evaluated in multiple other settings, including NASH, advanced colorectal cancer, pancreatic cancer, myelofibrosis, and idiopathic pulmonary fibrosis.

Obeticholic Acid

Another agent purported to have antifibrotic properties, and of therapeutic potential in PSC, is obeticholic acid (OCA; 6α-ethyl chenodeoxycholic acid, formerly INT-747), a semisynthetic analogue of the endogenous bile acid, chenodeoxycholic acid (CDCA). Chenodeoxycholic acid is the endogenous potent ligand for farnesoid X receptor (FXR), yet OCA, as well as its conjugated glycine and taurine derivatives, has been shown to be 100 times more potent than CDCA to activate FXR. Ursodeoxycholic acid does not activate FXR. This receptor, also known as the bile acid receptor, is a nuclear receptor expressed in a wide range of cells, including small bowel enterocytes, hepatocytes, and biliary epithelium. The main role of FXR is regulation of intracellular bile acids, through a negative feedback cycle, with ligand bound FXR bringing about efflux of bile acids from hepatocytes into bile, a reduction of bile acid synthesis from cholesterol, and a reduction of hepatocellular uptake of bile acids. Additionally it has a substantial role in lipid and glucose metabolism. Animal data have suggested that FXR also modulates fibrosis, and agonism with OCA has been shown in rats to have an antifibrotic effect. The only study looking at OCA and effect on fibrosis in humans is the Farnesoid X Receptor (FXR) Ligand Obeticholic Acid in NASH Treatment (FLINT) Trial, a multicenter, double-blind, placebo-controlled clinical trial of obeticholic acid in NASH. In this study, there was a statistically significant decrease in liver fibrosis score on histology at 72 weeks, although the actual absolute change in score was very small. It is not clear how much of an impact FXR agonism has on fibrosis in human liver disease, but it clearly warrants more investigation. It is worth noting, however, that a separate study of several different mouse models of fibrosis failed to show that FXR knockout protected against fibrosis, particularly biliary fibrosis animal models. However, it has been shown to have a beneficial biochemical effect in a clinical trial in PBC. The main side effects include hypercholesterolemia and pruritus, but it is a novel therapeutic agent that merits investigation in PSC, and a clinical trial is currently underway in PSC in the United States.

All-Trans Retinoic Acid

All-trans retinoic acid (atRA) is a derivative of vitamin A, and has various anti-inflammatory and immune modulatory properties. It is currently licensed for inflammatory conditions such as rheumatoid arthritis and psoriasis, as well as a treatment in acute promyelocytic leukemia. An animal study showed that combination treatment of atRA with UDCA, as compared with either atRA or UDCA alone, in bile duct ligated mice significantly reduce liver fibrosis on histology, reduced the expression of marker genes for liver fibrosis, duct proliferation, and inflammation and reduced hepatic bile acid pool levels. Accordingly, a phase 1 clinical trial is currently underway of atRA in patients with PSC.

Altering Bile Acid Composition

norUrsodeoxycholic Acid

24-norUrsodeoxycholic acid (norUDCA) is a synthetic bile acid with a similar structure to UDCA, but with one fewer methylene in its side chain. From animal studies, again using the Abcb4 (−/−) model, formally called Mdr2 (−/−), it appears to have multiple effects on biliary physiology. As compared with UDCA, norUDCA has a relative resistance to conjugation, and a proportion of unconjugated norUDCA is secreted into
the canaliculi, promptly pronated by a hydrogen ion, and then reabsorbed back into the cholangiocyte, thereby generating a bicarbonate ion, and then is secreted back into the bile via the hepatocyte. This repeated pathway through the hepatocyte, a so-called cholehepatic shunt, sets up a bile acid-dependent, bicarbonate-rich choleresis, which in mouse models appears to have a beneficial effect on fibrosis and other biliary processes, unlike the choleresis promoted by UDCA (see Fig. 3) A phase II double-blind, placebo-controlled randomized trial of norUDCA in PSC is currently underway.

Apical Sodium-Dependent Bile Acid Transporter Inhibitors

Another novel therapeutic strategy altering bile acid composition and flow is to reduce the exposure of biliary epithelia to supposedly toxic bile acids by inhibiting their reabsorption in the ileum. This can be potentially achieved by inhibiting the apical sodium-dependent bile acid transporter (ASBT), a transmembrane protein localized on the luminal surface of ileal enterocytes, which is the predominant pathway for bile acid active reabsorption from the lumen into the enterocyte. Studies in the Abcb4 (−/−) mouse model have shown that inhibition of ASBT brings about reduced hepatic profibrogenic gene expression, an upregulation of anti-inflammatory and antifibrogenic genes, and a reduction in bile acid pool size and composition in the liver, with improved liver histology and a reduction in the extent of fibrosis.

A potential dose-limiting side effect of inhibiting bile acid reabsorption, given this increases the fecal bile acid load, is diarrhea. A phase II clinical trial in PSC is currently underway with ASBT inhibitor SHP625 (formerly LUM001), and this drug is also being assessed in trials of pruritus in PBC.

Peroxisome Proliferator-Activated Receptor-α Agonists

There is current interest in bezafibrate as a potentially effective therapeutic agent in cholestatic liver diseases including PBC and PSC. Bezafibrate acts as a ligand of peroxisome proliferator-activated receptor α (PPARα), an intranuclear receptor involved in lipid metabolism. Peroxisome proliferator-activated receptor α promotes the expression of the multidrug resistance 3 (MDR3) gene, and increases P-glycoprotein levels in bile duct canaliculi. In turn, P-glycoprotein increases the phospholipid levels in bile juice, which forms micelles with toxic hydrophobic bile acids, thereby helping to prevent damage to bile ducts.

There is increasing evidence for efficacy of bezafibrate in PBC, with a current large placebo-controlled clinical trial of bezafibrate underway in PBC. There have been four small retrospective case reports of bezafibrate lowering liver enzymes in PSC, and recently a small Japanese prospective single-arm open-label study of 11 patients also showed some efficacy after 12 weeks of bezafibrate in PSC. All patients had improvements of their ALP and gamma-glutamyl transferase, with 64% also having improvement in transaminases. It must be noted that only 2 of 11 patients had concomitant ulcerative colitis, and whether these results can be reproduced in other populations of PSC remains to be seen, but further trials are warranted.

Fig. 3 Microphotographs of mouse liver histology specimens showing the amelioration of sclerosing cholangitis by norUDCA in Abcb4 (−/−) mice. Photos in Panel (A) show hematoxylin and eosin staining. Photos in panel (B) show Sirius red staining with significant fibrosis in red. Note the significant periductal fibrosis seen in the knockout mouse, as compared with the partial resolution in the knockout mouse fed UDCA, and resolution of fibrosis in the mouse given norUDCA. WT, control diet-fed wild-type mouse; KO, knockout mouse (Abcb4 (−/−)); UDCA, ursodeoxycholic acid; norUDCA, nor ursodeoxycholic acid; pv, portal vein; bd, bile duct (Fickert et al., 2006; figure reproduced with permission from Elsevier).
Manipulating Gut-Homing Immune Cells

There is mounting evidence that gut-homing T cells may play a role in the pathogenesis of PSC, in keeping with the common coexistence of IBD with PSC. Expression of chemokine receptor CCR9, along with the integrin α4β7, normally is induced on the cell surface of T lymphocytes primed in mesenteric lymph nodes, imprinting them with the capacity to travel to the gut and take up residence in the intestinal lamina propria. This migration into the tissue involves CCR9 first recognizing and binding to its ligand, CCL25, which is constitutively expressed in the small intestine. This interaction causes the T cell to bind to and roll along the endothelium, and it causes activation of α4β7 on the T-cell surface, which then binds to its ligand mucosal addressin cell adhesion molecule-1 (MAdCAM-1). Other adhesion molecules besides MAdCAM-1 are involved in recruitment of effector T cells to the gut, especially in inflammation, including vascular adhesion protein-1 (VAP-1), which is not only an adhesion molecule, but also an ectoenzyme with potent amine oxidase activity. This arrests the T lymphocyte, and it is extruded through the epithelium into the lamina propria where it may carry out its functions (see Fig. 4).

Ordinarily, the expression of MAdCAM-1 and CCL25 is restricted to the intestinal endothelium, rendering CCR9+ T cells fairly specific for the gut, with no expression in the liver. However, it has been shown in human PSC explants that there is aberrant expression of MAdCAM-1 and CCL25, and approximately 20% of the intrahepatic T cells are CCR9+ α4β7+, while there are virtually no CCR9+ α4β7+ T cells present in healthy livers and other liver-disease controls. The explanation for these findings is unknown, but may involve activation of the enzymatic activity of VAP-1 and upregulated expression of MAdCAM-1 on the hepatic sinusoidal epithelium, thus facilitating recruitment of these cells into the liver.

There are multiple agents currently available or in development that target various aspects of this pathway. Vedolizumab is a monoclonal antibody against α4β7, which is currently licensed for use in ulcerative colitis. There are specific agents that have been developed against CCR9 (CCX282B); MAdCAM-1, and VAP-1; currently an open-label phase II clinical trial is underway evaluating BTT1023, a VAP-1 inhibitor, in PSC.

Manipulating Gut Microbiome

Antibiotics

Antibiotic therapy has undergone resurgence in recent years as a potential therapy in PSC, after a few small trials and case series using agents such as vancomycin, metronidazole, and/or minocycline dating 20 to 50 years ago.

A possible mechanism in which antibiotics may have a role is by altering the gut microbiota and thereby reducing exposure of the biliary epithelium to pathogenic antigens. The “leaky gut” theory, with increased translocation of colonic bacteria and endotoxins, possibly due to concomitant IBD, to the liver via the portal vein, has been suggested to be important in the pathogenesis of PSC. There are numerous pathogen recognition receptors in cholangiocytes, such as nucleotide-binding oligomerization domain (NODs) and all known Toll-like receptors (TLRs). These receptors can recognize pathogen associated molecular patterns (PAMPs) in the bile, which may have been secreted into the canaliculi (from the portal circulation) or from ascending infection. In turn, this leads to increased expression of a variety of innate immune response genes including profibrogenflammatory mediators, and ultimately development of hepatobiliary inflammation and fibrosis. This theory is supported by early rat models of small bowel bacterial overgrowth producing PSC-like biliary inflammation and strictures.

The largest study of antibiotics in PSC compared metronidazole (MTZ) and UDCA acid to MTZ alone for 36 months in 80 patients. The addition of MTZ to UDCA therapy significantly improved liver function tests, the Mayo Risk Score, and liver histology scores, with a trend toward inhibition of progression of ERCP changes. A subsequent small pilot study demonstrated a benefit of both low- and high-dose vancomycin as compared with low- or high-dose MTZ, with particular...
efficacy of lowering ALP (40–43% reduction at 12 weeks), and with fewer side effects.\textsuperscript{91} Finally, a recent open-label pilot study of 16 PSC patients treated with rifaximin, a nonabsorbed antibiotic, for 12 weeks failed to show an ALP reduction, and 3 patients withdrew due to adverse events.\textsuperscript{92}

There is an ongoing trial evaluating the efficacy of vancomycin in children with PSC, with a scientific exploratory side arm evaluating the effects of vancomycin on the microbiota and immune system in these patients.\textsuperscript{93}

### Fecal Microbiota Transplantation

Also in planning stages is a clinical trial of fecal microbiota transplantation (FMT) in patients with PSC.\textsuperscript{94} This is an exciting and novel therapy, based on the assumption that the microbiome in PSC is unique and potentially contributory to the pathogenesis of the disease, research on which is currently active in several centers around the world. Fecal microbiota transplantation has an established role in \textit{Clostridium difficile}-associated diarrhea, where dysregulation of the microbiome is a key etiological factor, and is also currently being trialed in IBD.\textsuperscript{95}

### Endoscopic Intervention

#### Biliary Dilatation and Stenting

Another aspect of the management of patients with PSC is how to investigate and treat dominant strictures. Ten to 50% of patients develop a dominant stricture during the course of their disease, which is defined as stenoses < 1.5 mm in diameter in the common bile duct and < 1 mm in the right and left hepatic duct.\textsuperscript{9} It is established that patients who develop a dominant stricture have a worse prognosis than those who do not.\textsuperscript{96} There are risks associated with performing an endoscopic retrograde cholangiopancreatography (ERCP)—both for the purposes of investigating for malignancy with biliary brushings for cytology and fluorescence in situ hybridization, as well as endoscopic dilatation and stenting. Therefore, it is often recommended to only investigate and intervene when there is significant cholestasis and/or a change in the clinical picture. On the other hand, there is some evidence that intervention with dilatation and/or stenting may possibly improve prognosis.\textsuperscript{97,98}

Additionally, it is not clear whether one should simply perform a balloon dilatation or insert a temporary biliary stent. There is a current randomized clinical trial in progress, entitled DILSTENT2 (Multicenter Randomized Trial Comparing Short-Term Stenting versus Balloon Dilatation for Dominant Strictures in Primary Sclerosing Cholangitis), comparing reintervention free survival between these two groups which hopefully will help guide future endoscopic interventions.\textsuperscript{99}

#### Topical Mitomycin C

Another endoscopic intervention is a current trial evaluating topical therapy with intrabiliary instillation of mitomycin C.\textsuperscript{100} Mitomycin C is an aziridine-containing a chemotherapeutic agent that is currently used intravenously and topically for a variety of cancers. It has been used to prevent scar formation following varied surgical interventions.\textsuperscript{101,102} Mitomycin C’s mechanism of action is to slow fibroblast cell division and proliferation, thereby reducing scar formation. The biliary strictures in PSC have a similar pathophysiology to strictures treated with mitomycin C elsewhere, and therefore may have a potential role in PSC. The primary aim of the study is to determine the efficacy of mitomycin C intrabiliary bolus on survival and the progression of PSC.

### Conclusion

Primary sclerosing cholangitis remains a difficult condition to manage with an unmet need for effective therapy. Designing and carrying out clinical trials in PSC can be challenging, but the productive collaboration between researchers and the pharmaceutical industry has led to a large number clinical trials either in planning or underway in PSC. There are several potential pathways that can be targeted therapeutically, such as antiﬁbrotics, alteration of bile acid composition, manipulation of the gut microbiome, attenuating the immune response, and endoscopic therapies. It is likely that an effective drug therapy for PSC will become available over the next decade.

### Abbreviations

- Abcb4: ATP-binding cassette, subfamily B, member 4
- ALP: alkaline phosphatase
- ASBT: apical sodium-dependent bile acid transporter
- atRA: all-trans retinoic acid
- CCR9: chemokine (C-C motif) receptor 9
- CDCA: chenodeoxycholic acid
- ERCP: endoscopic retrograde cholangiopancreatography
- FXR: farnesoid X receptor
- FMT: fecal microbiota transplantation
- FUT-2: fucosyltransferase 2
- GWAS: genome-wide association studies
- HLA: human leukocyte antigen
- IBD: inflammatory bowel disease
- Lox12: lysyl oxidase-like 2
- LT: liver transplantation
- MAdCAM-1: mucosal addressin cell adhesion molecule
- Mdr2: multidrug resistance protein 2
- MHC: major histocompatibility complex
- MR: magnetic resonance
- MTZ: metronidazole
- NASH: nonalcoholic steatohepatitis
- NOD: nucleotide-binding oligomerization domain
- norUDCA: norursodeoxycholic acid
- OCA: obeticholic acid
- PAMP: pathogen-associated molecular patterns
- PBC: primary biliary cholangitis
- PSC: primary sclerosing cholangitis
- TLR: toll-like receptors
- UC: ulcerative colitis
- UDCA: ursodeoxycholic acid
- VAP-1: vascular adhesion protein-1
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