



Published in final edited form as:

Curr Opin Gastroenterol. 2017 May ; 33(3): 149–157. doi:10.1097/MOG.0000000000000352.

Emerging pharmacologic therapies for primary sclerosing cholangitis

Angela C. Cheung, Konstantinos N. Lazaridis, Nicholas F. LaRusso, and Gregory J. Gores

Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA

Abstract

Purpose of review—The only currently approved treatment for primary sclerosing cholangitis (PSC) is liver transplantation, with a median time to transplant of 12–18 years after diagnosis. There are a number of emerging drugs that have the potential to meet this critically unmet need that will be summarized and discussed herein.

Recent findings—Although the cause of PSC is unknown, there are a number of novel therapeutics under development. These drugs target presumed pathogenic mechanisms largely extrapolated from ex-vivo and in-vivo preclinical models, as well as translational observations.

Summary—Future therapeutic strategies for PSC may include a multitude of complex pathogenic mechanisms encompassing pathways of immunomodulation, the microbiome and inflammation-related fibrosis.

Keywords

bile acids; management; primary sclerosing cholangitis; therapies

Introduction

Classic primary sclerosing cholangitis (PSC) is a progressive, cholestatic liver disease of unknown cause, characterized by an inflammatory, fibro-obliterative process that may affect both the extrahepatic and intrahepatic bile ducts. The epidemiology, pathophysiology and general management of adult and pediatric PSC was recently reviewed [1,2]. The only available curative therapy is liver transplantation; up to 12.7% of patients will die on the waitlist, whereas 15–25% of transplanted patients will develop recurrent disease [3,4]. The current review will consider the key publications relevant to the subject of emerging pharmacologic therapies in PSC.

Although the cause of PSC is unknown, there are several prevailing hypotheses that have driven the search for novel therapeutics. The current therapeutic pipelines for PSC are based on four categories: bile acid pool modification ('toxic-bile' hypothesis) (summarized in Fig. 1 [5] and Table 1); intestinal microbiome modification ('leaky gut' hypothesis);

Correspondence to Gregory J. Gores, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Tel: +1 507 284 0686; gores.gregory@mayo.edu.

Conflicts of interest: There are no conflicts of interest.

immunomodulation of receptors that potentiate recruitment of intestinally derived lymphocytes to the hepatobiliary milieu ('aberrant gut lymphocyte homing' hypothesis) (summarized in Fig. 2) and lastly, modification of pathways involved in liver fibrogenesis.

The challenge of primary sclerosing cholangitis trials

The discovery of effective therapies for PSC has been hampered by lack of knowledge regarding its pathogenesis. This impacts the rate of therapeutic development and limits the identification of key surrogate endpoints and the creation of animal models that can recapitulate the complex nature of PSC [6,7]. Robust surrogate endpoints for PSC are urgently needed as clinical endpoints such as transplant-free survival or decompensation require lengthy follow-up and large patient cohorts that are virtually impossible to achieve in clinical trials. *In lieu* of hard clinical endpoints, alkaline phosphatase (ALP) has often been used as a surrogate measure of outcome, but as discussed below, this is controversial [8]. Better biomarkers for cholestasis and/or biliary fibrosis are clearly needed for this disease. Also, we need the capability to identify patients with rapidly progressive disease and preferentially enroll these patients into clinical trials.

Lessons from ursodeoxycholic acid studies

Although originally, administration of exogenous bile acid therapy was postulated to replace toxic endogenous bile with a more nontoxic form [i.e. ursodeoxycholic acid (UDCA)], it was later discovered that bile acids are not simply passive bystanders, but are signaling molecules that participate in maintaining their own homeostasis [9]. In animal models, UDCA has been demonstrated to have effects on the secretion of bile acids through Ca^{2+} , protein kinase C, mitogen-activated protein kinase- and integrin-dependent mechanisms, leading to an increase in bile salt export pump (BSEP) and multidrug resistance-associated protein 2 (MRP2) [10–14]. UDCA also stimulates HCO_3^- secretion, potentiating the 'biliary HCO_3^- umbrella', a constitutive mechanism that protects cholangiocytes from the injurious effects of hydrophobic bile [15,16]. It has negligible effects on the synthesis of bile acids [17].

Despite numerous studies on the utility of the synthetic bile acid UDCA in PSC, its use remains highly controversial [18,19]. Clearly, high-dose UDCA (28–30 mg/kg/day) worsens outcomes with greater progression to liver transplantation and the development of varices despite biochemical improvement in serum ALP, highlighting the uncertainty of ALP as a surrogate marker [20]. Furthermore, despite studies demonstrating that lower doses of UDCA (13–25 mg/kg/day) are associated with significant improvement in serum ALP – these studies failed to demonstrate improvements in transplant-free survival [21,22]. Significantly, stratification of patients into those with or without improvement in ALP (i.e. normalization or a drop in ALP to <1.5 times the upper limit of normal) demonstrate that patients have improved survival regardless of whether this biochemical change occurs spontaneously or following treatment with UDCA [23–24,25,26]. Due to the uncertainty around the true effect of UDCA, and the lack of a biomarker that may identify those who are more likely to have a biochemical response to UDCA, the use of UDCA in PSC remains controversial [18,19,27,28]. In children, the association between ALP and outcomes is even less clear as ALP levels vary with both age and sex due to fluctuations in the bone-derived

isoenzyme [29]. The experience with UDCA highlights the difficulty in designing PSC trials and the vulnerability of relying on a surrogate biomarker such as ALP.

Emerging therapies and trials

The following sections will outline the novel therapies currently under investigation for PSC, starting with those that modulate bile acids, followed by those that modulate the microbiome, immunomodulatory processes and finally fibrogenesis.

*nor*Ursodeoxycholic acid

24-*nor*Ursodeoxycholic acid (*nor*UDCA, Dr Falk Pharma GmbH, Freiburg, Baden-Württemberg, Germany) is a derivative of UDCA that lacks a methylene group, providing resistance to conjugation with taurine or glycine [30]. As a weak acid, unconjugated *nor*UDCA can be passively absorbed by cholangiocytes and secreted by hepatocytes, unlike UDCA, which in its unconjugated form can only be absorbed through the apical sodium bile acid transporter (ASBT) [31]. This allows *nor*UDCA to efficiently avoid full enterohepatic circulation, instead undergoing a process called ‘cholehepatic shunting’, in which bile acids are reabsorbed by cholangiocytes and returned to hepatocytes rather than undergoing active transport across the terminal ileum [32,33]. This leads to significantly greater choleresis than with UDCA [32]. In addition, *nor*-UDCA causes choleresis of more hydrophobic bile, with a significant increase in biliary glutathione and bicarbonate secretion in mouse models [34]. Unlike UDCA, *nor*UDCA can also increase the expression of basolateral efflux pumps (i.e. Mrp4 and Mrp3) and upregulate phase I and II detoxification enzymes (Sult2a1, Ugt1a1, Cyp2b10 and Cyp3a11), the latter leading to a significant decrease in serum bile acids [34].

In a 12-week phase II dose finding study, 159 patients were randomized to placebo or a daily dose of *nor*UDCA of 500, 1000 or 1500mg (NCT01755507) [35]. Intention-to-treat analysis demonstrated a significant reduction (12.3–26.0%) in serum ALP, compared with the placebo group. Similar changes in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were noted. Thus, *nor*UDCA may be a promising treatment for PSC due to its apparent lack of toxicity and greater choleric effects when compared with UDCA; a phase III study is necessary to examine the effectiveness of this drug in PSC.

Obeticholic acid

In 2016, obeticholic acid (OCA, Intercept Pharmaceuticals, New York City, New York, United States) was approved for use in primary biliary cholangitis, a cholestatic liver disease of presumed autoimmune origin that afflicts the interlobular and septal bile ducts; it is currently undergoing investigation in PSC (NCT02177136) [36]. OCA, a ligand for the farnesoid X receptor (FXR), has over 100 times greater potency for FXR than its endogenous analog, chenodeoxycholic acid [37]. OCA is postulated to reduce toxic bile production and induce secretion through FXR-mediated pathways. FXR is expressed in the liver and the small intestine (highest levels in the terminal ileum) [5]. Activation of FXR inhibits CYP7A1 (the rate limiting step of bile acid production) both directly, through translational activation of the short heterodimer protein (SHP), as well as indirectly, through the release of fibroblast growth factor (FGF)-19, which binds to FGF-4 on hepatocytes and leads to additional CYP7A1 inhibition [5,38,39]. OCA also decreases exposure to toxic bile

by upregulating BSEP, MDR2/3, MRP2 and OST α/β , which leads to increased canalicular bile secretion [40–42]. And finally, OCA also induces the expression of SULT2A1 and UGT1A1 [43,44]. These processes combined should limit hepatocyte accumulation of toxic bile acids, thereby reducing liver injury and potentially ameliorating the pathogenesis of PSC.

Fibrates

Fibrates are peroxisome proliferator-activated receptor (PPAR) agonists that were originally designed for treatment of hyperlipidemia and have recently been reviewed as potential therapies in cholestatic liver disease [45]. Each fibrate has a different affinity for individual PPAR receptors, of which there are three isoforms (α , β/δ and γ), with bezafibrate having equal activity with all three isoforms and fenofibrate having 10-fold higher selectivity for PPAR- α than PPAR- γ [46]. PPARs act as ligand-activated transcription factors, and once activated, they form a heterodimer with the retinoid X receptor and bind distinct DNA-response elements [45]. Similar to OCA, fibrates can downregulate bile acid synthesis (by suppressing CYP7A1 and CYP27A1) and stimulate canalicular secretion (by increasing expression of MDR2/3, MRP2) [45]. Fibrates may also act similarly to *norUDCA* by upregulating bile acid detoxification enzymes such as UGT1A1 and SULT2A1 [45].

Two pilot studies evaluating the efficacy of fibrates in PSC have been published [47,48]. Together, these include 21 patients treated over 6–12 months. Patients demonstrated significant decreases in ALP, with adverse events that included myalgias, nausea and worsening of psoriasis. Larger, placebo-controlled studies are warranted.

Apical sodium bile acid transporter inhibitors

Bile acids undergo enterohepatic circulation, with reabsorption of more than 95% of bile acids occurring at the terminal ileum via ASBT in the brush border membrane [49]. Two animal studies involving *Mdr2*^{-/-} mice have demonstrated that ASBT inhibitors reduce serum bile acid levels and profibrogenic gene expression, while improving hepatic biochemical profiles (i.e. ALP and ALT) [50,51]. A phase 2 study of an ASBT inhibitor (SHP625/Lum001; Lumena Pharmaceuticals, San Diego, California, United States) in PSC demonstrated significant reductions in bile acids from baseline, but no significant change in ALP and other liver biochemistries (NCT02061540) [52].

Antimicrobial therapy and modulation of the microbiome: the 'leaky gut' hypothesis

Failure of the intestinal barrier is posited to lead to bacterial translocation into the classically sterile portal and biliary system via the gut-liver axis, thereby exposing biliary epithelium to foreign microbial antigens [53]. Supportive evidence for this hypothesis includes studies demonstrating the presence of bacteria in the bile of explanted livers, as well as the presence of *Helicobacter pylori* in hilar hepatic ducts and antibodies against Chlamydia species lipopolysaccharide in the sera of PSC patients [54–57].

Exposure to bacterial products triggers pattern recognition receptors such as Toll-like receptors, causing cholangiocytes to assume an activated phenotype, leading to the release of cytokines and chemokines like TNF- α , IL-6 and IL-8, as well as growth factors and other

signaling molecules [58]. This proinflammatory state may precipitate cholestasis and periductular fibrosis [58].

In turn, bacteria that comprise the intestinal microbiome may be influenced by bile composition. Recently, it has been demonstrated that increases in taurocholic acid secretion induced by a diet high in milk-fat may potentiate an abundance of *Bilophila wadsworthia*, a sulphate-reducing bacteria associated with ulcerative colitis [59]. This suggests that changes in bile acid composition may alter the intestinal microbiota and lead to dysbiosis, an aberrant microbial ecology that may cause disease through alterations in immune homeostasis [60].

In addition to their antimicrobial effects, antibiotics such as minocycline have been shown to have anti-inflammatory properties that may provide additional therapeutic actions in PSC. The clinical efficacy of vancomycin with metronidazole (NCT01085760) or without metronidazole (NCT01802073, NCT02605213 and NCT02137668), minocycline and rifaximin (Salix Pharmaceuticals, Raleigh, North Carolina, United States) have all been under recent or current investigation.

Vancomycin has been evaluated in three studies (total patients: 14 pediatric, 17 adult) in doses ranging from 50 mg/kg/day (pediatric, treatment for mean 54±43 months) to 150mg three to four times daily (adult, treatment for 12 weeks) [61,62]. The latter study also investigated metronidazole 250 or 500 mg three times daily. In children, vancomycin was associated with a reduction in ALT and gamma-glutamyl transferase (GGT). In adults, both doses were associated with decreased ALP. Counter-intuitively, only low-dose vancomycin and metronidazole led to decreased bilirubin and Mayo PSC risk scores.

In an open-label study evaluating rifaximin (550-g bid) in 16 patients over 12 weeks, there were no significant improvements in serum ALP, bilirubin, GGT or Mayo PSC risk score [63]. Conversely, an open-label study of minocycline (100-mg bid) over 1 year demonstrated a significant improvement in serum ALP and Mayo PSC risk score, with no changes in bilirubin or albumin [64]. Minocycline's therapeutic effects may be in part because of its antiinflammatory and antiapoptotic properties [65]. It can also decrease inducible nitric oxide synthase, which is overexpressed in PSC and deleterious to cholangiocytes, and it also upregulates IL-10, a potent anti-inflammatory cytokine that limits auto-reactivity [66–69].

Fecal microbiota transplantation, probiotics and beyond

If modulation of the microbiome becomes a key component in the therapeutic arsenal for PSC, it is likely paramount that it is targeted toward the development of distinct intestinal microbial profiles, rather than a broad-spectrum destruction of the resident flora. This is exemplified by a recent study demonstrating that germ-free *Mdr2^{-/-}* mice have worsening fibrosis, ductular reaction and ductopenia, with higher ALP, AST and bilirubin compared with conventionally caged mice [70]. Senescence, which has been implicated in the pathogenesis of PSC, was also worse in germ-free models and was abrogated by the addition of UDCA, a metabolite of commensal flora. This demonstrates that microbial metabolites may play a vital protective role in preventing injury to the biliary epithelium, suggesting that

an alternative route to novel PSC therapeutics may involve targeted modification of metabolomics profiles which in healthy hosts are normally microbially derived.

Another major concern regarding antibiotic therapy is the evolution of antibiotic resistance, such as vancomycin-resistant enterococcus [71,72]. Ideally, future clinical trials will include studies to elucidate specific microbial metabolic pathways that could be targeted, thus eliminating the need for chronic antimicrobial treatment.

Future therapies may also include fecal microbiota transplantation (FMT) (NCT02424175) or the use of probiotics (NCT00161148). Fecal transplantation has been shown to be effective for diarrhea due to recurrent *Clostridium difficile*, but the long-term consequences of this approach are unclear [73]. Similarly, pooled data from two randomized controlled studies involving patients with ulcerative colitis suggest that FMT may be of benefit; however, randomized, placebo-controlled studies are needed to further validate its effectiveness in inflammatory bowel disease (IBD) [74■].

Immunomodulatory agents: the ‘aberrant gut lymphocyte’ hypothesis

The hypothesis postulates that intestinally derived lymphocytes aberrantly express receptors that allow for recruitment to the hepatobiliary system in which they incite a proinflammatory cascade [75]. Mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1), an endothelial cell adhesion molecule expressed on mesenteric lymph nodes and in vessels of the lamina propria of the intestinal milieu, may be integral to this aberrant signaling process [76]. MAdCAM-1 permits the recruitment of lymphocytes into the intestinal mucosa by binding to the $\alpha 4\beta 7$ integrin and has been implicated in IBD pathogenesis [77]. MAdCAM-1 is not constitutively expressed in the liver, but it appears to be inappropriately expressed on liver endothelium in PSC [76]. This allows gut-derived lymphocytes traveling through the enterohepatic circulation to bind to cholangiocytes, then infiltrate and incite local inflammation [75]. The adhesion of lymphocytes is further potentiated by vascular adhesion protein-1 (VAP-1), which is constitutively expressed on hepatic endothelial cells and upregulated in individuals with IBD [76,78].

There have been a number of molecules developed for IBD that may have a therapeutic effect in PSC. One of the first was natalizumab (Biogen, Cambridge, Massachusetts, United States), which targets the $\alpha 4$ integrin and can associate with either $\beta 1$, which can bind to vascular cell adhesion molecule 1, or $\beta 7$, which can bind to MAdCAM-1 [79]. Unfortunately, natalizumab caused reactivation of the John Cunningham virus leading to progressive multifocal leukoencephalopathy (attributed to the inhibition of $\alpha 4\beta 1$) and has since been discontinued [80,81]. Studies evaluating vercirnon, a CCR9 inhibitor (ChemoCentryx, Mountain View, California, United States), failed to consistently reach primary endpoints in Crohn's disease, and so further drug development has ceased [82]. Therapies currently under investigation for IBD, which may gain relevance in PSC, are etrolizumab (a monoclonal antibody against $\beta 7$) (NCT01461317 and NCT02394028) (Roche Holding AG, Basel, Switzerland) and PF-00547659 (a selective inhibitor of MAdCAM-1; Shire Pharmaceuticals, St. Helier, Jersey) [83–85]. Vedolizumab (a mAb against the $\alpha 4\beta 7$ integrin; Takeda Pharmaceutical Company Limited, Chuo-ku, Osaka, Japan) was approved by the Federal Drug Administration for ulcerative colitis and Crohn's

disease in 2014 and is currently under investigation for PSC (EudraCT2014-003942-28) [86–88]. BTT1023 (Biotie Therapies, Turku, Finland), an inhibitor against VAP-1, is also currently under investigation (NCT02239211).

Antifibrogenic therapies

The evolving interest in antifibrogenic therapies in noncholestatic liver disease has naturally given rise to investigations into their utility in cholestatic liver disease.

Chemokine receptor 2/chemokine receptor 5 inhibitors

Chemokine receptor 2 (CCR2) and chemokine receptor 5 (CCR5) are instrumental to liver fibrogenesis [89]. Located on monocytes/macrophages, Kupffer cells and hepatic stellate cells (HSC), they bind chemokine ligand type 2 and 5, leading to release of TNF- β , which then stimulates collagen production by activated HSCs [90■]. Cenicriviroc, a dual CCR2/CCR5 antagonist (Takeda Pharmaceutical Company Limited, Chuo-ku, Osaka, Japan and Tobira Therapeutics, San Francisco, California, United States), is currently under investigation for PSC (NCT02653625).

Simtuzumab

Simtuzumab (Gilead Sciences, Foster City, California, United States) is a mAb against *LOXL2*, an enzyme that promotes the formation of cross-linkages between collagen fibers as well as the activation and recruitment of fibroblasts [91]. It is increased in hepatitis B, hepatitis C, NASH and animal models of liver fibrosis [92,93■]. A randomized, placebo-controlled trial was recently completed, and published results are pending (NCT01672853), but given preliminary results, further drug development is on hold [94■].

Conclusion

There are a number of pharmacologic therapies under development or in clinical trials for PSC, which target the different proposed pathogenic pathways. The future of PSC treatment is highly promising, though it is important that future studies integrate biomarker discovery into their design, given the lack of clarity around the ideal surrogate endpoint in PSC, as well as tools to improve risk stratification.

Acknowledgments

None.

Financial support and sponsorship The authors have no conflicts of interest relevant to this article. This work was supported by NIH grants DK63947 (to G.J.G.), NIH/NIDDK DK57993 and the Mayo Center for Cell Signaling in Gastroenterology grant DK84567 (P30) (to N.F.L.), DK84960 (to K.N.L.), the Chris M. Carlos and Catharine N. Jockisch Carlos Foundation for PSC, and the Mayo Clinic.

References and Recommended Reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■ ■ of outstanding interest

- 1 ■ Lazaridis KN, LaRusso NF. Primary sclerosing cholangitis. *N Engl J Med.* 2016; 375:1161–1170. This is a review of the management, proposed pathogenesis and management of primary sclerosing cholangitis (PSC) in adults. [PubMed: 27653566]
- 2 ■ Mieli-Vergani G, Vergani D. Sclerosing cholangitis in children and adolescents. *Clin Liver Dis.* 2016; 20:99–111. This is a review of the management, proposed pathogenesis and management of sclerosing cholangitis in the pediatric population, which includes a discussion regarding patients with overlapping features of autoimmune hepatitis. [PubMed: 26593293]
- 3 ■ Singal AK, Fang X, Kaif M, et al. Primary biliary cirrhosis has high wait-list mortality among patients listed for liver transplantation. *Transpl Int.* 2016 [Epub ahead of print] This study highlights the mortality rate for patients with PSC on the transplant waitlist, which remains relatively high given that it is the only treatment option currently available.
- 4 ■ Gordon FD, Goldberg DS, Goodrich NP, et al. Recurrent primary sclerosing cholangitis in the Adult-to-Adult Living Donor Liver Transplantation Cohort Study: comparison of risk factors between living and deceased donor recipients. *Liver Transpl.* 2016; 22:1214–1222. This study demonstrates that a significant number of patients with PSC will develop recurrent disease following liver transplantation, which is critically important given that many will require retransplantation. [PubMed: 27339253]
5. Fickert P, Pollheimer MJ, Beuers U, et al. Characterization of animal models for primary sclerosing cholangitis (PSC). *J Hepatol.* 2014; 60:1290–1303. [PubMed: 24560657]
- 6 ■ ■ Ponsoen CY, Chapman RW, Chazouilleres O, et al. Surrogate endpoints for clinical trials in primary sclerosing cholangitis: review and results from an International PSC Study Group consensus process. *Hepatology.* 2016; 63:1357–1367. This article highlights the critical importance of including the exploration and validation of surrogate markers in drug development and clinical trials. Through a Delphi consensus process, it was determined that histology, alkaline phosphatase (ALP) and transient elastography are the key surrogate markers available to date, but even these require further validation. [PubMed: 26418478]
7. Kim WR, Therneau TM, Wiesner RH, et al. A revised natural history model for primary sclerosing cholangitis. *Mayo Clin Proc.* 2000; 75:688–694. [PubMed: 10907383]
8. Hofmann AF. The continuing importance of bile acids in liver and intestinal disease. *Arch Intern Med.* 1999; 159:2647–2658. [PubMed: 10597755]
9. Bouscarel B, Fromm H, Nussbaum R. Ursodeoxycholate mobilizes intracellular Ca^{2+} and activates phosphorylase a in isolated hepatocytes. *Am J Physiol.* 1993; 264:G243–G251. [PubMed: 8447407]
10. Bouscarel B, Gettys TW, Fromm H, et al. Ursodeoxycholic acid inhibits glucagon-induced cAMP formation in hamster hepatocytes: a role for PKC. *Am J Physiol.* 1995; 268:G300–G310. [PubMed: 7864127]
11. Schliess F, Kurz AK, vom Dahl S, et al. Mitogen-activated protein kinases mediate the stimulation of bile acid secretion by tauroursodeoxycholate in rat liver. *Gastroenterology.* 1997; 113:1306–1314. [PubMed: 9322526]
12. Haussinger D, Kurz AK, Wettstein M, et al. Involvement of integrins and Src in tauroursodeoxycholate-induced and swelling-induced choleresis. *Gastroenterology.* 2003; 124:1476–1487. [PubMed: 12730886]
13. Paumgartner G, Beuers U. Mechanisms of action and therapeutic efficacy of ursodeoxycholic acid in cholestatic liver disease. *Clin Liver Dis.* 2004; 8:67–81. vi. [PubMed: 15062194]
14. Jazrawi RP, de Caestecker JS, Goggin PM, et al. Kinetics of hepatic bile acid handling in cholestatic liver disease: effect of ursodeoxycholic acid. *Gastroenterology.* 1994; 106:134–142. [PubMed: 8276175]
15. Beuers U, Hohenester S, de Buy Wenniger LJ, et al. The biliary HCO₃⁻ umbrella: a unifying hypothesis on pathogenetic and therapeutic aspects of fibrosing cholangiopathies. *Hepatology.* 2010; 52:1489–1496. [PubMed: 20721884]
16. Ellis E, Axelson M, Abrahamsson A, et al. Feedback regulation of bile acid synthesis in primary human hepatocytes: evidence that CDCA is the strongest inhibitor. *Hepatology.* 2003; 38:930–938. [PubMed: 14512880]

17. Chapman R, Fevery J, Kalloo A, et al. Diagnosis and management of primary sclerosing cholangitis. *Hepatology*. 2010; 51:660–678. [PubMed: 20101749]
18. European Association for the Study of the Liver. EASL clinical practice guidelines: management of cholestatic liver diseases. *J Hepatol*. 2009; 51:237–267. [PubMed: 19501929]
19. Lindor KD, Kowdley KV, Luketic VA, et al. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. *Hepatology*. 2009; 50:808–814. [PubMed: 19585548]
20. Lindor KD. Ursodiol for primary sclerosing cholangitis. Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. *N Engl J Med*. 1997; 336:691–695. [PubMed: 9041099]
21. Mitchell SA, Bansl DS, Hunt N, et al. A preliminary trial of high-dose ursodeoxycholic acid in primary sclerosing cholangitis. *Gastroenterology*. 2001; 121:900–907. [PubMed: 11606503]
22. Stanich PP, Bjornsson E, Gossard AA, et al. Alkaline phosphatase normalization is associated with better prognosis in primary sclerosing cholangitis. *Dig Liver Dis*. 2011; 43:309–313. [PubMed: 21251891]
23. Lindstrom L, Hultcrantz R, Boberg KM, et al. Association between reduced levels of alkaline phosphatase and survival times of patients with primary sclerosing cholangitis. *Clin Gastroenterol Hepatol*. 2013; 11:841–846. [PubMed: 23353641]
24. Rupp C, Rossler A, Halibasic E, et al. Reduction in alkaline phosphatase is associated with longer survival in primary sclerosing cholangitis, independent of dominant stenosis. *Aliment Pharmacol Ther*. 2014; 40:1292–1301. [PubMed: 25316001]
25. Hilscher M, Enders FB, Carey EJ, et al. Alkaline phosphatase normalization is a biomarker of improved survival in primary sclerosing cholangitis. *Ann Hepatol*. 2016; 15:246–253. This retrospective cohort study demonstrated that normalization of alkaline phosphatase can occur in nearly 50% of patients with PSC within a year of diagnosis, and that this is an independent predictor of transplant-free and neoplasia-free survival. [PubMed: 26845602]
26. Lindor KD, Kowdley KV, Harrison ME, et al. ACG clinical guideline: primary sclerosing cholangitis. *Am J Gastroenterol*. 2015; 110:646–659. quiz 660. [PubMed: 25869391]
27. Tabibian JH, Lindor KD. Ursodeoxycholic acid in primary sclerosing cholangitis: if withdrawal is bad, then administration is good (right?). *Hepatology*. 2014; 60:785–788. [PubMed: 24752961]
28. Turan S, Topcu B, Gokce I, et al. Serum alkaline phosphatase levels in healthy children and evaluation of alkaline phosphatase z-scores in different types of rickets. *J Clin Res Pediatr Endocrinol*. 2011; 3:7–11. [PubMed: 21448327]
29. Beuers U, Trauner M, Jansen P, et al. New paradigms in the treatment of hepatic cholestasis: from UDCA to FXR, PXR and beyond. *J Hepatol*. 2015; 62:S25–37. [PubMed: 25920087]
30. Hofmann AF, Zakko SF, Lira M, et al. Novel biotransformation and physiological properties of norursodeoxycholic acid in humans. *Hepatology*. 2005; 42:1391–1398. [PubMed: 16317695]
31. Gurantz D, Schteingart CD, Hagey LR, et al. Hypercholerisis induced by unconjugated bile acid infusion correlates with recovery in bile of unconjugated bile acids. *Hepatology*. 1991; 13:540–550. [PubMed: 1999323]
32. Kip NS, Lazaridis KN, Masyuk AI, et al. Differential expression of cholangiocyte and ileal bile acid transporters following bile acid supplementation and depletion. *World J Gastroenterol*. 2004; 10:1440–1446. [PubMed: 15133850]
33. Fickert P, Wagner M, Marschall HU, et al. 24-norUrsodeoxycholic acid is superior to ursodeoxycholic acid in the treatment of sclerosing cholangitis in Mdr2 (Abcb4) knockout mice. *Gastroenterology*. 2006; 130:465–481. [PubMed: 16472600]
34. Trauner M, Fickert P, Hirschfield G, et al. Norursodeoxycholic acid improves cholestasis in primary sclerosing cholangitis: results of a phase II dose finding study. *J Hepatol*. 2015; 64:S208–S209.
35. Hirschfield GM, Mason A, Luketic V, et al. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. *Gastroenterology*. 2015; 148:751–761. ; e8. [PubMed: 25500425]
36. Pellicciari R, Fiorucci S, Camaioni E, et al. 6 α -ethyl-chenodeoxycholic acid (6-ECDCA), a potent and selective FXR agonist endowed with anticholestatic activity. *J Med Chem*. 2002; 45:3569–3572. [PubMed: 12166927]

37. Schaap FG, Trauner M, Jansen PL. Bile acid receptors as targets for drug development. *Nat Rev Gastroenterol Hepatol*. 2014; 11:55–67. [PubMed: 23982684]
38. Thomas C, Pellicciari R, Pruzanski M, et al. Targeting bile-acid signalling for metabolic diseases. *Nat Rev Drug Discov*. 2008; 7:678–693. [PubMed: 18670431]
39. Inagaki T, Choi M, Moschetta A, et al. Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. *Cell Metab*. 2005; 2:217–225. [PubMed: 16213224]
40. Ananthanarayanan M, Balasubramanian N, Makishima M, et al. Human bile salt export pump promoter is transactivated by the farnesoid X receptor/bile acid receptor. *J Biol Chem*. 2001; 276:28857–28865. [PubMed: 11387316]
41. Boyer JL, Trauner M, Mennone A, et al. Upregulation of a basolateral FXR-dependent bile acid efflux transporter OSTalpha-OSTbeta in cholestasis in humans and rodents. *Am J Physiol Gastrointest Liver Physiol*. 2006; 290:G1124–G1130. [PubMed: 16423920]
42. Kast HR, Goodwin B, Tarr PT, et al. Regulation of multidrug resistance-associated protein 2 (ABCC2) by the nuclear receptors pregnane X receptor, farnesoid X-activated receptor, and constitutive androstane receptor. *J Biol Chem*. 2002; 277:2908–2915. [PubMed: 11706036]
43. Song CS, Echchgadda I, Baek BS, et al. Dehydroepiandrosterone sulfo-transferase gene induction by bile acid activated farnesoid X receptor. *J Biol Chem*. 2001; 276:42549–42556. [PubMed: 11533040]
44. Edwards J, Zhang Y, Jackson J, et al. Obeticholic acid does not affect the hepatic metabolism of hormonal birth control in human sandwich cultured hepatocytes. *Hepatology*. 2016; 64:201A–202A. This abstract demonstrates that obetichoic acid increases transcription of UGT1A1.
45. Ghonem NS, Assis DN, Boyer JL. Fibrates cholestasis. *Hepatology*. 2015; 62:635–643. [PubMed: 25678132]
46. Willson TM, Brown PJ, Sternbach DD, et al. The PPARs: from orphan receptors to drug discovery. *J Med Chem*. 2000; 43:527–550. [PubMed: 10691680]
47. Chazouilleres O, Corpechot C, Gaovar F, et al. Fenofibrate improves liver tests in primary sclerosing cholangitis with incomplete response to ursodeoxycholic acid. *Hepatology*. 2010; 52:488A.
48. Dejman A, Clark V, Martin P, et al. Fenofibrate improves alkaline phosphatase in primary sclerosing cholangitis. *Gastroenterology*. 2013; 144:S1028–S1029.
49. Dawson PA, Lan T, Rao A. Bile acid transporters. *J Lipid Res*. 2009; 50:2340–2357. [PubMed: 19498215]
50. Baghdasaryan A, Fuchs CD, Osterreicher CH, et al. Inhibition of intestinal bile acid absorption improves cholestatic liver and bile duct injury in a mouse model of sclerosing cholangitis. *J Hepatol*. 2016; 64:674–681. This study of *Mdr2*^{-/-} mice demonstrated that pharmacologic inhibition of apical sodium bile acid transporter (ASBT) results in a reduction of bile acid secretion, ALP, aspartate aminotransferase, hepatic expression of proinflammatory and profibrogenic markers, leading to decreased histologic evidence of bile duct injury and fibrosis. [PubMed: 26529078]
51. Miethke AG, Zhang W, Simmons J, et al. Pharmacological inhibition of apical sodium-dependent bile acid transporter changes bile composition and blocks progression of sclerosing cholangitis in multidrug resistance 2 knockout mice. *Hepatology*. 2016; 63:512–523. This study of *Mdr2*^{-/-} mice recapitulated the same findings as the above study. [PubMed: 26172874]
52. Shire Pharmaceuticals. Dublin: Shire Pharmaceuticals; 2016 Apr 29. Shire delivers strong Q1 2016 results with double-digit growth in revenue and Non GAAP earnings per ADS. press release <https://www.shire.com/-/media/shire/shireglobal/shirecom/pdffiles/newsroom/2016/q1-2016-er-2016-04-29.pdf> In a press release, Shire outlined the results of their open-label phase 2 investigating the use of an ASBT inhibitor in PSC, which demonstrated that patients had significant decreases in serum bile acids and pruritus scores, but not in ALP or other liver function tests [Accessed 15 December 2016]
53. Tabibian JH, O'Hara SP, Lindor KD. Primary sclerosing cholangitis and the microbiota: current knowledge and perspectives on etiopathogenesis and emerging therapies. *Scand J Gastroenterol*. 2014; 49:901–908. [PubMed: 24990660]

54. Olsson R, Bjornsson E, Backman L, et al. Bile duct bacterial isolates in primary sclerosing cholangitis: a study of explanted livers. *J Hepatol*. 1998; 28:426–432. [PubMed: 9551680]
55. Krasinskas AM, Yao Y, Randhawa P, et al. *Helicobacter pylori* may play a contributory role in the pathogenesis of primary sclerosing cholangitis. *Dig Dis Sci*. 2007; 52:2265–2270. [PubMed: 17393314]
56. Ponsioen CY, Defoer J, Ten Kate FJ, et al. A survey of infectious agents as risk factors for primary sclerosing cholangitis: are Chlamydia species involved? *Eur J Gastroenterol Hepatol*. 2002; 14:641–648. [PubMed: 12072598]
57. Bjornsson ES, Kilander AF, Olsson RG. Bile duct bacterial isolates in primary sclerosing cholangitis and certain other forms of cholestasis – a study of bile cultures from ERCP. *Hepatogastroenterology*. 2000; 47:1504–1508. [PubMed: 11148988]
58. O'Hara SP, Tabibian JH, Splinter PL, et al. The dynamic biliary epithelia: molecules, pathways, and disease. *J Hepatol*. 2013; 58:575–582. [PubMed: 23085249]
59. Rowan FE, Docherty NG, Coffey JC, et al. Sulphate-reducing bacteria and hydrogen sulphide in the aetiology of ulcerative colitis. *Br J Surg*. 2009; 96:151–158. [PubMed: 19160346]
60. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev Immunol*. 2009; 9:313–323. [PubMed: 19343057]
61. Davies YK, Cox KM, Abdullah BA, et al. Long-term treatment of primary sclerosing cholangitis in children with oral vancomycin: an immunomodulating antibiotic. *J Pediatr Gastroenterol Nutr*. 2008; 47:61–67. [PubMed: 18607270]
62. Tabibian JH, Weeding E, Jorgensen RA, et al. Randomised clinical trial: vancomycin or metronidazole in patients with primary sclerosing cholangitis – a pilot study. *Aliment Pharmacol Ther*. 2013; 37:604–612. [PubMed: 23384404]
63. Tabibian JH, Gossard A, El-Youssef M, et al. Prospective clinical trial of rifaximin therapy for patients with primary sclerosing cholangitis. *Am J Ther*. 2017; 24:e56–e63. In this 12-week, open-label pilot study of rifaximin in patients with PSC, there was no significant change in ALP or other liver function tests, suggesting that rifaximin may not be an effective treatment in PSC, possibly due to its indiscriminate effects on the intestinal microbiota. [PubMed: 24914504]
64. Silveira MG, Torok NJ, Gossard AA, et al. Minocycline in the treatment of patients with primary sclerosing cholangitis: results of a pilot study. *Am J Gastroenterol*. 2009; 104:83–88. [PubMed: 19098854]
65. Garrido-Mesa N, Zarzuelo A, Galvez J. Minocycline: far beyond an antibiotic. *Br J Pharmacol*. 2013; 169:337–352. [PubMed: 23441623]
66. Amin AR, Attur MG, Thakker GD, et al. A novel mechanism of action of tetracyclines: effects on nitric oxide synthases. *Proc Natl Acad Sci U S A*. 1996; 93:14014–14019. [PubMed: 8943052]
67. Jaiswal M, LaRusso NF, Burgart LJ, et al. Inflammatory cytokines induce DNA damage and inhibit DNA repair in cholangiocarcinoma cells by a nitric oxide-dependent mechanism. *Cancer Res*. 2000; 60:184–190. [PubMed: 10646872]
68. Ledebor A, Sloane EM, Milligan ED, et al. Minocycline attenuates mechanical allodynia and proinflammatory cytokine expression in rat models of pain facilitation. *Pain*. 2005; 115:71–83. [PubMed: 15836971]
69. Henriksen EK, Melum E, Karlsen TH. Update on primary sclerosing cholangitis genetics. *Curr Opin Gastroenterol*. 2014; 30:310–319. [PubMed: 24565892]
70. Tabibian JH, O'Hara SP, Trussoni CE, et al. Absence of the intestinal microbiota exacerbates hepatobiliary disease in a murine model of primary sclerosing cholangitis. *Hepatology*. 2016; 63:185–196. This murine study utilizing the *Mdr2*^{-/-} model demonstrated that the commensal intestinal microbiota play a crucial role in preventing biliary injury, and that microbial metabolites may be implicated in this process. Novel pathogenic pathways and corresponding biomarkers and therapeutics may be derived from further investigations into the unique role of the intestinal microbiota in biliary homeostasis. [PubMed: 26044703]
71. O'Driscoll T, Crank CW. Vancomycin-resistant enterococcal infections: epidemiology, clinical manifestations, and optimal management. *Infect Drug Resist*. 2015; 8:217–230. [PubMed: 26244026]

72. Jones RN. The impact of antimicrobial resistance: changing epidemiology of community-acquired respiratory-tract infections. *Am J Health Syst Pharm.* 1999; 56:S4–11.
73. Koenigsnecht MJ, Young VB. Faecal microbiota transplantation for the treatment of recurrent *Clostridium difficile* infection: current promise and future needs. *Curr Opin Gastroenterol.* 2013; 29:628–632. [PubMed: 24100717]
74. Moayyedi P. Fecal transplantation: any real hope for inflammatory bowel disease? *Curr Opin Gastroenterol.* 2016; 32:282–286. This systematic review summarizes the evidence available for the use of fecal microbiota transplantation in inflammatory bowel disease, which, to date, is limited to two clinical trial in ulcerative colitis and four case series in Crohn's disease, highlighting the need for additional controlled randomized clinical trials. [PubMed: 27152872]
75. Adams DH, Eksteen B. Aberrant homing of mucosal T cells and extra-intestinal manifestations of inflammatory bowel disease. *Nat Rev Immunol.* 2006; 6:244–251. [PubMed: 16498453]
76. Grant AJ, Lalor PF, Hubscher SG, et al. MAdCAM-1 expressed in chronic inflammatory liver disease supports mucosal lymphocyte adhesion to hepatic endothelium (MAdCAM-1 in chronic inflammatory liver disease). *Hepatology.* 2001; 33:1065–1072. [PubMed: 11343233]
77. Briskin M, Winsor-Hines D, Shyjan A, et al. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. *Am J Pathol.* 1997; 151:97–110. [PubMed: 9212736]
78. Salmi M, Kalimo K, Jalkanen S. Induction and function of vascular adhesion protein-1 at sites of inflammation. *J Exp Med.* 1993; 178:2255–2260. [PubMed: 8245796]
79. Ghosh S, Goldin E, Gordon FH, et al. Natalizumab for active Crohn's disease. *N Engl J Med.* 2003; 348:24–32. [PubMed: 12510039]
80. Adelman B, Sandrock A, Panzara MA. Natalizumab and progressive multifocal leukoencephalopathy. *N Engl J Med.* 2005; 353:432–433. [PubMed: 15947083]
81. Van Assche G, Van Ranst M, Scot R, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med.* 2005; 353:362–368. [PubMed: 15947080]
82. Wendt E, Keshav S. CCR9 antagonism: potential in the treatment of Inflammatory Bowel Disease. *Clin Exp Gastroenterol.* 2015; 8:119–130. [PubMed: 25897254]
83. Rosenfeld G, Parker CE, MacDonald JK, et al. Etrolizumab for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev.* 2015:CD011661.
84. D'Haens, G., Lee, S., Tarabar, D., et al. OP022 anti-MAdCAM-1 antibody (PF-00547659) for active refractory Crohn's disease: Results of the OPERA study. European Crohn's and Colitis Organization Conference, Journal of Crohn's and Colitis; Barcelona, Spain. 2015;
85. Vermeire, S., Sandborn, W., Danese, S., et al. OP021 TURANDOT: a randomized, multicenter double-blind, placebo-controlled study of the safety and efficacy of anti-MAdCAM antibody PF-00547659 (PF) in patients with moderate to severe ulcerative colitis (UC). European Crohn's and Colitis Organisation Conference, Journal of Crohn's and Colitis; Barcelona, Spain. 2015;
86. Federal Drug Administration (FDA). FDA approves Entyvio to treat ulcerative colitis and Crohn's disease. May 20.2014 news release.
87. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2013; 369:699–710. [PubMed: 23964932]
88. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med.* 2013; 369:711–721. [PubMed: 23964933]
89. Seki E, de Minicis S, Inokuchi S, et al. CCR2 promotes hepatic fibrosis in mice. *Hepatology.* 2009; 50:185–197. [PubMed: 19441102]
90. Lefebvre E, Moyle G, Reshef R, et al. Antifibrotic effects of the dual CCR2/CCR5 antagonist cenicriviroc in animal models of liver and kidney fibrosis. *PLoS One.* 2016; 11:e0158156. This study demonstrated that cenicriviroc (a dual chemokine receptor 2/chemokine receptor 5 antagonist), when used in three rodent models of fibrosis (thioglycollate-induced peritonitis, diet-induced nonalcoholic steatohepatitis and renal fibrosis), significantly reduced macrophage recruitment, collagen expression and deposition and thus may be useful in preventing disease progression in PSC. [PubMed: 27347680]

91. Barry-Hamilton V, Spangler R, Marshall D, et al. Allosteric inhibition of lysyl oxidase-like-2 impedes the development of a pathologic microenvironment. *Nat Med.* 2010; 16:1009–1017. [PubMed: 20818376]
92. Vadasz Z, Kessler O, Akiri G, et al. Abnormal deposition of collagen around hepatocytes in Wilson's disease is associated with hepatocyte specific expression of lysyl oxidase and lysyl oxidase like protein-2. *J Hepatol.* 2005; 43:499–507. [PubMed: 16023247]
- 93■ Ikenaga N, Peng ZW, Vaid KA, et al. Selective targeting of lysyl oxidase-like 2 (LOXL2) suppresses hepatic fibrosis progression and accelerates its reversal. *Gut.* 2017 Epub ahead of print. This murine study demonstrated that lysyl oxidase-like 2 (LOXL2) is overexpressed in fibrosis, with particularly high levels localized to fibrotic septa, with pharmacologic inhibition of LOXL2 leading to decreased collagen deposition and histologic evidence of fibrosis, as well as diminished ductular reaction, indicating that it may limit both hepatic and biliary fibrosis.
- 94■ Third Quarter 2016 Gilead Sciences Earnings Conference Call. [Accessed 7 January 2017] Gilead Sciences. Nov 1. 2016 <http://investors.gilead.com/phoenix.zhtml?-P=irol-eventDetails&c=69964&eventID=5237083>The results of the randomized, placebo-controlled clinical trial evaluating the safety and efficacy of simtuzumab are yet to be published; however, during a conference call to investors, it was stated that further drug development is on hold

Key Points

- PSC is an incurable, fibro-obliterative disease that affects the large bile ducts in the liver, the only treatment of which is currently liver transplant.
- Novel therapeutics under development target four proposed pathways of PSC pathogenesis: bile acid pool modulation, intestinal microbiome modification, immunomodulation of receptors that potentiate hepatic infiltration of gut-derived lymphocytes, and inhibition of fibrogenesis.
- The lack of a strong surrogate marker continues to hamper therapeutic development in PSC, as traditional clinical endpoints (i.e. decompensation, death and liver transplant) require infeasible follow-up times and cohort sizes.
- It is critical that future therapeutic studies include discovery and validation pathways for novel biomarkers and tools to stratify disease severity.

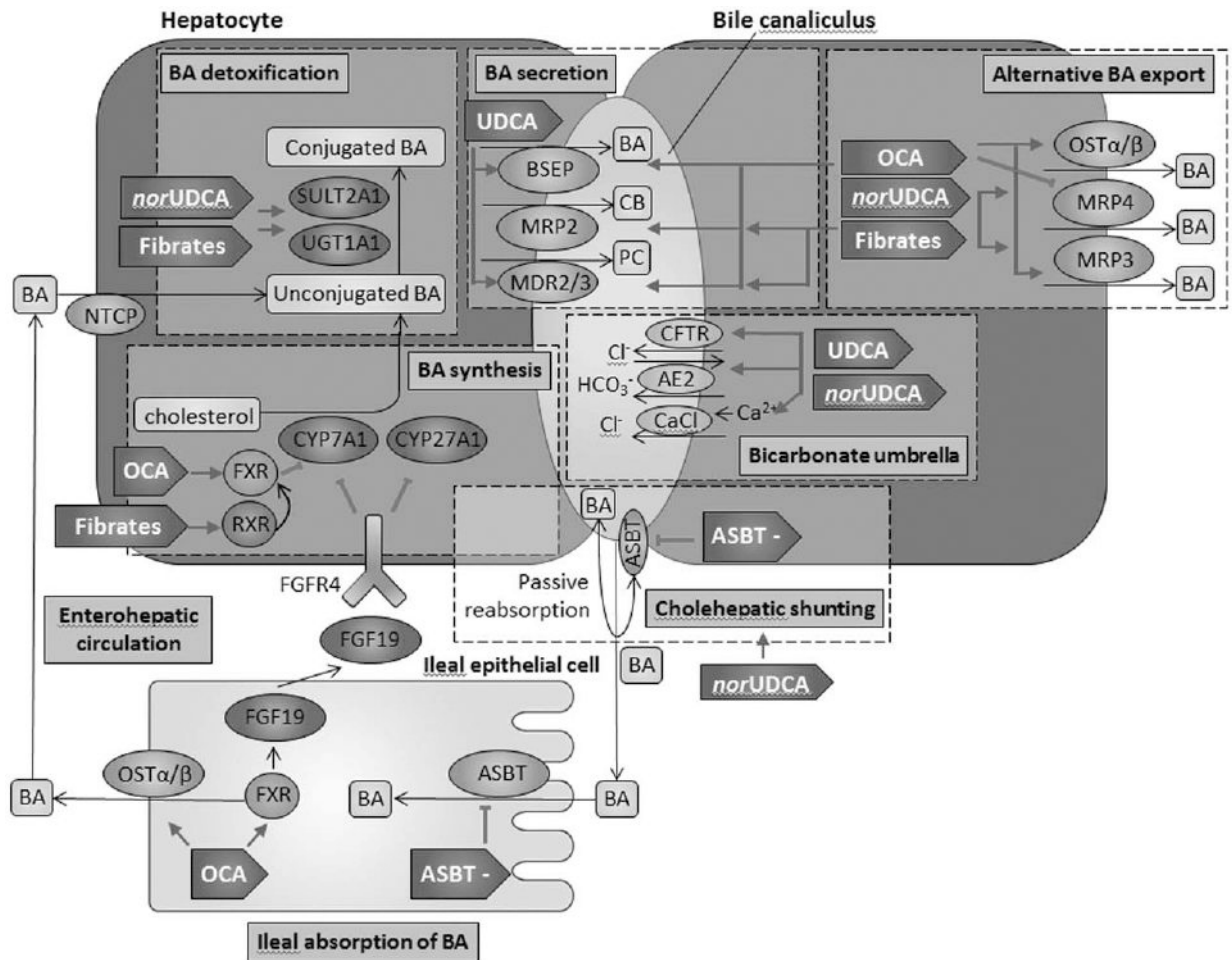


Figure 1.

Current and emerging therapies for primary sclerosing cholangitis that modulate bile acid synthesis, detoxification, secretion and reabsorption. AE2, $\text{Cl}^-/\text{HCO}_3^-$ anion exchanger 2; ASBT, apical sodium-bile acid transporter; ASBT⁻, apical sodium-bile acid transporter inhibitor; BA, bile acids; BSEP, bile salt export pump; CaCl , Ca^{2+} -dependent chloride channel; CB, conjugated bilirubin; CFTR, cystic fibrosis transmembrane conductance regulator; FGF19, fibroblast growth factor 19; FGFR4, fibroblast growth factor receptor 4; FXR, farnesoid X receptor; MDR2/3, multidrug resistance 2/3; MRP2, multidrug resistance-associated protein 2; MRP3, multidrug resistance-associated protein 3; MRP4, multidrug resistance-associated protein 4; NTCP, sodium/taurocholate cotransporting polypeptide; *nor*UDCA, 24-*nor*Ursodeoxycholic acid; OCA, obetichoic acid; OST α/β , organic solute transporter α/β ; PC, phosphatidylcholine; PSC, primary sclerosing cholangitis; RXR, retinoid X receptor; SULT2A1, sulfotransferase family 2A member 1; UDCA, ursodeoxycholic acid; UGT1A1, uridine diphosphate-glucuronosyltransferase family 1 member A1. Modified from [5].

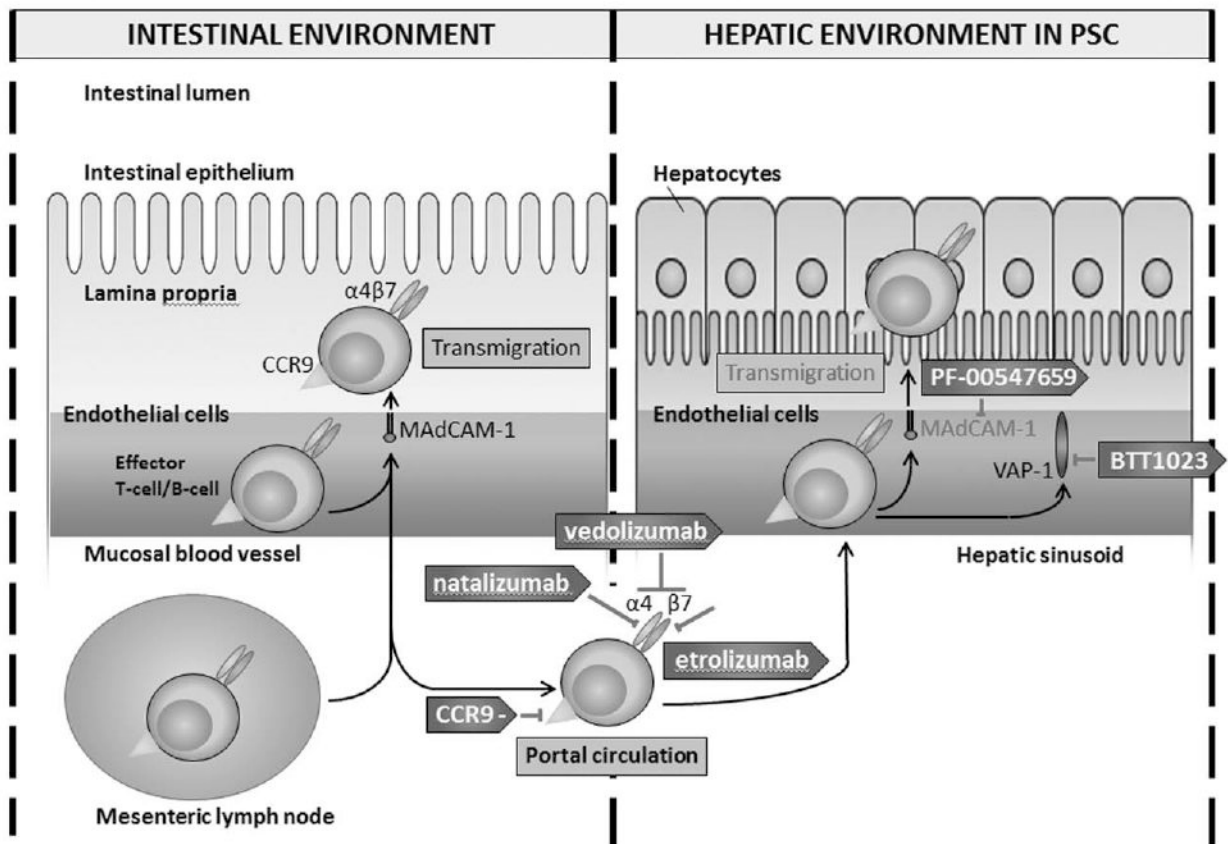


Figure 2.

Therapies that are proposed to inhibit the transmigration of gut-derived lymphocytes into the hepatic environment in primary sclerosing cholangitis. In primary sclerosing cholangitis, mucosal vascular addressin cell adhesion molecule 1 is aberrantly expressed. This allows aberrant binding and transmigration of gut-derived lymphocytes via $\alpha 4\beta 7$ integrin. Binding and transmigration is further enhanced by vascular adhesion protein-1, which is constitutively present on hepatic endothelial cells and allows lymphocyte recruitment. CCR9-, chemokine receptor 9 inhibitor; MAdCAM-1, mucosal vascular addressin cell adhesion molecule 1; PSC, primary sclerosing cholangitis; VAP-1, vascular adhesion protein-1.

Table 1
Potential therapeutics for primary sclerosing cholangitis that modulate bile acids

Process	Targets	Drug			
		UDCA	UDCA <i>nor</i>	OCA	Fibrates ASBT-
BA synthesis	FXR		✓		
	RXR				✓
	CYP7A1		✓		✓
	CYP27A1		✓		✓
BA detoxification	SULT2A1		✓		✓
	UGT1A1		✓		✓
BA secretion	BSEP	✓			
	MRP2			✓	✓
	MDR2/3			✓	✓
Alternative BA export	OST α / β			✓	
	MRP4		✓		✓
	MRP3		✓		✓
Bicarbonate umbrella	CFTR	✓			
	AE2	✓			
	CaCl	✓			

Process	Targets	Drug				
		UDCA	norUDCA	OCA	Fibrates	ASBT-
Cholehepatic shunting	ASBT					✓
Enterohepatic circulation	ASBT					✓
	FXR			✓		
	OST α/β (ileal)			✓		
	FGF19			✓		

Checkboxes indicate where each drug acts on individual targets. ASBT, apical sodium-bile acid transporter; ASBT⁻, apical sodium-bile acid transporter inhibitor; BA, bile acids; BSEP, bile salt export pump; CaCl₂, Ca²⁺-dependent chloride channel; CFTR, cystic fibrosis transmembrane conductance regulator; FXR, farnesoid X receptor; MDR2/3, multidrug resistance 2/3; MRP2, multidrug resistance-associated protein 2; MRP3, multidrug resistance-associated protein 3; MRP4, multidrug resistance-associated protein 4; norUDCA, 24-norursodeoxycholic acid; OCA, obeticholic acid; OST α/β , organic solute transporter α/β ; PSC, primary sclerosing cholangitis; RXR, retinoid X receptor; SULT2A1, sulfotransferase family 2A member 1; UDCA, ursodeoxycholic acid; UGT1A1, uridine diphosphate-glucuronosyltransferase family 1 member A1.