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Drug Therapies for Chronic Cholestatic Liver Diseases

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Abstract

Though ursodeoxycholic acid (UDCA) remains the baseline treatment for most cholestatic liver diseases, UDCA treatment leaves approximately one-third of patients with primary biliary cholangitis (PBC) and all patients with primary sclerosing cholangitis (PSC) at risk for disease progression. New anticholestatic agents, including nuclear receptor agonists, choleretics, and bile acid synthesis suppressors, will likely increase response rates to therapy in PBC and PSC. Strategies that target early immune-mediated injury have so far been disappointing, hampered by the lack of biomarkers to detect early disease states, which then could profit from immunomodulatory therapy. Future concepts need to personalize treatments according to disease stage, progression, and phase, and to combine multiple drugs to target different pathogenic pathways.

INTRODUCTION

PBC: primary biliary cholangitis

PSC: primary sclerosing cholangitis

UDCA: ursodeoxycholic acid

Chronic cholestatic liver diseases comprise a complex spectrum of hereditary and acquired hepatobiliary disorders, which may manifest from infancy to adulthood with clinical signs of jaundice, elevated bile acids, and, in some cases, impaired bile flow. The disease course is heterogeneous and manifests with various pathogenetic features ranging from earlier immune-mediated injury and later bile acid–induced and inflammation-induced toxic injury, to late adaptive responses and fibrotic repair. A recently suggested pathophysiological concept for chronic cholestatic liver disease, which particularly applies to primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), proposes that cholestatic disease development follows an ascending pattern, starting with an immune-modulated necro-inflammation in some large (in PSC) or small (in PBC) bile ducts (1). This early nonsymptomatic or symptom-poor cholangitic phase may precede clinically overt cholestasis with jaundice by years, but eventually there will be local toxic injury from bile leakage and bile acid–mediated inflammatory response. Adaptive anticholestatic events on the level of the biliary tree, the canalicular network, and the hepatocytes may successfully compensate for parenchymal injury and further mitigate symptoms. This may be one reason for the long, symptom-poor natural course of diseases of this type before overt cholestasis, cirrhosis, and portal hypertension eventually develop in more progressed and end-stage disease (1). This may also be a reason why anticholestatic therapies are initiated relatively late in the course of disease and explain why new therapeutic concepts, added after failure of primary treatment, often fail to meet expectations, as they are simply initiated too late. From a therapeutic point of view, anticholestatic strategies should be multimodal and ideally include immune-modulating, anti-inflammatory, bile acid toxicity–reducing, and antifibrotic properties, with an emphasis on immunogenic objectives earlier and antitoxic and antifibrotic targets later in the course. **Supplemental Table 1** gives an overview of the potential drug targets in chronic cholestatic liver diseases. This review particularly focuses on the new advanced therapeutic concepts for the two main chronic cholestatic liver diseases with still unknown etiology in adulthood, namely PBC and PSC. An overview on rare and childhood chronic cholestatic liver diseases is given in **Supplemental Table 2**.

Supplemental Material >

Ursodeoxycholic acid (UDCA) monotherapy is the primary anticholestatic drug for several cholestatic liver diseases, including PBC, intrahepatic cholestasis of pregnancy, and liver involvement in cystic fibrosis; for other cholestatic entities, UDCA alone does not work, particularly not for PSC (2, 3). UDCA has multiple sites of action to counteract cholestasis. It shows immunomodulatory effects by interfering with major histocompatibility complex class I/II presentation as well as anti-inflammatory effects on macrophages (2, 3). UDCA reduces bile acid–mediated toxicity because of its antiapoptotic and endoplasmic reticulum stress–relieving properties and by induction of a bicarbonate-rich biliary choleresis, which lowers toxic bile acid concentrations and counteracts biliary stasis. UDCA also enhances hepatocellular adaptation by upregulating bile acid–transporting systems and reducing bile acid synthesis (2, 3). Overall, UDCA shows anticholestatic qualities at different disease stages and phases on the hepatocytic and bile duct levels.

Why do we need additional therapy? In PSC, UDCA has no survival- or transplantation-free survival benefit. In PBC, complete responders to UDCA therapy have normal life expectancy (4), but 25–50% of the patients do not have a satisfactory response to UDCA treatment, and 15% may develop cirrhosis-associated, non-neoplastic complications (5). We accordingly need to develop and establish novel drug regimens for PBC and PSC and also determine who is at risk for disease progression and requires personalized additive treatment, based on disease stage. Correct risk stratification will obviously play a major role in treatment decisions.

PRIMARY BILIARY CHOLANGITIS

PBC is a rare chronic autoimmune liver disease characterized by the progressive destruction of intrahepatic bile ducts and eventually leading to clinically overt cholestasis and biliary cirrhosis. It mainly affects middle-aged women, with a female-to-male ratio of 10:1, an incidence between 0.3 and 5.8 per 100,000 persons, and a prevalence of 2–20 per 100,000 inhabitants (6). Diagnosis is made based on positive antimitochondrial antibodies (AMAs) and elevated alkaline phosphatase (AP) levels or, in AMA-negative PBC cases (~5% of PBC cases), histologically by typical histopathological features in liver biopsy (7). In most patients, PBC progresses slowly, but the clinical course may differ greatly between individual patients. In a cohort of UDCA-treated patients (not subdivided into responders or nonresponders), the rate of histological progression from fibrosis to cirrhosis after five years was 4%, 12%, and 59% of patients for stages I, II, and III, respectively (8), and 10-year transplant-free survival was 77% (9). Future advanced personalized therapeutic concepts will call for the identification of low-risk patients, who usually remain at low risk regardless of intervention, and high-risk patients, who may not respond adequately to standard therapy and will be candidates for advanced therapies.

AMA: antimitochondrial antibody

Individual prognostic markers are young age and probably also being male, both of which are associated with a reduced chance of biochemical response to UDCA treatment (10, 11). Interestingly, AMA titers are not associated with prognosis (11), but the PBC-specific antinuclear gp-210 antibodies are associated with a sixfold increase in disease progression, death, or transplantation (12). The strongest independent predictors of long-term outcome and survival are AP, as a marker of biliary injury and ductular reaction, and bilirubin, as a marker of ductopenia (in later disease) (11, 13). Currently, the most established and simplest prognostic model is biochemical response to UDCA therapy, because of the well-established link between AP levels on treatment and long-term outcome (4). Depending on the different models that define different thresholds for bilirubin, transaminases, and AP after 6–24 months after UDCA start (7), the percentage of incomplete response to UDCA varies between 25% and 50%, but these simple scores only dichotomize patients into responders or nonresponders. More advantageous continuous scoring systems such as the UK-PBC Risk Score (14) and Globe Score (15) additionally include platelets, age, and albumin, i.e., markers of disease activity and stage, and continuously quantify the risk in relation to time, i.e., risk after 3, 5, 10, or 15 years. Unfortunately, the continuous scoring systems do not define any definite thresholds, a persisting major disadvantage for therapeutic study designs.

Another obstacle of these prognostic models, which stratify according to UDCA treatment response, is the several-month-long waiting period for the UDCA response. Newer pretreatment prediction models can avoid the delay until UDCA treatment takes effect (16), and with pretreatment identification, patients with high risk of nonresponse could immediately be offered second-line treatments. Fibrosis can be assessed rapidly with liver stiffness measurement by transient elastography. A threshold >9.6 kPa (F4-fibrosis) is associated with a fivefold greater risk for future liver decompensation or liver transplantation (LTX) and a linear progression of >2 kPa/annum with an eightfold greater risk of liver decompensation (17). Liver stiffness, however, occurs later in the disease course when fibrotic repair processes have already taken place, while in the early phase, immune-mediated mechanisms dominate and the potential for response to treatment and prevention of complications is greater. In the future, more personalized risk stratifications, particularly for immune-targeted therapies, might also include evaluation of cytokines/chemokines or specific immune pathways and/or genomic testing and will most likely require modern machine learning technology due to the level of complexity, as recently shown for PSC (18).

Disease development in PBC requires a permissive genetic background (i.e., female sex, genetic risk alleles), exposure to an as yet undefined environmental trigger (e.g., bacterial mimics,

xenobiotic chemicals), and loss of immune tolerance to a conserved mitochondrial antigen, which leads to uncontrolled immune activation against pyruvate dehydrogenase complex E2 (6). A comprehensive (graphic) overview on the putative sequence of pathogenetic events is provided in the current PBC guidelines by the European Association for the Study of the Liver (EASL) (7). An imbalance between effector and regulatory immune activity results in continuous biliary injury, which eventually manifests clinically as progressive liver disease (19). Conceptually, stage-dependent therapy in PBC can be divided into interventions that target the early autoimmune response, interventions that target the resulting cholestatic hit to the bile ducts and prevent further biliary injury, and interventions that are directed against secondary fibrotic changes as a repair response to ongoing biliary injury. **Table 1** provides a comprehensive overview of drugs that are already approved, in clinical use, or in clinical trials for the treatment of PBC.

Immunomodulatory Therapy

The liver in PBC is densely infiltrated with $CD4^+$/$CD8^+$ T and B lymphocytes, and the portal tracts are rich in proinflammatory cytokines and chemokines also secreted by inflamed cholangiocytes (referred to as reactive bile duct epithelial cells) (20). Agents with broad immunosuppressive activity such as prednisolone (21, 22), methotrexate (23), azathioprine (24), cyclosporine (25), or mycophenolate (26) did not, however, show convincing beneficial results in PBC, nor did depletion of B cells with the anti-CD20 antibody rituximab (27, 28). More specific intervention of the autoimmune response in PBC could occur at the critical steps in the development of an autoimmune response, which include antigen presentation, T cell differentiation and proliferation, and recruitment of effector cells (20). The challenge for immunotherapy in PBC is to balance efficacy of the immunomodulatory action on the disease with immunocompromising the organism (20).

Ustekinumab. Genome-wide association studies in PBC patients revealed a strong association for the interleukin (IL)12 and downstream Janus kinase (JAK)/STAT signaling pathways (29–31), which supported findings in cytokine profiles and immunohistochemical analysis of PBC patients (32, 33). IL12, which is produced by activated antigen-presenting cells, modulates $CD4^+$ T helper lymphocyte induction via IFNγ and IL23. Inhibition of IL12 signaling enables the suppressive functions of T cells in a proinflammatory environment. Ustekinumab is a monoclonal antibody that targets IL12/23 and is already approved for Crohn's disease and psoriasis. The clinical phase 2 trial with ustekinumab in PBC, however, failed to show a therapeutic response in PBC patients with UDCA nonresponse (34). Ustekinumab therapy did not reach the primary end point of a 40% AP reduction and resulted only in a modest decrease in AP (median 12%) after 28 weeks (34). This study was concerned with advanced disease states, since most patients had moderate-to-severe liver fibrosis, and it was expected that immune injury would have been more prominent in less severe disease states. The downstream JAK/STAT pathway is currently targeted with baricitinib, already approved for rheumatoid arthritis, in a phase 2 study in UDCA nonresponders.

FFP104. FFP104 blocks CD40/CD40L interaction between T and B cells and inhibits immune responses farther upstream than cytokine inhibitors like TNF-α and IL23 blockers. The interaction of $CD4^+$ T helper lymphocytes and B cells is required for the specific antibody response in PBC. Results of this phase 1/2 study have not yet been reported.

E6011. The chemokine-adhesion molecule CX3CL1 (fractalkine) plays an important role in the recruitment of mononuclear cells to intralobular bile ducts and is elevated in the serum of PBC

Table 1 Drugs for the treatment of primary biliary cholangitis

Drug	Dosage	Mechanism	Side effects	Reference(s); clinical trial(s)
Approved				
UDCA	13–15 mg/kg/day	Hydrophilizing bile acid pool, choleretic, antiapoptotic	Rare: diarrhea, flatulence, modest weight gain	124–129
Obeticholic acid	5–10 mg/day; dose reduction in cirrhosis	Semisynthetic FXR ligand, transcriptional regulation of genes involved in bile acid metabolism, repression of bile acid synthesis, bicarbonate choleresis, anti-inflammatory properties	Pruritus, HDL reduction, narrow dose range in cirrhosis leads to caution in advanced/ decompensated liver cirrhosis	42, 43, 130
In clinical use				
Bezafibrate (not approved in the United States)	400 mg/day	Weak pan-PPAR ligand (α, γ, δ); downregulation of bile acid synthesis, anti-inflammatory, biliary phospholipid secretion, antiprurinergic	Increased transaminases, renal dysfunction, myalgia	48, 54, 56, 131
Fenofibrate	160–200 mg/day	PPAR-α ligand (PPAR-α mainly expressed in liver and in metabolic active tissues); downregulation of bile acid synthesis, anti-inflammatory, biliary phospholipid secretion	Increased transaminases, renal dysfunction, myalgia	57, 132–134
Budesonide	9 mg/day	GR and PXR agonistic effects, detoxification and suppression of bile acid metabolism, stimulation of AE2 and bicarbonate secretion	Increased risk for portal vein thrombosis in cirrhosis, steroid side effects (but less than prednisolone)	63–65; Eudra CT 2007-004040-70
PPAR agonists in clinical trials				
Seladelpar (MBX-8025)		PPAR-δ ligand, PPAR-δ ubiquitously expressed, downregulation of bile acid synthesis, modulation of bile acid transport and metabolism, choleretic, anti-inflammatory	Grade 3 increase in aminotransferases	58; NCT03602560 (phase 3), NCT03301506 (phase 3), NCT02955602 (phase 2)
Elafibranor		PPAR-α/δ agonist, downregulation of bile acid synthesis, anti-inflammatory, biliary phospholipid secretion, choleretic	NA	135; NCT03124108 (phase 2)
Saroglitazar magnesium		PPAR-α/γ agonist, PPAR-γ mainly expressed in immune cells and adipose tissue	PPAR-γ side effects include weight gain, edema, bone fractures	136; NCT03112681 (phase 2)

(*Continued*)

Table 1 (*Continued*)

Drug	Dosage	Mechanism	Side effects	Reference(s); clinical trial(s)
FXR agonists in clinical trials				
Cilofexor (GS-9674)		Synthetic nonsteroidal FXR ligand, transcriptional regulation of genes involved in bile acid metabolism, repression of bile acid synthesis	NA	NCT02943447 (phase 2)
Tropifexor (LJN452)		Synthetic nonsteroidal FXR ligand, transcriptional regulation of genes involved in bile acid metabolism, repression of bile acid synthesis	NA	137; NCT02516605 (phase 2)
EDP-305		Synthetic nonsteroidal FXR ligand, transcriptional regulation of genes involved in bile acid metabolism, repression of bile acid synthesis	NA	138; NCT03394924 (phase 2)
Modulators of bile acid metabolism in clinical trials				
LUM001		ASBT inhibitor, interrupts enterohepatic circulation of bile acids in the ileum (primary end point: improvement in pruritus)	Diarrhea, upper gastrointestinal complaints	NCT01904058 (phase 2)
NGM282		Nontumorigenic FGF19 mimetic, suppresses bile acid synthesis	Diarrhea, nausea, headache	47; NCT02135536 (phase 2b), NCT02026401 (phase 2)
Inhibitors of cytokine signaling in clinical trials				
Baricitinib (LY3009104)		JAK1/2 inhibitor, inhibits cytokine signaling via the JAK/STAT pathway; approved for rheumatoid arthritis	Increase of LDL cholesterol, upper respiratory infections	NCT03742973 (phase 2)
Modulators of immune cell interaction in clinical trials				
Etrasimod (APD334)		Sphingosine-1-phosphate inhibitor, reduces lymphocyte (T cell) migration, proliferation, and differentiation	NA	NCT03155932 (phase 2)
Rituximab		Anti-CD-20 antibody, B cell depletion, main indication in oncology and rheumatoid arthritis	Infections, immune system disorders, skin disorders	27, 28, 139
Abatacept (Orencia)		Blocks CD80/CD86 of antigen-presenting cells, inhibits T cell activation by blocking the second activating signal from antigen-presenting cells; approved for rheumatoid arthritis	Infections (upper respiratory tract), elevated transaminases	37

(*Continued*)

Table 1 (*Continued*)

Drug	Dosage	Mechanism	Side effects	Reference(s); clinical trial(s)
Ustekinumab		Anti-IL12/23 monoclonal antibody, reduces activation of NK and T cells; approved for psoriasis and Crohn's disease	NA	34; NCT01389973 (phase 2), end point not reached
E6011		Antifractalkine/CX3CL1 antibody, inhibits chemotaxis and adhesion	NA	NCT03092765 (phase 2) terminated (sponsor decision, non-safety related)
FFP104		Anti-CD40 antibody, CD40L is required for generating optimal $CD4^+$ and $CD8^+$ T cell responses through activation of dendritic cells	NA	140; NCT02193360 (phase 1/2)
Mesenchymal stem cells		Modulatory effects on various lymphoid cells	NA	141; NCT03668145
Various drugs in clinical trials				
S-adenosyl-methionine		Replenishing methyl pools, detoxification reactions	None reported	142
Tetrathio-molybdate		Copper chelating drug, intended to treat Wilson's disease, trials in various cancers	NA	143; NCT00805805 (phase 3)
Truvada and Kaletra		Highly active antiretroviral therapy, intended to target betaretroviruses	NA	144; NCT01614405
Antifibrotic drugs in clinical trials				
GKT137831		Nox1/4 inhibitor, reduces ROS production and fibrosis	NA	69; NCT03226067 (phase 2)
Preclinical drugs				
NTCP inhibitors		Inhibits hepatocellular uptake of bile acids	NA	145
*nor*UDCA		Bicarbonate-rich choleresis	NA	NA

Abbreviations: AE2, anion exchanger 2; ASBT, apical sodium bile salt transporter; FXR, farnesoid X receptor; GR, glucocorticoid receptor; HDL, high-density lipoprotein; IL, interleukin; LDL, low-density lipoprotein; NA, not available; NK, natural killer; PPAR, peroxisome proliferator–activated receptor; PXR, pregnane X receptor; ROS, reactive oxygen species; UDCA, ursodeoxycholic acid.

patients (35), in line with the generation and persistence of a portal lymphocytic infiltration (35). E6011 is an antifractalkine antibody that is currently being investigated in a phase 2 trial in PBC patients nonresponsive to UDCA; results are not yet out.

Abatacept. Abatacept is a fusion protein that contains part of the extracellular domain of CTLA4, which binds the signaling molecules CD80/CD86 on antigen-presenting cells and prevents the activation of effector T cells, which is needed for an immune response. A single case study of a patient with PBC and concomitant rheumatoid arthritis (for which abatacept is licensed) has shown improvement of the liver disease (36). However, in a phase 3 trial in UDCA nonresponders

or patients intolerant of UDCA, only 1 out of 16 treated patients met the co-primary end point defined as either AP normalization or a >40% reduction from baseline (37). Overall, abatacept was well tolerated but was ineffective in achieving biochemical responses associated with improved clinical outcomes (37).

*nor*UDCA: *nor*ursodeoxycholic acid

OCA: obeticholic acid

FXR: farnesoid X receptor

FGF19: fibroblast growth factor 19

ASBT: apical sodium bile salt transporter

PPAR: peroxisome proliferator–activated receptor

Etrasimod. Etrasimod is a selective sphingosine-1-phosphate (S1P) receptor (S1PR) modulator targeting S1P receptor subtypes 1, 4 and 5. Selective binding with S1PR1 is believed to inhibit a specific subset of activated lymphocytes from migrating to sites of inflammation. The result is a reduction of circulating T and B lymphocytes that leads to anti-inflammatory activity. Results of this phase 2 clinical trial in UDCA nonresponders have not yet been reported.

Therapies Targeting Bile Acid Metabolism

Bile acid metabolism can be targeted at different levels: strategies to increase choleresis via stimulation of bicarbonate-rich bile flow [e.g., UDCA, *nor*ursodeoxycholic acid (*nor*UDCA), obeticholic acid (OCA), fibrates], strategies to reduce bile acid pool size [farnesoid X receptor (FXR) agonists, fibroblast growth factor 19 (FGF19) mimetics, apical sodium bile salt transporter (ASBT) inhibitors, peroxisome proliferator–activated receptor (PPAR) ligands], and strategies to change bile acid composition (UDCA, *nor*UDCA, PPAR ligands). Most drugs act on several levels or indirectly impact other ones. At earlier disease stages, biliary injury, ductopenia, and fibrosis are less severe. The presence of a high percentage of intact bile ducts is a key determinant of the efficacy of choleretic therapies.

Ursodeoxycholic acid. UDCA is the first-line therapy in PBC, and all novel therapies are primarily intended as add-on therapy to UDCA (7). The 25–50% of PBC patients who do not respond adequately to UDCA are at increased risk for progressive disease, particularly when diagnosed at later stages (38). Since nonresponders to UDCA therapy nonetheless profit from therapy compared to untreated patients, they should also receive lifelong UDCA treatment (39).

Obeticholic acid and other FXR agonists. FXR is a nuclear hormone receptor and transcription factor that is naturally activated by hydrophobic bile acids, with chenodeoxycholic acid (which is the predominating bile acid in cholestasis) as its most potent endogenous ligand. FXR represents the central integrator of bile acid homeostasis and, once activated, reduces cellular bile acid levels. Part of the repressive effects of FXR agonists on bile acid synthesis in the liver depends on intestinal induction of the endogenous enterokine FGF19. Additional beneficial effects include stimulation of bile acid transporters, which reduce hepatocellular bile acid concentrations, and anti-inflammatory properties. Although FXR activation by endogenous bile acid accumulation is intended to counteract potentially toxic bile acid levels, its endogenous activation in chronic cholestatic liver disease is apparently too weak for disease self-limitation. Synthetic and semisynthetic FXR agonists with higher affinity and potency to activate FXR have been successfully tested in animal models of cholestasis (40).

OCA is a semisynthetic derivate of natural chenodeoxycholic acid with a 100-fold higher affinity to FXR (41). It is approved as a second-line treatment in PBC for UDCA nonresponders or patients who do not tolerate UDCA. The POISE trial tested the effects of OCA in UDCA patients with AP levels >1.67 upper limit of normal (ULN). Twelve-month OCA treatment on top of UDCA reduced AP below 1.67 ULN in 47% and 46% of patients in the 10 mg and 5–10 mg dose-titrating study arms, respectively, but only 7% normalized their AP levels (42). The most

prominent side effect was dose-dependent pruritus in more than 50% of the patients, leading to discontinuation of therapy in (only) 1% of patients in the low-dose titrating arm but in 10% of the 10 mg treatment arm. In a separate study OCA also proved to be effective as a monotherapy without UDCA (43). In clinical practice, OCA is started at 5 mg/day and then dose titrated to 10 mg/day at six months, depending on tolerability (7). Another concern with OCA is the reduction of high-density lipoprotein and increase of low-density lipoprotein cholesterol levels. This is less problematic in PBC patients but may be of greater concern in the ongoing OCA trials in patients with nonalcoholic fatty liver disease (NAFLD) who are at increased risk for cardiovascular diseases (44). Incorrect daily dosing of OCA in patients with Child's class B and C cirrhosis has led to detrimental outcomes and a black box warning from the US Food and Drug Administration. Cirrhotic patients should begin with 5 mg OCA once a week up to a maximum dose of 10 mg twice a week after careful dose titration. Several other nonsteroidal FXR agonists such as tropifexor, cilofexor, and EDP-305 are currently being tested in clinical phase 2 PBC trials. These drugs are supposed to have more potent effects on intestinal FXR but fewer pruritogenic side effects.

FGF19 mimetics. FGF19 is an enterokine that is naturally released from the terminal ileum upon intestinal FXR activation. It has insulin-like postprandial effects, but after traveling to the liver via the portal vein it robustly suppresses hepatic bile acid de novo production and thus the bile acid pool size (45). There are concerns about the mitogenic potential of natural FGF19, but a mimetic of FGF19 called NGM282 is nontumorigenic (46). In a clinical phase 2 trial in UDCA nonresponders, NGM282 administered subcutaneously for 28 days significantly improved AP and transaminase levels compared to placebo. The main side effects were mild, with diarrhea dominating, but no aggravation of pruritus (47). An extended trial has been completed, but the results have not yet been reported.

Fibrates and other PPAR ligands. Among the most promising pharmacological options for the treatment of PBC and PSC are PPAR-α ligands. Fibrates have shown clinical improvements in PBC patients in small clinical trials and one larger multicenter trial (48). PPARs are a class of nuclear receptors that sense fatty acids and exist in three isotypes: PPAR-α, PPAR-γ, and PPAR-β/δ, with different tissue distribution (49). Fibrates are, with the exception of the weak pan-PPAR agonist bezafibrate, specific PPAR-α activators. PPAR-α is mainly expressed in hepatocytes, where PPAR-α ligands increase multidrug resistance protein 3 (MDR3) expression and insertion into the canalicular membrane of hepatocytes, stimulating biliary phospholipid secretion and rendering bile less aggressive (50–52). This bile duct protective effect is further supported by the reduction of bile acid synthesis, induction of bile acid detoxification (50), and anti-inflammatory properties (53). In the largest prospective two-year trial with bezafibrate in UDCA nonresponders, bezafibrate achieved AP normalization in 67% of UDCA nonresponders compared to UDCA/placebo (48). In addition, bezafibrate significantly reduces pruritus and liver stiffness (48, 54, 55), but data on long-term outcomes need to be collected. In an eight-year prospective observation study, bezafibrate/UDCA did not improve survival, but it was accompanied by significantly increased serum creatinine levels (56). Bezafibrate is not available in the United States, but smaller trials with the specific PPAR-α agonist fenofibrate show comparable results (57). Seladelpar is a specific ligand for PPAR-δ, which is additionally expressed in cholangiocytes, stellate cells, Kupffer cells, and macrophages. It reduces endogenous bile acid synthesis and also has potent anti-inflammatory and choleretic capacities. In a recent phase 2 trial in UDCA-nonresponsive PBC patients, seladelpar completely normalized AP levels in all of them, but the study was terminated prematurely

when three patients developed a reversible grade 3 transaminase increase (58). Clinical phase 3 trials with seladelpar at reduced dosage are ongoing. Elafibranor is a dual PPAR-α/δ agonist that showed promising preclinical effects in patients with nonalcoholic steatohepatitis (NASH) (59) and is now being evaluated in PBC as well. Next-generation fibrates like the pan-PPAR ligand lanifibranor, with its promising antifibrotic effects (60), will be potential future candidates for PBC treatment.

GR: glucocorticoid receptor

PXR: pregnane X receptor

AE2: anion exchanger 2

LOXL2: lysyl oxidase–like 2

Budesonide. Budesonide is a synthetic corticosteroid with a high first-pass effect in the liver. Budesonide is agonistic to the nuclear receptors GR (glucocorticoid receptor) and PXR (pregnane X receptor). The combined administration of UDCA and glucocorticoids stimulates expression of anion exchanger 2 (AE2), which is important in the generation of biliary bicarbonate (61). The progression rate of PBC under UDCA therapy was significantly linked to single nucleotide polymorphisms in the anion exchanger 2 (*AE2*) gene, and certain *AE2* gene variants are an independent prognostic factor in PBC (62). However, the efficacy of budesonide in PBC is unclear, and the report on a larger phase 3 trial is not yet available (7, 63–65); in any case, cirrhotic patients are at increased risk of developing portal vein thrombosis under budesonide treatment.

Antifibrotic Therapy

Fibrosis is regarded as a later pathogenetic event in the disease course. Specific antifibrotic strategies likely will not alter ongoing immune-mediated injury but may be adjunctive in patients with advanced liver disease to prevent further progression and to avoid LTX. Trials with the lysyl oxidase–like 2 (LOXL2) inhibitor simtuzumab in PSC and NAFLD were discouraging (66–68), and there is currently only one clinical trial using a Nox1/4 inhibitor to target fibrosis in PBC (69–71). Yet it is reasonable to assume that anti-inflammatory treatment strategies will likely have secondary beneficial effects on fibrosis in the long-term. Some of the aforementioned new drugs are predicted to have additional direct antifibrotic potential, such as OCA (72) or PPAR ligands (60, 73).

PRIMARY SCLEROSING CHOLANGITIS

Since LTX currently is the only definitive treatment for progressive and complicated PSC, we need novel medical treatment strategies. In contrast to PBC, PSC primarily affects the large bile ducts, specifically the extrahepatic ducts in most cases, and represents a precancerous condition. The risk for cholangiocellular carcinoma as well as colorectal cancer in PSC patients with concomitant inflammatory bowel diseases (IBDs) is significantly increased (74, 75). PSC is rarer than PBC, with an incidence rate between 0.4 and 2.0 per 100,000 people per year. Histologically, PSC is characterized by multifocal bile duct strictures resulting from progressive, chronic pericholangitis. IBD is usually present in PSC patients, but the IBD phenotype is regarded as distinct from ulcerative colitis or Crohn's disease and increasingly referred to as PSC-IBD (75).

PSC presents at least in part as an immune-mediated disease; however, similar to PBC, untargeted immunosuppressive therapy has no proven benefit in PSC (74–76). UDCA was shown to improve histology and/or serum biochemistry in PSC patients, but there are no convincing positive effects on hard clinical end points such as transplant-free survival (77–79). High-dose UDCA treatment has even been associated with increased mortality (80). The American Association for the Study of Liver Diseases warns against the use of UDCA in PSC, while the American College of Gastroenterology and EASL follow a more liberal strategy and only discourage UDCA doses

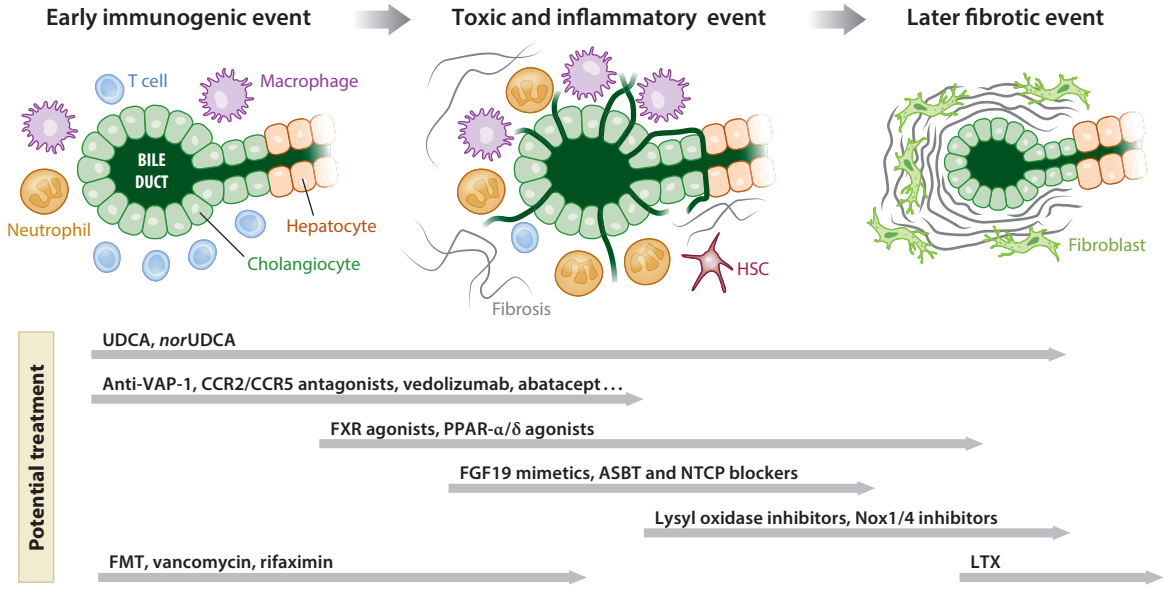

Figure 1

Potential synergistic anticholestatic treatment opportunities. Cholestatic liver disease may develop as an early immune-modulated necro-inflammation in smaller or larger bile ducts and may ascend to smaller biliary units and hepatocytes, where bile leakage and bile acid–mediated inflammatory responses result in local toxic injury and adaptive responses. Finally, biliary fibrosis, cirrhosis, and portal hypertension may develop. Since spatiotemporal progression likely varies even in different areas of the liver, synergistic treatment concepts will be required. Potential synergistic anticholestatic treatment may include multimodal choleretic UDCA or bicarbonate-rich, choleresis-inducing *nor*UDCA as a backbone therapy. Additional immune-modulatory treatment designs may dominate earlier disease stages and phases, followed by bile acid toxicity–reducing, bile acid pool–reducing, and anti-inflammatory strategies. At later stages, antifibrotic plans may be added. Abbreviations: ASBT, apical sodium bile salt transporter; FGF19, fibroblast growth factor 19; FMT, fecal microbiota transplantation; FXR, farnesoid X receptor; HSC, hepatic stellate cell; LTX, liver transplantation; *nor*UDCA, *nor*ursodeoxycholic acid; PPAR, peroxisome proliferator–activated receptor; UDCA, ursodeoxycholic acid; VAP-1, vascular adhesion protein 1. Figure adapted with permission from Reference 152.

beyond 28 mg/kg/day (77, 81–83). Effective PSC monotherapy is unlikely to be achieved, and the search for a precision treatment is hampered by numerous factors such as the heterogeneous phenotypical presentation of PSC, the imprecise and late diagnosis of PSC by the current gold standard of endoscopic retrograde cholangio-pancreaticography (ERCP) and magnetic resonance cholangio-pancreaticography (MRCP), and the lack of a specific disease cause. These facts significantly impede optimal study design regarding appropriate end points and readouts and further processing of successful PSC treatment trials (84, 85). Nevertheless, recent encouraging discoveries of novel PSC drug targets [e.g., vascular adhesion protein 1 (VAP-1), LOXL2, and gut-derived microbes such as pore-forming *Klebsiella pneumonia*] together with the development of new drugs modulating bile formation, composition, and intestinal uptake, as outlined for PBC above, significantly stimulated a veritable boom in PSC treatment trials (as summarized in **Table 2**) (86, 87). Similar to PBC, we think that PSC patients will most likely also need stage-dependent treatment strategies instead of a one-fits-all therapy (as outlined in **Figure 1**), but we still lack a clear (biomarker-guided) concept. Theoretically, effective medical treatment in PSC may include synergistically acting anticholestatic *nor*UDCA, UDCA, and fibrates in combination with drugs that target the inflammatory gut-liver axis containing biologics, antibiotics, sulfasalazine, and fecal microbiota transplantation (FMT).

VAP-1: vascular adhesion protein 1

FMT: fecal microbiota transplantation

Table 2 Drugs for the treatment of primary sclerosing cholangitis

Drug	Dosage	Mechanism	Side effects	Reference(s); clinical trial(s)
In clinical use				
UDCA	13–15 mg/kg/day	Hydrophilizing bile acid pool, choleretic, antiapoptotic	Rare: diarrhea, flatulence, modest weight gain; high-dose UDCA (25 mg/kg) not recommended due to adverse effects	80, 146, 147
FXR agonists in clinical trials				
Obeticholic acid		Semisynthetic FXR ligand, transcriptional regulation of genes involved in bile acid metabolism, repression of bile acid synthesis, bicarbonate choleresis, anti-inflammatory properties	Pruritus, HDL reduction, narrow dose range in cirrhosis; therefore, caution is recommended in advanced/ decompensated liver cirrhosis	NCT02177136 (phase 2)
Cilofexor (GS-9674)		Synthetic nonsteroidal FXR ligand, transcriptional regulation of genes involved in bile acid metabolism, repression of bile acid synthesis		91; NCT02943460 (phase 2)
PPAR agonists in clinical trials				
Bezafibrate	400 mg/day	Weak pan-PPAR ligand (α, γ, δ); downregulation of bile acid synthesis, anti-inflammatory, biliary phospholipid secretion	Increased transaminases, renal dysfunction, myalgia	102, 103; NCT02701166 (phase 3)
Fenofibrate	160–200 mg/day	PPAR-α ligand (PPAR-α mainly expressed in liver and in metabolically active tissues), downregulation of bile acid synthesis, anti-inflammatory, biliary phospholipid secretion		102; NCT01142323 (phase 1,2)
Modulators of bile acid metabolism in clinical trials				
*nor*UDCA		Synthetic bile acid, generates a bile acid–dependent bicarbonate-rich choleresis		101; NCT01755507 (phase 3)
LUM001		ASBT inhibitor, interrupts enterohepatic circulation of bile acids in the ileum		NCT02061540 (phase 2)
All-*trans*-retinoic acid		Reduction of bile acid synthesis and anti-inflammatory properties		99; NCT01456468, NCT03359174
NGM282		Nontumorigenic FGF19 mimetic, suppresses bile acid synthesis		93; NCT02704364 (phase 2)

(*Continued*)

Table 2 (*Continued*)

Drug	Dosage	Mechanism	Side effects	Reference(s); clinical trial(s)
Modulators of immune cell interaction in clinical trials				
BTT1023 (timolumab)		Antibody against vascular adhesion protein 1, which is important for gut homing of T cells		106; NCT02239211 (phase 2)
Cenicriviroc		Inhibitor of chemokine receptor 2 and 5, inhibits recruitment of monocytes and macrophages		107; NCT02653625 (phase 2)
Vidofludimus		Inhibitor of dihydroorotate dehydrogenase, inhibits pyrimidine synthesis, reduces cytokine release from T cells, promotes apoptosis		NCT03722576 (phase 2)
Anti-inflammatory drugs in clinical trials				
Sulfasalazine		Prodrug for sulfapyridine and 5-aminosalicylate, anti-inflammatory action by inhibiting arachidonic acid metabolism		NCT03561584 (phase 2)
Curcumin		Pleiotropic actions, anti-inflammatory, PPAR-γ agonistic, choleretic, modulation of NFκβ		NCT02978339 (phase 1/2)
Gut microbiome modulators in clinical trials				
Vancomycin		Gut-selective antibiotic, alters gut microbiota, reduces innate immune responses		148, 149; NCT01802073, NCT02605213, NCT03710122, NCT02137668, and more (phase 3)
Rifaximin		Gut-selective antibiotic, alters gut microbiota, reduces innate immune responses		NCT01695174
Fecal microbiota transplantation		Replaces existing gut microbiome with that of a healthy donor		119
Probiotics		NA		150
Antifibrotic drugs in clinical trials				
Simtuzumab		Antibody against LOXL2, which is required for collagen crosslinking		66

(*Continued*)

Table 2 (*Continued*)

Drug	Dosage	Mechanism	Side effects	Reference(s); clinical trial(s)
Various drugs in clinical trials				
HTD1801		No chemical formulation available; mechanism of action is lipid modulation		NCT03333928, NCT03678480 (phase 2)
DUR-928		Endogenous small molecule, epigenetic regulator with a role in lipid metabolism, inflammation, and cell survival		NCT03394781 (phase 2)
Docosahexaenoic acid		Supposedly increases PPAR signaling		151; NCT00325013 (phase 1)
Orbcel-C		Infusion with mesenchymal stromal cells		NCT02997878 (phase 2a)
Hymecromone		Hyaluronic acid synthesis inhibitor, choleretic		NCT02780752 (phase 1/2)
Cancer chemoprevention drugs in clinical trials				
Erlotinib		Inhibitor of human EGFR type 1 tyrosine kinase; for PSC patients with trisomy 7		NCT00955149 (phase 1)
Biliary strictures in clinical trials				
Mitomycin C		Antineoplastic alkylating agent causing cross-linking of DNA and inhibition of DNA synthesis; for treatment of biliary strictures during ERCP		NCT01688024

Abbreviations: ASBT, apical sodium bile salt transporter; EGFR, epidermal growth factor receptor; ERCP, endoscopic retrograde cholangiopancreaticography; FXR, farnesoid X receptor; HDL, high-density lipoprotein; LOXL2, lysyl oxidase–like 2; NA, not available; PPAR, peroxisome proliferator–activated receptor; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid.

Much earlier diagnosis of PSC will be needed for future successful treatment of PSC. Redefinition of diagnosis and clinical work-up will therefore be critical (in analogy to changing the nomenclature of PBC from primary biliary cirrhosis to primary biliary cholangitis and already allowing diagnosis when AP is elevated and AMA antibodies are positive). For instance, a cholestatic enzyme pattern in patients (especially male) with mild to moderate, primarily right-sided colitis may represent an early hint for cholangiopathies. This would require a high level of clinical suspicion for patients presenting with abdominal pain and unexplained increased AP/gamma glutamyl transferase (GGT) levels, even in the absence of diarrhea, since the rest of the colon may compensate for the inflamed parts. Diagnostically, this should lead to early and liberal measurement of stool calprotectin and colonoscopy. Efforts to develop novel diagnostic tools allowing earlier diagnosis should be stepped up, since MRCP and ERCP as the current gold standard for PSC diagnosis only detect the late disease stages with fibrotic/sclerotic bile ducts.

The following list of therapeutic options is arbitrary and fragmentary due to space limitations, since, due to the dynamics in the field and the lack of high quality phase 3 clinical trials, any prioritization would currently be more than premature.

Therapies Targeting Bile Acid Metabolism

OCA was tested in a phase 2a, double-blind, placebo-controlled trial (AESOP trial) in 77 PSC patients for 24 weeks with AP-dependent titrating doses of 1.5–3 mg/day and 5–10 mg/day, respectively. Both doses reduced AP levels by 22% overall. In PSC patients with baseline UDCA medication, OCA significantly decreased serum AP levels by about 15%. In those patients without UDCA treatment, 30% showed somewhat greater AP reduction. The gravest side effect of OCA was again dose-dependent pruritus, causing discontinuation of the study in 4 of 25 patients in the high-dose group. A two-year, open-label, long-term extension of the study is ongoing (88). Whether OCA will have any positive or negative effects on the risk of cholangiocellular or colorectal cancer in humans is open to question but will need special attention and careful surveillance (89). This should also be critically followed for the potential use of intestinal ASBT inhibitors. Concerning FXR as a drug target, substantial species differences between mice and humans have to be considered when translating results from animal models (90).

ATRA: all-*trans*-retinoic acid

RXR: retinoid X receptor

Cilofexor (GS-9674), a synthetic nonsteroidal FXR agonist, was recently tested in a phase 2 placebo-controlled study in noncirrhotic PSC patients (91). Synthetic nonsteroidal FXR agonists were designed to achieve a higher degree of receptor specificity, fewer adverse effects, less enterohepatic circulation with improved bioavailability, and favorable extrahepatic effects (92). In a 12-week study, 52 patients were randomized to receive two different doses of cilofexor (100 mg or 30 mg) or placebo orally. Cilofexor 100 mg led to dose-dependent significant reductions in serum AP (21%) and GGT (30%). Adverse events were similar between cilofexor- and placebo-treated patients. It is important to note that pruritus was more frequent in the placebo group and the rate of pruritus in the cilofexor groups was low (91). It will be interesting to see how cilofexor will perform in phase 3 PSC trials.

NGM282, an engineered nontumorigenic FGF19 analog, was recently tested in a placebo-controlled phase 2 trial in 62 PSC patients for 12 weeks (93). The authors found no significant differences in the mean change from baseline AP levels between NGM282 and placebo. Surprisingly, fibrosis biomarkers that predict transplant-free survival, including the Enhanced Liver Fibrosis test score and Pro-C3, were significantly improved in the NGM282 group. The ambivalent results of this interesting study are hard to interpret, as discussed in an accompanying thoughtful editorial (94). This study also promptly stimulated a discussion on the study end points for clinical PSC trials, and the clinical relevance of changes in AP levels was called into question (95). We can look forward to seeing whether NGM282 will move on to phase 3 trials after the interesting results on fibrosis markers in this phase 2 trial.

All-*trans*-retinoic acid (ATRA) activates the FXR/retinoid X receptor (RXR) nuclear receptor complex, leading to repression of bile acid synthesis (96). Based on promising preclinical results in bile duct–ligated rats and Abcb4 ($Mdr2^{-/-}$) mice (97, 98), ATRA was tested in a pilot study in 15 PSC patients who received UDCA in combination with ATRA for 12 weeks. This study did not meet the primary end point of a 30% reduction in serum AP levels, although there was a significant decrease in serum alanine aminotransferase and bile acid synthesis (99). Lower-dose ATRA is currently being investigated in a phase 2 study.

*nor*UDCA is a side chain–shortened UDCA derivate, which induces profound bicarbonate-rich choleresis via cholehepatic shunting (100). In a phase 2a clinical trial, *nor*UDCA significantly reduced serum AP levels dose dependently (101). In all, 161 patients were included to receive either 500, 1,000, or 1,500 mg/day of *nor*UDCA or placebo for 12 weeks. *nor*UDCA reduced AP levels up to 26% in the 1,500 mg/day group, thus reaching the primary end point. The most frequent adverse events in the *nor*UDCA treatment arms were abdominal pain, fatigue, nasopharyngitis, headache, and pruritus, which were similar compared to placebo. Based on its excellent safety

profile, *nor*UDCA may represent an attractive partner for combination therapy in PSC patients. Currently, a phase 3 trial of *nor*UDCA is recruiting PSC patients in Europe.

Fibrates

As in PBC, there is a growing number of studies testing fibrates in PSC patients, since increased biliary phospholipid secretion together with the anti-inflammatory and antifibrotic effects of fibrates are expected to improve disease course (102–104). In general, published data from mostly small and observational studies or retrospective analyses are promising, but published randomized controlled trials are lacking and urgently awaited.

Immunomodulatory Therapies

There is a long list of failed immunosuppressive treatments for PSC and explanations for their failure (76). Several novel strategies designed to act selectively on recently identified immunotargets in PSC are about to be tested.

Timolumab, a fully human monoclonal anti-VAP-1 antibody, currently has the most solid theoretical backbone. VAP-1 expression was shown to be significantly induced in PSC patients, and there is also positive preclinical evidence for anti-VAP-1 treatment. Treatment with an anti-VAP-1 antibody successfully prevented fibrosis in murine models of liver injury (105). Timolumab (BTT1023) is currently being tested in a phase 2 clinical trial (BUTEO trial) (106).

Cenicriviroc, a CCR2/CCR5 antagonist, showed anti-inflammatory and antifibrotic effects in preclinical NASH animal models as well as in Abcb4 ($Mdr2^{-/-}$) mice as a model for sclerosing cholangitis (107). Cenicriviroc 150 mg/day for 24 weeks was tested in 24 patients in a phase 2 trial (PERSEUS trial). The study was completed in 2017, but results have not yet been published.

Vedolizumab, an anti-α4β7 integrin monoclonal antibody, is used in IBD. The ligand for α4β7 integrin, MADCAM-1, was also found in the hepatic sinusoidal endothelium in PSC (108). Vedolizumab, by blocking α4β7 integrin, might therefore block MADCAM-1-induced migration of gut-derived, activated T cells to the liver in PSC patients. The impact of vedolizumab on PSC was disappointing (109–111). Pooled data from PSC-IBD patients treated with vedolizumab collected by the international PSC study group from several European and North American centers also showed no evidence for a biochemical response to vedolizumab in the majority of patients (112, 113). In a subset of patients with cirrhosis and a trend towards higher baseline AP levels, serum level of AP decreased by 20% or more. This, however, did not correlate with changes in liver synthetic function (112).

Antifibrotic Therapy

Two different doses of simtuzumab, targeting LOXL2 as an important stabilizer of the extracellular matrix and chemoattractant, administered over 96 weeks were investigated in a placebo-controlled phase 2b study that included 234 PSC patients, half of whom had bridging fibrosis or cirrhosis at baseline (66). There was no effect on liver fibrosis as determined by various tests, including liver histology and measurement of hepatic collagen. All in all, this study did not show any benefit of simtuzumab for PSC and it is questionable whether this drug will have any future (68).

Antibiotics and FMT

Most PSC patients suffer from concomitant IBD, which is distinct from solitary ulcerative colitis and Crohn's disease. In addition, there is an increasing body of evidence about changes in the gut microbiota such as dysbiosis and also the appearance of specific gut-derived pathobionts that may

play a critical role in PSC pathogenesis (87, 114). The therapeutic concept of modulating the gut flora via antibiotics, FMT, or pre/probiotics in PSC-IBD patients has attracted considerable interest.

The best-studied antibiotic in PSC is vancomycin, which is poorly absorbed when administered orally. First controlled trials, case series, and case reports in both adults and children reported a significant drop in AP (115). Nevertheless, the published evidence, with a relatively small number of treated patients and a lack of long-term and hard clinical end points, does not currently allow for the recommendation of vancomycin as a long-term PSC treatment.

Rifaximin and minocycline may also be attractive in this indication. Rifaximin showed no significant improvements in serum AP, bilirubin, GGT, or Mayo risk score in 16 PSC patients (116). In 40 patients with common variable immunodeficiency (as a model disease for a so-called leaky gut), rifaximin did not rebalance dysbiosis and had no effects on markers of systemic inflammation (117). An open-label study of minocycline in 16 PSC patients over one year demonstrated significant improvements in serum AP and Mayo PSC risk score (118).

FMT was recently tested in 10 PSC-IBD patients (119). There were no related adverse events, and 30% of patients showed a 50% decrease in AP levels. However, results and effects of FMT are hard to interpret because FMT protocols differed substantially. The potential risks and diagnostic and therapeutic standards for the performance of FMT have only recently been published (120). Reports on FMT must be reviewed and discussed very carefully, since they differ substantially regarding the route and frequency of application; preparation of the transplanted stool; use or abstinence of upstream antibiotic treatment; randomization; and, probably most importantly, well-defined control groups. Surprisingly, there is currently no FMT trial registered on ClinicalTrials.gov (**https://clinicaltrials.gov/**) actively recruiting PSC-IBD patients. In summary, we think there is currently no clear scenario to describe whether FMT will be useful in PSC-IBD patients, but FMT may prematurely reach clinics, since it is already discussed intensively in patient forums.

COMPLICATIONS OF CHRONIC LIVER DISEASES

Many patients are symptomatically more affected by complicating cholestasis-associated symptoms such as pruritus or fatigue. These symptoms, particularly pruritus, can be aggravated by drugs (e.g., OCA), while other drug regimens may have alleviating effects (e.g., fibrates, ASBT inhibitors). The discussion of novel treatment concepts for cholestasis-associated symptoms is beyond this review, and the reader is referred to excellent recent reviews specifically dedicated to this topic (121–123). In addition, **Supplemental Table 3** provides a comprehensive overview of drugs that are clinically used to treat complications of chronic liver diseases.

Supplemental Material >

OUTLOOK

The most promising drugs in the immediate pipeline for the treatment of cholangiopathies either stimulate bile flow as their main principle of action or decrease bile acid pool size. There remains a substantial percentage of patients who will not completely respond to novel treatment regimes. In the near future, new treatment strategies and clinical trials will combine drugs that are choleretic and target impaired bile flow with drugs that reduce bile acid accumulation and decrease bile acid pool size to maximize overall anticholestatic effects. The prototypical compounds are the FXR ligands, which appear to combine both effects: substantial suppression of bile acid synthesis and increase of bile acid–independent bile flow. Advanced concepts would combine the most powerful drugs to induce bicarbonate-rich choleresis, such as *nor*UDCA, with the most powerful drugs to suppress bile acid pool size, such as FGF19 mimetics or ASBT inhibitors, and may have real

potential to heal cholestasis. Surgical treatment strategies in severely cholestatic children with hereditary cholestatic defects also suggest that total biliary diversion might be a treatment option to avoid LTX, but the surgery is complex, and postsurgical complications can occur. Notably, some of these pharmacological approaches can be combined. As such, a combination of ASBT inhibitors with FGF19 agonists may be a therapeutic way to pharmacologically mimic total biliary diversion and thus provide another rationale to combine new anticholestatic drugs to eventually heal cholestasis. These anticholestatic treatments, however, are aimed to heal already injured biliary structures and do not address early immunological attacks as the cause of the disease. In the medium-term future, new treatments will have to be immunomodulatory, which presumes novel biomarkers to identify early disease states. In the long-term future, personalized treatment concepts will be based on the individual genetic and immunologic risk background assessed by machine learning algorithms.

CONCLUSIONS

For almost 40 years, UDCA has dominated the therapeutic field as the only approved anticholestatic drug, with various less well-characterized anticholestatic properties. In the last few years, however, with a more detailed understanding of immunological aspects in disease development and bile acid signaling properties, a range of new compounds entered the clinical stage. Currently, therapeutic concepts include either single drugs with pleiotropic effects or single drugs, which very specifically intervene with a distinct pathogenetic feature. Likewise, current clinical trials include a one-pill-fits-all strategy. More advanced anticholestatic therapies and new treatment concepts have to take disease stages (i.e., disease progression) and phases (i.e., time course) as well as spatiotemporal variability within the liver into account and need to combine specific drugs to target different pathogenic pathways at different time points (**Figure 1**). Another important issue in personalizing future therapy will be the individualization of risk stratification beyond the measurement of AP levels after first-line treatment.

DISCLOSURE STATEMENT

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