A Review of Therapies for Primary Biliary Cholangitis

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Abstract: Primary biliary cholangitis (PBC) is a rare, chronic, progressive autoimmune cholestatic liver disease that can lead to cirrhosis if left untreated. Ursodeoxycholic acid remains the standard first-line therapy; however, approximately 40% of patients exhibit an inadequate or partial biochemical response, and approximately 5% to 10% of patients are intolerant to the drug. Consequently, there remains a substantial need for effective second-line agents. Until recently, obeticholic acid (OCA) and fibrates were the only available second-line therapies. However, the therapeutic landscape for PBC has evolved significantly with the US Food and Drug Administration conditional approval of elafibranor and seladelpar as second-line therapies for patients without cirrhosis. Notably, OCA has been withdrawn as an available treatment option, further shifting the current treatment paradigm. This article aims to examine the current pharmacologic landscape of first-line and second-line PBC treatments, with an emphasis on clinical considerations and strategies for individualized treatment selection to optimize patient outcomes.

Keywords
Primary biliary cholangitis, ursodeoxycholic acid, elafibranor, seladelpar, fibrates

Primary biliary cholangitis (PBC), formerly referred to as primary biliary cirrhosis, is a chronic autoimmune disease characterized by progressive destruction of the intralobular bile ducts in the liver, ultimately leading to cirrhosis, liver failure, and death if left untreated.[1] PBC predominantly affects women with a female:male ratio of 9:1.[2] Over the past decade, the incidence and prevalence of PBC have shown notable increase worldwide with the highest prevalence in North America (21.81 per 100,000 persons) and then in Europe (14.59 per 100,000 persons).[3] The global prevalence of PBC is estimated to be 18.1 cases per 100,000 people, with an incidence of 1.8 per 100,000 person-years.[4] PBC in men is associated with delayed diagnosis and lower survival rates, possibly owing to lower clinical suspicion.[5,6]

The etiopathogenesis of PBC remains incompletely understood and is considered multifactorial, involving complex interactions among genetic susceptibility, environmental factors, and immune dysregulation.[7] It is recognized that the pathogenesis involves T-lymphocyte–mediated attack on the bile ducts, as well as antimitochondrial antibodies (AMAs), which target the E2 subunit of the pyruvate dehydrogenase complex

(PDC-E2).[8,9] The diagnosis of PBC is confirmed by the presence of 2 of 3 criteria: (1) elevated alkaline phosphatase (ALP) level and either (2) the presence of AMAs (≥1:40) or PBC-specific antinuclear antibodies Sp100 and gp210 or (3) histologic evidence of nonsuppurative destructive cholangitis.[10-12] Other characteristic clinical features include elevated serum immunoglobulin M, hypercholesterolemia, pruritus, sicca syndrome, and fatigue.[10]

The symptoms associated with PBC can significantly diminish a patient's quality of life. The most common reported symptoms include progressive fatigue, cholestatic pruritus, dry mucous membranes, and abdominal discomfort.[13] Ursodeoxycholic acid (UDCA) has been shown to alter the natural course of PBC and reduce the risk of liver transplant and death, leading to its approval as a first-line therapy in 1997, as discussed in detail in the following section.[14] Subsequent research established the prognostic significance of serum ALP and bilirubin levels, forming the basis for long-term risk stratification in patients with PBC.[15] A landmark study of 4845 patients demonstrated that elevated ALP and bilirubin levels 1 year after initiation of UDCA therapy were associated with worse outcomes.[16] Specifically, an ALP level greater than 2 times the upper limit of normal (ULN) was associated with decreased 10-year transplant-free survival compared with patients with an ALP level no more than 2 times the ULN (62% vs 84%, respectively).[16] Similarly, a bilirubin level greater than 1 times the ULN was associated with lower 10-year transplant-free survival compared with patients with a bilirubin level no more than 1 times the ULN (41% vs 86%, respectively).[16] Subsequent research showed that having bilirubin levels less than 0.6 times the ULN is associated with the lowest risk for liver transplant and/or death.[17]

Several risk calculators and criteria are used for predicting prognosis or treatment response as well as risk of adverse outcomes in patients with PBC. The Global Assessment of Liver Outcomes (GLOBE) score includes age, total bilirubin level, ALP, albumin, and platelets to interpret transplant-free survival.[18] The UK-PBC score consists of total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST), ALP after 12 months of UDCA, albumin, and platelets to estimate the risk of requiring liver transplant in 5, 10, or 15 years while receiving UDCA treatment.[19] The POISE criteria are defined as serum ALP less than 1.67 times the ULN with a 15% reduction from baseline and normal total bilirubin and have been used in all three phase 3 clinical trials that led to conditional US Food and Drug Administration (FDA) approval of second-line therapies for PBC.[5]

Although UDCA continues to be the first-line treatment for PBC and has been shown to alter the natural history of the disease, approximately 40% of patients are inadequate UDCA responders who do not achieve an adequate biochemical response, and another 5% to 10% experience side effects with UDCA, necessitating the need for second-line therapies.[20] Notably, inadequate UDCA responders have been shown to exhibit a higher risk of liver-related complications and mortality compared with UDCA responders.[21] Early identification of inadequate UDCA responder status is therefore essential to optimize clinical outcomes through timely initiation of second-line therapies.

Obeticholic acid (OCA; Ocaliva, Intercept) received conditional approval from the FDA in 2016 as a second-line therapy for patients with an incomplete response to UDCA monotherapy.[22] Although the COBALT trial did not demonstrate significant improvement in transplant-free survival or other clinical outcomes, substantial real-world data suggested that OCA conferred clinical benefit over no treatment.[23] However, concerns regarding hepatotoxicity in patients with cirrhosis subsequently emerged and in 2018, the FDA issued a black box warning restricting its use in patients with cirrhosis or clinically significant portal hypertension, which led to a label modification.[24] In late 2024, the FDA further cautioned that OCA may cause hepatotoxicity even in patients without cirrhosis, consequently leading to a voluntary withdrawal of the drug from the market by the manufacturer in September 2025.[25,26] OCA is no longer available for prescription for treatment of PBC.

Patients previously treated with OCA therefore require transition to alternative second-line therapies. The options for second-line treatment of PBC currently available include elafibranor (Iqirvo, Ipsen), seladelpar (Livdelzi, Gilead), bezafibrate, and fenofibrate. Elafibranor, a dual peroxisome proliferator-activated receptor (PPAR)-α/δ agonist, and seladelpar, a PPAR-δ agonist, were conditionally approved by the FDA in 2024 based on the findings of phase 3 clinical trials.[4] In addition, bezafibrate and fenofibrate are available for use as off-label treatment options.[27,28] This has expanded the therapeutic options available for patients with PBC. This article aims to summarize the current literature on first-line and second-line therapies in PBC.

First-Line Treatment

UDCA has been approved for the treatment of PBC in the United States since 1997.[18] UDCA exerts its therapeutic effects by reducing the concentration of toxic hydrophobic bile acids and oxidative stress on hepatocytes, thereby providing cytoprotective benefits.[15,29] It has been shown to slow the histologic progression of the disease, improve survival, and delay the need for liver transplant.[15] In 2019, an analysis encompassing 3902 patients with a median follow-up period of 7.8 years demonstrated that

treatment with UDCA significantly reduced the risk of liver transplant or mortality.[30] One study showed that the probability of remaining free of extensive fibrosis or cirrhosis after UDCA treatment was 76% and 61% after being treated for 4 and 8 years, respectively.[31]

Inadequate UDCA responder status has been defined as persistently elevated ALP levels greater than 1.67 times the ULN or abnormal bilirubin levels after 1 year of therapy.[32] Persistent ALP elevation has been correlated with an increased risk of end-stage liver disease and mortality compared with patients with an adequate response to UDCA therapy.[33] Additionally, a subset of patients cannot tolerate UDCA owing to adverse effects such as abdominal cramping, diarrhea, hair loss, weight gain, and allergic reactions or worsened pruritus.[29] Patients with an inadequate response and those who are intolerant to UDCA are candidates for second-line therapy, which is discussed in the following section.

Second-Line Treatments

Obeticholic Acid

OCA, a selective farnesoid X receptor agonist, was conditionally approved by the FDA as a second-line treatment in 2016 to be used in conjunction with UDCA based on the findings of the POISE trial.[34] This phase 3, 12-month, double-blind, randomized, placebo-controlled trial reported that 46% of patients in the 5 mg to 10 mg group, 47% in the 10 mg group, and 10% in the placebo group met the POISE criteria.[34] The most common side effects reported were pruritus, worsening fatigue, gastrointestinal issues, thyroid dysfunction, dizziness, and arthralgia.[34] In 2021, the FDA issued a warning restricting its use in patients with advanced liver disease characterized as Child-Pugh class B and C.[35]

The phase 3b/4 COBALT trial, a double-blind, randomized controlled trial, reported no difference between OCA and placebo in the primary clinical endpoints of time to death, liver transplant, Model for End-Stage Liver Disease score greater than 15, uncontrolled ascites, or hospitalization for hepatic decompensation in the intent-to-treat analysis, with a hazard ratio of 1.1.[24] The study was limited by informative censoring and functional unblinding with treatment crossover from placebo to active therapy, which confounded the results and reduced the power of the study.[24] To address these limitations, the treated group in the COBALT trial was compared with an external control group.[20] In this analysis, the primary endpoint of an adverse liver outcome occurred in 10.1% of OCA patients and 21.5% of non-OCA patients.[24] However, given persistent concerns about safety and lack of efficacy in the COBALT trial, the drug was voluntarily withdrawn by the manufacturer in September 2025 and is no longer available for prescription for PBC treatment in the United States.[27]

Role of Fibrates

Guidelines from the American Association for the Study of Liver Diseases, which were last updated in 2021, recommended fibrates as an off-label alternative therapy for patients with PBC without cirrhosis who have an inadequate response to UDCA.[28] The most commonly used fibrates are bezafibrate (which is not available in the United States) and fenofibrate.

Bezafibrate is thought to modulate all 3 PPAR isoforms (α, δ, and γ) with differing affinities to exert anti-inflammatory and antifibrotic effects.[29,36] Most available data with bezafibrate are from studies conducted in Europe, Canada, and Japan. The BEZURSO trial was a 24-month, phase 3, double-blind, placebo-controlled study with 100 patients who were assigned to bezafibrate or placebo in addition to ongoing treatment with UDCA.[37] The primary outcome, defined as normal levels of total bilirubin, ALP, aminotransferases, and albumin (according to the Paris-II criteria), as well as a normal prothrombin index, was achieved in 31% of the patients in the bezafibrate plus UDCA group compared with 0% in the placebo plus UDCA group.[37] The study also noted significantly improved ALP levels in 67% of patients in the bezafibrate group compared with 2% in the placebo group.[37] A higher proportion of patients in the bezafibrate group achieved complete biochemical response, and improvements in pruritus and surrogate markers of fibrosis were also observed. Common adverse effects noted were increased serum AST and ALT levels and myalgias if taken in combination with statins.[37] An extensive observational study in Japan involving 3908 patients showed that the addition of bezafibrate to UDCA was associated with improved transplant-free survival as predicted by the GLOBE score.[38]

Fenofibrate, which is available in the United States, is a selective PPAR-α agonist that regulates how the body processes fats leading to reduction in triglycerides and low-density lipoprotein while increasing high-density lipoprotein.[29,36] In a prior study involving 20 patients who were inadequate UDCA responders treated with fenofibrate for 48 weeks, 55% of patients had a greater than 40% reduction in ALP or normalization of ALP levels.[39] In a separate prospective study in China involving 117 patients, one group received a combination of UDCA and fenofibrate while the other was treated with UDCA alone.[40] Among those given the combination therapy, 81.4% experienced a reduction or normalization of ALP levels, compared with 64.3% in the UDCA-only group in 12 months.[40] Fibrates have also been shown to decrease cholestatic itch by reducing bile acid synthesis and decreasing the levels of autotaxin, which may correlate with severity of itch.[41] In a

Table. Comparison of Elafibranor and Seladelpar

	Elafibranor	Seladelpar
Mechanism of action	Dual PPAR-α/δ agonist[57]	Selective PPAR-δ agonist[58]
Key efficacy findings	The ELATIVE trial achieved 57% placebo-corrected composite biochemical response at 12 months and 15% ALP normalization[43]	The RESPONSE trial achieved 42% placebo-corrected composite biochemical response at 12 months and 25% ALP normalization[47]
Pruritus	WI-NRS not significantly improved compared with placebo in patients with moderate-to-severe itch. Possible favorable trends in other itch measures[59]	WI-NRS significantly improved at 6 months compared with placebo in patients with moderate-to-severe itch. Possible favorable trends in other itch measures[47]
Fatigue	Improvement in fatigue with treatment compared with placebo in double-blind phase[43,47]	Improvement in fatigue among patients with severe itch (NRS ≥7) compared with placebo in double-blind phase[43,47]
Contraindications	Not recommended in decompensated cirrhosis[57,58]	Not recommended in decompensated cirrhosis[57,58]
Warnings	• Myalgia, myopathy, and rare rhabdomyolysis (higher risk with statins) • Fractures (6%) • Fetal toxicity, requires contraception • Drug-induced liver injury, including autoimmune-like hepatitis[57,58] • Hypersensitivity reactions • Avoid in complete biliary obstruction	• Fractures (4%) • ALT/AST elevations at higher doses, monitor LFTs • Avoid in complete biliary obstruction[57,58]
Drug interactions	Drug interactions as a weak CYP3A4 inducer with hormonal contraceptives leading to contraceptive failure or other interactions with HMG-CoA reductase inhibitors, rifampin, and bile acid sequestrants[57,58]	Drug interactions with OAT3 inhibitors, strong CYP2C9 inhibitors, dual moderate CYP2C9 and moderate-to-strong CYP3A4 inhibitors, and BCRP inhibitors. Other interactions with rifampin and bile acid sequestrants[57,58]
Safety information	Common adverse events include weight gain, diarrhea, abdominal pain, nausea, arthralgia, muscle pain, GERD, rash[57,58]	Common adverse events include headache, abdominal pain, nausea, distension, dizziness[57,58]

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCRP, breast cancer resistance protein; GERD, gastroesophageal reflux disease; LFT, liver function test; NRS, numeric rating scale; OAT3, organic anion transporter 3; PPAR, peroxisome proliferator-activated receptor; WI-NRS, Worst Itch Numeric Rating Scale.

cohort of 74 individuals with cholestatic pruritus of moderate-to-severe intensity in the randomized, double-blind, placebo-controlled FITCH trial, 45% of those receiving bezafibrate reported at least a 50% improvement in pruritus vs 11% in the placebo group.[41] However, neither bezafibrate nor fenofibrate are currently FDA-approved for treatment of patients with PBC.

Selective Peroxisome Proliferator-Activated Receptor Agonists

The Table summarizes the currently available PPAR agonists, which are the only FDA-approved second-line therapies for noncirrhotic patients with PBC. These selective PPAR agonists are discussed further in the following sections.

Elafibranor Elafibranor is a dual PPAR-α/δ agonist that was conditionally approved by the FDA in June 2024 for the treatment of PBC either as monotherapy or as combination therapy with UDCA.[5] PPAR-α activation regulates the transcription of genes involved in bile acid synthesis, resulting in reduction of bile acids, upregulation of detoxification pathways, and increased biliary excretion, which causes decreased bile acid–induced hepatocellular toxicity.[5] The dual activation of PPAR-α and PPAR-δ is also thought to exert anti-inflammatory effects, in part by downregulating nuclear factor kappa B signaling pathways, which are implicated in cholestatic liver injury.[42]

Elafibranor received accelerated conditional approval for use as monotherapy or as a combination therapy in patients with inadequate response to UDCA owing to its

known rapid reduction in ALP.[5] The ELATIVE trial was a 52-week, randomized, double-blind, placebo-controlled study evaluating elafibranor in 161 patients with PBC who had an inadequate response to UDCA.[43] Participants received either elafibranor 80 mg once daily or placebo, in addition to background therapy with UDCA. The primary endpoint, defined as the POISE criteria, was met by 51% of patients in the elafibranor group compared with 4% in the placebo group (P<.0001).[43] In addition, 15% of patients achieved a secondary endpoint of normalization of ALP level at 52 weeks compared with 0% in the placebo group.[43] The study found no statistically significant difference in Worst Itch Numeric Rating Scale scores for worst itch between patients receiving placebo and those receiving elafibranor after 1 year, although there was a suggestion of improvement in pruritus in some measures of itch.[43] The most commonly reported adverse events included generalized myalgias with or without creatine phosphokinase elevations and gastrointestinal discomfort, including nausea, vomiting, diarrhea, and abdominal pain.[43] Elafibranor has not yet been evaluated among patients with cirrhosis, and its use in this population is therefore not currently recommended.[44] A confirmatory trial is underway to further assess the safety and efficacy of elafibranor among patients with PBC and cirrhosis.

Seladelpar Seladelpar was conditionally approved by the FDA in 2024 as a second-line treatment for PBC in patients who exhibit an inadequate response to UDCA.[45] It acts as a selective PPAR-δ agonist, promoting transcriptional regulation of genes involved in lipid metabolism and bile acid homeostasis.[46] This activity helps reduce bile acid synthesis and inflammation, the two key contributors to cholestatic liver injury in PBC.[46]

The 12-month, randomized, double-blind, placebo-controlled RESPONSE trial evaluated 193 patients with PBC who had an incomplete response or were intolerant to UDCA.[47] All participants continued background therapy with UDCA while the treatment arm received seladelpar 10 mg once daily.[47] The POISE criteria were met by 62% of patients in the seladelpar group, compared with 20% in the placebo group (P<.001).[47] Among participants with a numeric rating scale (NRS) of at least 4, seladelpar showed statistically significant improvement in pruritus score (NRS 0-1) in 26.5% of patients in 12 months compared with 0% in the placebo group.[47] Additionally, ALP normalization was achieved in 25% of patients treated with seladelpar in 12 months compared with 0% receiving placebo.[47] The most frequently reported adverse effects included fatigue, headache, abdominal pain, nausea, abdominal distention, and arthralgia in the seladelpar group.[47] The drug has not yet been studied in patients with cirrhosis, but a clinical trial is underway assessing its safety and efficacy in this patient population.

Upcoming Medications in Clinical Trials

Saroglitazar, a dual PPAR-α/γ agonist, showed promise in a phase 2 proof-of-concept trial.[48] Treatment with 2 mg and 4 mg doses, administered either as monotherapy or in combination with UDCA, resulted in 71% and 69% of patients meeting the POISE criteria, respectively.[48] A phase 2b/3 clinical trial is currently in progress.[49]

Pemafibrate, a selective PPAR-α modulator, is currently under investigation as a potential treatment option for patients with PBC.[50] The acidic side chain in its molecular structure makes it 2500 times more potent than fenofibrate.[51] In a cohort of 33 individuals, 12 months of combination therapy of UDCA plus pemafibrate resulted in significant reductions in serum AST, ALT, gamma-glutamyltransferase (GGT), and ALP levels across both the add-on and switch treatment groups. Additionally, the mean GLOBE score decreased from 0.37 to 0.01 (P<.05).[52] A small single-center, retrospective observational study in Japan included 12 patients with chronic kidney disease (estimated glomerular filtration rate [eGFR] lower than 30 mL/min/1.73 m^2) who were started on low-dose pemafibrate (0.1 mg/day) treatment for hypertriglyceridemia.[53] Serum ALT, ALP, and GGT levels were significantly decreased (P=.0034, .002, .001, respectively), whereas serum AST and creatine kinase levels did not change significantly.[53] Serum creatinine, eGFRs, and urinary protein levels after treatment were not significantly different from those before treatment, which suggests that pemafibrate might have a role in patients with chronic kidney disease.[53] A phase 2 randomized, placebo-controlled trial is currently in progress to evaluate the safety and efficacy of 2 dosing regimens of pemafibrate.[54]

Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 1 (NOX1) and NADPH oxidase 4 (NOX4) are enzymes primarily involved in the production of reactive oxygen species, which plays a key role in the development of liver fibrosis.[55] NOX1 and NOX4 initiate apoptotic pathways and promote the transformation of hepatic stem cells into myofibroblast-like cells.[55] Setanaxib, a dual NOX1/4 inhibitor, is currently being evaluated in a phase 2b clinical trial involving 76 participants. After 24 weeks of treatment, improvements in ALP levels were observed in 19% and 14% of patients receiving 1600 mg and 1200 mg doses, respectively.[55]

Role of Corticosteroids

The role of budesonide as an adjunctive therapy for PBC remains unclear. A randomized, placebo-controlled, 36-month trial enrolled 62 patients who were assigned to

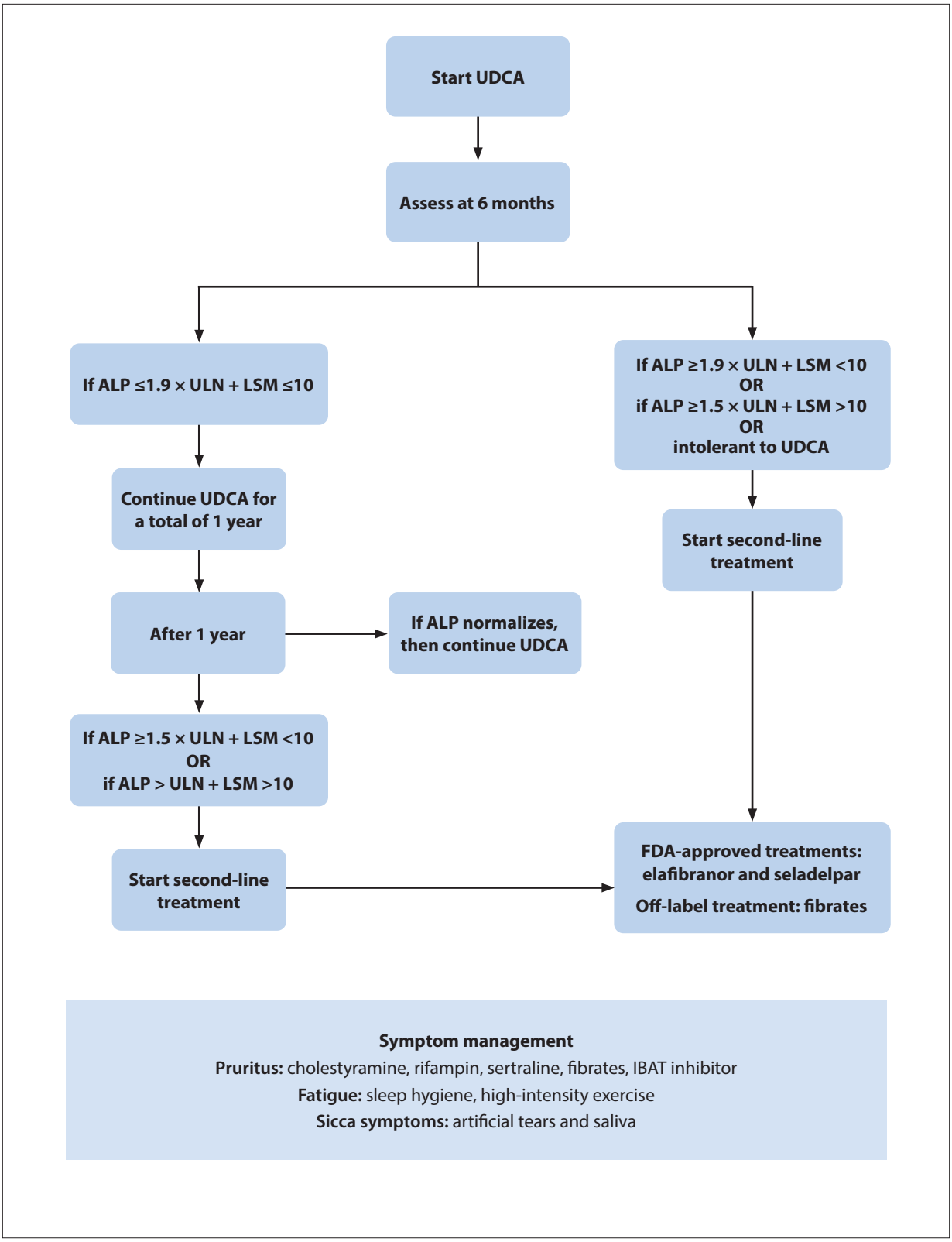

Figure. Algorithm for the management of PBC patients without cirrhosis.

ALP, alkaline phosphatase; FDA, US Food and Drug Administration; IBAT, ileal bile acid transporter; LSM, liver stiffness measurement; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

budesonide vs placebo in a 2:1 ratio.[56] The primary endpoint was defined as an improvement in liver histology and absence of fibrosis progression.[56] Reduction in ALP level was achieved in 35% of patients compared with 9% in the placebo group (P=.023), and no significant improvement in histology was noted.[56] Although the utility of using budesonide for PBC remains a topic of discussion, its use is recommended primarily for patients with overlapping autoimmune conditions such as autoimmune hepatitis.[29] Because long-term budesonide therapy can increase risk of bone loss, its use is limited.

Approach to Patients With Primary Biliary Cholangitis

The treatment goals in PBC are evolving toward achieving a complete biochemical response defined by normalization of ALP, AST, and ALT and, ideally, a total bilirubin level below 0.6 mg/dL.[17] It is likely that multidrug combinations with different mechanisms of action may be required. UDCA should be first-line therapy for both cirrhotic and noncirrhotic patients, followed by reassessment at 6 months to determine biochemical response. Patients with an ALP level no more than 1.9 times the ULN and liver stiffness measurement (LSM) no more than 10 kPa may continue UDCA for a full year, after which normalization of ALP supports ongoing monotherapy. Noncirrhotic patients with an inadequate biochemical response, defined as ALP at least 1.9 times the ULN with LSM less than 10 kPa or ALP at least 1.5 times the ULN with LSM more than 10 kPa, should add second-line therapy (or monotherapy if intolerant to UDCA). FDA-approved options include seladelpar and elafibranor for noncirrhotic patients. Fibrates may be considered as off-label treatment for patients unable to receive seladelpar or elafibranor. Because there are no FDA-approved second-line therapies for PBC patients with cirrhosis, clinical trials should be considered for such patients. Symptom-directed management remains essential throughout care, particularly for pruritus, fatigue, and sicca symptoms. A proposed algorithm for management of PBC without cirrhosis is presented in the Figure.

Conclusion

The therapeutic landscape of PBC has expanded considerably over the past year, providing new treatment avenues for patients who fail to achieve optimal outcomes with UDCA as first-line therapy. Following the withdrawal of OCA, elafibranor and seladelpar currently represent the only FDA–conditionally approved second-line therapies, with both agents demonstrating efficacy in improving biochemical responses, alleviating symptoms, and slowing disease progression. Although the treatment of PBC has progressed remarkably over the past 2 decades, there remains an unmet need for therapies to improve symptoms such as pruritus and fatigue and to achieve the aspirational goal of complete biochemical normalization of the liver. In the future, we hope to have additional treatment options to help patients obtain the maximum length and quality of life with this chronic and progressive liver disease.

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