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REVIEW

Primary Biliary Cholangitis: Promising Emerging Innovative Therapies and Their Impact on GLOBE Scores

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Abstract: Primary biliary cholangitis (PBC), previously referred to as primary biliary cirrhosis, is an autoimmune disorder leading to the destruction of intra-hepatic bile ducts. If untreated, progressive bile duct damage and cholestasis can lead to ductopenia and result in cirrhosis. Ursodiol, the first drug approved for PBC, has changed the natural history of this disease and improved patient outcomes. Subsequently, several new prediction models incorporating a response to ursodiol were developed. These include the GLOBE score, which was shown to predict long-term outcomes in patients with PBC. In 2016, obeticholic acid (OCA) became the second drug to be approved by the FDA, predominantly based on improvement in alkaline phosphatase (ALP) levels. This trial has subsequently influenced the design of clinical trials. Several drugs are currently being evaluated as therapeutic options for PBC, with improvement in ALP being a main endpoint. In this review, we will discuss the impact of new therapies on GLOBE scores in patients with PBC.
Keywords: PBC, GLOBE scores, treatments, therapeutic options

Introduction

Primary biliary cholangitis (PBC) is an autoimmune disorder wherein intrahepatic bile ducts are targeted by lymphocytes.[1] This results in periportal inflammation and cholestasis and may ultimately lead to cirrhosis and complications of chronic liver disease.[1] The incidence and prevalence of PBC varies by region: the highest prevalence was reported to be in North America (21.81 per 100,000 persons), followed by Europe (14.59 per 100,000 persons), and the lowest prevalence was reported in the Asia-Pacific region (9.82 per 100,000 persons).[2] Primary biliary cholangitis predominantly affects women, although men comprise approximately 10% of cases.[3,4] More recent studies have shown increased prevalence among men in recent years.[5] Men with PBC have a worse prognosis, possibly due to delayed disease recognition.[6]

There have been significant advances that have improved the staging, natural history, prognostication, and treatment of PBC in recent years.[7] An important development is a change in the name from "primary biliary cirrhosis" to "primary biliary cholangitis" in recognition of the fact that most patients with the disease do not have cirrhosis.[8] Multiple risk stratification scores based on new predictive models and novel therapeutic options have been developed that have improved the management of primary biliary cholangitis.[9] This article will discuss the approved treatments and emerging therapeutic options for managing PBC.

Pathophysiology

Before discussing the therapeutic options for PBC, it is pertinent to understand the pathophysiology of this disease. Biliary epithelial cells (BECs) form the lining of the biliary tree and play a role in bile formation.[10] This process is mediated via apical and basolateral exchangers and transmembrane channels.[10] Studies have also reported that a defect in the "Biliary bicarbonate umbrella" may be responsible for initiating injury in primary biliary cholangitis.[11] Normal BEC

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cellular integrity is maintained by appropriate bicarbonate production. Anion exchanger-2 (AE2), a chloride-bicarbonate exchange port expressed by BEC, regulates intracellular pH and biliary HCO3 secretion.[12–14] This bicarbonate layer is protective against the acidic environment produced by bile acids. In patients with PBC, there is a downregulation of AE2, leading to an alkaline intracellular environment.[15,16] This leads to the acidification of bile salts, rendering them more hydrophobic and cell membrane permeable, sensitizing the BECs to bile-salt-induced apoptosis.[17]

Apoptosis of BECs is a key step in the pathogenesis of PBC. In normal patients, during apoptosis, PDC-E2 in the BECs is modified through the covalent binding of glutathione.[18] In patients with PBC, this modification does not occur, and mitochondrial PDC-E2 remains immunologically intact,[18] which is recognized by circulating anti-mitochondrial antibodies (AMA), present in 90–95% of patients with PBC.[19] The antimitochondrial antibody (AMA) targets PDC-E2 within the apoptotic BECs,[19,20] resulting in antigen–antibody complexes and widespread immune activation. The inflammatory infiltrates comprise CD4+ T cells, CD8+ T cells, B lymphocytes, plasma cells, and variable eosinophils.[21] They localize around the portal tracts and recognize antigenic sequences within the mitochondrial complexes, leading to targeted biliary injury.[22,23] Regulatory T cells (Treg) cells are also reduced in patients with PBC, a defect that facilitates the autoimmune process.[24] Following initial bile duct injury, the process of cholestatic injury and cell death persists in PBC, eventually leading to the destruction of intrahepatic bile ducts, cholestasis, and fibrosis.

Approved Treatments and the Risk Stratification Scores

Ursodeoxycholic Acid (UDCA)

Ursodiol has been a component of traditional Chinese medicine for over 3000 years.[25] Ursodeoxycholic acid (UDCA) was the first drug approved by the US FDA for primary biliary cirrhosis in 1997.[26] UDCA is absorbed by passive non-ionic diffusion, mainly in the small intestine.[27] It is then extracted from the portal circulation by the liver, where it undergoes conjugation with glycine and taurine,[28] and is then secreted into the bile and undergoes enterohepatic circulation.[27]

Multiple possible mechanisms of action of UDCA have been described. (1) UDCA replaces more toxic hydrophobic bile acids and protects injured cholangiocytes by reducing their concentration in the bile. (2) UDCA also stimulates the bile acid secretion and detoxification of hydrophobic bile acids. (3) UDCA immunomodulates the humoral immune system (4) and may inhibit the apoptosis of hepatocytes.[29]

UDCA has been shown to alter the natural course of PBC.[30] EASL guidelines recommend the administration of ursodiol at a dose of 13–15 mg/kg/day in patients with PBC.[31] A cohort study including 3902 patients with PBC found that treatment with UDCA prolonged liver transplant-free survival; irrespective of the stage of the disease, UDCA significantly reduced the risk of LT or death (hazard ratio-0.46, 95% CI-0.40–0.52, $p<0.001$).[32] The findings were confirmed in a meta-analysis of seven randomized controlled trials and six reports of their follow-up.[33] Long-term treatment with UDCA, compared to placebo, reduced the incidence of liver transplantation and death. Common side effects of UDCA include hair thinning, weight gain, and flatulence.[34]

Risk-Stratification Scores

Before the approval of ursodiol for the prognostication of patients with PBC, multiple prediction models were developed.[35–42] Christensen et al were the first to develop a prediction model and reported that elevated bilirubin, older age, and cirrhosis were independently associated with poor prognosis.[39] Dickson et al, in 1989, developed the Mayo Risk Score (MRS) for predicting prognosis in PBC patients.[36] They reported that bilirubin, albumin, prothrombin time, age, and severity of edema were independent predictors of prognosis.[36] This model was initially developed to assess the ideal time for a liver transplant but was later adjusted in 1994 to predict a 2-year prognosis.[37]

The scores mentioned above, developed in the pre-UDCA era, were not useful after the approval of ursodiol, as ursodiol altered the natural course of the disease.[32,33] Multiple studies reported that ursodiol use was associated with improved ALP and bilirubin levels, which are markers of disease activity.[43,44] Lammers et al, in their study of 4845 patients from the Global PBC Study Group, reported that ALP levels and bilirubin are markers of disease activity in PBC and can predict long-term survival.[44] In this study, ALP >2 ULN and bilirubin >ULN were noted to be independent

predictors of liver transplantation and death.[44] ALP levels and bilirubin levels one year after the use of UDCA were shown to predict long-term outcomes.[44]

Subsequently, multiple scores assessing biochemical response criteria to UDCA, such as the Barcelona, Rotterdam, Paris, and Toronto criteria, were developed.[45–49] Information regarding these scores is presented in Table 1. Prediction models incorporating more variables were then developed to improve prognostication in patients with PBC. The GLOBE score was introduced in 2015 by the GLOBE-PBC Study Group.[50] This score was developed using a cohort of 2488 UDCA-treated patients and was validated in 1634 UDCA-treated patients. This score consists of age at baseline as well as total bilirubin (TB), ALP, albumin, and platelet count after 12 months of ursodiol.[50] This score estimates the risk of liver transplantation or mortality after a year of UDCA therapy. It is available on GLOBAL-PBC website (https://www.globalpbc.com/globe), and their calculator is presented in Figure 1. Multiple subsequent studies have reported that this score is beneficial in assessing the risk of worse outcomes in UDCA-treated patients over a longer period.[51–53] Another score, the UK-PBC score, was developed using 1916 UDCA-treated patients and validated in a cohort of 1249 UDCA-treated patients.[54] This score included baseline albumin, platelet count, bilirubin, aminotransferases, and alkaline phosphatase one year after treatment with UDCA. Both models have been shown to be superior in predicting outcomes in UDCA-non responders than Barcelona, Paris I/II, and Rotterdam criteria.[55]

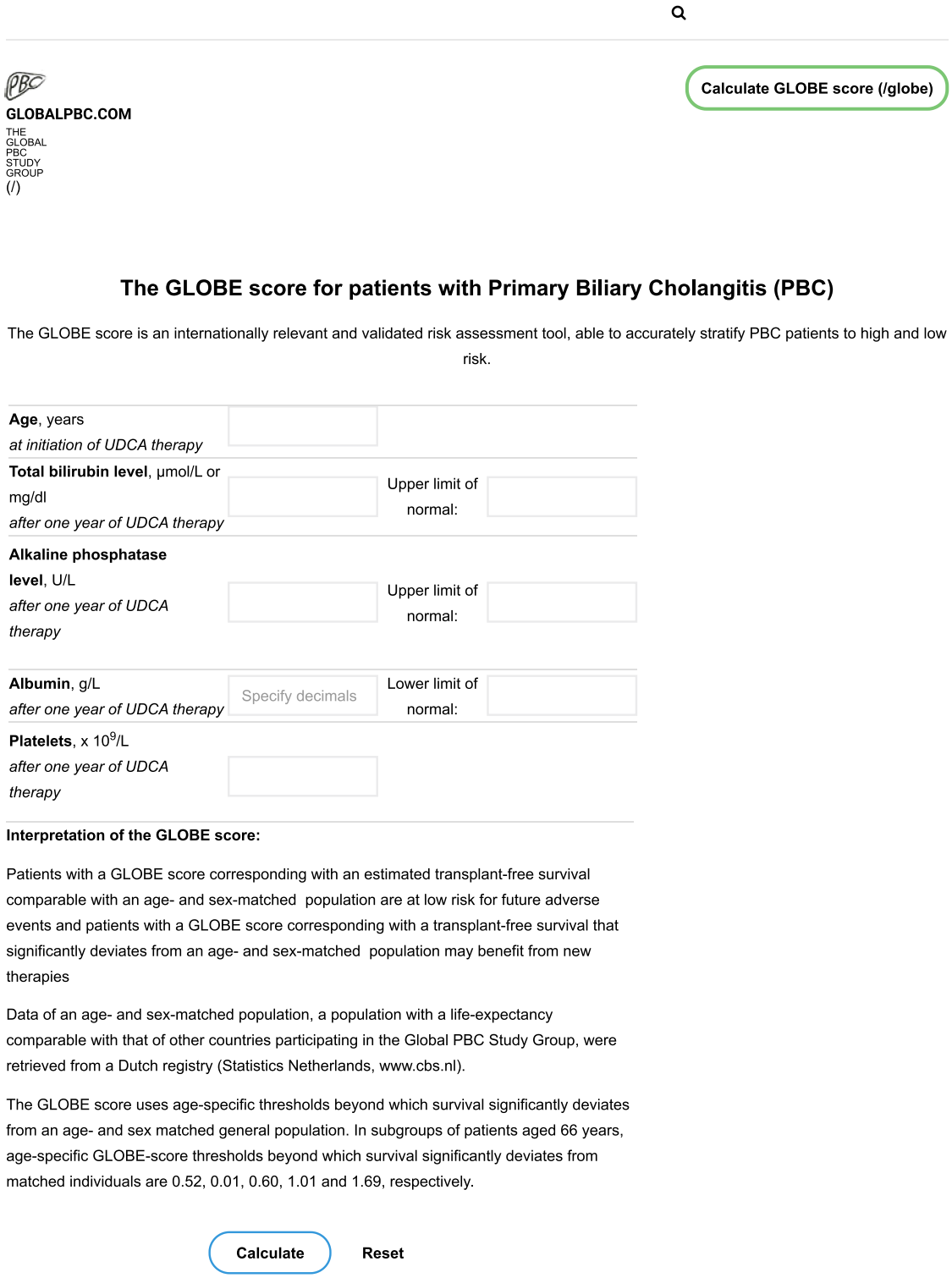
Obeticholic Acid (OCA)

Based on the previous studies and biochemical response criteria, it was noted that patients who did not achieve biochemical remission with UDCA had worse outcomes.[45–49] About 40% of the patients on UDCA are non-responders, defined as ALP >1.67 ULN, after UDCA therapy.[56] This led to the need to develop other therapeutic targets for managing patients with PBC.

In 2016, obeticholic acid (OCA) was approved for the treatment of PBC by the FDA as an adjunctive agent to UDCA or monotherapy in UDCA-intolerant patients.[57] Obeticholic acid is derived from chenodeoxycholic acid and imparts 100 times the increased agonism for the farnesoid X receptor (FXR) than endogenous chenodeoxycholic acid.[58] FXR activation inhibits the transcription of CYP7A1, which decreases the synthesis of bile acids.[59] FXR agonist has also been shown to regulate bile acids through enterohepatic circulation.[59] Activation of FXR agonists increases the secretion of fibroblast growth factor-19 (FGF-19), which also inhibits bile acid synthesis.[59]

Table 1 Risk Stratification Scores in the Post-UDCA Era

Criteria	Months After Starting UDCA	Incomplete Response Criteria
Binary Criteria		**Variables Included**
Rochester	6	ALP> 2XULN
Barcelona	12	ALP>ULN or less than 40% decrease in ALP
Paris-I	12	ALP >3ULN, AST >2 ULN, or T.Bili>ULN
Paris-II	12	ALP>1.5XULN, AST>1.5XULN or TB>1 mg/dl
Rotterdam	12	TB>ULN or Albumin<LLN
Toronto	24	ALP>1.67 X ULN
Continuous Criteria		
GLOBAL-PBC	12	TB, ALP, Albumin and platelet count after 12 months of ursodiol. Age at baseline
UK-PBC	12	TB, ALP, and AST (or ALT) after 12 months of ursodiol use. Albumin and platelets at baseline



GLOBALPBC.COM
THE GLOBAL PBC STUDY GROUP
(/)

Calculate GLOBE score (/globe)

The GLOBE score for patients with Primary Biliary Cholangitis (PBC)

The GLOBE score is an internationally relevant and validated risk assessment tool, able to accurately stratify PBC patients to high and low risk.

Age, years *at initiation of UDCA therapy*			
Total bilirubin level, µmol/L or mg/dl *after one year of UDCA therapy*		Upper limit of normal:	
Alkaline phosphatase level, U/L *after one year of UDCA therapy*		Upper limit of normal:	
Albumin, g/L *after one year of UDCA therapy*	Specify decimals	Lower limit of normal:	
Platelets, x 10^9/L *after one year of UDCA therapy*			

Interpretation of the GLOBE score:

Patients with a GLOBE score corresponding with an estimated transplant-free survival comparable with an age- and sex-matched population are at low risk for future adverse events and patients with a GLOBE score corresponding with a transplant-free survival that significantly deviates from an age- and sex-matched population may benefit from new therapies

Data of an age- and sex-matched population, a population with a life-expectancy comparable with that of other countries participating in the Global PBC Study Group, were retrieved from a Dutch registry (Statistics Netherlands, www.cbs.nl).

The GLOBE score uses age-specific thresholds beyond which survival significantly deviates from an age- and sex matched general population. In subgroups of patients aged 66 years, age-specific GLOBE-score thresholds beyond which survival significantly deviates from matched individuals are 0.52, 0.01, 0.60, 1.01 and 1.69, respectively.

Calculate Reset

Figure 1 GLOBE risk calculator on the GLOBAL-PBC website. Reproduced with permission from GlobalPBC.com.

In the POISE trial, a Phase 3 trial comparing OCA vs placebo in addition to UDCA in 216 patients with PBC, 46–47% of patients receiving OCA achieved the primary endpoint (alkaline phosphatase <1.67 times the upper limit of normal and normalization of total bilirubin) compared to 10% of the patients in the control group ($p<0.001$).[60] FDA

approval of the drug based on the reduction in the level of the surrogate marker ALP, which, as discussed previously, has been documented to be a marker of transplant-free survival.[44] The open-label extension of this trial revealed that the results were durable after six years of follow-up.[61] This study reported that patients treated with OCA had greater transplant-free survival than real-world controls. Another study assessing obeticholic acid monotherapy over six years found that individuals treated with 10 mg of OCA had a 53.9% reduction in alkaline phosphatase compared to 0.8% in the placebo group.[62] A post hoc analysis by Harms et al in the POISE study reported that 12 months of OCA treatment resulted in the reduction of APRI and GLOBE scores.[63] They reported that in patients who had GLOBE score >0.3 at baseline, the use of OCA 5-1 mg was associated with a greater percentage of patients achieving a GLOBE score <0.3, compared to placebo (27% vs 6%). Furthermore, a lower proportion of patients in the OCA treated group with GLOBE score≤0.3 at baseline were noted to progress to GLOBE score >0.3, compared to placebo (3–13% vs 33%).[63]

Pruritus is the most common side effect associated with OCA use.[60] The underlying mechanism of action for this symptom is unknown. This side effect has been noted to be dose dependent. A 68% of the patients in the 10 mg group and 56% in the 5–10 mg range experienced placebo as a side effect in the POISE trial.[60] Hepatotoxicity secondary to OCA use has been identified and postulated to be dose-related in patients with more advanced liver disease.[64,65] Due to these findings, OCA is now contraindicated in patients with child Class B and C cirrhosis, and a black box warning has been issued to the medication packaging.[66] Close monitoring of liver function tests is recommended in patients taking OCA. OCA use has also been shown to affect lipoprotein metabolism, with an increase in total cholesterol and LDL-cholesterol, and a decrease in HDL-C and triglycerides (TG).[67]

Emerging Therapies

Several subsequent studies have followed a study design similar to the POISE study. Most trials have documented changes in the ALP levels, with some studies reporting GLOBE scores. Even though some studies have not reported GLOBE scores, changes in the ALP translate to changes in the GLOBE score. In the following section, we will discuss the impact of emerging therapeutic options on ALP and GLOBE scores based on the published data.

Peroxisome Proliferator-Activated Receptors (PPAR) Agonists

Fibrates are FDA approved for treating patients with hyperlipidemia.[68] These drugs target peroxisome proliferator-activated receptors (PPAR). There are three isoforms of PPAR- α, δ, and γ, with fibrates differing in their affinity for each isoform.[69] PPARα induces the expression of genes involved in bile acid and lipid metabolism.[69] Its induction also results in the downregulation of genes involved in immune-related pathways.[70] PPARγ and δ activation has anti-inflammatory and anti-fibrotic properties.[70,71]

Given the mechanism of action of fibrates, they have been evaluated as a potential treatment option in patients with PBC. It was first noted in the 1960s that clofibrate use could reduce serum ALP, but this specific property of fibrates remained ignored before it was rediscovered in the 1990s.[72] In 1999, a study by Iwasaki et al reported, for the first time, that the use of bezafibrate alone or in combination with UDCA was able to decrease or normalize ALP levels and improve related symptoms.[73] Since then, multiple unblinded small-sized controlled studies in Japan and Western countries have consistently confirmed the role of fibrates in patients with PBC.[74–82] The BEZURSO trial comparing bezafibrate to placebo showed that 14 of 45 patients who had an incomplete response to ursodeoxycholic acid (UDCA) achieved the primary endpoint of biochemical remission at month 24 (defined as normalization of total bilirubin, ALP, aminotransferases, albumin concentrations, and prothrombin index) after receiving a daily dose of 400 mg bezafibrate, compared with none of the 39 patients who received UDCA and placebo ($p<0.001$).[83] Liver stiffness measured by vibration-controlled transient elastography showed a decrease of 15% in the bezafibrate (BZF) group compared to an increase of 22% in the placebo group.[83] Some adverse effects noted in the trial were myopathy and increased serum creatinine. Three patients were also noted to have a severe elevation of aminotransferases resolved after discontinuing bezafibrate.[83] Tanaka et al, in their study of 3908 patients receiving UDCA, reported that the using UDCA-BZF combination reduced the risk of all-cause as well as liver-related mortality. The requirement for LT was also reduced in the study.[84] The Japan Primary Biliary Cholangitis Study Group showed that patients who received the combination of bezafibrate and UDCA had significantly increased transplant-free survival than predicted by the GLOBE score calculated before initiating bezafibrate.[85] In this study, the mean GLOBE score improved from 0.504 (+/-0.08) before combination therapy to 0.115 (+/-0.085), after one year of combination therapy. Their study suggested that addition of bezafibrate to UDCA improves the long-term prognosis in

patients with PBC.[85] Information regarding the drugs currently under evaluation as well as their effect on GLOBE scores is presented in Table 2.

Fenofibrate has also been studied as an add-on therapeutic option in patients with PBC.[86–90] A recent meta-analysis by Guoyun et al reported that combining fenofibrate and UDCA could decrease ALP and GGT in UDCA-refractory patients with PBC.[89] The data regarding the impact of fenofibrate on GLOBE scores is mixed. A study by Wang et al reported that the addition of fenofibrate to UDCA resulted in an improvement in the GLOBE and UK-PBC scores.[90] On the contrary, Duan et al in their study of 39 patients with PBC, refractory to UDCA reported that 2-year combination therapy with UDCA and fenofibrate was not associated with improvement in the UK-PBC risk score and GLOBE score.[91] Further studies are needed to estimate the true effect of fenofibrate on GLOBE scores. Fibrates have also been beneficial in decreasing pruritus, a common symptom in patients with PBC.[92,93]

AASLD guidelines currently recommend that fibrates be considered an "off-label" alternative therapy for patients with PBC who have an inadequate response to ursodiol.[94] Other PPAR agonists are also in development. PPAR-δ, present in biliary epithelial cells, is involved in cholesterol trafficking and excretion.[94] The receptor induces the expression of ABCA1, a phospholipid-transporting ATPase responsible for cholesterol efflux from biliary epithelial cells.[95] PPAR-δ also plays a role in the macrophage clearance of apoptotic cells and reduces exposure to self-antigens.[96,97] Seladelpar has been noted to be a potent, selective agonist of PPAR-δ.[98] Seladelpar use was associated with a 53–63% reduction in ALP concentration compared to a 2% reduction in patients not taking the drug.[98] Another trial evaluating 25 patients with Child-Pugh A cirrhosis showed that response in ALP concentrations in patients with cirrhosis was comparable to those without cirrhosis.[99] There were no treatment-related adverse events during the 52-week study period. A phase 3 randomized placebo-controlled study (ENHANCE: NCT03602560) in 265 patients with PBC who were intolerant or UDCA non-responders reported that the use of seladelpar 10 mg resulted in normalization of ALP in 27% of the patients in the treatment group compared to placebo.[100] An improvement in the total bilirubin and symptoms such as pruritus was also noted.[100] This study was stopped prematurely because of the concern of hepatotoxicity noted during the end-of-treatment biopsy of the NASH study with seladelpar.[101] A subsequent review showed no drug-related clinical, biochemical, or histological evidence of liver injury.[102] Subsequently, trials of seladelpar for PBC were resumed.[102] Another study reported that seladelpar treatment for one year was associated with improved symptoms such as fatigue and pruritus.[103] A recent study by Hansen et al reported an improvement in the GLOBE score after two years of treatment with seladelpar.[104] This study reported that seladelpar use resulted in a mean change (SD) from baseline in GLOBE score of −0.417

Table 2 Therapies for PBC and Their Impact on GLOBE Scores

Drug	Impact on Globe Score
Obeticholic acid	Improvement in GLOBE scores
Bezafibrate	Improvement in GLOBE scores
Fenofibrate	Conflicting Data
Seladelpar	Improvement in GLOBE scores
Elafibranor	Improvement in GLOBE scores
Saroglitazar	No data on GLOBE scores, but will likely improve it based on improvement in the ALP levels noted
NOX inhibitors	No data on GLOBE scores, but will likely improve it based on improvement in the ALP levels noted
Non-bile FXR agonists	No data on GLOBE scores. It is likely that the real impact on long-term survival is not reflected by GLOBE scores because of the ability of FXR agonists to induce ALP transcription
Aldafermin	No data on GLOBE scores, but will likely improve it based on improvement in the ALP levels noted
Budesonide	Slight improvement in the GLOBE scores
IBAT inhibitors	No data on the GLOBE scores. It is less likely to impact GLOBE scores, as it does not impact ALP levels

(0.27). This change corresponded to 34% lower likelihood of requiring liver transplantation or death, compared to no prior treatment with seladelpar.[104]

Elafibranor (GFT505), first used in treating non-alcoholic steatohepatitis (NASH), is a dual PPARα and δ agonist.[105] The drug was subsequently evaluated in a Phase 2 trial as an adjunctive treatment for patients with PBC who did not respond to UDCA.[106] Patients who received elafibranor showed a 41–68% reduction in ALP compared with a 3% increase in those receiving a placebo ($p<0.001$). Secondary composite endpoints including ALP <1.67 times the upper limit of normal, more than 15% decrease in ALP, and normal total bilirubin levels were met in 67–79% of patients receiving elafibranor, compared to 6.7% of the patients in the placebo group.[106] This randomized placebo-controlled trial of elafibranor revealed that elafibranor increased the estimated transplant-free survival at 5, 10, or 15 years using a composite GLOBE score.[106] A phase 3 study ELATIVE comparing the effect of elafibranor in patients with PBC is currently underway (ELATIVE- NCT04526665). Data on therapies currently in phase 3 trials is presented in Table 3. The drugs currently being evaluated in phase 3 clinical trials are provided in Table 2.

Saroglitazar is a dual PPAR-α and PPAR-γ agonist that has shown promising results in mouse models of NASH.[107] In a phase 2 study (EPICS), saroglitazar use was associated with a 50% decrease in ALP levels in 81 patients who did not respond to UDCA.[108] An open-label phase-3 study evaluating saroglitazar as a potential treatment for PBC was terminated early because of a lack of enrollment.[109] In this 16-week study of 7 patients, treatment with saroglitazar resulted in a rapid reduction in ALP levels at week 4. Another trial (EPICS-III) is currently enrolling patients (NCT05133336).

NOX Inhibitors

Nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase (NOX) 1 and NOX4 are key enzymes involved in the development of liver fibrosis.[110] TGF-beta, through NOX1 and NOX4 signaling, initiates apoptosis of hepatocytes.[111] They also mediate the differentiation of hepatic stem cells to myofibroblasts.[110]

Setanaxib (GKT137831) is a NOX1 and NOX4 inhibitor.[112] It has been shown to be beneficial in patients with doxorubicin-induced cardiotoxicity.[112] It is currently being evaluated as a management option for patients with idiopathic pulmonary fibrosis (NCT03865927) and primary biliary cholangitis. Interim efficacy results of the phase 2 clinical trial in 111 patients showed that the use of GKT137831 was associated with improvement in the markers of cholestasis, inflammation, and liver fibrosis.[113] Their phase 2 study did not report GLOBE scores, but they likely improved based on the improvement in the ALP levels noted in the study.[113] Due to the positive results, a phase 2/3 clinical trial, TRANSFORM (NCT05014672), is currently underway and open to enrollment. It is planned that 318 patients with PBC will be randomized to setanaxib 1200 mg, 600 mg, and placebo in a 1:1:1 fashion for 52 weeks.

Table 3 Drugs Currently in Phase 3 Clinical Trials for the Management of PBC

Drug	NCT	Mechanism of Action	Primary Endpoint
Seladelpar	NCT04620733	PPAR-delta agonist	• ALP<1.67 ULN • >15% reduction in ALP • Total bilirubin <ULN
Saroglitazar	NCT05133336	PPAR alpha and gamma agonist	• ALP<1.67 ULN • >15% reduction in ALP • Total bilirubin <ULN
Elafibranor	NCT04526665	PPAR-alpha and delta agonist	• ALP<1.67 ULN • >15% reduction in ALP • Total bilirubin <ULN
Setanaxib	NCT05014672	NOX 1 and 4 inhibitors	• ALP<1.67 ULN • >15% reduction in ALP • Total bilirubin <ULN
Linerixibat	NCT04950127	ASBT inhibitors	• Monthly itch scores over 24 weeks

Non-Bile Acid FXR Agonists

Non-steroidal farnesoid X receptor (FXR) agonists have been evaluated for patients with PBC. These include tropifexor (LJN452), cilofexor (GS-9674), and EDP-305.

Tropifexor has been evaluated in a phase 2 trial of 61 patients.[114] In this study, tropifexor use was associated with an improvement in ALP and GGT levels. Tropifexor use was associated with a 26–72% reduction in GGT from baseline compared to placebo.[114] The most frequent adverse event in the study was pruritus. An increase in mean VAS itch score and median PBC-40 itch domain scores was noted in patients receiving tropifexor.[114] It was also noted that although the mean ALP was reduced, the ALP remained above the upper limit of normal value in all the treatment groups.[114] It has been previously reported that FXR activation can induce ALP gene transcription, which may confound the downstream effects of ALP reduction.[113–116] Since ALP is a component of GLOBE scores, this may impact the assessment of long-term prognosis in patients with PBC when GLOBE score or UK-PBC scores are used.

Cilofexor (GS-9674) has been shown to be beneficial in patients with NASH and PSC.[117,118] A phase 2 study involving 71 patients with PBC, with ALP greater than 1.67 times the upper limit of normal (ULN) and elevated serum total bilirubin, showed that cilofexor was associated with significant improvement in ALP and GGT.[119] The most common adverse event was grade 2 or 3 pruritus, noted in patients on high-dose cilofexor.[119]

In the INTREPID study, a 12-week trial comparing EDP-305 to placebo reported a reduction of ALP in 45% of patients on EDP-305 compared to 11% in the placebo group. The study, however, did not meet its primary endpoint of a 20% reduction in ALP.[120]

FGF-19 Analogues

Ileal enterocytes primarily produce FGF-19 in response to bile acid exposure.[121] After reaching the liver, it binds to FGFR4/ßKlotho and inhibits hepatic bile acid synthesis by suppressing CYP7A1.[121] FGF-19 is a crucial regulator of lipid and glucose metabolism.[122] FGF-19 agonist suppresses lipogenesis and gluconeogenesis[122] and promotes fatty acid oxidation and glycogen synthesis.[122] Murine models have shown that deficiency of FGF15/19 and receptor FGFR4 resulted in increased production of cholesterol-7-alpha-hydroxylase, increased bile acid turnover, and impaired gall bladder filling.[123]

Aldafermin (NGM282) is a subcutaneously administered analog of FGF-19.[124] It is non-mitogenic and is being developed as a therapeutic option for treating primary sclerosing cholangitis (PSC), PBC, and NASH.[124–126] A double-blind phase 2 trial evaluating 45 patients with PBC with inadequate response to UDCA for 28 days reported that aldafermin significantly reduced ALP levels from baseline.[126] The most common side effect of aldafermin reported in the phase 2 study was gastrointestinal disorders. A 21% of patients receiving NGM282 0.3 mg and 43% receiving NGM282 3 mg developed diarrhea.[126] A phase 2b study evaluating the effect of extended treatment with NGM282 for 24 weeks in PBC patients has been completed, with results pending (NCT02135536).

Budesonide

Budesonide is a potent corticosteroid with a high first-pass metabolism in the liver, resulting in fewer systemic side effects.[127] Budesonide and UDCA, when used together, have been noted to increase the expression of biliary chloride/bicarbonate anion exchanger 2.[128] This increases bicarbonate secretion and stabilizes the biliary bicarbonate umbrella.[128]

A phase 3 trial reported that combination therapy with budesonide and UDCA was not associated with improved liver histology, but an improvement in biochemical markers of disease was demonstrated when secondary analyses were performed.[129] A small change in the GLOBE score of 0.3 was also noted in the budesonide group.[129] It is recommended that budesonide use is avoided in patients with cirrhosis due to uncontrolled systemic shunting of the drug and increased risk of portal vein thrombosis.[130]

IBAT Inhibitors

Pruritus is a frequent symptom reported in 60–70% of patients.[131,132] Previous studies have shown that UDCA is ineffective in improving this symptom.[133] Normally, primary bile acids undergo extensive enterohepatic circulation with reabsorption of 95% of the bile acids secreted into the duodenum.[134] Apical sodium-dependent transporters (ASBT and IBAT) play a role in the

reabsorption of bile acids in the ileum.[134] Since bile acids have been implicated among pruritogenic substances in patients with PBC,[135] Ileal bile acid transport (IBAT) inhibitors by decreasing the reabsorption of bile acids have been hypothesized to reduce itching.[136] Phase 2 GLIMMER trial evaluated linerixibat in 147 patients with PBC and moderate itching.[136] Although no statistically significant difference was noted in the worst daily itch scores between linerixibat and placebo, the study reported a statistically significant change in the monthly itch scores from baseline in patients on linerixibat 40 mg, 90 mg, and 180 mg compared to placebo.[136] Diarrhea was the most frequent adverse event in this study. The GLIMMER study did note a higher change in serum ALP concentrations from baseline, but the differences were not clinically significant.[136] Since the mechanism of action does not decrease bile acid synthesis, it is less likely that an improvement in the ALP levels will be noted in patients on IBAT inhibitors.[136] Based on the findings of GLIMMER trial, a phase 3 clinical trial GLISTEN is underway (NCT-04950127). Maralaxibat, another IBAT inhibitor, has been evaluated in a phase 2 trial.[137] In this study, no significant reductions in the itching scores were noted between the patients on placebo and on maralixibat. There were no significant differences in the changes in the level of ALP between placebo and maralixibat.[137] Another trial evaluating volixibat in patients with PBC is underway, with results awaited (NCT05050136).

Other Drugs

Multiple other drugs such as immunomodulators, anti-retroviral therapy, antioxidants and mesenchymal stem cells[138–150] are currently being evaluated as therapeutic options for the management of PBC. Majority of these studies are limited to small sample of patients and only report reductions in the ALP. We believe that further large-population studies are needed, before the impact of these drugs on GLOBE scores can be studied. A diagram depicting the drugs currently approved as well as those under investigation is presented in Figure 2.

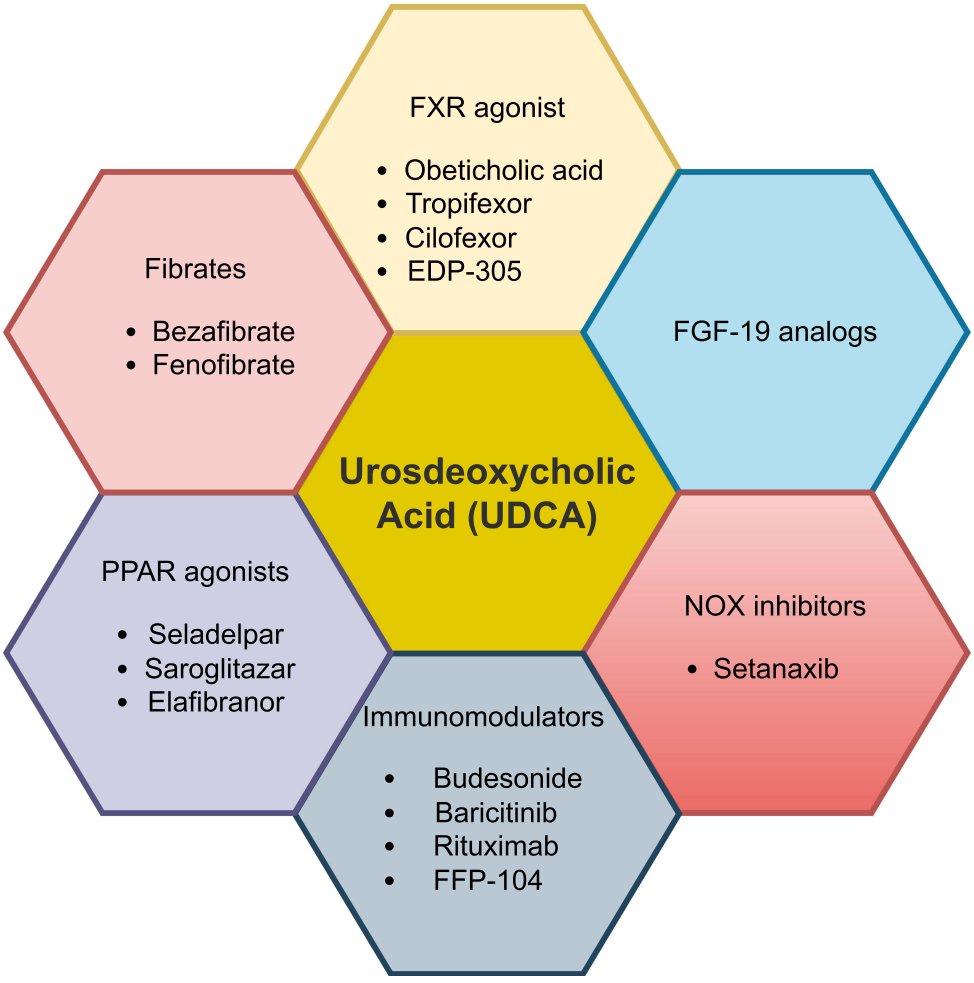


Figure 2 The current and potential therapies for the management of PBC.

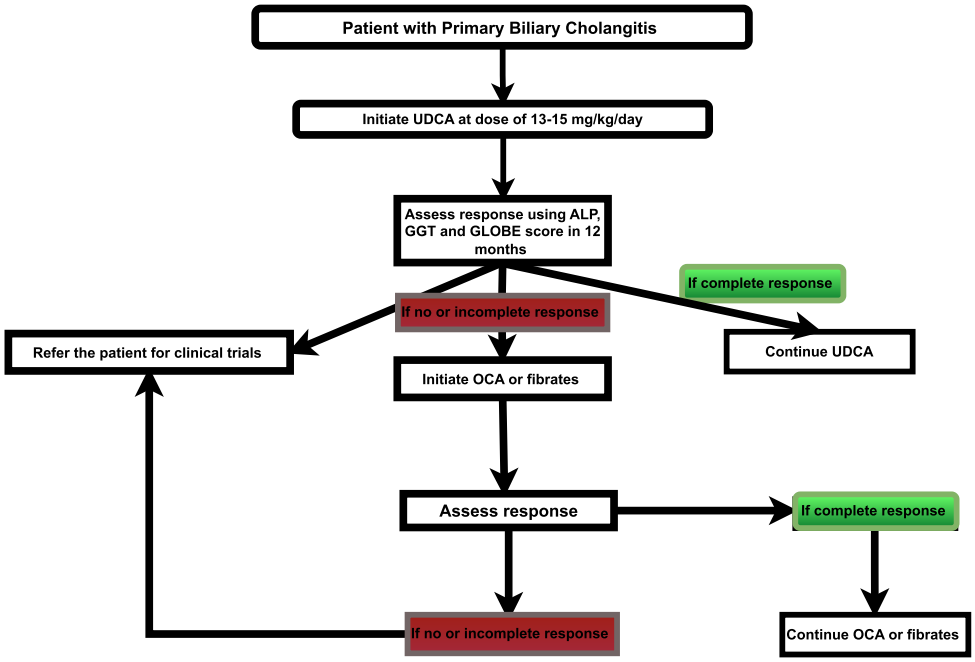


Figure 3 Flowchart describing the approach to a patient with PBC.

Conclusion

In summary, there have been substantial advances in the understanding of the pathophysiology, management, and prognostication models in patients with PBC. The approval of ursodiol and obeticholic acid has changed the natural history of PBC and the drug development processes for this rare disease. The drugs currently under investigation have a reduction in ALP as a primary endpoint in majority of the trials. Furthermore, the development of prognostication tools such as GLOBE scores and UK-PBC scores have improved our insight into the long-term outcomes. These scores are also currently being used as surrogate markers in clinical trials for the development of upcoming therapeutic options. We speculate that the approval of these upcoming therapies in the next decade will further change the management and help patients who do not respond to ursodiol and obeticholic acid. In addition, a flow diagram is provided in Figure 3 to assist the physicians in understanding how to approach PBC management.

Disclosure

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