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Advances in pharmacotherapy for primary biliary cirrhosis

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Abstract

Introduction—Primary Biliary Cirrhosis (PBC) is a chronic autoimmune liver disease mostly seen in middle aged women characterized by progressive non-suppurative destruction of small bile ducts resulting in intrahepatic cholestasis, parenchymal injury, and ultimately end stage liver disease. Despite major breakthroughs in our understanding of PBC, there remains only one FDA-approved agent for treatment: ursodeoxycholic acid (UDCA) to which one third of patients are unresponsive.

Areas covered—Biochemical response to treatment with UDCA is associated with excellent survival rates in PBC patients. However, there is a need for alternative treatments for non-responders. Results from human epidemiological and genetic studies as well as preclinical studies in PBC animal models have provided a strong impetus for the development of new therapeutic agents. In this review, we discuss the recent advances in translational research in PBC focusing on promising therapeutic approaches, namely immune-based targeted therapies and agents targeting the synthesis and circulation of bile acids.

Expert opinion—We are in a new era for the development of novel therapies for PBC. Data on fibrates, budesonide, and obeticholic acid offer encouragement for non-responders to UDCA.

Keywords

Primary Biliary Cirrhosis; ursodeoxycholic acid; FXR agonists; biologics

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The authors' preference for publication is US spellings.

The authors have enrolled patients in some cited trials (NCT01473524, NCT00746486, NCT01389973, NCT01430429)

1.0 INTRODUCTION

In 1851, Addison and Gull described three patients with light skin lesions, jaundice and enlarged livers; one of these patients later developed yellowish plaques around her eyes and finger joints. A century later, Ahrens and his colleagues coined the term Primary Biliary Cirrhosis (PBC) to describe jaundice, hepatomegaly and pruritus affecting middle aged women, in the absence of apparent obstruction of the large bile ducts [1, 2].

Since then, our understanding of PBC has grown considerably: anti-mitochondrial antibodies (AMA), which are present in 80% or more of PBC patients have been identified and the autoantigens recognized by them have been cloned [3, 4]. The major targets of AMAs, the E2 component of mitochondrial dehydrogenases, particularly the pyruvate dehydrogenase complex (PDC-E2), have been rigorously defined at the molecular level [3, 5, 6]. Moreover, autoreactive CD4+ and CD8+ T cell responses present in human peripheral blood and liver have been dissected [7–10]. Epidemiological and genetic studies, including Genome Wide Association Studies (GWAS), have delineated several crucial environmental factors and cellular pathways involved in the pathophysiology of the disease [11, 12].

There have been enormous advances in understanding the pathophysiology of PBC, including cloning of the major mitochondrial autoantigen, development of animal models, and refinement in dissection of effector pathways [13–18].

Despite the great progress made in understanding the disease, a major breakthrough in treatment has yet to be realized [19]. The only FDA-approved agent for the treatment of PBC is still ursodeoxycholic acid (UDCA), which was introduced in 1987. A complete biochemical response to UDCA is associated with both improved survival and liver histology [20–22]. However, while UDCA therapy has a marked impact on clinical outcomes in PBC, up to 40% of patients have an insufficient response to UDCA and accordingly have a significantly increased risk of developing an adverse outcome, such as liver transplantation or death [21, 23]. Several studies have proposed various criteria as predictors of treatment success with UDCA [20, 21, 23–27]. Recent studies of large patient cohorts from France and the United Kingdom have demonstrated that reduction of the alkaline phosphatase (ALP) and aspartate transaminase (AST) to < 1.5 times the upper limit of normal (ULN) and a normal total bilirubin after 1 year of UDCA therapy (Paris II criteria) is associated with significantly better transplant-free survival [28]. Numerous therapies including newer biologics have been studied in the one third of PBC patients who are incomplete responders to UDCA with little success. Importantly, an increased dose of UDCA in patients who had incomplete response to UDCA was not found to be of any benefit in this subpopulation of patients [21].

In this review we will summarize recent advances in therapeutics and potential imminent breakthroughs that may accelerate the development of therapies in PBC. We will focus both on bile acid-based therapies and the new therapeutic approaches originated from the discoveries of immune pathways in PBC. Indeed, while in the incipient stages of the disease, the immunological breach of tolerance is most significant, in later stages, cholestasis plays an important role in the recurring hepatic injury where the prime targets for novel

therapeutics focus on limiting the cytotoxic effects of bile acids at the level of the liver parenchyma [19, 29, 30].

2.0 PAST AND PRESENT: BILE ACID SIGNALING

In cholestatic conditions including PBC, the hydrophobic bile acids accumulate within the liver parenchyma contributing to hepatic injury. Multiple mechanisms of bile acid injury include: direct cytotoxic effects due to cell membrane solubilization, bile-induced reactive oxygen species (ROS), recruitment of mononuclear cells through the release of chemoattractant cytokines, upregulation of the expression of MHC class I on hepatocytes (rendering them more vulnerable to immune destruction), and induction of hepatocyte apoptosis (by direct activation of Fas). When given at therapeutic doses, UDCA, a hydrophilic bile acid occurring naturally in humans normally constituting less than 5% of the bile acid pool changes the composition of this pool by increasing the fraction UDCA. Experimental evidence suggests that UDCA protects cholangiocytes against cytotoxicity of hydrophobic bile acids, resulting from changes in the phospholipid-rich micelles, reduction of bile acid cytotoxicity of bile and decrease of the concentration of hydrophobic bile acids [31]. In addition, UDCA upregulates the anion exchanger 2 (AE2) transporter involved in biliary bicarbonate secretion resulting in less toxic bile [32]. Further, UDCA helps to reinstate antioxidant defenses mediated by glutathione-related upregulation of γ-glutamyl cysteine synthetase [33]. Other possible mechanisms of action of UDCA include its inhibition of apoptosis [34] and reported immunomodulatory effects that can be partially accounted for by its effect on the glucocorticoid receptor [35].

UDCA is currently the only drug approved for the treatment of patients with PBC. Several clinical studies support the assertion that UDCA not only improves biochemical indices, but also delays histologic progression and improves survival without transplantation. In fact, the transplant-free survival of UDCA treated PBC patients who respond to UDCA is comparable to that of the general population [21, 36]. Indeed both AASLD and EASL guidelines recommend the use of UDCA in PBC patients [37, 38]. Yet, one third of PBC patients do not respond to UDCA [21] and the efficacy of UDCA in terms of overall survival and progression to end stage liver disease is still unclear [39].

2.1 Bile acids as nuclear receptor ligands in the liver cell signaling

In the last two decades, endogenous bile acids have been identified as natural ligands for previously identified nuclear receptors. These receptors include the farnesoid X receptor (FXR), the pregnane X receptor (PXR), the constitutive androstane receptor (CAR) and the vitamin D3 receptor (VDR). As nuclear receptors, they translocate to the cell nucleus upon activation, bind to hormone response elements (HSR) and control the expression of certain genes. Once activated by bile acids, FXR translocates to the cell membrane, dimerizes with the retinoid X receptor (RXR) and induces the expression of small heterodimer partner (SHP) which regulates *de novo* bile acid synthesis and transport by inhibiting the expression of the CYP7A1 gene [40] and increasing the expression of multidrug resistance-associated protein 3 (MDR-3) [41]. Eventually, FXR is involved in the regulation of hepatic bile acid production and flow and the modulation of hepatic inflammation, fibrosis and regeneration (Figure 1). FXR is also an important regulator of the enterohepatic circulation of bile acids

at the level of hepatocytes and enterocytes [42]. FXR activation in hepatocytes down-regulates bile acid uptake [43] and indirectly stimulates bile salt export pump (BSEP, also known as ABCB11) [44]. In enterocytes, FXR induces the release of FGF-19, an ileal hormone that is released into the portal circulation and ultimately regulates bile acid synthesis, acting through the FGFR4/Klotho-β receptor complexes in the liver to inhibit CYP7A1 [45]. FXR is also an important inhibitor of hepatic inflammation, as evident by the spontaneous liver injury, inflammation and increased sensitivity to NF-κB activation seen in in FXR-deficient mice (Figure 1) [46].

Another recently discovered bile acid receptor is the transmembrane G protein–coupled receptor (TGR-5) expressed on macrophages, biliary epithelial cells (BEC), sinusoidal endothelial cells, gallbladder epithelium, and in brown adipose tissue and muscle. Activation of TGR-5 by bile acids result in inhibition of the NF-κB-mediated expression of proinflammatory genes in macrophages and Kupffer cells in hepatic tissue [47]. Some evidence also suggests a protective role against liver carcinogenesis through the negative regulation of STAT3 [48]. The favorable effects of bile acid receptor activation have made these receptors attractive targets for drug development over the last decade.

2.2 Bile Acid Pharmacotherapies

Obeticholic acid (OCA) (6-alpha-ethyl-chenodeoxycholic acid) (INT-747) is a semi-synthetic analogue of chenodeoxycholic acid with a 100-fold higher affinity for FXR [49]. OCA is notable for decreasing bile synthesis by directly suppressing CYP7A1 and inducing FGF-19, FGF-15 in mice, release to promote bile excretion by acting on various bile transporters [50]. OCA also may ameliorate portal hypertension through an increase in eNOS production, modulate liver regeneration and have anti-fibrotic effects [51]. FXR activation by OCA also has important anti-inflammatory effects evident by reduced cytokine production [52]. Two Phase 2 studies of OCA in PBC have been completed and the 1-year double blind, placebo controlled phase of a Phase 3 trial (POISE) evaluating OCA for the treatment of PBC patients with an incomplete biochemical response to UDCA has concluded recently (NCT01473524). Response rates (intended as alkaline phosphatase reduction, a surrogate marker of damage progression [27]) to OCA or placebo given in addition to UDCA in the Phase 3 trial were 10% with placebo compared to 47% with 10 mg OCA and 46% with 5 mg OCA with titration to 10 mg OCA (both OCA groups $p < 0.0001$ vs. placebo). The placebo group experienced a mean decrease in ALP from baseline of 5%, compared to a mean decrease of 39% in the 10 mg OCA dose group and 33% in the 5–10 mg OCA titration group (both OCA groups $p < 0.0001$ vs. placebo). Pruritus is the most severe and common side effect reported during the trial (up to 70% of patients). It is dose-dependent and has led to therapy discontinuation at high-dosage of OCA, but seems to be well tolerated at the lowest effective dosage. The POISE study is currently in a long-term safety extension phase [53].

Another steroidal semi-synthetic bile acid analogue INT-767 is a dual FXR and TGR5 agonist [54]. It has been shown to modulate the activity of monocytes and macrophages [55], to reduce inflammation though the inactivation of NF-κB via a protein kinase A dependent manner, and to reduce liver injury by promoting biliary bicarbonate excretion

[56]. A TGR-5 selective agonist, INT-777 has been shown to increase bile flow in animal models [57]. Regulating bile acid synthesis is also being attempted through a recombinant variant of FGF-19 (NGM-282). As noted above, FGF-19 plays an important role in suppressing bile synthesis and promoting hepatocyte proliferation [58]. A phase 2 clinical trial to evaluate the use of NGM-282 in PBC patients is currently ongoing (NCT02026401).

Finally, inhibition of the Ileal Bile Acid Transporter (IBAT, or ASBT) may result in increased excretion of bile. Indeed, ASBT inhibitors have been developed but, as far as we know, they have not yet been tested in cholestatic liver diseases (Table 1).

2.3 Fibrates

Fibrates are carboxylic acids that have been used as hypolipidemic agents for decades. They exert their effect by acting on nuclear transcription factors of the peroxisome proliferator-activated receptors (PPARs) family. Several mechanisms of action suggest that fibrates might be beneficial in PBC. Mediated via PPARα, fibrates upregulate MDR-3 and FXR, therefore may inhibit bile salt synthesis, reduce IL-1-induced C-reactive protein expression on hepatocytes, and inhibit NF-κB through the induction of IκBα expression. Through their activity on PPARδ, fibrates activate PGC-1α, which increases FXR activity. Fibrates also up-regulate bile acid efflux transporters and the ileal bile acid binding protein (I-BABP). Finally, it has recently been suggested that fibrates may act as a dual PPAR and PXR agonist. In the last two decades, several clinical trials have shown that fibrates have anti-cholestatic effects accompanied by decreases in inflammatory markers and relief from itching when combined with UDCA in PBC patients who were refractory to UDCA therapy [59–61]. Two different fibrates have been tested in PBC, Bezafibrate, a pan-PPAR isoform agonist, and fenofibrate which is a PPARa specific agonist; whereas Bezafibrate is approved in Europe and Japan, only fenofibrate is available in the USA. Although the results of these studies seem consistent, most of them included only a small number of patients [62]. The results of phase III studies are currently awaited.

3.0 NEAR FUTURE: THE IMMUNE NETWORK

The serologic hallmark of PBC is the presence of antibodies to mitochondria, i.e. AMA, especially to PDC-E2. PBC is considered a model autoimmune disease because of the homogeneity between patients and the high specificity of AMAs. However, over the past decade there has been great progress on defining the multi-lineage response to PDC-E2, including immunological definition of the antigenic epitopes, the nature of reactive autoantibodies, the characterization of T-cell responses [7–9], and the crucial role of the innate immune system [29]. Moreover pathway-based analysis of GWAS on PBC has confirmed that key immune mechanisms such as TNF signaling and antigen processing and presentation may underlie the genetic predisposition known to exist in PBC [63]. The effector mechanisms of PBC are indeed a multi-orchestrated response [64], and a better understanding of effector mechanisms will suggest new approaches to clinical intervention.

3.1 IL-12 and IL-23 axis

Interleukin-12 (IL-12) is a heterodimer composed of two subunits: IL-12p35 and IL-12p40 subunits. It is produced by antigen presenting cells (APCs) and drives the differentiation of T lymphocytes into a pro-inflammatory T helper (Th1) phenotype [30]. The importance of the IL-12/Th1 pathway in PBC has been suggested by a mouse model of PBC [65] and human genetic studies, which have identified predisposing polymorphism associated with genes downstream of the IL-12/Th1 signaling cascade [66, 67]. Interleukin-23 (IL-23) is composed of an IL-12p40 subunit that is shared with IL-12 and an IL-23p19 subunit. IL-23 drives the development of Th17 cells [68, 69] and is implicated in a number of autoimmune diseases, including PBC [70, 71]. While both Th1 and Th17 play cardinal roles in PBC pathogenesis, advanced disease stages are characterized by Th17 skewing emphasizing the potential importance of targeting the IL-23/Th17 axis [17].

The monoclonal antibody ustekinumab targets the IL-12p40 and therefore exerts its effect on both the IL-12/Th1 as well as the IL-23/Th17 axes. Ustekinumab is of therapeutic benefit in psoriasis and in trials for Crohn's disease. A phase II trial, aiming to test the efficacy and safety of ustekinumab in PBC patients (NCT01389973) showed a modest decrease in ALP, enhanced liver fibrosis (ELF) score and bile concentration, none of the patients achieved the predefined primary endpoint of ALP reduction from baseline of >40% or ALP normalization [72]. Given the strong evidence of an essential role for IL12 and IL23 in PBC [30], studies with agents specifically targeting either IL-12 or IL-23 may have different outcomes.

3.2 CTLA-4 Agents

Under physiological conditions, T-cell activation requires not only engagement of the T cell receptor with it cognate antigen presented by an MHC, but also a second signal from co-stimulatory molecules, including the cytotoxic T lymphocyte antigen 4 (CTLA-4) on T cells. In addition to MHC-peptide complexes, APCs express membrane proteins (CD80 and CD86) that bind to the CD28 co-receptor expressed on T-cells and produce a co-stimulatory signal further enhancing their activation. When CD80/86 interact with CTLA-4 on T cells instead of CD28, they convey an inhibitory signal to the T-cell. Importantly, CTLA-4 binds to CD80/86 with greater affinity than CD28 limiting T cell activation. As a consequence, cytokine production is reduced, cell cycle progression inhibited, TCR signaling down-modulated, and activation of B cells and macrophages decreased. Moreover, CTLA-4 is crucial for the function of $Foxp3^+$ T regulatory cells (Tregs), which mediate immune tolerance.

These properties of CTLA-4 as well as preclinical studies in mouse models of PBC [73] suggest a strong rationale for CTLA4-based therapy in PBC. Two chimeric CTLA-4-Ig proteins have been approved in recent years; abatacept for the treatment of rheumatoid arthritis and belatacept for the prevention of acute rejection in kidney transplant patients. This has triggered [73]a Phase 2 study to evaluate the use of abatacept in PBC patients with an incomplete biochemical response to UDCA (NCT02078882).

3.3 CD40-CD40L Signaling

CD40 is expressed on all APCs, binds to its natural ligand CD40L, which is expressed primarily on activated CD4+ T cells, and after cell activation is up-regulated [74]. Moreover, CD40 is constitutively expressed by B cells and its interaction with CD40L is critical for immunoglobulin (Ig) class-switching [75]. Dysregulation of CD40-CD40L has been documented in various autoimmune diseases [76]. In the context of PBC, CD40 activation induces Fas/FasL-mediated apoptosis of biliary epithelial cells (BEC) [77] and recent findings suggest that epigenetic changes in the CD40L could account for a defect in class switching resulting in the high titers of IgM seen in PBC patients [78]. Agents against CD40L are a promising means to target autoreactive T-cells [79], but, have only been tested in animal models. Interestingly, anti-CD40L has been shown to decrease activated CD8+ T-cells and hepatic NK-T cells and to ameliorate inflammation and bile duct destruction in an animal model of autoimmune cholangitis [80].

3.4 CXCL-10: T-Cell Recruitment

The CXC motif chemokine 10 (CXCL10), or Interferon-γ-inducible protein-10 (IP-10), plays a role in the recruitment of T-cells during biliary injury [81] and demonstrated to be involved in the pathogenesis of PBC [82]. Unfortunately, a trial targeting CXCL-10 with anti-CXCL10 (NI-0801) in PBC patients was not able to demonstrate a clinical efficacy (NCT01430429).

3.5 Regulatory T-Cell Activity

Regulatory T cells (Tregs) have been long known to mediate tolerance and different subtypes of Tregs have been implicated in the pathogenesis of PBC, including CD8+ CD28− Tregs [83] and the more studied CD4+ CD25+ Tregs [84]. Moreover, CD25 (IL-2Rα) -deficient mice develop PBC-like features [85] and a child with congenital IL-2Rα (CD25) deficiency presented PBC-like liver disease and AMAs [86]. Low dose IL-2 therapy might have beneficial effects on the Treg population in a variety of conditions [87, 88] and successful induction of remission in a patient with systemic lupus erythematosus has been reported. A clinical trial is currently underway to study the efficacy of low-dose IL-2 therapy in a host of autoimmune diseases (NCT01988506). Cell therapy is an alternative approach to reinstitute Treg activity. In the child with IL-2Rα deficiency, allogenic stem cell transplantation resolved his PBC [86]. In addition, adoptive transfer of wild type Tregs can reduce inflammatory cytokine production and prevent disease in a mouse model of PBC [89, 90].

3.6 B-cells

Although T-lymphocytes are considered the main mediators of tissue damage in PBC, the role of B cells is strongly suggested by the presence of highly specific AMA in more than 90% of patients, and the high titers of IgM that are frequently seen in the sera of patients [2, 78]. However, it is important to highlight that while the production of antibodies has an important diagnostic value, it does not correlate with disease severity [91]. However, in addition to antibody production, antigen presentation by B-cells plays an important role in T-cell mediated autoimmunity. Moreover, B-cells secrete cytokines including interferon-γ

and IL-4 and have a suppressive role on Tregs. Indeed, the beneficial effect of B-cell depletion in T cell mediated autoimmune diseases has been attributed to the attenuated T-cell activation, and the effect this depletion has on Treg cells.

Depletion of B-cells with anti-CD20 therapy has yielded some positive results in murine models [92] as well as in PBC patients, using Rituximab, with suboptimal response to UDCA [93] with significant improvement seen in both biochemical and immunologic markers (NCT00364819). Yet, depletion of B-cells can be a double-edged sword. Pretreatment of mice with anti-CD20 prior to induction of a PBC-like illness with xenobiotic immunization exacerbates the disease [92]. In addition, in a genetic model of PBC expressing a dominant negative TGF-β receptor II transgene, B-cell deficiency through genetic manipulation leads to a more severe liver inflammation [94]. A plausible explanation for these seemingly contradictory results may lay in the different subsets of B-cells, i.e. reactive B cells versus regulatory B cells, and in the role that each of these subsets play at different stages of disease progression. While B effector cells seem to contribute to disease progression, regulatory B cells may be protective against disease initiation, including IL-10 producing B-cells [95].

3.7 Budesonide And Immunosuppressive Agents

Although combination of UDCA with a glucocorticoid might have more favorable results compared to UDCA monotherapy [96], initial trials with prednisolone resulted in a high incidence of adverse effects, especially loss of bone density, that precluded its use [97, 98]. As a result, clinical trials of budesonide, a glucocorticoid with a higher receptor affinity and a higher first-pass metabolism, have been conducted and shown to improve both biochemical and histological markers [99, 100]. Yet, in late stage PBC budesonide results in high serum levels that are associated with serious adverse effects [101]. A phase 3 trial is currently underway for the evaluation of budesonide in UDCA-refractory PBC patients (ClinicalTrials.gov Identifier: NCT00746486).

Other immunosuppressive agents assessed for PBC treatment including methotrexate [102] and azathioprine, which is currently recommended only in the overlap syndrome of PBC with autoimmune hepatitis [103, 104]. Mycophenolate mofetil, an inhibitor of T- and B-cells proliferation, has also been evaluated with conflicting results [105]. The cumulative body of evidence is currently insufficient to support the use of any of these agents in PBC patients.

Several other potential therapies are not discussed herein as the data is too preliminary and/or confidential. We should note that Moexipril, an angiotensin-converting enzyme inhibitor, has been studied in conjunction with UDCA but demonstrated no beneficial effect [106]. Combivir, an antiretroviral agent, is under investigation in PBC, but its rationale and any conclusive data remain elusive [107]. Colchicine and methotrexate have a long history in the treatment of PBC [108–110], but their mechanisms of action and their roles, if any, are unclear. Finally, other drugs like tetrathiomolybdate [111], and the use of mesenchymal stem cells have been studied but again require more detailed analyses and there is insufficient data for discussion [112]. It is also important to note that PBC is associated with

systemic symptoms, including pruritus, fatigue, and bone density impairment, all of whom still lack specific treatments [113].

4.0 EXPERT OPINION

Since the FDA approval of UDCA over twenty years ago, there was little to be offered to PBC patients beyond the conventional UDCA therapy. For those patients that do not respond to UDCA there are currently no options to delay the progression of PBC to liver failure, death, or liver transplant. Interestingly, although PBC has a strong autoimmune pathogenesis, immunosuppressive drugs have not shown a beneficial effect. We hypothesize that such drugs would need to be utilized during the earliest phases of disease development, at the time when tolerance is broken. However, patients present with clinical symptoms several or more years after detection of autoantibodies and thus it has been difficult to treat patients during the first phases of disease. On the other hand, and during the last decade, there have been significant advances in our understanding of the pathogenesis and immunobiology of PBC. Epidemiological studies, GWAS and preclinical testing of new agents using PBC animal models have led to the development of new agents and a great number of clinical trials in PBC over recent years. Indeed the clinical trials presented in this review herald a new era of specifically targeted therapies that are based on sound understanding of the immunological and bile acid-related mechanisms that drive disease initiation and progression (Table 1). Clearly, the challenge is the design of high quality clinical trials, with molecules chosen on the basis of structure function and mechanisms of action if we are to develop successful new therapeutics. It is no trivial matter to obtain approval for an orphan disease like PBC and particularly a disease which progresses over years to decades. There is required persistence and a balance between the ideal and the practical.

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HIGHLIGHTS BOX

- For decades UDCA has been the only approved therapy for PBC, and although responders to UDCA have a good prognosis and survival rate, 30% of patients are still in need of therapy.
- Epidemiological studies, GWAS have identify specific molecular pathways that are potential therapeutic targets; preclinical testing of new agents using PBC animal models have led to the development of new agents and clinical trials in PBC. We are in a new era for the therapy of this chronic liver disease.
- Obeticholic acid (OCA) is a semi-synthetic analogue of chenodeoxycholic acid with a strong affinity for farnesoid X receptor (FXR). Response rates to OCA, given in addition to UDCA, in a Phase 3 trial seem are promising.
- Several mechanisms of action suggest that fibrates might be beneficial in PBC. However most studies include only a small number of patients and more data are needed.
- The effector mechanisms of PBC are a multi-orchestrated response involving both innate and adaptive immunity. A number of biologics targeting specific immune pathways are being tested in PBC, aimed at regulating pathogenic mechanisms involved in disease perpetuation.

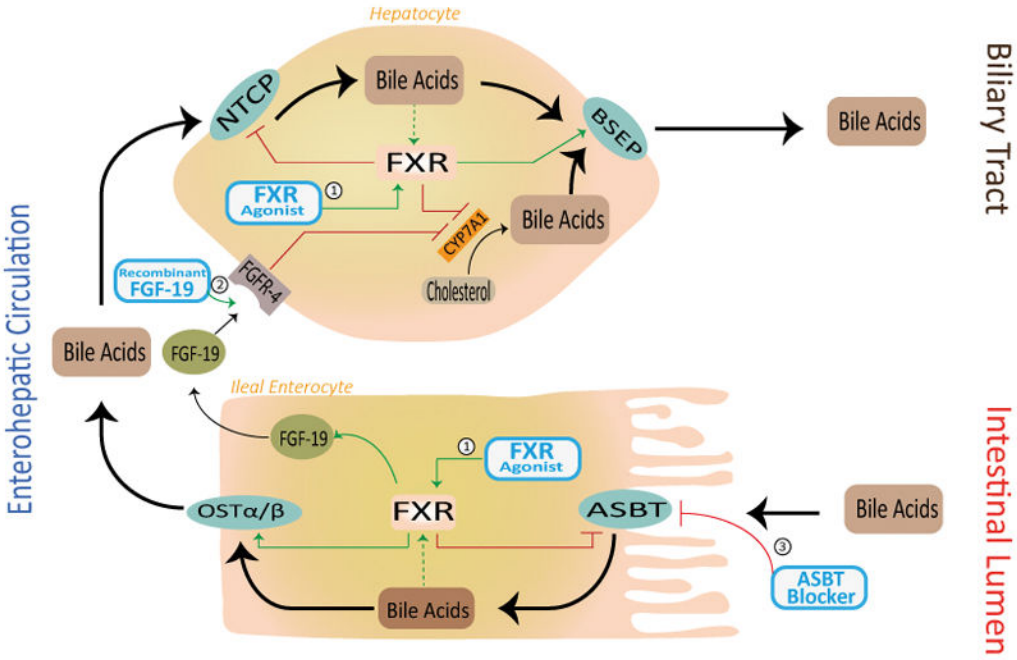

Figure 1. Bile acid based new therapeutics for PBC

(1) FXR-agonists exert their effect both on enterocytes and hepatocytes, inhibiting de novo synthesis of bile acids and promoting their excretion. (2) Recombinant FGF-19 interacts with the FGFR-4 receptor expressed on hepatocytes to inhibit bile acid synthesis. (3) ASBT blocker interferes with the reabsorption of bile acids from the intestinal lumen.

Dashed green line: not all bile acids can activate the FXR receptor (see text).

ASBT: Apical Sodium-dependent Bile acid Transporter. Ostα/β: Organic Solute Transporter α and β. NTCP: Na+ - Taurocholate Cotransporting Polypeptide. BSEP: Bile Salt Export Pump. FXR: Farnesoid X Receptor. FGF-19: Fibroblast Growth Factor-19. FGFR-4: Fibroblast Growth Factor Receptor-4.

Table 1

Beyond UDCA – Future Therapeutic Approaches for PBC

Treatment Approach	Mechanism	Class of molecule	Rationale	Typical Molecule(s)	References
Immunological	Targeting B–cells	Anti-CD20	The role of B-cells in PBC is not reduced to antibody production. B-cells can also act as antigen presenting cells, secrete important cytokines (including IL-4 and IFNγ) and suppress Tregs.	Rituximab	NCT00364819*
	Targeting Autoreactive T-Cells	Anti-IL12/IL23	Th1/IL-12 and Th17/IL-23 axis involvement in PBC has been confirmed by GWAS. Later stages are marked by Th17 skewing.	Ustekinumab	NCT01389973*
		Chimeric CTLA4	Chimeric CTLA4 proteins bind to the the B7 molecules on T-cells and prevent their interaction with CD28; thus blocking the second stimulus.	Abatacept Betalecept	NCT02078882*
		Anti-CD40	CD40 activation induce Fas/FasL-mediated apoptosis of biliary epithelial cells.	FFP104	NCT02193360*
		Anti-CXCL-10	CXCL-10 is important for the recruitment of T-cells during biliary injury.	NI-0801	NCT01430429*
	Enhancing Regulatory T-Cells	Low dose IL-2	Low dose IL-2 therapy might enhance Treg population. A clinical trial is currently underway to check the efficacy of low-dose IL-2 therapy in other autoimmune diseases (including Sclerosing Cholangitis). Therapeutic applicability to PBC is yet to be cleared.	Aldesleukin	NCT01988506*
		Cellular Therapy	Reinstitution of the Treg population might be possible with allogenic stem cell transplantation or adoptive transfer of wild type Tregs.		
Bile Acid Based	Activating Bile Acid Regulatory Mechanisms	FXR-Agonists	Nuclear Receptor Agonists (of which the most studied are FXR-agonists) feed on the regulatory mechanisms for bile acid synthesis and circulation, decreasing de novo synthesis and promoting excretion.	OCA, INT767, GW4064, WAY-362450, GSK2324, Fexaramine, PX-102	NCT01473524*
		Agonists of Other Nuclear Receptor	Activation of other nuclear receptors might have similar effects to those of FXR activation.	Rifampin, Hypricum, Vitamin D3	
		TGR5 agonists	Activation of the transmembrane TGR5 has been shown to increase bile flow in different animal models.	INT767, INT777	
		Recombinant FGF-19	Feeding on the FGF19/FGFR4 regulatory axis inhibits bile acid synthesis	NGM-282	NCT02135536* NCT02026401*
	Direct bile acid transporter blockers	ASBT Inhibitor	Inhibition of the Ileal Bile Acid Transporter (IBAT, or ASBT) may result in increased excretion of bile.	A4250	
Other	Activation of Key Nuclear Transcription Factor (PPAR)	Fibrates	Fibrates upregulate the expression of MDR-3, have anti-inflammatory effects, may increase FXR	Bezafibrate, Fenofibrate	NCT01654731*

Treatment Approach	Mechanism	Class of molecule	Rationale	Typical Molecule(s)	References
			activity and have shown to upregulate different bile acid transporters. activity and have shown to upregulate different bile acid transporters.		
	Steroidal Anti-inflammatory Agents	Glucocorticoids	Budesonide is a potent anti-inflammatory agent and at the same time has high first pass metabolism.	Budesonide	NCT00746486*

* These can be looked up at: *ClinicalTrials.gov*