Future Therapies for Primary Sclerosing Cholangitis

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Introduction

Primary sclerosing cholangitis (PSC) is a hepatobiliary disorder characterized by bile duct destruction and hepatic fibrosis [1, 2]. It is a chronic liver disease with progression to cirrhosis and eventual liver failure [1–4]. It carries increased risk for bile duct, colorectal, and gallbladder cancer that appears to be unrelated to disease severity or stage [5–7]. There is heterogeneity in its presentation and often occurs in association with inflammatory bowel disease (IBD) [1, 2, 8, 9]. More recently, recognition of specific clinical subtypes of PSC has led to improved classification of the disease [10]. It is, therefore, imperative to recognize these clinically distinct phenotypes within the context of novel therapeutics for PSC.

A number of drugs such as colchicine, methotrexate, pencillamine, pirfenidone, azathioprine, tacrolimus, budesonide, and prednisolone have been studied in PSC patients to prevent disease progression [11]. Many of the studies that reported promising results initially were open label and performed in an uncontrolled fashion with a small number of patients. Subsequent randomized controlled trials with a larger size have unfortunately failed to reproduce the initial positive results. The most commonly studied agent is ursodeoxycholic acid (UDCA) and is believed to slow the progression of fibrosis in cholestatic liver disease based on literature from primary biliary cirrhosis clinical trials [12, 13]. The European Association for the Study of Liver (EASL) has no "specific recommendation for the general use of UDCA in PSC," whereas the American Association for the Study of Liver Diseases (AASLD) concluded that "in adult patients with PSC, we recommend against the use of UDCA,": both positions reflective of negative RCTs [14, 15]. A landmark, long-term, randomized, double-blind, placebo-controlled multi-center study using high-dose UDCA performed in the United States in 150 adults with PSC was terminated after 6 years as the frequency of adverse events (i.e., death, liver transplantation, cirrhosis, esophageal varices, and cholangiocarcinoma) was significantly higher in the active than in the placebo group, irrespective of biochemical improvement [16]. The increase in adverse events appeared to occur primarily in patients with the early stage disease compared with similar patients in the placebo group [17]. There are no current effective therapies for PSC, and unfortunately, none except dilation of biliary stricture by endoscopic retrograde cholangiography or liver transplantation have altered the course of the disease significantly [18]. Therefore, a significant unmet medical need still exists for

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novel agents for the treatment of PSC and its subsequent complications.

Pathogenesis and Opportunities for Therapeutic Targets

Significant breakthroughs in the understanding the mechanisms involved in liver injury have led to several promising therapeutic agents that are currently under evaluation. Due to common downstream mechanisms of liver injury and fibrogenesis, the same therapeutic agents are undergoing evaluation for chronic liver diseases of various etiologies. A brief overview of the pathophysiology is essential to understand the rationale for investigation of the novel therapies for the treatment of PSC (Fig. 12.1).

Gut-Liver Axis in PSC and IBD

The liver plays a critical role in the immune surveillance against bacterial translocation or absorption of bacterial endotoxins into the portal circulation. Since the intestinal and biliary

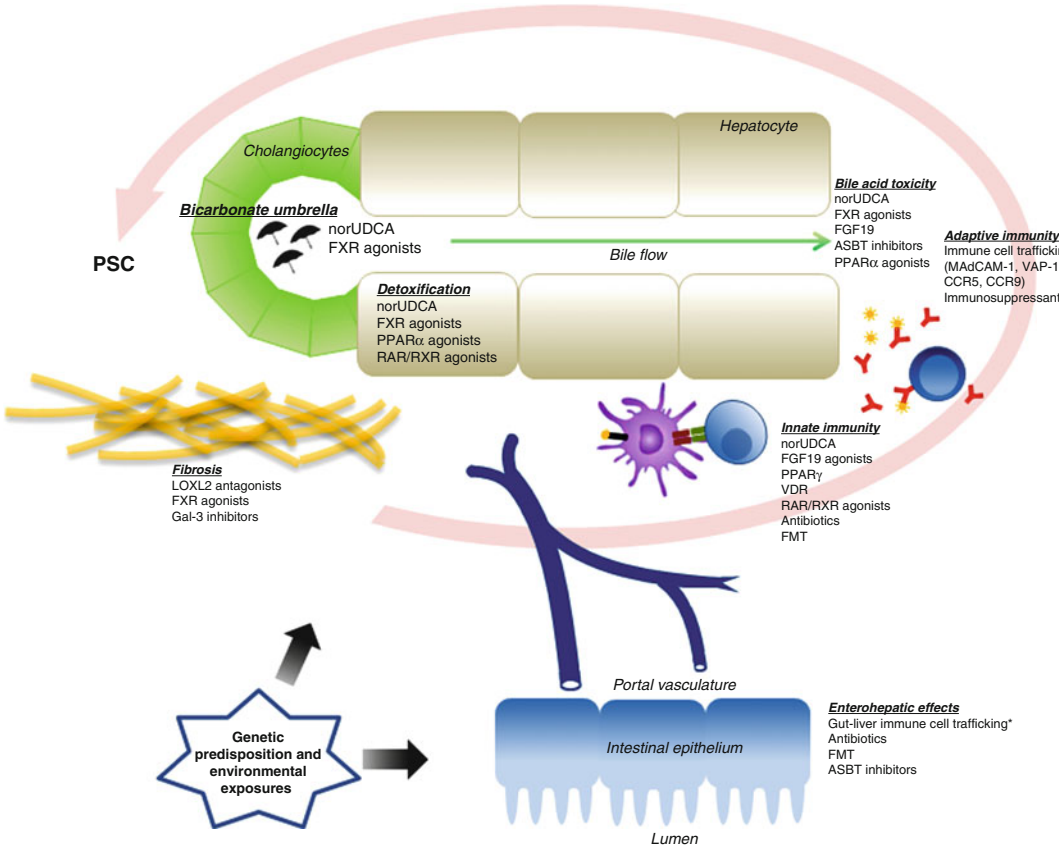

Fig. 12.1 A schematic overview of possible therapeutic targets, underlying mechanistic pathways, and pathogenesis of PSC: bile acid composition, detoxification, gut microbiota, hepatic fibrosis, adaptive and innate immune system activation, and immune cell trafficking represent areas in which a number study compounds and available drugs may exert therapeutic potential in the disease course. *FXR* farnesoid X receptor, *PPARa* peroxisome proliferator-activated receptor alpha, *VDR* vitamin D receptor, *RAR/RXR* retinoic acid receptor and retinoid X receptor, *LOXL2* lysyl oxidase-like 2, *ASBT* apical sodium-dependent bile acid transporter, *FMT* fecal microbiota transplantation, *FGF* fibroblast growth factor, *MAdCAM-1* mucosal vascular addressin cell adhesion molecule 1, *VAP* vascular adhesion protein, *CCR5* chemokine receptor type 5, *CCR9* chemokine receptor type 9

epithelia are continuous, any alterations in gut mucosal immunity ("leaky gut") or microbiome (dysbiosis) may, therefore, lead to heightened innate immune activation (liver-gut crosstalk) resulting in hepatobiliary injury (Fig. 12.1).

One of the hypotheses for the pathogenesis of PSC is the cross-reactive immunity to an antigen leading to immune-mediated gut and biliary inflammation from the enterohepatic circulation of gut-activated T lymphocytes. During intestinal inflammation, naive lymphocytes are imprinted with gut tropism by intestinal dendritic cells localized in the intestinal mucosa via integrin ligand, mucosal vascular addressin cell addressin molecule 1 (MAdCAM-1) and gut-specific chemokine, and CCL25-dependent mechanisms. Normally, these molecules are highly restricted to the gut, where they drive selective recruitment of gut-specific T and B cells and the expression the CCL25, chemokine receptor CCR9, and the integrin combination, α4β7, which binds to MAdCAM-1. It is suggested that in a genetically predisposed individual, gut dysbiosis and intestinal inflammation with translocation of enteric pathogens beyond the mucosal barrier lead to activation of endogenous molecules termed damage-associated molecular patterns (DAMPS) [19–21]. Due to aberrant gut tropism seen in PSC, DAMP-associated activation of innate immunity and hepatic expression CCL25 and MAdCAM-1 result in the recruitment of mucosal effector lymphocytes bearing a "gut-trophic" phenotype. Additionally, the adhesion molecule and ectoenzyme vascular adhesion protein (VAP-1) are upregulated during chronic inflammation and support both lymphocyte adhesion through upregulation of several endothelial adhesion molecules, including MAdCAM-1, on sinusoidal endothelium [22, 23]. Also, it catabolizes amine substrates secreted by gut bacteria and contributes to reactive oxygen species generation. After entering the liver, effector cells use chemokine receptors such as CCR9 to respond to chemokines secreted by epithelial target cells resulting in cell-mediated immunological attack and bile duct destruction (Fig. 12.1). Hepatobiliary damage is likely enhanced by the action of toxic bile acids and heightened DAMP activation resulting in cellular production of inflammatory cytokines that act as ligands for chemokine receptors leading to downstream processes such as autophagy, apoptosis, and fibrosis [19, 24–26].

Therapeutic Targeting of the Gut-Liver Axis

Gut Microbiome

The importance of the commensal microbiota and its metabolites in protecting against biliary injury was recently highlighted in an animal model [27]. The critical role of gut dysbiosis is increasingly being recognized in IBD and liver disease pathogenesis through alterations in the mucosal immune system and activation of DAMPs. Gut dysbiosis represents a modifiable therapeutic target through the use of antibiotics, probiotics, or fecal microbiota transplantation. Initial positive reports with improvement in liver biochemistries after oral administration of antibiotics in combination with ursodiol have led to three prospective studies to date. In the first study, 80 patients with PSC were randomized to 3 years of UDCA (15 mg/kg per day) plus metronidazole or UDCA alone [28]. This study showed the superiority of combination therapy in the improvement in alkaline phosphatase, Mayo PSC risk score, and histology. One of the well-conducted double-blind, randomized pilot study randomized, 35 adult PSC patients to low-dose vancomycin (125 mg four times a day), high-dose vancomycin (250 mg four times a day), low-dose metronidazole (250 mg three times a day), or high-dose metronidazole (500 mg three times a day) [29]. Low-dose and high-dose vancomycin were superior to metronidazole and achieved significant decreases in serum alkaline phosphatase levels at 12 weeks [29]. In another pilot study, 16 adult patients with PSC were treated with minocycline, 100 mg orally twice daily, for a year. A modest improvement in serum alkaline phosphatase levels and Mayo risk score was observed with treatment but there was no improvement in serum bilirubin and albumin [30]. However, a recent pilot study of 16 patients PSC and UC with oral rifaximin (550 mg twice a

day) has failed to show any biochemical improvement [31]. Future studies are therefore needed to understand how the antimicrobial spectra and other properties of antibiotics might determine their utility in treating PSC. Studies with oral vancomycin and fecal microbiota transplantation are currently planned (Table 12.1).

Gut Adhesion Molecules and Enterohepatic Circulation

Gut adhesion molecules are very attractive targets for pharmaceutical intervention, and given their enterohepatic expression in PSC, there is a possibility that agents that block the α4β7 – MAdCAM-1 – is expected to result in amelioration of ongoing chronic inflammation. Vedolizumab is a recombinant humanized IgG1 antibody constructed from the murine antibody Act-1, previously developed for use in patients with IBD. It inhibits adhesion and migration of leukocytes into the gastrointestinal tract by preventing the α4β7 integrin subunit from binding to MAdCAM-1. Therefore, the safety and efficacy of vedolizumab for the treatment of PSC in patients with underlying IBD is a matter of interest. Similarly, the VAP-1-blocking agent, BTT1023, is currently under investigation in phase 2 clinical trial in PSC patients with stable IBD (Table 12.1).

Bicarbonate Umbrella and Toxic Bile Acids in PSC

Bile acids are cholanic acid derivatives that act as detergents and are responsible for facilitating the absorption of dietary lipids, fat-soluble vitamins and for maintaining cholesterol homeostasis. The formation of bile acids is initiated in hepatocytes and mediated by cholesterol 7 α-hydroxylase (CYP7A1) [32]. Bile composed primarily of water, various ions, and solutes and is released into bile canaliculi on the apical side of hepatocytes. The bile acids flow through the canals of Hering before continuing through the biliary epithelium [32]. Despite continuous exposure to millimolar levels of hydrophobic bile salt monomers, the cholangiocytes are protected from damage due to a biliary HCO3- umbrella [33–37]. The formation of bicarbonate umbrella is mediated through transmembrane G-protein couple receptor (TGR5) [38]. Bile acids are stored in the gallbladder, and are then secreted into the duodenum where they are metabolized by enteric bacteria. Approximately, 95 % of these bile acids are absorbed in the terminal ileum and are then transported back to the liver via the portal vein for recycling [32]. These conjugated bile acids will be secreted back into the bile pool. This process is known as the enterohepatic shunt [32]. However, unconjugated bile acids are absorbed by the cholangiocytes and returned to the hepatocytes via the peribiliary vascular plexus in a process known as the cholehepatic shunt [32]. After synthesis, bile acids are conjugated with either glycine or taurine, which decreases the toxicity of bile and makes it more soluble [32]. In the liver, bile acids activate a nuclear receptor, farnesoid X receptor (FXR), that results in inhibition of CYP7A1 [32]. In the intestine, FXR induces an intestinal hormone, fibroblast growth factor 19 (FGF19), which activates hepatic FGF receptor 4 (FGFR4) signaling to inhibit bile acid synthesis resulting in decreased levels of 7ahydroxy-4-cholesten-3-one (C4) and endogenous bile acids (Fig. 12.1) [32].

Therapeutic Targeting of Toxic Bile

Because of the important processes that bile acids regulate through activation of receptors, bile acid derivatives and drugs that target these receptors are under development for the treatment of several diseases, including cholestatic liver disease and metabolic syndrome [39–41].

UDCA Derivative

24-norursodeoxycholic acid (*nor*UDCA) is a derivative of UDCA and is formed after removal of a methylene side group. This small alteration of the native compound establishes novel bile acid properties, enabling *nor*UDCA to overcome previous functional limitations of UDCA. *nor*UDCA is passively absorbed by cholangiocytes and subsequently undergoes extensive cho-

Table 12.1 List of novel therapeutic agents that are currently under evaluation for treatment of PSC. Brief overview of mechanism of action, route of administration, and details of the study design with primary efficacy endpoints are listed in the following table

Investigational drug (ClinicalTrials.gov identifier)	Mechanism of action	Administration	Clinical research phase	Sample size and study duration	Elevated alkaline phosphatase (AlkP) as inclusion criteria	Primary efficacy endpoint	Status	Estimated study completion date	Company
Simtuzumab (NCT01672853)	Monoclonal antibody against lysyl oxidase-like 2 (LOXL2)	Subcutaneous inj weekly	Phase 2b	$N=225$, 96 weeks	Not required	Change from baseline in morphometric quantitative collagen on liver biopsy	Active, not recruiting	July 2016	Gilead Sciences
LUM001 (NCT02061540)	apical sodium-dependent bile acid transporter inhibitor (ASBTi)	Oral, once daily	Phase 2	$N=20$, 14 weeks	Not required	Change from baseline in liver biochemistries, bile acids, and pruritus	Active, not recruiting	December 2015	Shire
norUDCA (NCT01755507)	Improve bicarbonate umbrella	Oral, once daily	Phase 2	$N=160$, 12 weeks	Not required	Decrease in AlkP levels	Unknown	March 2014	Dr. Falk Pharma GmbH
Obeticholic acid (NCT02177136)	FXR agonism	Oral, once daily	Phase 2	$N=75$, 24 weeks	AlkP at baseline ≥2xULN	Decrease in AlkP levels	Recruiting	June 2019	Intercept Pharmaceuticals
BTT1023 (NCT02239211)	Human monoclonal antibody (BTT1023) which targets the vascular adhesion protein (VAP-1)	IV infusion, every 14 days	Phase 2	$N=41$, 120 days	AlkP at baseline >2xULN	Decrease in AlkP levels	Recruiting	March 2017	Biotie Therapies Corp
Mitomycin C (NCT01688024)	Nucleic acid synthesis inhibitors, antineoplastic agent	Delivery into biliary tree via ERCP, as needed	Phase 2	$N=130$, 2 years	Not required	Improvement in Mayo Risk Score	Recruiting	September 2017	Investigator initiated

(continued)

Table 12.1 (continued)

Investigational drug (ClinicalTrials.gov identifier)	Mechanism of action	Administration	Clinical research phase	Sample size and study duration	Elevated alkaline phosphatase (AlkP) as inclusion criteria	Primary efficacy endpoint	Status	Estimated study completion date	Company
Vancomycin (NCT02605213)	Improve gut dysbiosis	Oral, every 6 h	Phase 4	$N=30$, 12 weeks	Not required	Decrease in AlkP levels	Recruiting	February 2016	Investigator initiated
Fecal Microbiota Transplantation (NCT02424175)	Improve gut dysbiosis	Single FMT	Phase 1, Phase 2	$N=5$, 12 weeks	AlkP at baseline >1.5xULN	>50% improvement in liver biochemistries 3 months after intervention	Not yet recruiting	June 2017	Investigator initiated, OpenBiome
Cenicriviroc (NCT02653625)	Dual CCR2 and CCR5 receptor inhibitor	Oral, once daily	Phase 2	$N=25$, 24 weeks	AlkP at baseline >1.5xULN	Decrease in AlkP levels	Not yet recruiting	June 2017	Tobira Therapeutics
All-trans retinoic acid (ATRA) (NCT01456468)	Active metabolite of vitamin A	Oral, twice daily	Phase 1	$N=30$, 3 months	AlkP at baseline elevated	Reduction in AlkP by at least 30%	Ongoing, but not recruiting	December 2015	Investigator initiated

lehepatic shunting [42, 43]. The physiologic result is increased cholangiocyte bicarbonate secretion and the creation of a possibly therapeutic "bicarbonate umbrella" in the biliary tree (Fig. 12.1). In fact, norUDCA resists taurine amidation, a property that increases its function in cholehepatic function compared to UDCA. *nor*UDCA has other unique features beyond UDCA, as it is more hydrophilic and thus less toxic to cholangiocytes and hepatocytes [44], but contains anti-lipotoxic, antiproliferative, antifibrotic, and anti-inflammatory effects [42, 45, 46]. Thus, *nor*UDCA has genuine potential to mitigate a number of steps in the pathogenesis of PSC and even complement mechanisms of bile acid detoxification and various overflow systems at the basolateral membrane [42, 46]. *nor*UDCA has mediated sclerosing cholangitis reversal in an experimental *Mdr2/Abcb4* knockout mouse model over a short study period, whereas the parent compound (UDCA) did not [45]. Human studies with norUDCA are underway, and results of phase 2 dose finding study (160 patients among 30 centers in Europe) are anticipated soon (Table 12.1). This study includes a primary outcome measure of change in serum alkaline phosphatase (AP) during the 12-week study, as well as secondary measures of the proportion of patients with at least 50% reduction in AP and rates of adverse events (NCT017555078).

Suppression of Bile Acid Biosynthesis

Bile acids, specifically those targeting the nuclear hormone receptor, FXR and the membrane associated G-protein couple receptor, TGR5 with high affinity, represent viable opportunities in the treatment of PSC [47]. Historically speaking, both targets (FXR and TGR5) have a rich history among autoimmune diseases. Specifically, TGR5 genetic polymorphisms have been associated with PSC and ulcerative colitis [48, 49], and FXR polymorphisms have been linked to inflammation and epithelial permeability in inflammatory bowel disease [50, 51]. FXR activation controls a number of downstream effects that enable cellular mechanisms to counteract biliary cholestasis via modulation of bile acid composition and inflammation. Activation of FXR not only leads to increased bile acid conjugation and excretion of bile from the hepatocyte into the canaliculi (also a bicarbonate rich choleresis) but contributes an additive role in the promotion of both phase I and phase II detoxification pathways [52–54]. UDCA and norUDCA are not ligands for FXR; however, 6-ethylchenodeoxcyholic acid (obeticholic acid (OCA) or INT-747) has strong receptor binding and activation profile [55, 56].

FXR agonist investigation in the *Mdr2/Abcb4* knockout mouse model has revealed significant mitigation of bile duct injury via diminished bile acid synthesis but also anti-inflammatory effects via FXR agonists (INT-767, similar FXR affinity as INT-747) [57]. Furthermore, overexpression of FXR in this model induced fibroblast growth factor 15 (or FGF19 in human) and suppressed the rate limiting enzyme-converting cholesterol to bile acids resulting in the cure of biliary injury [58]. OCA use is currently under investigation in a phase 2, blinded and randomized, placebo-controlled trial of the efficacy and safety in patients with PSC (NCT02177136). This study, estimated completion in June 2019, seeks to recruit a total of 75 subjects at 1:1:1 ratio into one of three treatment arms (Table 12.1). Two active compound groups include a daily OCA dose of 1.5 mg titrated to 3 mg and daily OCA dose of 5 mg titrated to 10 mg. The primary outcome measures include the effect of the compound on serum alkaline phosphatase as well as safety profile.

TGR5 and FGF19 also represent theoretic PSC therapeutic targets via roles in modulation of biliary composition and inflammation [59, 60]. TGR5, once activated, inhibits inflammation in part by suppression of NF-kb signaling [59] but also has a role in bile composition via cholangiocyte sensing bile sensing and bicarbonate secretion via cystic fibrosis transmembrane conductance regulator (CTFR) and anion exchange 2 (AE2) [61]. TGR5 has no current trials underway but a dual agonist of FXR, and TGR5 (INT-767) is currently undergoing preclinical evaluation. In the future, when targeted TGR5 compounds are available for treatment of cholangiopathies, off-target effects will have to be considered [62]. FGF19 expression is

increased after FXR activation, resulting in a multitude of metabolic effects including suppression of bile acid synthesis and anti-inflammatory activity [63, 64]. Currently, NGM282, a recombinant protein with an amino acid sequence of 95.4% identical to that of human FGF19, is currently under evaluation for PBC and PSC based on robust efficacy with no evidence of proliferative activity in a preclinical model (Table 12.1) [60].

Retinoic acid, an active metabolite of vitamin A, has been implicated in a number cellular processes including proliferation, differentiation, immunomodulation, and anti-inflammatory effects via activation of RXR and RAR [65, 66]. Furthermore, all-trans retinoic acid (atRA) causes an antifibrotic effect in bile duct ligation rats and carbon tetrachloride-induced liver fibrosis in vivo, yet the mechanistic pathway remains unclear [67, 68]. The administration of atRA resulted in repression of the rat CYP7A promoter, a finding that was potentiated by coadministration of UDCA. Evaluation of atRA in *Mdr2*/*Abcb4* knockout mice demonstrated reduced plasma levels of alkaline phosphatase, bile salts, duct proliferation, and inflammation in animals 12 weeks of age [69]. UDCA combined with atRA is currently being tested in an open-label trial for PSC patients with a primary outcome measure of alkaline phosphatase reduction over 3 months. Enrolled subjects continue UDCA at 15 mg/kg/day with the addition of oral atRA in two divided doses at 45 mg/m [2] (NCT01456468) (Table 12.1). Additionally, PPARα agonists have been evaluated in cholestatic liver disease since canalicular phospholipid translocator MDR3 is responsive to PPARα stimulation. Fibrates are potent PPARα agonist and increase MDR3 insertion into the canalicular membrane causing increased secretion of phosphatidylcholine resulting in the protection of cholangiocytes against bile acid toxicity. Additional mechanisms that may play a beneficial role include suppression of CYP7A1 and induction of CYP3A, each critical for bile salt synthesis and detoxification [70, 71]. Alterations in liver function and concerns related to cholestatic jaundice and cholelithiasis have unfortunately dampened the enthusiasm for the use of these agents in PSC [72].

Depletion of Bile Acid Pool

Apical sodium-dependent bile acid transport inhibitors (ASBTi) are also an exciting class of compounds that may provide another therapeutic option in PSC. Depletion of the bile acid pool through ASBTi can ultimately repress FXR-FGR signaling [73]. The action of ASBT inhibitors (LUM001, A4250 or SC-435), when tested in mouse models, was found to reduce the bile acid pool along with potentially toxic hydrophobic bile acids drastically [73, 74]. Furthermore, profibrogenic gene transcription was reduced as well as histologic fibrosis in this murine model [73]. An open-label phase II trial of LUM001, an ASBTi, in patients with PSC, is estimated to be completed in late 2015 (Table 12.1). This daily dosed compound is under evaluation with primary endpoints of safety and tolerability as well as adverse events in a 14-week study (NCT02061540).

Etiology-Independent Therapeutic Agents

Therapeutic Agents Against Fibrogenesis

Collagen cross-linking is an essential process for fibrotic matrix stabilization, a contributor to fibrosis progression, a limitation to the reversibility of liver fibrosis, and a potential therapeutic target. Lysyl oxidase-like 2 (LOXL2), a member of the LOX family with lysyl oxidase activity, is absent from adult healthy tissues and induced in disease [75]. Preclinical data using mouse models of biliary fibrosis suggested that a therapeutic anti-LOXL2 antibody significantly inhibited the progression of liver fibrosis prompting its evaluation in PSC [76]. A monoclonal antibody against lysyl oxidase-like 2 (LOXL2) in subjects with PSC is currently under evaluation (Table 12.1). Galectin-3 is a β-galactoside-binding lectin that has both intracellular effects (antiapoptotic, macrophage differentiation) and extracellular functions (chemokinetic/chemotactic factor) that are relevant to the physiopathology of PSC due to higher levels of expression of Gal-3 by in macrophages. Gal-3 is important for macrophage function in fibrotic disease including regulation of alternative activation of macrophages

[77]. Gal-3 inhibition is correlated to decreased monocyte/macrophage recruitment, cytokine production, and increased macrophage apoptosis [77]. Intravenous administration of galectin-binding drug GR-MD-02 is therefore expected to interfere with increased Gal-3-mediated inflammation and fibrogenesis seen in PSC.

Therapeutic Agents Against Inflammation and Cell Injury

The inflammation that occurs in the bile duct via translocation of enteric pathogens beyond the mucosal barrier interact with Toll-like receptors on the bile duct epithelial cells leading to increased production of inflammation cytokines, including ligands for CCR2 and CCR5 [78]. The cardinal feature of inflammation is the tissue recruitment of leukocytes, a process that is mediated predominantly by chemokines via their receptors on migrating cells. CCR2 and CCR5, two CC chemokine receptors, are important players in the trafficking of monocytes/macrophages such as monocyte chemotactic protein 1 (MCP-1) that is relevant to disease pathogenesis of PSC [79]. Overexpression of MCP-1 was observed in cholestatic liver diseases and PSC preclinical models [80, 81]. A potent, selective inhibitor of dual inhibitor of CCR2 and CCR5, currently under evaluation for the treatment of nonalcoholic steatohepatitis (NASH) and HIV may be an attractive candidate for treatment of PSC (Table 12.1) [82]. Finally, few studies have reported increased levels of serum keratin 18 fragment levels in patients with PSC suggesting the critical role of apoptosis in the pathogenesis of PSC [83, 84]. Liver-targeted caspase inhibitors could be an attractive treatment option for these patients and may be safely tolerated even in those with concomitant inflammatory bowel disease.

Safety and Tolerability of Novel Therapeutic Agents

The two key aspects of the evaluation of any investigational drug are safety – risk to the patient as assessed by laboratory testing, physical exam, adverse clinical events, and tolerability – the degree to which overt adverse effects can be tolerated by the patient.

In general, the novel therapeutic agents currently under evaluation have been previously investigated in patients with primary biliary cholangitis or non-alcoholic steatohepatitis (NASH) leading to recognition of the usual treatment-emergent adverse events (TEAEs) such as headache, abdominal pain, nausea, vomiting, diarrhea, somnolence, and elevated liver tests. In general, these TEAEs have been classified as either mild or moderate in severity. Some TEAEs, however, are drug specific and may affect the tolerability of the drug. In patients with PBC and NASH, who received treatment with OCA, a dose-dependent pruritus has been observed. Interestingly, increased liver enzymes and liver-related TEAEs including jaundice and acute cholecystitis were observed in patients with doses excess of 20 mg of OCA per day. In patients with PSC and dominant stricture resulting in inadequate bile flow, there could be an accumulation of OCA. The current study evaluating OCA for the treatment of PSC excludes patients with recent dominant stricture and also evaluates low-dose OCA between 1.5 and 10 mg per day. Alterations in lipid profile such as an increase in total cholesterol and low-density lipoprotein cholesterol were seen in NASH patients and a decrease in high-density lipoprotein cholesterol in both NASH and PBC. Although the clinical significance of these lipid changes remains unclear, the three deaths in OCA arm appear to be related to cerebro- and cardiovascular disease in the NASH (FLINT) trial. Although the main function of FGF19 is mediated through the negative control of bile acid synthesis, promotion of glycogen synthesis, lipid metabolism, and protein synthesis, there is concern about the tumorigenic potential due to high binding affinity for FGF receptor 4 whose expression correlates with progression of CCA. Another TEAE that may be of clinical relevance is diarrhea that may occur with ASBTi due to excess bile acids in the colon resulting in choleretic diarrhea. Lastly, in one study using oral minocycline for 1 year, a quarter of the study subjects withdrew due to intolerance.

Limitations of Current Approaches to the Development of Future Therapies for PSC

There is significant interindividual variability in progression, and prognosis depends on the clinical phenotype and stage of PSC at the time of initial diagnosis. For this reason, earlier attempts using any single test or a variable to predict survival in PSC patients failed due to lead time or length-time bias. Subsequent development of mathematical models of multivariable regression has allowed for an improved estimation of survival [85]. The long time required for the occurrence of sufficient hard outcomes such as death, liver failure, or cholangiocarcinoma requires the availability of a validated biomarker. Unfortunately, for a phase 2 clinical trial with novel therapeutic agents, a robust surrogate endpoint that can reliably assess response to therapy is essential to move the field forward. Alkaline phosphatase has been used as the primary endpoint in most trials but the recent termination of the multi-center study using high-dose UDCA due to increase frequency of adverse events (i.e., death, liver transplantation, cirrhosis, esophageal varices, and cholangiocarcinoma) in the active arm, despite improved alkaline phosphatase [16] has lead to major confusion. Despite this limitation, the majority of the studies require a baseline elevation in alkaline phosphatase of 1.5–2 times the upper limit of normal as the inclusion criteria to show an improvement in the clinical trial. An expert panel recently concluded that there is insufficient data to support any one biomarker and a combination of biomarkers is perhaps necessary [86]. With the exception of a few, all clinical trials are open to recruitment of patients with typical PSC and exclude other phenotypes such as small duct PSC and PSC with features of AIH (Table 12.2). Lastly, the majority of clinical trials exclude patients who are pregnant, breast feeding, hepatic decompensation, recent history of cholangitis, dominant stricture, chronic kidney disease, concomitant chronic liver disease and moderately active inflammatory

Table 12.2 Class of agents that are currently under evaluation for treatment of various phenotypes of primary sclerosing cholangitis (PSC)

	Therapeutic targeting of gut-liver axis			Therapeutic targeting of toxic bile acids					Other agents		
PSC phenotypes	Integrin α4β7 antagonist	VAP-1 blocking agent	Antibiotics and FMT	UDCA derivative	FXR agonist	ASBTi	Non-FXR nuclear receptor agonists	FGF-19 agonist	LOXL2 inhibitor	Galectin-3 inhibitor	Chemokine receptor antagonists
Typical	X	X	X	X	X	X	X	X	X	X	X
Atypical											
Small duct PSC								X			
PSC/AIH overlap											X
PSC/IBD	X	X	X	X	X			X	X	X	X

bowel disease possibly due to lack of data at this early stage of drug development.

Conclusion

PSC is a rare disease with no approved therapy. Recent breakthroughs in the understanding of the pathogenesis of PSC and other chronic liver disorders have led to several novel targets for treatment of PSC. These breakthroughs have unleashed the long-awaited arrival of novel therapeutic agents that not only delay the progression of the disease but also reverse the existing damage. It is very critical that these novel agents provide long-lasting, life-prolonging, and potentially curative treatment for patients with PSC.

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