REVIEW ARTICLE: REVIEW ARTICLE

Evolving Concepts of Treatment Targets for Primary Biliary Cholangitis: A Global Perspective

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Abstract In Brief

Primary biliary cholangitis (PBC) is a chronic cholestatic disease that if left untreated can progress to cirrhosis, end-stage liver disease, liver transplantation and, ultimately, death. PBC occurs worldwide, with rising prevalence in the North American, European, and Asia-Pacific regions. Ursodeoxycholic acid (UDCA) is the globally recommended first-line treatment, but up to half of UDCA-treated patients do not respond adequately. Fortunately, the PBC treatment landscape has evolved, and new treatments with novel mechanisms of action are available for patients with inadequate response to UDCA, but questions remain. Different treatment strategies have emerged in recent years from major societies across the globe regarding treatment targets, timing of treatment response assessment, management of hepatic and extrahepatic manifestations, and choice of second-line therapies. Drug availability also has global variation. Nine international PBC experts, representing the United States, Canada, Europe, Asia, Africa, and Central/South America, collaborated to formulate opinions about the unanswered questions related to treatment targets in PBC. The result of this expert review is a global perspective on terminology related to the definition of responses to treatment, risk stratification, and

treatment targets that can guide clinicians to optimize PBC treatment worldwide.

INTRODUCTION

Primary biliary cholangitis (PBC) is a slowly progressive, immune-mediated cholestatic liver disease that, if left untreated, typically progresses to cirrhosis, end-stage liver disease, liver transplantation and, ultimately, death (1–6). Common symptoms associated with PBC include cholestatic pruritus and debilitating fatigue (1–5). PBC affects adults of all ages, genders, races, and ethnicities (1), but is much more prevalent in middle-aged women (7,8). Initially described in populations of European descent, data demonstrate that PBC occurs throughout the globe (1,8–12). The prevalence of PBC has risen steadily over time in the North American, European and Asia Pacific regions (1,9,13–15), with a current estimated pooled global prevalence of 14.6 per 100,000 persons (9). Notably, this is based primarily on data generated from North America and Europe, as there is a lack of population-based studies concerning PBC disease frequency in Africa and South America, although real-world data have been recently published about the features of PBC in Latin American patients (16). Despite the scarcity of data, minor differences seem to exist in prevalences by race, with lower rates reported in African Americans compared with Hispanic and non-Hispanic White patients (8).

The European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases, and the Brazilian Society of Hepatology recommend that the goals of PBC treatment are to prevent disease progression and complications of cirrhosis and to manage the symptoms associated with PBC (specifically, fatigue and pruritus), ultimately improving patient quality of life (2,3,17,18). Although other regions of the globe have not generated specific PBC recommendations, clinicians tend to follow the EASL and American Association for the Study of Liver Diseases recommendations. Ursodeoxycholic acid (UDCA) is the globally recommended first-line treatment (2,3,5,19,20), but nearly half of UDCA-treated patients do not respond adequately to treatment, and a small percentage do not tolerate UDCA (21,22). For these patients, second-line therapies have become available (23–25). However, choosing the appropriate patients for second-line treatment has become an important issue. Complicating this decision process are the multiple criteria based on biochemical responses and other risk factors as well as a number of predictive scores, algorithms, and models to predict patient outcomes in

response to treatment (21,26–33). Most of these criteria assess response to UDCA after 12 months of treatment, but emerging evidence suggests that decisions can be made earlier (34–37).

In addition to slowing progression of liver disease, treatment of patients with PBC has also been directed at the prevalent symptoms, particularly pruritus and fatigue. UDCA does not significantly improve either symptom (38), and no therapies have demonstrated efficacy to relieve fatigue (39,40) short of liver transplantation (41). Recent progress in the treatment of pruritus has included the use of peroxisome proliferator-activated receptor (PPAR) agonists (3), also used to prevent liver disease progression, and novel intestinal bile acid transport inhibitors (42).

Despite these major developments in PBC, there is no consensus regarding treatment response criteria and their relationship to clinically relevant long-term outcomes, particularly in patients with less advanced disease or higher baseline levels of alkaline phosphatase (ALP). Furthermore, drug availability also has global variations, thus there is a need to have a consensus on terminology and treatment targets regardless of the chosen therapies.

APPROACH

Members of the Chronic Liver Disease Foundation, a nonprofit 501(c) (3) educational organization dedicated to raising awareness of liver disease, identified 9 international PBC experts representing the United States, Canada, Europe, Asia, Africa, and Central/South America. This international expert panel reviewed surrounding evidence and participated in interactive discussions, with the focus on analyzing the second-line treatment landscape, identifying gaps in and limitations to PBC treatment knowledge, and formulating opinions about the unanswered questions in the treatment targets for PBC. The result is this expert perspective review, which presents opinions from an international panel of experts on terminology and treatment targets in PBC.

Risk stratification after UDCA treatment

Since the 1990s, UDCA has been used for the treatment of PBC (43) and, across the globe, remains the recommended first-line therapy at a dose of 13–15 mg/kg/d (2,3,5,19,20). Initially, UDCA was developed and approved by the United States (US) Food and Drug Administration to dissolve gallstones (2). When reductions in ALP were observed in UDCA-treated patients, it was ultimately investigated for use in PBC and demonstrated that it reduced the need for liver transplantation and improved survival (44). UDCA can be

administered at any stage of PBC in patients with abnormal liver biochemistries, but earlier interventions correlate with better biochemical response and clinical outcomes (45), reinforcing the need for early diagnosis and treatment.

In 2014, Lammers and colleagues performed a large, international meta-analysis that included 4,845 patients with PBC and treated with UDCA. Individual patient data were used to evaluate whether levels of ALP and bilirubin after UDCA treatment correlated with liver transplantation or death. After 1 year of UDCA treatment, there was a direct correlation between ALP and total bilirubin with the risk death or liver transplant. Patients with ALP levels ≤2.0 times the upper limit of normal (ULN) had an 84% 10-year transplant-free survival compared with 62% for those with levels >2.0 times the ULN ($P < 0.0001$), although no specific cutoff value had better prognostic ability than others. Similarly for total bilirubin, a level 1.0 times the ULN best predicted patient transplant-free survival, with an 86% 10-year transplant-free survival compared with 41% for those with levels >1.0 times the ULN ($P < 0.0001$). This and other data led to the acceptance of ALP and total bilirubin as surrogate end points in clinical trials (46).

Other predictors of clinical outcomes include persistent PBC symptoms (3) and disease stage determined either by liver biopsy or liver stiffness (47). Liver stiffness measurement (LSM), assessed by vibration-controlled transient elastography, is one of the best measures to stage the progression of PBC and, as such, a baseline LSM and longitudinal assessment are encouraged. LSM can also be used to risk-stratify patients independent of biochemical response to UDCA (2–4). One study found that patients with a liver stiffness greater than 9.6 kPa were 5 times more likely to have disease progression, with clinical decompensation, death, or transplant (48). Liver biopsy is not indicated as a means to stage the disease or to monitor response to UDCA therapy (2,3).

The PBC treatment landscape

Over the past decade, the farnesoid X receptor agonist obeticholic acid (OCA) (22), and the PPAR agonists, elafibranor (35) and seladelpar (36), became commercially available for the treatment of PBC in several parts of the world. Furthermore, the use of bezafibrate has been widely and successfully used off-label. The accelerated/conditional approval of OCA in the United Kingdom (UK) and Europe in 2016, and more recently of elafibranor and seladelpar, were based on the results of randomized controlled trials demonstrating significantly greater biochemical responses

compared with placebo among patients treat with UDCA or intolerant to UDCA and who had an ALP greater than 1.67 × the ULN (see Biochemical responses to PBC treatment of more information on the primary end point) (22,35,36). In 2024 the European Medicines Agency recommended revoking the conditional authorization for OCA, and in the United States, the Food and Drug Administration declined full approval for OCA because of the inability to demonstrate long-term improvements in clinical outcomes (49), which ultimately led to the voluntary withdrawal of OCA from the US market (50). In addition to these approved therapies, a randomized controlled trial for the off-label use of the PPAR agonist bezafibrate showed biochemical improvements in patients with PBC who did not adequately respond to UDCA (51), and real-world data demonstrate improvements in long-term outcomes (52). Other fibrates, including fenofibrate, ciprofibrate, and pemafibrate, have also been used worldwide as off-label second-line therapy in patients with PBC (2,4,19).

Despite progress in the PBC treatment landscape, approximately 20% of patients with a PBC diagnosis do not receive or do not intend to receive treatment (53). A study in the UK found that EASL guideline adherence is low among healthcare providers, leading to inadequate drug dosing, among other real-world consequences (54). A large population-based study of almost 9,000 patients, also based out of the UK, reaffirmed that less than half of the patients meeting criteria for second-line treatment were appropriately referred (55). The challenges related to the global availability of novel therapies further impede optimal care for patients with PBC (Table 1).

Table 1. Global availability of second-line primary biliary cholangitis treatments

Drug	US	Canada	Europe	Asia/Pacific	Africa	Latin America
Obeticholic acid	x[a]	✓	x[b]		x[c]	
Elafibranor	✓	✓	✓			✓
Seladelpar	✓	✓	✓			
Bezafibrate		✓	✓	✓	✓	✓
Fenofibrate	✓	✓	✓	✓	✓	✓
Ciprofibrate						✓
Pemafibrate				✓[d]		

[a]Obeticholic acid has been voluntarily withdrawn from the US market.
[b]The United Kingdom and Switzerland have Obeticholic acid available because they are not part of the European Union and do not refer to the European Medicines Agency.
[c]It is possible to import this drug for select patients with the use of special permits.
[d]Used off-label as second-line treatment in Japan.

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Bezafibrate		✓	✓	✓	✓	✓
Fenofibrate	✓	✓	✓	✓	✓	✓
Ciprofibrate						✓
Pemafibrate				✓[d]		

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Biochemical responses to PBC treatment

With these new therapies, choosing the appropriate patients for second-line treatment has become an important issue. Multiple criteria based primarily on biochemical responses can be used to identify patients who remain at risk of clinical outcomes despite UDCA treatment and might benefit from a second-line treatment. A number of predictive models have also been developed to predict patient risk after UDCA treatment considering additional factors, including age and evidence of advanced liver disease such as albumin and platelet count (21,26–32).

The current treatment strategy for PBC involves risk stratification and response-guided therapy. The latter involves assessing the response to UDCA treatment at 1 year after treatment initiation and determining the

need for additional treatment based on that assessment. Recently, however, it has been argued that a decision can be made earlier based on personalized assessment of the patient's risk factors. A retrospective study proposed that determination at 6 months of treatment was similar to 1 year (56), and the phase 3 trials of OCA, seladelpar, and elafibranor demonstrate that most of the reduction in ALP occurs within 4 weeks of starting treatment (34–36). Furthermore, a study from China determined that treatment response to UDCA could be predicted based on biochemical parameters (ALP ≤ 2.5 × ULN and aspartate aminotransferase ≤ 2 × ULN, and total bilirubin ≤ 1 × ULN; Xi'an criteria) 1 month after the initiation of UDCA administration (37). In a retrospective international cohort study including 1,333 patients with PBC receiving second-line treatment (646 on OCA; 685 on fibrates), delay in starting second-line treatment—along with the presence of cirrhosis and higher ALP at the start of second-line treatment—were associated with worse outcomes, supporting early initiation of second-line treatment (57).

Treatment response, regardless of the criteria, is primarily determined by the improvement in ALP and total bilirubin, and response criteria can be broadly categorized into continuous (Globe, UK PBC) and dichotomous (Paris I, Rotterdam, Toronto, Paris II, Barcelona; Table 2) (21,26–33). Dichotomous criteria named after the region of the population studies were developed in the 2000s to identify at-risk patients after UDCA treatment (21,29–32,37). Later, large cohort studies by the Global PBC Group and the UK PBC Group modeled prognostic scores for predicting the risk of transplant-free survival and hepatic decompensation-free survival, respectively, after UDCA treatment (26,33). Taken together, the general consensus is that liver biochemical tests are reliable surrogate markers for predicting long-term prognosis.

Table 2. Continuous and dichotomous scoring systems to UDCA

Classification	Scoring system	Details
Continuous	UK-PBC (33)	Bilirubin, ALP, and AST or ALT at 12 mo Albumin and platelet count at baseline
	GLOBE (26)	Bilirubin, ALP, albumin, and platelet count at 12 mo Age at baseline
Dichotomous	**Response after 1 month of treatment with UDCA**	
	Xi'an (37)	ALP ≤ 2.5 × ULN and AST ≤ 2 × ULN and TBIL ≤ 1 × ULN
	Response after 6 mo of treatment with UDCA	
	Rochester (27)	ALP < 2 × ULN or Mayo score < 4.5
	Ehime (28)	Decrease in GGT > 70% and GGT < 1 × ULN
	Response after 12–24 mo of treatment with UDCA	
	Barcelona (29)	Decrease in ALP > 40% and ALP < 1.0 × ULN
	Paris-I (30)	ALP < 3 × ULN or AST < 2 × ULN or bilirubin ≤ 1.0
	Rotterdam (21)	Bilirubin < 1 × ULN and albumin > 1 × ULN
	Toronto (31)	ALP ≤ 1.67 × ULN after 2 yr on UDCA

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; PBC, primary biliary cholangitis; UCDA, ursodeoxycholic acid; ULN, upper limit of normal.

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	Rochester (27)	ALP < 2 × ULN or Mayo score < 4.5
	Ehime (28)	Decrease in GGT > 70% and GGT < 1 × ULN
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	Barcelona (29)	Decrease in ALP > 40% and ALP < 1.0 × ULN
	Paris-I (30)	ALP < 3 × ULN or AST < 2 × ULN or bilirubin ≤ 1.0
	Rotterdam (21)	Bilirubin < 1 × ULN and albumin > 1 × ULN
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ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; PBC, primary biliary cholangitis; UCDA, ursodeoxycholic acid; ULN, upper limit of normal.

Table 2. Continuous and dichotomous scoring systems to UDCA

Multiple criteria, however, have generated confusion surrounding the terminology for treatment targets (Figure 1). The phase 3 PBC OCA International Study of Efficacy (POISE) used a primary outcome of the composite end point of an ALP <1.67 × ULN, equivalent to an ALP of

approximately 200 IU, with a decrease of at least 15% from baseline and total bilirubin within ULN, frequently termed as the POISE criteria (22). All current phase 3 clinical trials have used the POISE criteria as the primary end point. Because ALP <1.67 × ULN with a decrease of at least 15% from baseline and total bilirubin within ULN has become the standard for PBC clinical trials, we propose that this should be referred to as a regulatory biochemical response.

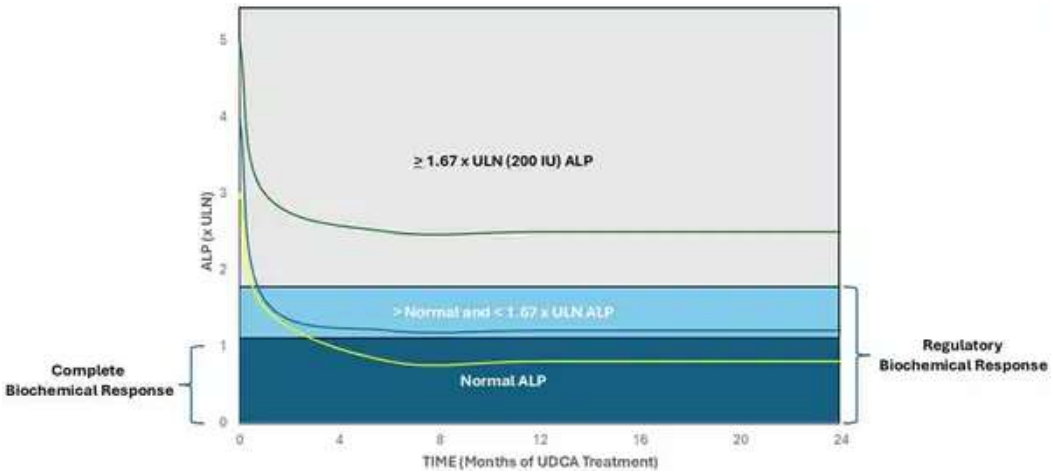

Figure 1. Representation of treatment responses based on serum alkaline phosphatase. Conceptualization of biochemical response definitions based on serum ALP after treatment. Typically, improvements in ALP occur rapidly and are maintained throughout therapy. A regulatory biochemical response is defined by an ALP < 1.67 × ULN with a normal total bilirubin. A complete biochemical response is defined by a normal ALP and a total bilirubin < 0.6 × ULN. An inadequate biochemical response is a clinical decision based on biochemical response and other clinical factors including age, disease stage, and comorbid conditions for which a second line therapy is indicated. ALP, alkaline phosphatase; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Recently, normalization of ALP has been proposed as a treatment target. A study by the Global PBC Group found that ALP normalization, rather than levels <1.67 × ULN, and bilirubin levels of ≤0.6 × ULN, rather than ≤ULN, were associated with a better long-term prognosis. The 10-year liver transplant-free survival rates of those with bilirubin levels ≤0.6 × ULN and ≤ULN at the 1-year treatment point were 91.3% and 79.2%, respectively (P < 0.001); similarly, ALP ≤ULN and ≤1.67 × ULN at the 1-year treatment point were 93.2% and 86.1%, respectively (P < 0.001) (58).

Another study demonstrated that among patients achieving a response to UDCA treatment according to the Paris-2 criteria (ALP and aspartate aminotransferase ≤1.5 × ULN, and normal bilirubin) (32), an ALP 1.1–1.5 × ULN was associated with a greater risk of transplantation or death compared with ALP ≤ULN, especially in patients with advanced fibrosis defined as an LSM > 10 kPa and in younger patients (59). In this study, patients with an ALP, gamma-glutamyl transpeptidase, and alanine aminotransferase < ULN and a total bilirubin ≤0.6 × ULN, were referred to as having a deep response. (59,60). We propose that normalization of the ALP and a total bilirubin < 0.6 × ULN should be referred to as a complete biochemical response.

Regardless of how response is defined, some key points should be kept in mind. First, even in patients who do not achieve a defined response, any reduction in ALP is associated with a reduction in clinical outcomes (61). In fact, second-line therapies reduce ALP approximately 40%–45% from baseline values regardless of the starting level of ALP. Thus, patients with a higher ALP at baseline may have a greater reduction in their risk of clinical outcomes (benefit) yet not meet dichotomous response criteria. To call these patients nonresponders would be inaccurate. Second, regulatory labeling indications for second-line agents are for patients with PBC who have an inadequate response to UDCA, without further defining what criteria should be used to determine an inadequate response. We propose that the term nonresponder should be avoided and that any response to treatment in which the treating provider does not consider the response to adequately reduce the risk of disease progression in an individual patient be referred to as an inadequate response.

DISCUSSION

Limitations in the current knowledge of PBC treatment

Despite the advances in PBC treatment and in the understanding of response to treatment, there are limitations in the current knowledge, which are discussed in detail throughout this section.

Surrogate end points are not validated for second-line treatments

Confirmation of the benefits of UDCA on long-term clinical outcomes required years-long trials of patients with advanced liver disease and meta-analyses of several large trials (38,44,62). Subsequently, ALP and total bilirubin have been used as prognostic markers for transplant-free survival in patients treated with UDCA (61). Similar findings from the real-world data

use of OCA and bezafibrate provide further validation of ALP and total bilirubin in PBC (63,64). This has allowed for the approval of second-line agents, including OCA, seladelpar, and elafibranor, conditional on confirmatory trials demonstrating clinical benefit. Failure to complete a confirmatory trial of OCA, however, has led to concerns about the feasibility of similar trials for seladelpar and elafibranor. Until ALP and total bilirubin or other surrogates are accepted by regulatory agencies as validated surrogate end points for full approval, confirmation of the safety and efficacy of these agents are more likely to come from well-conducted studies of real-world evidence.

Clinical trials are inclusive for patients with ALP > 1.67 × ULN

Recent clinical trials for second-line PBC therapies have included only patients with ALP > 1.67 × ULN (22,35,36). This leaves a gap in understanding the efficacy and safety of these agents in patients with less elevated or normal ALP but with other markers of disease activity (eg, mild total bilirubin elevations, increased LSM) (65). Ongoing studies of elafibranor and seladelpar in patients with ALP 1–1.67 × ULN will close this gap in patients with mild biochemical abnormalities. In addition, up to one third of patients with metabolic dysfunction-associated steatotic liver disease (MASLD) present with elevated ALP (66) and over 40% of patients with PBC have concomitant MASLD (67). With the rising prevalence of MASLD (68,69), these studies will address the question of whether mild ALP elevations in patients with PBC may be attributed to steatosis as opposed to PBC.

Clinical trials exclude patients with decompensated cirrhosis, advanced cirrhosis and PBC/autoimmune hepatitis overlap

Pivotal clinical trials in patients with PBC have excluded patients with decompensated cirrhosis (eg, ascites, encephalopathy, varices) or advanced cirrhosis (eg, Child-Pugh B/C) and those with PBC/autoimmune hepatitis (AIH) overlap (22,34–36,45). Patients with decompensated or advanced cirrhosis have been excluded because of safety concerns and difficulty assessing treatment efficacy in end-stage disease, but this gap limits treatment guidance for patients at the highest risk of adverse outcomes. Current real-world evidence has not supported the efficacy of fibrates in advanced cirrhosis (70), and OCA is contraindicated in patients with cirrhosis and portal hypertension (71).

Patients with PBC/AIH overlap syndrome are often excluded to maintain trial homogeneity because their unique pathology complicates end point assessment. In these patients, the sensitivity of conventional PBC-based biochemical response criteria (eg, Paris, Barcelona) for assessing UDCA

efficacy remains debatable. These patients often receive concurrent immunosuppressive therapy, which may improve inflammatory control but introduce complex safety profiles (72). Lack of randomized trials in patients with overlap syndrome limits the strength of treatment recommendations. Real-world data may provide additional information in this setting (73,74).

Long-term adverse effects of PBC treatments are largely unknown

Long-term adverse effects of most PBC treatments (eg, OCA, fibrates, PPAR agonists) are largely unknown because of limited follow-up in clinical trials that prevents robust evaluation of the cumulative risks. UDCA, as a first-line medication, exhibits almost no side effects with long-term use (2). Among second-line therapies, however, several concerns of potential long-term safety have arisen. Pruritus stands out as the most common adverse reaction with OCA, significantly impacting patients' quality of life. OCA also carries a black-box warning restricting its use in cirrhotic patients with portal hypertension because of the risk of hepatic decompensation (23). Concerns related to OCA's effects on lipid metabolism also require ongoing investigation. Fibrates have been used for decades to treat metabolic conditions and have known renal and muscle-related toxicities with long-term use. Seladelpar and elafibranor were both well tolerated in the pivotal clinical trials. Although rare, transient hepatotoxicity has been associated with both drugs. Interestingly, a small percentage of patients treated with either seladelpar or elafibranor have trauma-related fractures, but this did not occur in patients administered placebo. The cause remains unknown and requires additional postmarketing surveillance.

Recurrent PBC treatment and the effectiveness of second-line therapy

Recurrent PBC (rPBC) after liver transplantation affects up to 50% of patients and is associated with decreased patient and graft survival (75). Early initiation of UDCA after transplant has been associated with significantly reduced risk of rPBC and graft failure (76). However, evidence supporting second-line treatments (eg, OCA, fibrates) in the posttransplantation setting remains limited to case series and retrospective studies (77). A recent study examined 21 patients with rPBC in North America and Europe, who received second-line therapy (10 patients administered OCA, 11 administered fibrates). Both OCA and fibrates were well-tolerated in the posttransplantation setting and led to improvement in liver biochemistries (78).

CONCLUSION

The variety of response criteria in the published literature and in clinical trials has made the terminology used to describe treatment responses and treatment targets in clinical practice challenging. Table 3 articulates proposed definitions to codify the responses that are generally encountered in clinical practice and treatment targets in PBC.

Table 3. Proposed definitions of treatment responses in patients with primary biliary cholangitis

Definitions
1. Because ALP < 1.67 ULN × with a decrease of at least 15% from baseline and total bilirubin within ULN has become the standard for PBC clinical trials, we propose that this should be referred to as a regulatory biochemical response. The criteria first used in the POISE trial have been and will likely continue to be an important response to measure, but in clinical practice has less relevance. Therefore, we recommend qualifying this as a regulatory biochemical response.
2. We propose that normalization of the ALP and a total bilirubin < 0.6 × ULN should be referred to as a complete biochemical response. A complete biochemical response is when ALP and total bilirubin are below the thresholds where there is a measurable increase in the risks of death or liver transplantation. Normalization of AST and ALT may also be considered as part of this definition in the absence of concomitant MASLD.
3. We propose that the term nonresponder should be avoided. Few if any patients with PBC do not have any improvement in liver biochemistries. Therefore, this term should be avoided. Importantly, even patients with an inadequate response derive benefit from treatment, which should be continued.
4. Any response to treatment in which the treating provider does not consider the response to adequately reduce the risk of disease progression in an individual patient be referred to as an inadequate response. Understanding that any persistent increase above the upper limit of normal may be associated with worse clinical outcomes, treating providers must consider several clinical factors to determine if an individual patient would benefit from the addition of a second-line agent.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MASLD, metabolic dysfunction–associated steatotic liver disease; PBC, primary biliary cholangitis; POISE, PBC OCA International Study of Efficacy; ULN, upper limit of normal.

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Table 3. Proposed definitions of treatment responses in patients with primary biliary cholangitis

The decision to initiate second-line treatment in patients with PBC must balance several aspects unique to each patient. For this reason, all patients should be risk stratified at diagnosis and periodically based on age, ALP, total bilirubin, and LSM. The need for second-line agents can be assessed as early as 6 months after starting UDCA and should be reassessed throughout the disease course.

In our opinion, second-line therapy should be considered in all patients with an ALP > 1.67 × ULN (approximately > 200 IU/L) and in those patients with an ALP 1–1.67 × ULN (approximately 115–200 IU/L) who are of younger age or with an LSM > 10 kPa. In addition, all patients with PBC who do not tolerate UDCA should be treated with a second-line agent.

Consideration must also be given to the risk of disease progression vs the risk of adverse effects, cost, and the burden of add-on therapies. The presence of other comorbid conditions and age may change this calculation. Furthermore, the presence of concomitant disease, such as MASLD, may increase the risk of disease progression while at the same time making the interpretation of biochemical response more challenging. As a general rule, however, our opinion is that patients at risk based on ALP, total bilirubin, and LSM values should be offered second-line treatment unless there is a compelling reason not to optimize treatment.

CONFLICTS OF INTEREST

Guarantor of the article: Christopher L. Bowlus, MD.

Specific author contributions: All of the authors have contributed in the following ways, with the group being led by C.L.B.: Drafted the proposed outline; Identified the most recent updates in PBC data; Developed and

agreed upon (over several discussions) the practical recommendations in the manuscript; C.L.B. drafted the manuscript and every author approved each draft, including the final draft.

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ABBREVIATIONS:

AIH

autoimmune hepatitis

ALP

alkaline phosphatase

EASL

European Association for the Study of the Liver

LSM

liver stiffness measurement

MASLD

metabolic dysfunction-associated steatotic liver disease

OCA

obeticholic acid

PBC

primary biliary cholangitis

POISE

PBC OCA International Study of Efficacy

PPAR

peroxisome proliferator-activator receptor

rPBC

recurrent PBC

UDCA

ursodeoxycholic acid

ULN

upper limit of normal

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Keywords:
primary biliary cholangitis; response; risk; treatment target; international

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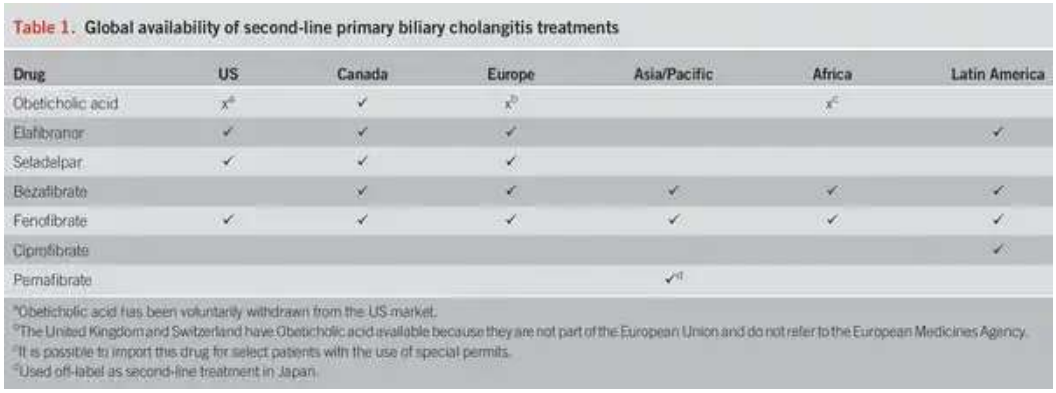

Table 1. Global availability of second-line primary biliary cholangitis treatments

Drug	US	Canada	Europe	Asia/Pacific	Africa	Latin America
Obeticholic acid	x[a]	✓	x[b]		x[c]	
Elafibranor	✓	✓	✓			✓
Seladelpar	✓	✓	✓			
Bezafibrate		✓	✓	✓	✓	✓
Fenofibrate	✓	✓	✓	✓	✓	✓
Ciprofibrate						✓
Pemafibrate				✓[d]		

[a]Obeticholic acid has been voluntarily withdrawn from the US market.
[b]The United Kingdom and Switzerland have Obeticholic acid available because they are not part of the European Union and do not refer to the European Medicines Agency.
[c]It is possible to import this drug for select patients with the use of special permits.
[d]Used off-label as second-line treatment in Japan.

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Fenofibrate	✓	✓	✓	✓	✓	✓
Ciprofibrate						✓
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Table 1. Global availability of second-line primary biliary cholangitis treatments

Table 2. Continuous and dichotomous scoring systems to UDCA

Classification	Scoring system	Details
Continuous	UK-PBC (33)	Bilirubin, ALP, and AST or ALT at 12 mo Albumin and platelet count at baseline
	GLOBE (26)	Bilirubin, ALP, albumin, and platelet count at 12 mo Age at baseline
Dichotomous	**Response after 1 month of treatment with UDCA**	
	Xi'an (37)	ALP ≤ 2.5 × ULN and AST ≤ 2 × ULN and TBIL ≤ 1 × ULN
	Response after 6 mo of treatment with UDCA	
	Rochester (27)	ALP < 2 × ULN or Mayo score < 4.5
	Ehime (28)	Decrease in GGT > 70% and GGT < 1 × ULN
	Response after 12–24 mo of treatment with UDCA	
	Barcelona (29)	Decrease in ALP > 40% and ALP < 1.0 × ULN
	Paris-I (30)	ALP < 3 × ULN or AST < 2 × ULN or bilirubin ≤ 1.0
	Rotterdam (21)	Bilirubin < 1 × ULN and albumin > 1 × ULN
	Toronto (31)	ALP ≤ 1.67 × ULN after 2 yr on UDCA

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; PBC, primary biliary cholangitis; UCDA, ursodeoxycholic acid; ULN, upper limit of normal.

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Table 2. Continuous and dichotomous scoring systems to UDCA

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