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An overview of recent treatment options for primary sclerosing cholangitis

Ioanna Mousavere[a], Georgios Kalampokis[b], Fotios Fousekis[a], Peter Karayiannis[c], Gerasimos Baltayiannis [a], Dimitrios Christodoulou[a]

University Hospital of Ioannina, Greece; University of Nicosia, Cyprus

Abstract

Primary sclerosing cholangitis (PSC) is a chronic hepatic dysfunction characterized by inflammatory and tissue-degenerative strictures of the biliary tree, leading to cirrhosis and cholangiocarcinoma. The pathophysiological mechanisms involve immune-mediated responses. Numerous treatment modalities targeting the inflammatory aspects have been suggested, but a consensus on the best treatment option is lacking. This study aims to review the most up-to-date treatment options for PSC.

Keywords Primary sclerosing cholangitis, treatment, management

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Introduction

Primary sclerosing cholangitis (PSC) is a rare and progressive hepatic disorder characterized by multifocal inflammatory and fibrotic bile duct strictures. The disease has genetic roots and is linked to autoimmunity. Over time, these strictures lead to fluctuating cholestasis, hepatic cirrhosis, and end-stage liver disease [1]. The diagnosis of PSC is made by identifying characteristic bile duct findings via magnetic resonance cholangiography and elevated levels of alkaline phosphatase (ALP), after ruling out other potential causes.

[a]Department of Gastroenterology, University Hospital of Ioannina, Greece (Ioanna Mousavere, Fotios Fousekis, Gerasimos Baltayiannis, Dimitrios Christodoulou); [b]Department of Internal Medicine, University Hospital of Ioannina, Greece (Georgios Kalampokis, Gerasimos Baltayiannis, Dimitrios Christodoulou[a]); [c]Department of Microbiology and Molecular Virology, University of Nicosia, Cyprus (Peter Karayiannis)

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Correspondence to: Ioanna Mousavere, Department of Gastroenterology, University Hospital of Ioannina, Greece, Stavrou Niarchou 1, Ioannina 45500, Greece,
e-mail: gianna_mousa@hotmail.com

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On biochemical testing, many patients exhibit ALP fluctuations. What is more, the various subgroups of PSC patients should be considered (e.g., small-duct PSC, PSC with ulcerative colitis or Crohn's colitis, etc.) [2-4], because they are likely to represent various forms of the same pathophysiological background and/or clinical picture (Tables 1, 2) [96-98]. Epidemiologically, the prevalence of PSC is from 1-16 per 100,000 in different societies, and its incidence might range from 1-1.3 cases per 100,000 [5]. Additionally, approximately 70% of the patients diagnosed with PSC have underlying inflammatory bowel disease (IBD). The prevalence of PSC-IBD has been estimated at 24 per 100,000 [6]. Moreover, patients with PSC-IBD are at increased risk of developing cholangiocarcinoma (CCA) and colorectal carcinoma [7,8]. It is estimated that 0.5-1.5% of patients with PSC develop CCA annually. For patients with PSC, the lifetime incidence of gallbladder carcinoma ranges from 3-14%, and the lifetime incidence of hepatocellular carcinoma ranges from 0.3-8%. Additionally, the epidemiological data on pancreatic cancer are insufficient; however, it has been suggested that incidence rates are 14 times higher in PSC patients with pancreatic cancer than in those without. Furthermore, the total frequency of hepatobiliary malignancies in patients with PSC is estimated to be around 13% [9]. PSC's pathogenesis still involves many unresolved questions and remains a scientific and clinical challenge. Genetic background, immune activation, bacterial infection and environmental exposures are the leading causes that have been investigated.

Pathophysiology

The pathogenesis of PSC involves a combination of environmental and genetic factors that contribute

Table 1 Clinical presentation of primary sclerosing cholangitis [96]

Symptom	% of patients
Asymptomatic	15-40
Fatigue	75
Pruritus	70
Jaundice	30-69
Hepatomegaly	34-62
Abdominal pain	16-37
Splenomegaly	30
Weight loss	10-34
Variceal bleeding	2-14
Ascites	2-10
Ascending cholangitis	5-28
Hyperpigmentation	25

Table 2 Prognostic factors of PSC [97,98]

Positive prognostic factors	Negative prognostic factors
Females in older age groups at the time of diagnosis	Females in younger age groups at the time of diagnosis or male patients
Mild symptoms of pruritus or fatigue	Persistent pruritus or fatigue
Response to UDCA	No response to UDCA
Minor probability of death (based upon revised Mayo risk score) or liver transplantation (based upon MELD score)	High probability of death (based upon revised Mayo risk score) or liver transplantation (based upon MELD score)
Specific ANA negative (anti-gp210 or anti-sp 100)	Specific ANA positive (anti-gp210 or anti-sp 100)
Small duct PSC	Presence of a dominant bile duct stricture
	Concurrent IBD

Revised Mayo risk score: AST levels, age, bilirubin, albumin, variceal bleeding

MELD score: serum sodium, bilirubin, INR, serum creatinine, dialysis at least twice in the past week

PSC, primary sclerosing cholangitis; ANA, antinuclear antibodies; UDCA, ursodeoxycholic acid; IBD, inflammatory bowel disease; MELD, model for end-stage liver disease; AST, aspartate aminotransferase

to alterations in bile acid composition and subsequent cholestasis [10] (Fig. 1). Additional factors implicated in the disease's pathogenesis include the gut microbiota [11] and autoimmune mechanisms [12], which play significant roles in inflammation, fibrosis and carcinogenesis in PSC.

Genome-wide association studies have identified over 20 genetic risk loci associated with PSC [12,13]. Recent evidence suggests that T-cells originating from the small and large intestine may migrate to the liver as a result of simultaneous gene expression of relevant lymphocyte homing components (e.g., MAdCAM-1) in both gut and liver [14]. These concentrated T-cells within the hepatic tissue contribute to biliary inflammation, leading to apoptosis and necrosis of cholangiocytes and ultimately resulting in hepatic fibrosis [15].

Gut-derived antigens presented by PSC-associated human leukocyte antigen (HLA) variants to T-cell receptors may participate in adaptive immune responses in the portal areas through molecular mimicry [16]. Certain HLA variants, such as HLA-B8, HLA-DR3, HLA-B and HLA-DRB1, have been associated with an increased risk of PSC. Gut leakage of proinflammatory byproducts of bacterial metabolism, such as lipopolysaccharides, also plays a role in the pathogenesis of the disease through innate immune responses [17]. It has been proposed that the gut microbiome of PSC may be involved in pathogenesis, potentially through non-absorbable antibiotic molecules and other manipulations of gut microbiota [18,19]. Bacteria and fungi colonization within the bile ducts may occur as a consequence of prolonged cholestasis and progressive endothelial damage, leading to a pathogenic biliary microbiome that further amplifies inflammatory responses and infections [20].

Toxicity of bile on hepatic cholangiocytes, resulting from cholestasis or alterations in bile composition within the bile ducts or colon, as well as impaired protective mechanisms (e.g., "bicarbonate umbrella"), play a key role in the inflammatory and fibrotic processes in the biliary tract [21-23]. The "toxic bile hypothesis" involves various molecules, chemokines and nuclear receptors that regulate bile acids, cholestasis and bile acid metabolism [24].

Regardless of the sequence of the aforementioned pathophysiological events, a common molecular pathway involving cellular crosstalk leads to the activation of stellate cells, and possibly portal myofibroblasts, ultimately resulting in hepatic fibrosis, collagen recruitment and scar tissue formation causing bile duct strictures [25]. These processes represent potential molecular targets for future antifibrotic treatments [26]. The clinical significance of the molecules and factors involved in the final manifestation of PSC is still largely unknown and may vary among different patient subgroups, depending on the clinical stage of the disease. Early-stage disease may present more treatment opportunities compared to later stages.

Treatment

Since the exact pathogenic mechanisms of PSC remain unclear, the disease is predominantly considered idiopathic [27], and the available treatments are limited in their efficacy. Liver transplantation is generally regarded as the gold standard treatment for PSC. However, several research studies suggest that pharmacological agents may also have a beneficial effect on disease progression [28] (Table 3).

Liver transplantation

Liver transplantation has been shown to be the most effective treatment option for individuals with advanced

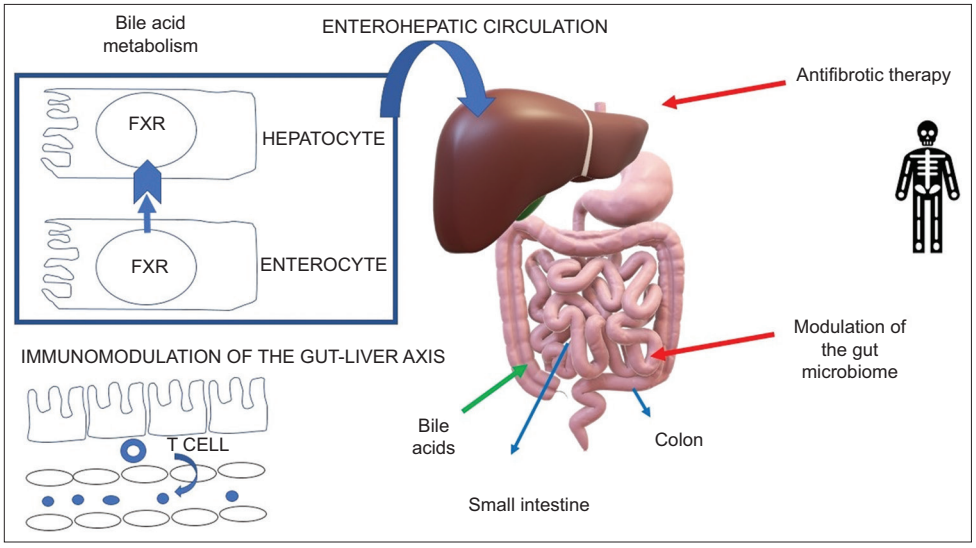

Figure 1 The new agents target the multiple pathways of the pathophysiology of primary sclerosing cholangitis. Upper right: agents for the production and the circulation of bile acids. Lower right: immunomodulators that stop T-cells from the gut causing inflammation in the liver. Upper left: antifibrotic therapy stops the hepatic fibrosis. Lower left: agents that regulate the gut microbiome
FXR, farnesoid X receptor agonists

PSC. The time between diagnosis and liver transplantation typically ranges from 20-25 years. It is important to note that patients who undergo liver transplantation after a diagnosis of PSC are susceptible to experiencing acute or chronic cellular rejection [29]. Furthermore, there is a risk of PSC recurrence (30-50%) following orthotopic liver transplantation, which may require a subsequent liver transplant. Recent studies have indicated a higher incidence of PSC recurrence in patients with PSC-IBD. Despite these challenges, liver transplantation remains the most effective therapy for advanced PSC [30], with end-stage patients (those with a Mayo risk score above 15) being suitable candidates for liver transplantation [31].

Although HLA serotyping generally does not significantly impact the clinical outcome of PSC transplantation, recent research suggests that liver transplants prescreened with HLA serotyping have a higher likelihood of successful outcomes. Certain HLA alleles, such as HLA-B7, HLA-B57, HLA-B75, HLA-DR13, HLA-DQB103, HLA-DRB104, and HLA-DQB107 in the recipient, and HLA-B55, HLA-B58, HLA-DRB107, and HLA-DR8 in the liver graft, have been associated with a higher risk of transplantation failure [32].

Endoscopic treatment

The clinical manifestation of dominant strictures, which can be either extrahepatic strictures with dimensions up to 1.5 mm in diameter, or intrahepatic strictures with dimensions larger than 1.0 mm in diameter [33], represents a frequent and high-risk complication of the pathophysiological process in PSC. The presence of dominant strictures is associated with a mean survival of 14 years for patients with PSC cholangitis, compared to 27 years for PSC patients without strictures [34]. Additionally, the presence of dominant strictures increases the risk of developing CCA [35]. Therefore, it is important for doctors to consider the risk of developing dominant strictures and the subsequent risk of CCA in cases where patients experience subacute worsening of right upper quadrant pain or laboratory abnormalities [36].

Balloon dilatation is considered the standard therapy of choice for patients with dominant strictures, although the use of stenting remains a matter of controversy [37].

Drug therapy

Ursodeoxycholic acid (UDCA)

UDCA is a hydrophilic bile acid and a chemical derivative of chenodeoxycholate that has been extensively studied for the treatment of PSC [38]. It is commonly used in the therapy of cholestatic liver disorders because of its protective effects on cholangiocytes, stimulation of hepatobiliary secretion, and ability to protect liver cells against bile acid-induced apoptosis [39]. Moreover, UDCA has been found to have genotoxic and aneugenic activity. It also inhibits enzyme activity and important biochemical pathways, including DNA repair and phagocytosis [40]. Previous studies have demonstrated that treatment with UDCA leads to a substantial improvement in liver function tests for patients with PSC [41]. The first randomized controlled trial of UDCA in PSC, conducted by Beuers *et al* in 1992, demonstrated that UDCA (13-15 mg/kg) was effective in reducing disease activity compared to placebo after 1 year of treatment [42]. Subsequent studies have examined the impact of UDCA at different dosages in PSC. Although biochemical parameters have improved in most studies, more data are needed to conclusively demonstrate improvements in "hard endpoints"

Table 3 Major studies regarding treatment options of primary sclerosing cholangitis

Treatment	Number of patients	Phase/study design	Dosage	Results	Study [ref.]
UDCA	14	RCT	13-15 mg/kg	67% reduction in ALP compared to placebo	Beuers *et al* [42]
	26	Double blind RCT	20 mg/kg	45.4% reduction in ALP compared to baseline	Michell *et al* [43]
	219	RCT	17-23 mg/kg	no effect	Olsson *et al* [44]
	150	Phase III	28-30 mg/kg	48.5% reduction in ALP compared to baseline	Lindor *et al* [45]
norUDCA	161	Phase II	500 mg, 1 g, 1.5 g	reduction in ALP	Fischer *et al* [52]
	300	Phase III	250 mg	change in ALP and histology	NCT03872921
OCA	77	Phase II	1.5-3 mg, 5-10 mg	reduction in ALP	Kowdley *et al* [56] AESOP trial
CILOFEXOR	52	Phase II	100 mg, 30 mg	safety and liver enzyme improvement	Trauner [57]
NGM282	62	Phase II	1 mg, 3 mg	reduction in ALP	Hirschfield [58]
ATRA	15	Pilot study	45 mg/m/d	30% reduction in ALP compared to baseline	Assis *et al* [60]
	2	Phase II	10 mg bd	reduction in ALP	NCT03359174
Bezafibrates	11	Phase II	200 mg BID	improvement in liver function test	Mizuno *et al* [66]
Bezafibrate or fenofibrate	20	Retrospective	400 mg or 200 mg	40% reduction in ALP compared to baseline	Lemoine *et al* [65]
Simtuzumab	237	Phase II	75 mg, 125 mg	No effect	Muir *et al* [69]
Timolumab	23	Phase II	8 mg/kg	25% reduction in ALP compared to baseline	BUTEO trial [71]
Cenicriviroc	24	Open label study	150 mg	reduction in ALP	PERSEUS trial [72]
Vedolizumab	102	Retrospective		20% reduction in ALP compared to baseline	Lynch [75]
Vidofludimus	14	Phase II	30 mg	Reduction in ALP	NCT03722576
Infliximab	24	Pilot study		Reduction in ALP	Hommes *et al* [81]
Metronidazole	80	Phase III		Reduction in ALP	Farkkila *et al* [49]
Vancomycin	102	Phase II/III		Reduction in ALP	NCT03710122 [86]
Rifaximin	16	Open label study	550 mg bd	Change in ALP	Tabibian *et al* [87]
Minocycline	16	Pilot study	100 mg bd	Change in biochemistry	Silviera *et al* [88]
FMT	10	Open label study		Safety and change in ALP	Allegretti *et al* [20]
Sulfasalazine	42	Phase II	500 mg bd	Reduction in ALP	NCT03561584
Curcumin	258	Open label study	750 mg bd	ALP <1.5 ULN	Eaton [90]
HTD 1801	59	Phase II	500 mg, 1 g	Reduction in ALP	NCT03333928
DUR-928	5	Phase II	10 mg, 50 mg	Reduction in ALP	NCT03394781
Docosahexaenoic acid	23	Open label study	800 mg bd	Reduction in ALP	Martin [92]

UDCA, ursodeoxycholic acid; norUDCA, 24-norUDCA; OCA, obeticholic acid; ATRA, all-trans retinoic acid; FMT, fecal microbiota transplantation; RCT, randomized controlled trial; ALP, alkaline phosphatase; bd, twice daily

For the trials with no reference use the link: https://clinicaltrials.gov/ for more information

such as patient survival, liver transplantation outcomes or progression to CCA.

A small cohort study by Mitchell *et al*, involving 26 PSC patients, showed a significant positive impact of UDCA (at a

dosage of 20 mg/kg/day), not only on liver tests but also on the cholangiographic appearance of the biliary tree as assessed by endoscopic retrograde cholangiopancreatography (ERCP) and liver fibrosis [43]. Another randomized controlled trial with 219 PSC patients treated with UDCA (dosage ranging from 17-23 mg/kg/day) or placebo did not demonstrate a significant improvement in the combined endpoint of "death or liver transplantation", although there was a significant reduction in both outcomes (31% and 34% reduction, respectively) [44]. Moreover, high doses of UDCA (28-30 mg/kg/day) have been associated with an increased risk of cirrhosis progression, development of varices, CCA, liver transplantation or death [45]. In addition, 3 meta-analyses also failed to show an effect of UDCA on mortality or liver transplantation [46]. Lastly, the most recent guidelines from the British Society of Gastroenterology recommend against long-term treatment of newly diagnosed PSC patients with UDCA [47].

Combination of UDCA and metronidazole (MTZ)

MTZ, an antibiotic, has shown promise in preventing PSC-like liver damage in animal models [48]. A randomized, placebo-controlled study involving 80 patients examined the effectiveness of combining UDCA with MTZ, compared to UDCA alone, in the progression of PSC. After a 3-year follow up, it was found that patients treated with the combination of UDCA/MTZ achieved significantly lower levels of serum ALP compared to those treated with UDCA and placebo. Additionally, the New Mayo Risk Score showed a remarkable decline only in the UDCA/MTZ group. In conclusion, the combination of MTZ with UDCA in PSC demonstrated a reduction in the New Mayo Risk Score, decreased serum ALP levels, and no progression in ERCP results [49]. Furthermore, another study showed that the combination of UDCA and MTZ resulted in better improvement of the liver histological stage compared to treatment with UDCA alone [50].

24-norUDCA

24-norUDCA is structurally similar to UDCA, but lacks a methylene group, making it resistant to conjugation. This characteristic allows norUDCA to be passively absorbed by liver cholangiocytes, move through the cholehepatic shunt, and stimulate bicarbonate-rich choleresis. Additionally, norUDCA has been found to have antilipotoxic, antiproliferative, antifibrotic, and anti-inflammatory properties, and it is less toxic to hepatocytes and cholangiocytes *in vitro* compared to UDCA, due to its hydrophilicity [51]. A phase II clinical trial involving 161 PSC patients who were not receiving concomitant UDCA therapy evaluated the efficacy of 3 oral doses of norUDCA and showed a significant dose-dependent reduction in ALP levels after 12 weeks, with no significant adverse events [52]. However, it is worth noting that some studies have raised concerns about possible disease progression attributed to the choleretic effects of norUDCA, especially in PSC patients with dominant strictures. Further research is needed to obtain solid scientific evidence in support of these findings. Lastly, a phase III double-blind, randomized clinical trial is currently underway, with the aim of recruiting patients from multiple centers worldwide (NCT03872921) to demonstrate the long-term efficacy of norUDCA.

Farnesoid X receptor agonists (FXR)

FXR, a nuclear bile acid receptor, has been found to play a role in cholestatic processes, including progressive familial intrahepatic cholestasis type 1 and intrahepatic cholestasis of pregnancy [53]. One of the critical functions of FXR is the downregulation of CYP7A1, the rate-limiting enzyme involved in bile acid production. Harmful feedback mechanisms involving FXR have been shown to significantly impact bile acid turnover. Hepatic FXR activation directly reduces the expression of the apical sodium-dependent bile acid transporter (ASBT) in enterocytes, while also increasing the secretion of fibroblast growth factor (FGF) 19. FGF19 then signals to hepatocytes via the portal blood circulation and activates the FGF receptor 4 (FGFR4) [54]. Like other bile acid receptors, FXR has pleiotropic effects that have experimentally demonstrated its involvement in regulating liver inflammation and metabolism at the cellular level [55].

Obeticholic acid (OCA) has been investigated in PSC patients in the AESOP trial, a randomized, double-blind, placebo-controlled phase II trial. The study included 77 PSC patients treated with titrating doses of 1.5-3 mg/day and 5-10 mg/day of OCA, or placebo, for 24 weeks, with a follow-up at 12 weeks. The results showed that serum ALP levels were significantly lower in the OCA group (at the dosage of 5-10 mg/day) compared to the placebo group. It is noteworthy that the effective dose of OCA is already being used in the treatment of PSC. Additionally, the impact of OCA (at a dosage of 5-10 mg/day) was found to be independent of UDCA administration, although a greater reduction in ALP was observed in patients who received OCA without UDCA. The main side-effect of the drug was dose-dependent pruritus, reported by 67% of patients in the OCA 5-10 mg/day group, 60% of patients in the OCA 1.5-3 mg/day group, and 45% of patients in the placebo group. Discontinuation due to pruritus was rare, with only 1 patient in the OCA 1.5-3.0 mg/day group and 3 patients in the OCA 5-10 mg/day group discontinuing the treatment [56]. Currently, a phase III trial is actively enrolling patients (NCT02177136) to evaluate the long-term efficacy of OCA in PSC.

Cilofexor (GS-9674), a non-steroidal FXR agonist, has demonstrated the ability to reduce hepatic bile acid secretion and potentially exert anti-inflammatory effects without the adverse effects associated with OCA administration. In a phase II randomized, double-blind, placebo-controlled trial, 52 non-cirrhotic PSC patients with ALP levels higher than 1.67 times the upper limit of normal were treated with cilofexor at a dosage of 100 mg/day. The results showed a significant decrease in ALP and γ-glutamyltransferase levels, as well as primary bile acid secretion, and the drug was well tolerated. It is worth noting that the trial had limitations, including the inclusion of only

large-duct PSC cases, without cirrhosis, and the low prevalence of IBD in the study sample [57].

NGM282, an analog of FGF19, has been studied in a phase II randomized, double-blind, placebo-controlled trial involving PSC patients with ALP levels higher than 1.5 times the upper limit of normal. Although no significant changes in ALP levels from baseline were observed, fibrosis biomarkers (as assessed by the Enhanced Liver Fibrosis test score and Pro-C3) showed significant improvement in the treatment group [58].

All-trans retinoic acid (ATRA), a medication currently used for the treatment of acne and acute promyelocytic leukemia, has been found to inhibit bile acid synthesis through the FXR/RXR nuclear receptor complex pathway [59]. The combination of UDCA (at a dosage of 15-23 mg/kg/day) and ATRA (at a dosage of 45 mg/m^2/day) was evaluated in a study involving 15 PSC patients. The results showed a 30% reduction in serum ALP levels and a significant decrease in ALP and C4 levels [60]. Another open-label phase II trial was conducted to assess the clinical efficacy and safety of a lower dose of ATRA. However, the study was terminated after enrolling only 2 participants, with only 1 completing the study (NCT03359174).

ASBT plays a crucial role in the reabsorption of conjugated bile acids in the terminal ileum. As mentioned earlier, the FXR exerts its effects, in part, by downregulating ASBT, thereby reducing the enterohepatic circulation of bile acids and the bile acid pool. Inhibition of ASBT has been shown to improve hepatic histology in animal models of cholestatic liver disease, suggesting a potential therapeutic effect in patients with PSC [61].

Maralixibat, an inhibitor of ASBT (LUM001), has been evaluated in a recent open-label phase II trial involving 27 PSC patients. Preliminary results indicate that there were no clinically significant changes in liver biochemical indices observed [62].

Peroxisome proliferator-activated receptor (PPARs)agonists

PPARs, especially PPAR-α, play a critical role in regulating liver transporters involved in bile homeostasis, making them promising targets for the treatment of cholestatic liver diseases. PPAR agonists have demonstrated anti-cholestatic effects, such as enhancing biliary phospholipid secretion, promoting mixed micelle formation through upregulation of MDR3, inhibiting bile acid synthesis, and upregulating bile acid detoxification [63]. These receptors are activated by a variety of lipophilic acids, including essential fatty acids, eicosanoids, phytanic acid, and palmitoylethanolamide. Like the FXR, PPARs have pleiotropic effects and interact with bile acid nuclear receptors, leading to anti-inflammatory and antifibrotic effects [64].

There have been an increasing number of studies investigating the clinical efficacy of fibrates in PSC. However, most of the available evidence comes from observational or retrospective analyses rather than primary studies.

Fenofibrate and bezafibrate have shown promise in the treatment of PSC. A recent retrospective study conducted in France and Spain demonstrated a 40% decrease in ALP levels and significant improvement in pruritus after treatment with fenofibrate (200 mg/day) or bezafibrate (400 mg/day), for a median duration of 1.5 years, in 20 PSC patients [65]. However, the study also noted a rebound in ALP levels after discontinuation of the PPAR agonist, which may be attributed to the occurrence of biliary stones, tolerability issues, or worsening of hepatic biochemistry. It is important to mention that liver stiffness, as measured by transient elastography, showed a significant increase during the study.

Another prospective study aimed to evaluate the clinical effectiveness of bezafibrate (200 mg b.i.d.) in 11 PSC patients. After 12 weeks of treatment, ALP levels were significantly improved in 7 of 11 (64%) patients and subsequently increased after treatment discontinuation [66]. Additionally, a phase III trial is currently underway to assess the safety and clinical effectiveness of bezafibrate compared to placebo in PSC patients with persistent cholestasis despite ongoing UDCA therapy. The results of this trial are expected to be reported in the near future.

Antifibrotic therapy

In spite of the fact that hepatic fibrosis is considered to be a crucial part of the pathophysiology of PSC, not many antifibrotic pharmacological agents have been studied so far.

Simtuzumab. Lysyl oxidase-like 2 (LOXL2), an enzyme that catalyzes the crosslinking of collagen and elastin fibers, thus strengthening the extracellular matrix structure, has been used in recent studies. Previous research had revealed that blood and liver LOXL2 in PSC patients was associated with disease progression [67]. What is more, the administration of a LOXL2 inhibitor in animal models (mice) was shown to lower the accumulation of hepatic and biliary fibrosis, as well as to accelerate its reversal [68]. On the other hand, no clinically significant amelioration in hepatic fibrosis was seen in a placebo-controlled, phase IIb trial testing simtuzumab, a LOXL2 inhibitor. In that specific trial, 234 patients with compensated PSC were randomized on a 1:1:1 basis to receive placebo, weekly subcutaneous injections of 75 mg of simtuzumab, or weekly subcutaneous injections of 125 mg of simtuzumab, for a total period of 96 weeks. The study failed to prove any significant clinical effectiveness of simtuzumab on the patients' hepatic collagen content (as measured by morphometry on hepatic biopsy material) or on the liver fibrosis stage (as measured by the Ishak fibrosis stage) [69].

Immunomodulators

Although PSC is an autoimmune liver disorder, the immunosuppressive medications commonly used have not shown clear clinical benefits in PSC patients [1]. However, there are ongoing studies investigating other immunomodulatory drugs for potential therapeutic effects in PSC.

Timolumab (BTT1023), a human monoclonal anti-VAP-1 antibody, has demonstrated the ability to prevent hepatic fibrosis in animal models of liver injury [70]. A recent phase II clinical trial called the BUTEO trial evaluated the clinical

efficacy of timolumab in PSC patients over a 78-day treatment period. The results of this trial are still pending publication (NCT02239211) [71].

Cenicriviroc, a CCR2/CCR5 antagonist, was examined in another phase II trial called the PERSEUS trial. The results showed a modest reduction in ALP levels (median 18%) after 24 weeks in 24 participating patients [72]. Cenicriviroc has also demonstrated significant anti-inflammatory and antifibrotic effects in animal models of non-alcoholic steatohepatitis and in Abcb4 (Mdr2−/−) mice [73].

Vedolizumab, a monoclonal antibody targeting the α4β7 integrin used in the treatment of IBD, has shown promise through its ability to inhibit leukocyte migration between intestinal and hepatic cells by targeting MADCAM-1, the ligand for α4β7 integrin [74]. However, retrospective analyses have shown mixed results, with some studies not demonstrating any improvement in hepatic biochemical indices in PSC patients with IBD treated with vedolizumab. In about 20% of the patients, a reduction of at least 20% in ALP levels was observed, but this outcome was independently associated with the presence of hepatic cirrhosis [75,76].

Vidofludimus, an inhibitor of dihydroorotate dehydrogenase that blocks replication of activated T- and B-cells and interferes with the JAK/signal transducer, has shown potential in a phase II open-label clinical trial. This trial evaluated the safety and clinical effectiveness of vidofludimus in 18 PSC patients over a 6-month period; it found that ALP levels normalized in 27.7% (3/11) of the patients at week 24 (NCT03722576).

These are all promising avenues of research, but further studies are needed to establish the efficacy and safety of these immunomodulatory drugs in the treatment of PSC.

Immunosuppressants

Limited research has been conducted on the use of other immunosuppressants in the treatment of PSC, and the available studies often lack placebo groups or have small cohorts with uncertain results. While some individual cases have suggested a decline in ALP levels with pharmacological treatment using azathioprine, mycophenolate mofetil, and tacrolimus, the clear clinical efficacy of these drugs in PSC remains largely questionable [77-80]. Additionally, a pilot study of orally administered budesonide in PSC showed minimal, if any, clinical efficacy and was associated with worsening osteoporosis.

Infliximab, a monoclonal antibody that inhibits tumor necrosis factor (TNF)-α and is commonly used in the treatment of severe IBD, has been studied in PSC. However, a small pilot study found that infliximab did not demonstrate clinical effectiveness in terms of reducing ALP levels, improving hepatic histology or alleviating PSC-related symptoms [81]. A retrospective study involving 141 patients with PSC and IBD indicated that anti-TNF agents had moderate clinical efficacy and did not worsen PSC symptoms or lead to specific side-effects, although there are currently no available data regarding hepatobiliary disease [82].

Overall, the evidence for the clinical efficacy of immunosuppressants in treating PSC is limited, and further research is needed to establish their effectiveness and safety in this condition.

Modulators of the gut microbiome

The role of the gut in the pathogenesis of PSC is still not fully understood. Early theories proposed a "leaky gut" concept, suggesting that bacterial components and byproducts passively enter the portal circulation and cause biliary inflammation. However, recent research indicates that there are specific interactions between the hepatic tissue and the gut microbiota, including potential crosstalk involving individual bacteria [83]. The precise mechanisms through which the gut microbiome may contribute to PSC, such as immunological stimulation or the effects of bacterial metabolites, remain largely unknown [84].

An important question is whether changes in the gut microbiome are a primary etiological factor for PSC, occur secondarily, or potentially both [11]. The gut microbiome plays a significant role in bile acid homeostasis and can greatly influence bile physiology. Therefore, alterations in the composition of the gut microbiota may have implications for reducing inflammation and fibrosis in the bile ducts.

Vancomycin, a glycopeptide antibiotic, has been found to have immunomodulatory effects by reducing T-cell cytokine production [85]. In 2 randomized trials involving PSC patients with or without IBD, vancomycin was compared to MTZ and placebo [86]. The results showed a significant decrease in ALP levels and Mayo score in the vancomycin-treated groups. Currently, a phase II multicenter clinical trial is underway, involving 102 patients with PSC, to evaluate ALP levels at 6, 12, and 18 months (NCT03710122). This trial aims to further investigate the potential therapeutic effects of vancomycin in PSC.

Rifaximin and minocycline have shown clinical effectiveness in treating PSC. A study involving 16 PSC patients found that rifaximin had no effect on reducing cholestatic markers or the Mayo score [87]. In contrast, minocycline significantly improved ALP levels and the Mayo score in participants [88].

Fecal microbiome transplantation (FMT) is another promising therapeutic option for PSC. In a small pilot study, PSC patients who underwent FMT experienced a ≥50% decrease in blood alkaline phosphatase levels in 3 of the participants. The efficacy of this treatment may be associated with the bacterial diversity in the gut and the engraftment of donor microbiota [20].

Probiotic supplementation therapy was evaluated in a small crossover randomized controlled trial (n=14, 3 months) involving PSC patients treated with a combination of 4 *Lactobacillus* and 2 *Bifidobacillus* strains [89]. The results showed no significant difference in ALP levels, other hepatic enzymes, or patient symptoms. A phase II trial has been registered (NCT00161148), but its completion status has not been verified for several years.

Other treatments

Sulfasalazine/curcumin. Several studies have investigated the use of anti-inflammatory drugs and supplements such

as sulfasalazine and curcumin in PSC patients. Currently, a multicenter, randomized, double-blinded, placebo-controlled trial is ongoing to assess the safety and clinical efficacy of sulfasalazine in the treatment of PSC. On the other hand, no significant improvement in cholestasis or hepatic symptoms was observed in patients receiving curcumin supplements [90].

A wide variety of other drugs, each with a different mechanism of action, may be important in the treatment of PSC. For example, HTD1801 is being studied in 2 ongoing phase II trials for its effects on lipid metabolism (NCT03333928, NCT03678480).

DUR-928, an endogenous epigenetic regulator, is being studied in a phase II trial in PSC patients for its anti-inflammatory effects, and its role in lipid metabolism and cell survival processes (NCT03394781) [91].

Supplementation with docosahexaenoic acid, which has been found to enhance peroxisome proliferator-activated receptor signaling, was associated with a significant reduction in ALP levels in PSC patients in a 12-month, open-label, pilot study (n=23) [92].

Hymecromone. An ongoing phase I/II trial is being conducted to assess the potential therapeutic efficacy of hymecromone, a hyaluronic acid synthesis inhibitor (NCT02780752) [93].

Bexotegrast (PNL-74809), an orally administered small-molecule inhibitor of αvβ6 and αvβ1 integrins, upregulated in the hepatic tissues of PSC patients, is being studied. These integrins act as activators of TGF-β, leading to increased collagen production and fibrosis. Another phase IIa, multicenter, randomized, double-blind, dose-ranging, placebo-controlled study was conducted to assess the safety, clinical tolerability, and pharmacokinetic properties of PLN-74809 in 84 participants with PSC and suspected hepatic fibrosis. The results of this study are yet to be published [94].

Selected mesenchymal stromal cells (Orbcel-C) are being investigated as a promising therapeutic option in an ongoing phase II trial (NCT02997878) [95].

Concluding remarks

PSC is a rare and partially understood chronic cholestatic and fibroinflammatory liver disorder that can lead to severe complications, such as cirrhosis, hepatic fibrosis and cancer. Recent advances in understanding its pathophysiology have identified new potential molecular targets, offering new treatment possibilities. In view of the complex nature of the disease, it is unlikely that a single pharmacological intervention can address all the treatment needs of PSC patients. Therefore, future therapeutic strategies for PSC are likely to involve a combination of multiple pharmacological agents targeting different molecular and biochemical pathways at various stages of the disease.

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