Primary Biliary Cholangitis and Primary Sclerosing Cholangitis Therapy Landscape

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Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are rare, and chronic cholestatic diseases that can progress to liver failure. The goals of treatment are to halt the progression of liver disease to cirrhosis and/or liver failure, and alleviate symptoms associated with these diseases. Ursodeoxycholic acid has historically been the first-line treatment of PBC, with obeticholic acid and fibrates used as second-line or adjunctive therapies. However, the treatment landscape is rapidly expanding. Recently, 2 new second-line agents gained US Food and Drug Administration approval for the treatment of PBC, and several other therapies remain under investigation with promising results. Although significant progress has been made in the development of therapies for PBC, there are no current approved treatments of PSC other than liver transplantation although several emerging therapies have shown encouraging results. This review outlines the current and upcoming treatments of PBC and PSC.

KEYWORDS: PBC; PSC; treatments; therapeutic options

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D458

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INTRODUCTION

Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are relatively rare diseases with a reported prevalence ranging from 0 to 16.2 per 100,000 for PSC and 1.91–40.2 per 100,000 individuals for PBC (1). The exact mechanisms that lead to the development of PBC are incompletely understood. PBC is an autoimmune disease characterized by immune-mediated destruction of medium and small-sized bile ducts (2,3). It is postulated that genetic and environmental factors trigger an autoimmune reaction directed toward the biliary epithelial cells (4). PSC is a rare, chronic, progressive, cholestatic disease characterized by inflammation, fibrosis, and stricturing of large and medium-sized intrahepatic and/or extrahepatic ducts, which can lead to progressive liver failure if left untreated (5). The prevalence of PSC is estimated to be quite low but may be increasing over time (6,7). Not much is known about the exact pathogenesis of PSC but genetic, environmental, and microbial factors have been implicated.

METHODOLOGY

The aim of this review was to examine emerging, novel treatments of PBC and PSC. A comprehensive literature search was conducted using PubMed, the Cochrane Library, Scopus, and ClinicalTrials.gov. Peer-reviewed articles focusing on existing and novel therapeutic approaches for both adult and pediatric patients with PBC and PSC were included. Preclinical studies were excluded.

Primary biliary cholangitis

The goal of therapy in PBC is to prevent its progression to cirrhosis, liver failure, liver transplantation, and death. Another goal of medical therapy is to improve the quality of life in patients by alleviating disabling symptoms such as fatigue, sicca complex, and pruritus. Currently, ursodeoxycholic acid (UDCA) is the only approved first-line therapy for PBC. Obeticholic acid (OCA) and elafibranor are approved as second-line agents for patients with an inadequate response to UDCA or as monotherapy in patients who are intolerant to UDCA (Figure 1). Serum alkaline phosphate (ALP) and bilirubin levels are reliable indicators of inflammation, disease severity, and response to treatment (8). Patients with ALP levels $>$ 2 times upper limit of normal (ULN) and elevated bilirubin levels at diagnosis are at increased risk of worse outcomes (9,10). In the next section of this review, we will review the current and upcoming treatments of PBC (Table 1).

Current treatments for PBC

Ursodeoxycholic acid. UDCA is the first-line treatment of PBC and has been shown to alter the natural history of the disease (11–13). It was first approved by the US Food and Drug Administration (FDA) in 1997 and works through several proposed mechanisms (14). UDCA is hydrophilic and acts to displace the more cytotoxic bile acids within bile, thereby safeguarding cholangiocytes from membrane damage (2). UDCA at a dose of 13–15 mg/kg/d for at least 12 months has been shown to improve survival free of liver transplant, irrespective of the severity of the

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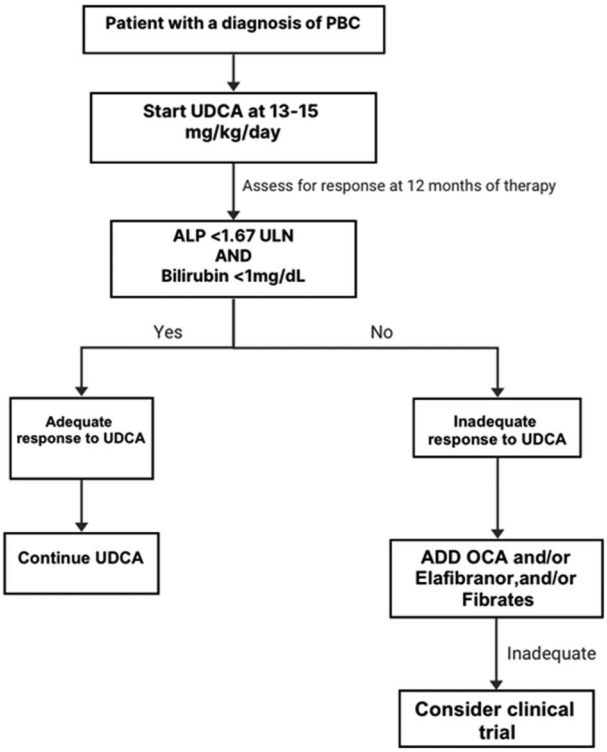

Figure 1. Current treatments for PBC. ALP, alkaline phosphate; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

disease (15). It is also associated with a decrease in ALP, total bilirubin, cholesterol, and immunoglobulin M levels in patients with PBC (12,13,16–19). Furthermore, treatment with UDCA for 2 years has also shown to delay histological progression of PBC (20). Response to UDCA is typically measured after 12 months of treatment (21) but can begin as early as 6 months, by measuring serum ALP and bilirubin levels, which have shown to closely correlate with the risk of liver transplant or death (8). Several criteria can be used to determine response to treatment with UDCA and these include Rochester I & II, Global Assessment of Liver Outcomes (GLOBE) Score, Toronto, Paris I & II, Rotterdam, UK PBC, and Barcelona (10,22–25). Approximately 40% of patients do not respond to UDCA (26), and a lack of biochemical response is associated with a 5-fold increase in the progression of disease to cirrhosis and a 3-fold increase in mortality (27). UDCA also does not demonstrate a consistent effect on the resolution of fatigue, pruritus, and bone disease associated with PBC (28). Around 5%–10% of patients are intolerant to UDCA due to adverse effects such as weight gain, hair thinning, and flatulence (29).

Obeticholic acid. OCA was approved in 2016 as a second-line treatment of PBC or as monotherapy in patients who are intolerant to UDCA (30). The US FDA granted approval based on a reduction in ALP as a surrogate end point under the agency's accelerated approval program that provides earlier access to promising drugs, while confirmatory trials are ongoing (30). A full approval from the US FDA would require improvements in clinical outcomes such as improved survival and delayed progression to cirrhosis, which have not yet been established (30).

OCA is a potent selective farnesoid X receptor (FXR) agonist. FXR agonism leads to increased excretion of bile acids into the bile, decreased ileal uptake of bile acids, and decreased synthesis of new bile acids (31). In the landmark Primary Biliary Cholangitis Obeticholic Acid International Study of Efficacy trial, which was a double-blind, placebo-controlled Phase 3 trial involving 216 patients who were either intolerant or had an inadequate response to UDCA, patients were randomized to receive OCA at a dose of 10 mg, OCA at a dose of 5 mg, or a placebo (32). Since ALP and bilirubin levels correlate with the risk of liver transplantation and death, they were used as surrogate markers for the progression of PBC. The primary end points of the trial were defined as a (i) decrease in the ALP levels to < 1.67 ULN, with at least a 15% reduction from the baseline, and (ii) maintaining bilirubin within ULN. At the end of 12 months, 46% in the 5 mg OCA group and 47% in the 10 mg OCA group reached the primary end point compared with 10% from the placebo group. These results were sustained in the 5-year open label extension of this trial, with patients on OCA demonstrating greater transplant-free survival than real-world controls (33). Subsequently, it was discovered that OCA was associated with hepatic decompensation and failure sometimes resulting in death or liver transplantation in patients with compensated cirrhosis with evidence of portal hypertension or decompensated cirrhosis. This led to a label change, and OCA now carries a black box warning for this subgroup of patients (34,35). OCA is associated with a dose-related risk of pruritus and may also be accompanied by a decrease in high-density lipoprotein and elevation of total cholesterol and low-density lipoprotein levels (32,36).

A subsequent confirmatory trial, the COBALT trial, was a multicenter, phase 3b/4, double-blind, randomized, placebo-

Table 1. Therapeutic agents currently in Phase 3 clinical trials for primary biliary cholangitis

Drug	NCT	Mechanism of action	Number of patients	Trial duration	Findings
Seladelpar	NCT04620733	PPAR-delta agonist	N = 112	12 mo	• 69% met POISE at 12 mo • 33% had normal ALP at 12 mo • Symptomatic improvement in pruritus
Saroglitazar	NCT05133336	PPAR-alpha/gamma agonist	N = 37	16 wk	• 71% met POISE
Setanaxib	NCT05014672	NOX1/4 inhibitor	N = 111	24 wk	24% decrease in ALP in patients with liver stiffness >0.6 kPa
Linerixibat	NCT04950127	IBAT inhibitor	N = 147	12 wk, extension in progress	Improved pruritus and insomnia

POISE Criteria is defined as ALP <1.67 times of ULN and normal total bilirubin.
ALP, alkaline phosphate; IBAT, ileal bile acid transporter; NADPH, nicotinamide adenine dinucleotide phosphate; NCT, National Clinical Trial; NOX1, NADPH oxidase 1; NOX4, NADPH oxidase 4; Primary Biliary Cholangitis Obeticholic Acid International Study of Efficacy; PPAR, peroxisome proliferator-activated receptors.

controlled trial that evaluated the long-term efficacy of OCA monotherapy in patients with PBC. The primary end point was defined as the time to first occurrence of a significant clinical event such as liver transplantation, all-cause death, or hospitalization for serious liver-related events. No statistically significant differences between OCA and placebo were noted on the primary end point. The trial was terminated early due to statistical futility, attributed to a high drop-out rate among placebo-treated patients who likely suspected their assignment to the placebo due to the lack of reduction in ALP levels (37). However, real-world evidence from several large databases suggested that the OCA treatment was associated with reduction in adverse clinical outcomes (33,38–40).

Fibrates. The American Association for the Study of Liver Diseases (AASLD) guidelines recommend fibrates as an "off-label" alternative therapy for patients with PBC who have an inadequate response to ursodiol (41). Fenofibrate and bezafibrate have been used as adjunctive treatment in Japan and Europe for some time (42–49). These drugs have pan-peroxisome proliferator-activated receptors (PPAR) activity that targets all 3 isoforms of PPAR with differing affinities (50). PPAR-alpha upregulates the expression of genes involved in bile and lipid metabolism and downregulates the genes involved in immune-related pathways (50). PPAR gamma and delta induce anti-inflammatory and antifibrotic properties (51,52).

Fenofibrate is a fibrate available in the United States (bezafibrate is not available in the United States). In a study involving 20 patients with an inadequate response to UDCA, 55% of patients who were treated with fenofibrate for 48 weeks met the Barcelona response criteria (>40% reduction in serum ALP levels or normalization of serum ALP levels) (42). In another study involving 117 treatment-naive patients, 81.4% patients on a combination of fenofibrate and UDCA met the Barcelona criteria at 12 months, compared with 64.3% in the UDCA-only group (53).

Bezafibrate has been used as a second-line therapy in Japan since the 2000s (54). Iwasaki et al (55) were the first to report that a combination of UDCA and bezafibrate resulted in normalization of ALP levels. A large observational study from Japan involving 3,908 patients compared the use of combination therapy (i.e. UDCA and bezafibrate therapy) with UDCA alone and showed that addition of bezafibrate to UDCA was associated with a significant improvement in transplant-free survival (54). Another study corroborated these findings, demonstrating that patients who received the combination therapy had significantly increased transplant-free survival than predicted by GLOBE scores. Specifically, the mean GLOBE scores improved from 0.504 ± 0.090 precombination therapy to 0.115 ± 0.085 ($P < 0.0001$) 1-year postcombination therapy (56).

The BEZURSO trial, a phase 3 randomized, double-blind, trial compared the combination of bezafibrate and UDCA with placebo in 100 patients with PBC who had an incomplete response to UDCA per the Paris-II criteria. The primary end point, defined as normalization of ALP, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin, albumin, and prothrombin time by month 24, was achieved by 31% patients in the combination therapy group, compared with none in the placebo group. In addition, 67% of patients in the bezafibrate plus UDCA group achieved normalization of ALP levels compared with 0% on the placebo group, and a 15% decrease in liver stiffness measured by vibration controlled transient elastography compared with an increase of 22% in the placebo group. Furthermore, a significant reduction in pruritus and fatigue was also reported in the bezafibrate group (57). Real-world data that studied the use of triple therapy i.e. a combination of UDCA, OCA, and bezafibrate in patients who were refractory to second-line therapy showed significant improvement in ALP, total bilirubin, and pruritus (58,59).

From a safety perspective, the use of fibrates at the recommended therapeutic doses can increase serum AST and ALT levels due to inhibition of CYP2CP enzyme (82). It has also shown to increase creatinine levels and can cause myalgia, especially if taken together with statins (60).

PPAR AGONISTS

Selective PPAR agonists are also under investigation for treatment of PBC. Elafibranor (GFT505), which is a dual PPAR alpha and delta agonist, received US FDA approval in June 2024 for the treatment of PBC in combination with UDCA for patients with inadequate response to UDCA alone or as a monotherapy in those who are unable to tolerate UDCA (61). The drug was evaluated in the multinational, double-blind, placebo-controlled phase 3 ELATIVE trial involving 161 patients with an inadequate response or intolerance to UDCA, who received either 80 mg of elafibranor or a placebo daily for a period of 52 weeks (23). The primary end point, defined as an ALP level < 1.67 times ULN, with a reduction of $\geq 15\%$ from baseline and normal total bilirubin levels was met in 51% of patients who received elafibranor, compared with 4% in the placebo group. In addition, 15% of patients who received elafibranor had normalization of ALP levels, compared with 0% in the placebo group. The drug was well tolerated with common side effects being abdominal pain, nausea, vomiting, and diarrhea.

Another potent drug in this category is seladelpar, which is a selective PPAR delta agonist that decreases bile acid synthesis and suppresses inflammatory cytokines (62). The phase 3 RESPONSE trial involving 193 patients compared the use of seladelpar with placebo in patients with PBC who had an incomplete response or were intolerant to UDCA (63). At 12 months, 61.7% of patients treated with seladelpar reached the primary end point, defined as a reduction in ALP to < 1.67 ULN and normalization of bilirubin levels, compared with 20% in the placebo group. In addition, patients on seladelpar exhibited statistically significant reduction in pruritus from baseline, compared with placebo. Based on these results, the US FDA granted an accelerated approval for seladelpar, in August 2024 (64).

Saroglitazar is a PPAR-alpha and gamma agonist and was examined in a phase 2 study (EPICS) involving 37 patients with an incomplete response or intolerance to UDCA. Patients were randomized to saroglitazar 2 mg/d, saroglitazar 4 mg/d, or placebo (65). After 4 weeks, 71% of patients reached the composite end point, with those in the 4 mg subgroup achieving a 50% reduction in ALP levels. However, the drug caused elevations in both ALT and AST in 4 patients (66).

NOX INHIBITORS

Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 1 (NOX1) and NADPH oxidase 4 (NOX4) are enzymes implicated in the production of reactive oxygen species, which plays a key role in the development of liver fibrosis (67). Setanaxib (GKT137831) is a NOX1 and NOX4 inhibitor. Interim efficacy results of a phase 2 trial involving 111 patients indicated that setanaxib significantly reduced ALP at 24 weeks ($P = 0.002$), compared with placebo. A mean change in gamma-glutamyl

transferase at 24 weeks, which was the primary end point at week 24, was not met (68).

BUDESONIDE

The role of budesonide as an adjunctive therapy to UDCA in the treatment of PBC remains inconclusive. In a randomized, placebo-controlled trial involving 62 patients with PBC who demonstrated an inadequate response to UDCA, patients were randomly assigned to receive either add-on budesonide or placebo in a 2:1 ratio for a duration of 36 months (69). The primary end points were defined as an improvement in liver histology and absence of fibrosis progression (69). The addition of budesonide did not result in significant histological improvement; however, it was associated with a reduction in the mean ALP levels, with 35% patients achieving complete normalization of ALP compared with 9% in the placebo group ($P = 0.023$) (69). Although the utility of budesonide in the treatment of PBC remains a subject of debate, it may hold therapeutic potential in cases involving overlap with autoimmune hepatitis.

PRIMARY SCLEROSING CHOLANGITIS

Unlike strides made in the treatment landscape of other chronic liver diseases, there are no approved medical therapies for PSC. Currently, liver transplantation is the only curative treatment and is reserved for patients with advanced liver disease (5,70). The next section of this review highlights the state of novel therapies currently under investigation (Table 2).

Ursodeoxycholic acid

In a randomized, double-blind, placebo-controlled study involving 105 patients with PSC, patients received either 13–15 mg/kg of UDCA or a placebo (17). At the end of 2 years, significant improvements in the levels of serum ALP, bilirubin, and liver histology were noticed in patients receiving UDCA, compared with placebo. However, no significant differences in the progression to cirrhosis or liver transplant and survival rates were observed (17). A subsequent Scandinavian study involving 219 patients who used a high-dose 17–23 mg/kg/d of UDCA reenforced these findings (71). Another randomized, controlled study investigated even higher doses of UDCA at 28–30 mg/kg/d in a long-term study of 150 patients with PSC (72). UDCA treatment was associated with reduction in ALP and AST. However, the higher UDCA doses were associated with serious adverse effects such as development of cirrhosis, varices, and need for liver transplant and the study was discontinued early due to the safety (repeat reference). Based on the results of this study, the AASLD recommends against the use of high-dose UDCA in PSC although lower doses (13–23 mg/kg) of UDCA may be considered in patients with persistently elevated ALP (70).

Norursodeoxycholic acid

Norursodeoxycholic acid (norUDCA) shows promise as an emerging treatment of PSC. It is a C23 homolog of UDCA and has a side chain that renders it resistant to conjugation (73). As a result, it undergoes cholehepatic shunting and has anti-inflammatory and antifibrotic effects (74). It also has direct immunomodulatory effects on CD8+ T cells (75).

A phase 2 trial involving 161 patients with PSC, with elevated serum ALP and without concurrent UDCA use, were randomized to receive norUDCA or a placebo for a period of 12 weeks (76). The primary end point was reduction in ALP levels from baseline at a 4-week follow-up after treatment. The use of norUDCA resulted in a 26% reduction in serum ALP levels compared with placebo. A large double-blind, randomized, multicenter, placebo-controlled phase 3 trial comparing 1,500 mg/d of norUDCA with placebo is currently underway (NCT02872921).

Fibrates

Fibrates activate PPARs, which inhibits bile acid synthesis and reduces bile acid toxicity in patients with PSC (77,78). In a randomized, double-blind, placebo-controlled trial involving patients with PSC, the use of fenofibrate reduced ALP levels by 66%, compared with 20% in the placebo group (79). In a retrospective study evaluating the addition of fenofibrate (200 mg/d) or bezafibrate (400 mg/d) in 24 patients with PSC who exhibited an incomplete response to UDCA, significant clinical and biochemical improvements were observed. The combination therapy resulted in a 41% reduction in AL levels and a marked decrease in pruritus (80). Other clinical trials involving bezafibrate (NCT04309773) and elafibranor (NCT05627362) are currently underway.

FXR AGONISTS

Bile acid FXR agonists

Obeticholic acid. OCA has also been studied as a potential treatment option for PSC. The phase 2 AESOP study evaluated the effect of OCA on the ALP levels in patients with PSC, compared with placebo (81). Although OCA decreased the levels of ALP by up to 25%, it was also associated with significantly higher rates of side effects such as pruritus (81).

Nonbile acid FXR agonists

Cilofexor. Cilofexor was evaluated in a phase 2, double-blind, placebo-controlled study involving 52 patients with large-duct PSC. Patients were randomized to receive cilofexor (100 mg, 30 mg) or placebo for 12 weeks. Patients who received cilofexor had a 21% or more reduction in ALP compared with placebo (82). However, the phase 3 study for cilofexor (PIRIMIS) was terminated early due to futility (83).

Table 2. Therapeutic agents currently in Phase 3 clinical trials for primary sclerosing cholangitis

Drug	NCT	Mechanism of action	Number of patients	Trial duration	Findings
Cilofexor	NCT03890120	Nonsteroidal FXR agonist	N = 190	12 mo	Terminated early due to futility
NorUDCA	NCT01755507	Cholehepatic shunting	N = 161	12 wk treatment followed by 4 wk follow-up	26% reduction in ALP compared with placebo.
Simvastatin	NCT04133792	HMG-CoA reductase	N = 700 (ongoing)	5 yr	Ongoing

ALP, alkaline phosphate; FXR, farnesoid X receptor; HMG-CoA, 3-ydoxy-3-Methyl-Glutaryl-Coenzyme A; NCT, National Clinical Trial; NorUDCA, norursodeoxycholic acid.

Berberine ursodeoxycholate (HTD1801). Berberine ursodeoxycholate (HTD1801) is an ionic salt of berberine and UDCA (84). Besides the anti-inflammatory and cytoprotective effects of UDCA, berberine has additional anti-inflammatory properties and antimicrobial activity, specifically against Klebsiella pneumonia, which is believed to play a role in the development of PSC (84,85). A Phase 2 study evaluated the safety and efficacy of HTD1801 in 55 patients with PSC over a period of 18 weeks (86). The primary end point was reduction in ALP levels from baseline at week 6. A significant decrease in mean serum ALP from baseline was observed with HTD1801 (−53 U/L ad −37 U/L), compared with placebo (98 U/L). These reductions sustained through week 18 for those who remained on HTD1801 therapy.

Fibroblast growth factor 19. Fibroblast growth factor 19 is an endocrine hormone that inhibits bile acid synthesis through FXR activation (87). However, its use in the treatment of PSC has been limited due to its hepatocarcinogenecity (88). NGM282 also known as M70 is an engineered, nontumorogenic analog of fibroblast growth factor 19 that was evaluated in a multicenter, phase 2, randomized, double-blind, placebo-controlled trial. At 12 weeks, no significant difference in ALP levels were observed compared with placebo; however, significant reductions in the levels of 7alpha-hydroxy-4-cholesten-3-one which is a marker of CYP7A1 activity and bile acid synthesis (mean differences of −9.4 ng/mL and −6.2 ng/mL) were observed compared with placebo (89).

CM-101. C-C motif chemokine ligand 24 is a proinflammatory, profibrotic chemokine that plays a role in the pathogenesis of liver fibrosis (90). CM-101 is a monoclonal antibody that clocks C-C motif chemokine ligand 24 and was shown to improve cholestasis, inflammation, and fibrosis in preclinical studies (91).

Vancomycin. Given the potential role of dysbiosis in biliary injury, antibiotics have been proposed to modulate the gut microbiome in PSC (92–94). In a small study involving 35 patients with PSC, 8 patients received oral vancomycin (OV) 125 mg 4 times a day, 7 patients received OV 250 mg 4 times a day, and the remaining received metronidazole. The group receiving higher dose of OV achieved a greater reduction in ALP levels at 12 weeks (92). Similarly, in a blinded, randomized, placebo-controlled trial involving 29 patients with PSC, 18 patients treated with OV 125 4 times daily demonstrated a statistically significant reduction in the PSC Mayo risk score (93). However, a large retrospective study involving 264 pediatric patients with PSC observed no differences in outcomes between patients who received OV or UDCA (94). Owing to the potential for antibiotic resistance and lack of sufficient clinical trials, the AASLD concluded that there was insufficient evidence to recommend OV in patients with PSC (70).

Bexotegrast. Bexotegrast is a novel antifibrotic agent that functions as a dual-selective inhibitor of αvβ6 and αvβ1 integrins, thereby inhibiting the activation of transforming growth factor-beta and reducing collagen production and fibrosis in the liver (95). The phase 2a INTEGRIS-PSC trial evaluated the safety and efficacy of bexotegrast in patients with PSC. At week 12, a statistically significant reduction in enhanced liver fibrosis score and PRO-C3 levels was seen in patients receiving 160 mg of bexotegrast compared with placebo. In addition, patients with elevated baseline ALP showed a dose-dependent reduction in ALP levels at 12 weeks along with stabilization of ALT, AST, and total and direct bilirubin levels (96).

Simvastatin. A case-control study from Sweden reported that patients with PSC who were on statin therapy had a reduced risk of liver transplant or death and all-cause mortality (97). A phase 3, randomized, double-blind, controlled PiSCATIN trial is currently underway and aims to evaluate the effect of simvastatin in PSC.

Emerging therapies targeting pruritus

Ileal bile acid transporter inhibitors. Ileal bile acid transporter inhibitors are upcoming treatment modality for pruritus. These agents block reabsorption of bile acids in the ileum, thereby interrupting enterohepatic circulation of bile acids resulting in increased fecal bile acid excretion (98,99).

In the phase 2 GLIMMER trial involving 147 patients with PBC and moderate pruritus, linerixibat demonstrated a statistically significant improvement in monthly itch scores from baseline compared with placebo over a period of 12 weeks (100). However, no statistically significant difference was noted in daily itch scores.

Maralixibat, another ileal bile acid transporter inhibitor, was evaluated in an open-label phase 2 clinical trial in 23 patients. The trial reported a significant decrease in mean serum bile acids by 16.7% along with significant reductions in ItchRO weekly sum scores from baseline by 12.6% in patients with pruritus at baseline and by 70% in patients with itchRO daily average score greater than or equal to 3 at baseline (101) (see Supplemental Figures 1–3, Supplementary Digital Content 1, http://links.lww.com/AJG/D458).

FUTURE DIRECTIONS

Our approach to treatment of PBC has evolved substantially and rapidly over the last several years. The incorporation of prognostic models into our management of PBC has led us to aim for focus on improving ALP and bilirubin levels; we are moving toward a goal of achieving complete normalization of liver biochemistries, and this appears increasingly attainable, although triple combination therapies may be needed. Transient elastography is now established as reliable tool of staging PBC, and liver biopsy has become unnecessary in most patients.

The therapeutic landscape and path to approval for new therapies in PSC remains arduous. Clinically meaningful end points in clinical trials continue to be actively debated among clinicians, researchers, and regulatory agencies, and the highly variable progression of the disease and the presence of competing risks due to inflammatory bowel disease and concomitant medications also complicate development of new treatments. Despite the unique challenges involved in the conduct and design of clinical trials in PSC, we remain optimistic that new therapies will also be developed for this rare but serious chronic liver disease.

CONFLICTS OF INTEREST

Guarantor of the article: Kris V. Kowdley, MD, FACG.

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