The impact of deep response to ursodeoxycholic acid in primary biliary cholangitis – should it be the new clinical standard?

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Purpose of review
This review explores the emerging concept of "deep response" in primary biliary cholangitis (PBC), defined by the normalization of biochemical markers, particularly alkaline phosphatase and bilirubin. It examines its potential as a new standard for disease management and its implications for long-term patient outcomes, health policies, and clinical decision-making.

Recent findings
Recent studies suggest that achieving a deep response significantly improves long-term outcomes in some patients with PBC. In particular, a significant complication-free survival gain was observed among patients who at baseline were at high risk for disease progression. However, limitations in data and the variability in patient populations pose challenges for universal adoption of this standard.

Summary
Deep biochemical response represents a promising new standard for optimizing PBC management, offering measurable goals for clinicians and potentially improved long-term outcomes for patients. However, further research is necessary to better define the appropriate biochemical thresholds, understand the risks of overprescribing, and identify patient subgroups that are most likely to benefit from this strategy.
A balanced, patient-centered approach incorporating deep response into comprehensive management could improve care for high-risk PBC patients.

Keywords
alkaline phosphatase normalization, deep response, primary biliary cholangitis, treatment

INTRODUCTION

Primary biliary cholangitis (PBC) is an autoimmune liver disease characterized by progressive destruction of the small intrahepatic bile ducts, leading to cholestasis, liver fibrosis, and ultimately cirrhosis and liver failure if left untreated. While the precise pathogenetic mechanisms underlying PBC remain incompletely elucidated, emerging evidence suggests that a complex interplay of genetic predisposition and environmental factors is likely responsible for the development and progression of this condition [1,2].

For over three decades, ursodeoxycholic acid (UDCA) has been the cornerstone of PBC. However, a significant proportion of patients either do not respond adequately to UDCA according to established response criteria [3–10], or cannot tolerate it, and therefore would benefit from additional therapies to improve biochemical parameters and clinical outcomes [11,12▪].

More recently, the concept of "deep response," defined as the normalization of biochemical markers of cholestasis, particularly alkaline phosphatase (ALP) and total bilirubin, has garnered significant research interest given growing evidence that some patients who are able to achieve this level of biochemical improvement may experience significantly better long-term outcomes compared to those who only achieve an adequate biochemical

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KEY POINTS

- Achieving deep response may improve complication-free survival specially among patients at high risk for primary biliary cholangitis progression.
- Despite its potential benefits, deep response is not yet universally recommended given limited data.
- Future research is needed to identify the patient subgroups that would benefit most from deep response and to refine biochemical thresholds for this strategy.
- Incorporating deep response into PBC management could optimize care, particularly for high-risk patients with advanced fibrosis.

response [13▪▪,14]. This review aims to explore the concept of "deep response" in PBC, evaluate its potential as a new clinical standard for disease management and its implications for long-term outcomes, health policies and clinical decision-making.

IMPACT OF URSODEOXYCHOLIC ACID USE AND EVALUATION OF TREATMENT RESPONSE

UDCA, a hydrophilic bile acid, is the current standard of care for PBC. It works through multiple mechanisms, including enhancing bile acid transport and detoxification, providing cytoprotective effects on cholangiocytes, and modulating immune responses [15]. UDCA has long been shown to improve biochemical parameters [16], delay histological progression [17], delay development of portal hypertension [18], and increase transplant-free survival rates in patients with PBC [19,20]. Corroborating these early findings, a large international cohort study demonstrated decreasing cumulative decompensation rates over time in UDCA responders. Specifically, patients who achieved biochemical response had a 10-year first complication risk of only 6.2%, compared to 32.4% in nonresponders [21]. Indeed, another study from the same group including 3902 patients with a median follow-up of 7.8 years, found that UDCA treatment significantly reduced the risk of liver transplant or death by 54% compared to untreated patients [22]. This benefit was observed regardless of disease stage, and UDCA doses higher than 13 mg/kg provided the greatest clinical benefit. Notably, even patients with suboptimal biochemical response to UDCA had better long-term outcomes than untreated patients, suggesting that therapy should be maintained despite this incomplete response. Furthermore, UDCA is generally well tolerated, making it a viable long-term treatment option.

However, while the majority of patients respond well to UDCA, approximately 40% do not achieve an adequate biochemical response or, more rarely, are unable to tolerate the medication [8]. These patients may require second-line therapies with a different mechanism of action to improve biochemical parameters and, eventually, clinical outcomes. Given the above benefits associated with use of UDCA, even in the setting of incomplete response, second-line therapies should be added-on to UDCA, instead of switched.

Achieving an adequate response to UDCA therapy has been a critical goal in the management of PBC. This can be evaluated trough several response criteria, which differ in the specific parameters and assessment times (Table 1, Supplemental Digital Content, http://links.lww.com/COG/A54). This lack of standardization complicates the universal application and comparison of treatment outcomes across studies and clinical settings. Moreover, studies have shown that even among patients who meet different response criteria, there is significant variability in long-term outcomes, with some experiencing continued disease progression and higher risk of liver transplantation or liver-related mortality. For instance, patients with a normal GLOBE score after 2 years of UDCA therapy but with ALP levels remaining above 2× upper limit of normal (ULN) exhibit significantly lower 10-year liver transplant-free survival compared to those with a normal GLOBE score and ALP levels below 2× ULN (82.6% vs. 90.8%, respectively) [14,23]. Similarly, higher total bilirubin levels within the normal range have been associated with diminished cumulative survival, even when other parameters such as the GLOBE score are favorable [14]. These findings support the growing recognition that achieving a robust biochemical response may be crucial for improving long-term prognosis in PBC patients.

Currently, patients are generally considered eligible for second-line therapies, where available, when their ALP levels remain elevated above 1.5–1.67× ULN, or if their total bilirubin levels exceed the ULN, after at least 12 months of UDCA therapy [1,2]. However, recent evidence suggests that pre-treatment ALP levels are strong predictors of UDCA response and long-term outcomes, offering an alternative approach to patient stratification [24]. Building on this insight, the UDCA Response Score, or Carbone score, was developed to predict response even before treatment begins and is derived from key clinical variables, including baseline ALP, bilirubin, transaminases, patient age, treatment time lag (i.e. longer interval from diagnosis to the start of

UDCA), and the change in ALP from diagnosis to the start of treatment. These variables were selected based on their strong correlation with UDCA response and histological markers of biliary injury, such as ductular reaction and intermediate hepatocytes, making the score a useful tool for early patient stratification [24]. Two other recent studies evaluated our ability to identify patients most likely to benefit from second-line therapy at an earlier timepoint. The Brazilian Cholestasis Study Group found no difference in the predictive ability of Toronto, Paris 2 or Rotterdam criteria when applied at 6 vs. 12 months [25], and the Global PBC Study Group found that patients with ALP levels >1.9× ULN at 6 months were highly unlikely to meet the POISE criteria for response at 1 year, with approximately 90% negative predictive value [26▪]. This earlier identification of incomplete responders allows for more individualized management, indicating a much needed shift towards a more proactive rather than reactive approach.

DEEP BIOCHEMICAL RESPONSE

Another important proposed shift in the care of people living with PBC is exactly how aggressive we should be in the pursuit of normalization of liver chemistries. The first robust evidence highlighting the benefits of achieving better biochemical profiles came from a large international cohort study showing that patients who attained bilirubin levels ≤0.6× ULN or normalized their ALP had the lowest risk of liver transplantation (LT) or death. Specifically, patients with bilirubin levels ≤0.6× ULN demonstrated a 10-year survival rate of 91.3%, compared to 79.2% for those with higher bilirubin levels (>0.6× ULN). Similarly, ALP normalization was associated with a 10-year survival rate of 93.2%, significantly improved when compared to 86.1% in those with ALP between 1.0 and 1.67× ULN, currently considered an adequate response [14].

More recently, another large retrospective study corroborated these findings. Using a cohort of 1047 patients with known adequate response to UDCA at baseline based on Paris II criteria, the authors compared long-term outcomes of those who achieved adequate responses (ALP 1–1.5× ULN) with those who attained deep response (ALP < ULN). ALP normalization was associated with a 7.6-month increase in complication-free survival over a 10-year period and a 50% reduction in the risk of serious liver-related complications, such as liver transplantation [13▪▪]. This beneficial effect was particularly pronounced in younger patients (age < 62 years) and those with advanced fibrosis (LSM > 10 kPa); patients meeting both criteria had an increment of 52.8 months in decompensation-free survival. For yet unclear reasons the study also found that ALP, rather than bilirubin, was the most consistent biochemical factor associated with improved outcomes. Subsequently, a Latin-American study including 297 patients found that roughly 1 in 5 patients reached a deep response, which in their study was defined as normalization of ALP and total bilirubin (instead of total bilirubin level <0.6× ULN). As expected, on multivariate analysis, the presence of cirrhosis and ALP elevation reduced the odds of response [27]. Importantly, the Carbone score was unable to identify patients more likely to achieve such deep response. Key findings from these studies are summarized in Table 1.

While these findings are compelling, a few important limitations should be considered. First, those are retrospective studies with significant amount of missing data and heterogeneous populations, thus requiring sophisticated statistical adjustments. As a result, the number of subjects with analyzable data becomes quite limited. Furthermore, clinical events are not regularly adjudicated. Second, one cannot be certain that the persistent ALP elevation was not due to an alternative etiology such as metabolic dysfunction-associated steatotic liver disease, for instance. More than 70% of the deaths (nearly half of the events) in the Corpechot *et al.* study were unrelated to liver disease, thus unlikely to be modified by more stringent treatment of PBC [13▪▪]. Finally, significant improvement in decompensation-free survival was only observed in the smaller subset of younger patients with advanced fibrosis.

As our understanding of the prognostic role of ALP in PBC has evolved, we have also seen a clear shift in drug development strategies. After publication of the POISE study for obeticholic acid (OCA) and its subsequent regulatory approval in 2016, other pivotal studies of proposed second-line drugs for PBC have adopted the same primary endpoint: a composite requiring a reduction in ALP levels to <1.67× ULN, with at least a 15% reduction from baseline in ALP, alongside normal bilirubin levels after one year of treatment [28–30]. This composite endpoint came to be known as the POISE criteria. However, since then, ALP normalization rate has been introduced as a key secondary endpoint in clinical trials, and in some studies, such as the BEZURSO trial, normalization of all liver chemistries became the primary endpoint [31]. Future analyses of open-label extension studies as well as post marketing studies focusing on long-term outcomes may reveal whether targeting deep response as a new clinical standard could enhance the survival benefit for PBC patients.

Table 1. Summary of key studies on deep response

Study	Design	Sample size	Population	Key endpoints	Follow-up duration	Key findings
Murillo Perez *et al.*, 2020	Retrospective cohort	2555	UDCA-treated and untreated patients with normal bilirubin levels *Patients with AIH-PBC overlap syndrome and those on second-line therapy were excluded.*	LT and all-cause mortality	Median 7.3 years [IQR 3.7–11.5]	– Bilirubin <0.63 ULN and ALP normalization were significantly associated with improved 10-year survival. – Patients with consistently low bilirubin levels showed reduced risk of LT or death.
Corpechot *et al.*, 2023	Retrospective cohort	1047	(1) Long-term treatment with UDCA of ≥12 months (2) Adequate biochemical response as defined by the Paris-2 criteria. *Patients with history of second-line therapies use, AIH-PBC overlap syndrome and decompensated cirrhosis were excluded.*	Liver-related complications, LT, liver-related and all-cause mortality	Mean 7.8 ± 5.9 years	– Deep response was linked to improved outcomes, especially in patients with advanced disease stages (LSM ≥ 10 kPa) and/or younger ages (≤ 62 years). – Overall population: complication-free survival gain of 7.6 months in 10 years – High-risk patients: complication-free survival gain of 52.8 months in 10 years
Cançado *et al.* 2024	Retrospective cohort	297	Long-term treatment with UDCA of ≥12 months *Patients with history of second-line therapy use, AIH-PBC overlap syndrome or any other concomitant liver disease, and UDCA dose different than 13–15mg/kg/day were excluded*	Deep response (normalization of ALP and TB levels 12 months after UDCA start date), and adequate response (according to Toronto criteria)	12 months	– 57.2% of patients achieved an adequate response, while 22.9% reached deep response. – The UDCA score had sensitivity of 65% (0.50, 0.78), specificity of 84% (0.77, 0.89), positive predictive value of 52% (0.39, 0.65), and negative predictive value of 89% (0.84, 0.94),

ALP, alkaline phosphatase; AIH, autoimmune hepatitis; AUROC, area under the receiver operating characteristic; LSM, liver stiffness measurement; LT, liver transplantation; PBC, primary biliary cholangitis; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

POTENTIAL IMPACT OF USING DEEP REPONSE AS A NEW STANDARD

Beyond its direct impact on complication-free survival and quality of life, understanding and striving for deep response in PBC provides another indirect benefit: a clear, measurable goal for clinicians, aiding in the optimization of treatment strategies and patient monitoring.

At present, several critical shortfalls have been identified in the care of people living with PBC. The UK-PBC audit revealed that while UDCA remains the cornerstone of PBC treatment, only 92% of diagnosed patients were receiving treatment and nearly one third were undertreated (i.e., UDCA dose <13 mg/kg/day) [32]. Similarly, a US study conducted by the Fibrotic Liver Disease (FOLD) Consortium reported that approximately 30% of PBC patients were not receiving UDCA despite its well established benefits [33]. As concerning, recent work from the Mayo Clinic showed that only one in four patients meeting criteria for second-line therapy were actually initiated on an FDA-approved drug, and one in five received off-label treatment with fenofibrate, thus leaving over 50% of eligible patients untreated [34]. This lack of access to second-line therapy was also evident on a real-world study comparing long-term outcomes of OCA-eligible patients to matched patients who actually received it. Using the Komodo Health claims database, the authors identified over 5000 eligible patients who had never received OCA, compared to 400 who had been on OCA [35].

Potentially magnifying these disparities in the United States, an updated epidemiology report identified significant regional variability, with higher prevalence rates observed in rural areas such as the mountain areas in the Midwest [36]. It is, therefore, expected, that any additional complexity in determining response criteria and identifying incomplete responders will further enhance these disparities. For a change in prescribing behavior to occur, we need to both increase general knowledge about PBC and facilitate motivation, by introducing more intuitive goals which can also be more easily automatized.

Likewise, it is important to also consider potential drawbacks and challenges of over-simplifying treatment goals. Implementing a complete normalization of ALP as a new standard of care would require significant investments in resources, infrastructure, and healthcare system changes that may not be feasible or equitable for all patients. Policymakers and stakeholders would need to carefully evaluate the cost-effectiveness and accessibility of therapies capable of achieving these more ambitious treatment targets. Moreover, there is a risk of over-treatment, where an excessive focus on numerical targets could overshadow other important aspects of patient-centered care, such as the individual's risk of disease progression, quality of life, and shared decision-making.

Another important caveat is cirrhosis. All second-line therapies should be used with caution in patients with cirrhosis, given the potential risk of hepatotoxicity and clinical decompensation. At present, OCA is contra-indicated in the presence of advanced cirrhosis or any evidence of portal hypertension [37] and the newly approved peroxisome proliferator-activated receptor (PPAR) agonists, elafibranor and seladelpar, are currently contra-indicated in decompensated cirrhosis as this population has not been sufficiently studied [38,39]. Therefore, this is a subset of patients with PBC for whom adding a second-line drug to push for ALP and bilirubin normalization would not be a consideration, defying the generalization of a deep response concept.

Professional organizations and policy-makers must weigh these tradeoffs and provide guidance that balances the benefits of deep response with the practical realities of clinical practice and healthcare system constraints. Ultimately, a measured and nuanced approach, incorporating deep response as one component of a comprehensive PBC management strategy, may be more prudent than mandating it as a new universal standard. Flexibility and individualization will be key to ensuring equitable access and optimizing outcomes for all PBC patients. A proposed management algorithm is presented in Fig. 1.

FUTURE DIRECTIONS AND RESEARCH NEEDS

As the concept of deep response gains traction in the PBC community, it will be important to carefully define the appropriate biochemical thresholds (for instance, total bilirubin within ULN vs. <0.6× ULN) and time points for assessing this endpoint. Additionally, further research is needed to establish the specific clinical correlates and long-term outcomes associated with achieving a deep response in PBC, and better characterizing the subgroups more likely to profit from this strategy. Nonetheless, the available evidence suggests that bringing this concept to the forefront of PBC management may lead to meaningful improvements in patient care and outcomes for certain patients: perhaps at this point in our understanding of PBC progression, one could consider aiming for normalization of ALP and total bilirubin in the subgroup of high-risk patients, namely younger patients and those with advanced

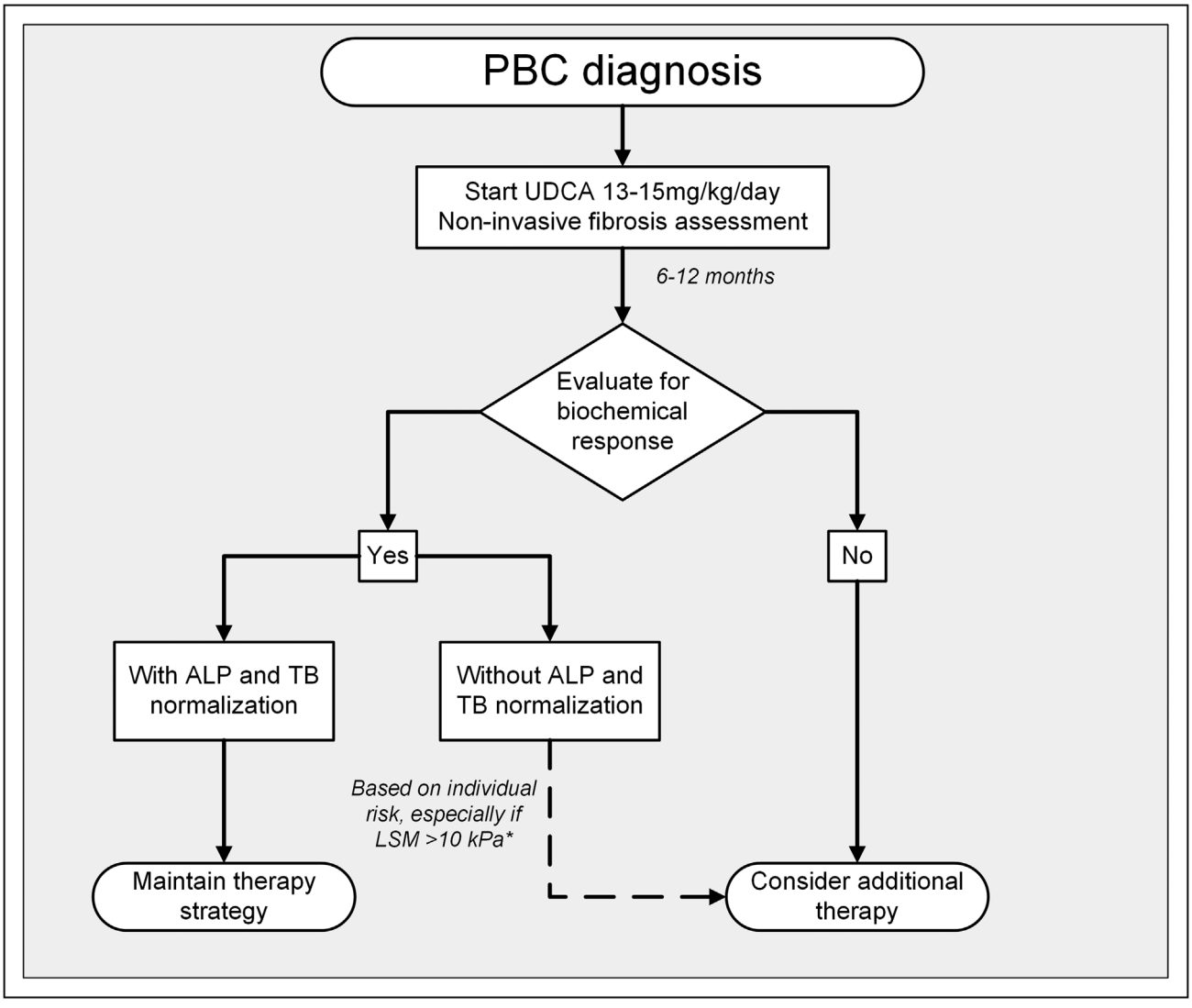

FIGURE 1. Algorithm for the management of primary biliary cholangitis following diagnosis. Upon diagnosis, patients should start treatment with UDCA at a dosage of 13–15 mg/kg/day, accompanied by a noninvasive assessment of liver fibrosis. After 6–12 months of therapy, biochemical response by any established response criteria (refer to Table 1, Supplemental Digital Content, http://links.lww.com/COG/A54) should be evaluated based on serum ALP and TB levels. If there is a response, patients with normalized ALP and TB can continue with the current treatment strategy. In cases where ALP and TB remain abnormal despite biochemical response, the patient's risk should be reassessed, particularly if LSM exceeds 10 kPa, indicating higher individual risk. Additionally, the clinical benefits of achieving a deep biochemical response diminish as age advances, and this should be weighed against the risks of treatment. In incomplete-responders, additional therapy should be considered. ALP, alkaline phosphatase; LSM, liver stiffness measurement; PBC, primary biliary cholangitis; TB, total bilirubin; UDCA, ursodeoxycholic acid. ∗ Patients with cirrhosis should be managed with caution. At this time, decompensated cirrhosis indicates a contra-indication to second-line therapy.

fibrosis, and in whom other reasons for persistent ALP elevation have been excluded. As always, caution is advised in the setting of cirrhosis, and those with decompensated cirrhosis are not currently eligible for second-line therapies. Continued investigation into its impact on disease progression, quality of life, and other clinically relevant endpoints will be crucial in solidifying the role of this approach in the management of PBC.

CONCLUSION

Achieving deep biochemical response represents a potentially transformative approach in PBC management, offering improved long-term outcomes for select patients. While normalization of ALP and bilirubin has been linked to reduced liver-related complications and better survival, further validation through robust data is necessary. Defining clear criteria to identify the patients most likely to benefit

and incorporating deep response into individualized, patient-centered care could help address gaps in current PBC management strategies.

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Conflicts of interest

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- ■ of special interest
- ■■ of outstanding interest

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