OPTIMIZING OUTCOMES IN PRIMARY BILIARY CHOLANGITIS

Seizing Opportunities to Address Unmet Needs through PPAR Agonists in the Second-line Setting



Frequently Asked Questions

Navigating the Diagnosis of Primary Biliary Cholangitis (PBC)

Is there a gold standard test to diagnose PBC?

A diagnosis of PBC requires at least 2 of 3 criteria to be met: 1) biochemical evidence of cholestasis with elevated alkaline phosphatase (ALP) activity; 2) presence of antimitochondrial antibodies (AMA); and/or 3) histopathologic evidence of nonsuppurative cholangitis involving the interlobular bile ducts. While liver biopsy may represent the closest diagnostic tool to a gold standard test for PBC, it is an imperfect assessment that only samples a limited portion of hepatic tissue. As a result, histopathologic evidence of nonsuppurative cholangitis may be missed and should not be solely relied upon to establish a diagnosis of PBC. Patients with elevated ALP levels and positive AMA may still meet diagnostic criteria for PBC if other extrahepatic causes of cholestasis have been excluded.

Should a liver biopsy be repeated if there is no evidence of non-suppurative cholangitis but there is a strong clinical suspicion for PBC?

Given that liver biopsy involves sampling only a limited portion of hepatic tissue, characteristic florid bile duct lesions and nonsuppurative cholangitis may not always be detected, even in patients with PBC. However, Dr. Gordon does not recommend repeat liver biopsy when there is strong clinical suspicion for PBC and sufficient information to fulfill its diagnostic criteria, including biochemical evidence of cholestasis and positive AMA serology.

Are Black patients with PBC more likely to test negative for PBC-specific autoantibodies?

Data from large U.S.-based PBC cohorts suggest that Black patients may be more likely to test negative for AMA despite having clinical features consistent with PBC. AMA negativity may raise concern for alternative diagnoses, such as sarcoidosis or other autoimmune conditions, which may lead to the under-recognition of PBC. Dr. Gordon emphasizes that in Black patients with compatible biochemical and histopathologic findings, clinicians should continue to consider PBC even in the absence of positive AMA serology.

Risk Stratification, Treatment Monitoring, and Predicting Ursodeoxycholic Acid (UDCA) Response

What are the key risk factors clinicians should assess for when managing patients with PBC?

Baseline and longitudinal ALP elevations, younger age at presentation, male sex, elevated bilirubin levels, and evidence of progressive liver fibrosis are poor prognostic indicators in PBC. To help assess fibrosis and risk stratification in clinical practice, vibration-controlled transient elastography can be used to evaluate liver stiffness, with increasing scores suggesting greater likelihood of disease progression and the potential need for earlier initiation of second-line therapy.

What patient characteristics predict or are associated with poor treatment response to UDCA?

Younger patients and those with advanced fibrosis, cirrhosis, or markedly elevated serum transaminases may be more likely to have a suboptimal response to UDCA. Additionally, baseline ALP levels may impact the likelihood of achieving treatment response thresholds commonly used in clinical trials. For example, patients with very high baseline ALP levels may have greater difficulty achieving predefined biochemical response targets compared with patients who begin treatment with more modest ALP elevations.

How is UDCA treatment failure defined, and which failure criteria do you use in practice?

There are multiple definitions and criteria for an inadequate response to UDCA, which often use relatively arbitrary biochemical thresholds—such as ALP levels ≥1.5 ×, 1.67 ×, or 2 × the upper limit of normal (ULN). These thresholds were derived from large datasets evaluating patients with PBC across varying ages and stages of fibrosis.

Dr. Mayo emphasizes the importance of a personalized approach when determining whether to initiate second-line therapy that extends beyond simply identifying inadequate biochemical response to UDCA. Additional considerations include patient preferences, insurance coverage, access to PPAR agonists, age, and stage of fibrosis. In patients with multiple risk factors for disease progression, earlier initiation of second-line therapy at lower biochemical response thresholds may be warranted.

Should clinicians aim for biochemical normalization?

While ALP thresholds such as 1.67 × ULN have historically been used to define biochemical response, the ideal therapeutic goal is ALP normalization whenever feasible. This is especially true for younger patients who have many more years to live with the disease and have the potential for progression, as well as those with advanced fibrosis and greater underlying disease activity. However, patients with markedly elevated baseline ALP levels may be unlikely to achieve complete normalization despite meaningful treatment response. In these cases, longitudinal improvements and the overall slope of ALP reduction over time may provide valuable insight into treatment effectiveness. Dr. Gordon notes that although UDCA response has traditionally been assessed after 12 months of treatment, many patients demonstrate their biochemical response within the first 6–9 months, potentially allowing for an earlier consideration of second-line therapy.

Are continuous scoring systems feasible to incorporate into daily practice?

The GLOBE and UK-PBC assessments are continuous risk scoring systems that clinicians can incorporate into clinical practice. While these tools are relatively quick and easy to calculate, time constraints in routine clinic workflows may make them challenging to readily implement. To help address this, Dr. Mayo recommends incorporating these assessments into pre-clinic check-ins or questionnaires that can then be integrated into the patient's overall evaluation and management plan. By estimating long-term risks of liver transplantation and mortality over 5-, 10-, or 15-year time increments, these tools may help support more informed shared decision-making between clinicians and patients. For example, such prognostic information can facilitate discussions regarding the potential benefits of earlier initiation of second-line therapy based on factors including patient age and biochemical profile.

Evidence and Clinical Experience with PPAR Agonists in PBC Care

How do you differentiate between PPAR agonists when selecting treatment for patients with PBC?

Both elafibranor and seladelpar demonstrated similar efficacy outcomes in their respective phase 3 clinical trials, including biochemical response and ALP improvement. Although these agents target different PPAR receptors—with elafibranor acting as a dual PPAR-α/δ agonist and seladelpar as a selective PPAR-δ agonist—these mechanistic differences have not translated into meaningful clinical differences in efficacy or safety to date. Both therapies have been generally well tolerated in both clinical trials and early real-world experience.

In the United States, treatment selection between available PPAR agonists is often influenced more by drug availability and insurance coverage than by clear differences in efficacy or safety. Manufacturers of both elafibranor and seladelpar offer patient assistance programs to help improve medication access, which Dr. Mayo recommends exploring when affordability is a barrier to treatment.

What has been your clinical experience using PPAR agonists in patients with PBC?

Drs. Mayo and Gordon report positive experiences with elafibranor and seladelpar in clinical trial and real-world practice settings, regarding both efficacy and safety. While gastrointestinal adverse effects may occur with either agent, these symptoms are often manageable and do not typically lead to treatment discontinuation.

Are PPAR agonists effective for the symptomatic treatment of pruritus and fatigue in PBC?

Clinical data suggest that both elafibranor and seladelpar may help improve pruritus and fatigue in patients with PBC, which is further supported by Dr. Mayo and Dr. Gordon's own clinical experiences. PPAR agonists are now the first pharmacologic class that has been shown in blinded, placebo-controlled trials to improve pruritus in PBC. However, treatment responses can vary considerably between patients, and there are currently no known predictive factors to identify which individuals will experience the greatest symptomatic benefit from PPAR agonist therapy. At present, available evidence is also insufficient to determine whether one PPAR agonist has more robust efficacy for

improving pruritus or fatigue, as differences in symptom outcomes may vary depending on the assessment tools and endpoints used across clinical trials.

Dr. Gordon emphasizes the importance of routinely assessing and actively asking patients about changes in pruritus and fatigue at each visit. For many patients, the chronicity of symptoms establishes a new baseline normality, which may lead to the underreporting of symptom burden unless specifically questioned. With therapies now demonstrating improvements in both itch and fatigue, Dr. Gordon highlights the importance of incorporating symptom assessment and quality-of-life discussions into routine PBC management.

Do insurance providers require step therapy or prior authorization for PPAR agonists?

In Dr. Mayo's clinical experience, insurance coverage for PPAR agonists is often based on whether patients meet the FDA-labeled indications for currently approved therapies, including elafibranor and seladelpar. Typically, this requires patients to have an ALP level ≥1.67 × ULN or elevated bilirubin despite at least 1 year of UDCA treatment, or UDCA intolerance. Prior authorization requirements are also common and may require appeals or additional documentation for approval.

However, some clinicians across the United States have successfully obtained insurance coverage for the off-label use of PPAR agonists in select patients with lower degrees of ALP elevation, particularly when there is concern for advanced fibrosis or significant symptom burden that may improve with therapy. Dr. Gordon similarly emphasizes that access to PPAR agonists can vary considerably depending on the insurer, with some payers demonstrating preferences for one agent over another and others closely evaluating baseline ALP criteria. Despite these challenges, Dr. Gordon reports that his overall experience obtaining access to PPAR agonists has been reasonably favorable, although coverage considerations may continue to evolve as clinical experience with these therapies expands.

If a patient is refractory to or experiences only a transient response with one PPAR agonist, would you consider switching to another in-class agent?

While phase 3 clinical trial data demonstrate similar efficacy between available PPAR agonists, there is no available data to determine whether switching from one PPAR agonist to another provides clinical benefit in patients with a transient, inadequate, or refractory treatment response.

Would you consider simultaneously starting a patient on UDCA and a PPAR agonist if they are at high-risk for liver transplantation?

In patients with immediate need or high risk for liver transplantation, referral for transplant evaluation may take priority over escalation of medical therapy. However, in patients who do not urgently require transplantation, Dr. Mayo recommends initiating treatment with UDCA alone rather than simultaneously starting UDCA and a PPAR agonist to avoid unnecessary polypharmacy, costs, and potential adverse effects. Consistent with current guideline recommendations and approved indications, treatment response to UDCA should be assessed before initiating second-line therapy with either elafibranor or seladelpar.

Would you consider a PPAR agonist for patients with PBC and autoimmune overlap?

In clinical trials evaluating elafibranor and seladelpar in patients with PBC, individuals with suspected autoimmune hepatitis (AIH) overlap were excluded, particularly those with markedly elevated alanine aminotransferase levels. As a result, there is a lack of clinical data regarding the safety and efficacy of PPAR agonists in patients with PBC-AIH overlap. When considering treatment approaches, Dr. Gordon emphasizes the importance of carefully establishing the underlying diagnosis. While antinuclear antibody positivity may occur in PBC, AMA positivity is uncommon in AIH. Evaluation of immunoglobulin (Ig) profiles, including elevated IgG levels in AIH and elevated IgM levels in PBC, may help differentiate these conditions. In patients with true autoimmune overlap, immunosuppressive therapies are often prioritized while PPAR agonists are generally not considered or recommended at this time.

Emerging Antipruritic Agents and Their Role Relative to PPAR Agonists

How are ileal bile acid transporter inhibitors (IBATis) being incorporated into treatment sequencing for pruritus management in PBC?

IBATis block the ileal bile acid transporter responsible for bile acid reuptake within the enterohepatic circulation, thereby increasing fecal bile acid excretion and helping reduce pruritus in cholestatic diseases. Compared with traditional bile acid sequestrants, IBATis are generally more potent and available in more patient-friendly oral formulations, such as twice-daily pills or capsules.

The first FDA-approved IBATi for the treatment of PBC-associated pruritus, linerixibat, received approval in March 2026. The optimal sequencing and relative role of IBATis compared with traditional antipruritic therapies (e.g., bile acid sequestrants, rifampin, opioid antagonists, selective serotonin reuptake inhibitors) in PBC management remain unclear. As clinical experience with IBATis continues to grow, their appropriate timing, positioning, and integration alongside therapies targeting the underlying disease process, such as PPAR agonists, will likely become better defined.

Should PPAR agonists be combined with traditional pruritus management initially or should symptomatic response be assessed first?

Dr. Mayo recommends prioritizing initiation of elafibranor or seladelpar in patients with inadequate biochemical response or intolerance to UDCA, given the importance of achieving disease control. PPAR agonists can also improve pruritus, with benefits sometimes observed within the first several weeks of treatment. As a result, clinicians may consider waiting approximately 2–12 weeks before escalating pruritus management with an additional agent. In contrast, patients with adequate biochemical responses to UDCA but persistent, burdensome pruritus may represent appropriate candidates for IBATi therapy.

If a patient has recently started on a PPAR agonist, symptomatic response should be assessed prior to adding an additional antipruritic agent. However, if a patient is already receiving treatment for pruritus (e.g., naltrexone, rifampin), these therapies may be continued when initiating a PPAR agonist. Over time, if pruritus improves or remains well controlled, de-escalation or discontinuation of the pre-existing antipruritic regimen may be considered. It is important to note, however, that there is a lack of clinical data to guide these treatment modifications.