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Review Article

Progress in the Management of Patients with Cholestatic Liver Disease: Where Are We and Where Are We Going?

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Abstract

Cholestatic liver disease is a group of diseases in which bile acid accumulates in the liver for various reasons, resulting in abnormal liver biochemical indicators and histological damage. Cholestasis can be divided into intrahepatic cholestasis and extrahepatic cholestasis, which will contribute to liver damage and progress to liver fibrosis and cirrhosis. Primary biliary cholangitis (PBC) and primary sclerosing cholangitis are the two most typical cholestatic liver diseases. Ursodeoxycholic acid is currently the first-line treatment for PBC, while obeticholic acid, budesonide and fibrates have also shown good potential in the treatment of PBC. There are currently no official drugs approved to treat primary sclerosing cholangitis, and the use of ursodeoxycholic acid may have certain clinical benefits. At present, progress has been made in new treatment directions for cholestatic liver disease, including fibroblast growth factor 19, cholestyramine, S-adenosyl-L-methionine, steroid drugs, farnesoid X receptor agonists, and more. Considerable progress has been made in the management of cholestatic liver disease but there are still many opportunities and challenges. In this review, we summarized the recommended guidelines for the management of cholestatic disease and the progress of new drug research and development, in order to provide an important reference for the clinical practice of cholestatic liver disease.

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Keywords: Cholestatic liver disease; Management; Ursodeoxycholic acid; Primary biliary Cholangitis; Primary sclerosing cholangitis; Ursodeoxycholic acid; Obeticholic acid.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BEC, biliary epithelial cell; ERCP, endoscopic retrograde cholangiopancreatography; FGF19, fibroblast growth factor 19; FXR, farnesoid X receptor; GGT, gamma-glutamyl transferase; IBD, inflammatory bowel disease; OCA, obeticholic acid; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PPAR, peroxisome proliferator-activated receptor; SAM-e, S-adenosyl-L-methionine; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

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Introduction

Cholestatic liver disease encompasses a spectrum of liver diseases characterized by impaired bile production, secretion, and excretion with various etiologies, leading to intrahepatic stasis and subsequent systemic reflux.[1] Bile acids are synthesized by hepatocytes and cholangiocytes. In an average healthy adult, the daily bile acid production is approximately 600 mL, with hepatocytes contributing around 450 mL and cholangiocytes accounting for approximately 150 mL.[1] Cholestasis can be either intrahepatic or extrahepatic. Intrahepatic cholestasis is primarily characterized by hepatocyte and cholangiocyte damage within the bile ducts, with no apparent evidence of obstructive lesions observed by imaging examination. The etiology of intrahepatic cholestasis encompasses immune dysfunction, viral infections, drug-induced injury, alcohol-related damage, etc. Extrahepatic cholestasis is characterized by damage or obstruction of the bile ducts, including septal (>100 μm), regional (300–400 μm), segmental (400–800 μm), left or right hepatic, or common bile ducts. Common causes of extrahepatic cholestasis are bile duct stones, malignant tumors of the pancreas or bile duct ampulla, or benign bile duct strictures.[2,3] Generally, the course of disease is divided into acute cholestasis if the course is less than 6 months or chronic cholestasis if it is more than 6 months. Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are the main types of chronic cholestatic liver disease.[4] In recent years, significant advancements have been made in understanding the pathogenesis and management of cholestatic liver disease, leading to a continuous increase in potential therapeutic targets and ongoing clinical trials. This review provides a comprehensive summary of the latest developments in the management of cholestatic liver disease.

Classification and diagnosis of cholestatic liver disease

According to the classification of etiology, cholestatic liver disease might be divided into intrahepatic or extrahepatic cholestatic liver disease. PBC and PSC are currently the main types of intrahepatic cholestatic liver disease but standardized diagnostic criteria for cholestatic liver disease have not been established. Several recent guidelines recommended using upper limit of normal (ULN) thresholds of alkaline phosphatase (ALP) level exceeding 1.5 × ULN and a gamma-glutamyl transferase (GGT) level exceeding 3 × ULN as indicators of cholestatic liver disease.[5,6] Elevated levels of

ALP and GGT are the most common early manifestations of cholestasis. Among liver enzymes, GGT has the highest sensitivity for diagnosing cholestasis. Generally, elevation of both ALP and GGT after ruling out other causes of liver injury such as alcoholism or infection, strongly suggests damage to hepatocytes and cholangiocytes, indicating the presence of cholestatic liver disease. Conversely, if only GGT is elevated while ALP remains within the normal range, it indicates damage specifically to bile canaliculi and bile duct cells. Finally, elevation of ALP without an increase in GGT usually excludes liver injury.[1] After abnormal biochemical manifestations are discovered, with other possible causes of liver damage being excluded, a diagnosis of cholestatic liver disease is made after comprehensive judgment based on biochemical results and imaging and endoscopy manifestations.

Treatment of cholestatic liver disease

The treatment of cholestatic liver disease is mainly etiological and symptomatic. First, the cause of cholestasis should be actively relieved. Surgical or endoscopic relief of obstruction is usually effective in patients with obstruction. For cholestasis caused by drugs, alcohol, etc., it is recommended to stop using the corresponding drugs and alcohol. Viral hepatitis should be given antiviral treatment. Cholestasis caused by immune dysfunction can be treated with ursodeoxycholic acid (UDCA).[1,5,6]

Additional drug therapy can effectively alleviate the symptoms of cholestasis by mitigating hepatocyte and cholangiocyte damage while regulating bile acid metabolism. Current pharmacological approaches for treating cholestasis primarily involve UDCA, obeticholic acid (OCA), budesonide, fibrates, S-adenosyl-L-methionine (SAM-e), cholestyramine, etc.[7,8] Given that PBC and PSC are the predominant types of cholestatic liver disease, this review focuses on pharmacological treatment of PBC and PSC.

Treatment of PBC

UDCA is the first-line therapy for PBC: Currently, UDCA is the only recommended first-line therapy for PBC. Evidence from many randomized controlled trials and meta-analyses shows that UDCA significantly improves the biochemical response of PBC, delays histological progression in the liver, and prolongs the liver transplant-free survival of patients.[3,9,10] UDCA is a physiological component of human bile acids but accounts for only 1–3% of the total endogenous bile acids in humans. When PBC patients and healthy volunteers are treated with therapeutic doses of UDCA (13–15 mg/kg/d), UDCA may account for up to 40% of total bile acids.[11] The recommended dose for PBC patients is 13–15 mg/kg/d. Clinical studies have confirmed that larger doses of UDCA (28–32 mg/kg/d) do not significantly increase the clinical benefits.[5,6] The safety of UDCA is generally satisfactory. PBC patients have good tolerance to UDCA, and only a few experience adverse events such as allergies and pruritus. If the patient tolerates UDCA and responds well, UDCA is recommended to use for life.[1,5,6]

Generally speaking, the therapeutic effectiveness of UDCA in PBC is mediated by four activities.[12,13] First, UDCA inhibits the synthesis of hydrophobic bile acids thereby reducing the damage caused by an excess of bile acids. UDCA is a natural bile acid that is not obviously cytotoxic even at concentrations of up to 500 μmol/L. After exogenous administration to patients with cholestasis, UDCA inhibits intestinal reabsorption of bile acids in the form of amidation products, thereby inhibiting the gut-liver circulation of bile acids. Consequently, the proportion of hydrophobic bile acids that re-enter the liver is greatly reduced and liver damage is significantly alleviated. Secondly, UDCA increases the production of non-liposoluble bile acids. As non-liposoluble bile acids cause less damage to bile duct cells than liposoluble bile acids, the reduced reabsorption of bile acids from the gut into the liver results in supplemental secretion of liposoluble bile acids by the liver. Liposoluble bile acids are less harmful to the liver and thus have a hepatoprotective role. In addition, the administration of UDCA enhances the secretion of bicarbonate by bile duct cells., thereby forming a barrier that protects endothelial cells from excessive bile-acid damage. Finally, UDCA reduces the apoptosis of cholangiocytes and exerts a protective function. Overall, UDCA has therapeutic activity in PBC by regulating the multiple aspects of bile acid metabolism, thereby reducing further damage and preventing further toxic bile acid damage.

Other therapies for PBC besides UDCA: Not all PBC patients respond well to UDCA, and about 40% of PBC patients fail to achieve effective biochemical improvement after using UDCA. Currently, the commonly accepted criterion for assessing a poor response to UDCA is an ALP level greater than 1.67 × ULN. Most clinical trials use 1 year of UDCA treatment as the period for evaluating drug response in PBC patients.[14] For PBC patients with a poor response to UDCA, the current recommendations of the EASL (2017), AASLD (2018) and APASL (2022) guidelines on second-line treatment of PBC include OCA, budesonide, and fibrates. Of these three drug classes, only OCA has been officially approved by EASL and AASLD for second-line treatment of PBC and budesonide and fibrates are currently used as off-label therapy.[5,14,15]

OCA is a semisynthetic bile acid analog and an FXR agonist that inhibits the synthesis of bile acids and relieves the symptoms of cholestasis. Multiple clinical trials have shown that for PBC patients with poor response to UDCA, adding or switching to OCA (5–10 mg/kg/d) significantly improves the biochemical response and delays the histological progression of PBC patients.[14,15] In a phase 3 trial of OCA in PBC patients with a poor response to UDCA, patients received either OCA or placebo in addition to continued UDCA. The primary endpoint occurred in more patients in the 5–10 mg group (46%) and the 10 mg group (47%) than in the placebo group (10%; $p<0.001$ for both comparisons).[16] The trial demonstrated the efficacy of OCA in patients who had had a poor response to UDCA. However, OCA treatment was associated with a higher rate of adverse events. Pruritus was more common in the OCA group than in the placebo group (56% of patients in the 5–10 mg group, 68% in the 10 mg group, and 38% in the placebo group). Serious adverse events occurred in 16% of the 5–10 mg group, 11% of the 10 mg group, and 4% of the placebo group.[16] Based on the results of the above clinical trials, OCA was approved by the Food and Drug Administration (FDA) for the treatment of PBC patients with a poor response or intolerance to UDCA but with close monitoring of the occurrence of adverse events. The main adverse events of OCA in PBC patients were pruritus and fatigue. The probability of pruritus caused by OCA increased as the treatment dose increased. Some patients stopped taking the drug because they did not tolerate pruritus, so special attention should be paid to the clinical application when OCA is used.[14]

Drugs that were not approved by the guidelines have had good results in the treatment of PBC, including fibrates and budesonide. Fibrates such as fenofibrate and bezafibrate are frequently used as an adjuvant treatment for PBC along with UDCA.[1,5,6] Fibrates are peroxisome proliferator-activated receptor (PPAR) agonists and bezafibrate and fenofibrate are widely licensed as PPAR agonists for the treatment of dyslipidemia.[17,18] After activation, PPARs inhibit bile acid synthe-

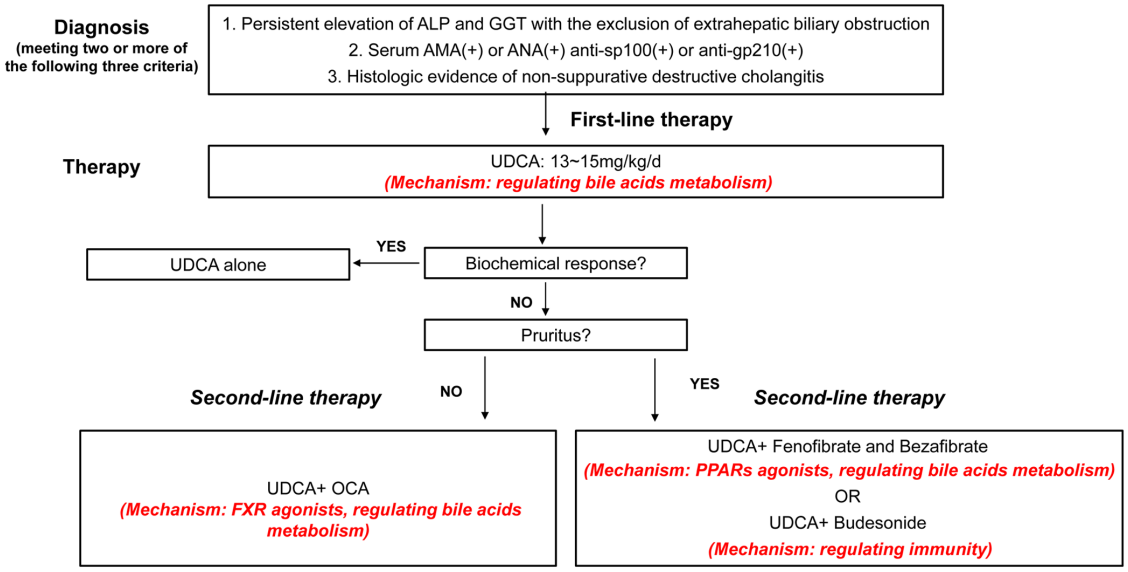

Fig. 1. Diagnosis and treatment strategy of PBC. ALP, alkaline phosphatase; AMA (+), anti-mitochondrial antibody positive; ANA (+), antinuclear antibody positive; anti-gp210(+), human glucoprotein 210 antibody positive; anti-sp100(+), sp100 nuclear antigen (sp100) antibody positive, FXR, farnesoid X receptor; OCA, obeticholic acid; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PPARs, peroxisome proliferator-activated receptors; UDCA, ursodeoxycholic acid; GGT, gamma-glutamyl transferase.

sis by downregulating the expression of bile acid synthase CYP7A1, which is the key regulator of bile acid synthesis. Several studies have shown that the use of fibrates as an adjunctive therapy to UDCA led to a more significant decrease in ALP of PBC patients, which was consistent with a trend of improving overall survival.[19–21] A 2016 retrospective study found that the addition of fenofibrate to PBC treatment significantly increased the rate of biochemical response to ALP in PBC patients with a poor response to UDCA (41% in fenofibrate group vs. 7% in UDCA group).[22] In a 24-month phase 3 trial (BEZURSO trial), Bezafibrate was administered at a dose of 400 mg daily to patients with an incomplete biochemical response after 12 months of UDCA treatment The ALP normalization rate was 67% in the treatment group compared with 2% in the placebo group (p<0.001).[23] The APASL guidelines (2022) recommend the addition of bezafibrate (400 mg/d) or fenofibrate (200 mg/d) to UDCA for the treatment of PBC patients with an incomplete response to UDCA. Adverse events of such combination therapy should be closely monitored, especially in PBC patients with cirrhosis.[14]

Studies have shown significant improvement of ALP and changes in liver histology in PBC patients treated with budesonide.[24–27] Hirschfield *et al*.[27] found that in PBC patients with a poor response to UDCA, the combination of UDCA and budesonide for 36 months did not improve the histological progression, but the proportion of patients with normal ALP (35%) was significantly higher than that in the placebo group (9%, p=0.023). The clinical trials are not large enough, so larger trials and more complete clinical trial evidence are needed to confirm the benefits of budesonide in the treatment of PBC. Budesonide (6–9 mg/day) is now recommended for the treatment of noncirrhotic PBC patients who do not respond well to UDCA in the APASL guidelines (2022).[14] A map of diagnosis and treatment strategies for PBC is shown in Figure 1.

Treatment of complications in PBC: Pruritus and fatigue are common complications in patients with PBC. Pruritus is one of the characteristic cholestatic symptoms of PBC, with approximately 80% of patients experiencing pruritus during the course of the disease.[5,6] It can occur at any stage of the disease process, but it is important to note that as liver disease worsens, pruritus improves. Cholestyramine is a bile-acid sequestrant, a nonabsorbable resin recommended for first-line treatment of pruritus.[5,6] However, it is worth noting that cholestyramine affects the absorption of UDCA, so it is generally used 4–6 hours before UDCA is taken.

The pregnane X receptor agonist rifampicin is the second-line choice for pruritus as it can alleviate pruritus in patients who are intolerant to cholestyramine or have no response to the first-line therapy.[28,29] However, rifampicin may affect coagulation function and vitamin K absorption, so it needs to be carefully tested during clinical use. The opioid receptor antagonist naltrexone is used as a third-line treatment for pruritus.[5,6] A few patients may have side effects such as nausea, vomiting, and mild pain when taking naltrexone. Naltrexone metabolites can accumulate in patients with decompensated liver disease and should be used carefully in such patients. These drugs should be used in small doses first and then gradually increased to avoid withdrawal effects.[14]

Fatigue is reported by more than 50% of PBC patients and is an important cause of impaired quality of life.[14] Fatigue is generally considered a normal response in patients with PBC (to be distinguished from hepatic encephalopathy in patients with advanced liver disease) and is not related to the severity of the disease. To date, there are few high-quality clinical trials in this area and there are no licensed treatments. It is generally recommended that patients may be able to improve fatigue caused by PBC by appropriate exercise.

Treatment of PSC

Currently there are no officially approved drug therapies for PSC: There are currently no officially approved drug therapy for PSC and the use of UDCA in patients with PSC is controversial. There is currently a lack of high-quality clinical trials to confirm that PSC patients can benefit from UDCA treatment.[1,5,6] The effect of UDCA at therapeutic doses (15–20 mg/kg/d) in slowing the progression of PSC may occur only in a subset of patients. Many clinical trials have con-

firmed that UDCA improves the clinical and biochemical indicators of PSC patients. The results indicated that low-dose UDCA (10–15 mg/kg/d) significantly improved biochemical indicators but did not improve the clinical endpoints of liver transplantation and death. Moderate doses of UDCA (17–23 mg/kg/d) improved the biochemical indicators in PSC patients but there is considerable controversy about the effectiveness in improving long-term prognosis. High-dose UDCA (>25 mg/kg/d) did not improve biochemical indicators in PSC patients but did increase the probability of adverse outcomes such as liver transplantation and death.[30,31]

There is currently insufficient clinical data on the treatment of PSC with other drugs. Some studies have shown that budesonide and prednisone improved the biochemical indicators in PSC patients.[32,33] However, no current guidelines recommend glucocorticoids in the routine treatment of PSC patients. In addition, some small studies have shown that immunosuppressants such as tacrolimus were effective in improving biochemical indicators in PSC patients.[34] Some studies have exploring the therapeutic effectiveness of antibacterial drugs in PSC such as vancomycin, but the samples of these clinical data are small and the results are not sufficient.[35]

Use of endoscopy to treat PSC is controversial: PSC may be complicated by esophageal and gastric varices as well as colitis, so screening for varicose veins is strongly recommended for PSC patients diagnosed with cirrhosis and portal hypertension.[6] Screening colonoscopy is recommended for all PSC patients. As the disease progresses, significant bile duct sclerosis and stricture may occur. In addition, about 30–50% of PSC patients will develop overt bile duct stenosis, the occurrence of which is often associated with a poor prognosis.[5,6] However, there is still no high-quality clinical evidence on the clinical benefit of interventional endoscopic treatment of bile duct stricture. The current consensus generally recommends that endoscopic retrograde cholangiopancreatography (ERCP) intervention should be avoided in PSC patients without obvious jaundice unless cholangiocarcinoma is suspected.[5,6] It is generally believed that the use of ERCP balloon dilation or stent implantation to relieve biliary obstruction may relieve biochemical conditions and pruritus in PSC patients. In patients undergoing ERCP for overt stenosis, pathological sampling of suspected stenosis must be performed. Biliary dilatation is preferred over biliary stent placement in patients undergoing ERCP for overt stenosis.

Liver transplantation is the most effective treatment for PSC patients.[1,5,6] Indications for liver transplantation in patients with PSC are similar to those of other chronic liver diseases, and include severe impairment of quality of life, complications of portal hypertension, and liver failure. Different guidelines recommend different indications for liver transplantation in PSC patients. In general, the long-term prognosis of PSC patients following liver transplantation is favorable. Numerous study findings have consistently demonstrated a post-transplant survival rate exceeding 70% in PSC patients.[6] PSC patients with decompensated cirrhosis and a Model for End-Stage Liver Disease score ≥15 or a Child-Turcotte-Pugh score of C should be evaluated for liver transplantation.[6] PSC patients should still be closely monitored for disease recurrence after liver transplantation.

Management of complications of PSC: The complications in PSC patients include cholangitis, metabolic bone disease, pruritus, fatigue, cholangiocarcinoma, etc.[36] Cholangitis is a common complication of PSC. Biliary tract bacterial infection has been reported in 55% of patients when undergoing liver transplantation. Previous ERCP clearly increases the risk of cholangitis especially when the stent is left in place. ERCP is a major risk factor for PSC cholangitis, and antibiotics should be used routinely in clinical practice. Moreover, osteopenia and osteoporosis are common in PSC, and patients with metabolic bone disease should routinely take vitamin D and calcium supplements. For the treatment of pruritus associated with PBC, medication with cholestyramine, rifampin, and naltrexone may be effective.

Cholangiocarcinoma is currently one of the most common causes of death in PSC patients who do not undergo transplantation.[37,38] The usual manifestations are epigastric pain, liver biochemical deterioration, jaundice, and elevated serum CA19.9. Chemotherapy remains the primary palliative treatment for patients with cholangiocarcinoma. Although resection may be curative, it is often not possible in PSC patients with intrahepatic malignancies.

Progress in the development drugs that target PBC and PSC

Novel therapeutic approaches are needed owing to incomplete UDCA responses observed in 35–40% of patients with PBC and the debated efficacy of UDCA in PSC patients. Currently, novel PBC treatment primarily involves four targets, modulation of bile acid metabolism, preservation of bile duct endothelial cell function, immune regulation, and mitigation of fibrosis (Fig. 2). Novel therapeutic targets for PSC treatment primarily revolve involves regulating fibrosis and microbiome. Phase III clinical trials of PBC and PSC therapies listed in the current FDA registry are summarized in Table 1.

Drugs designed to regulate bile acids metabolism in PBC: In terms of bile acids metabolism, reducing bile acid synthesis bile acids circulation, and increasing bile acids excretion may be effective treatment strategies. The synthesis of bile acids primarily occurs in hepatocytes, with the CYP7A1 gene serving as the pivotal regulatory factor of the process. After being synthesized, bile acids are secreted by liver cells into bile ducts and flow into the intestine. In the intestine, bile acids are metabolized from primary bile acids into secondary bile acids, which are then reabsorbed into the blood through intestinal epithelial cells and returned to the liver for recycling.[39,40] FXR, PPARs, and FGF19 have been shown to be important regulators of bile circulation.[12,17] The FXR gene is the bile sensor of liver cells. After liver cells are stimulated by bile acids, activation of FXR inhibits the expression of CYP7A1, thereby reducing the formation of bile acids. FXR agonists are the most investigated drug target for cholestatic liver disease. There are steroid and nonsteroid FXR agonists. OCA is a representative FXR agonist, and frequent side effects of this group of drugs are pruritus and increase of low-density lipoprotein. Cilofexor is a nonsteroidal FXR agonist, that has shown improvement in the ALP response of PBC patients. However, clinical trial data are insufficient, and further study with analysis of more extensive data is needed.[41]

The PPAR family has an important role in bile acid synthesis. PPAR agonists, represented by fibrates, have been effective in PBC patients, and are recommended by some guidelines as second-line treatment for PBC patients with poor response to UDCA. At present, some new PPARs agonists are also under clinical study for PBC. Seladelpar is a selective PPAR-δ agonist and elafibranor is a PPARα/δ agonist that has been tested in recent clinical trials.[42,43]

Fibroblast growth factor 19 (FGF19) was found to have good potential in PBC patients. An increase in intestinal FGF19 concentration was found to activate the FGFR4 pathway in the liver and suppress CYP7A1 gene expression, thereby inhibiting cholestasis.[44] NGM282 is a synthetic analog of FGF19 that has been evaluated in phase 2 clinical trials in patients with PBC and PSC. It reduced ALP levels in 50% of the treat-

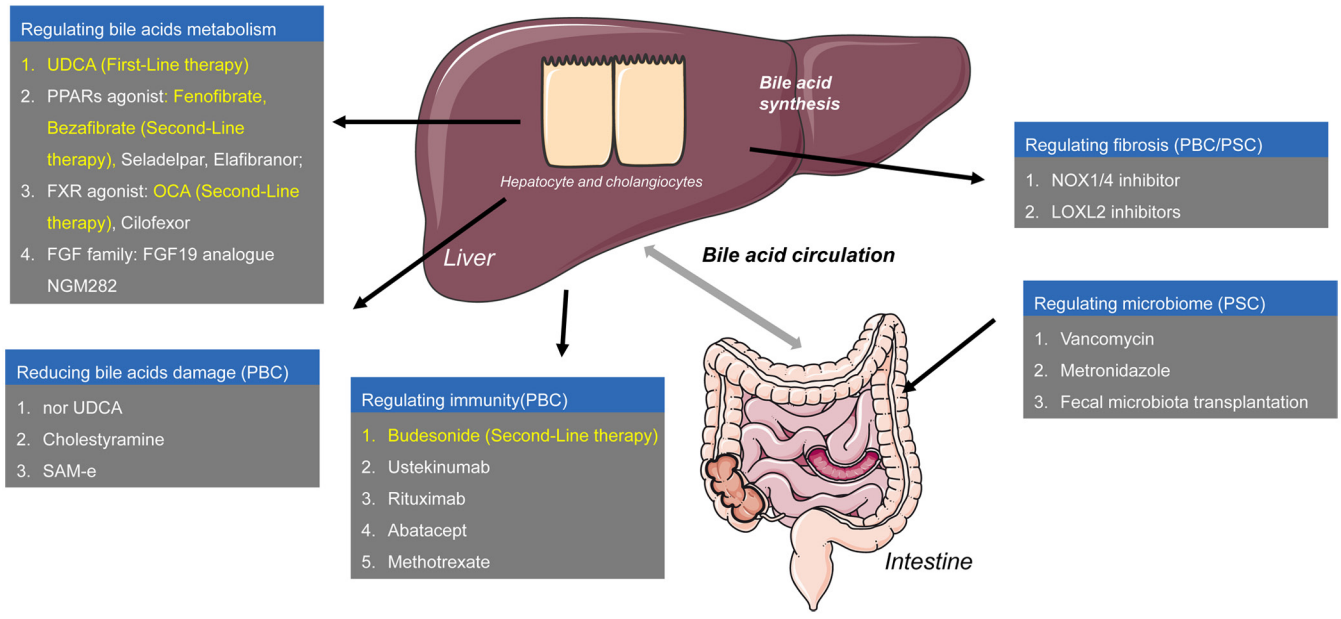

Fig. 2. Therapeutic targets for cholestatic liver diseases. FGF19, fibroblast growth factor 19; OCA, obeticholic acid; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PPARs, peroxisome proliferator-activated receptors; SAM-e, S-adenosyl-L-methionine; UDCA, ursodeoxycholic acid; NOX, NADPH oxidases; LOXL2, Lysyl Oxidase Like 2.

ed patients compared with only 7% of those given a placebo group.[45] Biochemical parameters of PSC patients improved in a clinical trial of NGM282.[46]

Drugs designed to regulate bile acid circulation and damage in PBC: A feasible approach to reducing bile acid circulation is the use of bile acid exchange resins. Cholestyramine has been effective in clinical practice. It improved the biochemical response as well as having a good therapeutic effect on pruritus in PBC patients.[5,6] UDCA has shown good therapeutic prospects in protecting against bile acid dam-

Table 1. Main phase III clinical trials on PBC and PSC

Target	NCT number	Drug	Condition	Population size, *n*	Dosage	Primary endpoints
PPAR agonists	NCT06016842	Elafibranor or placebo	PBC	450	80 mg/d	EFS (maximum duration of 7 years)
PPAR agonists	NCT06051617	Seladelpar or placebo	PBC and compensated cirrhosis	192	10 mg/d	EFS (36 months)
PPAR agonists	NCT03301506	Seladelpar	PBC	500	5 mg/d, 10 mg/d	Adverse events AND Biochemical response
PPAR agonists	NCT05751967	(Fenofibrate or placebo) +UDCA	PBC	150	200 mg/d+UDCA	Biochemical response
PPAR agonists	NCT05133336	Saroglitazar Magnesium or placebo	PBC	192	1 mg/d, 2 mg/d	Biochemical response
FXR agonist	NCT05450887	(OCA or placebo) ±UDCA	PBC	156	5 mg/d±UDCA	Biochemical response
NOX inhibitor	NCT05014672	Setanaxib or placebo	PBC	318	1,200 mg/d	Biochemical response
Bile acid	NCT03872921	Nor UDCA or placebo	PSC	300	1,500 mg/d	Biochemical response and histological improvements
PPAR agonists	NCT04309773	(Bezafibrate or placebo) +UDCA	PSC	104	400 mg/d	Biochemical response
Antibiotic	NCT03710122	Vancomycin or placebo	PSC	102	Not reported	Biochemical response

EFS, event-free survival; FXR, farnesoid X receptor; OCA, obeticholic acid; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PPAR, peroxisome proliferator-activated receptors; UDCA, ursodeoxycholic acid; NOX, NADPH oxidases.

age. 24-Norursodeoxycholic acid (NorUDCA) is a derivative of UDCA. Its metabolism differs significantly from UDCA in that it is not conjugated to taurine or glycine. NorUDCA has been found to cause the bile duct endothelium to secrete more bicarbonate, which plays a cell-protective role.[47] SAM-e is a naturally occurring methyl donor that helps maintain cell membrane integrity. SAM-e has been found to inhibit bile salt-induced apoptosis *in vitro*, and has been effective in the treatment of PBC.[48]

Drugs designed to regulate immunity in PBC: Currently, there is a prevailing agreement that PBC and PSC are autoimmune-related, highlighting the potential therapeutic for immune modulation as a therapeutic avenue. Cortisol hormone drugs including budesonide, have been shown effective for the clinical treatment of PBC.[21,27] Methotrexate (a folate reductase inhibitor) and mycophenolate mofetil (an inosine monophosphate dehydrogenase inhibitor) have also been investigated for the treatment of PBC or PSC but no good therapeutic effect has been found.[49,50]

Other studies have evaluated the role of biological agents in the treatment of PBC, including mesenchymal stem-cell therapy, monoclonal antibody therapy, etc. They explored corresponding therapeutic effects but their potential has not yet been demonstrated.[51] At present, clinical studies of biological agents for the treatment of PBC include ustekinumab, rituximab, and abatacept but their clinical effectiveness has not been demonstrated. The pathogenesis of PBC may be different from that of traditional autoimmune diseases.[52–54]

Drugs designed to regulate fibrosis in PBC

Similar to other chronic liver diseases, both PBC and PSC have a progressive course leading to the development of liver fibrosis. Therapeutic agents targeting liver fibrosis may thus be effective in advanced stages of PBC and PSC. Setanaxib (GKT831) is a NOX1/4 inhibitor that inhibits NADPH oxidases 1 and 4. Previous studies have shown that it alleviated the development of liver inflammation and fibrosis in mice with PBC and can improve fibrosis and cholestasis. In a phase 2 clinical study of Setanaxib in PBC patients, patients received either Setanaxib or placebo in addition to UDCA. The results revealed a significant decrease in GGT level and liver stiffness in patients treated with 400 mg Setanaxib, suggesting reductions in cholestasis and fibrosis.[55]

Drugs designed for PSC

Clinical trials for PSC are difficult due to the lack of standardized and applicable inclusion criteria, as well as clinical endpoints. Clinical trials for drugs to treat PSC are similar to those for PBC, and include FXR agonists, PPAR agonists, and others. Currently, there are no approved drug treatments for PSC, so liver transplantation remains an important means of treating the disease. It is believed that PSC may be related to the disruption of certain physiological processes in the gastrointestinal tract, as patients with PSC often present with concurrent intestinal dysfunction such as inflammatory bowel disease (IBD).[56] Consequently, clinical trials targeting the gut microbiota of PSC patients should be paid more attention. Several ongoing clinical trials have demonstrated that antibiotic interventions, such as vancomycin or metronidazole, have the potential to improve biochemical markers in PSC patients.[57,58] Furthermore, fecal microbiota transplantation has shown promise as a therapeutic approach for treating PSC patients, and has been found to improve biochemical parameters. However, evidence from large clinical studies is needed to support the. effectiveness of antibiotic therapy and fecal microbiota transplantation.

Summary

Cholestatic liver disease is characterized by excessive cholestasis leading to biochemical index disorders and liver histopathological damage. PBC and PSC are the most common types of cholestatic liver disease and have some similar pathological similarities. As our understanding of the mechanisms behind PBC deepens, we are developing more accurate and effective treatments. UDCA is approved as a first-line treatment for PBC and can significantly improve patients' biochemical outcomes and delay the progression of the histological course. OCA is approved for the treatment of PBC patients with poor response to UDCA and has also shown good therapeutic effects. Fibrates and budesonide have also shown promising results as off-label treatments for PBC, and are often used in conjunction with UDCA.

Pruritus and fatigue are common adverse reactions of PBC. Cholestyramine is currently the recommended first-line treatment for pruritus. Rifampicin and naltrexone are recommended as second-line treatments, both of which have shown good therapeutic effects. There is currently no ideal treatment for fatigue but appropriate exercise and nutritional supplements may be effective.

The development of drugs for PBC currently focuses on regulating bile acid metabolism, protecting cholangiocyte function, and regulating immune function. Certain drugs, including fibrates, PPAR activators, UDCA, and others, have demonstrated therapeutic potential and are worthy of special attention, but there is still no clear direction for drug development for PSC treatment. Owing to a lack of high-quality clinical research results, no drugs have been approved for the treatment of PSC. In clinical practice, UDCA has been effective in improving biochemical indicators of PSC, and endoscopic treatment may alleviate the symptoms of PSC obstruction. Liver transplantation remains the most effective treatment for PSC patients.

Drug therapy for PBC and PSC has made advances but it still does not meet the demands of clinical practice. Although some PBC therapies that improve serum biochemical indicators and long-term prognosis are available, the exploration of more effective solutions is needed. An ideal treatment for PSC is urgently needed. The main reason for this unmet clinical need is the unclear mechanisms exploration of etiology in PBC and PSC.

The pathophysiology of PBC is largely elucidated and recent studies have focused on the initiating factors of the disease. It is generally accepted that PBC is a disease driven by both genetic and environmental factors, and is closely related to autoimmune dysfunction. For reasons that have not yet been elucidated, mitochondria in biliary epithelial cells (BECs) are attacked, leading to BEC dysfunction, bile duct injury, and cholestasis. A characteristic biochemical change in PBC patients is antimitochondrial antibody BEC seropositivity. One of the urgent questions to be answered is that although mitochondria are present in all nucleated cells, why are mitochondria in BECs but not other cells attacked in PBC patients.[58,59] Study of this immunological mechanism is important for the development of new drugs that can target PBC and represents a new direction. The immune system may play an important role in the development of new drugs for PBC. Protection of BEC function is thought to be important. Because increased BEC apoptosis leads to bile duct dysfunction, the inhibition of BEC apoptosis is of great significance.[60] It is also important to note that PBC is more common in women than in men.[61] Does this suggest that sex hormones may be involved in the progression of PBC? Targeting the role of sex hormones in the progression of PBC is also an important direction for subsequent drug research

and development.

Recent studies of the etiology of PSC have focused on the correlation of PSC and IBD. There is a controversy about whether PSC and IBD are two independent diseases or the same disease manifests in different organs. A lot of clinical evidence shows that the two diseases are similar, but further investigation is needed to determine a causal relationship between the two diseases. Although there is a strong correlation between the two diseases, a number of clinical trials have confirmed that drugs suitable for IBD have very limited benefits for the treatment of PSC, which suggests that pathophysiology of PSC differs from that of IBD.[62,63] It is very important to optimize the design of new drugs and to explore appropriate therapeutic drug targets. There is no satisfactory animal model of PSC disease, which limits the progress of new drug development.[64] Development of suitable animal models of PSC is also a direction of future research.

To sum up, this article reviewed current management strategies of cholestatic liver disease, especially PBC and PSC, and the direction of drug development. We hope that safe and effective drugs for cholestatic liver disease will gradually emerge.

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Conflict of interest

LGL has been an Associate Editor of *Journal of Clinical and Translational Hepatology* since 2013. The other author has no conflict of interests related to this publication.

Author contributions

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