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Proposed therapies in primary biliary cholangitis

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Abstract

Primary biliary cholangitis (PBC), previously known as primary biliary cirrhosis, is a model autoimmune disease with chronic cholestasis characterized by the hallmark of anti-mitochondrial antibodies and treated with ursodeoxycholic acid (UDCA). However, approximately 20-40% of patients incompletely respond to UDCA and have an increased risk of disease progression. Although there have been significant advances in the immunobiology of PBC, these have yet to be translated into newer therapeutic modalities. Current approaches to controlling the immune response include broad immunosuppression with corticosteroids as well as targeted therapies directed against T and B cells. In contrast, ameliorating cholestasis is the focus of other therapies in development, including obeticholic acid. In this article the authors will discuss ongoing clinical trials and, in particular, the rationale for choosing agents that may effectively target the aberrant immune response.

Keywords

Primary biliary cirrhosis; treatment; UDCA; obeticholic acid; budesonide; fibrates; biologic agents; pruritus; fatigue

Introduction

There have been major advances in our understanding of the immunobiology of primary biliary cholangitis (PBC), the recent designation for what was previously known as primary

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biliary cirrhosis, beginning with the cloning and identification of the major mitochondrial autoantigens [1] and followed by the identification of T and B cell epitopes, development of animal models, and elucidation of genetic and epigenetic components that lead to autoimmune cholangitis [2-21]. However, a major gap remains between the investigative immunology and introduction of new treatments for the unmet needs of PBC[22, 23]. The current paradigm for the treatment of PBC began in 1987 with the introduction of ursodeoxycholic acid (UDCA) [24]. Interestingly, the efficacy of UDCA and its use in cholestasis was discovered by serendipity; it had been used to prevent cholesterol supersaturation by increasing the bile acid content and decreasing the ratio of cholesterol to bile acid [25, 26]. Chemical dissolution of cholesterol gallstones was demonstrated using UDCA in patients with chronic hepatitis and, importantly, led to improvement of liver biochemistries [27].

Subsequently, several randomized controlled trials with UDCA and meta-analyses have been performed and UDCA remains the only therapy approved for use in PBC by the Food and Drug Administration (FDA) and the only drug recommended for the treatment of PBC by both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of Liver Diseases (EASL). The data supporting these recommendations include the observations that: a) UDCA delays histological progression and time to transplantation [28, 29]; b) patients treated with UDCA have a better prognosis than those untreated [30, 31]; and c) patient with a biochemical response to UDCA as defined by several criteria have the same probability of survival as the general population [32]. However, despite these criteria, one meta-analysis of 16 randomized clinical trials concluded that UDCA offers no advantage in terms of mortality or liver transplantation rates in patients with PBC [33]. Moreover, 20-40% of PBC patients do not have a biochemical response to UDCA; the precise frequency being dependent upon criteria employed[24, 25, 32, 34, 35]. Regardless, recent large cohort studies have noted the clear associations between the level of serum alkaline phosphatase and bilirubin with UDCA and transplant-free survival [36, 37]. Based upon the correlation between improvements in alkaline phosphatase and bilirubin with UDCA therapy, current clinical trials utilize these biochemical responses as surrogate markers of clinical efficacy. Thus, there is a significant unmet need for PBC patients with an incomplete response to UDCA. Therapeutic targets generally involve bile acid metabolism, immune responses, and anti-fibrotic agents. In the remaining portion of this text we will discuss several new therapies under investigation.

Bile Acid Directed Therapies

Although PBC has all the hallmarks of a classic autoimmune disease, the most effective agents to date have targeted the impaired end organ function, namely bile acid stasis. Bile secretion is regulated by a complex network of adenosine triphosphate-binding cassette (ABC) transporters on the hepatocyte canalicular membrane. Synthesis and transport of bile salts are further regulated by transcriptional and post-transcriptional mechanisms. In particular, two nuclear receptors, the bile acid receptor or farnesoid X receptor (FXR) and the oxysterol receptor or liver X receptor (LXR) play a pivotal role in transcriptional regulation of the genes encoding these proteins [38, 39].

Obeticholic acid (OCA), an FXR agonist is a derivative of the chenodeoxycholic acid (CDCA) that has shown promise for the treatment of cholestatic conditions. A double-blind study of 165 patients with PBC, who had an inadequate response to UDCA, were randomly assigned to groups given 10 mg, 25 mg, or 50 mg doses of OCA or placebo, once daily for 3 months. An open-label extension of the trial in which 78 patients were enrolled and 61 completed the first year was also performed [40]. OCA, in daily doses ranging from 10 to 50 mg significantly reduced levels of ALP, γ-glutamyl transpeptidase, and alanine aminotransferase, compared with placebo. Pruritus was the only adverse effect that required a reduction of the dosage of OCA in PBC patients. A phase III study (POISE, NCT02308111) was started thereafter comparing 3 treatment groups; 10 mg daily, 5 mg daily titrated to 10 mg daily; and placebo, in a randomized, double-blind fashion for 1 year followed by an open label long term safety extension. The primary endpoint of the study included reduction in serum alkaline phosphatase (ALP) to < 1.67× ULN with a ≥ 15% reduction from baseline and a normal bilirubin level after 12 months of therapy. Preliminary results of the double-blind phase of the study have reported the proportion of patients meeting the primary endpoint was: 10% in the placebo group, 47% in the 10 mg OCA group and 46% in the 5-10 mg OCA group (both dose groups $p < 0.0001$ vs placebo) in an intention to treat analysis. A second phase III study of higher risk patients evaluating the effects of OCA on clinical outcomes was recently launched (NCT02308111). Pruritus, the main adverse effect of OCA in the PBC trials appears to be dose dependent and was also noticed in a trial of OCA for non-alcoholic steatohepatitis [11]. The mechanism of pruritus has not been explained, but activation of the autotaxin pathway or activation of the TGR5 bile acid receptor by OCA are possible pathways [41]. Currently, OCA is the leading candidate for the next approved therapy for PBC, something that has been lack for 2 decades.

Several other drugs under development in the FXR pathway include NGM282 (NCT02135536), LJN 452 (NCT02516605), and PX-102 (NCT01998672). Another agent targeting bile acids, tauroursodeoxycholic acid (TUDCA) promotes bicarbonate-rich hypercholeresis and may have benefits over UDCA [42]. TUDCA was studied in a recent randomized controlled trial in China (NCT01829698) with the results yet to be published [43]. Further, 24-nor-UDCA, a side-chain shortened derivate of UDCA inducing a bicarbonate-rich hypercholeresis and which in experimental models of cholestasis has a pronounced anti-inflammatory and anti-fibrotic effect [44, 45] is currently under investigation in a double-blind, randomized, placebo-controlled phase II trial in patients with primary sclerosing cholangitis is ongoing (NCT01755507). PBC is an obvious additional therapeutic area for the potential use of 24-*nor*-UDCA.

Targeting of the enterohepatic circulation of bile acids as a means of reducing the absorption of cholesterol has been an area of research for many decades. Molecules specifically targeting the intestinal apical sodium dependent bile acid transporter (ASBT) have more recently been repurposed for the potential use in PBC. Specifically, A4250, which showed promise in the multidrug resistant 2 (Mdr2)-deficient mouse model of primary sclerosing cholangitis, and LUM-001 are in phase 2 studies in PBC (NCT02360852 and NCT01904058, respectively).

Fibrates

An interesting therapeutic approach is the use of fibrates (bezafibrate or fenofibrate) to improve the response to UDCA in patients who do not have a complete response. Fibrates induce peroxisome proliferator-activated receptor α (PPARα)-UDP-glucuronosyltransferases (UGTs) signaling axis which is an important determinant of bile acid homeostasis [46] and may act through several mechanisms including: promoting the expression of MDR3 by binding to specific PPAR response elements in gene promoter and subsequently induce biliary phospholipid secretion; down-regulation of bile acid synthesis inhibiting CYP7A1 and CYP27A1; regulating detoxification of bile acids by up-regulation of different transporters (SULT 2A1, ASBT, MRP3, MRP4); altering the ratio of cholic acid/chenodeoxycholic acid by promoting the expression and activity of CYP8B1; and reducing inflammation by inhibiting NF-KB translocation with subsequent reduction of VCAM-1 expression that mitigates leukocyte adhesion and transendothelial migration [46].

A number of small clinical studies have assessed the potential efficacy of fibrates in PBC [47-72] (Table 1). Firstly, in 1999 Iwasaki et al. reported a significant improvement in the biochemical profile and disease symptoms after adding bezafibrate in PBC that were non-responders to UDCA. Since 1999, over 30 studies including both small pilot and long-term randomized controlled studies have been published on bezafibrate and fenofibrate in UDCA null or partial responders patients. Collectively these studies suggest efficacy in reducing alkaline phosphatase, gamma-glutamyl transferase and IgM when bezafibrate or fenofibrate is given in combination with UDCA [73]. Recently, a meta-analysis including 84 patients from 6 long-term randomized studies concluded that combination therapy with fenofibrate and UDCA is more effective than UDCA alone in reducing alkaline phosphatase, gamma-glutamyl transferase, immunoglobulin M and triglycerides but not pruritus in PBC [74]. Moreover, there was no increase in adverse events with combination therapy [74]. Other studies report heartburn, nausea, arthralgias, transient aminotransferase elevations (to 2-5 × the upper limit of normal), and mild, transient pruritus with the use of fenofibrate [51, 62, 67]. In the bezafibrate studies, there was an increase in creatinine, mild myalgias and isolated cases of nausea and heartburn [57, 61]. A recent long-term prospective study from Japan reported an increased risk of renal dysfunction and mild muscle pain that required dose reduction or discontinuation and correlated with long-term combination therapy with bezafibrate and UDCA compared to UDCA monotherapy [54]. We should note that in one study, no differences in number and intensity of adverse events in patients treated with bezafibrate or fenofibrate in combination with UDCA were reported [50].

Currently, a phase III prospective, double blind, randomized study of bezafibrate in combination with UDCA (BEZURSO) in PBC patients with incomplete responses to UDCA monotherapy is ongoing (NCT01654731). The results, expected at the end of 2016, are eagerly awaited.

Immunomodulatory Agents

PBC is an autoimmune disease and both innate and acquired immunity are involved in pathogenesis [16, 17, 20, 21, 75-77]. The upstream process of bile duct injury in PBC follows the breakdown of tolerance to E2 proteins of the pyruvate dehydrogenase complex

(PDC). However, results of immunosuppressive drugs to date have either been ineffective or had unacceptable adverse effects. Those studied in randomized-controlled trials include corticosteroid [78], azathioprine [79], cyclosporine [80, 81], methotrexate [82], and mycophenolate mofetil (MMF) [83]. In general, these studies were disappointing. Budesonide, a synthetic steroid with a high first-pass hepatic metabolism and high affinity for the glucocorticoid receptor, has been proposed in combination with UDCA as second-line therapy (Table 2) [84-87] In a double blind controlled trial including 20 patients with pre-cirrhotic histological stage, UDCA plus budesonide (3 mg orally three times daily) was superior to UDCA plus placebo after 2 years of treatment[85]. The favorable end-points included a significant amelioration in liver function tests and liver histology. In a 3 year open-label trial, oral budesonide (3 mg twice a day) combined with UDCA treatment was superior to UDCA monotherapy, not only in amelioration of liver function tests, but also in histologic improvement of fibrosis [87]. In a pilot trial including 22 non-responders to UDCA, with a mean duration of 46 months, budesonide failed to add any additional benefit to UDCA; moreover, it was shown that budesonide could aggravate underlying osteopenic bone disease [84]. In a small pilot study including 15 patients with PBC (with a suboptimal response to UDCA), budesonide was administered in combination with both UDCA and MMF; patients also received supplementation with calcium and vitamin D. A normalization of liver enzymes was obtained in 41% of cases [86]. It should be stressed, however, that budesonide is contraindicated in cirrhosis due to its potential to induce portal vein thrombosis [88]. A phase III randomized placebo-controlled trial comparing budesonide (3 mg three times daily plus) and UDCA (12-16 mg/Kg body weight) to placebo and UDCA in PBC is currently ongoing (NCT00746486). Currently, the use of a corticosteroid with or without azathioprine is only recommended for the PBC and AIH overlap syndrome [89, 90].

Biologic therapy

In contrast to immunomodulators, biologic therapies off the potential for more specific immunosuppression leading to greater efficacy with lower risk of adverse effects. Despite multiple potential targets and therapeutics developed for other more common autoimmune diseases, few biologic agents have been studied in PBC.

One approach that has been taken was the targeting of B-cell cells with rituximab, a chimeric monoclonal antibody specific for human CD20 that depletes B cells by complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity (Table 3) [91]. In an open-label study including 6 patients with PBC and an incomplete response to UDCA, treatment with rituximab led to significant reductions in serum alkaline phosphatase up to 36 weeks following treatment and reversed several immunologic abnormalities [92]. A second open-label study in 14 patients with PBC refractory to UDCA also demonstrated a significant reduction in alkaline phosphatase (median decrease 16%) at 6 months together with a reduction in serum IgM and AMA levels [93]. Pruritus improved in 60% of patients, with only 8% of subjects experienced a worsening of pruritus. Although rituximab was well tolerated, the size of the effect was limited in both studies leading both to conclude that rituximab has limited efficacy in PBC for the treatment of liver disease but an ongoing study is being performed for the treatment of fatigue (NCT02376335) [94].

Based upon genome wide association studies identifying the IL-12 pathway as susceptibility genes and other evidence linking IL-12 and IL-23 mediated Th1/Th17 signaling pathway with the etiopathogenesis of PBC, a trial of ustekinumab, a humanized monoclonal antibody directed against interleukins 12 and 23 through the shared interleukin 23p40 chain, was initiated in PBC [6, 95]. In this phase II multi-center study evaluating the efficacy and safety of ustekinumab in 20 patients with PBC, no patient achieved the primary endpoint of a reduction in serum alkaline phosphatase of at least 40% at week 12 or 28 (NCT01389973).

The pathogenesis of PBC is primarily attributed to auto-reactive T cells [96-98], the activation of which requires co-stimulatory signaling via CD28 by engagement with CD80 or CD86 on antigen presenting cells [99]. Cytotoxic T-lymphocyte antigen 4 (CTLA-4) is induced on the T-cell surface 24–48 hours after activation and attenuates CD28-mediated co-stimulation as a means to prevent over reactivity [100]. CTLA-4 immunoglobulin (CTLA-4 Ig) is a recombinant fusion protein comprising a fragment of the Fc domain of human IgG1 and the extracellular domain of human CTLA-4 [101-104] and in its soluble form inhibits T-cell activation by selectively modulating co-stimulation by binding to CD80/86, and blocking its interaction with CD28. CTLA-4 Ig has been investigated in 2 murine models of PBC including the xenobiotic-induced model and the transgenic model expressing a dominant negative TGF-β receptor II (dnTGFβRII)[105]. CTLA-4 Ig treatment, started one day before the immunization with the xenobiotic 2-octynoic acid, completely inhibited the PBC-like bile duct damage, AMA production and intra-hepatic T-cell infiltrates [105]. When given after induction of PBC, CTLA-4 Ig did not reduce the AMA but did significantly reduce the liver inflammation. Interestingly, in the dnTGF-βRII model which also develops severe colitis, CTLA-4 Ig improved the liver inflammation but exacerbated the colitis. Currently, a clinical trial with CTLA-4 Ig (abatacept) is ongoing in PBC patients with an incomplete response to UDCA or intolerant to UDCA (NCT02078882).

CXCL10 (also known as interferon-γ-inducible 10-kd protein or IP-10) can attract T lymphocytes by binding CXCR3 expressed on activated $CD4^+$ T cells [106]. In the pathogenesis of PBC, recruitment of lymphocytes in the portal tracts has a pivotal role, while Th1 cells expressing IFN-γ are mainly present in the inflammatory infiltrate around the injured bile ducts. CXCL10 is specifically produced in inflammatory areas where it may help recruit T cells to the hepatic lesions [107]. An open-label multicenter study with NI-0801, a human anti-CXCL10 monoclonal antibody, was performed in 40 PBC patients with an incomplete response to UDCA (NCT01430429), but the study was terminated due to lack of efficacy.

The CD40-antagonist monoclonal antibody, FFP104, blocks the interaction of the CD40-CD40L signal, an important receptor-ligand interaction during activation of antigen presenting cells, induces a variety of downstream effects, such as surface T cell priming, B-cell terminal maturation, and immunoglobulin (Ig) class-switching [108]. A phase I/II open label multicenter, pilot dose escalation study in PBC patients is ongoing with an estimated completion date is December 2016 (NCT02193360).

Anti-fibrotic treatment

Multiple factors are involved in the pathogenesis of disease progression [109]. One aim is to inhibit or reverse fibrosis. This issue has been recently reviewed by Trautwein et al [110]. An interesting target for treatment is integrin αVβ6, which is uniquely up-regulated in activated cholangiocytes and plays an important role in the progression of biliary fibrosis [111]. In an experimental model of cholestasis it has been shown that inhibition of αVβ6 integrin by a non-peptide specific antagonist, significantly inhibited the progression of biliary fibrosis [112]. A humanized monoclonal antibody, STX-100, which inhibits αVβ6, is currently under study to treat pulmonary fibrosis in a phase II study (NCT01371305) and chronic allograft nephropathy (NCT00878761). Moreover, simtuzumab, a monoclonal antibody inhibitor of lysyl oxidase homolog 2 (LOXL2), is being used in experimental human studies in NASH and primary sclerosing cholangitis (NCT01672879 and NCT01672853). Finally, pentoxiphylline (PTX), a methylxanthine derivative that inhibits pro-inflammatory cytokines, has potential anti-fibrotic effects [113], is currently being studied in a clinical trial including PBC patients non responsive to UDCA, but no data are available (NCT01249092).

Stem cells

Umbilical cord mesenchymal stem cells (UC-MSC) have received significant attention because of their potential modulation of the immune system by increasing the number of T-regulatory cells and blocking clonal expansion of activated T cells. Mesenchymal stem cells have been studied to treat several autoimmune diseases [114-117], including PBC [116, 117]. A randomized study in PBC is now ongoing comparing 12 weeks of treatment with UC-MSC and UDCA and 12 weeks of placebo and UDCA (NCT01662973). In contrast, hematopoietic stem cell transplantation has been proposed as a way to “reset” the immune system following high-dose chemotherapy to ablate, or nearly ablate, the immune system. A phase I study (NCT00393185) is ongoing in PBC patients with end-stage liver disease with pruritus unresponsive to medical therapy or with more than 50% probability of dying or needing a liver transplant. Patients are treated with high dose cyclophosphamide, fludarabine and alemtuzumab, a monoclonal antibody to CD52 that is cytotoxic to mature lymphocytes, followed by infusion of stem cells previously collected from a patient's sibling.

Symptomatic treatments

In addition to the long term progression of liver fibrosis, patients with PBC also have a reduced quality of life due to associated symptoms including fatigue and pruritus (Table 5). Modafinil has been studied for fatigue in PBC in 3 pilot studies in which it was administered orally at an initial dose of 100 mg, with an increasing dosage to 200 mg if tolerated [118, 119]. The results were promising in all three trials, with an improvement in at least 70% of cases. The duration of follow-up ranged between 2 and 15 months. However, a long-term follow-up of patients included in one original study [120] found that 66% of patients failed to tolerate modafinil long-term, but those who tolerated it had an improvement in their quality of life [121].

Pruritus is a common symptom of PBC and can range from mild to severe. Its pathogenesis is unclear, but for many years it was thought to be caused by accumulation of pruritogens

produced within the liver and normally excreted in the bile. However, pruritus is not present in all patients with cholestasis; tends to fluctuate during the course of the disease; and has a circadian rhythm with maximum peak in the evening [122]. Many endogenous substances associated with pruritus, including opioid peptides and serotonin together with bile acids have been studied as a potential targets for pruritus (Fig. 1). Cholestyramine, a bile acid sequestrant, can ameliorate the pruritus of PBC patients and is recommended as first-line therapy [123]. Through similar mechanism, the ASBT inhibitor LUM001 is being studied for the treatment of pruritus in PBC and other conditions of cholestasis. Rifampicin is a strong hepatic drug metabolizing enzyme (DME) inducing agent and nuclear receptor-pregnane X receptor (PXR) agonist, which can inhibit bile acid synthesis through PXR [124]. Several studies suggest that rifampicin may be effective for controlling pruritus in PBC patients [125, 126], but can cause potentially serious adverse effects in approximately 10% of patients, including drug-induced hepatitis, hemolysis, renal impairment and metabolic interference with other agents (i.e. antidepressants) [127]. Opiate antagonists have been shown to ameliorate pruritus in several trials, including a double-blind, randomized, placebo-controlled study of naloxone infusions [128]. The role of opioid receptors as a target for pruritus therapy has not been completely elucidated; indeed, a scientific hypothesis suggests that plasma from patients with cholestasis and pruritus contains a factor that might induce itching by a central opioid-mediated mechanism [129]. An unexpectedly beneficial side effect of sertraline on pruritus was reported in a cohort of PBC patients [130]. Following this observation, an open-label study to determine a dose with optimal efficacy and tolerability was designed [131]. After a washout period, 12 patients were included in a randomized, double-blind, placebo-controlled trial. Itch scores, evaluated using a visual analog scale, improved in patients taking sertraline, but worsened in those taking placebo [131]. A validation of this study has never been performed. In our experience, approximately 30% of patients with PBC and severe pruritus respond to sertraline administration (data unpublished).

One study [132] may shed light on the pathogenesis of pruritus in cholestasis. Lysophosphatidic acid (LPA), a bioactive phospholipid produced extracellularly by autotaxin (ATX), is a potential mediator of pruritus specifically due to cholestasis. In addition, colesevelam, a bile salt sequestrant, but not placebo, effectively reduced total serum bile salts and fibroblast growth factor 19 (FGF19) levels in cholestatic patients, but only marginally altered pruritus intensity and ATX activity [132]. When patients with severe pruritus underwent molecular adsorbents recirculation system (MARS) or nasobiliary drainage, the pruritus was reduced, and simultaneously autotaxin levels were dropped, demonstrating a significant correlation between improvement of itching and reduction in autotaxin activity [132]. Therefore, LPA-receptor blockers and ATX inhibitors should be considered for future evaluation in the treatment of pruritus in cholestasis [133]. In addition to LUM001, two other agents are now under study for controlling pruritus in cholestatic liver diseases: GSK2330672 and NGM282. GSK2330672 is a highly potent, non-absorbable apical sodium-dependent bile acid transporter inhibitor which has been recently studied for its properties in the treatment of type 2 diabetes [134]. A randomized, double-blind cross-over placebo-controlled trial to assess safety and tolerability of GSK2330672 in subjects with PBC and symptoms of pruritus is ongoing. The total duration of the study will be 45

days (for screening and treatment) (NCT01899703). NGM282, an engineered protein variant of the human hormone FGF19, is a potent regulator of bile acid synthesis. A phase I/II, open multicenter study in patients with PBC is ongoing (NCT02026401).

Expert Commentary

UDCA has been the main treatment for PBC during the last 25 years. Following the introduction of UDCA, the natural history of PBC has dramatically changed, causing an improvement in transplant-free survival in patient responders to UDCA. However, up to 40% of patients do not respond to UDCA, with consequently higher risk of disease progression and mortality. Many new agents have been proposed for the treatment of PBC, targeting different aspects of its pathogenesis, primarily targeting autoimmunity, cholestasis, and symptoms that affect the quality of life. The majority of the trials are still ongoing. None of the new drugs, however, have demonstrated a “revolutionary” treatment for PBC.

Five-year view

PBC is a relatively common cholestatic liver disease, easy to be diagnosed, with a long natural history and a slow progression to end-stage liver disease. Nevertheless, multiple factors are involved in the pathogenesis of disease progression, including genetic factors. Management of PBC during the next five years should take into account that the new approach to PBC patients should focus on risk stratification for disease progression. Thus, emerging therapies will be applied tailoring the individual risk of patients in fibrosis progression and in improvement of quality of life. The concept of irreversibility of cirrhosis is not a “dogma”, hence future clinical trials must keep into account that regression of fibrosis is a critical important end-point to be considered.

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References

Reference annotations

* Of interest

** Of considerable interest

1*. Gershwin ME, Mackay IR, Sturgess A, et al. Identification and specificity of a cDNA encoding the 70 kd mitochondrial antigen recognized in primary biliary cirrhosis. J Immunol. 1987; 138:3525–31. [PubMed: 3571977] [Original paper reporting the identification of the antimitochondrial antibody antigen.]

2. Beuers U, Gershwin ME. Unmet challenges in immune-mediated hepatobiliary diseases. Clin Rev Allergy Immunol. 2015; 48:127–31. [PubMed: 25820618]

3. Bian Z, Miao Q, Zhong W, et al. Treatment of cholestatic fibrosis by altering gene expression of Cthrc1: Implications for autoimmune and non-autoimmune liver disease. J Autoimmun. 2015

4. Han Y, Jiang Z, Chen Z, et al. Pathogen-expanded CD11b+ invariant NKT cells feedback inhibit T cell proliferation via membrane-bound TGF-beta1. J Autoimmun. 2015; 58:21–35. [PubMed: 25592391]

5. Hirschfield GM, Siminovitch KA. Genetics in PBC: what do the “risk genes” teach us? Clin Rev Allergy Immunol. 2015; 48:176–81. [PubMed: 24744192]
6. Yang CY, Ma X, Tsuneyama K, et al. IL-12/Th1 and IL-23/Th17 biliary microenvironment in primary biliary cirrhosis: implications for therapy. Hepatology. 2014; 59:1944–53. [PubMed: 24375552]
7. Invernizzi P. Liver auto-immunology: the paradox of autoimmunity in a tolerogenic organ. J Autoimmun. 2013; 46:1–6. [PubMed: 24012346]
8. Katsumi T, Tomita K, Leung PS, et al. Animal models of primary biliary cirrhosis. Clin Rev Allergy Immunol. 2015; 48:142–53. [PubMed: 25771770]
9. Kawata K, Yang GX, Ando Y, et al. Clonality, activated antigen-specific CD8(+) T cells, and development of autoimmune cholangitis in dnTGFbetaRII mice. Hepatology. 2013; 58:1094–104. [PubMed: 23532950]
10. Leung PS, Wang J, Naiyanetr P, et al. Environment and primary biliary cirrhosis: electrophilic drugs and the induction of AMA. J Autoimmun. 2013; 41:79–86. [PubMed: 23352659]
11. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet. 2015; 385:956–65. [PubMed: 25468160]
12. Lleo A, Oertelt-Prigione S, Bianchi I, et al. Y chromosome loss in male patients with primary biliary cirrhosis. J Autoimmun. 2013; 41:87–91. [PubMed: 23375847]
13. Lleo A, Zhang W, McDonald WH, et al. Shotgun proteomics: identification of unique protein profiles of apoptotic bodies from biliary epithelial cells. Hepatology. 2014; 60:1314–23. [PubMed: 24841946]
14. Pollheimer MJ, Fickert P. Animal models in primary biliary cirrhosis and primary sclerosing cholangitis. Clin Rev Allergy Immunol. 2015; 48:207–17. [PubMed: 25172178]
15. Sun Y, Zhang W, Li B, et al. The coexistence of Sjogren's syndrome and primary biliary cirrhosis: a comprehensive review. Clin Rev Allergy Immunol. 2015; 48:301–15. [PubMed: 25682089]
16. Wang L, Sun Y, Zhang Z, et al. CXCR5+ CD4+ T follicular helper cells participate in the pathogenesis of primary biliary cirrhosis. Hepatology. 2015; 61:627–38. [PubMed: 25042122]
17. Wang YH, Yang W, Yang JB, et al. Systems biologic analysis of T regulatory cells genetic pathways in murine primary biliary cirrhosis. J Autoimmun. 2015; 59:26–37. [PubMed: 25701076]
18. Webb GJ, Siminovitch KA, Hirschfield GM. The immunogenetics of primary biliary cirrhosis: A comprehensive review. J Autoimmun. 2015
19. Yang CY, Leung PS, Adamopoulos IE, et al. The implication of vitamin D and autoimmunity: a comprehensive review. Clin Rev Allergy Immunol. 2013; 45:217–26. [PubMed: 23359064]
20. Yao Y, Yang W, Yang YQ, et al. Distinct from its canonical effects, deletion of IL-12p40 induces cholangitis and fibrosis in interleukin-2Ralpha(−/−) mice. J Autoimmun. 2014; 51:99–108. [PubMed: 24651036]
21. Zhang H, Liu Y, Bian Z, et al. The critical role of myeloid-derived suppressor cells and FXR activation in immune-mediated liver injury. J Autoimmun. 2014; 53:55–66. [PubMed: 24721598]
22. Lindor KD, Gershwin ME, Poupon R, et al. Primary biliary cirrhosis. Hepatology. 2009; 50:291–308. [PubMed: 19554543]
23. European Association for the Study of the L. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol. 2009; 51:237–67. [PubMed: 19501929]
24. Poupon R, Chretien Y, Poupon RE, et al. Is ursodeoxycholic acid an effective treatment for primary biliary cirrhosis? Lancet. 1987; 1:834–6. [PubMed: 2882236]
25. Admirand WH, Small DM. The physicochemical basis of cholesterol gallstone formation in man. J Clin Invest. 1968; 47:1043–52. [PubMed: 5645851]
26. Wang DQ, Carey MC. Characterization of crystallization pathways during cholesterol precipitation from human gallbladder biles: identical pathways to corresponding model biles with three predominating sequences. J Lipid Res. 1996; 37:2539–49. [PubMed: 9017506]

27. Leuschner U, Leuschner M, Sieratzki J, et al. Gallstone dissolution with ursodeoxycholic acid in patients with chronic active hepatitis and two years follow-up. A pilot study. Dig Dis Sci. 1985; 30:642–9. [PubMed: 4006646]

28**. Corpechot C, Carrat F, Bonnand AM, et al. The effect of ursodeoxycholic acid therapy on liver fibrosis progression in primary biliary cirrhosis. Hepatology. 2000; 32:1196–9. [PubMed: 11093724] [Randomized clinical trial demonstrating that UDCA prevented progression of liver fibrosis in PBC.]

29. Lindor KD, Jorgensen RA, Therneau TM, et al. Ursodeoxycholic acid delays the onset of esophageal varices in primary biliary cirrhosis. Mayo Clin Proc. 1997; 72:1137–40. [PubMed: 9413293]

30. Kuiper EM, Hansen BE, de Vries RA, et al. Improved prognosis of patients with primary biliary cirrhosis that have a biochemical response to ursodeoxycholic acid. Gastroenterology. 2009; 136:1281–7. [PubMed: 19208346]

31. Floreani A, Caroli D, Variola A, et al. A 35-year follow-up of a large cohort of patients with primary biliary cirrhosis seen at a single centre. Liver Int. 2011; 31:361–8. [PubMed: 21059170]

32**. Pares A, Caballeria L, Rodes J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic Acid. Gastroenterology. 2006; 130:715–20. [PubMed: 16530513] [Established the long term outcome of PBC patients treated with UDCA who had a biochemical respones to UDCA versus those who did not.]

33. Gong Y, Huang Z, Christensen E, et al. Ursodeoxycholic acid for patients with primary biliary cirrhosis: an updated systematic review and meta-analysis of randomized clinical trials using Bayesian approach as sensitivity analyses. Am J Gastroenterol. 2007; 102:1799–807. [PubMed: 17459023]

34. Corpechot C, Abenavoli L, Rabahi N, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology. 2008; 48:871–7. [PubMed: 18752324]

35. Beuers U, Lindor KD. A major step towards effective treatment evaluation in primary biliary cirrhosis. J Hepatol. 2011; 55:1178–80. [PubMed: 21703168]

36. Lammers WJ, van Buuren HR, Hirschfield GM, et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. Gastroenterology. 2014; 147:1338–49. e5. quiz e15. [PubMed: 25160979]

37. Carbone M, Sharp SJ, Flack S, et al. The UK-PBC risk scores: Derivation and validation of a scoring system for long-term prediction of end-stage liver disease in primary biliary cirrhosis. Hepatology. 2015

38. Makishima M, Okamoto AY, Repa JJ, et al. Identification of a nuclear receptor for bile acids. Science. 1999; 284:1362–5. [PubMed: 10334992]

39. Rader DJ. Liver X receptor and farnesoid X receptor as therapeutic targets. Am J Cardiol. 2007; 100:n15–9. [PubMed: 18047847]

40**. Hirschfield GM, Mason A, Luketic V, et al. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. Gastroenterology. 2015; 148:751–61. e8. [PubMed: 25500425] [Phase 2 study of obeticholic acid establishing efficacy in improving liver biochemistries in PBC patients with an inadequate response to UDCA.]

41. Neuschwander-Tetri BA. Targeting the FXR nuclear receptor to treat liver disease. Gastroenterology. 2015; 148:704–6. [PubMed: 25724453]

42. Invernizzi P, Setchell KD, Crosignani A, et al. Differences in the metabolism and disposition of ursodeoxycholic acid and of its taurine-conjugated species in patients with primary biliary cirrhosis. Hepatology. 1999; 29:320–7. [PubMed: 9918905]

43. Uriz M, Saez E, Prieto J, et al. Ursodeoxycholic acid is conjugated with taurine to promote secretin-stimulated biliary hydrocholeresis in the normal rat. PLoS One. 2011; 6:e28717. [PubMed: 22194894]

44. Fickert P, Wagner M, Marschall HU, et al. 24-norUrsodeoxycholic acid is superior to ursodeoxycholic acid in the treatment of sclerosing cholangitis in Mdr2 (Abcb4) knockout mice. Gastroenterology. 2006; 130:465–81. [PubMed: 16472600]

45. Fiorotto R, Scirpo R, Trauner M, et al. Loss of CFTR affects biliary epithelium innate immunity and causes TLR4-NF-kappaB-mediated inflammatory response in mice. Gastroenterology. 2011; 141:1498–508. 1508, e1–5. [PubMed: 21712022]
46. Ghonem NS, Assis DN, Boyer JL. Fibrates and cholestasis. Hepatology. 2015; 62:635–43. [PubMed: 25678132]
47. Akbar SM, Furukawa S, Nakanishi S, et al. Therapeutic efficacy of decreased nitrite production by bezafibrate in patients with primary biliary cirrhosis. J Gastroenterol. 2005; 40:157–63. [PubMed: 15770399]
48. Day AP, Feher MD, Chopra R, et al. The effect of bezafibrate treatment on serum alkaline phosphatase isoenzyme activities. Metabolism. 1993; 42:839–42. [PubMed: 8102192]
49. Dohmen K, Mizuta T, Nakamuta M, et al. Fenofibrate for patients with asymptomatic primary biliary cirrhosis. World J Gastroenterol. 2004; 10:894–8. [PubMed: 15040040]
50. Dohmen K, Tanaka H, Haruno M. Effectiveness of fenofibrate in comparison to bezafibrate for patients with asymptomatic primary biliary cirrhosis. Fukuoka Igaku Zasshi. 2013; 104:350–61. [PubMed: 24511666]
51. Han XF, Wang QX, Liu Y, et al. Efficacy of fenofibrate in Chinese patients with primary biliary cirrhosis partially responding to ursodeoxycholic acid therapy. J Dig Dis. 2012; 13:219–24. [PubMed: 22435507]
52. Hazzan R, Tur-Kaspa R. Bezafibrate treatment of primary biliary cirrhosis following incomplete response to ursodeoxycholic acid. J Clin Gastroenterol. 2010; 44:371–3. [PubMed: 19881358]
53. Honda A, Ikegami T, Nakamuta M, et al. Anticholestatic effects of bezafibrate in patients with primary biliary cirrhosis treated with ursodeoxycholic acid. Hepatology. 2013; 57:1931–41. [PubMed: 22911624]
54. Hosonuma K, Sato K, Yamazaki Y, et al. A prospective randomized controlled study of long-term combination therapy using ursodeoxycholic acid and bezafibrate in patients with primary biliary cirrhosis and dyslipidemia. Am J Gastroenterol. 2015; 110:423–31. [PubMed: 25732417]
55. Itakura J, Izumi N, Nishimura Y, et al. Prospective randomized crossover trial of combination therapy with bezafibrate and UDCA for primary biliary cirrhosis. Hepatol Res. 2004; 29:216–222. [PubMed: 15288014]
56. Iwasaki S, Akisawa N, Saibara T, et al. Fibrate for treatment of primary biliary cirrhosis. Hepatol Res. 2007; 37(Suppl 3):S515–7. [PubMed: 17931214]
57. Iwasaki S, Ohira H, Nishiguchi S, et al. The efficacy of ursodeoxycholic acid and bezafibrate combination therapy for primary biliary cirrhosis: A prospective, multicenter study. Hepatol Res. 2008; 38:557–64. [PubMed: 18452482]
58. Kanda T, Yokosuka O, Imazeki F, et al. Bezafibrate treatment: a new medical approach for PBC patients? J Gastroenterol. 2003; 38:573–8. [PubMed: 12825134]
59. Kita R, Takamatsu S, Kimura T, et al. Bezafibrate may attenuate biliary damage associated with chronic liver diseases accompanied by high serum biliary enzyme levels. J Gastroenterol. 2006; 41:686–92. [PubMed: 16933007]
60. Kurihara T, Niimi A, Maeda A, et al. Bezafibrate in the treatment of primary biliary cirrhosis: comparison with ursodeoxycholic acid. Am J Gastroenterol. 2000; 95:2990–2. [PubMed: 11051391]
61. Lens S, Leoz M, Nazal L, et al. Bezafibrate normalizes alkaline phosphatase in primary biliary cirrhosis patients with incomplete response to ursodeoxycholic acid. Liver Int. 2014; 34:197–203. [PubMed: 23998489]
62. Levy C, Peter JA, Nelson DR, et al. Pilot study: fenofibrate for patients with primary biliary cirrhosis and an incomplete response to ursodeoxycholic acid. Aliment Pharmacol Ther. 2011; 33:235–42. [PubMed: 21083674]
63. Liberopoulos EN, Florentin M, Elisaf MS, et al. Fenofibrate in primary biliary cirrhosis: a pilot study. Open Cardiovasc Med J. 2010; 4:120–6. [PubMed: 20556204]
64. Miyaguchi S, Ebinuma H, Imaeda H, et al. A novel treatment for refractory primary biliary cirrhosis? Hepatogastroenterology. 2000; 47:1518–21. [PubMed: 11148991]

65. Nakai S, Masaki T, Kurokohchi K, et al. Combination therapy of bezafibrate and ursodeoxycholic acid in primary biliary cirrhosis: a preliminary study. Am J Gastroenterol. 2000; 95:326–7. [PubMed: 10638623]

66. Nakamuta M, Enjoji M, Kotoh K, et al. Long-term fibrate treatment for PBC. J Gastroenterol. 2005; 40:546–7. [PubMed: 15942724]

67. Ohira H, Sato Y, Ueno T, et al. Fenofibrate treatment in patients with primary biliary cirrhosis. Am J Gastroenterol. 2002; 97:2147–9. [PubMed: 12190200]

68. Ohmoto K, Mitsui Y, Yamamoto S. Effect of bezafibrate in primary biliary cirrhosis: a pilot study. Liver. 2001; 21:223–4. [PubMed: 11422787]

69. Ohmoto K, Yoshioka N, Yamamoto S. Long-term effect of bezafibrate on parameters of hepatic fibrosis in primary biliary cirrhosis. J Gastroenterol. 2006; 41:502–3. [PubMed: 16799896]

70. Takeuchi Y, Ikeda F, Fujioka S, et al. Additive improvement induced by bezafibrate in patients with primary biliary cirrhosis showing refractory response to ursodeoxycholic acid. J Gastroenterol Hepatol. 2011; 26:1395–401. [PubMed: 21443659]

71. Walker LJ, Newton J, Jones DE, et al. Comment on biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology. 2009; 49:337–8. author reply 338. [PubMed: 19035342]

72. Yano K, Kato H, Morita S, et al. Is bezafibrate histologically effective for primary biliary cirrhosis? Am J Gastroenterol. 2002; 97:1075–7. [PubMed: 12003404]

73. Cuperus FJ, Halilbasic E, Trauner M. Fibrate treatment for primary biliary cirrhosis. Curr Opin Gastroenterol. 2014; 30:279–86. [PubMed: 24625898]

74. Zhang Y, Li S, He L, et al. Combination therapy of fenofibrate and ursodeoxycholic acid in patients with primary biliary cirrhosis who respond incompletely to UDCA monotherapy: a meta-analysis. Drug Des Devel Ther. 2015; 9:2757–66.

75. Wu SJ, Yang YH, Tsuneyama K, et al. Innate immunity and primary biliary cirrhosis: activated invariant natural killer T cells exacerbate murine autoimmune cholangitis and fibrosis. Hepatology. 2011; 53:915–25. [PubMed: 21374662]

76. Bernuzzi F, Fenoglio D, Battaglia F, et al. Phenotypical and functional alterations of CD8 regulatory T cells in primary biliary cirrhosis. J Autoimmun. 2010; 35:176–80. [PubMed: 20638239]

77. Kita H. Autoreactive CD8-specific T-cell response in primary biliary cirrhosis. Hepatol Res. 2007; 37(Suppl 3):S402–5. [PubMed: 17931194]

78. Wolfhagen FH, van Buuren HR, Schalm SW. Combined treatment with ursodeoxycholic acid and prednisone in primary biliary cirrhosis. Neth J Med. 1994; 44:84–90. [PubMed: 8202208]

79. Wolfhagen FH, van Hoogstraten HJ, van Buuren HR, et al. Triple therapy with ursodeoxycholic acid, prednisone and azathioprine in primary biliary cirrhosis: a 1-year randomized, placebo-controlled study. J Hepatol. 1998; 29:736–42. [PubMed: 9833911]

80. Lie TS, Preissinger H. [Successful treatment of primary biliary cirrhosis with cyclosporin]. Dtsch Med Wochenschr. 1990; 115:698–702. [PubMed: 2335133]

81. Wiesner RH, Ludwig J, Lindor KD, et al. A controlled trial of cyclosporine in the treatment of primary biliary cirrhosis. N Engl J Med. 1990; 322:1419–24. [PubMed: 2184355]

82. Combes B, Emerson SS, Flye NL, et al. Methotrexate (MTX) plus ursodeoxycholic acid (UDCA) in the treatment of primary biliary cirrhosis. Hepatology. 2005; 42:1184–93. [PubMed: 16250039]

83. Treiber G, Malfertheiner P. Mycophenolate mofetil for the treatment of primary biliary cirrhosis in patients with an incomplete response to ursodeoxycholic acid. J Clin Gastroenterol. 2005; 39:837–8. author reply 838. [PubMed: 16145353]

84. Angulo P, Jorgensen RA, Keach JC, et al. Oral budesonide in the treatment of patients with primary biliary cirrhosis with a suboptimal response to ursodeoxycholic acid. Hepatology. 2000; 31:318–23. [PubMed: 10655252]

85*. Leuschner M, Maier KP, Schlichting J, et al. Oral budesonide and ursodeoxycholic acid for treatment of primary biliary cirrhosis: results of a prospective double-blind trial. Gastroenterology. 1999; 117:918–25. [PubMed: 10500075] [First study to demonstrate efficacy of budesonide in PBC patients not repsonding adequately to UDCA.]

86. Rabahi N, Chretien Y, Gaouar F, et al. Triple therapy with ursodeoxycholic acid, budesonide and mycophenolate mofetil in patients with features of severe primary biliary cirrhosis not responding to ursodeoxycholic acid alone. Gastroenterol Clin Biol. 2010; 34:283–7. [PubMed: 20417047]
87. Rautiainen H, Karkkainen P, Karvonen AL, et al. Budesonide combined with UDCA to improve liver histology in primary biliary cirrhosis: a three-year randomized trial. Hepatology. 2005; 41:747–52. [PubMed: 15754377]
88. Hempfling W, Grunhage F, Dilger K, et al. Pharmacokinetics and pharmacodynamic action of budesonide in early- and late-stage primary biliary cirrhosis. Hepatology. 2003; 38:196–202. [PubMed: 12830002]
89. Chazouilleres O, Wendum D, Serfaty L, et al. Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy. Hepatology. 1998; 28:296–301. [PubMed: 9695990]
90. Yoshioka Y, Taniai M, Hashimoto E, et al. Clinical profile of primary biliary cirrhosis with features of autoimmune hepatitis: Importance of corticosteroid therapy. Hepatol Res. 2014; 44:947–55. [PubMed: 23879195]
91. Reff ME, Carner K, Chambers KS, et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood. 1994; 83:435–45. [PubMed: 7506951]
92*. Tsuda M, Moritoki Y, Lian ZX, et al. Biochemical and immunologic effects of rituximab in patients with primary biliary cirrhosis and an incomplete response to ursodeoxycholic acid. Hepatology. 2012; 55:512–21. [PubMed: 22006563] [First use of a biologic agent for the treatment of PBC demonstrating that B cel depletion led to significant biochemical improvements in PBC patients with an incomplete response to UDCA.]
93. Myers RP, Swain MG, Lee SS, et al. B-cell depletion with rituximab in patients with primary biliary cirrhosis refractory to ursodeoxycholic acid. Am J Gastroenterol. 2013; 108:933–41. [PubMed: 23649186]
94. Freeman HJ. Colitis associated with biological agents. World J Gastroenterol. 2012; 18:1871–4. [PubMed: 22563166]
95. Lleo A, Gershwin ME, Mantovani A, et al. Towards common denominators in primary biliary cirrhosis: the role of IL-12. J Hepatol. 2012; 56:731–3. [PubMed: 22005588]
96. Shimoda S, Van de Water J, Ansari A, et al. Identification and precursor frequency analysis of a common T cell epitope motif in mitochondrial autoantigens in primary biliary cirrhosis. The Journal of clinical investigation. 1998; 102:1831–40. [PubMed: 9819369]
97. Kita H, Lian ZX, Van de Water J, et al. Identification of HLA-A2-restricted CD8(+) cytotoxic T cell responses in primary biliary cirrhosis: T cell activation is augmented by immune complexes cross-presented by dendritic cells. The Journal of experimental medicine. 2002; 195:113–23. [PubMed: 11781370]
98. Kita H, Matsumura S, He XS, et al. Quantitative and functional analysis of PDC-E2-specific autoreactive cytotoxic T lymphocytes in primary biliary cirrhosis. The Journal of clinical investigation. 2002; 109:1231–40. [PubMed: 11994412]
99. Lenschow DJ, Walunas TL, Bluestone JA. CD28/B7 system of T cell costimulation. Annual review of immunology. 1996; 14:233–58.
100. Collins AV, Brodie DW, Gilbert RJ, et al. The interaction properties of costimulatory molecules revisited. Immunity. 2002; 17:201–10. [PubMed: 12196291]
101. Teng GG, Turkiewicz AM, Moreland LW. Abatacept: a costimulatory inhibitor for treatment of rheumatoid arthritis. Expert opinion on biological therapy. 2005; 5:1245–54. [PubMed: 16120053]
102. Rozelle AL, Genovese MC. Efficacy results from pivotal clinical trials with abatacept. Clinical and experimental rheumatology. 2007; 25:S30–4. [PubMed: 17977486]
103. Davis PM, Abraham R, Xu L, et al. Abatacept binds to the Fc receptor CD64 but does not mediate complement-dependent cytotoxicity or antibody-dependent cellular cytotoxicity. The Journal of rheumatology. 2007; 34:2204–10. [PubMed: 17787038]
104. Linsley PS, Brady W, Grosmaire L, et al. Binding of the B cell activation antigen B7 to CD28 costimulates T cell proliferation and interleukin 2 mRNA accumulation. The Journal of experimental medicine. 1991; 173:721–30. [PubMed: 1847722]

105*. Dhirapong A, Yang GX, Nadler S, et al. Therapeutic effect of cytotoxic T lymphocyte antigen 4/immunoglobulin on a murine model of primary biliary cirrhosis. Hepatology. 2013; 57:708–15. [PubMed: 22996325] [Demonstration of the potential efficacy of CTLA-4 Ig in an animal model of PBC.]

106. Hyun JG, Lee G, Brown JB, et al. Anti-interferon-inducible chemokine, CXCL10, reduces colitis by impairing T helper-1 induction and recruitment in mice. Inflamm Bowel Dis. 2005; 11:799–805. [PubMed: 16116313]

107. Nishioji K, Okanoue T, Itoh Y, et al. Increase of chemokine interferon-inducible protein-10 (IP-10) in the serum of patients with autoimmune liver diseases and increase of its mRNA expression in hepatocytes. Clin Exp Immunol. 2001; 123:271–9. [PubMed: 11207658]

108. Herve M, Isnardi I, Ng YS, et al. CD40 ligand and MHC class II expression are essential for human peripheral B cell tolerance. J Exp Med. 2007; 204:1583–93. [PubMed: 17562816]

109. Locke GR 3rd, Therneau TM, Ludwig J, et al. Time course of histological progression in primary biliary cirrhosis. Hepatology. 1996; 23:52–6. [PubMed: 8550048]

110. Trautwein C, Friedman SL, Schuppan D, et al. Hepatic fibrosis: Concept to treatment. J Hepatol. 2015; 62:S15–24. [PubMed: 25920084]

111. Inamine T, Nakamura M, Kawauchi A, et al. A polymorphism in the integrin alphaV subunit gene affects the progression of primary biliary cirrhosis in Japanese patients. J Gastroenterol. 2011; 46:676–86. [PubMed: 21116829]

112. Popov Y, Patsenker E, Stickel F, et al. Integrin alphavbeta6 is a marker of the progression of biliary and portal liver fibrosis and a novel target for antifibrotic therapies. J Hepatol. 2008; 48:453–64. [PubMed: 18221819]

113. Peterson TC, Davey K. Effect of acute pentoxifylline treatment in an experimental model of colitis. Aliment Pharmacol Ther. 1997; 11:575–80. [PubMed: 9218085]

114. Woodworth TG, Furst DE. Safety and feasibility of umbilical cord mesenchymal stem cells in treatment-refractory systemic lupus erythematosus nephritis: time for a double-blind placebo-controlled trial to determine efficacy. Arthritis Res Ther. 2014; 16:113. [PubMed: 25166210]

115. Ma L, Zhou Z, Zhang D, et al. Immunosuppressive function of mesenchymal stem cells from human umbilical cord matrix in immune thrombocytopenia patients. Thromb Haemost. 2012; 107:937–50. [PubMed: 22398715]

116. Wang L, Li J, Liu H, et al. Pilot study of umbilical cord-derived mesenchymal stem cell transfusion in patients with primary biliary cirrhosis. J Gastroenterol Hepatol. 2013; 28(Suppl 1): 85–92. [PubMed: 23855301]

117. Wang L, Wang L, Cong X, et al. Human umbilical cord mesenchymal stem cell therapy for patients with active rheumatoid arthritis: safety and efficacy. Stem Cells Dev. 2013; 22:3192–202. [PubMed: 23941289]

118. Jones EA. Personal view: a potential novel treatment for fatigue complicating chronic liver disease--how should its efficacy be evaluated? Aliment Pharmacol Ther. 2006; 23:1113–6. [PubMed: 16611271]

119. Ian Gan S, de Jongh M, Kaplan MM. Modafinil in the treatment of debilitating fatigue in primary biliary cirrhosis: a clinical experience. Dig Dis Sci. 2009; 54:2242–6. [PubMed: 19082890]

120. Kaplan MM, Bonis PA. Modafinil for the treatment of fatigue in primary biliary cirrhosis. Ann Intern Med. 2005; 143:546–7. [PubMed: 16204174]

121. Hardy T, MacDonald C, Jones DE, et al. A follow-up study of modafinil for the treatment of daytime somnolence and fatigue in primary biliary cirrhosis. Liver Int. 2010; 30:1551–2. [PubMed: 20536714]

122. Bergasa NV. Pruritus in primary biliary cirrhosis: pathogenesis and therapy. Clin Liver Dis. 2008; 12:385–406. [PubMed: 18456187]

123. Moritoki Y, Lian ZX, Lindor K, et al. B-cell depletion with anti-CD20 ameliorates autoimmune cholangitis but exacerbates colitis in transforming growth factor-beta receptor II dominant negative mice. Hepatology. 2009; 50:1893–903. [PubMed: 19877182]

124. Li T, Chiang JY. Mechanism of rifampicin and pregnane X receptor inhibition of human cholesterol 7 alpha-hydroxylase gene transcription. Am J Physiol Gastrointest Liver Physiol. 2005; 288:G74–84. [PubMed: 15331348]

125. Ghent CN, Carruthers SG. Treatment of pruritus in primary biliary cirrhosis with rifampin. Results of a double-blind, crossover, randomized trial. Gastroenterology. 1988; 94:488–93. [PubMed: 3275568]

126. Podesta A, Lopez P, Terg R, et al. Treatment of pruritus of primary biliary cirrhosis with rifampin. Dig Dis Sci. 1991; 36:216–20. [PubMed: 1988266]

127. Prince MI, Burt AD, Jones DE. Hepatitis and liver dysfunction with rifampicin therapy for pruritus in primary biliary cirrhosis. Gut. 2002; 50:436–9. [PubMed: 11839728]

128. Bergasa NV, Alling DW, Talbot TL, et al. Effects of naloxone infusions in patients with the pruritus of cholestasis. A double-blind, randomized, controlled trial. Ann Intern Med. 1995; 123:161–7. [PubMed: 7598296]

129. Bergasa NV. The pruritus of cholestasis: facts. Hepatology. 2015; 61:2114. [PubMed: 25345776]

130. Browning J, Combes B, Mayo MJ. Long-term efficacy of sertraline as a treatment for cholestatic pruritus in patients with primary biliary cirrhosis. Am J Gastroenterol. 2003; 98:2736–41. [PubMed: 14687826]

131. Mayo MJ, Handem I, Saldana S, et al. Sertraline as a first-line treatment for cholestatic pruritus. Hepatology. 2007; 45:666–74. [PubMed: 17326161]

132. Kremer AE, van Dijk R, Leckie P, et al. Serum autotaxin is increased in pruritus of cholestasis, but not of other origin, and responds to therapeutic interventions. Hepatology. 2012; 56:1391–400. [PubMed: 22473838]

133. Beuers U, Kremer AE, Bolier R, et al. Pruritus in cholestasis: facts and fiction. Hepatology. 2014; 60:399–407. [PubMed: 24807046]

134. Wu Y, Aquino CJ, Cowan DJ, et al. Discovery of a highly potent, nonabsorbable apical sodium-dependent bile acid transporter inhibitor (GSK2330672) for treatment of type 2 diabetes. J Med Chem. 2013; 56:5094–114. [PubMed: 23678871]

Key issues

- PBC is a model autoimmune disease with chronic cholestasis with a slow progression towards end-stage liver disease. At least 50% of patients complain of symptoms which alter the quality of life, including fatigue and pruritus.
- UDCA has changed the natural history of PBC patients dramatically, however, up to 40% of patients only partially or incompletely respond to UDCA.
- There are subgroups of patients with a more aggressive disease accompanied by complication of portal hypertension.
- Several new agents have been identified as new therapies, targeting cholestasis, autoimmunity, fibrosis and symptoms which alter the quality of life.
- Future research will look at combining therapies with UDCA, as well other agents including obeticholic acid and/or new biologic treatment.

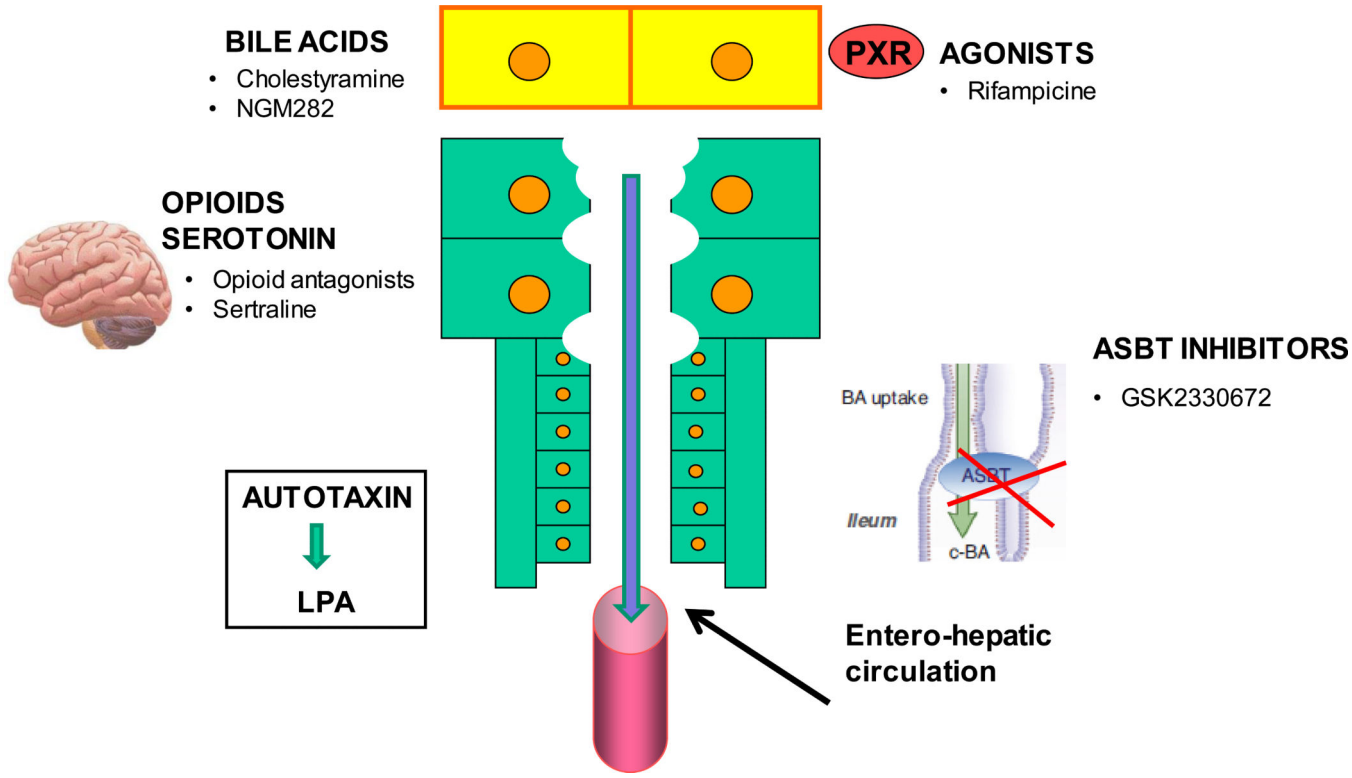

Figure 1.
Targets of pruritus in cholestasis.

Table 1

Studies involving fibrates in PBC

Drug	Studies (n)	Daily dose (mg)	Patients (n)	Combination with UDCA	Outcome	Adverse Events
Bezafibrate	20	200-400	2-45	18 studies	Reduction of ALP, GGT, IgM, AST, ALT, fatigue, pruritus, total cholesterol, TG, serum markers of fibrosis, APRI score, liver stiffness unchanged	Increase in serum creatinine, mild myalgia in 2 studies, mild GI discomfort (nausea or heartburn) in 2 studies
Fenofibrate	7	80-200	7-22	7 studies	Reduction of ALP, GGT, IgM, AST, ALT, pruritus, AMA, serum cholesterol, TG, IL1,6, increase of Apo AII e Apo CII	Severe erosive esophagitis in 1 study, increase in AST and ALT in 1 study, increase in serum creatinine in 1 study

ALP, alkaline phosphatase; GGT, gamma glutamyl transferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AMA, anti-mitochondrial antibodies; APRI, AST-platelet ratio index.

Table 2

Studies involving Budesonide in PBC

Author	Patients	Trial	Duration	Outcome
Leuschner[85]	20	Double blind, 2 groups: 1) UDCA+Bud (3 mg tid) 2) UDCA + placebo	2 years	Significant improvement in LFTs in group 1; improvement in liver histology
Rautiainen[87]	77	Randomized, 2 groups: 1) UDCA+Bud (3 mg bds) 2) UDCA alone	3 years	Improvement in liver histology in group 1
Angulo[84]	22	UDCA + Bud Pilot	A mean of 46 months	No efficacy
Rabahi[86]	15	UDCA + Bud + MMF	3 years	Normalization of LFTs in 41% of cases; improvement in liver histology
NCT00746486	?	Phase III randomized placebo-controlled trial with UDCA (12-16 mg/Kg of body weight + (Bud 3mg tid vs UDCA + placebo)	3 years	ongoing

UCDA, ursodeoxycholic acid; Bud, budesonide; MMF, mycophenolate mofetil.

Table 3

Studies with Rituximab in PBC

Author	Patients	Trial	Duration	Outcome
Tsuda[92]	6	Open-label	2 doses of 1000 mg separated by 2 weeks and follow-up of 52 weeks	Reversion of several immunologic abnormalities and significant reduction of ALP up to 36 weeks
Myers [93]	14	Open-label	2 doses of 1000 mg separated by 2 weeks and follow-up for 6 months	Effective B-cell depletion 1n 13 patients, significant reduction of ALP at 6 months, improvement in pruritus in 60% of patients at 12 months

ALP, alkaline phosphatase.

Table 4

Current studies with stem cells in PBC

Trial	Type	Criteria	Protocol
NCT00393185	Phase I	End-stage PBC with more than 50% or dying or need for liver transplant in the following 36 months	Treatment with high dose cyclophosphamide, Ffudarabine and alemtuzumab followed by infusion of UC-MSC
NCT0166293	PhaseI/II	PBC with cirrhosis and liver failure	12 weeks of UC-SMS + UDCA vs placebo UDCA

UC-MSC=Umbilical cord mesenchymal stem cells

Table 5

Pilot studies with modafinil for daily somnolence in PBC

Author	Patients	Daily dose	Duration	Outcome
Kaplan[120]	5	100-200 mg	15 months	Improvement
Jones[121]	21	100 mg then titration	2 months	Significant improvement
Gan[119]	43	100-200 mg	3 days (if effective indefinitely)	73% effective