Update on Pharmacotherapies for Cholestatic Liver Disease

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Cholestatic liver diseases are conditions with impaired bile formation and/or flow due to genetic, immunologic, environmental, or other causes. Unless successfully treated, this can lead to chronic liver injury and end-stage liver disease. Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) embody the most prominent adult cholestatic liver diseases with regard to incidence, morbidity, and mortality. A considerable proportion of patients with PBC and PSC experience progressive liver disease and ultimately liver-related death due to a paucity of effective pharmacotherapy; however, novel pharmacologic developments offer substantial promise in this regard. Here, we provide a brief review and update on current and emerging pharmacotherapies for PBC and PSC. (HEPATOLOGY COMMUNICATIONS 2017;1:7-17)

Introduction

Cholestatic liver disease encompasses an array of human disorders and syndromes in which there is impairment of bile formation and/or flow due to genetic, immunologic, environmental, or other causes. This impairment can be localized to microscopic hepatic canaliculi, intrahepatic biliary ductules, segmental ducts, or large intrahepatic and extrahepatic bile ducts and may be secondary to congenital or acquired defects in, injury to, or disruption of cholangiocytes and other hepatic cell types.

The most common and prominent adult cholestatic liver diseases from a clinical and public health perspective are primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). In large part due to a paucity of effective pharmacotherapies, PBC and PSC have considerable morbidity and mortality and constitute a major indication for orthotopic liver transplantation (LT). In this brief review, we provide an overview of PBC and PSC and an update highlighting current and investigational pharmacotherapies.

Overview of PBC

CLINICAL FEATURES AND EPIDEMIOLOGY

PBC is an autoimmune disease of the liver characterized by destruction of the small intrahepatic bile ducts.[(1)] It primarily affects middle-aged women, with a reported female-to-male ratio of 10:1. The incidence and prevalence of PBC have been reported to be 0.33-5.8 per 100,000 people and 1.9-40.2 per 100,000

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; AMA, antimitochondrial antibodies; AST, aspartate aminotransferase; BA, bile acid; BMD, bone mineral density; CD, clusters of differentiation; CTLA4, cytotoxic T lymphocyte antigen 4; EASL, European Association for the Study of the Liver; FDA, US Food and Drug Administration; FGF19, Fibroblast growth factor 19; FXR, farnesoid X receptor; GGTP, gamma-glutamyl transpeptidase; IBD, inflammatory bowel disease; IL, interleukin; LOXL2, Lysyl oxidase homolog 2; LT, liver transplantation; OCA, obeticholic acid; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; UC, ulcerative colitis; UDCA, ursodeoxycholic acid; VAP1, vascular adhesion protein 1.

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people, respectively,[2] and recent reports suggest that the incidence of PBC is rising.[3] PBC is commonly seen in association with other autoimmune diseases, such as scleroderma, thyroid dysfunction, rheumatoid arthritis, and autoimmune hepatitis (AIH).[4]

DIAGNOSIS

The diagnosis of PBC is made, after excluding all other causes of cholestasis, based on biochemical evidence of cholestasis (typically a serum alkaline phosphatase [ALP] level $\geq$ 1.5 times the upper limit of normal) coupled with the presence of anti-mitochondrial antibodies (AMA).[5] AMA, a highly specific antibody, is found in nearly 95% of all PBC patients and is rarely found in healthy individuals.[6] Liver biopsy may be needed in equivocal cases to confirm histologic features of PBC and can also provide an assessment of disease activity and stage.

NATURAL HISTORY

PBC is a major cause of liver-related morbidity and mortality in Western societies. Although the majority of patients with PBC (up to 70%) are asymptomatic at the time of diagnosis, up to 89% will develop PBC-related symptoms during an average follow-up period of up to 17.8 years after PBC diagnosis.[5] Progression to cirrhosis and liver failure (variceal hemorrhage, ascites, hepatic encephalopathy, and hyperbilirubinemia) during a 5-year follow-up has been reported to be 15% in a well-characterized cohort of PBC patients.[7] Survival is markedly decreased in patients who progress to these clinical complications. For example, after the development of varices, 3-year survival has been found to be 59% and only 46% after an episode of esophageal variceal bleeding.[8] As with patients with cirrhosis due to other etiologies, PBC patients with cirrhosis are also at increased risk for hepatocellular carcinoma.[9]

Importantly, asymptomatic PBC patients have been found to have better long-term survival than those who present with (or develop) symptoms.[10] Likewise, survival of patients with early stage PBC who respond to ursodeoxycholic acid (UDCA), for years the only US Food and Drug Administration (FDA)-approved pharmacotherapy for PBC, is comparable to the general population.[11] Unfortunately, only a fraction of patients with PBC will begin UDCA therapy at an early stage and experience excellent biochemical response[12]; the remainder of patients represent an increased-risk group for which novel therapies are needed, as will be reviewed below.

Overview of PSC

CLINICAL FEATURES AND EPIDEMIOLOGY

PSC is an idiopathic disease of the liver that results in fibro-obliterative destruction of the intrahepatic and/or extrahepatic bile ducts.[13] PSC can affect pediatric[14] as well as adult patients, has a 2.5:1 male-to-female predominance, and is commonly (75%) associated with inflammatory bowel disease (IBD), particularly ulcerative colitis (UC).[15] The reported incidence and prevalence rates for PSC range from 0-1.3 per 100,000 people per year and 0-16.2 per 100,000 people, respectively.[2] Although population studies are limited, available data suggest that the incidence of PSC is rising.[16]

DIAGNOSIS

The diagnosis of PSC is established when any two of the three following criteria are met: (1) biochemical evidence of cholestasis (elevated serum ALP $\geq$ 1.5 times the upper limit of normal), (2) cholangiographic changes of PSC, and/or (3) histologic abnormalities consistent with PSC.[17] In the proper clinical context (e.g., a young male with IBD and a cholestatic serum

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TABLE 1. Therapies (Established or Undergoing Clinical Trial Evaluation) in PBC

Agent	Type of Clinical Trial(s), Past or Present	Main Results/Comments (from Prior Clinical Trials)	Status at Present
Ursodeoxycholic acid	Randomized placebo controlled	Improves liver biochemistries, including ALP, and liver transplant- free survival. 40% have incomplete response to UDCA	FDA approved (1997) as first-line therapy
Obeticholic acid	Randomized placebo controlled	Improves liver biochemistries, including ALP, GGTP, and bilirubin. Effects on hard clinical outcomes are yet to be elucidated	FDA approved (2016) as combination therapy, in addition to UDCA, or as single agent in those unable to tolerate UDCA
Budesonide	Open label; randomized placebo controlled	Improves liver biochemistries, including ALP. No significant effects on bone mineralization. Use in cirrhotic stage PBC is contraindicated	Undergoing evaluation
Fibrates	Open label and randomized clinical trials	Improves liver biochemistries, including ALP, as well as PBC- related symptoms.	Undergoing clinical evaluation
Antivirals	Open label; randomized placebo controlled	Improves liver biochemistries, including ALP	Undergoing clinical evaluation
Ustekinumab	Open label	Modest reduction in ALP, probably more effective in early stage PBC	————
Abaacept	————	No clinical trial data. Improved histological abnormalities in animal models.	Undergoing clinical evaluation
NGM282	————	No clinical trial data. Improves liver histological abnormalities in animal models of PBC	Undergoing clinical evaluation
LUM001	Open label; randomized	Results have not been published yet	Study completed

biochemical profile), a characteristic cholangiographic appearance can negate the need for a liver biopsy. Of note, AIH overlap occurs more frequently in pediatric PSC than adult PSC[18] and is an important diagnosis to rule out because this subset of patients might benefit from treatments directed against AIH (not discussed).

NATURAL HISTORY

In both children and adults, PSC can progress to end-stage liver disease, even in the absence of intervening symptoms. The median survival free of LT from the time of PSC diagnosis is estimated at 15-20 years, although significant interindividual variation exists.[19-23] PSC is an important cause of morbidity and mortality; in Norway, it is the leading indication for LT.[24] Unlike PBC, PSC significantly increases the risk of cholangiocarcinoma and gallbladder adenocarcinoma, either of which can arise before the onset of cirrhosis.[25] Moreover, PSC has been found to be a robust risk factor for colorectal adenocarcinoma, especially when PSC and IBD co-exist.[26]

To date, there is no FDA-approved pharmacotherapy for PSC. This is related in part to the unclear

TABLE 2. Therapies Undergoing Clinical Trial Evaluation in PSC

Agent	Type of Clinical Trial(s), Past or Present	Main Results/Comments (from Prior Clinical Trials)	Status at Present
Obeticholic acid	Randomized placebo controlled	————	Undergoing clinical evaluation
NGM282	Randomized placebo controlled	————	Undergoing clinical evaluation
LUM001	Randomized placebo controlled	Results have not been published yet	Study completed
Vancomycin/Metronidazole	Open label in children; randomized in adults	Improves liver biochemistries, Mayo risk score; improves cholangiographic abnormalities on magnetic resonance imaging studies in children	Undergoing clinical evaluation in children and adults
Nor-ursodeoxycholic acid	Randomized placebo controlled	————	Undergoing clinical evaluation
BTT1023	Randomized placebo controlled	————	Undergoing clinical evaluation
Lysyl oxidase homolog 2	Randomized placebo controlled	————	Undergoing clinical evaluation

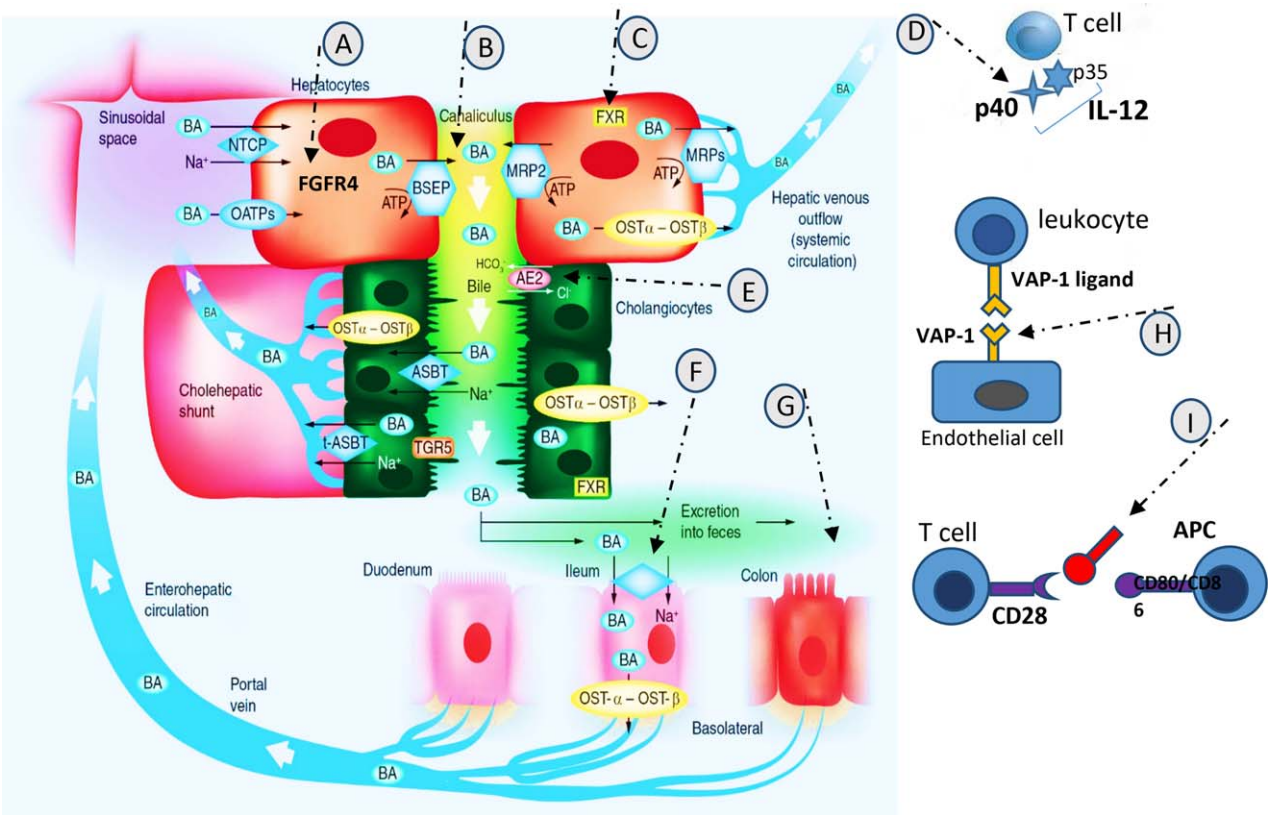

FIG. 1. Illustration of drugs and their proposed target site(s) in PBC and PSC. (A) NGM282; (B) fibrates, nor-UDCA, and UDCA; (C) obeticholic acid; (D) ustekinumab; (E) budesonide; (F) LUM001; (G) antibiotics in PSC; (H) BTT1023; (I) abatacept. Abbreviations: AE2, anion exchanger 2; ASBT, apical sodium bile acid transporter; ATP, adenosine triphosphate; BSEP, bile salt export pump; FGFR4, fibroblast growth factor receptor 4; MRP, multidrug resistance protein; NTCP, sodium/taurocholate co-transporting polypeptide; OATPs, organic anion transporting polypeptide; OST-α and β, organic solute transporter α and β; t-ASBT, truncated version of ASBT; TGR5, G protein-coupled bile acid receptor 1. (A portion of this figure is adapted from Tabibian JH, Lindor KD. Primary sclerosing cholangitis: a review and update on therapeutic developments. Expert Rev Gastroenterol Hepatol 2016;7(2):103-114. PMID: 23363260 with permission. Copyright Mayo Foundation for Medical Education and Research. All rights reserved.)

pathogenesis of the disease, heterogeneity in patient phenotypes (e.g., pediatric PSC versus adult PSC), and challenges with designing adequately powered clinical trials.

Established and Emerging Therapies for PBC and PSC

Extensive research has been performed and is ongoing to identify safe and effective pharmacotherapies for cholestatic liver disease. In this section, we provide a synopsis on current and investigative treatment for PBC and/or PSC, some of which may have a role in both diseases (summarized in Tables 1 and 2 and Fig. 1).

UDCA

UDCA, a naturally occurring bile acid, has been extensively studied in both PBC and PSC. Several randomized placebo-controlled clinical trials have shown that UDCA improves liver biochemistries and LT-free survival in PBC.[12,27-33] UDCA is one of two drugs that are approved by the FDA for treatment of PBC and is currently recommended as the first-line option by the American Association for the Study of Liver Diseases (AASLD)[5] and the European Association for the Study of the Liver (EASL) for all PBC patients.[34]

In PSC, the role of UDCA is unproven. Initial reports of open-label clinical trials showed that UDCA is safe.[35-38] Moreover, the use of UDCA (dose range from 13-15 mg/kg body weight) in PSC results in

improvement of serum liver biochemistries. Unfortunately, two large, randomized, placebo-controlled clinical trials using higher UDCA doses (17-23 mg/kg body weight [39] and 28-30 mg/kg body weight[40]) did not demonstrate a clinical benefit in PSC patients; one of these clinical trials was prematurely terminated due to excess rates of serious adverse events in the (high-dose) UDCA group compared to the placebo group.[40] Given the lack of clear evidence supporting UDCA use in PSC, the AASLD recommends against it, whereas EASL states "...the limited data does not yet allow a specific recommendation for the general use of UDCA in PSC." Nevertheless, a subset of PSC patients may sustain benefit from UDCA, but this is a topic of uncertainty and contention.[41] With this in mind and given the differences in pediatric versus adult PSC, it is worth noting that a phase I, multicentral, open-label clinical trial of UDCA in children with PSC is underway (clinicaltrials.gov identifier: NCT01088607).

FARNESOID X RECEPTOR AGONISTS

Farnesoid X receptors (FXRs), a group of nuclear hormone receptors distributed in the liver, intestines, and kidneys, have been found to play a critical role in bile acid (BA) metabolism. Particularly, activation of FXRs has been shown to down-regulate the expression of cholesterol 7-alpha hydroxylase (CYP7a1), a key and rate-limiting enzyme in the BA synthesis pathway.[42] Obeticholic acid (OCA; 6-ethyl chenodeoxycholic acid) is a potent FXR agonist and was recently approved by the FDA for the treatment of PBC in patients with an incomplete response to UDCA.

In an early clinical trial of OCA in PBC patients who had an incomplete response to UDCA, 165 subjects were randomly assigned to OCA at 10 mg, 25 mg, 50 mg, or placebo once daily for 3 months, followed by an extended period of treatment with OCA (for those who tolerated OCA) for 12 months.[43] Study subjects continued their same prerandomization UDCA dose throughout the clinical trial. Significant reductions in liver biochemistries (ALP, gamma-glutamyl transpeptidase [GGTP], aspartate aminotransferase [AST], and bilirubin levels) have been observed across all OCA treatment arms compared to the placebo group. Specifically, ALP levels decreased by 21%-25% on average from baseline values compared with only 3% in the placebo group, and 69% (68/99) of patients in the OCA arms had at least 20% reduction in ALP levels from baseline compared with 8% (3/37) in the placebo group. Pruritus, the main side effect in this study, was reported in 72% of those in the OCA arms (92/127) compared to 50% (19/38) in the placebo group, and the incidence/severity of pruritus was dose dependent (lowest in the 10-mg arm). ALP levels continued to decline in the extended open-label trial.

Most recently, in a phase III clinical trial of OCA, 217 PBC patients (of whom 93% received UDCA at baseline and throughout the clinical trial) who demonstrated inadequate responses or intolerance to UDCA were randomly assigned to receive either OCA at a dose of 10 mg/day (n = 73), 5 mg/day for 6 months with an increase to 10 mg/day if applicable (based on the patient's biochemical response, side effects, and whether or not the patient achieved the primary endpoint; n = 71), or placebo (n = 73).[44] After 12 months of treatment, the primary endpoint (serum ALP < 1.67 times the upper limit of the normal range, a reduction of at least 15% from baseline, and a normal total bilirubin level) occurred in 47% of the 10-mg group, 46% of the 5-mg to10-mg group, and in 10% of the placebo group. Pruritus occurred more frequently in the OCA than the placebo group (68% in the 10-mg group, 56% in the 5-mg to 10-mg group, and 38% in the placebo group. The percentage of patients who had a reduction of at least 15% from baseline in the serum ALP was higher in the 10-mg group (77%) and in the 5-mg to 10-mg group (77%) than in the placebo group (29%). Seven patients (10%) in the 10-mg group discontinued OCA due to pruritus, whereas only 1 patient (1%) in the 5-mg to 10-mg group discontinued OCA due to pruritus. None of the patients in the placebo group discontinued the regimen due to pruritus.

The safety and biochemical efficacy of OCA in PSC remains less known but is an area of interest. This is currently being investigated in a 24-week, double-blind, placebo-controlled, phase II clinical trial in patients with PSC (NCT02177136).

BUDESONIDE

Budesonide has been evaluated as adjunct therapy to UDCA in a few clinical trials in PBC patients. In an open-label clinical trial,[45] the addition of budesonide to UDCA in PBC patients with an inadequate response to UDCA resulted in deterioration of bone mineral density (BMD) and no biochemical improvement. Two randomized controlled clinical trials have shown that budesonide in addition to UDCA is safe

and well tolerated, with mild adverse effects on BMD.[46,47] Moreover, the addition of budesonide to UDCA resulted in significant improvement in liver biochemistries in PBC patients when compared to those who received UDCA alone. Budesonide should not be used in patients with cirrhotic-stage PBC because of increased risk of portal vein thrombosis.[48] The mechanism of action of budesonide in PBC remains to be elucidated; one study showed that steroids improve bile flow in the affected bile ducts by increasing the local bicarbonate secretion by means of up-regulating the gene encoding for the Cl-/HCO3 exchanger anion exchanger 2.[49] EASL currently recommends that budesonide could be considered in patients with early stage PBC with suboptimal response to UDCA.[34] This approach (UDCA + budesonide) is currently being investigated in a phase II, randomized, controlled clinical trial (NCT00746486).

FIBRATES

Fibrates (fenofibrate and bezafibrate) are commonly used for the treatment of hyperlipidemia for the modulation of lipid metabolism. The mechanism of action of fibrates in cholangiopathies is unknown; however, a few studies have shown that fibrates could reduce the hepatobiliary damage that occurs with PBC, possibly through improving the bile flow, increasing the hydrophilicity of bile acids, detoxifying bile acids, and reducing the amount of bile acids circulating to and from the liver.[50-53] Systematic meta-analysis studies have revealed that fibrates in addition to UDCA significantly improve liver biochemistries compared to UDCA alone in PBC patients with suboptimal response to UDCA, and this combined approach might offer survival benefit.[52-54] A phase III, randomized, controlled trial of bezafibrate in addition to UDCA is underway (NCT01654731). Whether the potential benefits of fibrates are applicable to PSC is an area that has very limited data.

ANTIVIRALS

Viral infections/proteins have been historically linked to PBC. In a pilot study examining the combination regimen of zidovudine + lamivudine in addition to UDCA versus UDCA + placebo, PBC patients in the antiretroviral regimen arm experienced a significant reduction in liver biochemistries compared to those in the placebo arm.[55-57] The long-term effects of antiretroviral drugs on the clinical and biochemical outcomes of PBC patients are under further investigation in a randomized, controlled, phase II clinical trial (NCT01614405).

USTEKINUMAB

Genome-wide association studies and animal models have revealed a potentially pathogenic role of the interleukin-12 (IL-12) pathway in the etiopathogenesis of PBC.[58,59] Ustekinumab (a monoclonal antibody directed against the p40 subunit of IL-12) has been evaluated in PBC patients who have had inadequate responses to UDCA. Although the vast majority of patients had significant reductions in serum levels of IL-17, IL-6, interferon gamma, and tumor necrosis factor alpha, these patients experienced only a modest reduction in serum ALP.[60]

ABATACEPT

T cells are thought to play a key role in the pathogenesis of PBC. The clusters of differentiation (CD)28/cytotoxic T lymphocyte antigen 4 (CTLA4):CD80/CD86 co-stimulatory pathway controls activation and proliferation of T cells and their direct effects on the antigen-presenting cells (APCs).[61,62] Abatacept, a CTLA4 immunoglobulin, blocks the interaction between CD28 (on T cells) and CD80/CD86 (on APCs), resulting in the attenuation of T-cell activity.[63] Preliminary data have shown that CTLA4 immunoglobulin decreases serum AMA, biliary lymphocyte infiltration, and bile duct damage in mice compared to placebo.[64] Abatacept is currently being evaluated in PBC patients with an incomplete biochemical response to UDCA (clinicaltrials.gov identifier: NCT02078882).

NGM282

Fibroblast growth factor 19 (FGF19) is an important regulator of BA biosynthesis. It interacts directly with FGF receptor 4, down-regulating the expression of CYP7a1. The end result is a decrease in BA biosynthesis, which is believed to be of therapeutic benefit in the cholangiopathies. NGM282 is an engineered version of FGF19. Preclinical experimental studies have shown a potential therapeutic role of FGF19 analogues in patients with cholestatic liver diseases. The safety and efficacy of NGM282 is currently being examined in patients with PBC (NCT02135536) and PSC (NCT02704364).

LUM001

Active absorption of BA occurs in the terminal ileum through the apical sodium-dependent BA transporter system. In this system, BAs are returned to the liver through the portal circulation. The circulation of BA from and to the liver is called the enterohepatic circulation. It has been proposed that the accumulation of hydrophobic "toxic" BA in liver tissue significantly contributes to the biliary damage that characterizes some cholangiopathies.[65] Thus, interrupting or modulating the enterohepatic circulation of BA might be of therapeutic benefit in patients afflicted with chronic cholestatic liver diseases.[66] This approach is currently being investigated in patients with PBC (NCT01904058, NCT02321306) and PSC (NCT02061540); the results have not yet been published.

ANTIBIOTICS/GUT MICROBIOME TARGETING

One hypothesis that has gained increasing attention is that the gut microbiome plays a role in the development of PSC. Portal vein bacteremia, leakage of bacterial toxins and metabolites through the disrupted intestinal epithelial lining, and alteration of the bile acid pool caused by bacterial metabolic activity have been suggested mechanisms.[67-69] Interestingly, treatment of experimental colitis with daily antibiotics led to resolving PSC-like hepatobiliary lesions,[70] further supporting this hypothesis. Absence of a commensal microbiome was recently found to exacerbate biliary injury in a mouse model of PSC.[71]

Over the last 2 decades, the application of high-throughput DNA-sequencing technology in gut microbiome analysis has improved the ability to rapidly, accurately, and (relatively) inexpensively assess the microbiome. Recently, several clinical studies using DNA-sequencing technology have found PSC patients to exhibit distinct gut microbiota compared to patients with UC alone and healthy controls. Specifically, *Escherichia, Fusobacterium, Lactobacillus, Entercoccus, Veillonella, Blautia*, Barnesiellaceae, and Lachnospiraceae have been found to be more abundant in PSC patients compared to UC patients and healthy controls, whereas reduced concentrations of Clostridiales II, *Prevotella, Roseburia*, and *Bacteroides* compared with UC patients and healthy individuals have been observed.[72-77]

Vancomycin has been studied in small case series of children with PSC and in a comparative trial versus metronidazole in adults with PSC.[78-81] In brief, the use of vancomycin with or without UDCA in PSC patients has been associated with improved liver biochemistries (including ALP in adults and GGTP in children). To date, there are no published randomized placebo-controlled clinical trials assessing the safety and efficacy of vancomycin in PSC patients. An open-label phase III clinical trial of vancomycin in pediatric PSC (NCT01802073) and a phase IV randomized placebo-controlled clinical trial of vancomycin in adults with PSC (NCT02605213) are currently ongoing. Fecal microbiota transplantation is another proposed therapeutic approach in patients with PSC and IBD that is under investigation (NCT02424175).

NOR-URSODEOXYCHOLIC ACID

Nor-UDCA, a C(23) homolog of UDCA with one fewer methylene group in its side chain, has shown a potential therapeutic benefit in PSC in an animal model, possibly through increasing the hydrophilicity of biliary bile acids, stimulating bile flow in injured bile ducts, and inducing detoxification routes for bile acids.[82] A phase II, randomized, placebo-controlled clinical trial of nor-UDCA in PSC patients has been completed, but results are yet to be published (NCT01755507).

BTT1023

The adhesion molecule vascular adhesion protein 1 (VAP1) is a membrane-bound amine oxidase that promotes leukocyte recruitment to the liver.[83] VAP1, in the presence of tumor necrosis factor alpha, is a prerequisite for aberrant expression of mucosal addressin cell adhesion molecule 1; this molecule recruits activated lymphocytes from the gut to the liver, and this process might be partially responsible for the biliary injury seen in PSC.[84] BTT1023, a fully human monoclonal anti-VAP1 antibody, is currently being tested in a phase II multicenter clinical trial in the United Kingdom (NCT02239211).

LYSYL OXIDASE HOMOLOG 2

Lysyl oxidase homolog 2 (LOXL2) is a secreted copper-dependent amine oxidase that modifies collagen and elastin. LOX deaminates the peptidyl lysine and hydroxylysine residues of collagen to form allysine; allysine condenses with other collagen aldehydes to create intramolecular and intermolecular crosslinking of collagen, which results in formation of collagen

fibers.[85] In the liver, this process is thought to be key in the pathogenesis of fibrosis. Simtuzumab (GS-6624), a humanized monoclonal antibody, inhibits fibrosis by binding to and inhibiting LOXL2. The effectiveness of GS-6624 in preventing progression of fibrosis in PSC patients is currently being examined in a phase II, randomized, placebo-controlled clinical trial (NCT01672853).

OTHER AGENTS/COMBINATION REGIMENS TESTED IN PBC AND PSC

There are agents that have been tried in PBC but have failed to show positive effects (clinical/biochemical response). Immunosuppressive agents (d-penicillamine, azathioprine, chlorambucil, colchicine, cyclosporine, prednisolone, and mycophenolate mofetil) have been examined in therapeutic clinical trials; however, they did not demonstrate clinical/biochemical efficacy and/or have been associated with serious adverse events.[86-92] A few drugs have been tested as add-on therapy to UDCA in PBC patients with suboptimal response to UDCA; the addition of colchicine did not offer further improvement in the liver biochemical profile,[93,94] and methotrexate was associated with severe side effects.[95-97] The addition of prednisolone to UDCA resulted in improved histologic abnormalities without a significant effect on liver biochemistries.[98] Thalidomide, an immunomodulating agent, did not result in clinical/biochemical improvement in a randomized placebo-controlled clinical trial.[99] Silymarin, an antioxidant, has been tried in PBC patients with an incomplete response to UDCA in an open-label clinical trial; no further improvement in clinical/biochemical profiles has been observed.[100]

Penicillamine, prednisone plus colchicine, methotrexate, budesonide, mycophenolate mofetil, tacrolimus, etanercept, and infliximab have been examined in PSC patients but either demonstrated no clinical/biochemical efficacy or resulted in serious adverse events.[101-111] Methotrexate and mycophenolate have been examined separately in combination with UDCA in PSC patients; no obvious clinical/biochemical benefits have been reported.[112,113]

Conclusion

Chronic cholestatic liver diseases remain important causes of morbidity and liver disease-related death worldwide and have become a major focus of research efforts. UDCA is approved for PBC by the FDA as a first-line therapeutic option and is recommended by the leading liver societies (AASLD and EASL). Despite its clinical efficacy, nearly 40% of PBC patients have an incomplete response to UDCA, and these patients are at risk for serious adverse outcomes. OCA, an FXR agonist, has recently been approved by the FDA as combination therapy (in addition to UDCA) in PBC patients who have an inadequate response to UDCA or as single therapy in PBC patients who are unable to tolerate UDCA; long-term outcomes of OCA in PBC remain to be elucidated. FDA-approved pharmacotherapy for PSC remains lacking, but OCA, oral antibiotics, and several other agents are actively being investigated in clinical trials in various phases. Similarly, additional pharmacotherapies for PBC continue to be sought, and as such, the pharmacoscape for PBC as well as PSC appears more promising and exciting.

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