



# Clinical Updates in Primary Biliary Cholangitis: Trends, Epidemiology, Diagnostics, and New Therapeutic Approaches

Artin Galoosian\*<sup>1</sup>, Courtney Hanlon<sup>2</sup>, Julia Zhang<sup>1</sup>, Edward W. Holt<sup>3</sup> and Kidist K. Yimam<sup>4</sup>

<sup>1</sup>Department of Medicine, California Pacific Medical Center, San Francisco, CA, USA; <sup>2</sup>Department of Medicine, University of Southern California Keck School of Medicine, Los Angeles, CA, USA; <sup>3</sup>Department of Transplant, Division of Hepatology, California Pacific Medical Center, San Francisco, CA, USA; <sup>4</sup>Director of the Autoimmune Liver Disease Program, Department of Transplant, Division of Hepatology, California Pacific Medical Center, San Francisco, CA, USA

## Abstract

Primary biliary cholangitis, formerly known as primary biliary cirrhosis, is a chronic, autoimmune, and cholestatic disease ameliorating the biliary epithelial system causing fibrosis and end-stage liver disease, over time. Patients range from an asymptomatic phase early in the disease course, to symptoms of decompensated cirrhosis later in its course. This review focuses on the current consensus on the epidemiology, diagnosis, and management of patients with primary biliary cholangitis. We also discuss established medical management as well as novel and investigational therapeutics in the pipeline for management of PBC.

**Citation of this article:** Galoosian A, Hanlon C, Zhang J, Holt EW, Yimam KK. Clinical updates in primary biliary cholangitis: Trends, epidemiology, diagnostics, and new therapeutic approaches. *J Clin Transl Hepatol* 2020;8(1):49–60. doi: 10.14218/JCTH.2019.00049.

## Introduction

Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is an autoimmune, T-cell-mediated condition affecting the biliary epithelial cells. The granulomatous destruction and subsequent necrosis of cholangiocytes creates an accumulation of inflammatory infiltrates, which eventually leads to cholestasis and fibrosis. Because of its cumulative nature, PBC can present as a spectrum of disease severity – from no symptoms to cholestasis to biliary cirrhosis resulting in end-stage liver disease. Patients may present

with symptoms of pruritus, fatigue, other autoimmune diseases (including Sjogren's syndrome, Hashimoto's thyroiditis and/or rheumatoid arthritis), decreased bone mineral density, hyperlipidemia, and xanthelasma.<sup>1,2</sup> Without a prompt diagnosis, treatment may be delayed; as such, the chronic inflammation and destruction of intrahepatic ducts contributes significantly to disease-related mortality and morbidity.

The terminological and paradigm shift from “primary biliary cirrhosis” to “primary biliary cholangitis” reflects a variety of changes within the PBC landscape in recent years, including understanding of its pathogenesis and development of novel therapeutics. Since the majority of patients with the diagnosis do not progress to cirrhosis, this change in the name was made to more accurately represent the histologic hallmarks of cholestasis and cholangitis.<sup>2</sup>

Despite ongoing efforts to improve treatment options for patients with PBC, disease progression to cirrhosis and liver-related complications contribute to recurrent hospitalizations, increased healthcare resource utilization, and increased morbidity and mortality overall.<sup>3</sup> Improvement in the diagnosis, detection of early-stage disease, and understanding different treatment modalities are essential to reducing disease burden and complications. Thus, the aim of this paper is to elucidate current trends in the epidemiology and diagnostic approaches of PBC by clarifying the current understanding of serologic and histologic factors associated with PBC. Additionally, we discuss the management of PBC, with use of both approved and investigational agents, and discuss how to identify at-risk patients to reduce late-stage complications, morbidity, and mortality.

## Epidemiology

The overall prevalence and incidence of PBC remains low compared to other liver disorders. PBC cases represented only 165 of the 8,250 liver transplantations done in 2018, according to the Organ Procurement and Transplantation Network.<sup>4,5</sup> Despite not being a leading indication for liver transplantation, the overall global rate of PBC incidence continues to rise, with a marked increase since the 1980s.<sup>4,6–8</sup> Originally, PBC was thought to be a very rare disease, largely because of small sample sizes and lack of large longitudinal studies; moreover, reported prevalence and incidence data have often been dramatically different between different studies and regions across the world (and even within different states in the USA).<sup>4</sup>

In the USA, there are currently no longitudinal studies on the epidemiology of PBC. In 2018, the Fibrotic Liver Disease

**Keywords:** Primary biliary cholangitis (PBC); Epidemiology; Treatment; UDCA; Obeticholic acid.

**Abbreviations:** AASLD, American Association for the Study of Liver Diseases; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; APRI, aminotransferase to platelets ratio index; ASBT, apical sodium-dependent bile acid transporter; AST, aspartate aminotransferase; CI, confidence interval; FDA, Food and Drug Administration; FGF, fibroblast growth factor; FXR, farnesoid X receptor; HCC, hepatocellular carcinoma; NASH, nonalcoholic steatohepatitis; norUDCA, norursodeoxycholic acid; NOX, NADPH oxidase; OCA, obeticholic acid; PBC, primary biliary cholangitis; PDC-E2, pyruvate dehydrogenase complex-dihydrolipoyltransacetylase; POISE, Perioperative Ischemic Evaluation Study; PPAR, peroxisome proliferator-activated receptor; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Received: 7 October 2019; Revised: 21 December 2019; Accepted: 1 January 2020

\*Correspondence to: Artin Galoosian, Department of Medicine, California Pacific Medical Center, 1101 Van Ness Avenue, Suite 1120, San Francisco, CA 94109, USA. Tel: +1-310-560-2155, E-mail: GaloosA@sutterhealth.org

Consortium reported a 12-year point prevalence of PBC of 23.9 per 100,000 persons, but even this number varied significantly by geographic region and patient demographics within the USA.<sup>9</sup> Their study found that prevalence increased by over 72% among women (33.5 to 57.8 per 100,000 persons) and by over 114% among men (7.7 to 15.4 per 100,000 persons) during the 12-year period. Studies from Europe and Asia have also generally reported a steadily increasing prevalence of PBC within as early as the past decade.<sup>10,11</sup>

### Geographic clusters

It is estimated that the incidence of PBC ranges from 0.33 to 5.8 per 100,000 persons, with the reported point prevalence ranging from 1.91 to 33.8 per 100,000 persons, with large differences seen in geographic region.<sup>12–15</sup> Data on specific epidemiological trends and global incidence is scarce, again largely due to the lack of a large longitudinal population-based studies and the marked geographic heterogeneity within different regions.<sup>4,8,16</sup>

Both genetic and environmental factors contribute widely to the pathogenesis of PBC, with epidemiologic data indicating variable prevalence rates of disease into distinct and different geographical areas, or clusters.<sup>17</sup> For example, the incidence of PBC developing in a well-defined population from Rochester, Minnesota (USA) was 4.5 per 100,000 person-years for women, and 0.7 per 100,000 person-years for men, with age and gender-adjusted prevalence for women being 65.4 per 100,000 persons and 12.1 per 100,000 persons for men.<sup>18</sup> Another study aimed to highlight the epidemiology of PBC in Hong Kong; this study found that the average age/sex adjusted annual incidence rate increased from 6.7 to 8.1 per million person-years and the age/sex adjusted prevalence increased from 31.1 to 82.3 per million between 2000 and 2015.<sup>14</sup>

Europe and North America have the highest reported prevalence of PBC worldwide, as reflected in the increasing rate of PBC-related hospitalizations over the last 30 years.<sup>7,16,19</sup> Recently, a large population-based analysis of both inpatient and outpatient registries in Sweden found that the prevalence of PBC increased steadily from 5.0 to 34.6 per 100,000 persons from 1987 to 2014, respectively.<sup>20</sup> Data collected from an Italian cohort between 2014 to 2015 reported that the point-prevalence of PBC was 27.9 per 100,000 people in Italy.<sup>21</sup>

In addition to the scarcity of large population-based studies, misdiagnoses and underreporting of patients may also contribute to the incidence and prevalence of PBC, as 5–10% of patients may be antimitochondrial antibody (AMA)-negative.<sup>16,22,23</sup> Despite these limitations, data support the observation that global rates of PBC are rising, as many countries continue to improve diagnostic accuracy, reporting measures, and surveillance of PBC patients.<sup>4,16,19,22,23</sup>

### Heterogeneity

Heterogeneity in prevalence can in part be explained by regional variation in diagnostic awareness or access to care; however, several studies have suggested that environmental exposures may play a role in the development of specific regional clusters of PBC.<sup>8,16,24</sup> Some studies support a high concordance among monozygotic twins and human leukocyte antigen alleles; yet, only about 15% of PBC variability has

been accounted for by genetics.<sup>16,25–29</sup> PBC frequently develops around the ages of 40–60 years, with women more commonly affected than men (at a ratio of 9:1).<sup>4,11,30</sup> This female-to-male ratio also persists in other countries, such as Taipei (9:1), Japan (9.1:1), and mainland China (6.82:1).<sup>31,32</sup> Although there is a female predominance, men who develop PBC tend to have a more severe and aggressive disease process with more severe lobular inflammation.<sup>33</sup> Men are also more likely to be unresponsive to the conventional first-line treatment, ursodeoxycholic acid (UDCA).<sup>33</sup>

### Etiopathophysiology

Significant progress has been made in understanding the immune responses involved in the pathophysiology of PBC. However, many aspects of the etiology and pathogenesis of the destruction of biliary epithelial cells remains incompletely explained.<sup>4,23,34</sup> It is known that PBC involves a predominantly T-cell mediated destruction of intrahepatic bile ducts, likely initiated when a genetically susceptible individual comes into contact with an antigen in the environment such as an infectious pathogen, medication or other compound, triggering an autoimmune event.<sup>2</sup>

Regardless of the autoimmune trigger, the disease begins with specific AMA targeting of the lipoic acid on the 2-oxo acid dehydrogenases, which are located on the inner mitochondrial membrane. This enzyme then targets the E2 subunit of the pyruvate dehydrogenase complex, which eventually leads to biliary epithelial cell destruction. In addition, peptides from viruses or bacteria that are structurally similar to pyruvate dehydrogenase complex-dihydrolipoyltransacetylase (referred to as PDC-E2) epitopes can trigger an autoimmune response through molecular mimicry.<sup>2,34–36</sup> An increase in PDC-E2 may lead to a loss of humoral tolerance and increases the differentiation of T-cells in the liver, resulting in damage to the intrahepatic biliary epithelial cells, scarring, fibrosis, and ductal destruction.<sup>2,34–36</sup> The exposure of extraductular liver parenchyma to bile acids contributes to hepatocyte injury, fibrosis, and eventually cirrhosis.

### Clinical manifestations of PBC

#### **Signs, symptoms, and associated autoimmune conditions**

The clinical presentation of PBC can vary greatly. Up to 50–60% of patients with PBC are asymptomatic at the time of diagnosis, and only present with abnormal liver function tests.<sup>37</sup> Fatigue is one of the most common symptoms, which is present in almost 80% of patients with PBC; however, there is no correlation between fatigue and disease severity or duration.<sup>2,19,22</sup> It is reported that 20% of these patients will have concomitant thyroid disorders, making it important for patients with PBC to get yearly thyroid function testing.<sup>2</sup> Pruritus is a common symptom of PBC, which tends to be worse at night, in the heat, and during pregnancy, and can affect up to 20–70% of patients.<sup>22,38</sup> Dermatologic findings including hyperpigmentation, jaundice, xanthomas, xanthelasmas, xerosis, and dermatographism are all common among patients with PBC.<sup>23,39</sup> Patients with PBC often have other rheumatologic or autoimmune diseases as well, most commonly Sjogren's syndrome and autoimmune thyroid diseases, which can affect up to 40–65% of patients.<sup>23,39</sup> About 5–10% of patients will also present with cutaneous scleroderma, and up to 10% of

patients may have concomitant rheumatoid arthritis.<sup>39</sup> During the end stages of PBC, patients may develop symptoms of portal hypertension, which is typically seen in patients with at least bridging fibrosis.<sup>22,30,40</sup>

### Natural history

The natural history and prognosis of PBC has changed and improved significantly over the last several decades. The disease, without any treatment, has gone from a slow, progressive disease resulting in liver fibrosis and cirrhosis to eventual hepatic decompensation and death, to a disease process with slower rates of progression and fibrosis, and higher rates of clinical remission.<sup>41,42</sup> This can be explained partially by both the earlier diagnosis and earlier treatment of PBC. Without treatment, the intrahepatic bile ducts are destroyed, causing bile acid to build up within the liver, leading to cholestasis. Cholestasis contributes to chronic granulomatous inflammation, which eventually leads to fibrosis and the subsequent development of cirrhosis and portal hypertension, along with its associated complications, including a predisposition to hepatocellular carcinoma (HCC).<sup>43</sup>

With increasing awareness and understanding of the natural history of the disease, as well as earlier diagnosis and prompt treatment initiation, the progression to fibrosis and cirrhosis among PBC patients is becoming increasingly rarer, as demonstrated by the decrease in the indications of liver transplantation for PBC patients.<sup>19,41,44</sup> The introduction and use of UDCA for treating PBC has impacted the natural history of the disease.

### Diagnostic criteria

#### Serological features

Environmental triggers and autoimmunity may play crucial immunologic roles in the development of PBC. The current etiologic understanding suggests that the development of PBC requires both a genetic predisposition and exposure to an unknown environmental trigger, thereby initiating the immunologic cascade that destroys biliary cells.<sup>5,38</sup> Autoantibodies are commonly found in patients with PBC and are often used to aid diagnosis. Approximately 90–95% of patients with PBC have detectable AMA, an autoantibody that targets lipoic acid present on the 2-oxo-acid dehydrogenase complexes within the inner mitochondrial membrane that has high disease specificity.<sup>23,27,45</sup> A large proportion of these patients also have elevated levels of antinuclear antibodies, alkaline phosphatase (ALP), polyclonal IgM, and inflammatory cytokines, which include TNF-alpha, IFN-gamma, IL-1, and IL-6.<sup>5,27,38,45–47</sup> Approximately 50% of patients are found to have antinuclear antibody positivity, most commonly of nuclear-rim or nuclear-dot patterns, which are highly specific for PBC.<sup>38,48</sup>

Between 5–10% of patients with PBC are AMA-negative, leading to potential misdiagnosis and under-treatment of the actual disease.<sup>16,22,23</sup> The American Association for the Study of Liver Diseases (AASLD) recently updated its practice guidelines to include the antibodies against sp100 and gp210 as serum markers, with the intent of helping to identify patients who are negative for AMA, via indirect immunofluorescence. These PBC-specific antinuclear antibodies are present in over 30% of AMA-negative patients, allowing for more accurate diagnosis in those who did not meet previous diagnostic guideline criteria.

### Liver biochemistry and diagnostic algorithm

Previous diagnostic guidelines focused on serologic, histologic, and immunologic testing for a diagnosis of PBC. In 2018, the AASLD released updated practice guidelines, in which they outlined the currently used diagnostic criteria for PBC.<sup>23</sup> Accordingly, a diagnosis of PBC today is established based on the presence of two of three of the following:

1. An elevated serum-based ALP level (>1.5 times the upper limit of normal (ULN))
2. Histologic evidence of chronic nonsuppurative biliary ductal destruction (florid duct lesion)
3. The presence of AMA at a titer of 1:40 or greater

ALP levels are not only used for diagnosis but are associated with both the severity of inflammation and ductopenia.<sup>49</sup> ALP levels also reflect markers of cholestasis, and higher levels of ALP are associated with higher risk of liver transplantation and death.<sup>50,51</sup> Similarly, aminotransferase and IgM levels reflect inflammation and the severity of periportal and lobular necrosis.<sup>49,52,53</sup> Bilirubin has also been studied in PBC as a potential early marker for hepatic dysfunction; in conjunction with low albumin and low platelets, an elevated serum bilirubin may precede the development of cirrhosis and portal hypertension, and has been shown to be an important biomarker to assess disease severity.<sup>49,52,53</sup> The discovery of more serologic markers known to be associated with PBC will aid considerably in the diagnosis of patients with atypical clinical presentations. Patients with symptoms typical for autoimmune-related biliary disease or patients with features of PBC-autoimmune hepatitis overlap syndrome may benefit from more accurate markers of disease. Patients may also present with dyslipidemia, particularly with an elevated high-density lipoprotein level.

#### Role of liver biopsy

As stated above, the diagnosis of PBC can be made on the basis of clinical features, liver biochemical and autoantibody testing, and imaging to exclude extrahepatic biliary obstruction. Liver biopsy is not required in most cases but can be helpful in cases without a certain diagnosis by evaluating for concomitant conditions such as autoimmune hepatitis and nonalcoholic steatohepatitis (NASH). Liver biopsy also holds prognostic value, based on disease activity and fibrosis stage. A classic histologic characteristic of PBC is chronic nonsuppurative cholangitis affecting the interlobular and septal bile ducts. Fibrosis in PBC can be staged using the METAVIR system, which is a four-point scale, in which stage 0 represents normal liver, stage 1 represents portal inflammation with or without florid duct lesions, stage 2 represents periportal fibrosis, stage 3 represents bridging fibrosis, and stage 4 represents cirrhosis.<sup>54,55</sup> The presence of cirrhosis is associated with a worse prognosis and increased risk of developing complications.

#### Radiographic features and noninvasive imaging modalities

Magnetic resonance cholangiopancreatography and/or magnetic resonance imaging are a noninvasive method of imaging the intrahepatic and extrahepatic biliary tree. These imaging modalities are not required but can aid in the exclusion of patients with other cholestatic liver diseases, such as primary sclerosing cholangitis (PSC), and to rule out concomitant pancreatic or biliary masses causing biliary obstruction.<sup>2,56</sup>

There are also newer imaging modalities, such as transient elastography, that evaluate disease progression, prognosis, and treatment response. Transient elastography-derived liver stiffness measurement has been used as a surrogate marker of liver fibrosis in PBC patients, allowing noninvasive monitoring over time.<sup>54</sup> A prospective performance analysis was completed in 2012 which showed the benefit of noninvasive testing using transient elastography in patients with PBC using UDCA. Using a generalized Cox linear regression model, the authors showed that, in general, patients had about an overall progression rate of  $0.48 + 0.21 \text{ kPa/year}$  ( $p = 0.02$ ).<sup>54</sup> A cutoff value of 2.1 kPa/year was associated with an 8.4-fold increased risk of liver decompensations, liver transplantations, or deaths ( $p < 0.001$ ).<sup>54</sup> Accuracy is limited in patients with ascites obesity. Progression of liver stiffness over time is predictive of poorer outcomes, and patients with response to UDCA showed improvement in liver stiffness scores.<sup>54,56</sup> The authors also purported that transient elastography is superior in determining liver fibrosis compared to using biochemical testing alone, which is important in the prognostication of PBC patients over time.

### PBC complications

Patients with PBC are at an increased risk of developing HCC, though at a lower rate compared to those with other chronic liver diseases.<sup>37,43</sup> In a multicenter study involving over 4,500 patients over a 40-year period, Trivedi *et al*.<sup>57</sup> showed that the incidence of HCC among PBC patients was 3.4 cases per 1,000 person-years. In particular, PBC patients with advanced age at diagnosis, advanced disease, male sex, and suboptimal response to UDCA are at higher risk for development of HCC.<sup>23</sup> However, biochemical nonresponse to treatment has been shown to be a significant predictor of future risk for developing HCC. According to one study, biochemical nonresponse to treatment for PBC after one year had a hazard ratio of 3.44 ( $p < 0.001$ ) in developing HCC on multivariate analysis.<sup>57</sup>

Development of HCC in patients with PBC is associated with notably worse transplant-free and overall survival.<sup>43</sup> Given this, PBC patients with known or suspected cirrhosis should receive screening ultrasounds for HCC with or without alpha fetoprotein at regular 6 month intervals. Development of portal hypertension can also occur in these patients with cirrhosis or in some patients before full-blown cirrhosis, given granulomatous inflammation leading to pre-sinusoidal portal hypertension.

PBC patients are also at higher risk of osteopenia and osteoporosis, mostly related to decreased bone formation and concomitant vitamin D deficiency, which places them at higher risk of fracture. Baseline bone mineral density scans should be done at diagnosis and then subsequent screening should be continued on the basis of risk.<sup>23,43</sup> General management includes calcium and vitamin D supplementation, encouraged weight-bearing exercises, and bisphosphonates to improve bone mineral density, though their effectiveness in PBC is not clear.<sup>23</sup> Because of chronic cholestasis, hyperlipidemia is common but rarely of clinical significance; lipid-lowering therapies should be considered in patients with other coexisting cardiovascular risk factors. Fat-soluble vitamin deficiencies are possible as well and can be treated with appropriate supplementation. Table 1 suggests a common follow-up schedule for patients with PBC in the primary care setting.

In terms of managing symptom complications, no good treatment exists for the treatment of fatigue in patients with

**Table 1. Follow-up schedule for patients with PBC in the primary care setting and the management of complications**

1. **Liver function testing** every 3 to 6 months (earlier if initiating treatment), including a complete metabolic panel, coagulation factors, and complete blood count to assess platelet levels
2. **Thyroid function** studies every year
3. **Bone mineral density, DEXA** scans every 2–4 years
4. **Fat soluble vitamin levels** yearly, including vitamins A, D, and K
5. **Upper endoscopy** every 1 to 3 years if patient has cirrhosis or if Mayo risk score  $>4.1$  (the 1-year risk of death was  $\sim 90\%$  in patients with a Mayo risk score  $>6.0$ )
6. **Abdominal ultrasound and alpha fetoprotein** in patients with known or suspected cirrhosis, including evidence of synthetic liver dysfunction in labs
7. **Screening for major depression and generalized anxiety disorder**

Abbreviations: DEXA, dual-energy X-ray absorptiometry; PBC, primary biliary cholangitis.

PBC. A randomized, double-blind, placebo-controlled study was conducted to evaluate the effects of modafinil with fatigue in patients with PBC, however no beneficial effects on fatigue were found when compared with placebo.<sup>58</sup> A clinical trial is currently in the enrollment phase to study the efficacy and impact of mindfulness-based interventions for the treatment of moderate to severe fatigue in patients with PBC (ClinicalTrials.gov Identifier: NCT03684187).

### Medical management

Without treatment, patients with PBC progress, on average, one histologic stage within 2 years.<sup>59</sup> Treatment of PBC is aimed at reducing symptoms of cholestasis, preventing fibrosis progression and avoiding complications of end-stage disease.<sup>23</sup> Previous data had shown the median survival of a patient with PBC not on treatment was dependent on symptoms, with median survival of symptomatic and asymptomatic patients of 7.5 years and 16 years, respectively.<sup>44,60</sup>

Recent data suggest, however, that asymptomatic patients with PBC often have less severe disease at diagnosis than those with symptomatic PBC; yet, the absence of symptoms alone is not associated with a better prognosis and does not show a mortality benefit.<sup>61</sup> Unlike other autoimmune diseases, biologic and immune-based therapies have not been shown to be effective in treating patients with PBC.<sup>62</sup> Herein, we describe approved treatments, off-label therapies, and drugs in development for the treatment of PBC (see Fig. 1 for a detailed schema of treatment options).

The main treatment paradigms of disease management for patients with PBC include slowing the progression of the disease and managing the symptoms and complications of chronic cholestasis. The only two Food and Drug Administration (FDA) medications that are approved for the treatment of PBC are UDCA and obeticholic acid (OCA); however, over the last several years, there have been several therapies, currently under different phases of clinical trials, that have been shown to be effective as both primary and adjuvant medications for the treatment of PBC. Herein, we will discuss the approved therapies for PBC, followed by the novel and investigational therapies that have been under clinical investigations over the last several years.

### Approved therapies: What is established

#### UDCA

UDCA is a naturally occurring, hydrophilic bile acid that was originally used for gallstone dissolution. It was noted that

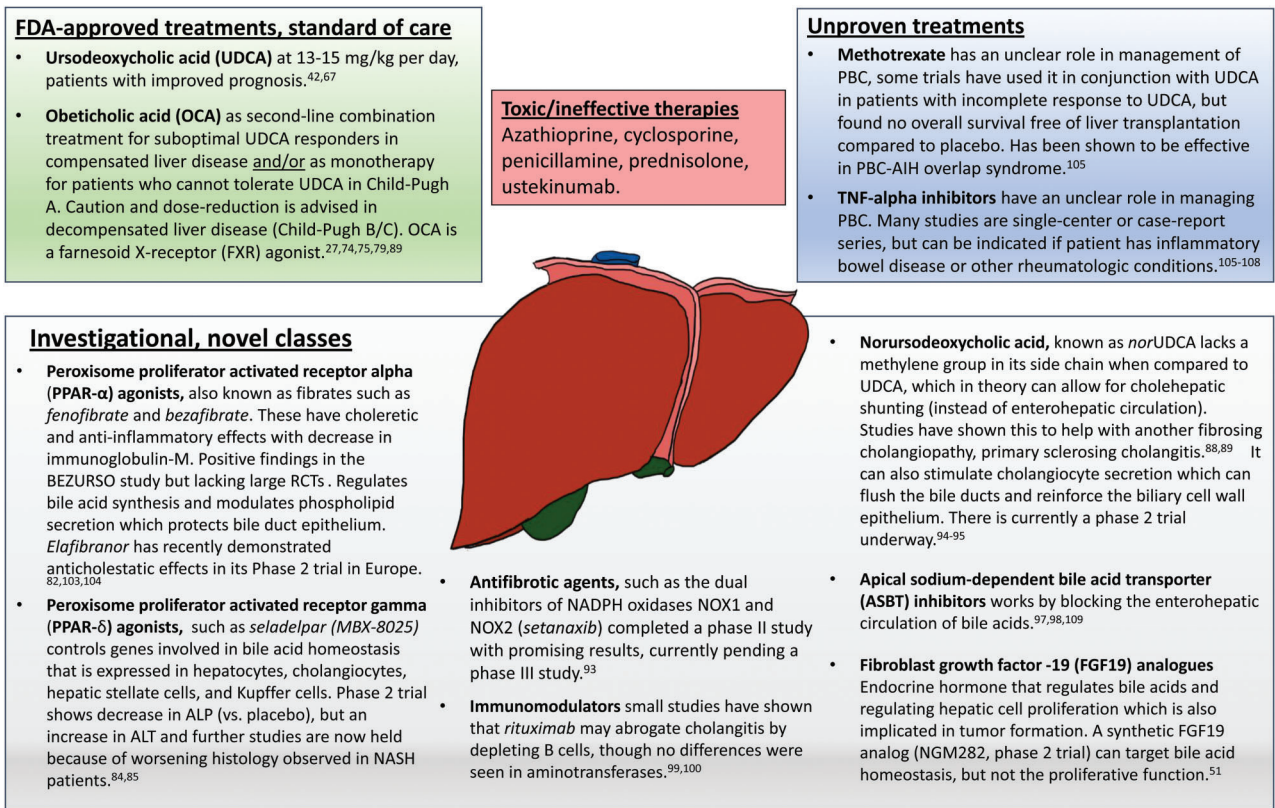


Fig. 1. Treatment modalities for primary biliary cholangitis: What we know in 2019.

patients treated with UDCA had associated decreases in their ALP levels, leading to the eventual approval for its treatment of PBC. UDCA is incorporated into the bile acid pool, replacing other more toxic bile acids and reducing inflammation, cholestasis and cell lysis.<sup>63</sup> Although UDCA has changed the landscape of PBC treatment, only 40% to 60% of patients with PBC respond adequately to UDCA.<sup>64</sup> However, because of its limited side effects (up to 2% report diarrhea and pruritus), current guidelines recommend UDCA as the first-line treatment for PBC, at a dose of 13–15 mg/kg/day.<sup>63</sup> Further, higher doses have not been shown to be effective in PBC.<sup>51</sup>

To investigate the impact of UDCA on the incidence of cirrhosis-related complications and on overall survival in PBC, Harms *et al.*<sup>65</sup> reviewed data from 16 liver centers in 10 countries in Europe and North America in the Global PBC Study Group. This large study found that early diagnosis and early treatment are independent protective factors in delaying PBC-related complications. Additionally, patients with higher aspartate aminotransferase to platelets ratio index (commonly known as the APRI) and patients who were UDCA nonresponders were both more likely to experience disease complications; patients who had both an elevated APRI score and proved to be UDCA nonresponders experienced a 10-year complication rate of 37.4% compared to 3.2% in those with a lower APRI score and a response to treatment.<sup>2,65</sup>

Guidelines continue to support the role of UDCA as first-line therapy for patients with PBC. After patients are placed on an adequate dose of UDCA, treatment response should be measured after 1 year of treatment. Disease response is defined by biomarkers such as ALP and total bilirubin, based

on the Rochester I, Barcelona, Paris I, Rotterdam, Toronto, Paris II, Rochester II, and Global treatment response criteria.<sup>42,50,52,53,66–68</sup> Although many models exist for determining risk of disease progression, including the GLOBE and UK-PBC risk scoring systems, there is insufficient evidence to recommend one scoring system over another.<sup>50,69,70</sup> Both the GLOBE and UK-PBC risk scoring systems were found to be predictive of cirrhosis-related complications based on a recent multicenter Turkish study.<sup>71</sup> Table 2 provides a review of current prognostication models.

Patients with incomplete biochemical response to UDCA and hence with risk of progressive liver disease and complications, should be evaluated for a second-line agent or be considered for available clinical trials.

### OCA

OCA was first approved in May 2017 to be used in conjunction with UDCA for PBC patients with an inadequate response to UDCA, or as monotherapy for those who cannot tolerate UDCA. OCA is a modified bile acid farnesoid X receptor (FXR) agonist which when activated, modulates various steps in bile acid homeostasis, which culminates in a decrease in bile acid synthesis and an increase in its clearance. The FXR agonist also plays an important role in down-regulating inflammatory signaling, which reduces inflammation and cholestasis in the liver.<sup>72</sup> Overall, OCA is well tolerated and has been shown to decrease ALP and total bilirubin.<sup>65,73,74</sup> In the landmark phase 3 Perioperative Ischemic Evaluation Study (POISE) trial, the primary

**Table 2. Assessment of biochemical response and prognostication after initiation of treatment, adapted from the 2018 Practice Guidelines from the AASLD<sup>23</sup>**

Criterion	Response criteria	Response time
<b>Mayo</b>	↓ Alkaline phosphatase <2 x ULN	6 months
<b>Barcelona</b>	↓ Alkaline phosphatase 40% from baseline or within normal limits	12 months
<b>Paris I</b>	↓ Alkaline phosphatase to < 3 x ULN, and decrease in aspartate aminotransferase <2 x ULN and normalized bilirubin	12 months
<b>Rotterdam</b>	Normalization of either bilirubin or albumin (one needed to be abnormal prior to treatment)	12 months
<b>Toronto</b>	Alkaline phosphatase <1.67 x ULN	24 months
<b>Paris II</b> (early stage PBC only)	↓ Alkaline phosphatase to <1.5 x ULN or aspartate aminotransferase <1.5 x ULN and normalized bilirubin	12 months
<b>Rochester II</b>	↓ Alkaline phosphatase <2 x ULN	12 months
<b>UK-PBC risk score</b>	Prognostic index; baseline albumin, platelet, bilirubin, alanine aminotransferase or aspartate aminotransferase, and alkaline phosphatase after 1 year on UDCA	12 months
<b>GLOBE score</b>	Prognostic index: baseline age, bilirubin, alkaline phosphatase, albumin, and platelet count after 1 year on UDCA	12 months

Abbreviations: AASLD, American Association for the Study of Liver Diseases; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

endpoint of an ALP level of less than 1.67 times the ULN range, with a reduction of at least 15% from baseline and a normal total bilirubin level met in an intention-to-treat analysis. The primary endpoint occurred in more patients in the 5–10 mg titration group (46%) and the 10 mg group (47%) than in the placebo group (10%;  $p < 0.001$  for both comparisons).<sup>74,75</sup> Changes in noninvasive measures of liver fibrosis did not differ significantly between either treatment group or the placebo group at 12 months. However, the most common adverse event of OCA is dose-dependent pruritus. Up to 56% of patients in the 5–10 mg titration group and 68% of patients in the 10 mg group discontinued OCA compared to 38% in the placebo arm.<sup>73,74</sup> Pruritus returned back to baseline during the open-label extension phase of the study. Despite the increase in pruritus, discontinuation rates remained low in either arm of the study, with 0% of patients in the placebo group versus 1% of patients discontinuing the drug in the 5–10 mg titration group and 10% of patients discontinuing the drug in the higher than 10 mg OCA dose group.<sup>76</sup> In addition, OCA has also been studied in Child-Pugh Class A PBC patients in the POISE trial, with ongoing study in those Child-Pugh Classes B and C with dose-reduction or caution for usage in Child-Pugh Classes B and C. The data show that plasma exposure to OCA and its active conjugates and metabolites increases significantly in patients with moderate to severe hepatic impairment.<sup>23</sup> For example, compared to patients with normal liver function, Child-Pugh Class A patients have a 1.1-fold increase in OCA conjugates compared to a 4-fold increase in Child-Pugh B and 17-fold increase in Child-Pugh C patients.<sup>77</sup> As such, it is recommended for Child-Pugh B and C patients to start patients on 5 mg OCA weekly; then, doses can be increased to 10 mg twice weekly (3 days apart) after 3 months.

Additionally, OCA has been showed to sustain improved liver biochemistry for up to 6 years in patients with PBC; the results of the 5-year open-label extension of the phase III, placebo-controlled POISE trial was reported most recently during the AASLD 2019 Liver Meeting. POISE included a 12-month double-blind phase with the 5-year open-label extension.<sup>78,79</sup> As many as 97.5% of patients (193 of 198 patients)

enrolled in the open-label extension and received OCA, but only 60% of patients completed 5 years of the OCA treatment and 52 patients who had received OCA in the double-blind phase of the trial completed 6 years of treatment after the open-label extension was complete. The mean total bilirubin remained stable through 72 months of OCA treatment, and throughout the study, there was no significant worsening in hepatic stiffness as measured by transient elastography in a subset of patients. During the open-label extension, only eight patients (4%) discontinued treatment due to pruritus.<sup>76</sup> Adverse events were consistent with the established safety profile of OCA in PBC, with no new safety observations during long-term treatment, out to 6 years.

Samur *et al.*<sup>80</sup> conducted a simulation analysis of the clinical impact and cost-effectiveness of OCA for the treatment of PBC. This study found that over a 15-year period, UDCA + OCA dual therapy could decrease the cumulative incidences of decompensated cirrhosis from 12.2% to 4.5%, of HCC from 9.1% to 4.0%, of liver-related mortality from 16.2% to 5.7%, and of liver transplantations from 4.5% to 1.2%. This combination also increased transplant-free survival from 61.1% to 72.9%.<sup>80</sup> Despite these substantial improvements in long-term outcomes, the authors concluded that OCA is not currently cost-effective, as the lifetime cost of PBC treatment would increase from \$63,000 to \$902,000 (a 1,330% increment) per patient.<sup>80</sup>

### Emerging therapies: What is new and what is in the pipeline

#### **Peroxisome proliferator-activated receptor- $\alpha$ and - $\gamma$ agonists**

The peroxisome proliferator-activated receptor (PPAR) subfamilies include  $\alpha$ ,  $\beta$ ,  $\delta$ , and  $\gamma$ , which regulate the transcription of various genes. PPAR- $\gamma$  is primarily found in the adipose tissue and the heart. An example of PPAR- $\gamma$  are the thiazolidinediones. PPAR- $\delta$  (also known as PPAR- $\beta$ ) is primarily found in the liver and in the peripheral tissues, and includes

drugs such as seladelpar (primarily PPAR- $\delta$  agonist). PPAR- $\alpha$  (i.e. fibrates), which is found in the liver, muscle, and kidneys, is involved in the beta oxidation of fatty acids and regulation of lipid metabolism. In addition, both PPAR- $\alpha$  and PPAR- $\delta$  are important regulators of bile acid homeostasis.<sup>72</sup> Both PPAR- $\alpha$  and PPAR- $\delta$  work by acting on transcription factors which reduce inflammation (thus lowering IgM) and increase bile acid excretion. The most common type of PPAR agonists are the fibrates, which include fenofibrate (more PPAR- $\alpha$  selective) and bezafibrate (pan-selective).

A recent trial of fibrates in PBC enrolled 100 Korean patients with UDCA-refractory PBC, including 71 patients who received UDCA monotherapy and 29 patients who received UDCA + fibrate therapy (either 160 mg/day fenofibrate or 400 mg/day bezafibrate). At follow-up after 18 months, the UDCA + fibrate group showed a higher probability of normalizing ALP levels compared to the UDCA monotherapy group (hazard ratio = 5.00, 95% confidence interval (CI): 2.87–8.73,  $p < 0.001$ ).<sup>81</sup> Another randomized controlled trial in Europe included 100 patients with PBC treated for 2 years with either UDCA + placebo or UDCA + bezafibrate (the BEZURSO trial).<sup>82</sup> In this study, combination therapy was associated with improvement in ALP and 30% of patients saw normalization on all liver function tests. The combination group in this study also reported improvement in pruritus. Bezafibrate, however, is not currently approved for use in the USA.

More recently, during AASLD's The Liver Meeting in 2019, it was published that bezafibrate was superior to placebo for the treatment of pruritus in cholestatic liver diseases, and authors concluded that it should be the first-line treatment of pruritus for patients with PBC and PSC, as determined from the Fibrates for Cholestatic ITCH Trial.<sup>83</sup> The primary endpoint of the study was a 50% reduction in pruritus on a visual analogue scale, and 43.7% of patients in the bezafibrate treatment arm achieved the primary endpoint compared to only 11% in the placebo arm ( $p = 0.003$ ).<sup>42</sup>

In addition, another pan-selective PPAR agonist, elafibranor, which targets both PPAR- $\alpha$  and PPAR- $\delta$ , has been studied in patients with PBC and results were discussed at the 2019 European Association for the Study of the Liver International Liver Congress Meeting. A phase 2 multi-center, double-blind, randomized, placebo-controlled clinical trial was reported to evaluate the efficacy and safety of elafibranor after 12 weeks of treatment in patients with PBC with inadequate response to UDCA. Forty-five patients were randomized into three arms: 1) elafibranor at 80 mg, 2) elafibranor at 120 mg, or 3) placebo. The primary endpoint of the study was a change in serum ALP at the end of 12 weeks compared to baseline. Both doses of elafibranor demonstrated a significant change in ALP, a decrease of 48% from baseline in the 80 mg group and 41% decrease in the 120 mg group; as expected, there was a ~3% increase in ALP from baseline in the placebo group. A key secondary endpoint from this trial was the responder rate for patients achieving the composite endpoint of serum ALP  $< 1.67 \times$  the ULN, and ALP decrease  $> 15\%$ , and total bilirubin  $< \text{ULN}$ . This secondary endpoint was achieved in approximately 67% patients for the 80 mg group ( $p = 0.001$ ) and 79% of patients in the 120 mg group ( $p < 0.001$ ), as compared to only 6.7% in the placebo group. As such, in July 2019, the USA FDA and the European Medicines Agency have granted Orphan Drug Designation to elafibranor for the treatment of PBC in addition to an upcoming phase 3 trial.

Seladelpar, a selective PPAR- $\delta$  agonist, has been studied in a randomized control trial of patients with PBC and NASH<sup>84</sup>

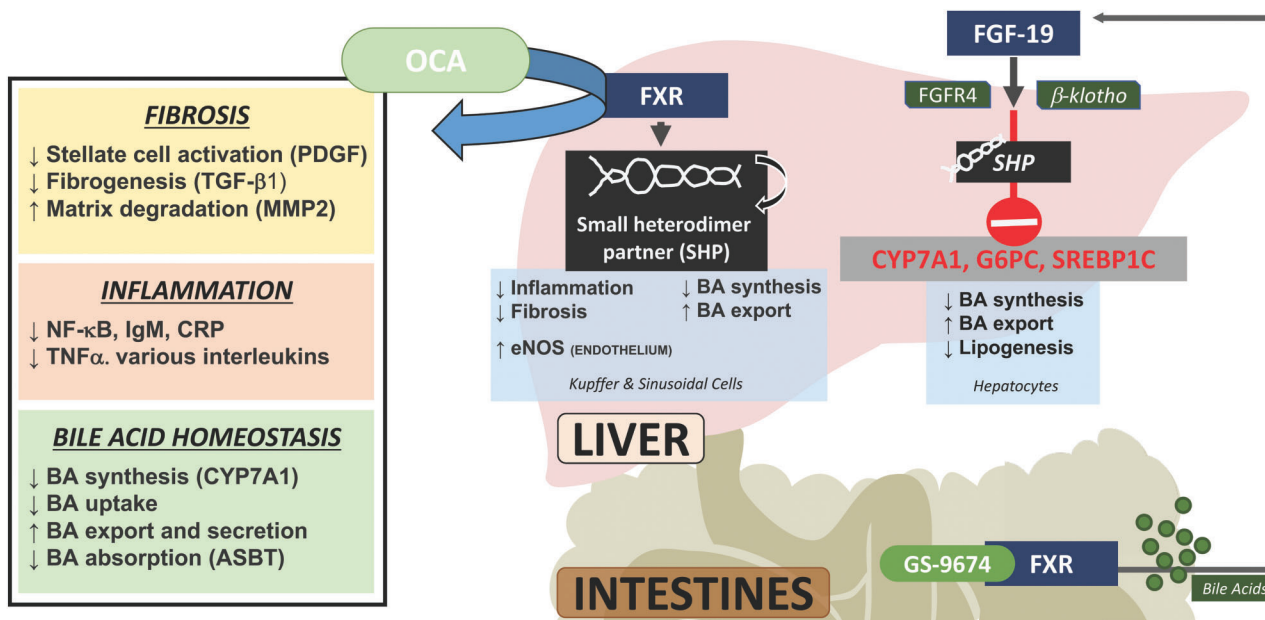
with primary endpoint of ALP levels  $< 1.67 \times$  the ULN in patients with PBC. In a phase II study, 70 patients were screened at 29 sites in North America and Europe. During the recruitment phase of the study, three of the seventy patients developed a reversible and asymptomatic increase in their alanine aminotransferase (ALT) levels (one patient on the 50 mg dose, and two on the 200 mg dose), ranging from just over 5- to 20-times the ULN. As such, the original study with higher doses was terminated, and a newer low-dose phase II study (5 mg and 10 mg of seladelpar groups) was initiated and the 12-week interim results were first published at the AASLD Liver Meeting in 2017,<sup>85</sup> showing 45% and 82% of patients on the 5 mg group and 10 mg group, respectively, achieved the primary endpoint. Additionally, 12% of the 5 mg group and 45% of the 10 mg group had ALP less than the ULN at week 12. This 12-week analysis also revealed improvements in other biochemical parameters as well, including significant decreases in ALT and cholesterol levels.<sup>85</sup> Given the promising results of the interim analysis, the study entered open enrollment extension phase to extend the duration, increase study participants, and add a 2 mg arm to assess the minimally effective dose.

Additionally, a phase III multicenter and international study (ENHANCE) was initiated at the end of 2018, and enrolled 265 patients by mid-November 2019. However, on November 25, 2019, the open-label extension phase of the study was placed on hold after a similar study which was evaluating the effectiveness of seladelpar in NASH patients found that patients receiving seladelpar had atypical histologic findings characterized as interface hepatitis. As such, although the interim data was promising, further investigations are placed on hold until investigators can try to identify a mechanism of action and to understand if the observed histological changes in patients taking seladelpar are NASH-specific or if this adverse event is universal among all liver disease etiologies.

### **Fibroblast growth factor-19 analogues (antifibrotic and anti-inflammatory)**

Fibroblast growth factor (FGF)-19 is an endocrine hormone that is induced by the activation of the FXR in ileal enterocytes.<sup>86</sup> After its activation, FGF-19 acts on hepatocytes to repress bile acid synthesis and gluconeogenesis, and to stimulate hepatic glycogenesis and protein synthesis (Fig. 2).<sup>86</sup> FGF-19 is part of a signaling pathway that regulates the enterohepatic response of bile acid synthesis. In the normal liver, FGF-19 expression is absent; however, in cholestatic liver diseases, FGF-19 expression is increased in the liver, in response to both extrahepatic and intrahepatic cholestasis.<sup>87</sup> Recent evidence also suggests an antifibrotic activity of FGF-19 analogues.<sup>87</sup> For example, FGF-19 is also involved in the regulation of proinflammatory cytokines in the cholangiocytes.<sup>87</sup> Serum levels of FGF-19 correlate with worse liver enzyme biochemistry levels; an elevated serum FGF-19 was also seen in UDCA nonresponders, allowing one study to conclude that PBC induces changes in bile acid synthesis and that FGF-19 levels correlate with liver disease severity in cholestatic liver diseases.<sup>88</sup> That same study found that administering an FGF-19 mimetic can increase circulating FGF-19 and thus suppress bile acid synthesis.

In a multicenter randomized, double-blind, placebo-controlled phase II clinical trial is investigating the use of NGM282 (FGF-19 analogue) for the treatment of PBC in



**Fig. 2. Steroidal and nonsteroidal FXR agonists and FGF-19 mechanism of action.** FXR is a nuclear hormone receptor that is highly expressed in the gastrointestinal tract, adrenal glands, kidneys, and the liver. FXR is the primary regulator of BA homeostasis. By activating FXR, OCA is a steroidal FXR agonist and it is expected to do three things: 1) decrease fibrosis by decreasing fibrogenesis, stellate cell activation, and increase matrix degradation, 2) decrease inflammation, and 3) regulate BA homeostasis by decreasing its synthesis, uptake and absorption, and increasing its secretion. GS-9674 is a nonsteroidal FXR agonist in the intestine, which triggers release of FGF-19 from the intestinal mucosa. FGF-19, which is an endocrine hormone, then binds to hepatic receptor complex tyrosine kinase FGFR4 and its co-receptor  $\beta$ -klotho, which inhibits the gene transcription of the CYP7A1 BA synthesis gene (encoding cholesterol 7- $\alpha$ -hydroxylase), the SREBP1c lipogenic gene (encoding sterol regulatory element-binding protein 1C), and the G6PC gluconeogenic gene (encoding the glucose-6-phosphatase catalytic subunit), leading to decreases in BA synthesis, lipogenesis, and gluconeogenesis. Concurrently, FXR in the liver induces SHP, a negative nuclear receptor, which in turn also inhibits gene transcription of CYP7A1, SREBP1c, and G6PC. Cilofexor (GS-9674) has been shown to significantly reduce fibrosis and portal hypertension in a murine model of nonalcoholic steatohepatitis, to have anti-inflammatory property *in vivo*, and to increase eNOS.

Abbreviations: BA, bile acid; eNOS, endothelial nitric oxide synthase; FGF, fibroblast growth factor; FXR, farnesoid X receptor; OCA, obeticholic acid; SHP, small heterodimer partner.

patients who had inadequate response to UDCA.<sup>51</sup> The authors conclude that the administration of NGM282 (14 patients in the 0.3 mg group, 13 patients in the 3 mg group, and 15 patients in the placebo group) reduced ALP levels and transaminase levels, as well as markers of cholestasis, hepatocellular injury and inflammation (IgM levels) in a follow-up of 28 days. The 0.3 mg group had an average of 15.9% decrease in ALP levels (95% CI: 3.9%–25.6%,  $p < 0.001$ ) versus an average of 19.0% decrease in ALP in the 3 mg group (95% CI: 6.7%–29.0%,  $p < 0.001$ ). However, longer length studies are needed to assess overall effectiveness and tolerability.

#### Other FXR agonists (nonsteroidal)

FXRs are nuclear hormone receptors that are integral in bilirubin metabolism, primarily in the liver. The most common FXR agonist studied and approved for treatment of PBC is OCA. Bile acids are the naturally occurring ligands of FXR. FXRs regulate the rate-limiting step in bile acid synthesis (Fig. 2).<sup>89</sup> FXR activation protects against cholestatic-induced liver injury, and other studies have shown a protective effect of FXR activation in patients with nonalcoholic fatty liver disease.<sup>89,90</sup> Additional FXR agonists are being investigated for PBC, including in a phase II dose-ranging, randomized, double-blind, placebo-controlled trial, currently recruiting participants to evaluate the safety, tolerability, pharmacokinetics, and efficacy of EDP-305 in patients with PBC with or

without incomplete response to UDCA (ClinicalTrials.gov Identifier: NCT03394924).

In a recent phase II, randomized, double-blind, placebo controlled trial of 71 patients, the safety, efficacy, and tolerability of cilofexor (GS-9674, which is a non-steroidal FXR agonist) evaluated in patients without advanced PBC. Fig. 2 shows the mechanism of action of this drug. This trial was completed recently, and the results of the phase II trial were presented at AASLD's The Liver Meeting in 2019. The authors demonstrated that patients treated with cilofexor at 100 mg had significant decreases (compared to placebo) in serum ALP, gamma-glutamyltransferase, and ALT levels (ALP mean reduction of -13.8%,  $p = 0.005$ ; gamma-glutamyltransferase mean reduction of 47.7%,  $p < 0.001$ ; ALT mean reduction of -17.8%,  $p = 0.08$ ).<sup>91</sup> The study also showed a significant reduction in primary bile acids compared to placebo (reduction of -30.5%,  $p = 0.0008$ ). At the same meeting, patient-reported outcomes in patients with PSC during treatment with cilofexor were reported.<sup>92</sup> Patient-reported outcomes are important markers in clinical outcomes and contribute greatly to the efficacy of a drug. During long-term treatment with 100 mg cilofexor, patients experienced improvement in some aspects of their patient-reported outcomes.<sup>92</sup>

#### Antifibrotic agents

Cholangiocyte injury and leakage of bile acid into the liver parenchyma are the key events in fibrosis progression in PBC



and other cholestatic liver diseases.<sup>93</sup> Hepatic stellate cell activation is ultimately the final common pathway in the formation of fibrosis in chronic liver diseases. NADPH oxidase (referred to as NOX) plays a role in stellate cell-mediated fibrogenesis. *In vivo* data has demonstrated that setanaxib (a dual inhibitor of NOX1 and NOX2) may be an effective antifibrotic drug in PBC.<sup>93</sup> Additional studies are needed, however, to prove the efficacy of this and other compounds in human patients.

#### **Norursodeoxycholic acid and tauroursodeoxycholic acid**

The molecular structure of norursodeoxycholic acid (norUDCA) is similar to UDCA, except that it lacks a methylene group in its side-chain. In theory, norUDCA can then allow for cholehepatic shunting of bile salts, instead of by enterohepatic circulation. norUDCA can also stimulate secretion of cholangiocytes found in bile ducts, which can help flush the ducts of bile salts and reinforce the ductal wall epithelium. The use of norUDCA as treatment has been shown to be beneficial in PSC, yet its usefulness in PBC has yet to be elucidated. Multiple animal studies have shown improvement in fibrosis and inflammation in mice with cholestatic liver diseases treated with norUDCA, including PBC.<sup>94,95</sup> A multicenter, double-blind trial in China comparing tauroursodeoxycholic acid and UDCA was completed in 2013 and showed that tauroursodeoxycholic acid was non-inferior to UDCA in biochemical response and had a better profile in mitigating symptoms associated with PBC.<sup>96</sup> Further studies are needed in the USA to account for external validity of this trial.

#### **Ileal apical sodium-dependent bile acid transporter inhibitors**

The apical sodium-dependent bile acid transporter (ASBT) is found in the brush-border membrane primarily expressed in the distal ileum. It is responsible for the reuptake of bile acids and the maintenance of the enterohepatic circulation. ASBT is up-regulated in PBC patients; therefore, the inhibition of ASBT may counteract the toxicity caused by bile acids. Studies have shown that by inhibiting ASBT, both cholestatic injury and fibrosis improves by increasing bile acid excretion in fecal matter.<sup>97</sup> There is currently a phase II trial underway that is comparing combination therapy of a selective ASBT inhibitor (lopixibat) with UDCA; the preliminary results, however, show poor effects on ALP and pruritus, though there are reductions in transaminases.<sup>98</sup>

#### **Immunomodulating agents**

Since PBC is an autoimmune disease, various immunological hallmarks have been implicated in its pathogenesis, including humoral, cytotoxic and the innate immune response in destroying the small bile ducts. Rituximab is an anti-CD20 monoclonal antibody that selectively decreases B cells and which has been used for years in other autoimmune diseases, such as rheumatoid arthritis, and other immune-mediated disorders.<sup>99</sup> Although this drug is used in other autoimmune disorders, a study evaluating 14 patients who did not respond to UDCA were given rituximab. Six months after starting infusion therapy, there was a decrease in auto-antibody production and a significant decrease in pruritus

but no significant decrease was observed in ALP levels.<sup>99</sup> Another phase II trial was completed in the UK to evaluate symptoms of fatigue in 71 patients with PBC.<sup>100</sup> Using an intention-to-treat analysis, this study found significant decrease in fatigue at 3 months between the rituximab and placebo arms (adjusted mean difference  $-0.9$ , 95% CI:  $-4.6-3.1$ ). Another open-label, active treatment study was recently completed in 2018, which studied the efficacy and safety of abatacept for the treatment of PBC in patients with incomplete response to UDCA. This study showed that, much like other biologic therapies, the treatment was ineffective in achieving biochemical responses associated with improved clinical outcomes.<sup>101</sup>

In addition, another biologic therapy has failed to show significant reductions in biochemical markers of cholestasis. A phase 2 open-label trial using ustekinumab, an anti-interleukin-12/23 monoclonal antibody, for PBC patients with inadequate response to UDCA showed a modest decrease in ALP after 28 weeks of therapy that was not significant, and overt proof-of-concept was not established per the *a priori* primary endpoint's proposed efficacy.<sup>45,102</sup>

#### **Conclusions, remarks, and future directions**

PBC is a chronic and slowly progressive cholestatic liver disease that is caused by the autoimmune and non-suppurative destruction of the bile ducts which can lead to fibrosis and eventually cirrhosis. Mainstay treatments include UDCA as first-line standard of care therapy, while OCA is used as an adjuvant therapeutic agent for patients with incomplete response to UDCA or as a first-line agent for patients who cannot tolerate UDCA. Although UDCA continues to be the mainstay treatment, UDCA leaves over one-third of patients at risk for disease progression by using methods described in Table 2. Other than UDCA and OCA, there are no other FDA-approved treatment agents for PBC at this time. As such, this review provides information regarding the promising therapeutic landscape for PBC, including many agents which are currently under clinical trials. New anticholestatic pharmacologic agents, such as PPAR agonists, choleretics, bile acid suppressants, antifibrotics and anti-inflammatories, provide promising outlooks for treatment of PBC and possibly other diseases of cholestasis and NASH. In addition, early emerging data indicates combination therapy may also contribute to the landscape of PBC treatments with improved efficacy and potential benefits in symptoms such as pruritus and fatigue, and in quality of life.

#### **Funding**

None to declare.

#### **Conflict of interest**

The authors have no conflict of interests related to this publication.

#### **Author contributions**

Formulated manuscript, drafting of the manuscript, responsible for organization of content, critical editing of manuscript (AG), writing of the manuscript, organization and formulation of content, major editing (CH), writing of the manuscript (JZ),

formulation and organization of drafts, major content revisions and additions, expert review, study supervision (EWH), formulation and organization of drafts, major content revisions and additions, expert review, study supervision (KKY).

## References

- [1] Sylvestre PB, Batts KP, Burgart LJ, Poterucha JJ, Wiesner RH. Recurrence of primary biliary cirrhosis after liver transplantation: Histologic estimate of incidence and natural history. *Liver Transpl* 2003;9:1086–1093. doi: 10.1053/jlts.2003.50213.
- [2] Younossi ZM, Bernstein D, Shiffman ML, Kwo P, Kim WR, Kowdley KV, *et al*. Diagnosis and management of primary biliary cholangitis. *Am J Gastroenterol* 2019;114:48–63. doi: 10.1038/s41395-018-0390-3.
- [3] Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, Williams JL, *et al*. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: Update 2018. *Gastroenterology* 2019;156:254–272.e11. doi: 10.1053/j.gastro.2018.08.063.
- [4] Podda M, Selmi C, Lleo A, Moroni L, Invernizzi P. The limitations and hidden gems of the epidemiology of primary biliary cirrhosis. *J Autoimmun* 2013;46:81–87. doi: 10.1016/j.jaut.2013.06.015.
- [5] Poordad F. Diagnosis, treatment, and monitoring of patients with primary biliary cholangitis. *Gastroenterol Hepatol (N Y)* 2016;12:561–564.
- [6] Hamlyn AN, Macklon AF, James O. Primary biliary cirrhosis: geographical clustering and symptomatic onset seasonality. *Gut* 1983;24:940–945. doi: 10.1136/gut.24.10.940.
- [7] Boonstra K, Kunst AE, Stadhouders PH, Tuynman HA, Poen AC, van Nieuwkerk KM, *et al*. Rising incidence and prevalence of primary biliary cirrhosis: a large population-based study. *Liver Int* 2014;34:e31–e38. doi: 10.1111/liv.12434.
- [8] McNally RJ, James PW, Ducker S, Norman PD, James OF. No rise in incidence but geographical heterogeneity in the occurrence of primary biliary cirrhosis in North East England. *Am J Epidemiol* 2014;179:492–498. doi: 10.1093/aje/kwt308.
- [9] Lu M, Li J, Haller IV, Romanelli RJ, VanWormer JJ, Rodriguez CV, *et al*. Factors associated with prevalence and treatment of primary biliary cholangitis in United States health systems. *Clin Gastroenterol Hepatol* 2018;16:1333–1341.e6. doi: 10.1016/j.cgh.2017.10.018.
- [10] Kim KA, Ki M, Choi HY, Kim BH, Jang ES, Jeong SH. Population-based epidemiology of primary biliary cirrhosis in South Korea. *Aliment Pharmacol Ther* 2016;43:154–162. doi: 10.1111/apt.13448.
- [11] Lleo A, Jepsen P, Morengi E, Carbone M, Moroni L, Battezzati PM, *et al*. Evolving trends in female to male incidence and male mortality of primary biliary cholangitis. *Sci Rep* 2016;6:25906. doi: 10.1038/srep25906.
- [12] Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. *J Hepatol* 2012;56:1181–1188. doi: 10.1016/j.jhep.2011.10.025.
- [13] Chuang N, Gross RG, Odin JA. Update on the epidemiology of primary biliary cirrhosis. *Expert Rev Gastroenterol Hepatol* 2011;5:583–590. doi: 10.1586/egh.11.66.
- [14] Cheung KS, Seto WK, Fung J, Lai CL, Yuen MF. Epidemiology and natural history of primary biliary cholangitis in the Chinese: A territory-based study in Hong Kong between 2000 and 2015. *Clin Transl Gastroenterol* 2017;8:e116. doi: 10.1038/ctg.2017.43.
- [15] Rautiainen H, Salomaa V, Niemelä S, Karvonen AL, Nurmi H, Isoniemi H, *et al*. Prevalence and incidence of primary biliary cirrhosis are increasing in Finland. *Scand J Gastroenterol* 2007;42:1347–1353. doi: 10.1080/00365520701396034.
- [16] Selmi C, Invernizzi P, Keeffe EB, Coppel RL, Podda M, Rossaro L, *et al*. Epidemiology and pathogenesis of primary biliary cirrhosis. *J Clin Gastroenterol* 2004;38:264–271. doi: 10.1097/00004836-200403000-00013.
- [17] Abu-Mouch S, Selmi C, Benson GD, Kenny TP, Invernizzi P, Zuin M, *et al*. Geographic clusters of primary biliary cirrhosis. *Clin Dev Immunol* 2003;10:127–131. doi: 10.1080/10446670310001626526.
- [18] Kim WR, Lindor KD, Locke GR 3rd, Therneau TM, Homburger HA, Batts KP, *et al*. Epidemiology and natural history of primary biliary cirrhosis in a US community. *Gastroenterology* 2000;119:1631–1636. doi: 10.1053/gast.2000.20197.
- [19] Carey EJ, Ali AH, Lindor KD. Primary biliary cirrhosis. *Lancet* 2015;386:1565–1575. doi: 10.1016/S0140-6736(15)00154-3.
- [20] Marschall HU, Henriksson I, Lindberg S, Söderdahl F, Thuresson M, Wahlin S, *et al*. Incidence, prevalence, and outcome of primary biliary cholangitis in a nationwide Swedish population-based cohort. *Sci Rep* 2019;9:11525. doi: 10.1038/s41598-019-47890-2.
- [21] Marzioni M, Bassaneli C, Ripellino C, Urbinati D, Alvaro D. Epidemiology of primary biliary cholangitis in Italy: Evidence from a real-world database. *Dig Liver Dis* 2019;51:724–729. doi: 10.1016/j.dld.2018.11.008.
- [22] Bowlus CL, Gershwin ME. The diagnosis of primary biliary cirrhosis. *Autoimmun Rev* 2014;13:441–444. doi: 10.1016/j.autrev.2014.01.041.
- [23] Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2018 practice guidance from the American Association for the study of liver diseases. *Hepatology* 2019;69:394–419. doi: 10.1002/hep.30145.
- [24] Ala A, Stanca CM, Bu-Ghanim M, Ahmado I, Branch AD, Schiano TD, *et al*. Increased prevalence of primary biliary cirrhosis near Superfund toxic waste sites. *Hepatology* 2006;43:525–531. doi: 10.1002/hep.21076.
- [25] Webb GJ, Siminovitch KA, Hirschfield GM. The immunogenetics of primary biliary cirrhosis: A comprehensive review. *J Autoimmun* 2015;64:42–52. doi: 10.1016/j.jaut.2015.07.004.
- [26] Cordell HJ, Han Y, Mells GF, Li Y, Hirschfield GM, Greene CS, *et al*. International genome-wide meta-analysis identifies new primary biliary cirrhosis risk loci and targetable pathogenic pathways. *Nat Commun* 2015;6:8019. doi: 10.1038/ncomms9019.
- [27] Hirschfield GM, Liu X, Xu C, Lu Y, Xie G, Lu Y, *et al*. Primary biliary cirrhosis associated with HLA, IL12A, and IL12RB2 variants. *N Engl J Med* 2009;360:2544–2555. doi: 10.1056/NEJMoa0810440.
- [28] Nakamura M, Nishida N, Kawashima M, Aiba Y, Tanaka A, Yasunami M, *et al*. Genome-wide association study identifies TNFSF15 and POU2AF1 as susceptibility loci for primary biliary cirrhosis in the Japanese population. *Am J Hum Genet* 2012;91:721–728. doi: 10.1016/j.ajhg.2012.08.010.
- [29] Liu JZ, Almarri MA, Gaffney DJ, Mells GF, Jostins L, Cordell HJ, *et al*. Dense fine-mapping study identifies new susceptibility loci for primary biliary cirrhosis. *Nat Genet* 2012;44:1137–1141. doi: 10.1038/ng.2395.
- [30] Flores A, Mayo MJ. Primary biliary cirrhosis in 2014. *Curr Opin Gastroenterol* 2014;30:245–252. doi: 10.1097/MOG.0000000000000058.
- [31] Chan CY, Lee SD, Huang YS, Wu JC, Tsai YT, Tsay SH, *et al*. Primary biliary cirrhosis in Taiwan. *J Gastroenterol Hepatol* 1990;5:560–565. doi: 10.1111/j.1440-1746.1990.tb01441.x.
- [32] Sakauchi F, Mori M, Zeniya M, Toda G. A cross-sectional study of primary biliary cirrhosis in Japan: utilization of clinical data when patients applied to receive public financial aid. *J Epidemiol* 2005;15:24–28. doi: 10.2188/jea.15.24.
- [33] Lohse AW, Weiler-Normann C. Not all PBC is the same! *Gastroenterology* 2013;144:494–497. doi: 10.1053/j.gastro.2013.01.032.
- [34] Tanakaa A, Leung PS, Young HA, Gershwin ME. Toward solving the etiological mystery of primary biliary cholangitis. *Hepatol Commun* 2017;1:275–287. doi: 10.1002/hep4.1044.
- [35] Walden HR, Kirby JA, Yeaman SJ, Gray J, Jones DE, Palmer JM. Xenobiotic incorporation into pyruvate dehydrogenase complex can occur via the exogenous lipoylation pathway. *Hepatology* 2008;48:1874–1884. doi: 10.1002/hep.22540.
- [36] Yeaman SJ, Kirby JA, Jones DE. Autoreactive responses to pyruvate dehydrogenase complex in the pathogenesis of primary biliary cirrhosis. *Immunol Rev* 2000;174:238–249. doi: 10.1034/j.1600-0528.2002.00021h.x.
- [37] Onofrio FQ, Hirschfield GM, Gulamhusein AF. A practical review of primary biliary cholangitis for the gastroenterologist. *Gastroenterol Hepatol (NY)* 2019;15:145–154.
- [38] Kaplan MM, Gershwin ME. Primary biliary cirrhosis. *N Engl J Med* 2005;353:1261–1273. doi: 10.1056/NEJMra043898.
- [39] Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ. Primary biliary cirrhosis. *Hepatology* 2009;50:291–308. doi: 10.1002/hep.22906.
- [40] Boberg KM, Chapman RW, Hirschfield GM, Lohse AW, Manns MP, Schrupf E. Overlap syndromes: The International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. *J Hepatol* 2011;54:374–385. doi: 10.1016/j.jhep.2010.09.002.
- [41] Lee YM, Kaplan MM. The natural history of PBC: has it changed? *Semin Liver Dis* 2005;25:321–326. doi: 10.1055/s-2005-916323.
- [42] Kuiper EM, Hansen BE, de Vries RA, den Ouden-Muller JW, van Ditzhuijsen TJ, Haagsma EB, *et al*. Improved prognosis of patients with primary biliary cirrhosis that have a biochemical response to ursodeoxycholic acid. *Gastroenterology* 2009;136:1281–1287. doi: 10.1053/j.gastro.2009.01.003.
- [43] Janmohamed A, Trivedi PJ. Patterns of disease progression and incidence of complications in primary biliary cholangitis (PBC). *Best Pract Res Clin Gastroenterol* 2018;34–35:71–83. doi: 10.1016/j.bpg.2018.06.002.
- [44] Springer J, Cauch-Dudek K, O'Rourke K, Wanless IR, Heathcote EJ. Asymptomatic primary biliary cirrhosis: a study of its natural history and prognosis. *Am J Gastroenterol* 1999;94:47–53. doi: 10.1111/j.1572-0241.1999.00770.x.
- [45] Hirschfield GM, Gershwin ME. The immunobiology and pathophysiology of primary biliary cirrhosis. *Annu Rev Pathol* 2013;8:303–330. doi: 10.1146/annurev-pathol-020712-164014.
- [46] Cheung AC, LaRusso NF, Gores GJ, Lazaridis KN. Epigenetics in the primary biliary cholangitis and primary sclerosing cholangitis. *Semin Liver Dis* 2017;37:159–174. doi: 10.1055/s-0037-1603324.
- [47] Xie YQ, Ma HD, Lian ZX. Epigenetics and primary biliary cirrhosis: a comprehensive review and implications for autoimmunity. *Clin Rev Allergy Immunol* 2016;50:390–403. doi: 10.1007/s12016-015-8502-y.

- [48] Worman HJ, Courvalin JC. Antinuclear antibodies specific for primary biliary cirrhosis. *Autoimmun Rev* 2003;2:211–217. doi: 10.1016/s1568-9972(03)00013-2.
- [49] Poupon R, Chazouillères O, Balkau B, Poupon RE. Clinical and biochemical expression of the histopathological lesions of primary biliary cirrhosis. UDCA-PBC Group. *J Hepatol* 1999;30:408–412. doi: 10.1016/s0168-8278(99)80098-1.
- [50] Lammers WJ, van Buuren HR, Hirschfield GM, Janssen HL, Invernizzi P, Mason AL, *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;147:1338–1349.e5; quiz e15. doi: 10.1053/j.gastro.2014.08.029.
- [51] Mayo MJ, Wigg AJ, Leggett BA, Arnold H, Thompson AJ, Weltman M, *et al*. NGM282 for treatment of patients with primary biliary cholangitis: A multicenter, randomized, double-blind, placebo-controlled trial. *Hepatology* 2018;2:1037–1050. doi: 10.1002/hep4.1209.
- [52] Corpechot C, Abenavoli L, Rabahi N, Chrétien Y, Andréani T, Johanet C, *et al*. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. *Hepatology* 2008;48:871–877. doi: 10.1002/hep.22428.
- [53] Corpechot C, Poujol-Robert A, Wendum D, Galotte M, Chrétien Y, Poupon RE, *et al*. Biochemical markers of liver fibrosis and lymphocytic piecemeal necrosis in UDCA-treated patients with primary biliary cirrhosis. *Liver Int* 2004;24:187–193. doi: 10.1111/j.1478-3231.2004.0918.x.
- [54] Corpechot C, Carrat F, Poujol-Robert A, Gaouar F, Wendum D, Chazouillères O, *et al*. Noninvasive elastography-based assessment of liver fibrosis progression and prognosis in primary biliary cirrhosis. *Hepatology* 2012;56:198–208. doi: 10.1002/hep.25599.
- [55] Goodman ZD. Grading and staging systems for inflammation and fibrosis in chronic liver diseases. *J Hepatol* 2007;47:598–607. doi: 10.1016/j.jhep.2007.07.006.
- [56] Kovač JD, Weber MA. Primary biliary cirrhosis and primary sclerosing cholangitis: an update on MR imaging findings with recent developments. *J Gastrointest Liver Dis* 2016;25:517–524. doi: 10.15403/jgld.2014.1121.254.vac.
- [57] Trivedi PJ, Lammers WJ, van Buuren HR, Parés A, Floreani A, Janssen HL, *et al*. Stratification of hepatocellular carcinoma risk in primary biliary cirrhosis: a multicentre international study. *Gut* 2016;65:321–329. doi: 10.1136/gutjnl-2014-308351.
- [58] Silveira MG, Gossard AA, Stahler AC, Jorgensen RA, Petz JL, Ali AH, *et al*. A randomized, placebo-controlled clinical trial of efficacy and safety: Modafinil in the treatment of fatigue in patients with primary biliary cirrhosis. *Am J Ther* 2017;24:e167–e176. doi: 10.1097/MJT.0000000000000387.
- [59] Locke GR 3rd, Therneau TM, Ludwig J, Dickson ER, Lindor KD. Time course of histological progression in primary biliary cirrhosis. *Hepatology* 1996;23:52–56. doi: 10.1002/hep.510230108.
- [60] Mitchison HC, Lucey MR, Kelly PJ, Neuberger JM, Williams R, James OF. Symptom development and prognosis in primary biliary cirrhosis: a study in two centers. *Gastroenterology* 1990;99:778–784. doi: 10.1016/0016-5085(90)90968-7.
- [61] Prince MI, Chetwynd A, Craig WL, Metcalf JV, James OF. Asymptomatic primary biliary cirrhosis: clinical features, prognosis, and symptom progression in a large population based cohort. *Gut* 2004;53:865–870. doi: 10.1136/gut.2003.023937.
- [62] Bahar R, Wong KA, Liu CH, Bowlus CL. Update on new drugs and those in development for the treatment of primary biliary cholangitis. *Gastroenterol Hepatol (NY)* 2018;14:154–163.
- [63] Floreani A, Mangini C. Primary biliary cholangitis: Old and novel therapy. *Eur J Intern Med* 2018;47:1–5. doi: 10.1016/j.ejim.2017.06.020.
- [64] Chascsa D, Carey EJ, Lindor KD. Old and new treatments for primary biliary cholangitis. *Liver Int* 2017;37:490–499. doi: 10.1111/liv.13294.
- [65] Harms MH, Lammers WJ, Thorburn D, Corpechot C, Invernizzi P, Janssen HLA, *et al*. Major hepatic complications in ursodeoxycholic acid-treated patients with primary biliary cholangitis: Risk factors and time trends in incidence and outcome. *Am J Gastroenterol* 2018;113:254–264. doi: 10.1038/ajg.2017.440.
- [66] Angulo P, Lindor KD, Therneau TM, Jorgensen RA, Malinchoc M, Kamath PS, *et al*. Utilization of the Mayo risk score in patients with primary biliary cirrhosis receiving ursodeoxycholic acid. *Liver* 1999;19:115–121. doi: 10.1111/j.1478-3231.1999.tb00020.x.
- [67] Parés A, Caballería L, Rodés J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic acid. *Gastroenterology* 2006;130:715–720. doi: 10.1053/j.gastro.2005.12.029.
- [68] Momah N, Silveira MG, Jorgensen R, Sinakos E, Lindor KD. Optimizing biochemical markers as endpoints for clinical trials in primary biliary cirrhosis. *Liver Int* 2012;32:790–795. doi: 10.1111/j.1478-3231.2011.02678.x.
- [69] Lammers WJ, Hirschfield GM, Corpechot C, Nevens F, Lindor KD, Janssen HL, *et al*. Development and validation of a scoring system to predict outcomes of patients with primary biliary cirrhosis receiving ursodeoxycholic acid therapy. *Gastroenterology* 2015;149:1804–1812.e4. doi: 10.1053/j.gastro.2015.07.061.
- [70] Carbone M, Sharp SJ, Flack S, Paximadas D, Spiess K, Adgey C, *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 cholangitis. *Hepatology* 2016;63:930–950. doi: 10.1002/hep.28017.
- [71] Efe C, Taşçılar K, Henriksson I, Lytyvyak E, Alakim F, Trivedi H, *et al*. Validation of risk scoring systems in ursodeoxycholic acid-treated patients with primary biliary cholangitis. *Am J Gastroenterol* 2019;114:1101–1108. doi: 10.14309/ajg.0000000000000290.
- [72] Santiago P, Scheinberg AR, Levy C. Cholestatic liver diseases: new targets, new therapies. *Therap Adv Gastroenterol* 2018;11:1756284818787400. doi: 10.1177/1756284818787400.
- [73] Erlinger S. Obeticholic acid in primary biliary cholangitis. *Clin Res Hepatol Gastroenterol* 2017;41:3–5. doi: 10.1016/j.clinre.2016.09.006.
- [74] Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, *et al*. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. *N Engl J Med* 2016;375:631–643. doi: 10.1056/NEJMoa1509840.
- [75] Hirschfield GM, Mason A, Luketic V, Lindor K, Gordon SC, Mayo M, *et al*. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. *Gastroenterology* 2015;148:751–761.e8. doi: 10.1053/j.gastro.2014.12.005.
- [76] Yimam KK, Bowlus CL. Obeticholic acid for the treatment of primary biliary cirrhosis. *Expert Rev Clin Pharmacol* 2014;2:1351–1358. doi: 10.1517/21678707.2014.964206.
- [77] Roda A, Aldini R, Camborata C, Spinozzi S, Franco P, Cont M, *et al*. Metabolic profile of obeticholic acid and endogenous bile acids in rats with decompensated liver cirrhosis. *Clin Transl Sci* 2017;10:292–301. doi: 10.1111/cts.12468.
- [78] Trauner MH, Nevens F, Shiffman ML, Drenth J, Bowlus CL, Vargas V, *et al*. Durable response in the markers of cholestasis through 36 months of open-label extension study of obeticholic acid in primary biliary cholangitis. *Gastroenterology* 2018;154:S-1211–S-1212. doi: 10.1016/S0016-5085(18)34002-2.
- [79] Nevens F, Shiffman ML, Drent JPH, Bowlus CL, Vargas V, Andreone P, *et al*. Durable response in the markers of cholestasis through 5 years of open-label extension study of obeticholic acid in primary biliary cholangitis. *Hepatology* 2019;70:1481A–1482A.
- [80] Samur S, Klebanoff M, Banken R, Pratt DS, Chapman R, Ollendorf DA, *et al*. Long-term clinical impact and cost-effectiveness of obeticholic acid for the treatment of primary biliary cholangitis. *Hepatology* 2017;65:920–928. doi: 10.1002/hep.28932.
- [81] Chung SW, Lee JH, Kim MA, Leem G, Kim SW, Chang Y, *et al*. Additional fibrate treatment in UDCA-refractory PBC patients. *Liver Int* 2019;39:1776–1785. doi: 10.1111/liv.14165.
- [82] Corpechot C, Chazouillères O, Rousseau A, Guyader D, Habersetzer F, Mathurin P, *et al*. A 2-year multicenter, double-blind, randomized, placebo-controlled study of bezafibrate for the treatment of primary biliary cholangitis in patients with inadequate biochemical response to ursodeoxycholic acid therapy (Bezurso). *J Hepatol* 2017;66:S89. doi: 10.1016/S0168-8278(17)30442-7.
- [83] de Vries E, Bolier R, Goet J, Pares A, Verbeek JPHM, Vree MD, *et al*. Bezafibrate is more effective than placebo in pruritus of chronic cholestasis: The fitz trial. *Hepatology* 2019;70:9A.
- [84] Jones D, Boudes PF, Swain MG, Bowlus CL, Galambos MR, Bacon BR, *et al*. Seladelpar (MBX-8025), a selective PPAR- $\delta$  agonist, in patients with primary biliary cholangitis with an inadequate response to ursodeoxycholic acid: a double-blind, randomised, placebo-controlled, phase 2, proof-of-concept study. *Lancet Gastroenterol Hepatol* 2017;2:716–726. doi: 10.1016/S2468-1253(17)30246-7.
- [85] Hirschfield G, Boudes P, Bowlus C, Gitlin N, Michael G, Harrison S, *et al*. Treatment efficacy and safety of seladelpar, a selective peroxisome proliferator-activated receptor delta agonist, in primary biliary cholangitis patients: 12- and 26-week analysis from an ongoing international, randomized, dose rasing phase 2 study. *J Hepatol* 2018;68:S105–S106. doi: 10.1016/S0168-8278(18)30429-X.
- [86] Kliewer SA, Mangelsdorf DJ. Bile acids as hormones: The FXR-FGF15/19 pathway. *Dig Dis* 2015;33:327–331. doi: 10.1159/000371670.
- [87] Li Z, Lin B, Lin G, Wu Y, Jie Y, Li X, *et al*. Circulating FGF19 closely correlates with bile acid synthesis and cholestasis in patients with primary biliary cirrhosis. *PLoS One* 2017;12:e0178580. doi: 10.1371/journal.pone.0178580.
- [88] Wunsch E, Milkiewicz M, Wasik U, Trottier J, Kempinska-Podhorodecka A, Elias E, *et al*. Expression of hepatic Fibroblast Growth Factor 19 is enhanced in Primary Biliary Cirrhosis and correlates with severity of the disease. *Sci Rep* 2015;5:13462. doi: 10.1038/srep13462.
- [89] Ali AH, Carey EJ, Lindor KD. Recent advances in the development of farnesoid X receptor agonists. *Ann Transl Med* 2015;3:5. doi: 10.3978/j.issn.2305-5839.2014.12.06.
- [90] Liu X, Green RM. Beyond Farnesoid X receptor to target new therapies for NAFLD. *Hepatology* 2017;66:1724–1726. doi: 10.1002/hep.29411.

- [91] Kowdley KV, Minuk GY, Pagadala MR, Gulamhusein A, Swain MG, Neff GW, *et al*. The nonsteroidal farnesoid x receptor (FXR) agonist cilofexor improves liver biochemistry in patients with primary biliary cholangitis (PBC): A phase 2, randomized, placebo-controlled trial. *Hepatology* 2019; 70:31A–32A.
- [92] Younossi ZM, Stepanova M, Nader F, Gulamhusein A, Hameed B, Thorburn D, *et al*. Patient-reported outcomes (PROS) in patients with primary sclerosing cholangitis (PSC) during treatment with cilofexor (GS-9674). *Hepatology* 2019;70:805A–806A.
- [93] Jiang JX, Venugopal S, Serizawa N, Chen X, Scott F, Li Y, *et al*. Reduced nicotinamide adenine dinucleotide phosphate oxidase 2 plays a key role in stellate cell activation and liver fibrogenesis in vivo. *Gastroenterology* 2010;139:1375–1384. doi: 10.1053/j.gastro.2010.05.074.
- [94] Beuers U, Trauner M, Jansen P, Poupon R. New paradigms in the treatment of hepatic cholestasis: from UDCA to FXR, PXR and beyond. *J Hepatol* 2015; 62:S25–S37. doi: 10.1016/j.jhep.2015.02.023.
- [95] Fickert P, Hirschfield GM, Denk G, Marschall HU, Altorjay I, Färkkilä M, *et al*. norUrsodeoxycholic acid improves cholestasis in primary sclerosing cholangitis. *J Hepatol* 2017;67:549–558. doi: 10.1016/j.jhep.2017.05.009.
- [96] Ma H, Zeng M, Han Y, Yan H, Tang H, Sheng J, *et al*. A multicenter, randomized, double-blind trial comparing the efficacy and safety of TUDCA and UDCA in Chinese patients with primary biliary cholangitis. *Medicine (Baltimore)* 2016;95:e5391. doi: 10.1097/MD.0000000000005391.
- [97] Baghdasaryan A, Fuchs CD, Österreicher CH, Lemberger UJ, Halilbasic E, Pählman I, *et al*. Inhibition of intestinal bile acid absorption improves cholestatic liver and bile duct injury in a mouse model of sclerosing cholangitis. *J Hepatol* 2016;64:674–681. doi: 10.1016/j.jhep.2015.10.024.
- [98] Mayo MJ, Pockros P, Jones D, Bowlus C, Levy C, Patanwala I, *et al*. Clarity: A phase 2, randomized, double-blind, placebo-controlled study of lopixibat chloride (formerly lum001), a novel apical sodium-dependent bile acid transporter inhibitor, in the treatment of primary biliary cirrhosis associated with itching. *J Hepatol* 2016;64:S197. doi: 10.1016/S0168-8278(16)00146-X.
- [99] Myers RP, Swain MG, Lee SS, Shaheen AA, Burak KW. B-cell depletion with rituximab in patients with primary biliary cirrhosis refractory to ursodeoxycholic acid. *Am J Gastroenterol* 2013;108:933–941. doi: 10.1038/ajg.2013.51.
- [100] Khanna A, Jopson L, Howel D, Bryant A, Blamire A, Newton JL, *et al*. Rituximab for the treatment of fatigue in primary biliary cholangitis (formerly primary biliary cirrhosis): a randomised controlled trial. Southampton (UK): NIHR Journals Library; 2018. doi: 10.3310/eme05020.
- [101] Bowlus CL, Yang GX, Liu CH, Johnson CR, Dhaliwal SS, Frank D, *et al*. Therapeutic trials of biologics in primary biliary cholangitis: An open label study of abatacept and review of the literature. *J Autoimmun* 2019;101:26–34. doi: 10.1016/j.jaut.2019.04.005.
- [102] Hirschfield GM, Gershwin ME, Strauss R, Mayo MJ, Levy C, Zou B, *et al*. Ustekinumab for patients with primary biliary cholangitis who have an inadequate response to ursodeoxycholic acid: A proof-of-concept study. *Hepatology* 2016;64:189–199. doi: 10.1002/hep.28359.
- [103] Webb GJ, Hirschfield GM. Work in progress: Drugs in development. *Clin Liver Dis* 2018;22:501–515. doi: 10.1016/j.cld.2018.03.004.
- [104] Dalekos G, Invernizzi P, Nevens F, Hans VV, Zigmund E, Andrade RJ, *et al*. Efficacy of GKT831 in patients with primary biliary cholangitis and inadequate response to ursodeoxycholic acid: Interim efficacy results of a phase 2 clinical trial. *J Hepatol* 2019;70:e1–e2. doi: 10.1016/S0168-8278(19)30002-7.
- [105] Kaplan MM, Bonder A, Ruthazer R, Bonis PA. Methotrexate in patients with primary biliary cirrhosis who respond incompletely to treatment with ursodeoxycholic acid. *Dig Dis Sci* 2010;55:3207–3217. doi: 10.1007/s10620-010-1291-5.
- [106] Ben AK, Dhahri R, Hana S, Fazaa A, Ouennich K, Kassab S, *et al*. Safety and efficacy of infliximab in primary biliary cirrhosis associated with rheumatoid arthritis. *Intern Med* 2017;7:250. doi: 10.4172/2165-8048.1000250.
- [107] Dimopoulou D, Dimitroulas T, Akriavidis E, Garyfallos A. Infliximab as a treatment option for patients with rheumatoid arthritis and primary biliary cirrhosis. *Rheumatol Int* 2015;35:1913–1916. doi: 10.1007/s00296-015-3366-2.
- [108] Resorlu H, Köllöç S, Isök S, Gokmen F. Successful infliximab therapy in a patient with comorbid spondyloarthritis, primary biliary cirrhosis and generalized morphea. *Acta Clin Belg* 2017;72:365–368. doi: 10.1080/17843286.2017.1290567.
- [109] Hegade VS, Jones DE, Hirschfield GM. Apical sodium-dependent transporter inhibitors in primary biliary cholangitis and primary sclerosing cholangitis. *Dig Dis* 2017;35:267–274. doi: 10.1159/000450988.