REVIEW

Primary biliary cholangitis: new treatments for an old disease

Hirsh D Trivedi,¹ Blanca Lizaola,² Elliot B Tapper,³ Alan Bonder¹

¹Liver Center, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA

²Department of Internal Medicine, St. Elizabeth's Medical Center, Brighton, Massachusetts, USA

³Department of Hepatology, University of Michigan, Ann Arbor, Michigan, USA

Correspondence to

Dr Alan Bonder, Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School, 110 Francis Street, Suite 8E, Boston, MA 02215, USA; abonder@bidmc.harvard.edu

Received 1 August 2016

Revised 4 October 2016

Accepted 17 October 2016

Published Online First

3 November 2016

ABSTRACT

Primary biliary cholangitis (PBC) is an immunological condition that causes a significant health disturbance and dramatically reduces the quality of life for those affected with the disease. It is a potentially fatal disease that can lead to multiple hepatic and extrahepatic complications. Having adequate therapeutic interventions that can improve the course of the disease is imperative in reducing the associated morbidity and mortality. Ursodeoxycholic acid (UDCA) is the gold standard therapy. However, it has been associated with suboptimal response rates in a significant proportion of patients. Despite UDCA, approximately 35%–40% of individuals with PBC still experience a progression of the disease, leading to liver failure and requiring liver transplantation. Recent studies of new pharmacological approaches have shown beneficial outcomes. Some of these agents can now be applied to a clinical scenario. In this review article, we will outline the new and emerging treatments for PBC.

INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic autoimmune, cholestatic condition. PBC can result in cirrhosis, liver failure and ultimately require liver transplantation.¹ Individuals with PBC suffer from significant morbidity^{2–3} and experience a multitude of non-specific symptoms. Of these, fatigue, bone disease and pruritus are common clinical manifestations that have a significant impact on quality of life.^{2–4} The several complications associated with this disease highlight the importance of having sufficient therapies for its management.

The therapy for PBC has evolved over the recent years. Ursodeoxycholic acid (UDCA) remains the conventional therapy.¹ It is recommended in any stage of PBC with elevated alkaline phosphatase (ALP) levels^{1–5} at an optimal dose of

13–15 mg/kg/day.⁶ UDCA not only markedly improves basic liver function tests^{7–8} but it also improves histological characteristics, delays the progression to cirrhosis and reduces the need for liver transplantation.^{9–13} The response to UDCA can be measured through histological or biochemical parameters. Although the definition of ‘biochemical response’ varies among different studies, many patients taking UDCA have shown an adequate improvement in biochemical parameters that has enhanced prognosis and long-term survival.^{14–15} However, evidence shows that 30%–40% of individuals have a suboptimal response to UDCA therapy and have an increased chance of complications and eventually require liver transplantation.^{15–16} These outcomes have led to further investigation of alternative therapies to optimise the management of PBC. In this article, we will review the current and investigational therapies, some of which can be applied to clinical practice.

MECHANISM OF PBC AND ITS THERAPY

The pathogenesis of PBC remains unknown. The toxic accumulation of bile acids, T cell-mediated toxicity and the interaction between mitochondrial auto-antigens and antimitochondrial antibodies are thought to play a key role and contribute to immune-mediated destruction of intrahepatic bile ducts.¹⁷ This leads to portal inflammation and fibrosis.¹⁷ UDCA, a naturally occurring bile acid, protects cholangiocytes from bile acid toxicity. Other endogenous bile acids have recently been discovered to act as natural ligands and bind to nuclear and membrane receptors. This interaction reduces the cytotoxic effects of bile acids. The newer therapeutic agents involve the

To cite: Trivedi HD, Lizaola B, Tapper EB, et al. *Frontline Gastroenterology* 2017;**8**:29–36.

targeting of these nuclear and membrane receptors to regulate bile acid synthesis and flow. Optimising the regulation of bile acids and minimising their toxic accumulation is the concept of therapy in PBC. The biochemical response is used to measure the efficacy of treatment and is a vital component to managing patients with PBC.

Measuring biochemical response

Serial histological evaluation by liver biopsy is often difficult when evaluating response to therapy. The measurement of biochemical response is more widely used. The definition of biochemical response has varied in the context of PBC. In 2011, a study of 165 patients with early-stage PBC defined an adequate biochemical response as a normal bilirubin level with ALP and aspartate aminotransferase (AST) levels <1.5 times the upper limit of normal at 6–12 months after initiation of therapy.¹⁸ A separate study, which analysed 187 patients prospectively, found that the biochemical response could be measured as early as 6 months into therapy.¹⁹ In a more recent meta-analysis with 4845 patients, individuals with an ALP level of ≤ 2 times the upper limit of normal at 1 year of initiation of therapy had the best-predicted outcomes.²⁰ In this analysis, a bilirubin level of 1 times the upper limit of normal at 1 year best predicted the patient's transplant-free survival.²⁰ Thus, monitoring the biochemical response is crucial in the management of PBC. It provides an objective way of

assessing therapeutic response and plays an important role in determining the efficacies of treatments. We recommend measuring biochemical response through blood tests every 3–6 months to best characterise response to therapy.²¹

The GLOBE score can also be used to monitor therapy for patients on UDCA and consists of the following variables: age, bilirubin level, albumin, ALP level and platelet count.²² This score is able to identify patients being treated with UDCA who would survive for 5 and 10 years with positive predictive values of 98% and 88%, respectively.²² Alternate treatment can be sought if prognosis is poor with UDCA. The current and investigational therapies for PBC are summarised in [table 1](#) and described in the subsequent sections of this review.

CURRENT THERAPIES

Farnesoid X receptor agonists

The observed suboptimal response rate with UDCA therapy has led to the development of a second-line treatment in PBC. The farnesoid X receptor (FXR) is an important nuclear receptor. When activated, it regulates bile acid physiology and reduces their toxic accumulation.^{45 46} Obeticholic acid (OCA) is a therapeutic FXR agonist that has shown encouraging biochemical results. Histological improvement with OCA has not yet been documented.

Several studies evaluated the effects of OCA therapy by measuring the biochemical response. For example,

Table 1 Therapeutic modalities for primary biliary cholangitis

Therapeutic agent	Mechanism of action	Clinical outcomes			
		Biochemical response	Histological response	Clinical application	References
Fibrates	Acts on PPARs family	Decrease in ALP, ALT and GGT	Not assessed	Yes (improves pruritus)	23, 24
Corticosteroids	Acts on PXR receptor	Yes (AIH/PBC overlap)	Yes (AIH/PBC overlap)	Limited due to adverse effects	25
Budesonide	Acts on glucocorticoid receptors	Decrease in liver enzymes, IgM and IgG; AMA remained same	Decrease in fibrosis and inflammation	Controversial in late-stage PBC	26, 27
Obeticholic acid	FXR agonist	Decrease in ALP, ALT, GGT and bilirubin	Not assessed	Yes	28–30
Anti-CD20 agents	Causes B cell depletion	Decrease in ALP, AMA and Ig	Not assessed	Not yet established	31
Additional therapies still undergoing investigation					
FGF 19	Suppresses bile acid synthesis	Studies on these agents have been primarily in animal models. Clinical outcomes in humans have not yet been evaluated.			32
INT-777 INT-767	Acts on TGR5 receptors				33–36
ASBT inhibitors	Reduces bile acid pool				37
CTLA-4 agents	Regulates inflammation				38
Anti-CD40 L agents	Reduces inflammation and biliary destruction				39
IL-12/23 activity modulators	Regulates inflammation				40–42
norUDCA	Reduces bile acid toxicity	Primarily tested in PSC. Further studies warranted in PBC.			43, 44

AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ASBT, apical sodium-dependent bile acid transporter; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GGT, gamma-glutamyl transferase; IL, interleukin; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; PSC, primary sclerosing cholangitis; PXR, pregnane X receptor; TGR, transmembrane G-protein coupled receptor; UDCA, ursodeoxycholic acid.

in one study of 59 patients with PBC, they assessed OCA monotherapy by measuring the change in serum ALP levels.²⁸ There was a significant reduction in serum ALP in the treatment group (44% in the 10 mg group, 37% in the 50 mg group; $p \leq 0.0001$) compared with the placebo group.²⁸ The efficacy of OCA treatment was also validated in an international study of 165 individuals with PBC who had persistently elevated ALP while on stable doses of UDCA.²⁹ Patients received concomitant OCA therapy while on UDCA and were randomly assigned to the following groups: placebo, 10 mg, 25 mg and 50 mg OCA.²⁹ There was a significant reduction in serum ALP levels in the treatment group (23.7% in the 10 mg group, 24.7% in the 25 mg group and 21% in the 50 mg group) compared with placebo (2.6%).²⁹ A significant reduction in serum gamma-glutamyl transferase (GGT) and serum alanine aminotransferase (ALT) levels were also observed in both of the above-mentioned studies.^{28 29}

A phase III clinical trial, the POISE trial, further validated the use of OCA as monotherapy or as combination therapy with UDCA.⁴⁷ A total of 217 patients with PBC and an inadequate response to UDCA were allocated to the following groups: placebo, OCA 10 mg daily or OCA 5 mg titrated up to 10 mg daily.⁴⁷ The primary endpoint, which was an ALP level <1.67 times the upper limit of normal, a normal bilirubin and at least a 15% decrease in serum ALP after 1 year of therapy, was met in 10% of the placebo group, 47% in the 10 mg OCA group and 46% in the 5–10 mg OCA group ($p \leq 0.001$).⁴⁷ Both groups taking OCA also met secondary endpoints with improvements in GGT, ALT and total bilirubin.⁴⁷ A double-blind randomised controlled trial in 2015 found that OCA therapy significantly reduced mean levels of serum ALP in patients who already showed an inadequate response to UDCA ($p \leq 0.0001$).³⁰ The most common adverse effect of OCA therapy in all of these studies was pruritus, which led to discontinuation in some cases.^{28–30} Interestingly, in POISE trial, pruritus was minimal in the group that started at the 5 mg dose of OCA.

The initial dose of OCA is 5 mg one time per day.⁴⁸ It can be increased to the maximum dose of 10 mg per day if there is inadequate reduction in ALP and/or total bilirubin at 3 months.⁴⁸ Dose adjustments are required in certain patients.⁴⁸ Those with Child-Pugh classes B and C liver disease should be started on 5 mg one time per week.⁴⁸ If there is an inadequate response at 3 months, the dose can be increased to 5 mg two times per week and subsequently 10 mg two times per week if necessary.⁴⁸ Dose adjustments of OCA should also be made in patients with severe pruritus associated with therapy.⁴⁸ The dose can be reduced to 5 mg every other day for patients who were taking 5 mg daily or 5 mg one time per day for patients who were taking 10 mg daily.⁴⁸ Another option is to stop therapy for 2 weeks before restarting

the medication at a reduced dosage.⁴⁸ If pruritus still persists, consider discontinuing OCA and seeking alternative therapies.

The histological response of OCA therapy has not been documented. Surrogate markers, such as ALP and bilirubin levels, can be used to reliably predict outcomes of liver transplantation or death in patients with PBC.²⁰ This evidence substantiates OCA as a relatively safe and efficacious treatment for patients with PBC who have not shown an adequate biochemical response with UDCA alone.

Fibrates

The mechanism of fibrates is not completely understood. Nuclear transcription factors of the peroxisome proliferator-activated receptors (PPARs) family appear to play some role.⁴⁶ This results in a cascade of events which reduces toxic bile.²⁴ Fibrate therapy has shown benefit when combined with UDCA. The anticholestatic effects of fibrates are associated with reduced inflammation and relief from pruritus when combined with UDCA therapy in patients with PBC who were previously refractory to UDCA alone.^{23 49–51} In 2014, Lens *et al*²³ demonstrated normalisation or decrease in ALP <1.5 times the normal levels at 3 months in 13 and 4 patients, respectively, with bezafibrate and UDCA combination therapy. There was also significant decrease in GGT and ALT, as well as improvement in pruritus.²³ Further studies investigating long-term outcomes.

Corticosteroids

Corticosteroids are beneficial in patients who have an overlap syndrome with PBC and autoimmune hepatitis (AIH).²⁵ In a meta-analysis of seven randomised controlled trials, patients with PBC and features of AIH had improved biochemical markers and histological grades with combination UDCA and corticosteroid therapy.²⁵ This, however, did not translate to an improved mortality rate or reduced rate of transplantation.²⁵ Corticosteroids have been historically associated with many adverse effects,⁵² such as osteoporosis, bleeding, worsening pruritus and diarrhoea.²⁵ The high rate of adverse events is a severe limitation to the use of corticosteroids in the treatment of PBC.

Budesonide, a glucocorticoid with extensive first-pass metabolism, can be considered in the treatment of PBC. Clinical trials have shown significant improvement in biochemical parameters and histology with the use of oral budesonide in combination with UDCA, particularly in patients with grades I–III fibrosis.^{26 27} In 2005, Rautiainen *et al*²⁷ studied the changes in biochemical markers and liver histology with UDCA (15 mg/kg/day) and budesonide (6 mg/day) combination therapy in a 3-year, prospective randomised study. The study found that fibrosis decreased by 25% in the combination group and increased by 70% in the UDCA group ($p = 0.0009$).²⁷

Inflammation decreased in both groups, but more so in the combination group at 34% ($p=0.02$), compared with only 10% in the UDCA group (statistically not significant).²⁷

Budesonide has been associated with serious adverse effects.^{53–54} In an open-label controlled trial, two out of seven patients with PBC stage IV developed portal vein thrombosis leading to early termination of the study.⁵³ In a separate study, budesonide was associated with worsening of osteoporosis in patients with PBC.⁵⁴ There was a significant decrease in bone mineral density at the lumbar spine from 0.912 ± 0.02 g/cm² before treatment to 0.893 ± 0.03 g/cm² after 1 year of treatment ($p \leq 0.001$).⁵⁴ Five patients in the study, who had bone mineral densities below the fracture threshold of 0.85 g/cm² and lost ≥ 0.03 g/cm² of bone mass at 6 months of therapy, were given etidronate.⁵⁴ Despite antiresorptive therapy, these patients were still found to have a significantly greater amount of bone loss after 1 year of treatment compared with the UDCA group.⁵⁴ The increased rate of adverse events is likely attributed to the high serum drug levels in cirrhotic patients with PBC.⁵³ Therefore, budesonide's use in clinical practice requires further investigation and should only be limited to earlier stages of disease.

INVESTIGATIONAL THERAPIES

The identification of multiple therapeutic targets within this multifaceted disease process has led to the development of multiple therapies in PBC, other than the ones listed above. The studies behind these treatments are preliminary and require further investigation.

Membrane receptor agonists

Membrane receptors can be targeted to modulate the regulation of bile. A recently discovered therapeutic target is TGR5, a transmembrane G-protein coupled receptor.⁴⁶ Int-767, a dual FXR and TGR5 agonist, and Int-777 are two agents that are currently undergoing investigation.^{33–36} Animal studies show that activation of this receptor inhibits inflammatory processes^{55–57} and minimises associated liver injury. It may also have a protective role in carcinogenesis of the liver.⁵⁸ Fibroblast growth factor 19 (FGF19) has also been discovered as a therapeutic target for patients with PBC. A recombinant form of FGF19, NGM 282, plays a role in suppressing bile acid synthesis and promoting hepatocyte proliferation.³² Other agents that target the apical sodium-dependent bile acid transporter (ASBT) are responsible for the ileal absorption of bile acids.³⁷ ASBT inhibitors disrupt the enterohepatic circulation of bile salts by decreasing their entry into enterocytes and reducing the circulating bile acid pool.³⁷

Interleukin-12 and interleukin-23

Interleukin-12 (IL-12) and IL-23 promote the development of proinflammatory T helper 1 (Th1) and 17 (Th17) cells.^{40–42} However, a monoclonal antibody, ustekinumab, which targets this pathway, has not shown promising results in a recent phase II trial.⁵⁹

CTLA-4 agents

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) agents have also been discovered as potential targets of therapy for PBC. These agents inhibit T cells and help minimise inflammation.⁴⁶ In a phase II trial by Dhirapong *et al*,³⁸ mice were immunised with 2-octynoic acid coupled to bovine serum albumin that led to the development of portal cellular infiltrates and high titers of antimitochondrial antibodies. These mice were then treated with CTLA-4 immunoglobulin and had a significant therapeutic benefit, which included decreased cellular infiltrates and biliary cell damage.³⁸

Anti-CD40L agents

The dysregulation of CD40–CD40L signalling has been implicated in a number of autoimmune diseases.⁶⁰ The CD40–CD40L interaction is essential for immunoglobulin class switching.⁶¹ Some evidence suggests that certain changes in CD40L lead to defective immunoglobulin class switching in patients with PBC, therefore resulting in elevated titres of IgM.⁶² In addition, the activation of CD40 can cause biliary epithelial cell apoptosis.⁶³ In one animal model with autoimmune cholangitis, an anti-CD40 L agent had improved inflammation and bile duct destruction.³⁹

Anti-CD20

B cells play a major role in the pathogenesis of PBC as well. This is evident by the presence of elevated IgM titres and antimitochondrial antibodies.^{62–64} Rituximab, an anti-CD20 agent, has shown some effects in patients with PBC who have had a suboptimal response to UDCA.³¹ Tsuda *et al*³¹ performed an open-label study of six patients with PBC who did not respond to UDCA and administered two doses of 1 gm of rituximab 2 weeks apart. The ALP levels significantly reduced up to 36 weeks after therapy.³¹ However, since there have been conflicting results in other studies,^{65–66} further investigation of anti-CD20 therapy is necessary.

PUTTING IT ALL TOGETHER

UDCA is beneficial for most patients and thus remains the standard of care for treatment of PBC.¹ Nonetheless, considering alternative agents when appropriate and having a heightened awareness of emerging therapies is essential to provide patients with an optimal outcome. New treatments, such as obeticholic acid, provide further opportunity for patients with UDCA-non-responsive PBC. **Figure 1**

Figure 1 This figure illustrates a stepwise approach to the management of PBC. AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ASMA, antismooth muscle antibody; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

provides a stepwise algorithm for the management of PBC.

The diagnosis of PBC is made on the basis of biochemical parameters with or without liver biopsy.¹ Liver biopsy can be used when the index of suspicion for PBC remains high despite inconsistent laboratory

results, or to exclude AIH/PBC overlap syndrome and other liver diseases.¹ Once the diagnosis is made, UDCA therapy should be initiated at a dose of 13–15 mg/kg/day.¹ While on UDCA treatment, the biochemical response should be measured. An adequate response is defined as an ALP level ≤ 2 times the

upper limit of normal and a serum bilirubin level of 1 times the upper limit of normal.²⁰ UDCA should be continued if these laboratory parameters are met. In the setting of an inadequate response, OCA can be added to the current dose of UDCA as combination therapy or used as monotherapy in those who do not tolerate UDCA. In the phase III POISE clinical trial, the biochemical response on OCA therapy was defined as an ALP level <1.67 times the upper limit of normal, with a normal serum bilirubin and at least a 15% decrease in the ALP level. If therapy still remains inadequate, alternative measures for treatment should be considered.

Many other treatments for PBC have been trialed in small uncontrolled studies. We recommend that agents such as methotrexate should only be considered once a patient has failed primary therapy with UDCA and OCA. Patients with AIH/PBC overlap syndrome can be treated with UDCA and corticosteroids or azathioprine,^{67–69} as there is currently no role for OCA therapy in these patients.

CONCLUSION

Treatment of PBC has advanced in the past several years and still continues to evolve. The discovery of multiple therapeutic targets has led to the ongoing development of several new agents. UDCA therapy has been the cornerstone of treatment for decades and remains the standard of care. It improves histological as well as biochemical parameters and has proven long-term benefit.^{7–13} However, a significant proportion of patients show a suboptimal response to UDCA, keeping them at increased risk of potentially fatal complications and requiring liver transplantation.^{15–16} OCA has provided a substantial opportunity for UDCA-non-responsive patients and can serve as second-line therapy. OCA and the upcoming therapies will hopefully continue to improve the outcomes of PBC by reducing its associated morbidity and improving the quality of life for these patients. The new therapies and their ongoing investigations provide an encouraging future in the treatment of PBC.

Contributors HDT wrote the article and performed the literature review. BL edited the article. EBT edited the article. AB had the idea for the article and is the corresponding author.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Lindor KD, Gershwin ME, Poupon R, *et al.* Primary biliary cirrhosis. *Hepatology* 2009;50:291–308.
- Jopson L, Jones DE. Fatigue in primary biliary cirrhosis: prevalence, pathogenesis and management. *Dig Dis* 2015;33 (Suppl 2):109–14.
- Kuo A, Bowlus CL. Management of symptom complexes in primary biliary cholangitis. *Curr Opin Gastroenterol* 2016;32:204–9.
- Glass LM, Su GL. Metabolic bone disease in primary biliary cirrhosis. *Gastroenterol Clin North Am* 2016;45: 333–43.
- European Association for the Study of the Liver. EASL clinical practice guidelines: management of cholestatic liver diseases. *J Hepatol* 2009;51:237–67.
- Angulo P, Dickson ER, Thorneau TM, *et al.* Comparison of three doses of ursodeoxycholic acid in the treatment of primary biliary cirrhosis: a randomized trial. *J Hepatol* 1999;30:830–5.
- Poupon R, Chrétien Y, Poupon RE, *et al.* Is ursodeoxycholic acid an effective treatment for primary biliary cirrhosis? *Lancet* 1987;1:834–6.
- Leuschner U, Fischer H, Kurtz W, *et al.* Ursodeoxycholic acid in primary biliary cirrhosis: results of a controlled double-blind trial. *Gastroenterology* 1989;97:1268–74.
- Poupon RE, Balkau B, Eschwege E, *et al.* A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. UDCA-PBC Study Group. *N Engl J Med* 1991;324:1548–54.
- Poupon RE, Lindor K, Cauch-Dudek K, *et al.* Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. *Gastroenterology* 1997;113:884–90.
- Poupon RE, Poupon R, Balkau B. Ursodiol for the long-term treatment of primary biliary cirrhosis. The UDCA-PBC Study Group. *N Engl J Med* 1994;330:1342–7.
- Poupon RE, Bonnard AM, Chrétien Y, *et al.* Ten-year survival in ursodeoxycholic acid-treated patients with primary biliary cirrhosis. The UDCA-PBC Study Group. *Hepatology* 1999;29:1668–71.
- Parés A, Caballería L, Rodés J, *et al.* Long-term effects of ursodeoxycholic acid in primary biliary cirrhosis: results of a double-blind controlled multicentric trial. UDCA-Cooperative Group from the Spanish Association for the Study of the Liver. *J Hepatol* 2000;32:561–6.
- 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.
- Parés A, Caballería L, Rodés J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic Acid. *Gastroenterology* 2006;130:715–20.
- 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.
- Gershwin ME, Ansari AA, Mackay IR, *et al.* Primary biliary cirrhosis: an orchestrated immune response against epithelial cells. *Immunol Rev* 2000;174:210–25.
- Corpechot C, Chazouillères O, Poupon R. Early primary biliary cirrhosis: biochemical response to treatment and prediction of long-term outcome. *J Hepatol* 2011;55: 1361–7.
- Zhang LN, Shi T-Y, Shi X-H, *et al.* Early biochemical response to ursodeoxycholic acid and long-term prognosis of primary biliary cirrhosis: results of a 14-year cohort study. *Hepatology* 2013;58:264–72.
- 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.

- 21 Kaplan MM, Bonder A, Ruthazer R, *et al.* Methotrexate in patients with primary biliary cirrhosis who respond incompletely to treatment with ursodeoxycholic acid. *Dig Dis Sci* 2010;55:3207–17.
- 22 Lammers WJ, Hirschfield GM, Corpechot C, *et al.* Development and validation of a scoring system to predict outcomes of patients with primary biliary cirrhosis receiving ursodeoxycholic acid therapy. *Gastroenterology* 2015;149:1804–12.e4.
- 23 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.
- 24 Cuperus FJ, Halilbasic E, Trauner M. Fibrate treatment for primary biliary cirrhosis. *Curr Opin Gastroenterol* 2014;30:279–86.
- 25 Zhang Y, Lu J, Dai W, *et al.* Combination therapy of ursodeoxycholic acid and corticosteroids for primary biliary cirrhosis with features of autoimmune hepatitis: a meta-analysis. *Gastroenterol Res Pract* 2013;2013:490731.
- 26 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.
- 27 Rautiainen H, Kärkkäinen 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.
- 28 Kowdley KV, Jones D, Luketic V, *et al.* An international study evaluating the farnesoid X receptor agonist obeticholic acid as monotherapy in PBC. *J Hepatol* 2011;54:S13.
- 29 Mason A, Luketic V, Lindor K, *et al.* Farnesoid-x receptor agonists: a new class of drugs for the treatment of PBC? An international study evaluating the addition of INT-747 to ursodeoxycholic acid. *J Hepatol* 2010;52:S1–2.
- 30 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.
- 31 Tsuda M, Moritoki Y, Lian Z-X, *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.
- 32 Wu X, Ge H, Lemon B, *et al.* FGF19-induced hepatocyte proliferation is mediated through FGFR4 activation. *J Biol Chem* 2010;285:5165–70.
- 33 Pellicciari R, Gioiello A, Macchiarulo A, *et al.* Discovery of 6alpha-ethyl-23(S)-methylcholic acid (S-EMCA, INT-777) as a potent and selective agonist for the TGR5 receptor, a novel target for diabetes. *J Med Chem* 2009;52:7958–61.
- 34 Miyazaki-Anzai S, Masuda M, Levi M, *et al.* Dual activation of the bile acid nuclear receptor FXR and G-protein-coupled receptor TGR5 protects mice against atherosclerosis. *PLoS ONE* 2014;9:e108270.
- 35 Rizzo G, Passeri D, De Franco F, *et al.* Functional characterization of the semisynthetic bile acid derivative INT-767, a dual farnesoid X receptor and TGR5 agonist. *Mol Pharmacol* 2010;78:617–30.
- 36 Baghdasaryan A, Claudel T, Gumhold J, *et al.* Dual farnesoid X receptor/TGR5 agonist INT-767 reduces liver injury in the Mdr2-/- (Abcb4-/-) mouse cholangiopathy model by promoting biliary HCO₃⁻(3) output. *Hepatology* 2011;54:1303–12.
- 37 Poupon R. ASBT inhibitors in cholangiopathies—good for mice, good for men? *J Hepatol* 2016;64:537–8.
- 38 Dhirapong A, Yang G-X, 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.
- 39 Tanaka H, Yang G-X, Iwakoshi N, *et al.* Anti-CD40 ligand monoclonal antibody delays the progression of murine autoimmune cholangitis. *Clin Exp Immunol* 2013;174:364–71.
- 40 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.
- 41 Cua DJ, Sherlock J, Chen Y, *et al.* Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. *Nature* 2003;421:744–8.
- 42 Aggarwal S, Ghilardi N, Xie M-H, *et al.* Interleukin-23 promotes a distinct CD4T cell activation state characterized by the production of interleukin-17. *J Biol Chem* 2003;278:1910–14.
- 43 Trauner M, Fickert P, Halilbasic E, *et al.* Lessons from the toxic bile concept for the pathogenesis and treatment of cholestatic liver diseases. *Wien Med Wochenschr* 2008;158:542–8.
- 44 Fickert P, Pollheimer MJ, Silbert D, *et al.* Differential effects of norUDCA and UDCA in obstructive cholestasis in mice. *J Hepatol* 2013;58:1201–8.
- 45 Denson LA, Sturm E, Echevarria W, *et al.* The orphan nuclear receptor, shp, mediates bile acid-induced inhibition of the rat bile acid transporter, ntcp. *Gastroenterology* 2001;121:140–7.
- 46 Mousa HS, Lleo A, Invernizzi P, *et al.* Advances in pharmacotherapy for primary biliary cirrhosis. *Expert Opin Pharmacother* 2015;16:633–43.
- 47 Nevens F, Andreone P, Mazzella G, *et al.* A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. *N Engl J Med* 2016;375:631–43.
- 48 Intercept Pharmaceuticals, I., Ocaliva (obeticholic acid) [prescribing information]. New York, NY. May 2016.
- 49 Honda A, Ikegami T, Nakamura M, *et al.* Anticholestatic effects of bezafibrate in patients with primary biliary cirrhosis treated with ursodeoxycholic acid. *Hepatology* 2013;57:1931–41.
- 50 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.
- 51 Hazzan R, Tur-Kaspa R. Bezafibrate treatment of primary biliary cirrhosis following incomplete response to ursodeoxycholic acid. *J Clin Gastroenterol* 2010;44:371–3.
- 52 Gallant C, Kenny P. Oral glucocorticoids and their complications. A review. *J Am Acad Dermatol* 1986;14(Pt 1):161–77.
- 53 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.
- 54 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.
- 55 Wang YD, Chen W-D, Yu D, *et al.* The G-protein-coupled bile acid receptor, Gpbar1 (TGR5), negatively regulates hepatic inflammatory response through antagonizing nuclear factor

- kappa light-chain enhancer of activated B cells (NF-kappaB) in mice. *Hepatology* 2011;54:1421–32.
- 56 Kawamata Y, Fujii R, Hosoya M, *et al.* A G protein-coupled receptor responsive to bile acids. *J Biol Chem* 2003;278:9435–40.
 - 57 Keitel V, Donner M, Winandy S, *et al.* Expression and function of the bile acid receptor TGR5 in Kupffer cells. *Biochem Biophys Res Commun* 2008;372:78–84.
 - 58 Chen WD, Yu D, Forman BM, *et al.* Deficiency of G-protein-coupled bile acid receptor Gpbar1 (TGR5) enhances chemically induced liver carcinogenesis. *Hepatology* 2013;57:656–66.
 - 59 Hirschfield GM, Gershwin ME, Strauss MJ, *et al.* P367 phase 2 study evaluating the efficacy and safety of Ustekinumab in patients with primary biliary cirrhosis who had an inadequate response to ursodeoxycholic acid. *Journal of Hepatology* 2014;60:S189–90.
 - 60 Goules A, Tzioufas AG, Manousakis MN, *et al.* Elevated levels of soluble CD40 ligand (sCD40L) in serum of patients with systemic autoimmune diseases. *J Autoimmun* 2006;26:165–71.
 - 61 Pessach IM, Notarangelo LD. X-linked primary immunodeficiencies as a bridge to better understanding X-chromosome related autoimmunity. *J Autoimmun* 2009;33:17–24.
 - 62 Lleo A, Liao J, Invernizzi P, *et al.* Immunoglobulin M levels inversely correlate with CD40 ligand promoter methylation in patients with primary biliary cirrhosis. *Hepatology* 2012;55:153–60.
 - 63 Afford SC, Ahmed-Choudhury J, Randhawa S, *et al.* CD40 activation-induced, Fas-dependent apoptosis and NF-kappaB/AP-1 signaling in human intrahepatic biliary epithelial cells. *Faseb J* 2001;15:2345–54.
 - 64 Kaplan MM, Gershwin ME. Primary biliary cirrhosis. *N Engl J Med* 2005;353:1261–73.
 - 65 Dhirapong A, Lleo A, Yang G-X, *et al.* B cell depletion therapy exacerbates murine primary biliary cirrhosis. *Hepatology* 2011;53:527–35.
 - 66 Moritoki Y, Lian Z-X, 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.
 - 67 Chazouilleres O, Wendum D, Serfaty L, *et al.* Long term outcome and response to therapy of primary biliary cirrhosis-autoimmune hepatitis overlap syndrome. *J Hepatol* 2006;44:400–6.
 - 68 Muratori P, Granito A, Pappas G, *et al.* The serological profile of the autoimmune hepatitis/primary biliary cirrhosis overlap syndrome. *Am J Gastroenterol* 2009;104:1420–5.
 - 69 Ozaslan E, Efe C, Heurgué-Berlot A, *et al.* Factors associated with response to therapy and outcome of patients with primary biliary cirrhosis with features of autoimmune hepatitis. *Clin Gastroenterol Hepatol* 2014;12:863–9.