Seladelpar and Elafibranor: The Second-Line Options for PBC After Ursodeoxycholic Acid Fails

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Primary biliary cholangitis (PBC) remains a chronic, progressive autoimmune liver disease that, if left untreated, can lead to cirrhosis and liver failure. Ursodeoxycholic acid (UDCA) has long been the cornerstone of therapy, improving biochemical parameters and delaying disease progression for many. But a significant proportion of patients, perhaps 30% to 40%, exhibit an inadequate response to UDCA, leaving them at elevated risk for adverse outcomes and an urgent need for additional therapeutic strategies.
This unmet need has driven the development of novel agents, with peroxisome proliferator-activated receptor (PPAR) agonists emerging as a key class. Seladelpar and elafibranor represent two such agents, offering distinct but complementary mechanisms of action to address the cholestasis, inflammation, and fibrosis characteristic of PBC.

KEY TAKEAWAYS

- The Pivot: New PPAR agonists, seladelpar and elafibranor, offer second-line options for PBC patients who do not respond adequately to UDCA.
- The Data: Both agents have demonstrated improvements in biochemical markers of cholestasis, including alkaline phosphatase and bilirubin levels.
- The Action: Clinicians should consider these agents for patients with an inadequate biochemical response to UDCA, aiming to reduce disease progression risk.

Primary biliary cholangitis is characterised by immune-mediated destruction of small intrahepatic bile ducts, leading to cholestasis and progressive liver damage. The disease predominantly affects women, typically presenting in middle age. Early diagnosis and treatment are critical to prevent progression to end-stage liver disease. UDCA works by altering the bile acid pool, reducing the hepatotoxicity of endogenous bile acids, and exerting immunomodulatory effects. Despite its established efficacy, a substantial subset of patients fails to achieve adequate biochemical response, defined by persistently elevated alkaline phosphatase (ALP) and/or bilirubin levels. These patients face a higher risk of liver-related complications, including decompensation, liver transplantation, and death.
The development of second-line therapies for PBC has focused on targeting different pathways involved in the disease pathogenesis. PPAR agonists, such as seladelpar and elafibranor, modulate gene expression involved in bile acid synthesis, transport, and inflammation. Seladelpar is a selective PPAR-delta agonist, while elafibranor is a dual PPAR-alpha/delta agonist. Both aim to improve cholestasis and reduce inflammation, thereby mitigating liver injury and

slowing disease progression. For a deeper understanding of liver diseases and their management, clinicians often consult comprehensive texts like Sherlock's Diseases of the Liver and Biliary System.

Targeting Cholestasis and Inflammation

Seladelpar's mechanism of action involves activating PPAR-delta, which plays a role in lipid metabolism, glucose homeostasis, and inflammation. In the context of PBC, PPAR-delta activation leads to increased expression of genes involved in bile acid detoxification and transport, facilitating the efflux of bile acids from hepatocytes. This action helps to reduce the accumulation of toxic bile acids, a hallmark of cholestasis. The drug also exerts anti-inflammatory effects, which can mitigate the immune-mediated damage to bile ducts. Patients receiving seladelpar typically show reductions in ALP, a key biochemical marker of cholestasis, and improvements in other liver function tests. The goal is to achieve an ALP level below 1.67 times the upper limit of normal, coupled with normal bilirubin, which is associated with improved long-term outcomes.

Elafibranor, as a dual PPAR-alpha/delta agonist, offers a broader spectrum of action. PPAR-alpha activation primarily influences fatty acid oxidation and lipid metabolism, which can be beneficial in PBC patients who often present with dyslipidemia. PPAR-delta activation mirrors some of the effects seen with seladelpar, promoting bile acid detoxification and transport. The combined activation of both PPAR subtypes aims to synergistically improve cholestasis, reduce inflammation, and potentially address metabolic comorbidities. Elafibranor has also demonstrated its ability to significantly lower ALP levels and improve other liver biochemical markers in patients who have not responded adequately to UDCA. The reduction in ALP is a critical surrogate endpoint, as it correlates with a lower risk of liver-related events.

Clinical Efficacy and Safety Profiles

Clinical development programs for both seladelpar and elafibranor have evaluated their efficacy and safety in patients with PBC who had an inadequate response or intolerance to UDCA. These programs have consistently shown that both agents lead to significant biochemical improvements. The primary efficacy endpoint in many of these studies is typically a composite of ALP reduction and normalisation of bilirubin, reflecting the direct impact on cholestasis. Patients treated with either seladelpar or elafibranor experience substantial reductions in ALP, often achieving the target levels associated with a better prognosis. The improvements are generally sustained over longer treatment periods, suggesting durable efficacy.

Beyond biochemical endpoints, these agents also aim to alleviate symptoms commonly associated with PBC, particularly pruritus. Pruritus can be debilitating for many patients, severely impacting quality of life. While direct anti-pruritic effects are not the primary mechanism, improvements in cholestasis can indirectly reduce pruritus. The safety profiles of seladelpar and elafibranor are generally favourable. Common adverse events are typically mild to moderate and may include gastrointestinal disturbances, such as nausea or abdominal pain, and fatigue. Some patients may experience transient elevations in transaminases, which usually resolve with continued treatment or dose adjustment. The incidence of serious adverse events is low, and both drugs are generally well-tolerated in the long term. For clinicians managing complex liver conditions, staying updated on the latest guidelines and treatment options is essential, as discussed in our coverage on alcohol policy action needed for liver disease.

Addressing the Unmet Need

The availability of seladelpar and elafibranor provides much-needed options for patients who do not achieve an adequate response to UDCA. Until recently, obeticholic acid (OCA), a farnesoid X receptor (FXR) agonist, was the primary second-line therapy. While effective, OCA is associated with dose-dependent pruritus, which can limit its use in some patients. The introduction of PPAR agonists offers alternative mechanisms of action and potentially different safety profiles, allowing for more personalised treatment approaches. This expanded therapeutic arsenal is important for managing a chronic disease like PBC, where long-term adherence and tolerability are paramount, as it directly impacts the ability to prevent disease progression and improve patient survival.

The choice between these second-line agents will depend on individual patient characteristics, comorbidities, and tolerability profiles. For instance, patients with significant dyslipidemia might benefit from elafibranor's PPAR-alpha activity. Those with severe pruritus might find seladelpar or elafibranor more tolerable than OCA. The ultimate goal is to halt or slow disease progression, prevent cirrhosis, and improve patient quality of life. Regular monitoring of liver biochemical markers remains essential to assess treatment response and adjust therapy as needed. The long-term impact on hard clinical outcomes, such as liver transplantation and mortality, will continue to be evaluated in ongoing studies and real-world data. Our previous reporting on EHR data identifying liver transplant patients at high risk of early graft loss highlights the importance of effective disease management.

These new therapies represent a significant step forward in PBC management. They provide clinicians with more tools to manage a complex and progressive disease, offering hope for improved outcomes for patients who previously had limited options beyond UDCA. The ongoing research into novel targets and combination therapies will further refine treatment strategies, moving towards a future where PBC progression can be effectively controlled for all patients. The open-label design of some earlier studies is an obvious caveat, but the consistent biochemical improvements across multiple trials lend confidence to the efficacy signals. Whether these benefits translate into a significant reduction in liver-related events in broader populations remains the critical unanswered question for future research.

CLINICAL IMPLICATIONS

The arrival of seladelpar and elafibranor marks a genuine expansion of our therapeutic toolkit for primary biliary cholangitis. For too long, clinicians have been left with limited options once ursodeoxycholic acid proved insufficient, forcing difficult choices between suboptimal control and therapies with significant side effect burdens. These new PPAR agonists provide distinct mechanisms, offering a more tailored approach to patients who are still at risk of progression.

The focus on biochemical endpoints, particularly ALP reduction, is a pragmatic one. While we await definitive long-term outcomes data on liver transplantation and mortality, the consistent and substantial improvements in these surrogate markers are encouraging. It means we have more levers to pull to reduce the inflammatory and cholestatic burden on the liver, which should, in theory, translate to better patient prognoses.

But the choice between these agents and existing second-line options like obeticholic acid will not be trivial. Clinicians will need to weigh the specific patient profile, including comorbidities, symptom burden (especially pruritus), and individual tolerability. This is not a one-size-fits-all scenario; it demands careful consideration of each drug's unique benefits and potential drawbacks. The expanded pipeline means more patients can find a therapy that works for them, but it also means more detailed decision-making for the prescribing physician.

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