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REVIEW

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Medical treatment of primary sclerosing cholangitis: What have we learned and where are we going?

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Abstract

It has proven difficult to establish robust evidence for significant clinical benefits of medical treatment in primary sclerosing cholangitis (PSC). For ursodeoxycholic acid, clinical practice guidelines only offer vague recommendations, leading to a situation of variable prescription rates depending on local reimbursement policies and physician preference. The difficulty in drug development in PSC is partly related to a poor understanding of critical disease processes with failure to identify relevant mechanisms of action of putative drugs. The variable disease course, both intra-individually and between individuals, and the lack of robust definitions of what success looks like for clinical trials in PSC have also contributed to the negative outcomes of trials performed. In this review article, we will discuss these uncertainties and challenges, building on key previous and ongoing clinical trials. Despite the lack of consensus for ideal phase II and phase III study designs, several trials for diverse compounds are currently ongoing, indicating a shift from therapeutic nihilism toward hope for people with PSC. While waiting for robust efficacy data for drugs currently being tested, the current lack of effective interventions should not motivate the prescription of compounds to people with PSC based on low-quality evidence.

Keywords: cholangiocarcinoma, clinical trials, inflammatory bowel disease, primary sclerosing cholangitis, surrogate endpoint

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic liver disease represented by progressive fibrosis of the intrahepatic and extrahepatic bile ducts.[1] The concentric biliary fibrosis is not specific to PSC and can also arise from chronic bile duct injury from diverse and identifiable causes (secondary sclerosing cholangitis),

Abbreviations: AIH, autoimmune hepatitis; CCA, cholangiocarcinoma; ELF, enhanced liver fibrosis; EMA, European Medical Agency; FDA, Food and Drug Administration; FGF19, fibroblast growth factor 19; FXR, farnesoid X receptor; IBD, inflammatory bowel disease; MRI, magnetic resonance imaging; OCA, obeticholic acid; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator–activated receptor; PROM, patient-reported outcome measure; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

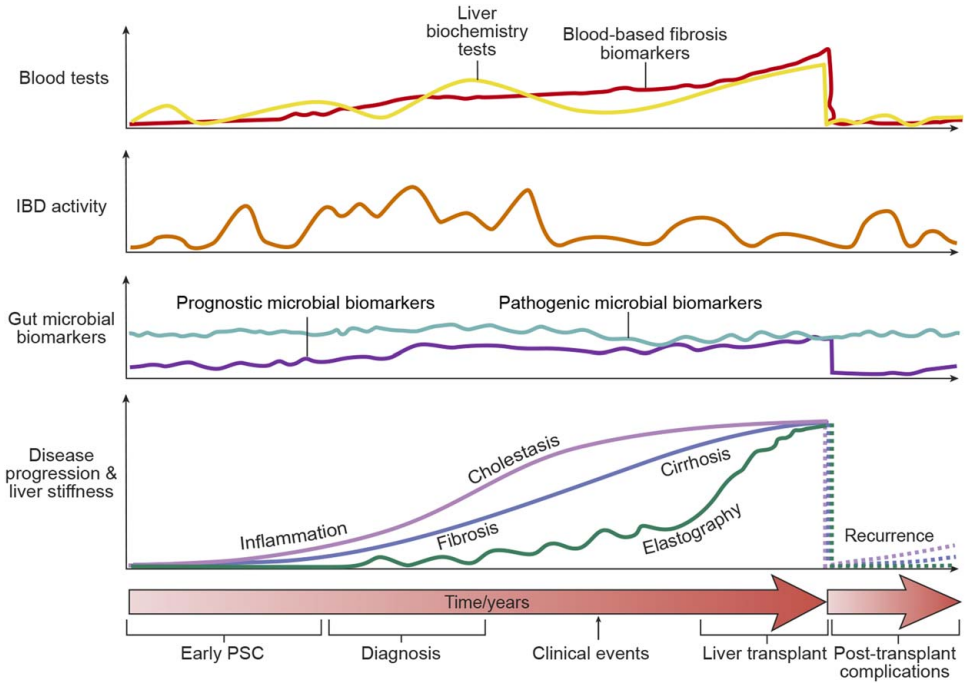

FIGURE 1 Schematic illustration of the natural history of PSC. Disease activity assessed by liver blood tests, ALP included, typically fluctuates (upper panel) despite underlying progression toward cirrhosis (lower panel). This variability influences the utility of liver blood tests as surrogate endpoints in clinical trials in PSC. IBD severity is also variable and may partially influence liver blood tests and PSC progression. Blood-based fibrosis markers (upper panel) show less spontaneous variability than ALP and typically increase throughout the disease course along with liver stiffness as measured by elastography (lower panel). Several gut-derived microbial biomarkers are also associated with prognosis in PSC (prognostic microbial biomarkers, eg, pyridoxal 5′-phosphate and trimethylamine-*N*-oxide), some of which may remain elevated after liver transplantation to exert pathogenic effects and influence the risk of PSC recurrence (pathogenic microbial biomarkers). As shown in the bottom timeline, there is typically a long asymptomatic period ("early PSC") before and after diagnosis. Common clinical events include bacterial cholangitis, cholangiocarcinoma or colorectal cancer, end-stage liver disease with portal hypertension and associated complications, and ultimately in most patients, the need for liver transplantation. After liver transplantation PSC may recur. Modified from Karlsen et al[1] and printed with permission from © Kari C. Toverud. Abbreviations: IBD, Inflammatory bowel disease; PSC, primary sclerosing cholangitis.

which must be excluded as part of making the diagnosis.[2] The cause of PSC is unknown, but chronic cholangitis often occurs in the context of inflammatory bowel disease (IBD), and there is also an increased frequency of other autoimmune and inflammatory diseases.[3] Pathophysiology likely involves an interplay between cholangiocytes, infiltrating immune cells, and cells involved in maintaining the extracellular matrix (stellate cells and portal myofibroblasts in particular), with possible contributions from bile acid toxicity and a range of proposed factors related to the gut microbiota.[1]

The natural history of PSC is inherently progressive, with most people in published PSC cohorts at some point reaching definite endpoints of liver transplantation or death. Progression is nevertheless slow, with a median time until these endpoints of more than 20 years in population-based cohorts, and highly variable with fluctuating disease severity (Figure 1). Cholestasis, bacterial cholangitis, and malignancies are common clinical events, in addition to those related to end-stage liver disease. The lifetime risk of hepatobiliary malignancies is up to 20% in some geographic areas,[4] and cholangiocarcinoma (CCA) represents an important cause of death in people with PSC due to lack of reliable surveillance strategies for early-stage neoplasia and CCA therapies. Symptom burden and medical costs related to bile duct strictures or comorbidities are considerable, particularly for advanced disease stages,[5] making PSC proportionally important despite its rarity.

Treatment aims in PSC are diverse (Box 1). Robust evidence for the impact of medical therapy on the

Box 1 The multifaceted treatment aims and considerations for drug interventions in primary sclerosing cholangitis

- achieve biochemical and serological improvement/remission;
- achieve radiological improvement/remission;
- achieve histological improvement/remission;
- reduce the number of clinical events;
- increase transplant-free survival;
- relieve symptoms (eg, pruritus and fatigue) and preserve the quality of life;
- avoid or minimize side effects;
- account for inflammatory bowel disease activity;
- account for the risk of cholangiocarcinoma and colorectal cancer;
- compatible with long-term treatment duration (decades).

progression of PSC has been hard to establish, as reflected by the lack of firm and consistent treatment recommendations in clinical practice guidelines.[2,6] Partially this may be due to an hitherto failure to identify relevant mechanisms of action of putative drugs.[7] The highly variable disease course and lack of validated surrogate endpoints could also have contributed to the negative outcomes of trials performed, leaving uncertainty as to potential efficacy even for candidate drugs previously scrutinized. For clinical trials after liver transplantation to prevent and treat recurrent PSC, the topic is even more complex, given the scarcity of patients, concurrent immunosuppressive treatment, and surgical sequelae.

The mentioned challenges significantly affect drug development programs in PSC, and both the pharmaceutical industry and academic investigators await consensus on phase II and phase III trial designs for exploring putative drugs and "a regulatory grade" toolbox for assessing efficacy. For clinicians and regulators, there is currently a significant risk of errors of "omission," that is, not adopting and approving a drug that is beneficial due to a level of evidence that is unattainable, as well as "commission," that is, approving a drug that is not beneficial or even harmful based on low-quality evidence. In the present article, we will expand on these uncertainties and challenges, building on a discussion of selected clinical trials (Table 1) rather than a systematic and comprehensive review. Statements and conclusions made throughout the article are not imperative but are meant to nurture a productive and critical discussion toward evidence-based consensus standards for clinical trials in PSC.

LEARNING EXPERIENCES FROM SELECTED CLINICAL TRIALS IN PSC

Ursodeoxycolic acid

Ursodeoxycholic acid (UDCA) is a naturally occurring hydrophilic bile acid with a potential beneficial impact on cholestatic liver disease, which is only partially understood.[18] While considered standard of care in primary biliary cholangitis (PBC), robust and trial-based evidence for an impact on clinical outcomes from UDCA in PSC is still missing,[19] and population-based registry data also remain conflicting as to a potential clinical benefit.[20,21]

The history of clinical trials on UDCA in PSC holds several learning experiences. The largest randomized placebo-controlled clinical trial involving UDCA in PSC to date included 218 adults with PSC who were randomized to receive UDCA 17–23 mg/kg per day (mg/kg/d) or placebo with a median follow-up of 38–42 months.[8] Results of the trial illustrate the status of UDCA in PSC; there was a tendency for improvement in ALT and ALP levels during the first 6 months; however, no statistically significant difference in clinical outcomes, symptoms, or quality of life was shown between the treatment and placebo arm. The study, however, failed to recruit the 346 participants needed to detect a predefined 50% reduction of primary events (death or liver transplantation) during the 5-year period of treatment, exemplifying also the logistical and practical challenges of clinical trials in a rare disease like PSC. In an extended follow-up analysis of 198 participants from the trial, normal ALP or ALP reductions $>40\%$ were reported to associate favorably with long-term clinical outcomes in PSC,[22] however with no evidence for such favorable outcomes to result from UDCA prescription; in fact, the best survival rate was found in participants with an ALP reduction assigned to placebo.

Dosing of UDCA in clinical trials in PSC has been variable, ranging from ~10–30 mg/kg/d.[19] Building from observations that biliary enrichment of UDCA increases up to a plateau at 22–25 mg/kg/d,[23] higher doses of UDCA were explored.[24] However, when a dose of 28–30 mg/kg/d was evaluated in 150 adults with PSC in a randomized, double-blinded controlled trial, an approximately 2-fold increased risk for death and liver transplantation was demonstrated in the UDCA group, and serious adverse events were also more common in the treatment arm.[9] Paradoxical to this outcome, but similar to other trials of UDCA in PSC, improvements in ALP and AST were still observed in the UDCA treatment group. The findings led to consistent recommendations against the use of high-dose UDCA in many areas, particularly in Northern Europe and the United States, to widespread UDCA discontinuation in both adult[25] and pediatric[26] settings. Clinical practice guidelines statements are currently vague for UDCA in PSC, however allowing for doses of 13–23 mg/kg/d (American Association for the Study of Liver Diseases [AASLD]) and 15–20 mg/kg/d (European Association for the Study of the Liver [EASL]), leading to a situation of variable prescription rates depending on local reimbursement policies and physician preference.

Norucholic acid

Norucholic acid (previously denominated nor-UDCA) is a side chain–shortened homologue of UDCA that has shown superior anticholestatic, anti-inflammatory, and antifibrotic properties compared to UDCA in animal models.[9] In PSC, norucholic acid was compared to placebo in a randomized multicenter phase II trial that evaluated the safety and efficacy of 12 weeks of treatment with oral norucholic acid (500, 1000, or 1500 mg/d) compared with placebo.[10] In this trial, 161 persons with PSC with elevated ALP and without concomitant UDCA treatment were included. Norucholic

TABLE 1 Summary of important phase II and phase III clinical trials investigating medical treatment of PSC

Study	Type	Intervention	Number of participants	Duration	Serum ALP level at inclusion	Primary endpoint	Liver biopsy Included
Olsson et al[8]	Phase III placebo-controlled RCT	UDCA	n110 UDCA 17–23 mg/kg/d, n109 placebo	5 y	ALP > ULN	Death or liver transplantation	No
Lindor et al[9]	Phase III placebo-controlled RCT	UDCA	n76 UDCA 28–30 mg/kg/d, n74 placebo	5 y treatment, trial ceased 6 y	ALP ≥ 1.5× ULN	Development of cirrhosis, varices, cholangiocarcinoma, liver transplantation, or death	Yes
Fickert et al. et al[10]	Phase II placebo-controlled RCT	Norucholic acid	n39 500 mg/d, n41 1000 mg/d, n39 1500 mg/d, n40 placebo	12 wk treatment, 4 wk follow-up	ALP ≥ 1.5× ULN	Mean relative change in ALP levels between baseline and end of study	No
NCT03872921 ongoing	Phase III placebo-controlled RCT	Norucholic acid	n303 1500 mg/d, placebo	2 y	ALP > 1.5× ULN	Partial normalization of ALP and no disease progression by liver histology between baseline and end of study	Yes
NCT04309773 ongoing	Phase III placebo-controlled RCT	Bezafibrate	n104 400 mg/d + UDCA 15–20 mg/kg/d, placebo + UDCA 15–20 mg/kg/d	24 mo	ALP ≥ 1.5× ULN	Proportion of patients with ALP < 1.5 × ULN and reduction of at least 15% from baseline, normal serum bilirubin, and no increase of liver stiffness at the end of the study compared to baseline	No
NCT05627362 ongoing	Phase II placebo-controlled RCT	Elafibranor	n68 80 mg, 120 mg, 80 mg + placebo, 120 mg + placebo	12 wk	ALP ≥ 1.5× ULN	Safety, clinically significant changes in laboratory parameters, vital signs, and ECG readings	No
Färkkilä et al[11]	Phase III placebo-controlled RCT	Metronidazole and UDCA	n39 metronidazole 600–800 mg/d + UDCA 15 mg/kg/d n41 placebo + UDCA 15 mg/kg/d	36 mo	ALP > ULN	Progression of PSC: change in liver blood tests, New Mayo Risk Score, liver histology, and cholangiographic findings	Yes
Tabibian et al[12]	Phase II RCT	Vancomycin or metronidazole	n8 vancomycin 125 mg × 4/d, n9 250 mg × 4/d, n9 metronidazole 250 mg × 3/d, n9 500 mg × 3/d	12 wk	ALP > 1.5× ULN	Decrease in ALP at 12 wk	No
NCT03710122 ongoing	Phase II and III placebo-controlled RCT	Vancomycin	n102 Vancomycin, placebo	18 mo	ALP ≥ 1.5× ULN	ALP level at 6, 12, and 18 mo, and 3 and 6 mo after treatment	No
Muir et al[13]	Phase II placebo-controlled RCT	Simtuzumab	n79 75 mg sc × 1/wk, n77 125 mg sc × 1/wk, n78 placebo sc × 1/wk	96 wk	ALP > ULN	Safety and mean change in hepatic collagen content assessed by morphometry between baseline and week 96	Yes

Trauner et al[14]	Phase II placebo-controlled RCT	Cilofexor	n22 100 mg/d, n20 30 mg/ d, n10 placebo	12 wk	ALP ≥ 1.67× ULN	Safety and tolerability of cilofexor	No
NCT03890120 ongoing[15]	Phase III placebo-controlled RCT	Cilofexor	n419 100 mg/d, placebo	96 wk	Any ALP value	Percentage of participants with progression of liver fibrosis at week 96	Yes
Hirschfield et al[16]	Phase II placebo-controlled RCT	Aldafermin	n21 1 mg/d, n21 3 mg/d, n20 placebo	12 wk	ALP > 1.5× ULN	Change in ALP from baseline to week 12	No
Kowdley et al[17]	Phase II placebo-controlled RCT	Obeticholic acid	n25 1.5–3 mg/d, n26 5–10 mg/d, n25 placebo	24 wk, 2 y safety extension	ALP ≥ 1.5× ULN	Change in ALP from baseline to week 24, and safety.	No
NCT04480840 ongoing	Phase II placebo-controlled RCT	Bexotegrast	n121 40 mg, 80 mg, 160 mg, 320 mg, placebo	Part 1 and 2, 12 wk each, Part 3, 24–48 wk	Any ALP value	Safety and tolerability	No
NCT04133792 ongoing	Phase III placebo-controlled RCT	Simvastatin	n560 40 mg/d, placebo	5 y	Any ALP value	Overall survival, listing for liver transplantation, time to first variceal bleeding, time to diagnosis of hepatobiliary cancer	No
CTIS 2023-505155-47-00 ongoing	Phase II placebo-controlled cross-over RCT	Pyridoxine	n26 40 mg/d, placebo	50 wk	ALP ≥ ULN	Difference in mean change of ALP between pyridoxine phase and placebo phase	No
NCT03561584 ongoing	Phase II placebo-controlled RCT	Sulfasalazine	n42 Initially 500 mg × 2/d, placebo	22 wk	ALP ≥ 1.67 × ULN	Proportion of patients with reduction of mean ALP < 1.5× ULN at the end of the study	No
NCT04595825 ongoing	Phase II placebo-controlled RCT	CM-101	n68 10 mg/kg every 3 wk, 20 mg/kg every 3 wk, placebo	15 wk	ALP ≥ 1.5× ULN	Safety and tolerability	No

Note: As an important disclaimer, details for the ongoing clinical trials at the time of writing, as indicated by their national clinical trial (NCT) or clinical trials information system (CTIS) number, are based on publicly available information on clinicaltrials.gov and the CTIS; the authors have not had access to detailed trial protocols. Numbers and details for these ongoing trials may thus differ from that of the detailed study protocol and eventual publications.

Abbreviations: ECG, electrocardiogram; d, day; mo, months; PSC, primary sclerosing cholangitis; RCT, randomized controlled trial; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; wk, weeks; y, years.

acid significantly reduced ALP values in all treatment arms compared to placebo, and the safety profile was comparable across groups. An ongoing phase III placebo-controlled study compares oral treatment with 1500 mg/d norucholic acid with placebo on PSC disease progression assessed by a decrease in ALP and liver histology as a combined primary endpoint (NCT03872921).

While the norucholic acid phase II trial required UDCA discontinuation for 8 weeks (so-called "wash-out"), the phase III trial inclusion criteria allow for a stable dose of UDCA not exceeding 20 mg/kg/d, with a justification to make final study results compatible with real-world settings, where UDCA prescription, despite conflicting evidence, commonly occurs. How this difference will influence study results can only be speculated, but the case made in the choice for the study design for the phase III trial exemplifies a principal challenge in clinical trials in PSC: how to deal with baseline therapy for which evidence is incomplete or absent? In our opinion, such baseline therapy should have a firm evidence base and broad recognition by clinical practice guidelines and regulators.

Peroxisome proliferator–activated receptor agonists

Peroxisome proliferator–activated receptors (PPARs, ie, PPARα, PPARβ/δ, and PPARγ) are a class of ligand-activated nuclear receptors that are interesting targets in cholestatic liver diseases based on their function as regulators of hepatic transporters involved in bile homeostasis.[27,28] PPAR agonists have demonstrated several mechanisms of action of potential benefit in PSC, including anticholestatic effects (eg, enhancement of biliary phospholipid secretion and mixed micelle formation, inhibition of bile acid production and secretion)[29] and additional pleiotropic effects through extensive cross-talk with other nuclear receptors involved in causing anti-inflammatory and antifibrotic effects.[30]

Beneficial effects of bezafibrate in PSC, a pan-PPAR agonist, were reported in several case series,[31–33] and similar reports were published for fenofibrate, a PPARα agonist.[33–36] One phase III randomized clinical trial investigating the effect on cholestatic pruritus of oral administration of bezafibrate 400 mg/d for 21 days to participants with either PSC or PBC reported improvement in liver blood tests as well as a significant reduction of pruritus in participants with PSC.[37] In PBC, 3 phase III trials have suggested clinical benefits from PPAR-agonists.[38–40] A phase III randomized placebo-controlled trial of bezafibrate in people with PSC on concomitant UDCA treatment (NCT04309773) and an industry-initiated phase II trial of elafibranor, a PPARα/δ agonist (NCT05627362) are currently ongoing. Development of the PPARδ agonist seladelpar has been temporarily paused in PSC (NCT04024813).

The use of PPAR agonists in cholestatic liver disease has a history spanning almost 25 years, predominantly involving off-label prescription. Safety concerns have included occasional creatinine increase, reports of ALT/AST flares with unclear attribution to the drug versus underlying liver disease, and muscle pain. While these issues are generally manageable, bezafibrate has seen significant discontinuation in clinical practice due to muscle-related side effects. Regulatory and licensing aspects of new compounds (like seladelpar and elafibranor) versus established but off-patent compounds (like bezafibrate and fenofibrate) in PBC will provide important learning experiences for PSC, where the payer's perspective on pricing in such a setting remains to be seen. Data are also likely to emerge to shed light on the relative importance of various PPAR subspecificities, in particular PPARα and PPARδ, both for potential efficacy as well as the frequency of side effects.

Antibiotics and gut-targeted therapies

A key role of the gut microbiome in PSC pathophysiology is highly likely,[41,42] but the exact mechanisms whereby the gut microenvironment interacts with biliary inflammation and peribiliary fibrogenesis are still under investigation. The potential impact is multifactorial, including effects from pathobiont or opportunists like *Klebsiella pneumoniae*, *Enterococci*, and *Veillonella* spp., along with altered gut microbial metabolism resulting from shifts in microbiome composition.[41] Several small trials have shown improvements in ALP from absorbable (eg, metronidazole) and non-absorbable (eg, vancomycin) antibiotics.[11,12,43–45] How these changes in liver blood tests relate to a potential impact on gut inflammation in IBD in PSC can so far only be speculated. In the pediatric setting, off-label vancomycin prescription for PSC has gained popularity.[46]

For a scientific topic, the discussion on vancomycin prescription and potential reimbursement has become quite tempered. Learned society clinical practice guidelines advise against long-term antibiotics in PSC except for recurrent bacterial cholangitis,[2,6] while advocacy is being made from both patient representatives and certain academic centers to implement vancomycin prescription in routine practice for PSC, even with associated reimbursement.[47,48] The discussion holds considerable relevance since the implicit consequence of routine prescription of vancomycin would be to compromise the type and volume of evidence normally required for the introduction of therapeutic modalities with the argument that PSC is rare and difficult to study.[49] The proof-of-concept vancomycin data

support a role of the gut microbiota in PSC pathophysiology, but from such proof-of-concept data to make short-cuts into clinical applications with associated concerns on long-term safety and efficacy is a route likely not to benefit patients. Adequately powered clinical trials for vancomycin (such as NCT03710122 and NCT05876182) are warranted, addressing distinctively efficacy for IBD versus liver disease in PSC, respectively. The underlying biological mechanisms responsible for vancomycin-associated effects must also be determined.

A range of other modalities is also being explored for manipulation of the gut microbiota in PSC and other liver and non-liver diseases.[41,42,50] Of particular interest are specific approaches, either targeting particular pathobionts, such as bacteriophage-mediated killing of *Klebsiella pneumoniae*,[51] or targeted correction of the metabolic consequences of microbiome perturbations through supplementation (eg, vitamin B6 supplementation) or in vitro and in vivo genetic engineering of bacterial features.[52–54] With time and an increased understanding of the exact roles of the gut microbiota in PSC, clinical trials based on such specific approaches are likely to replace broad approaches like antibiotics and fecal microbiota transplantation.

The farnesoid X receptor-fibroblast growth factor 19 signaling pathway

Reductions of ALP levels from the farnesoid X receptor (FXR) agonist obeticholic acid (OCA) in PBC brought attention to the potential utility of the FXR-fibroblast growth factor 19 (FGF19) signaling pathway and suppression of bile acid synthesis in the treatment of other cholestatic liver diseases. In PSC, the intent-to-treat population in the phase II placebo-controlled OCA trial comprised placebo (n = 25), OCA 1.5–3.0 mg (n = 25), and OCA 5–10 mg (n = 26), with significant improvements in ALP observed in the 5–10 mg treatment arm.[17] Corroboration of this proof-of-concept came from the phase II trial of the nonsteroidal FXR agonist cilofexor (previously called GS-9674), including 100 mg (n = 22), 30 mg (n = 20), or placebo (n = 10) arms, with significant reductions in ALP observed for the 100 mg treatment arm.[14] For the 47 individuals in the open-label extension of this trial, a total of 15 withdrew for a variety of reasons; the week 96 ALP reductions were not statistically significant,[55] and a small but statistically significant increase in the enhanced liver fibrosis (ELF) test values was noted.[55]

The future of OCA therapy in PBC is uncertain at the time of writing due to the European Medical Agency (EMA) suggestion to revoke the conditional marketing approval for OCA based on the COBALT study (https://www.ema.europa.eu/en/news/ema-recommends-revoking-conditional-marketing-authorisation-ocaliva),[56] along with the US Food and Drug Administration (FDA) vote to potentially refrain from full approval. Should these suggestions result in the withdrawal of the label, OCA has nevertheless provided valuable learning experiences on the challenges associated with drug development and regulatory pathways in rare cholestatic liver diseases and, more specifically, on the potential relevance of drugs targeting the FXR-FGF19 pathway.[54] Furthermore, the academic debate resulting from the COBALT study[57] expands on the blurred relationship between improvement of liver blood tests and long-term clinical benefits in both PBC and PSC, as well as the inherent problems in designing controlled trials to provide confirmatory data following conditional or accelerated approval. The problem of retaining trial participants on perceived placebo in such trials, which was likely part of the reason for the failure of the COBALT study, will be similar in PSC.[57]

For the FGF19 analog aldafermin (previously called NGM282), a phase II placebo-controlled trial in 62 individuals with PSC yielded though-provoking results.[16] While ALP levels remained stable, there were significant reductions in a serum marker of fibrogenesis, the cleaved amino-terminal propeptide of type III collagen (pro-C3). Additionally, the ELF test, which includes 3 parameters - procollagen III amino-terminal peptide (PIIINP), tissue inhibitor of matrix metalloproteinase 1 (TIMP-1), and hyaluronic acid - showed reductions, with the most notable decrease observed in the PIIINP component. Furthermore, bile acid synthesis, as indicated by C4 levels, was significantly suppressed, consistent with findings from other trials of aldafermin.[58]

There appear several learning experiences from these data. First, with 3 different compounds interfering with the FXR-FGF19 signaling pathway showing signals in either ALP or fibrosis biomarkers, the relevance of this pathway for treatment in PSC warrants further scrutiny. Second, the data from the aldafermin trial raise the intriguing question of “What does success look like?” in clinical trials of PSC. Is it perceivable that a stable ALP and reductions in fibrogenesis represent such a scenario of treatment success? Further understanding of the prospective behavior of the ELF test and pro-C3 from natural history cohorts and the long-term clinical implications of this behavior will help shed light on this question. Finally, as discussed further below, experience with the regulatory pathway for OCA in PBC certainly holds relevance also in PSC.

Relevance of IBD medication

Treatment of IBD in PSC should follow general recommendations, and optimal treatment of IBD as such is important in itself, as shown by the relationship between gut inflammation and an intact colon on

pretransplant and posttransplant PSC severity.[59–61]. The close association between PSC and IBD, however, opens the possibility that IBD therapy might also have direct effects on liver disease in PSC.[1,41,62,63]

Controlled studies on treatment with biologics and immunosuppressive drugs prescribed for IBD in PSC are scarce, and meta-analyses of data overall show ineffectiveness on liver disease severity.[64,65] The majority of the underlying studies are, however, retrospective case series and with a limited number of participants, often with a selection biased toward people with PSC and an active IBD in need of treatment. Reports on associations between azathioprine and beneficial outcomes in PSC are interesting and warrant further investigation.[20,66] An ongoing trial is also specifically assessing the influence of sulphasalazine on PSC (NCT03561584).

In a detailed investigation of individuals with PSC receiving adalimumab (n = 31) and infliximab (n = 110) on the indication of IBD in PSC (PSC-IBD), some improvement of ALP was demonstrated in the adalimumab group with a 15% median reduction at 3, 6, and 12 months.[67] A positive IBD response at 3 months was however predictive of a lower ALP level at 12 months, raising the possibility that this effect of adalimumab on ALP levels was merely due to a reduction of intestinal inflammation.[67] Similar reasoning was made for the observations on tofacitinib (n = 43),[68] where individuals on continued therapy—presumably due to efficacy for IBD activity— showed ALP improvements, and the IBD response to tofacitinib significantly correlated with ALP changes.

A significant amount of translational research suggested the involvement of α4β7-integrin on lymphocytes with MAdCAM1 in the liver in recruiting gut-activated lymphocytes to extraintestinal manifestations in IBD, PSC included.[69–71] Despite the plausibility of these biological data, the largest study up to now investigating the liver effects of α4β7-inhibition in people with PSC receiving vedolizumab on the basis of their IBD (n = 102) found no evidence for a biochemical response after 14 weeks follow-up.[72] While ALP decreased by 20% or more in a subset (20.6%) of individuals, there was also an increase in ALP of 20% or more in 41.6% of the individuals.

The disappointments associated with immunosuppressive drugs and IBD-related biologics are furthered by the paradoxical recurrence of PSC after liver transplantation, despite tacrolimus-based immunosuppression regimens with or without concomitant mycophenolate and corticosteroids.[73] The key learning experience appears to be that control of IBD is relevant, but for now little clarity exists as to whether biological pathways of relevance to achieving IBD remission or other immunological pathways also could be targeted to halt disease progression in PSC. A key question remains open for the suitability of ALP as an indicator for clinical benefits from any of these therapies, and further studies of the relationship between IBD therapeutic benefits and progression of PSC using other surrogate endpoints such as the ELF test or pro-C3 are warranted.

Other avenues of ongoing drug development in PSC

Several other avenues of drug development in PSC are ongoing (Table 1) and reviewed elsewhere.[74] Of particular conceptual interest is the phase II bexotegrast (previously called PLN-74809, NCT04480840), the phase III simvastatin (NCT04133792),[75] the phase II CM-101 (NCT04595825), and the phase II pyridoxine (CTIS 2023-505155-47-00) trials. Inhibitors of the apical sodium-dependent bile acid transporter (also called ileal bile acid transporter and SLC10A2) such as odevixibat and volixibat (NCT04663308) are also being explored,[76] with a strong emphasis on patient-reported outcome measures (PROMs), particularly reduction of pruritus.

Bexotegrast is conceptually interesting because it is the first antifibrotic drug trial in PSC since the failure of simtuzumab to show benefit,[13,77] however, with a different mechanism of action (bexotegrast is an αvβ6/αvβ1 integrin inhibitor). Safety was the primary endpoint of the trial, which was met and has been reported in abstract form,[78] but secondary analysis of data from the study might indicate clinically relevant influences on the ELF test and pro-C3 in the treatment group (https://ir.pliantrx.com/news-releases/news-release-details/pliant-therapeutics-announces-positive-safety-and-exploratory-0), along with a stable ALP. The simvastatin trial is interesting given its choice of a primary endpoint related to clinical outcomes (death, listing for liver transplantation, time to first variceal bleeding, and time to hepatobiliary cancer diagnosis), as will be further discussed below.[75] The CM-101 phase II trial is of interest due to the novelty of its mechanism of action,[79] targeting the profibrotic and proinflammatory chemokine CCL24.[80,81] Finally, the vitamin B6 supplementation trial is of mechanistic interest due to its reliance on molecular data on the gut microbiome in PSC.[54,82]

THE PROS AND CONS OF ALP IN PSC

An elevated serum ALP level above the upper limit of normal (ULN) is part of the diagnostic criteria of PSC in adults in the EASL, but not in the AASLD clinical practice guidelines.[2,6] According to the AASLD guidelines, the cholangiographic features of PSC, along with the exclusion of secondary sclerosing cholangitis, is sufficient for making a diagnosis, accounting for the fact that a significant proportion of individuals with PSC may have normal ALP levels.[83,84] As PSC is

increasingly diagnosed at earlier disease stages along with increased attention and magnetic resonance imaging (MRI) availability and quality, omission of the elevated ALP criterion of the diagnosis, as now implemented in the AASLD guidelines, may be particularly relevant. High levels of ALP are associated with a more severe disease stratum, while normal levels are associated with a better prognosis.[85,86] ALP is thus included in several prognostic models for PSC, including the Amsterdam-Oxford score,[87] the UK-PSC score,[88] and the PREsTO score.[89] However, the intraindividual variability of ALP is considerable, and spontaneous normalization of ALP frequently occurs.[77,83,90,91]

Biology of ALP

ALPs are glycoproteins bound to the plasma membrane and are widely distributed in nature.[92] In humans, zinc and magnesium serve as significant cofactors for their biological activity. ALPs exist in 4 different isoforms: intestinal ALP, placental ALP, germ cell ALP, and liver/bone/kidney (ie, tissue-nonspecific) ALP.[92,93] Over 80% of the ALPs in serum originate from the liver and bone. Although ALPs are found in numerous tissues, their exact physiological function remains largely unknown.[94] Elevated activity in the circulation is a marker for skeletal remodeling or hepatobiliary disease, but clinical variations in serum ALP levels also commonly occur in endocrine disorders such as thyroid disease, hematological diseases, malnutrition, and vitamin deficiencies.[94] Genetic variation, for instance related to bile acid transport and glycobiology, associates with ALP levels in apparently healthy individuals.[92,95,96] It is currently unknown to what extent ALP serves an integral part of cholestatic liver disease pathophysiology or merely represents a marker of biliary injury, altered bile composition, and cholestasis.[92]

Behavior of ALP in PSC

Along with PSC disease flares, ALP and other liver blood tests (transaminases and bilirubin in particular) are potentially affected by incident bacterial cholangitis, high-grade and clinically significant bile duct strictures and associated endoscopic treatment, concomitant features of autoimmune hepatitis (AIH), and IBD activity and treatment of IBD.

The variability of serum ALP levels in PSC over time is large (Figure 1). Data from the simtuzumab trial demonstrated that ALP varies up to 20% over 1 and 2 years.[13,77] At 2 years, more than a 40% reduction of ALP was observed in 16% of individuals with baseline ALP exceeding 2× ULN, and 18% in those having ALP exceeding 3× ULN.[77] These data provide important food for thought on what a change in ALP and other biomarkers over a 3–48-month clinical trial period means in terms of clinical outcomes a decade later—which is the projected horizon in a slowly progressing disease such as PSC.

Spontaneous normalization of ALP is common, and low ALP levels are associated with a more favorable prognosis in PSC. Several studies have shown that levels of ALP $<1.5\times$ ULN are linked to a lower risk of complications compared to levels above 1.5× ULN.[84,90] Reduction in ALP values might also be associated with improved transplantation-free survival in people with PSC,[22,91] regardless of the presence of high-grade strictures.[97] In one of these studies, ALP reductions $>40\%$ were reported to associate favorably with long-term outcomes in PSC.[22] A 5-year longitudinal follow-up of 113 individuals with PSC compared ALP, liver stiffness measurement, and the ELF test over time.[90] Sixteen percent of these individuals changed the category using a cutoff of 1.5× ULN. Progression measured by the ELF test and liver stiffness, however, occurred only in individuals with an ALP level above 1.5× ULN.

One study of newly diagnosed PSC individuals followed for 10 years revealed that 40% normalized their ALP during follow-up, while 60% had continuously elevated levels. Those with high ALP levels at diagnosis were more likely to reach clinical endpoints (CCA, liver transplantation, and death). In addition, they had more advanced PSC, as evidenced by higher fibrosis stages, Mayo risk scores, and bilirubin levels.[91] An extended follow-up analysis of 198 participants from the Scandinavian UDCA trial revealed that responders—defined as individuals who achieved at least a 40% decrease in ALP levels or consistent normalization after one year—had better 10-year transplant-free survival compared to nonresponders.[22] Interestingly, the most favorable outcomes were observed in individuals receiving a placebo and spontaneously normalized their ALP levels. Similar findings were reported in a UK PSC population, where an improvement in ALP to below 1.5× the upper limit of normal (ULN) was associated with better outcomes, comparable to those with complete ALP normalization.[98]

In summary, there is an association between low, normalized, and improvement of ALP to levels below 1.5× ULN and a favorable outcome in PSC. However, whether medical treatment that leads to an improved ALP during a clinical trial period of up to two years reduces the risk of long-term clinical complications and future need for liver transplantation remains to be proven, and ALP should not, in isolation, be considered a valid surrogate endpoint in clinical trials in PSC.

INCLUSION AND EXCLUSION CRITERIA IN CLINICAL TRIALS OF PSC

The choice of inclusion and exclusion criteria in clinical trials in PSC warrants several considerations, including the mechanisms of action of candidate drugs to be

tested. A selection of disease-specific inclusion and exclusion criteria for clinical trials in PSC are listed in Table 2. In general, the exclusion of very mild disease (ie, small duct PSC), concomitant AIH, or IgG4-associated cholangitis is normally recommended. Moderately increased IgG and IgG4 levels and positive autoantibodies (eg, ANA and SMA) in PSC are not uncommon, and such individuals should not be excluded if overt overlapping disease is excluded.[2]

Disease stage

The disease stage at which a study drug has the best chance of proving efficacious warrants considerations from several perspectives. As illustrated in Figure 1, there is increasing fibrosis with advanced disease, both peribiliary ("onion-skin fibrosis") and in the liver parenchyma. As such, early disease stages of PSC with only minimal fibrosis may warrant different types of interventions than that of later disease stages and may be the optimal time for disease interventions aiming for reversal and even resolution of PSC. However, studies using inclusion criteria allowing very early and mild disease are likely to fail due to slow disease progression and lack of surrogate biomarkers for progression at such stages. Small-duct PSC represents one end of the PSC disease spectrum, and behaves less progressively and is therefore usually an exclusion criterion in clinical trials in PSC.[99,100] The definition of "early PSC"

TABLE 2 Typical inclusion and exclusion criteria for clinical trials in PSC

	Discussion points
Inclusion criteria	
Age 18–75 years	There is no reason not to include people from 16 years of age, but the increased frequency of features of AIH must be accounted for
A confirmed diagnosis of large-duct PSC	An MRCP/MRI is required and should not be older than 6–12 months to be able to stage the disease and exclude high-grade strictures and manifest cholangiocarcinoma
ALP level $>1.5\times$ ULN	Normal serum ALP does not exclude advanced or progressive disease, and up to 50% of people with PSC may not fulfill this criterion.
Colonoscopy to ascertain IBD status	Presence and type of IBD may affect the disease course in PSC
Stable IBD treatment	IBD activity and IBD therapy may influence liver blood tests, and/or PROMs and quality of life in PSC
Discontinued or stable dose of UDCA	UDCA is commonly prescribed in PSC, and UDCA discontinuation or change in dose can influence liver blood tests
Exclusion criteria	
Small-duct PSC	Small duct PSC has a different natural history than large duct and may represent a separate disease entity
Secondary causes of sclerosing cholangitis	This typically includes significant gallstone disease requiring endoscopic intervention, which may also occur in the context of PSC
History or presence of other competing liver diseases	These include viral hepatitis, AIH, MASLD, Wilson's disease, hemochromatosis, ALD, α1-antitrypsin deficiency, congenital biliary disease
Previous liver transplantation	Represents a clinical endpoint, and clinical trials to prevent or treat recurrent PSC warrant special considerations
Previous hepatobiliary malignancy	Represents a clinical endpoint, and cholangiocarcinoma has a high recurrence risk
Signs of portal hypertension or decompensated cirrhosis	Represent a clinical endpoint
Recurrent bacterial cholangitis	Influences surrogate endpoints (liver blood tests and LSM) and with a risk of accelerating disease progression
ALT or AST $>5\times$ ULN	AST and ALT levels $>5\times$ ULN in PSC are uncommon and may represent other underlying conditions (AIH, DILI, etc) and also make the detection of trial-relevant DILI difficult
Ongoing moderate or severe inflammation of IBD	Active gut inflammation affects liver blood tests and requires treatment that can affect outcome measures
Concomitant therapies that can interact with the study drug or affect the endpoint	Typically drugs such as fibrates or rifampicin are used to treat pruritus, or long-term antibiotic treatment (including vancomycin)
Current or recent history of colorectal all-grade dysplasia and cancer	Individuals considered cured from colorectal cancer are usually eligible

Abbreviations: AIH, autoimmune hepatitis; ALD, alcohol-associated liver disease; DILI, drug-induced liver injury; IBD, inflammatory bowel disease; LSM, liver stiffness measurement; MASLD, metabolic dysfunction–associated steatotic liver disease; MRCP/MRI, magnetic resonance cholangiopancreatography/magnetic resonance imaging; PROMs, patient-reported outcome measures; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

(Figure 1) is still unclear but usually includes individuals with only minimal elastography elevations, minor cholangiographic changes, no symptoms, and sometimes a low ALP. Importantly, individuals with such features of early PSC represent a large and increasing proportion of the overall PSC population,[90,101] and additional inclusion criteria may be considered in future trials to allow for the participation of such individuals. Determining which of these individuals have a concomitant predisposition for progression during follow-up and thus are in need of medical therapy remains unknown. Liver stiffness measurements,[102,103] serum bile acid profiles,[104] and increased serum fibrosis and fibrogenesis biomarkers (eg, the ELF test and pro-C3) with specific cutoff levels that need to be identified[7,90,105,106] could represent criteria for including such individuals.

Very advanced PSC is also typically avoided in most clinical trials, under the assumption that disease at some point becomes irreversible or is dominated by irreversible features. In decompensated cirrhosis and a setting with frequent recurrent bacterial cholangitis and repeated need for endoscopic interventions, the disease may be considered to have reached a point where medical treatment that targets PSC-specific aspects of pathophysiology is unlikely to change the ultimate clinical outcome. Child-Pugh class B or C or decompensated liver disease, as defined by a history of variceal bleeding, history of encephalopathy or ascites, anticipated need for liver transplantation within 6 months or already listing for liver transplantation, presence of cirrhosis and portal hypertension with low platelet counts, and a spleen size above 14 cm and presence of varices are therefore all common and relevant exclusion criteria.

Bacterial cholangitis with fevers is frequent in PSC, but there is no consensus definition of cholangitis as a clinical event.[107] Studies usually exclude individuals with a recent history of bacterial cholangitis ($\leq$12weeks) and endoscopic treatment for bile duct stenosis $\leq$12 weeks before inclusion or planned within 12 weeks after randomization. An episode of bacterial cholangitis influences common surrogate endpoints (eg, liver blood tests and liver stiffness), and endoscopic dilatation of biliary strictures will improve liver blood tests and liver function unrelated to any concomitant medical intervention. A consensus definition of cholangitis, potentially on the basis of patient symptoms as much as other parameters, and refinement of cholangitis as an exclusion criterion in relevant studies, including strategies to appropriately account for individuals with clinically relevant, high-grade strictures, would facilitate the inclusion of more severe forms of PSC into clinical trials for therapies of particular relevance to this group.

In current practice, a baseline or recent MRI that will identify high-grade strictures, as well as potential CCA, signs of cirrhosis, portal hypertension, and providing a general evaluation of the bile ducts, is advisable. With improving technology and the use of targeted contrast agents, as well as artificial intelligence–informed or computerized image analysis (eg, MRCP+),[108–112], MRI-based surrogate endpoints for disease stability ("no worsening") or progression may become feasible and enable further stratification of the cholangiographic disease stage at inclusion by the use of validated scoring systems.[113,114] Reporting MRI standards should be used[115] and continuously revised according to technological developments.

Liver blood tests and ALP on inclusion

Based on the data suggesting that an ALP cutoff at approximately $<$1.5× ULN associates with a milder disease course in PSC,[97,98] this has frequently been used as an inclusion criterion in clinical trials in PSC (Table 1).[10,16] The choice of the ALP cutoff has also been influenced by reminiscent criteria in PBC, where cutoffs for ALP of 1.5× ULN or 1.67× ULN have been widely accepted as a valid inclusion criterion for "non-responders" to UDCA therapy.[116] The threshold at which ALP after 1 year had the best prognostic value was evaluated in a Dutch study, which concluded that 1.3× ULN appeared as the most optimal threshold (and at levels $>$2.5× ULN, the hazard of reaching an endpoint seemed to level off).[117] While some studies argue an optimal cutoff for ALP versus negative outcomes in PSC may be higher (ie, 2.4× ULN),[88] there appear to be only minimal improvements in risk stratification capacity above approximately ALP $>$1.5× ULN.

The main argument against using an ALP threshold as an inclusion criterion is the known fluctuations and even spontaneous normalization in a significant proportion of people with PSC.[84] This concern adds to observations of data from a prospective Norwegian study where ~50% of the participants had ALP levels below 1.5× ULN,[90] and a Swedish cohort where stable low levels of ALP were found over time.[101,118] An inclusion criterion rendering almost 50% of the patient population ineligible for study inclusion furthermore poses concerns about the generalizability of findings from clinical trials in individuals with elevated ALP. There is also an element of circular logic surrounding the use of an elevated ALP as an inclusion criterion, meaning that in trials where ALP reduction is part of the primary endpoint, the baseline level needs to be increased.

Out of 3 ongoing phase III trials in PSC, 2 (the 24 months norucholic acid vs. placebo [NCT03872921] and the 24 months trial of bezafibrate and UDCA vs. placebo [NCT04309773]) use the 1.5× ULN threshold for inclusion, whereas a third trial (60 months simvastatin vs. placebo, NCT04133792) does not use an ALP $>$1.5× ULN elevation as an inclusion criterion.[75] In the future, ALP either needs to be substantiated as a

surrogate biomarker for disease severity in PSC far beyond the current conflicting situation or abandoned due to its obvious shortcomings.

ALT or AST $>5\times$ ULN in the last 12 weeks is a common exclusion criterion. AST and ALT $>5\times$ ULN are not very common in PSC unless there are particularly pronounced concomitant features of AIH or adverse drug reactions. Such individuals should not be included in clinical trials of PSC.

Serum bilirubin level is challenging to incorporate along with other inclusion/exclusion criteria but has been used in some trials (eg total bilirubin >3.0 mg/dL at screening or baseline, or both total bilirubin levels $>$ ULN within the last 6 months before baseline and a rise of this level by more than 50% within the last 6 months before baseline in the phase II norucholic acid trial[10]). As a biomarker for late-stage disease, but also disease complications such as clinically relevant strictures and CCA, bilirubin might rather be handled along with imaging-based criteria of such complications and general definitions of end-stage liver disease. The same argument can be made for serum albumin level as a separate exclusion criterion.

IBD and CCA

Due to the high prevalence of IBD in PSC,[1] presence and activity of IBD and associated treatments can affect PSC and liver blood tests and consequently need to be handled upon inclusion. In most PSC trials, a colonoscopy is mandatory in all individuals, and if IBD is known to be present, a colonoscopy should have been performed within the last 24 months. Ongoing moderate or severe inflammation in IBD are relevant exclusion criteria since active gut inflammation may affect liver blood tests and requires treatment that potentially could affect outcome measures. Any ongoing treatment for IBD should be at stable dosing for at least 12 weeks.[20,67,72,119] Current or history of colorectal cancer or all-grade dysplasia described at the last colonoscopy should also be an exclusion criterion, while individuals cured from colorectal cancer by colectomy without recurrence for at least 5 years are usually considered eligible. To the extent feasible, CCA should be excluded, and an MRI <6–12 months before trial participation is implemented in most protocols.

UDCA at inclusion

As elaborated above, a large proportion of people with PSC are treated with UDCA despite insufficient evidence for its efficacy.[120] Concomitant treatment with UDCA in clinical trials is therefore often accepted and, by some regulatory authorities, paradoxically even considered as standard clinical practice. Furthermore, if discontinuation of UDCA is used as an inclusion criterion, individuals with PSC may hesitate to participate, hampering recruitment. A change in the dosing of UDCA or discontinuation may affect liver blood tests. A delay of study drug exposure or so-called "wash-out" period is therefore warranted if dosing has been changed or discontinued.[25,26] The appropriate length of a wash-out period after UDCA discontinuation is unclear but should likely be at least 8 weeks.[10] If no discontinuation of UDCA is performed, a stable dose for more than 6 months has been proposed preferable.

The topic of concomitant UDCA in PSC trials illustrates a potential barrier to drug development in PSC, where baseline therapy, favored by people with PSC and physicians, may hold insufficient evidence for prescription, on top of which new therapies are now tested. To what extent this situation may confound data on efficacy of new compounds can only be speculated.

SURROGATE ENDPOINTS IN CLINICAL TRIALS IN PSC—ALP AND BEYOND

A surrogate endpoint in clinical trials is generally defined as a clinically meaningful endpoint that measures the feelings, functions, or survival of diseased individuals.[121] In PSC, accepted clinically meaningful endpoints are the transplant- and cancer-free survival or survival free from liver decompensation. Any surrogate endpoint in PSC needs to predict either of these outcomes. The heterogeneity in disease severity and overall slow progression of PSC make the most relevant outcomes (death, liver transplantation, and hepatobiliary cancer) challenging outcome measures due to the low incidence of these events in phase II and III studies of common size and duration.

Before a surrogate biomarker is ultimately accepted by regulatory authorities, it must predict so called "meaningful" clinical benefit.[122,123] As of yet, robustly validated and regulatory adopted surrogate biomarkers to predict long-term clinical outcomes in PSC are lacking.[121,124] In 2016, the International PSC Study Group published a Delphi-based consensus statement on surrogate endpoints promoting ALP, histology, and elastography as promising candidates.[124] Since then, a considerable amount of data on serum fibrosis biomarkers, including the ELF test and pro-C3, and liver stiffness have been published.[125,126]. Bile acid profiles is another example which takes UDCA treatment into account and is associated with hepatic decompensation.[104] Such non-invasive measures of fibrosis are favored by study participants over liver biopsy. Still, there is not enough data to support one surrogate endpoint for treatment response over another, and none is generally approved by regulatory authorities to support accelerated approval (FDA) or conditional market authorization (EMA) of new drugs in PSC.

The advantages and disadvantages of different endpoints are discussed below and are summarized in Table 3. Likely the field will have to cope for some time still with the need to use composite endpoints comprising several of these biomarkers and events. Despite various still ongoing consensus processes to introduce standards for clinical trials in PSC,[127] there is no shortcut around the severe need for significantly more data on the performance and behavior of all surrogate biomarkers for clinical outcomes in PSC.

ALP as an endpoint

ALP has been widely used as a surrogate endpoint in PSC trials (Table 1). There has been a significant transfer of experiences from PBC, as illustrated by the widespread use of an ALP cutoff of 1.5× ULN as an indicator for the evaluation of treatment efficacy.[116] First-line PBC treatment with UDCA improves ALP and prevents hepatic complications.[116] For nonresponders to UDCA, conditional approval of second-line treatment with OCA in PBC was based on results from the POISE trial, a phase III, randomized, double-blind placebo-controlled study which demonstrated a significant, sustained reduction in ALP,[128] and its inclusion criteria and endpoints set standards for further trials in PBC (the POISE criteria). However, full approval of OCA depended on the requirement to confirm meaningful benefits through clinical outcomes, such as hepatic decompensation or liver transplantation,[129–131]. With the results of the COBALT study,[56] despite challenges related to recruitment and retainment, the journey of ALP as a surrogate biomarker for long-term benefits in PBC has reached a temporary impasse that remains unresolved. In PSC, which is even rarer than PBC and characterized by a more heterogeneous disease behavior, the limitations of ALP as a biomarker are even more evident.

Although ALP is associated with prognosis in PSC and can be used for disease stratification, in our opinion, its high inter-individual variability, imperfect correlation with short-term disease progression (especially in early stages), and frequent spontaneous reductions or normalizations make change in ALP levels insufficient as a measure for treatment efficacy. This is especially true for short-term phase II studies sensitive to such variation. For example, in the dose-finding safety phase II trial of

TABLE 3 Pros and cons of potential endpoints in clinical trials in PSC

Endpoint	Biomarker	Pros	Cons
Cholestasis	ALP	− Increased levels associated with more severe disease − Reduction/normalization associated with a more favorable outcome	− High variability − Spontaneous normalization occurs − Disease progression despite normal levels − Affected by endoscopic intervention
Liver blood tests	AST, ALT, bilirubin, bile acid profiles	− Increased levels associated with more severe disease − Reduction/normalization associated with a more favorable outcome	− Affected by PSC complications (high-grade strictures) and associated treatment − Affected by IBD activity − Affected by drugs, including DILI
Histology	Fibrosis stage	Nakanuma and CPA associated with prognosis	High variability—patchy distribution of fibrosis, invasive, not used clinically
Liver stiffness	VCTE MRE	Noninvasive, associated with prognosis	High variability MRE low availability
Serum fibrosis markers	ELF test, pro-C3, others	Noninvasive, associated with prognosis	Missing data on natural history variability
Imaging	Anali Score, District Score, Spleen Size, Quantitative MRCP	Promising, including artificial intelligence–assisted reading opportunities	High inter-reader variability
PROMs and quality of life questionnaires		Measures symptom burden and quality of life features which are important for individuals with PSC	− PSC-specific PROMs and quality of life assessments not universally validated −Strong influence by comorbidities such as IBD and CCA risk
Cholangitis	Symptoms, fevers	− Common clinical event − Indicates more severe disease	No consensus definition, but can be included as part of PROMs
Composite hard endpoints	Death, liver transplantation, variceal bleeding, and hepatobiliary malignancies	Most relevant for the assessment of clinically meaningful benefits from any drug/intervention	Low feasibility for new drugs due to slow disease progression and low number of events during trial duration

Abbreviations: CCA, cholangiocarcinoma; CPA, collagen proportionate area; ELF test, enhanced liver fibrosis test; IBD, inflammatory bowel disease; MRE, magnetic resonance elastography; MRCP, magnetic resonance cholangiopancreatography; pro-C3, cleaved amino-terminal propeptide of type III collagen; PROMs, patient-reported outcome measures; PSC, primary sclerosing cholangitis; VCTE, vibration-controlled transient elastography.

cilofexor in PSC, ALP was significantly decreased.[14] However, in the subsequent open-label extension, ALP reduction did not remain significant (while other liver blood tests were significantly improved in treated individuals).[55] In the high-dose UDCA trial in PSC, ALP (and AST) levels decreased more significantly in the treatment group than in the placebo group, but these improvements in liver blood tests were not associated with a decrease in hard endpoints and the study was prematurely stopped for safety reasons.[9] In the simtuzumab trial, ALP levels were not associated with the fibrosis stage on histology.[13] Such examples illustrate the difficulty of relying on ALP as a surrogate endpoint in the setting of clinical trials in PSC. Spontaneous ALP variations can potentially lead to misinterpretation of treatment effects whereby potentially important and relevant drugs for the treatment of PSC can end up being dismissed, despite their effectiveness, and vice versa. As such, better surrogate endpoints than ALP should be used.

Liver biopsy versus noninvasive assessments of liver fibrosis

Liver fibrosis regression on liver biopsy is often a valid and appropriate endpoint for chronic liver diseases with predominant parenchymatous manifestations such as metabolic dysfunction–associated steatotic liver disease.[132] With its unequal manifestations throughout the biliary tree, liver biopsy findings in PSC are often unevenly distributed, with a mixture of late-stage and early-stage lesions even being found in the same liver. Despite the patchy distribution, liver biopsy findings have nevertheless been shown to associate with PSC outcomes,[133–135] with the most robust associations found for collagen proportionate area and the Nakanuma scoring system. There has been support from regulatory authorities for liver biopsy in clinical trials in PSC,[121] which led to the inclusion of liver biopsy assessments in both the phase IIb simtuzumab trial and the phase III norucholic acid trial. Clinicians and people with PSC have been reluctant to a biopsy-based endpoint orientation in PSC, given the fact that liver biopsy is rarely clinically indicated (only in cases of suspected overlap with AIH or other liver diseases) and not part of the diagnostic criteria.

A growing body of research has highlighted the utility of serum-based fibrosis tests in predicting clinical outcomes in PSC.[136] The ELF test has been the most extensively studied,[105,125] but there is also an increasing amount of data supporting the use of the fibrogenesis biomarker pro-C3,[106,126] including evidence from clinical trials.[16,137] Both the ELF test and pro-C3 correlate strongly with liver stiffness,[90,126] which also show robust associations with clinical outcomes,[102,103] as well as with histological stage.[137] Given the increasing data on liver stiffness and serum-based fibrosis tests in PSC, even to the extent of being incorporated in learned society guidelines for prognostication in PSC,[138] along with questionable features of liver biopsy regarding sampling error and ethical considerations, we believe noninvasive tests of liver fibrosis will replace liver biopsy in clinical trials for PSC in the near future.

Cholangitis

Bacterial cholangitis is a common clinical event in PSC and can be considered as a clinical endpoint. The use of cholangitis in the setting of clinical trials is hampered by the lack of its definition in PSC (see above).[124] The UK PSC patient organization has developed a smartphone app for people with PSC where they can register their perceived cholangitis attacks. To include cholangitis as one component of symptom burden assessments by patients in clinical trials is likely a pragmatic way to deal with the inability of experts to agree on a definition.

Imaging

Imaging, and in particular MRI, as a prognostic tool is receiving increased attention but has so far not been used as a primary endpoint in PSC trials. Various types of imaging findings are associated with prognosis. Signs associated with disease progression are increasing spleen size and other signs of portal hypertension, intrahepatic bile duct dilatation, the severity of biliary strictures and dilatations and delayed relatives contrast enhancement or presence of potential functional strictures, and quantitative MRI scores (eg, MRCP+).[110,113,114,139–142] Neither in the phase III bezafibrate versus placebo study nor in the PRIMIS study (cilofexor, phase III)[15] is MRI listed among the endpoints. In the norucholic phase III trial, MRI is an optional explorative endpoint, and in the simvastatin phase III (NCT04133792) trial, MRI is listed as a secondary endpoint.[75] Further development and evaluation of MRI using computerized interpretation of images with or without application of artificial intelligence or the use of targeted contrast agents make imaging a highly interesting and potentially prosperous area for the development of future surrogate endpoints in PSC.

PROMs and quality of life assessment

The patient's voice is increasingly heard in PSC.[120,143,144] Along with respectful implementation of “people first language” in trial protocols and scientific publications,[145] for example, “people with PSC” rather than “PSC patients,” this has paved the way for the development of PSC-specific PROMs to assess

symptom burden and quality of life. There is no current consensus on which scoring systems to apply in clinical trials for PSC, and the emphasis is put on validated, generic scoring systems for quality of life (eg, SF-36), bowel symptoms (eg, IBD-Q), or specific symptoms such as pruritus (eg, worst itching intensity numerical rating scale, ie, the NRS).[146]

There is ongoing activity to develop PSC-specific PROM tools and quality of life questionnaires.[147,148] Existing examples include the Simple Cholestatic Complaints Score.[149–151] With an emphasis on regulatory acceptance for implementation in clinical trial settings, a new symptom assessment questionnaire is under development by the US patient organization (PSC Partners Seeking a Cure), focusing on abdominal pain and fatigue.[152] Another initiative is aiming for an even more comprehensive assessment of the quality of life for people with PSC.[153]

Once relevant validation and regulatory approval are in place, consensus on how to implement the PSC-specific PROMs and quality-of-life assessments in relevant trial protocols needs to be developed. PROMs might even be included as part of a composite primary endpoint. For widespread implementation, accepted protocols for translation (eg, forward and backward translations) must subsequently be applied for as many languages as possible.

Composite hard endpoints

The use of a composite hard endpoint creates the best evidence for treatment efficacy. However, performing such trials is challenging given the longer study period and the large number of participants needed. This imposes a risk of recruitment failure, meaning that the trials end up underpowered. This happened in the Scandinavian UDCA trial, where only 7.5% reached the primary endpoint of death or liver transplantation.[8] Expanded hard endpoint criteria were employed in the high-dose UDCA trial (28–30mg/kg/d), which used the development of cirrhosis, varices, CCA, liver transplantation, or death as a primary composite endpoint.[9] In the ongoing phase III simvastatin trial, death liver transplantation, hepatobiliary cancer, or variceal bleeding is used.[75]

To include CCA as part of a composite endpoint in clinical trials is problematic. Hepatobiliary cancer can occur at any time point during the disease course in PSC and will occur occasionally in trials regardless of the intervention. Risk factors for CCA are the presence of high-grade or rapidly progressive strictures, old age, and a recent PSC diagnosis.[1,4,154] Although the lifetime risk of hepatobiliary malignancy is high and a common cause of death in PSC, the yearly incidence in PSC after the first year after diagnosis is low.[101,155] Progressive fibrosis and the need for liver transplantation are much more common and important as endpoints. In a Swedish study following 512 persons with PSC prospectively for 5 years, 16 persons developed hepatobiliary cancer and 54 needed a transplant.[101] Given the relative impact on mortality in PSC,[156] it may be argued that CCA should still be included. To the extent feasible, CCA should be excluded at baseline to avoid undetected malignancy that is already present before exposure to the study drug.

Due to the great challenges to perform large and long-term studies in PSC, composite hard endpoints are less likely to be used in PSC trials although desirable. Large-scale and long-term real-world data of surrogate endpoints need to compensate for this.

WHERE ARE WE GOING?

Several trends are notable from the above discussions. First, there is a significant number and diversity of clinical trials ongoing. This means that people with PSC have the opportunity to—and should be offered to—participate in these trials, a key point that is now even emphasized by clinical practice guidelines.[2] Implicit to this orientation is an imminent abandoning of therapeutic nihilism in PSC, which became prevalent following the disappointment from the high-dose UDCA trial and subsequent controversies. Importantly, in management-related conversations with people with PSC, a clear distinction needs to be made between experimental interventions in the context of controlled, clinical trials and evidence-based routine prescriptions. The discussion on vancomycin illustrates this point very clearly,[47,49] and the current lack of effective interventions should not leave people with PSC at risk of well-intended exposure to clinical interventions which are based on low-quality evidence.

Second, beyond the evaluation of specific interventions, the ongoing clinical trials are slowly building knowledge on the utility and behavior of candidate surrogate endpoints. The subsequent scrutiny of the simtuzumab trial has been a model example of how to utilize data from negative clinical trials to forward the field in this regard,[13,77] showing, for instance, the superior stability over time of the ELF test (3%–4% spontaneous variability) to ALP (12%–20% spontaneous variability). Furthermore, the accumulating data on the behavior of exploratory endpoints such as the ELF test and pro-C3 in the context of clinical trials are also helpful, as illustrated by promising trends in these biomarkers in the aldafermin[16] and bexotegrast[78] trials. A provocative position would be that such trends are exactly what success in PSC should look like: a reduction in biliary and liver fibrogenesis and, ultimately, even a potential reversal of existing fibrosis. With further knowledge of the natural behavior and long-term prognostic utility of such noninvasive biomarkers of fibrosis, the field may ultimately be able to move away from the use of liver biopsy in clinical trials in PSC, which is long overdue.

Third, despite the shortcomings of ALP, including the high frequency of individuals with PSC with low or normal levels of ALP, the association between high levels and a more severe disease stratum appears undisputable. Prioritizing trials to high-risk strata holds some rationale yet reduces the generalizability of findings to a real-world PSC population. We anticipate an intermediate stage in the evolution of clinical trials in PSC, where ALP will still be used for participant stratification and as an inclusion criterion, but where the primary endpoints will be noninvasive measures of fibrogenesis and possibly also PROMs. In a subsequent stage, ALP will be totally replaced by noninvasive biomarkers of PSC severity and MRI-based measures of disease severity, stage, progression, or regression, backed by data for such measures that are acknowledged by relevant regulatory authorities. However, importantly, as learned from the lesson of OCA in PBC, the final word on efficacy for any compound is not said until robust data on clinical benefit are at hand, a conclusion which is as likely to be supported by real-world data as much as controlled trials following accelerated or conditional approval.[57] Long-term use of artificial intelligence tools for clinical decision-making and evaluation of quality of care will likely replace traditional real-world data studies in the future and further strengthen the evidence for or against the efficacy of a specific treatment.

In addition, to receive robust outcome data and avoid repeating the lapse seen in PBC, new insights into how the short-term behavior of candidate prognostic biomarkers can be projected into long-term clinical outcomes is a prioritized area of research. However, the nature of PSC running in flares with unexpected events driving disease makes the development of surrogate biomarkers for disease outcomes even more challenging than in PBC, which has a more predictable, linear disease course. In PSC, there is an opportunity to take advantage of previous and ongoing longitudinal data and biobank collections to test and validate the noninvasive markers. There are such collections available with the FICUS study from France and the SUPRIM study from Sweden.[103,118] In the latter, also longitudinal MRI data was collected, making this a potential resource for validation of MRI-based measures of PSC progression. The Worldwide Integration of Natural History Databases (WIND) project initiated by the US PSC patient organization and the Strategic Prospective Scandinavian PSC Biobank & Cohort (ScandPSC) project are examples of 2 ongoing natural history cohort initiatives offering similar research opportunities. These projects have the ambition, for subsets of the cohorts, to serve as external controls (synthetic control arms), for real-world data and even trials on promising interventions.[131]

There is a major responsibility with the PSC research community to ensure that ongoing data collections, surrogate endpoints analysis, and symptom score questionnaires adhere to requirements and guidelines posed by regulatory authorities to ensure that scientific output is valid for clinical trial applications and subsequent regulatory considerations. Consensus processes on clinical trial design also need to pay attention to this aspect,[124,127], and consensus without such evidence is likely to be of limited value. With increasing harmonization in phase II and III study design in PSC, there are growing opportunities to utilize alternative study designs, such as adaptive platform trials,[157,158] to minimize placebo exposure, simultaneously study different compounds and maximize the utility of patient trial participation. Platform trials are being applied in other rare diseases (eg, scleroderma, NCT06195072) and may help overcome an increasing phenomenon of "trial competition" as the number of compounds entering clinical trials in PSC is increasing while eligible patients remain scarce—challenges which are common to all rare diseases.[159] The current and hypothetical future landscape of clinical trials in PSC is summarized in Box 2.

Box 2 Current and future features of clinical trials in primary sclerosing cholangitis (PSC). Abbreviations: ELF test, enhanced liver fibrosis test; MRI, magnetic resonance imaging; pro-C3, cleaved amino-terminal propeptide of type III collagen; PROMs, patient-reported outcome measures

Current and near future	After 2030
● Increasing number of phase II trials— typically runs 3–6 months ● Increasing number of phase III trials— typically runs 1–2 years ● Fibrosis markers (eg, the ELF test, pro-C3, and liver elastography) replacing ALP and liver biopsy as surrogate biomarkers for clinical benefit based on emerging data from several natural history cohorts ● Computerized MRI analysis with or without artificial intelligence applications are included in study protocols to accelerate the development of additional surrogate endpoints ● PSC-specific PROMs and quality of life questionnaires which are accepted by regulatory authorities are implemented as co-primary or secondary endpoints in clinical trials ● Debate and controversy on the use of ursodeoxycholic acid in control arms due to its low level of evidence	● Established standards for inclusion/exclusion criteria and surrogate endpoints allow for adaptive platform trials to be increasingly used in PSC ● The prediction of surrogate biomarkers for hard endpoints are established and accepted by regulatory authorities leading to predictable pathways for conditional or accelerated approvals ● Control arms are shared between trials and trial data supported by extensive data from prospectively collected natural history cohorts (eg, WIND, ScandPSC) ● Real-world data studies are replaced by automatically generated data from health care systems supported by real-time artificial intelligence assessments

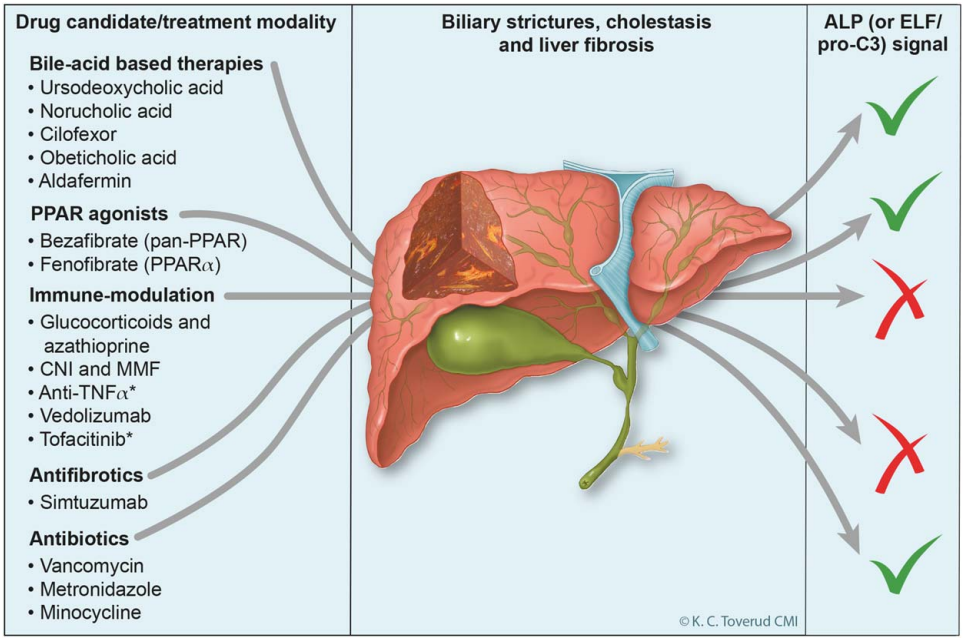

FIGURE 2 Various types of medical treatment have been tested for clinical benefit in primary sclerosing cholangitis. So far, none of these have been shown to significantly halt the development of biliary strictures and the development of end-stage liver disease. Several treatment modalities have, however, shown to influence ALP levels or other surrogate biomarkers potentially associated with clinical events, such as the ELF test and serum levels of pro-C3. Despite strong data to support the involvement of autoimmune mechanisms in PSC development, immunosuppressive drugs and biological treatments have yet to show similar effects. However, the variable quality and mostly retrospective nature of these studies mean that it cannot be concluded that immune-targeted therapy will not benefit people with PSC. Only one antifibrotic drug has so far been reported in a peer-reviewed article (simtuzumab). More data for all drug categories are warranted. *For adalimumab and tofacitinib, improved ALP values have been reported in conjunction with a reduction in inflammatory bowel disease activity and sustained prescription, respectively. Modified from Vesterhus and Karlsen[7] and printed with permission from Kari C. Toverud. Abbreviations: CNI, calcineurin inhibitors; ELF, enhanced liver fibrosis; MMF, mycophenolate mofetil; PPAR, peroxisome proliferator–activated receptor; pro-C3, cleaved amino-terminal propeptide of type III collagen; PSC, primary sclerosing cholangitis.

The broad mechanistic basis of potential therapeutics in PSC as illustrated in Figure 2 raises the discussion on what the future might look like as to combination therapies. While a combination of nonredundant therapeutic approaches might be needed to obtain sufficient clinical impact in PSC, it is too early to speculate what might comprise the ideal and complementary composition of a future drug regimen in PSC, and adaptive platform study designs seem a useful approach when such combinations will be investigated. What moreover will be important for the field is that each component of such a regimen is based on robust evidence, otherwise trial activity in PSC will be confounded by insufficiently justified prescriptions sustained throughout clinical trials. The relevance of such prescriptions as confounders, occult or overt, to the extent they influence relevant surrogate biomarkers, is illustrated by one of the hypotheses on why the COBALT study in PBC failed, that is, participants assigned to placebo were potentially treated with some form of second-line therapy.[57] In PSC, there are additional layers of complexity as given by the widespread UDCA prescription in clinical trials, even in the absence of regulatory approval for UDCA, as well as treatment for concomitant IBD with potential influence on liver blood tests.

In summary, and for good reasons, the pharmaceutical industry has been hesitant to engage in clinical trials in PSC due to the lack of phase II and III study designs accepted by the regulatory authorities and validated, surrogate biomarkers for accelerated approval and conditional market authorization. With increasing confidence and consensus on clinical trial design and utilization of new and validated surrogate endpoints, and the accumulating experience from several ongoing trials, this is likely to change. The unmet need from the patient's perspective is huge, and the business case for drug development should be attractive from both a health systems and industrial point of view. For people with PSC, there is now a firm basis to claim that there is hope on the horizon.

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CONFLICTS OF INTEREST

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