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Review Article

Treatment of primary sclerosing cholangitis

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ABSTRACT

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by progressive fibro-stenotic strictures and destruction of the biliary tree. Currently, there is no effective treatment which can delay its progression or ameliorate the transplant-free survival. Moreover, a major chontroversy in PSC is whether to use UDCA. More recently, novel pharmacological agents emerged aiming at: i) modulation of bile composition; ii) immunomodulation; iii) targeting the gut microbiome; iv) targeting fibrosis. Successful PSC therapy, however, will be most likely a personalized combination of different drugs plus endoscopic treatment. This review aims at offering an overview on the experimental pharmacological strategies currently exploited for PSC treatment.

1. Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease, whose hallmarks are inflammation, fibrosis and destruction of intra and extrahepatic bile ducts which can lead to cirrhosis. The disease is heterogeneous and characterized by several phenotypes: i) large duct PSC; ii) small duct PSC; iii) paediatric PSC; iv) PSC associated with inflammatory bowel disease (IBD); v) high IgG4 PSC; vi) overlap syndrome between PSC and autoimmune hepatitis (AIH) [1]. Individuals with PSC display increased risk for hepatobiliary malignancies, whereas those with IBD-associated PSC present a risk also for colorectal cancer. In general, the clinical course of PSC is highly variable. The classic or "large duct" PSC is the most common, comprising around 90% of the PSC population; small duct PSC has a slower progression towards cirrhosis, a better prognosis and less risk of development of cholangiocarcinoma [2]. However, despite significant efforts, to date there is no medical treatment able to prolong the time of liver transplantation, which still represents the only effective therapeutic option in late-stage disease [3]. Here we summarize the pharmacologic approach to PSC focusing on the more recent options to current clinical trials (Tables 1 and 2). The most important strategies include: 1) bile composition modulators; 2) immune modulators; 3) anti-fibrotics; 4) manipulation of microbiome.

2. Bile composition modulators

2.1. Ursodeoxycholic acid (UDCA)

The mechanisms of action of UDCA include: 1) stimulation of hepatocellular secretion; 2) stimulation of cholangiocellular secretion; 3) anti-apoptotic effects; 4) reduction of bile toxicity [4]. UDCA exerts its mechanisms of action by interacting with nuclear receptors, i.e., retinoid X receptor (RXR), peroxisome proliferator-activated receptor a (PPARα) and pregnane X receptor (PXR), all of which transcriptionally modulate bile formation [4]. Low dose UDCA (13–15 mg/Kg/day) improves biochemistry but there is no chance in survival [5]. Median dose UDCA (17–23 mg/Kg/day) improves biochemistry, there is a trend towards improvement in survival [6]. A US multicentre study enroled 150 PSC patients receiving high dose UDCA (28–30 mg/kg/day), but was prematurely interrupted due to evident lack of efficacy [7]. The mechanism underlying the negative clinical outcomes in patients receiving UDCA at high dose (28–30 mg/kg/day) has not been elucidated, but it has been hypothesized that the increased production of hydrophobic bile acids can be involved. Despite these unfavourable results, UDCA at medium dosage continues to be prescript in many countries of Europe. Interestingly, a prospective study evaluating the ef-

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Table 1
Main registered trials for PSC cited in the text (excluding antibiotics).

Drug	Phase	NCT number	Status	N. patients
nor-UDCA	Phase III	03,872,921	Ongoing	300
OCA	Phase II	02,177,136	Completed	76
ATRA	Phase II	01,456,468	Completed	15
Cilofexor	Phase II	02,943,460	Completed	52
Cilofexor	Phase III	03,890,120	Ongoing	400
Marilixibat	Phase II	02,061,540	Completed	27
Bezafibrate	Phase III	01,654,731	Completed	100
Bezafibrate	Phase II	04,309,773	Ongoing	104
Cenicriviroc	Phase I PSC/IBD	02,653,625	Completed	20
Timolumab	Phase II	02,339,211	Ongoing	59
Vedolizumab	Phase III	03,035,058	Withdrawn	–
NGM282	Phase II	02,704,364	Completed	62
Simvastatin	Phase II	04,133,792	Ongoing	700
Simtuzumab	Phase II	01,672,853	Completed	234

Table 2
Registered trials with antibiotics for PSC.

Drug	Design	NCT number	Status	N. patients
Vancomycin	Phase III	01,802,073	Completed	34
Vancomycin	Post-OLT	03,046,901	Withdrawn	No participants
Vancomycin	Phase II/III vs placebo for 18 months	03,710,122	Ongoing	102
Vancomycin	Phase IV Vs placebo for 12 weeks	2,608,213	Ongoing	30
Vancomycin	Phase I (PSC and biliary atresia)	02,137,668	Ongoing	200
Vancomycin	Phase I	1,322,386	Completed	32
Vancomycin	Phase I PSC/IBD	02,464,020	Completed	8
Minocycline	Phase I	00,630,942	Completed	16
Rifaximin	Phase I	01,695,174	Completed	16
Rifaximin	Phase II	01,904,409	Completed	420

fect of UDCA withdrawal in a small group (26 patients) with PSC treated with low or moderate dose UDCA, showed a significant deterioration in liver biochemistry and increase of Mayo Risk score for PSC after 3 months of withdrawal [8]. However, it should be underlined that UDCA did not prove prolonged overall survival, or transplant-free survival, or reduction in cholangiocarcinoma development. In a systematic review of 8 randomized trials (592 patients) no significant reduction of risk of death, treatment failure, or liver histology was observed [9].

Interestingly, in a prospective study carried out in Japan, 278 patients with PSC were treated with UDCA [10]. The median observational period was 5.1 years (2.3–7.4 yrs). A multivariate analysis demonstrated the association between prolonged liver transplant-free survival ($P=0.003$) and reduction of biliary tract cancer ($P=0.012$) and UDCA treatment. However, despite these important results, a large-scale cohort with an international collaboration is required to produce more convincing evidence for long-term therapy with UDCA in PSC.

2.2. nor-*UDCA*

nor-UDCA is an UDCA derivative characterized by a relative resistance to amidation, enabling its chole-hepatic shunting [4] and increasing the production of bicarbonate. This leads to the creation of a more hydrophilic and less toxic environment for liver parenchymal cells. nor-UDCA demonstrated antiproliferative, antifibrotic and anti-inflammatory properties in experimental mouse models of PSC [11,12]. In a placebo-controlled phase II clinical trial including 161 patients with PSC from 12 European countries [13], three doses (500 mg/day, 1000 mg/day or 1500 mg/day) of oral nor-UDCA were administered for 12-weeks followed by a 4-week follow-up. The primary efficacy endpoint was the mean relative change in alkaline phosphatase (ALP) levels between baseline and end of treatment visit. *nor*-UDCA significantly reduced ALP levels in the 500, 1000, and 1500 mg/day groups ($P=0.029$, $P=0.003$, and $P=0.0001$ with respect to placebo, respectively). Similar dose-dependant results were observed also for transaminases and GGT. The safety profile was similar in the 3 groups. In particular, severe adverse side effects occurred in 7 patients in the 500 mg/day, 5 patients in the 1000 mg/day, 2 in the 1500 mg/day and 3 in the placebo group. These results showed that nor-UDCA can be considered for PSC treatment. A larger phase III study expected to enrol 300 patients with PSC and comparing *nor*-UDCA 1500 mg/day to placebo for 2 years is ongoing and no results are available so far (NCT03872921).

2.3. Obeticholic acid

Obeticholic acid (OCA) is a steroidal farnesoid X receptor (FXR) agonist registered as second-line treatment for patients with primary biliary cholangitis non responders or intolerant to UDCA [14]. FXR is a nuclear receptor with high expression levels in the liver and gut playing a pivotal role in the regulation of bile acid synthesis and the prevention of their accumulation [15]. Its mechanism relies on the control of the expression of bile salt export pump (BSEP) expression on the canalicular membrane of hepatocytes and organic solute transporters (OST) α and β in the distal portion of the gut and bile ducts. Furthermore, FXR induces the expression of small heterodimers proteins, also known as nuclear receptor superfamily 0, probably playing a role in the control of bile acid transport and metabolism at the transcriptional level [15]. Besides its role in the regulation of bile acid transport, OCA exerts other therapeutic effects, i.e. anti-inflammatory and antifibrotic properties [16]. A randomized, placebo-controlled phase II study (AESOP study, NCT02177136) was performed in 76 patients randomized to placebo ($n=25$), OCA 1.5–3 mg ($n=25$), or 5–10 mg ($n=26$) [17]. Treatment continued for 24 weeks, and for 2 years thereafter when patients were switched to long-term safety extension phase, considering as primary endpoints change in ALP (from baseline to week 24), and safety. At week 24 serum ALP was significantly reduced in the higher dose group vs placebo ($P<0.043$) but not in the lower dose group. The total bilirubin remained stable and reduction in ALP was maintained during the long-term extension phase. The most common adverse effect was pruritus which was recorded as mild to moderate. The overall incidence of pruritus was greater in the two groups of treated patients (67% and 60% in OCA 5–10 mg and 1.5–3 mg, respectively) compared to placebo (46%). Four patients discontinued treatment due to pruritus during the double-blind phase, and 3 patients during the long-term extension phase. Further 10 patients discontinued treatment during the extension phase for blood bilirubin increase (N.4), liver function tests abnormalities (N.5) and ascites (N.1). In summary, the treatment showed only a significant reduction in ALP with OCA 5–10 mg, but more robust endpoints are needed to recommend OCA treatment in PSC.

2.4. All-Trans retinoic acid plus UDCA

All-Trans retinoic acid (ATRA) is an evolutionarily conserved, permissive activator of the nuclear receptor complex FXR/RXR [18]. ATRA is related to vitamin A and has been used for many years as a typical medication of skin conditions such as acne and psoriasis. In an experimental mouse model od 2-week bile duct obstruction by the research group at Yale University School of Medicine, animals treated with ATRA with or without UDCA had marked reduction

in nevrosis, decreased hepatic fibrosis and markers of inflammation associated with a 50% decrease in the bile acid pool size, and decrease in bile duct proliferation [19]. A pilot study with ATRA (45 mg/m^2/day) was given with moderate dose UDCA to 15 PSC patients non completely responding to UDCA (NCT01456468) [20]. The treatment was administered for 12 weeks, followed by a 12-week washout, during which patients were given UDCA monotherapy. The primary endpoint (30% reduction in serum ALP) was not reached. However, serum levels of ALT and the bile acid intermediate C4 significantly decreased. This result may provide the basis for further investigating ATRA or repurposed drug in PSC.

2.5. Non-bile acid FXR agonists

Cilofexor (GS9674) is a potent and selective nonsteroidal, synthetic FXR agonist which has demonstrated anti-inflammatory and antifibrotic effects in experimental preclinical models [21]. A phase II double-blind, placebo-controlled study has been performed in large-duct PSC patients without cirrhosis [22]. Patients were randomized to three arms, receiving orally either 100 mg ($n=22$), 30 mg ($n=20$) or placebo ($n=10$) once daily for 12 weeks. All patients ($n=52$) had serum ALP at least 1.67 higher than the upper limit and total bilirubin $\leq$ 2 mg/dl at baseline. After 12 weeks of treatment, cilofexor 100 mg led to significant reductions in serum ALP, GGT, AST/ALT compared to placebo. Adverse events were similar in the three study groups. In summary, cilofexor affects relevant clinical endpoints associated with PSC and is a potential drug with a mechanism of action distinct from UDCA. A phase III, randomized double-blind, placebo-controlled study with cilofexor in non-cirrhotic subjects with PSC is currently ongoing (NCT03890120).

2.6. ASBT inhibitors

Targeting apical sodium-dependant bile acid cotransporter (ASBT) is a novel approach for cholangiopathies. ASBT inhibitors selectively block the bile acid (BA) transporter ASBT, located on the apical side of ileal enterocytes thereby inhibiting BA re-uptake. As a result, BAs spill over into the colon and are lost via faeces [23]. This mechanism reduces the amount of BAs returning to the liver *via* the portal circulation. The effects of ASBT inhibitors have been studies in two experimental models of sclerosing cholangitis [24,25]. In these murine models, ASBT inhibition led to increased faecal secondary BA and increasing in BA synthesis, whereas and bile duct injury and both markers of inflammation and fibrosis were attenuate. ASBT inhibitors for the treatment of cholestasis includes A4250 (lopixabat), SC-435 (odevixibat), marilixibat (formerly called LUM001) and GSK2330672 (linerixabat). A pilot open label study to evaluate the safety, tolerability and efficacy of marilixibat in 27 patients with PSC has been completed (CAMEO Study-NCT02061540). Preliminary data showed minimal reduction in ALP and total bilirubin and in itch score. However, adverse events developed, such as diarrhoea and gastrointestinal symptoms (clinicaltrials.gov/ct2/show/results/NCT02061540).

3. Modulators of inflammation

3.1. Fibrates

Fibrates are agonists of the peroxisome proliferator-activated receptor (PPAR-α), a member of the nuclear receptor superfamily. PPARs account for 3 isoforms, i.e., α, β/δ, and γ, encoded by distinct genes and characterized by peculiar distribution. Fenofibrate stimulates both transcription and translation of the transporter multidrug resistance protein 3 (MDR3) and increases the biliary excretion of phosphatidylcholine [26], improving biomarkers of cholestasis. The drug bezafibrate is a dual PPARα/γ and pregnane X receptor (PXR) agonist [27].

The BEZURSO trial (Phase III placebo-controlled study in which the use of Bezafibrate in Combination with UDCA has been evaluated) employed for the first time a fibrate for the treatment of PBC. In this 24-month study, the second-line use of bezafibrate with UDCA led to a rate of complete biochemical response which was higher than that observed in the placebo group [28]. An improvement in symptoms and a reduction of surrogate markers of fibrosis was also observed. Adverse reactions of fibrates are increased creatinine levels, heartburn, and transient elevation of transaminases. PBC patients treated with clofibrate showed gallstone formation (possibly due to repression of bile acid synthesis) and paradoxic hypercholesterolaemia [29], but these reactions have not been observed during treatment with fenofibrate or bezafibrate.

A small pilot study experimented the oral administration of bezafibrate (400 mg/day) to 7 patients with PSC [30]. In 3 patients the level of all hepatobiliary enzymes decreased after 6 months (ALP decreased to 40% from baseline). Subsequently a prospective trial was conducted with the same dosage of bezafibrate in 11 patients for 12 weeks [31]. Bezafibrate improved liver function tests in 64% of patients. Six weeks after cessation of bezafibrate, enzyme levels significantly increased once more ($P<0.01$).

In a retrospective study from Paris and Barcelona 20 patients with PSC and an incomplete response to UDCA were given bezafibrate (400 mg/day) or fenofibrate (200 mg/day). After a mean follow-up of 1.56 years, a reduction of ALP by 41% and an amelioration of other liver tests was observed; pruritus significantly decreased as well [32]. Bezafibrate for 24 months (BEZASCLER – NCT04309773) phase III, randomized, double-blind, placebo-controlled trial evaluating both efficacy and safety of bezafibrate in PSC patients with persistent cholestasis despite standard UDCA therapy is ongoing. The estimated enrolment consists of 104 participants randomized into 2 arms: i) UDCA therapy plus Bezafibrate 400 mg/day; ii) UDCA plus placebo. The primary endopoint is the proportion of patients with serum ALP $<$1.5 ULN, a reduction of at least 15% from baseline at month 24, the normalization of serum bilirubin and the absence of liver stiffness increase with respect to baseline. Secondary measures are safety, quality of life, score of pruritus, fatigue score, biochemical parameters, occurrence of clinical events and transplant free survival.

The effect of bezafibrate on pruritus was investigated in a double-blind, randomized, placebo-controlled trial (FITCH) enroling 70 PBC, PSC and secondary sclerosing cholangitis patients with moderate to severe pruritus [33]. The primary endpoint was $\geq$50% reduction of pruritus (scored on visual analogue scale). Bezafibrate (400 mg/day) led in 45%, to primary endpoint and this effect was significantly higher than that observed in placebo subjects (11%; $P=0.003$). It has been demonstrated that fibrates ameliorate cholestasis-associated pruritus by a mechanism which is autotaxin-independent [34]. No definite factors associated to the benefit of fibrates have been found [35]. However, bezafibrate was more effective for patients with preserved liver function when it was prescribed before progression of liver fibrosis and failure to UDCA [35].

Recently, a study performed in patients with PBC and PSC with incomplete response to UDCA showed that the addition of fenofibrate reduced bile acid synthesis and favourably improved serum bile acids augmenting the concentration of less toxic moieties and in general normalizing the levels of bile acids toward levels typical of healthy controls [26]. Moreover, these findings suggest that PPARα is integrally involved in the regulation of bile acid metabolism during cholestasis and represents an important target for the treatment of patients with chronic cholestasis. A small pilot study in 8 patients with PSC showed that even a low dosage

of fenofibrate (160 mg/day) for 6 months was effective in reducing serum levels of ALP and ALT [36].

3.2. Cenicriviroc

Cenicriviroc (CVC) is a novel dual antagonist of C–C chemokine receptor type 2 (CCR2) and C–C chemokine receptor type 5 (CCR5), which are the main receptors for monocyte chemotactic protein-1 (MCP-1) and RANTES. It has been observed that MCP-1 expression is increased in cholangiocytes and livers from PSC patients [37]. Thus, it has been thought that blocking the activation of MCP-1 may act as a therapeutic strategy for PSC. A phase II, single-arm, open-label exploratory study was performed in 24 participants with PSC, 20 of whom completed the 24 week study (NCT02653625 – Perseus Study) [38], considering as primary endpoint the percent change in ALP, while secondary efficacy endpoints were the proportion of patients obtaining ALP normalization and the overall response. A limited reduction (median 18%) of ALP was observed after 24 weeks. At least one adverse effect was reported in 83% of patients, the most frequent being rash, fatigue and dizziness. Taken together, these data showed modest changes with cenicrivoroc in patients with PSC and the need of future studies with a robust design and strong endpoints.

3.3. Timolumab

Timolumab (BTT-1023; SI-3106; SI636) is a fully human, monoclonal, anti-vascular adhesion protein 1 (VAP-1) antibody which diminishes leucocyte entry to site of inflammation. In PSC Timolumab may have the potential to impact inflammation and fibrosis. A phase II single-arm with Timolumab is still ongoing (BUTEO, NCT02339211). Fifty-nine participants with PSC are planned to receive 8 mg/Kg i.v. infusion every 14 days for a total of 7 infusions. The primary endpoint is the decline of ALP from baseline to day 99. Secondary outcomes include safety and tolerability (recording serious adverse events, liver function tests, tests of liver fibrosis and quality of life questionnaires.

3.4. Vedolizumab

Vedolizumab is a biological agent blocking the $\alpha 4\beta 7$ integrin, a protein implicated in the pathophysiology of PSC [39]. Since $\alpha 4\beta 7$ can promote lymphocyte infiltration into the colon, it has been hypothesized that vedolizumab can induce clinical remission in patients with inflammatory bowel disease (IBD) associated with PSC. A large International study collected retrospectically data from European and North American centres participating in the International PSC Study Group [40]. In particular, in this study were enroled 102 PSC and IBD patients who received at least 3 doses of vedolizumab (median treatment duration: 412 days). Serum ALP decreased by 20% or more in a subset of 21 patients (20.6%). The 56.8% of patients with available endoscopic data had a good response of IBD. Liver-related adverse reactions, including bacterial cholangitis, cirrhosis decompensation or transplantation occurred in 21 patients (20.6%). In conclusion, vedolizumab does not appear to improve the liver biochemistry of patients with IBD and concomitant PSC.

Furthermore, a retrospective multicentre study on 34 patients with PSC and concomitant IBD (16 Crohn's disease, 18 ulcerative colitis) failed to demonstrate significant changes in liver biochemistry, whereas remission of Crohn's disease was reached in 55% and of ulcerative colitis in 29% of cases [41]. Interestingly, a phase III trial with vedolizumab for patients with PSC and concomitant IBD was withdrawn in early 2018 (NCT03035058).

3.5. NGM282 (Aldafermin)

The candidate drug NGM282, also known as M70, is an analogue of the endocrine gastrointestinal hormone Fibroblast Growth Factor 19 (FGF19), which plays a pivotal role in the modulation of bile acid metabolism. Its mechanism comprises the inhibition of the enzyme CYP7A1, which catalyzes the first and rate-limiting reaction in the classic pathway of bile acid synthesis. Since its circulating concentration increases in PSC patients, it has been suggested that FGF19 may be considered a pharmacological target in this disease. However, its therapeutic potential is hampered by its well-known carcinogenicity, since both experimental evidence and clinical observations [42] linked this hormone to hepatic cancer. Therefore, NGM282 has been developed as a non-tumorigenic option. Several clinical trials have been performed and are currently ongoing evaluating the therapeutic potential of NGM282 liver diseases of different etiologies. One double-blind placebo-controlled trial has been dedicated to PSC (NCT02704364), and its results have been published in 2019 [43]. This trial enroled 62 PSC patients, who were randomly assigned to three study arms, i.e., placebo, NGM282 (1 mg), and NGM282 (3 mg). NGM282 did not affect alkaline phosphatase levels of PSC patients, which was the primary outcome, but had an impact on hepatic fibrosis and inflammation, when non-invasive markers of fibrosis, such as ProPC3, ELF score and its individual components PIIINP and TIMP-1, were considered beyond standard liver function indicators. Furthermore, a decrease of the fourth component of complement (C4) and circulating bile acids could also be observed in NGM-282-treated patients.

4. Anti-fibrotics

4.1. Anti-NOX

Data obtained in a preclinical model of PSC, the *Mdr2*$^{-/-}$ mouse, indicated that the targeted inhibition of the enzymes NADPH oxidases (NOXs) can be considered as a strategy for the treatment of cholestatic fibrosis. These NOX family comprises a set of 7 electron-transporting membrane enzyme isoform [44] producing reactive oxygen species (ROS). This approach is straightforward since, besides an uncontrolled inflammatory cascade, the generation of ROS is known to play a pivotal role in hepatic tissue remodelling and fibrosis [45]. The NOX isoforms expressed in the liver are mainly NOX1, NOX2, and NOX4. To date, NOX inhibitors are currently in preclinical and clinical development for different hepatic diseases. In particular, GKT137831 (Setanaxib) has been the first NOX1/4 selective inhibitor to enter the clinic as a candidate drug, after a careful evaluation in several preclinical models of inflammatory and fibrotic hepatic disorders, such as carbon tetrachloride (CCl4)-induced liver injury and high fat diet-induced NASH [46]. Setanaxib demonstrated also clinical evidence of anti-fibrotic activity in a Phase II clinical trial in PBC patients (NCT03226067). In this study, setanaxib led to a 22% reduction in liver stiffness, whereas only a 4% increase was observed in the placebo group ($p = 0.038$), providing a clinical proof of concept for the efficacy of this compound and highlighting its potential anti-fibrotic action in other liver diseases, such as PSC.

4.2. Statins

There is increasing evidence that statins can be beneficial in patients affected by chronic and cholestatic diseases. Besides lowering cholesterol, statins exert multiple positive effects by different pleiotropic mechanisms involving inflammation, fibrosis, and coagulation. Taken together, these effects concur in potentially improve chronic liver disease. Furthermore, statins have been as-

sociated with beneficial effects on markers of cholestasis in patients with cholestatic liver disease. Clinical evidence of the protective role exerted by statins on PSC patients has been provided by a population-based cohort of Swedish patients, in which the use of statins has been associated with decreased risks of death or liver transplantation [47]. However, the use of these drugs did not show benefits to PBC patients [48]. A clinical trial (PiSCATIN, NCT04133792) is currently ongoing (recruiting since October 2020) to evaluate the effect of simvastatin on the prognosis of PSC. This has been designed as a randomized, double-blind, placebo controlled multicentre study, expecting to enrol 700 PSC patients. They will be tested for daily intake of 40 mg simvastatin or placebo for 5 years to study the effect of the long-term intake of simvastatin on PSC prognosis. The considered outcomes are death, liver transplantation, cholangiocarcinoma or bleeding from oesophageal varices.

4.3. Simtuzumab

Simtuzumab is a monoclonal antibody directed against lysyl oxidase-like 2 (LOXL2) which catalyses the cross linkage of collagen and elastin, thereby mediating stabilization of the fibrotic matrix [49]. Simtuzumab has been demonstrated to reduce progression of liver fibrosis in murine models [49,50] and in clinical studies including patients with viral hepatitis and non- alcoholic steatohepatitis [51,52]. In a phase 2b, dose-ranging, randomised, double-blind, placebo-controlled study, 234 patients with PSC were enroled to receive weekly subcutaneous injections of simtuzumab 75 mg, simtuzumab 125 mg or placebo for 96 weeks [53]. The primary endpoint was mean change in hepatic collagen content assessed by morphometry between baseline and week 96. Additional endpoints included change in histological fibrosis stage and the frequency of PSC-related clinical events. At week 96 neither dose of simtuzumab led to significant reduction of fibrosis content, fibrosis stage, progression to cirrhosis, or frequency of clinical events. In summary, simtuzumab, although well tolerated, did not provide significant benefit in clinical, histological or biochemical endpoints in patients with PSC.

5. Manipulation of microbiome

The role of microbiota is increasingly being recognized as critical importance in chronic cholangiopathies, especially in PSC. Indeed, an altered microbiota composition has been observed in PSC, independently from IBD [54–56]. Moreover, there is emerging evidence that targeting the microbiome may alter the course of the disease to delay or even stop disease progression [57]. The immunologic gut-liver axis in PSC may be modulated fundamentally via the gut microbiome.

5.1. Antibiotics

Antibiotics represent the typical drugs for manipulation of gut microbiome. In general, there are 2 types of antibiotics: a) non-absorbable and b) absorbable. Non-absorbable antibiotics exert endotoxin-lowering and anti-inflammatory effects rather than changing the composition of microbiota and include rifaximin, paromomycin and neomycin. Currently they are employed in cirrhotic patients for spontaneous bacterial peritonitis (SBP) prophylaxis. A phase II study of rifaximin soluble solid dispersion in patients with early decompensated cirrhosis showed that 40 mg immediate release formulation could reduce hospitalization and death, because of reduction of cirrhosis complications [58]. Absorbable antibiotics cross the intestinal barrier to achieve therapeutic serum concentrations and are currently used for spontaneous bacterial peritonitis prophylaxis [59] and for the management of acute recurrent cholangitis. Moreover, the British Society Gastroenterology guidelines recommend the prophylactic use of antibiotics for patients with PSC undergoing endoscopic retrograde cholangiopancreatography [60].

With the aim of targeting the microbiome two RCTs and an open label study have been performed in adult patients with PSC. Eighty patients were randomised to 36 months of UDCA (15 mg/Kg/day) plus metronidazole or UDCA alone [61]. A significant reduction in ALP, Mayo risk score, and histologic stage and grade was reported in the group with metronidazole plus UDCA. An open-label study has been performed in 16 patients with PSC treated for 12 months with minocycline; a significant decrease in ALP was noticed, but 25% of patients withdrew from the study due to intolerance to minocycline [62]. Finally, a double-blind, randomized, pilot study was conducted in 35 patients randomized in 4 groups: low-dose vancomycin (125 mg 4 times daily), high-dose vancomycin (250 mg 4 times daily), low-dose metronidazole (250 mg 3 times daily), high-dose metronidazole (500 mg 3 times daily). Low-dose and high-dose vancomycin groups were superior to metronidazole and achieved a significant reduction in ALP [63]. In paediatric patients with PSC and associated ulcerative colitis vancomycin was used in a recent cohort study [64]. Interestingly, in the International Paediatric PSC Consortium Registry, 85% of children receive off-label treatment with one or both of UDCA and oral vancomycin. Data from this Registry have been recently analysed [65]. Two hundred sixty-four patients (88 each with oral vancomycin therapy [OVT], UDCA, or observation) were assessed. Neither OVT nor UDCA showed improvement in outcomes compared to strategy observation. In particular, patients progressed to end stage liver disease at similar rates. Favourable outcome was associated with having a mild phenotype of PSC and minimal hepatic fibrosis.

Actually, several controlled studies employing antibiotics for PSC are ongoing (Table 2). Certainly, antibiotics can modulate microbiome which only one pathogenic aspect regarding PSC and probably should be one of the first therapeutic approach. It is rather impossible that monotherapy in PSC might have a benefit on the abnormalities of biliary tree; moreover, there are a number of considerations regarding the limited effect of UDCA in a variety of clinical conditions (the association with inflammatory bowel disease, the overlap with autoimmune hepatitis, the small duct variant, the cystic dilatation variant). Thus, a combined approach with different agents will be the future strategy for the management of PSC.

5.2. Intestinal faecal microbiota transplantation

Intestinal microbiota transplantation has been proposed to treat liver disease and cirrhosis [58,66]. An open pilot study using faecal microbiota transplantation (FMT) has been recently conducted in 10 patients with PSC, concurrent IBD and ALP >1.5 x the upper limit of normal [67]. This study included the evaluation of liver enzymes, stool microbiome, and also metabolomic analyses at baseline and week 1, 4, 8, 12 and 24 after FMT. The primary outcome was *safety*, and the secondary outcome was *decrease in ALP levels ≥50% from baseline by week 24 post FMT*. Overall, 3 out 10 patients experienced $a \geq 50\%$ decrease in ALP levels, which was correlated with an increase in bacterial diversity and engraftment, and the FMT was a safe procedure.

5.3. Treatment for PSC/AIH overlap syndrome

In children with autoimmune sclerosing cholangitis treatment with steroids and azathioprine in association with UDCA is beneficial for the parenchymal inflammatory lesions, but is less effective in the control of bile duct damage [68]. The prognosis of autoimmune cholangitis is worse than that of AIH because of progres-

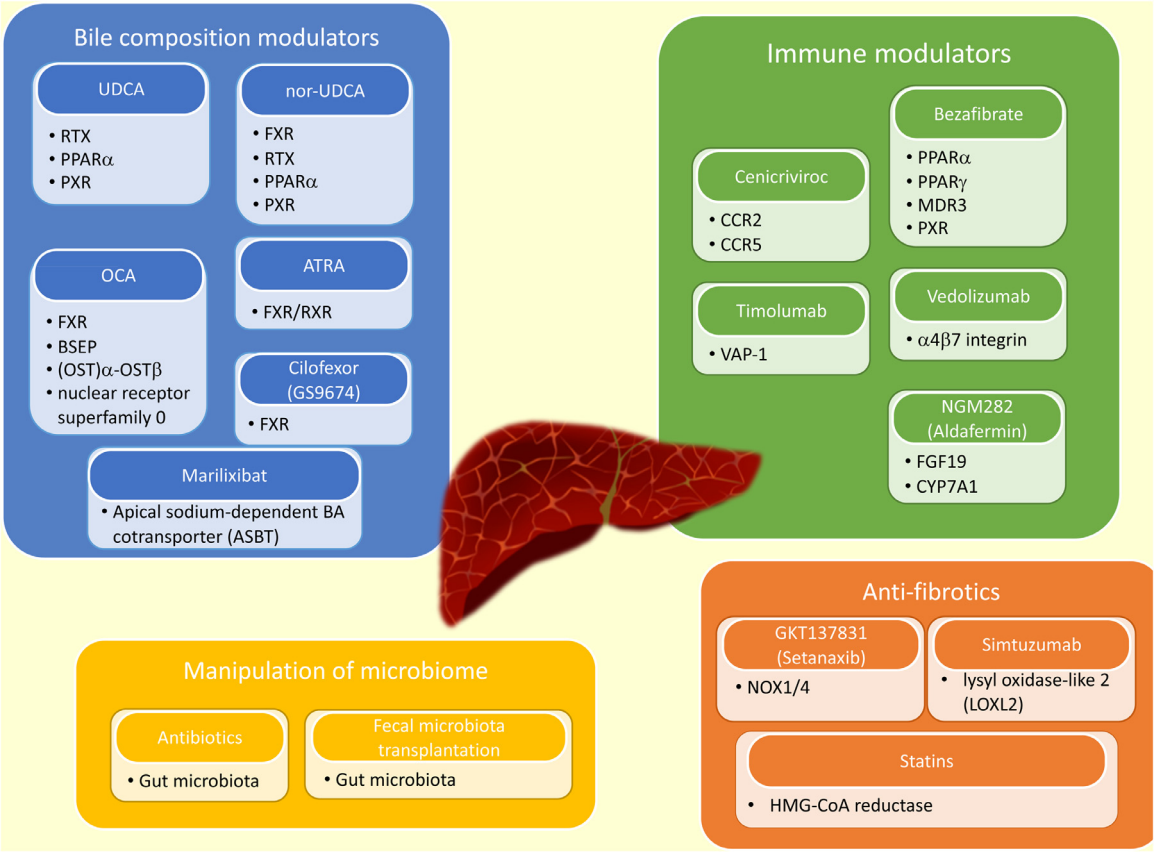

Fig. 1. Classes of drugs used for PSC and their pharmacological targets.

sion of cholangiopathy, and 20% of patients eventually require liver transplantation [68]. The combination approach with UDCA plus immunosuppressive therapy is recommended also for adults with PSC/AIH overlap syndrome by EASL guidelines [69]. However, the diagnosis of PSC/AIH overlap syndrome requires an accurate evaluation. A positive response was observed in a prospective study including only 7 patients with PSC/AIH overlap syndrome administered with prednisolone (from an initial dose 0.5 mg/Kg/day to 10–15 mg/day) and azathioprine (50–75 mg/day) plus UDCA (15–20 mg/Kg/day) [70]. This group of patients demonstrated an improved survival when compared to a parallel group of 34 patients with classical PSC treated with UDCA as monotherapy (follow-up 7–8 years) [70]. The EASL guidelines recommend UDCA and immunosuppressive therapy for patients with PSC/AIH overlap syndrome, although it is emphasized that this therapeutic option is not evidence-based [71]. Accordingly, also AASLD recommend the use of corticosteroids and other immunosuppressive agents in these patients [72].

6. Conclusions

Several types of agents targeting bile composition, immunomodulation, fibrosis or the gut microbiome have been conducted in PSC patients so far (Fig. 1, Tables 1 and 2). The ideal treatment scheme for PSC is probably a combination of different drugs targeting different pathogenic mechanisms. The majority of them have shown beneficial effects on biochemical endpoints. No data are available on robust endpoints, such as amelioration of endoscopic changes or transplant-free survival. Indeed, the absence of valid surrogate outcomes and the lack of good prognostic models can affect the clinical trial investigations on new experimental drugs. To discuss this important issue the International PSC Study Group initiated a consensus process to identify appropriate candidate surrogate endpoints for clinical trials [73]. This consensus process yielded histology, ALP, transient elastography and combinations thereof as the most likely candidate parameters for clinical trials. Nevertheless, in our opinion, more robust endpoints should be considered in near future, including the assessment of changes in abnormalities of the biliary tree. In this view, the Amsterdam-Oxford model for PSC could be useful for a valuable approach at different timepoints during follow-up of patients [74]. It should be stressed that other new natural history models for PSC have been introduced. These models, however, are limited by the prediction of hepatic decompensation rather than solid clinical endpoints such as liver transplantation, death, or cholangiocarcinoma. In conclusion, the definition of specific risk profiles is of importance for the identification of PSC subgroups that may have an unfavourable disease course, or for the selection of patients to be enroled in clinical trials.

Declaration of Competing Interest

Annarosa Floreani has received advisory board fees from Intercept

Sara De Martin declares no conflict of interest that pertain to this work

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