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Position Paper

AISF practice guidance on the treatment of primary biliary cholangitis: A 2026 update

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ABSTRACT

Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic liver disease that, if untreated or inadequately treated, may progress to advanced fibrosis, cirrhosis, and liver-related complications. Although ursodeoxycholic acid (UDCA) remains the cornerstone of first-line therapy and improves transplant-free survival, an important proportion of patients show an inadequate biochemical response, and many continue to experience substantial symptoms, particularly pruritus and fatigue, with a major impact on quality of life. In recent years, the therapeutic landscape of PBC has evolved following the withdrawal of obeticholic acid and the availability of selective PPAR agonists, including elafibranor and seladelpar. At the same time, disease management has shifted beyond a dichotomous definition of biochemical response toward a risk-based and holistic approach integrating biochemical response, fibrosis stage, liver stiffness, and patient-reported outcomes. Therapeutic targets should be individualized according to age, disease stage, symptom burden, and risk of progression, distinguishing between "adequate" and "complete" biochemical response and supporting earlier treatment escalation in high-risk and symptomatic patients. This updated AISF guidance provides an evidence-based framework for PBC management in 2026 and beyond, reviewing therapeutic goals, response criteria, second-line therapies, and management in specific settings, including cirrhosis, pregnancy, variant syndromes, and metabolic comorbidities, emphasizing a patient-centred approach and highlighting unmet needs and future directions.

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1. Introduction

Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic liver disease characterized by progressive destruction of the interlobular bile ducts, leading to chronic cholestasis and ultimately cirrhosis, and liver-related complications in the absence of effective treatment [1,2]. Although traditionally considered rare, the global burden of PBC has increased over recent decades, likely reflecting improved diagnostic awareness, a broader use of sensitive serological markers, and longer patient survival due to therapeutic advances. The disease typically affects women more frequently than men and presents in middle to older age groups, with a growing proportion of diagnoses occurring in patients aged over 60 years, adding complexity to disease management due to comorbidities [3–8]. However, a higher proportion of patients are currently diagnosed at an earlier stage of disease, reflecting improved awareness and earlier biochemical detection [3,7]. PBC incidence and prevalence estimates vary by geography, but pooled data suggest a global prevalence of approximately 18 cases per 100.000 people and an incidence around 1.8 per 100.000 person-years [9].

First-line therapy with ursodeoxycholic acid (UDCA) has been a major advance, shown to improve liver biochemistries, delay histologic progression, and prolong transplant-free survival, particularly when initiated early in the disease course [2,10,11]. Nonetheless, up to 40% of patients exhibit an inadequate biochemical response to UDCA, and many continue to experience symptom burden, including fatigue, pruritus, and sicca complex, which significantly impair their quality of life [8,12,13]. To address unmet therapeutic needs, in 2016 obeticholic acid (OCA) emerged as the first approved second-line agent. However, tolerability limitations and safety concerns in advanced disease have emerged as significant issues, and ultimately OCA marketing authorization has been withdrawn by the European Medicines Agency (EMA) due to the failure of the trial that aimed to demonstrate the impact of OCA treatment on hepatic solid endpoints [14,15].

Recently, the landscape of PBC therapy has broadened further with the development and regulatory accelerated approvals of se-

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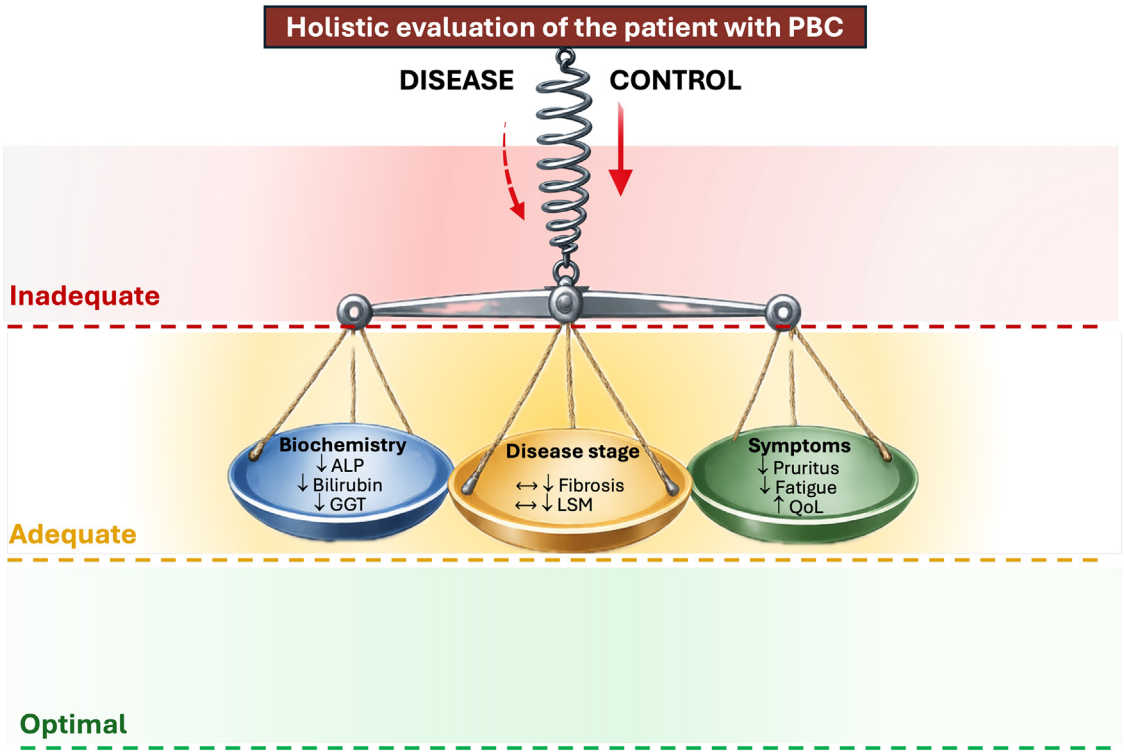

Fig. 1. Holistic approach in primary biliary cholangitis (PBC). The goals of PBC management should target three key domains, *i.e.*, biochemical parameters, disease stage and symptoms, to achieve optimal disease control and improve quality of life. ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase; LSM = Liver Stiffness Measurement; PROs = patient-reported outcomes; QoL=Quality of life.

lective peroxisome proliferator-activated receptor (PPAR) agonists, including elafibranor, a dual PPAR-α/δ agonist, and seladelpar, a PPAR-δ agonist, which have shown positive effects on alkaline phosphatase (ALP) reductions and biochemical response rates in phase 3 studies [16,17]. These agents offer new mechanisms of action targeting cholestasis and inflammation beyond farnesoid X receptor (FXR) modulation and represent an important therapeutic opportunity for patients with a suboptimal response, or intolerance, to UDCA [18].

However, the evolution of available therapeutic options coincides with increasing regulatory complexity, heterogeneity in access across jurisdictions, and a shifting paradigm toward individualized, patient-centred care. In particular, lessons learned from the OCA experience highlight the importance of weighing efficacy against tolerability and long-term outcomes in diverse patient subsets [8,18,19]. In parallel, the recognition that biochemical response alone may not fully capture disease trajectory or patient experience has catalysed interest in more nuanced goals of care that encompass symptom control, patient-reported outcomes (PROs), and risk stratification beyond surrogate biomarkers.

In 2024, AISF produced a position paper on the management of patients with PBC [2]. In light of the recent evolution toward a holistic and phenotype-based approach to the management of PBC, as well as the latest developments in the therapeutic armamentarium, this AISF guidance seeks to offer an updated, evidence-based, and clinically focused framework for PBC treatment in 2026 and beyond. The objectives are to:

1. Define therapeutic goals and response paradigms, integrating classic biochemical endpoints with emerging concepts of "adequate response" and "complete response" and phenotype-driven risk stratification.
2. Evaluate current therapies, in particular second-line agents such as PPAR agonists and a mention to other investigational molecules, with a focus on efficacy, safety, symptom management, and individualized therapy selection.
3. Address clinical challenges and special conditions encountered in routine practice, including cirrhosis, pregnancy, variant syndrome, and metabolic comorbidities.
4. Highlight outstanding unmet needs and future directions in research, regulatory alignment, and equitable access to novel therapies.

2. Current therapeutic goals in PBC

Therapeutic targets in PBC have evolved from a purely biochemical "response/non-response" concept (*e.g.*, Paris II, POISE criteria) toward a phenotype-informed strategy that aims to minimize long-term liver-related outcomes by achieving the best possible disease control, and to address patient's symptoms and quality of life through a "holistic approach" [2] (Fig. 1).

In practice, the current management integrates three parallel targets: biochemical response, fibrosis stabilization/regression, and symptom control assessed with validated PROs.

2.1. Risk stratification

PBC is generally characterized by a relatively homogeneous clinical presentation, typically affecting middle-aged women with chronic cholestasis. However, disease stage, severity, symptom burden, and response to therapy may vary considerably among patients, resulting in different prognostic phenotypes and therapeutic needs [18,20]. Younger patients, males, subjects with advanced fibrosis or bilirubin-predominant cholestatic disease, patients with severe symptom burden (particularly pruritus), and those with PBC-autoimmune hepatitis (AIH) variant generally represent higher-risk phenotypes requiring closer monitoring and a more aggressive therapeutic approach [18,20]. A subset of patients

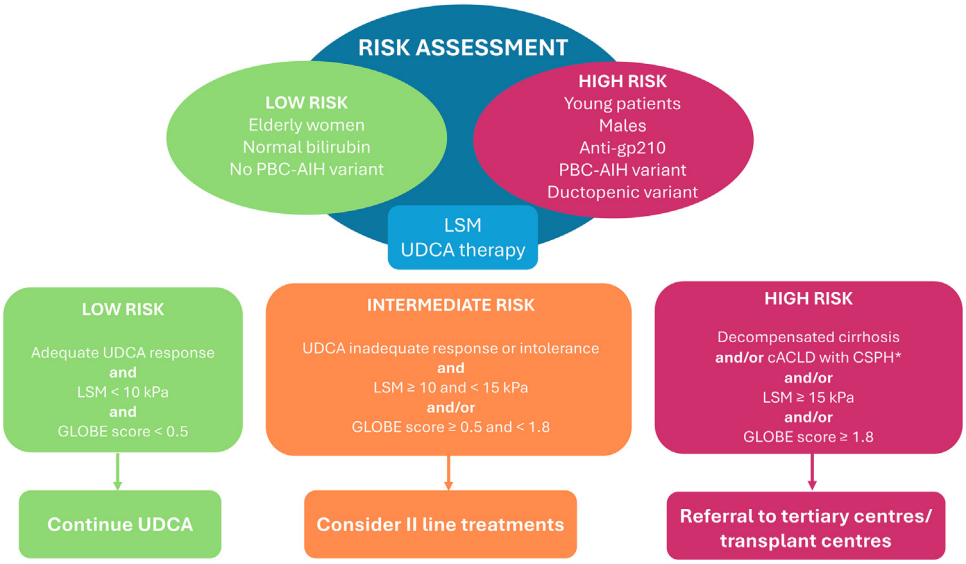

Fig. 2. Risk-based management in primary biliary cholangitis (PBC). Integration of baseline characteristics, biochemical response to UDCA, liver stiffness measurement (LSM), and prognostic scores enables patient stratification into low-, intermediate-, and high-risk categories, that guide the most appropriate clinical management. ANA = antinuclear antibodies; AIH = autoimmune hepatitis; UDCA = Ursodeoxycholic acid; LSM = Liver Stiffness Measurement at transient elastography; cACLD = compensated advanced chronic liver disease; *CSPH: clinically significant portal hypertension (further detailed in paragraph 4.2).

may present with a premature ductopenic phenotype characterized by disproportionate cholestasis and bilirubin elevation despite limited fibrosis progression [21]. Conversely, older patients with mild disease burden and stable biochemical responses may reflect a long-standing but slowly progressive disease course. Recognizing these clinical trajectories may support a more personalized and patient-centred management strategy.

Risk stratification should consider multiple factors that influence patients' prognosis: clinical and demographic features, biochemical markers, disease stage and presence of symptoms are the key elements (Fig. 2).

Clinical and demographic features

- Age at diagnosis: patients with younger age at onset have a higher likelihood of non-response to first-line treatment with UDCA and may experience more intense symptoms [20,22,23]. Owing to their longer life expectancy, these patients face a higher cumulative risk of poor outcomes and may thus require closer monitoring and early consideration of add-on strategies in the setting of suboptimal response.
- Sex: men may present later and with more advanced disease [20]. Diagnostic delay should be avoided by appropriately screening for PBC young men with cholestasis, and fibrosis cofactors (*i.e.*, metabolic dysfunction-associated steatotic liver disease and alcohol-associated liver disease) should be actively addressed. Moreover, advanced disease in men is associated with higher hepatocellular carcinoma (HCC) risk compared to women [24].

Biochemical and serological markers

- ALP and gamma-glutamyl transferases (GGT): are biomarker of cholangiocyte injury and validated surrogate markers of clinical outcome, with a stronger predicting weight after treatment with UDCA [25,26].
- Elevated bilirubin: a marker of cholestasis, advanced disease stage and severe ductopenia [21], is a strong short-medium term prognostic predictor.
- Aspartate and Alanine Aminotransaminases (AST, ALT): are biomarker of hepatocyte injury and are often mildly elevated in patients with PBC. When elevations are disproportionate to cholestatic markers and/or fail to decline in parallel with cholestatic indices after first-line therapy, this should raise suspicion for the PBC-AIH variant [27], and prompt consideration of liver biopsy [27]. The PBC-AIH variant has prognostic implications and requires specific management, as it has an independent risk for clinical endpoints [28].
- Gp210 antibodies: are associated with more aggressive disease progression in some cohorts and can refine risk profiling [29,30].

Disease stage

Fibrosis stage at diagnosis and the evolution during monitoring is prognostically relevant. In patients with early-stage PBC, the main goals are to achieve sustained biochemical response, prevent fibrosis progression, and maintain quality of life. Prognosis is generally favourable in patients with complete biochemical response and absence of advanced fibrosis [22,23]. Nevertheless, regular follow-up remains important, including periodic assessment of liver biochemistry, liver stiffness, and symptom burden, as disease progression or loss of response may still occur over time [31,32]. Conversely, patients with advanced fibrosis have an increased risk of clinical events, irrespective of response to first-line therapy. Disease stage should be assessed at baseline and in periodic re-evaluations using non-invasive tools, complemented by liver biopsy in selected cases [2].

- Liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE): a widely available, non-invasive tool routinely used in clinical practice as a surrogate marker of liver fibrosis and prognosis. It is a surrogate of histological fibrosis and can support outcome prediction. At diagnosis, dual cut-offs of $\leq$ 6.5 kPa and $>$ 11 kPa allow exclusion or confirmation of advanced fibrosis/cirrhosis [33]. Moreover, LSM improves survival prediction beyond biochemical response, prognostic scores, and age [31,34]. At baseline, it is independently associated with adverse outcomes, with 8 kPa and 15 kPa as suggested thresholds to stratify patients into low-, intermediate-, and high-risk groups [34]. By adopting a simpler dichotomous approach, a LSM $\geq$10 kPa identifies patients at increased

risk of hepatic decompensation [31,35,36]. Moreover, a LSM ≥10 kPa during follow-up predicts decompensation independently of biochemical response to UDCA according to Paris II criteria [31]. Consistently, current EASL guidelines on non-invasive tests recommend a 10 kPa LSM threshold to identify patients with advanced disease [35]. The risk of a first decompensation event rises from 10 kPa and increases progressively according to the Baveno VII "rule of five" [37]: patients with baseline LSM 10–15 kPa and 15.1–20 kPa have a 6-fold and 25-fold higher risk, respectively, compared with those <10 kPa [31]. In addition, longitudinal LSM has prognostic value in PBC with relative changes over time associated with variations in risk of serious clinical events [38].

- Liver biopsy: remains the reference standard for fibrosis staging, but is currently recommended only when disease-specific auto-antibodies are absent and/or a variant syndrome or hepatic comorbidities are suspected [39–41]. Histologically, PBC is characterized by chronic nonsuppurative destructive cholangitis affecting small intrahepatic bile ducts, progressive ductopenia, portal inflammation, and fibrosis. Traditionally, histological staging has been assessed using systems such as Ludwig and Scheuer classifications, which stratify disease progression from portal inflammation to cirrhosis [39,42]. More recently, the Nakanuma staging and grading system has gained relevance because it incorporates not only fibrosis but also bile duct loss and cholestatic activity, thus providing a more comprehensive assessment of disease severity and prognosis [40,43].

2.2. Biochemical response criteria: "adequate" and "complete" response

The first-line therapy for patients with PBC is UDCA at 13–15 mg/kg/day. UDCA therapy improves prognosis independently of biochemical response [11,44]. However, the improvement of liver biochemistry on UDCA is one of the strongest predictors of long-term outcomes in PBC.

How to define response

Biochemical response to UDCA is traditionally assessed after 12 months of treatment using either categorical (dichotomous) [45–50], or continuous criteria [22,23]. Among dichotomous definitions, the Toronto-derived POISE criteria (ALP <1.67 x upper level of normal (ULN), ALP reduction ≥15% and normal bilirubin) are particularly relevant because POISE is the endpoint used in phase 3 trials supporting approval of second-line therapies [16,17,51], and have been referenced in reimbursement pathways in some countries.

Alongside dichotomous definitions, continuous risk scores, *i.e.*, the GLOBE score [23] and UK PBC score [22], provide an accurate estimate of overall and liver-related survival, respectively. At the time being, such scores are applied for trial design and as secondary endpoints in clinical trials, other than for patient's counselling in clinical practice.

Current thinking also emphasizes a "deep response" criterion: beyond a dichotomous responder/non-responder classification, lower cholestatic markers -particularly ALP- translate into better prognosis. Large international registry analyses from Global PBC Study Group showed that ALP normalization and/or bilirubin ≤0.6 × ULN are linked to a significantly lower risk of clinical events [52]. In a subsequent analysis, normal serum ALP was associated with a significant absolute gain in complication-free survival at 10 years (mean 7.6 months, 95% CI: 2.7–12.6; $p = 0.003$), whereas bilirubin <0.6 mg/dL was not confirmed as an independent prognostic factor [53], leaving the latter objective, at present, desirable but not mandatory. In a subgroup analysis of the same study, this association remained significant in patients with liver stiffness ≥10 kPa and/or age ≤62 years, with a 10-year absolute gain in complication-free survival of 52.8 months (95% CI: 45.7–59.9; $p < 0.001$) when both conditions were met [53]. Notably, biochemical response is dynamic: some patients might lose response during follow-up and face an increased risk of adverse outcomes, underscoring the value of achieving and maintaining a lower-risk biochemical state over time [32].

Considering this evidence, the most recent view is to define a response as "adequate" when bilirubin is within the normal range (<1 mg/dL) and ALP meets the response criteria according to Paris II or, at least, Toronto criteria (<1.5 x ULN or <1.67 x ULN, respectively); and as "complete" when ALP is also within the normal range (<ULN). An adequate response appears to be an acceptable target in older patients with non-advanced fibrosis who do not experience disease-related symptoms such as pruritus and fatigue. Conversely, in younger patients and/or those with LSM ≥10 kPa, prompt escalation to second-line therapy should be considered, and the ideal target should be a complete response. Likewise, early consideration of an upgrade to second-line therapy, even in the presence of an acceptable biochemical response, seems reasonable in patients with symptoms that negatively impact quality of life.

When to define response

Regarding timing of response assessment, while 12 months remains the standard timepoint, earlier evaluation may be useful in higher-risk patients. Registry-based evidence suggests that patients with ALP >1.9 × ULN at 6 months have an approximately 90% probability of not meeting POISE response criteria at 12 months [54], supporting consideration of earlier add-on strategies in selected cases. Additional tools aiming at earlier risk identification include the UDCA Response Score (URS), which predicts the probability of response at 12 months before starting UDCA using baseline ALP, bilirubin, aminotransferases, age at diagnosis, and time from diagnosis to treatment initiation [12].

Earlier assessment of response and achievement of a complete response should be pursued in patients with high-risk profile. In parallel, closer monitoring is warranted to ensure sustained response and reduce the risk of complications during follow-up. Biochemical response should indeed be assessed throughout the entire follow-up, as patients may lose it over time, even if it was achieved early at 12 months. Loss of response during follow-up is associated with changes in the risk of liver transplantation or death [32].

2.3. Symptom assessment and patient-reported outcomes

The assessment of patients' symptoms and the use of PROs are increasingly important to support a holistic approach to PBC care, as symptoms substantially affect quality of life and inform clinical management. Symptom burden is an integral part of patient assessment and should be considered when selecting therapy and tailoring follow-up.

In the last decade, regulatory agencies have strongly encouraged the inclusion of symptoms-based PRO endpoints in clinical trials. Several instruments have been developed, but only few have undergone appropriate validation and psychometric testing in PBC populations [55].

- PBC-40 is a questionnaire covering six domains: fatigue, emotional, social and cognitive function, general symptoms and itch, developed and validated to study health related quality of life of PBC patients [56]. This questionnaire assesses symptoms over the last 4 weeks.
- PBC-27 is a shortened version, validated in Italian, that could be used in clinical practice [57].
- The 5-D Itch scale comprises five domains: duration, degree, direction, disability, and distribution, with each domain accounting for 5 points. The domain scores are then added together for

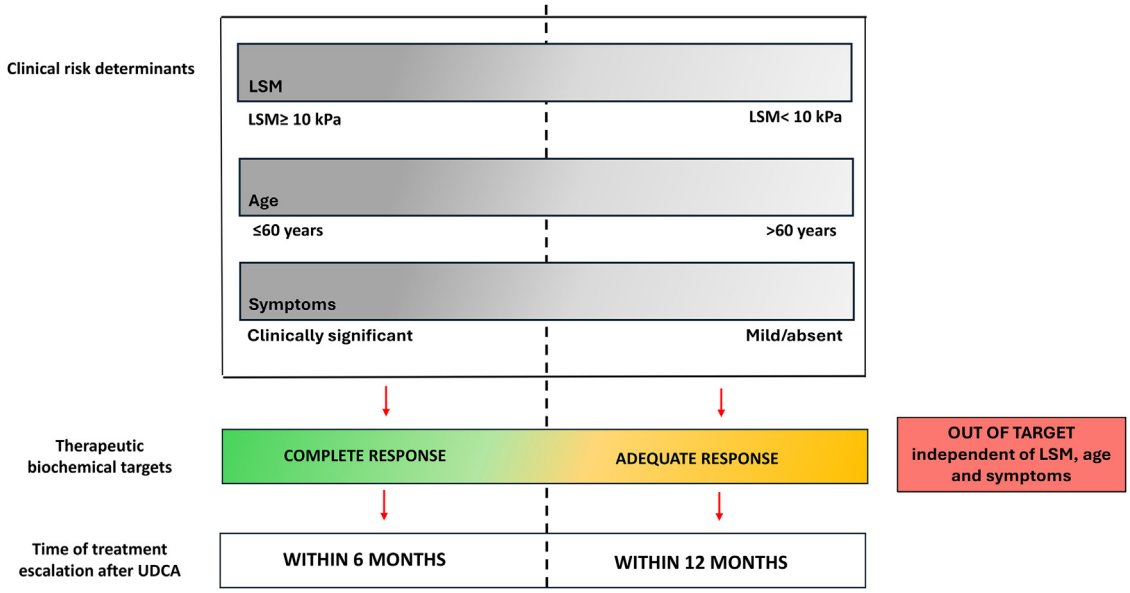

Fig. 3. Determinants of treatment escalation in primary biliary cholangitis (PBC). Integration of age, liver stiffness measurement (LSM), and symptom burden may help guide the choice and the timing of treatment escalation beyond UDCA when therapeutic targets are not achieved. Although current evidence does not allow the definition of precise criteria, younger age, higher stiffness, and more impactful symptoms should guide both the adoption of more stringent therapeutic targets and a more rapid escalation to second-line therapy. Adequate response (ALP <1.5 -or, at least- 1.67 X ULN and normal bilirubin) may be acceptable in older (age > 60 years), asymptomatic patients (mild/absent symptoms) with mild fibrosis (LSM < 10 kPa). In contrast, younger (age ≤ 60 years) and/or advanced-fibrosis patients (LSM ≥ 10 kPa) should be considered for early second-line therapy, with the ideal target being complete response (normal ALP and bilirubin). Likewise, symptomatic patients (clinically significant symptoms) may warrant prompt escalation despite an acceptable biochemical response.

a total 5-D score, potentially ranging from 5 (no pruritus) to 25 (most severe pruritus) [58].

- Patient-Reported Outcomes Measurement Information System (PROMIS) [59] is a tool created to collect rigorously PROs in different languages. Symptoms evaluated are pain, fatigue, physical functioning, emotional distress, and social role participation that have a major impact on quality-of-life across a variety of chronic diseases. The application of this tool is research, with the goal to standardize PROs and therefore allow greater comparability of studies.
- Clinical Global Impression of Severity Scale for Primary Biliary Cholangitis (CGI-S-PBC) is a new tool to evaluate symptom severity [60,61], currently used in the ongoing Phase IIa trial of golexanolone [62].

2.4. A comprehensive evaluation to guide escalation to second-line therapy

The therapeutic goal of achieving an adequate or complete response is driven by risk stratification, which primarily takes into account specific clinical characteristics (particularly age and LSM). When the predefined therapeutic target is not achieved, the timing of escalation to second-line therapy should also be aligned with the patient's risk profile. Moreover, in the presence of debilitating symptoms (pruritus/fatigue), it seems reasonable to consider the introduction of a second-line treatment with potential impact on these symptoms also in cases where an adequate biochemical response would otherwise be considered acceptable, or the introduction of therapies specifically targeting pruritus (*e.g.*, bezafibrate or ileal bile acid transporter inhibitors [IBAT-i], when available for this indication—see below) in patients with a complete biochemical response. Although these considerations are not yet sufficiently robust to be translated into precise algorithms, they nonetheless represent useful guiding elements in the decision-making process toward second-line therapeutic approaches (Fig. 3).

3. Second-line treatments for PBC: PPAR agonists and beyond

OCA, a FXR agonist, was the first second-line therapy available in Italy for the treatment of PBC patients with an inadequate response to UDCA. OCA has been widely used in Italy, and the cohort of patients treated with OCA has enabled the generation of important real-world evidence on the effectiveness and safety of the drug [63–66]. However, for some limitations of the drug mentioned above and due to regulatory issues discussed above, its marketing authorization has been withdrawn by the EMA [15]. Consequently, OCA is currently not available in Italy and will not be addressed further in this guidance.

This document will instead focus on available emerging therapies, namely elafibranor and seladelpar, which currently represent the backbone of second-line treatment. Fibrates will also be discussed, more specifically bezafibrate, although it should be emphasized that their use in the treatment of PBC is off-label. A brief reference will also be made to other agents currently under development.

3.1. PPAR agonists: mechanistic rationale

PPARs are nuclear receptors that regulate bile-acid detoxification, lipid metabolism, inflammation, and fibrogenesis. There are three isotypes of PPARs (PPAR-α, PPAR-γ, PPAR-δ), encoded by different genes, with various tissue specificity and actions [67]. In particular, activation of PPAR-α, that in the liver is expressed in hepatocytes, enhances peroxisomal and mitochondrial fatty-acid oxidation, inhibits expression of pro-inflammatory cytokines, and most importantly modulates bile acids metabolism by inhibiting bile acid synthesis, increasing their secretion, and reducing their toxicity due to activation and induction of multidrug resistance protein 3 gene [67,68]. PPAR-δ is located in hepatocytes, cholangiocytes, hepatic stellate cells, and Kupffer cells, and its activation at hepatocyte level improves mitochondrial function and lipid metabolism, thus decreasing steatosis, while at cholangiocyte level

Table 1
Main baseline characteristics and outcome of patients included in the Elafibranor, Seladelpar, and Bezafibrate phase III studies in patients with Primary Biliary Cholangitis.

	Elafibranor	Seladelpar	Bezafibrate
N (drug/placebo)	108/53	128/65	50/50
Baseline ALP (mean ± SD)	322 ± 151	292 ± 171	243 ± 114
Baseline ALP (x ULN)	3.1	2.3	1.8
Biochemical response at week-52 (%)*	51.0 (55/105)	61.7 (79/128)	31.0 (16/50)
Difference (drug *versus* placebo) (%)	47.0 (95%CI: 32–57)	41.7 (95%CI: 27.7–53.4)	31 (95%CI: 10–50)
ALP normalisation at week-52 (%)	15.0	25.0	67.0
Biochemical response at week-104 (%)	55.7 (34/61)	69.4 (68/98)	-
ALP normalisation at week-104 (%)	13.1 (8/61)	28.6 (28/98)	-
Biochemical response at week-156 (%)	84.6 (11/13)	70.0 (20/29)	-
ALP normalisation at week-156 (%)	38.5 (5/13)	24.1 (7/29)	-

Abbreviations: ALP, alkaline phosphatase; SD, standard deviation; ULN, upper limit of normal. *Biochemical response for elafibranor and seladelpar: alkaline phosphatase level <1.67 times the ULN, with a decrease of ≥15% from baseline, and a total bilirubin level ≤1.0 times the ULN. *Biochemical response for Bezafibrate: normal levels, alkaline phosphatase, aminotransferases, of total bilirubin, albumin, and normal prothrombin index.

regulates transport and absorption of bile compounds, and its activation in Kupffer cells modulates inflammatory pathways [67,68].

From the therapeutic standpoint, dual or selective PPAR activation addresses both cholestasis and parenchymal liver injury, and contributes to improvement of inflammation, in line with current concepts of treating PBC as a systemic cholestatic, inflammatory, and fibrotic disease.

3.2. Currently available PPAR agonists for the treatment of patients with PBC

The PPAR agonists currently available on the market that have met the primary endpoint in phase III trials are elafibranor and seladelpar (recently conditionally approved for the treatment of patients who are inadequate responders or intolerant to UDCA) and bezafibrate (used off-label) [16,17,69]. The baseline biochemical features of the patients included in the phase III registration trials with elafibranor and seladelpar, and in the placebo-controlled phase III trial with bezafibrate, together with their main outcomes, are reported in Table 1.

3.3. Elafibranor and seladelpar

Phase III studies of elafibranor and seladelpar had the same primary composite biochemical endpoint, *i.e.*, the POISE criteria at week 52, that was achieved in 51.0% of patients who received elafibranor 80 mg daily *versus* 4.0% of those who received placebo, and in 61.7% of patients who received seladelpar 10 mg daily *versus* 20.0% who received placebo [16,17]. In both trials, no clinically relevant safety concerns have emerged. The most commonly reported adverse events with both elafibranor and seladelpar were gastrointestinal in nature, predominantly including abdominal pain and abdominal distension. There was a trend toward more frequent reporting of nausea and vomiting with elafibranor compared with placebo, and of headache with seladelpar compared with placebo [16,17]. A transient increase in aminotransferases during the first weeks of treatment with PPAR agonists can be observed and may be related to enzymatic induction rather than toxicity, and in registration studies an increase >3 X ULN occurred in 0.9% of patients treated with elafibranor (*versus* 3.8% placebo) and 7.0% of those treated with seladelpar (*versus* 10.8% placebo) [16,17,70]. Furthermore, the potential for increase in creatine phosphokinase (CPK) (at least >3 X ULN) should also be considered, as this event occurred in 4 patients (3.7%) *versus* 0% placebo and 2 patient (1.6%) *versus* 1.5% placebo of patients treated with either elafibranor or seladelpar, respectively [16,17]. Lastly, a numerical imbalance in bone fractures was observed between the treatment and placebo groups (elafibranor 6%, seladelpar 4%, and none in placebo in both studies), although clinical context and bone biomarker data suggest this may be due to baseline patient risk, *i.e.*, higher rates of osteoporosis and most fractures due to accidental falls, rather than to a direct effect of the drugs. Indeed, analysis of Dual-Energy X-ray Absorptiometry scans and bone turnover markers showed no negative impact of elafibranor compared with placebo on bone mineral density or bone metabolism over 52 weeks [71]. Consistently, the 4.1 fractures per 100 patient-years observed in the registration study with seladelpar was in line with the expected rate for the aging PBC patient population, and longer follow-up data showed a downward trend at the second (3.0 *per* 100 patient-years), and third year (2.7 *per* 100 patient-years) [72]. This notwithstanding, given the nature of the disease, bone health and fractures risk should be adequately assessed before and during treatment as part of patients' standard of care [2].

The registration studies of both drugs were followed by an open-label extension period whose preliminary results have recently been made available [73–75]. Interim results from the long-term, open-label extension study of elafibranor now provide >3-year treatment data, showing sustained improvement in cholestasis markers [73,76]. Indeed, biochemical response and ALP normalisation at week-104 was achieved in 34/61 (55.7%) and 8/61 (13.1%) of patients receiving continuous elafibranor, with corresponding figures of 11/13 (84.6%) and 5/13 (38.5%) at week-156 [73]. More recent interim data from the ELATIVE open-label extension further supported the durability of response, with overall POISE response and ALP normalisation rates at week 182 of 72.1% (31/43) and 18.6% (8/43), respectively [76]. These long-term findings should, however, be interpreted with caution given the very small number of evaluable patients at later time points. Non-invasive fibrosis surrogates such as LSM and enhanced liver fibrosis (ELF) scores showed a stable, or favourable, trajectory [73]. Likewise, 24-month data of patients continuously treated with seladelpar showed maintained efficacy with 68/98 (69%) of patients with POISE response and 28/98 (28.6%) with ALP normalisation, with corresponding figures of 20/29 (69%) and 7/29 (24.1%) at month-36 [75]. Furthermore, in the subset of patients who received open-label seladelpar with at least one post-baseline LSM available, 85% of participants maintained or improved LSM, with a median change from baseline of −0.2 kPa (−2.9%) among 114 participants with data available at month-36 [77]. All in all, the results of the open-label extension of the registration studies of PPAR agonists were consistent with initial results, and demonstrated continuous efficacy of the drugs, with safety signals over the extension period that were consistent with the double-blind phase for both drugs, with no new pattern of treatment-emergent adverse events [73–76].

As far as symptoms are concerned, in patients with moderate-to-severe pruritus (worst itch numeric rating scale [WI-NRS]≥4) at baseline, seladelpar determined a statistically significant reduction in pruritus at 6 months (−1.5, −2.5 to −0.5; $p = 0.005$), with a sustained response through 12 months, including across multiple

itch-related quality-of-life tools (5-D itch scale, PBC-40 itch domain) [17]. On the contrary, in patients with moderate-to-severe pruritus at baseline, elafibranor did not significantly improve pruritus against placebo [−0.78 (−1.99 to 0.42), $p = 0.20$], although some secondary measures [5-D itch scale: −3.0 (−5.5 to −0.5), $p = 0.02$; PBC-40 itch domain: −2.3 (−4.0 to −0.7), $p = 0.007$) showed improvement favouring elafibranor [16]. Open-label extensions of the studies showed consistent results for seladelpar, with 56.0% of patients with moderate-to-severe pruritus continuously treated showing a meaningful improvement (*i.e.*, reduction of at least 3 points) in WI-NRS [78]. Seemingly, elafibranor showed improving trends in pruritus-related outcomes [73], with more recent long-term data indicating sustained improvement through week 156 in patients with baseline moderate-to-severe pruritus (WI-NRS mean [SD] change: −4.1 [2.3]; $n = 23$), although the number of evaluable patients remained limited [76].

Fatigue is another relevant and often invalidating symptom that may affect up to 37% of patients with PBC, and whose prevalence is mostly independent of disease stage and biochemical response to treatment [79,80]. Although no specific and definite treatment is available for the treatment of fatigue in patients with PBC, both elafibranor and seladelpar reported positive results in symptom relief. In particular, elafibranor has shown a clinically meaningful improvement in fatigue, assessed using the Patient-Reported Outcome Measurement Information System (PROMIS) Fatigue Short Form 7a (PFSF 7a) and the PBC-40 Fatigue domain, that was not necessarily linked to resolution of pruritus, while seemed to be associated with changes in proteins linked to mitochondrial function [81,82]. On another note, in patients treated with seladelpar, studies identified an improvement in fatigue mainly as a result of clinically relevant improvement in pruritus, that in turn was associated with improvement in quality of sleep, and sustained benefit in activities of daily living [83].

Taken together, the results of second-line treatment with PPAR agonists and their open-label extensions showed high-level biochemical efficacy, a growing body of long-term safety data, and emerging evidence for fibrosis stabilisation and symptom improvement, in particular pruritus. Unfortunately, in clinical practice, individualisation of treatment can be hardly based on these results due to the absence of a direct comparison between the two drugs. Indeed, as of today, the best evidence available is provided by a systematic review and network meta-analysis that indirectly compared elafibranor, seladelpar and OCA in UDCA-inadequate responders [84]. However, further data from large real-world cohorts are needed before therapeutic choices can be tailored based on specific patient profiles.

Lastly, despite the lack of any direct evidence to support this approach, it appears reasonable to suggest that patients with PBC who experience intolerance or an insufficient response to one PPAR agonist to achieve the desired treatment goals may be offered an alternative PPAR agonist.

3.4. Bezafibrate

Bezafibrate is a pan- (α-δ-γ)-PPAR agonist that acts suppressing bile acid synthesis (via CYP7A1 inhibition), increasing biliary phospholipid secretion to neutralize toxic bile acids, and that exerts anti-inflammatory and anti-fibrotic effects on the biliary epithelium. Bezafibrate has been extensively used as an off-label treatment for patients with PBC and inadequate response to UDCA [85]. In a non-controlled study carried out in 49 patients with ALP >1.5 x ULN after at least 12 months of adequate treatment with UDCA, bezafibrate 400 mg daily led to ALP normalisation in 86% of patients at 12-month [86]. In this same study, among 31 patients receiving paired liver biopsies at baseline and after 5 years of treatment, it was associated with a significant improvement in Ludwig histological score and with a decrease in the proportion of patients with cirrhosis (from 19% to 3%) [86]. Larger, non-controlled studies from Japan showed that bezafibrate treatment of inadequate responders to UDCA is associated with a reduction in solid endpoints such as liver-related mortality and need for liver transplantation [87].

In the investigator-initiated Phase III BEZURSO trial, patients with inadequate biochemical response to UDCA according to Paris-2 criteria were randomised to bezafibrate or placebo. Bezafibrate achieved the primary endpoint of complete biochemical response at 24 months in a substantial proportion of patients, whereas no patients in the placebo arm met this endpoint [69] (Table 1). In addition, treatment was associated with marked improvements in ALP normalisation, liver stiffness, and ELF score, together with reductions in pruritus and fatigue, while quality-of-life scores did not differ [69]. Bezafibrate was generally well tolerated. Adverse events included mild and reversible increases in serum creatinine (5% *versus* 3% decrease in placebo), myalgia (20% *versus* 10% placebo), and occasional elevations in aminotransferases, without reports of serious liver-related adverse events or rhabdomyolysis [69]. Regarding the safety of fibrates, however, in a recent analysis of 566 patients from the Italian PBC Registry treated with OCA and/or fibrates in a real-world context, fibrates showed greater efficacy in terms of ALP reduction compared to OCA, but were associated with a higher rate of early discontinuation (12.6%*vs* 5.4%), mainly due to intolerance or unspecified toxicity [88]. Moreover, the BEZURSO population differed from those enrolled in the ELATIVE and RESPONSE trials owing to differences in inclusion criteria and study design, which limit direct cross-trial comparisons [84]. This issue has been highlighted in recent discussions on the role of bezafibrate in PBC management [89–91].

Overall, the availability of in-label second-line therapies for the treatment of PBC has markedly reduced the need to use off-label compounds such as bezafibrate or fenofibrates as second-line agents for the treatment of PBC. The only clinical scenario in which a therapeutic dilemma may still arise is represented by patients who were initiated on bezafibrate therapy in the past, have achieved a complete biochemical response, and demonstrate good tolerability. In such cases, treatment decisions may benefit from an individualized risk–benefit assessment that takes into account both regulatory status and the observed treatment response, provided that patients are adequately informed about the availability of in-label alternatives and that ongoing clinical and biochemical monitoring is ensured over time.

3.5. Other investigational molecules

Saroglitazar is a dual PPAR-α/γ agonist currently under clinical development for PBC [92,93]. In a seamless phase 2b/3 randomized trial (EPICS-III), treatment with saroglitazar 1 mg/day for 52 weeks significantly improved the proportion of patients achieving the composite biochemical endpoint (difference *vs* placebo 48.5%, $p < 0.001$) and met the key secondary endpoint of ALP normalization [92]. These findings are currently available as preliminary topline data and await confirmation in full peer-reviewed publications.

Beyond PPAR agonists, other investigational molecules with distinct mechanisms of action are currently in development for the management of patients with PBC, with the potential for clinical implementation in the foreseeable future [94–99]. Among these, non-steroidal FXR agonists, *i.e.*, cilofexor and tropifexor, have been evaluated in phase II studies in patients with PBC and inadequate response to UDCA, showing reductions in ALP and other markers of cholestasis [100,101]. However, their clinical development has not yet progressed to phase III, and the available studies remain limited by their small size and short duration, with pruri-

tus emerging as a relevant adverse event [102–107]. The NOX1/4 inhibitor Setanaxib has shown signals of biochemical improvement, reductions in liver stiffness and fatigue in selected patient subgroups in phase II and IIb/III studies, despite failing to meet its primary endpoint and requiring further confirmation of efficacy and tolerability [94–99]. If validated, it may represent a first antifibrotic-oriented adjunct to cholestasis-directed therapies. Ileal bile acid transporter inhibitors (IBAT-i), such as linerixibat, interrupt enterohepatic bile acid circulation and have demonstrated symptomatic efficacy for cholestatic pruritus in patients with moderate-to-severe PBC [108,109]. Notably, the drug has just been approved by FDA for the treatment of cholestatic pruritus in patients with PBC [110]. Overall, these agents illustrate a potential future paradigm of personalised combination therapy targeting cholestasis, fibrosis, and symptoms, although most of them currently remain investigational.

4. Treatment in specific conditions

There are specific recommendations to consider in patients with PBC presenting with advanced liver disease, special clinical conditions, or relevant comorbidities. These include guidance on the use of first- and second-line therapies in the presence of cirrhosis and portal hypertension, the non-invasive assessment and management of portal hypertension, and treatment during pregnancy. Additional recommendations address the management of PBC/AIH variant syndrome and the safe use of PBC therapies in patients with chronic kidney disease, dyslipidemia, bone disease, and altered glycaemic control, emphasizing a tailored approach based on disease severity and associated conditions.

4.1. Cirrhosis with/without portal hypertension

UDCA is recommended as first-line therapy in PBC, regardless of the grade of liver fibrosis or the presence of cirrhosis and portal hypertension [111]. Indeed, a metanalysis conducted by the Global PBC Study and UK-PBC study groups in 2019 described the positive impact of UDCA on clinical outcomes even in patients with advanced disease, demonstrating its efficacy in preventing liver transplantation or death [11]. Recently approved PPAR-agonists, elafibranor and seladelpar, have shown their efficacy in inducing biochemical response across all fibrosis stages, including advanced fibrosis or cirrhosis [16,17,84,112]. For seladelpar, safety and efficacy have not been established in patients with moderate or severe hepatic impairment: treatment discontinuation should be considered if liver function deteriorates to Child–Pugh class B, and its use is not recommended in Child–Pugh C patients [113]. In contrast, elafibranor does not require dose adjustment in patients with moderate hepatic impairment (Child–Pugh class B), although its safety and efficacy in severe hepatic impairment have not been established and its use is therefore not recommended in Child–Pugh C patients [114]. Ultimately, in the absence of more extensive data on this patient population, it seems reasonable to recommend that PPAR agonists be used with caution in patients with compensated cirrhosis and portal hypertension.

Timely referral for liver transplantation (LT) is a key component in the management of patients with advanced PBC. Indeed, outcomes after LT are generally excellent, with survival rates comparable or even superior to those observed for other transplant indications [115,116]. Referral to a transplant center is needed at the occurrence of clinical features such as persistent hyperbilirubinemia (typically >3–5 mg/dL), clinically significant portal hypertension, hepatic decompensation or HCC [117,118]. In the absence of specific exceptions, LT is considered indicated in patients with MELD score >15 [119], as in other chronic liver diseases.

Several disease-specific prognostic models, including the Mayo Risk Score, UK-PBC score, and GLOBE score, have shown execellent prognostic performance [120]. However, their routine use in transplant decision-making remains heterogeneous across centers and healthcare systems, and no data exist on their potential usefulness as list prioritization tools.

Patients with confirmed or suspected cirrhosis should undergo 6-monthly HCC surveillance with abdominal ultrasound, in keeping with the general standard recommended across aetiologies[1]; advanced fibrosis or cirrhosis remains the main risk factor in PBC, with male sex and coexisting metabolic or viral cofactors potentially increasing individual risk [121,122]. Nonetheless, the incidence of HCC in cirrhotic PBC patients does not exceed 1.5% per year [123,124], and thus lies close to the threshold conventionally used to define cost-effective surveillance [125], and robust randomised evidence supporting a survival benefit of surveillance is still lacking [126]. Larger cohort studies, stratified by the different risk factors, are therefore warranted to define the incidence of HCC in PBC more precisely and to support a more tailored surveillance strategy. Ultrasound remains the reference tool, whereas the incremental role of alpha-fetoprotein is still debated [127,128].

4.2. Portal hypertension assessment and management in PBC patients

Real-world evidence suggests that Baveno VI criteria can also be applied to PBC patients, allowing up to 40% of esophagogastroduodenoscopies to be avoided [129,130]. However, a more recent study from the Italian PBC Registry including 293 patients demonstrated a reduced performance of elastography-based criteria in this setting. Specifically, Baveno VI and expanded Baveno VI criteria showed suboptimal accuracy in ruling out high-risk varices (HRV), while Baveno VII criteria underperformed in the non-invasive rule-out of clinically significant portal hypertension (CSPH). This limitation was particularly pronounced in patients with more severe cholestasis (ALP $\geq$1.5 $\times$ ULN), in whom the missed diagnosis rate of HRV reached 15.5% and 14.5% when applying Baveno VI and expanded Baveno VI, and 18.7% for CSPH when applying Baveno VII criteria. In contrast, the Rete Sicilia Selezione Terapia (RESIST) criteria, based on biochemical parameters (platelet count and serum albumin) rather than liver stiffness, demonstrated markedly superior performance for HRV rule-out in this subgroup, with a missed diagnosis rate of only 3.1% [131]. The reduced accuracy of stiffness-based thresholds across all these criteria may be explained, at least in part, by the coexistence of a pre-sinusoidal component of portal hypertension, characteristic of chronic cholestatic liver diseases, which can uncouple liver stiffness values from true portal pressure. Pending further validation of non-invasive tools specifically tailored to the PBC context, the assessment of portal hypertension and decisions regarding primary prophylaxis with non-selective beta-blockers (NSBBs), preferably carvedilol [37], should rely on a multiparametric approach integrating clinical, biochemical, and elastography-based parameters, with esophagogastroduodenoscopy indicated whenever non-invasive criteria yield discordant or indeterminate results.

4.3. Pregnancy

EASL and AASLD guidelines support the continued use of UDCA in pregnant women with PBC throughout all trimesters of pregnancy and during breastfeeding, as it is not associated with adverse maternal or fetal outcomes and has a well-established safety profile [132,133]. Fibrates may be used after the first trimester, but safety data remain limited [134]. Regarding the newly approved PPAR-agonists, seladelpar use is not recommended due to insufficient data from human pregnancies, while elafibranor is

contraindicated due to concerning findings from animal studies [113,114].

4.4. PBC/AIH variant

PBC-AIH variant affects fewer than 10% of patients with PBC and is associated with a higher risk of cirrhosis at presentation and accelerated disease progression if inadequately treated [135,136]. Whether it represents a true overlap syndrome or a variant of a dominant underlying disease remains debated. A recent Delphi consensus favours the latter interpretation and endorses the definition of "PBC-AIH variant" [137]. Presentation may be simultaneous or sequential, highlighting the need for ongoing phenotypic reassessment throughout the disease course [138].

The diagnosis relies on a combination of biochemical, serological and histological features. Liver biopsy is mandatory [137]. Clinically, the PBC-AIH variant should be suspected at diagnosis in patients with disproportionate transaminase elevation, elevated IgG, and positivity for AIH-related autoantibodies (anti-SMA, anti-dsDNA, anti-SLA/LP) [139]. Under UDCA therapy, the variant should be reconsidered when transaminases rise out of proportion to cholestatic markers after 6–12 months of treatment. Neither the Paris nor the Zhang criteria are formally endorsed, as most real-world variant patients do not fulfil them [136,138].

Regarding treatment, immunosuppressive therapy is indicated in patients with severe interface hepatitis (Ishak 4), where UDCA alone is insufficient to control the hepatitic component [140,141]. In patients with moderate interface hepatitis (Ishak 2–3), the decision should be individualised, balancing inflammatory activity, fibrosis stage and the risks of corticosteroid therapy, particularly relevant in middle-aged women. Treatment targets should follow current guidance for both PBC and AIH.

4.5. Chronic kidney disease

UDCA is not excreted by the kidney and does not require dose adjustment in chronic kidney disease [1]. Fibrates have been associated with a modest, reversible increase in serum creatinine in patients with mild-to-moderate CKD (eGFR 30–60 ml/min/1.73 m^2), without evidence of long-term adverse effects on kidney function or increased risk of end-stage kidney disease [142], so their use is not contraindicated. No dose adjustment is required in patients with renal impairment for either seladelpar or slafibranor [113,114]. In the ELATIVE trial, elafibranor was associated with mild, reversible increase in serum creatinine, without significant impact on estimated glomerular filtration rate or cystatin C^{16}. For seladelpar, no adverse events related to changes in renal function have been reported [17].

4.6. Dyslipidemic patients

A significant proportion of patients with PBC develop hypercholesterolemia during the disease due to chronic cholestasis, which impairs biliary cholesterol excretion. A lipid-lowering therapy should be offered to PBC patients with dyslipidemia based on their cardiovascular risk. Statins are safe in PBC patients, even in the presence of advanced fibrosis or cirrhosis, but they should be used with caution in case of hepatic decompensation [2]. The PPAR agonists class, including fibrates and the recently approved seladelpar and elafibranor, exert significant effects on lipid metabolism; therefore, their use in PBC patients with dyslipidemia provides a dual benefit on cholestatic parameters and lipidic profile [143]. There is no contraindication to using statins in combination with these treatments when additional lipid-lowering therapy is needed [16,17]. However, due to the higher rates of CPK elevation compared with placebo reported in the previous section, the prescribing information for elafibranor recommends checking CPK levels before initiating treatment and monitoring them during therapy, particularly in patients who are already receiving statin treatment.

4.7. Bone disease

Osteopenia and osteoporosis are frequent complications of PBC due to chronic cholestasis leading to reduced absorption of fat-soluble vitamins, including vitamin D. In patients with PBC, osteoporosis risk assessment and treatment should follow current dedicated clinical practice guidelines. Oral bisphosphonates can be prescribed in PBC patients with osteoporosis unless contraindicated by acid reflux or the presence of esophageal varices with a high bleeding risk [10]. Emerging evidence supports the use of denosumab in PBC-related osteoporosis, but long-term data are limited [144].

4.8. Altered glycaemic control/diabetes

PPAR agonists are able to modulate glycaemic control primarily through effects on insulin sensitivity and lipid metabolism [2]. Clinicians may take advantage of this effect when prescribing a PPAR agonist in PBC patients with metabolic syndrome, insulin resistance, or diabetes. No clinically relevant drug–drug interactions are currently known that would contraindicate the concomitant use of elafibranor or seladelpar with antidiabetic agents in patients with PBC [113,114]. However, caution is warranted when combining these agents with thiazolidinediones, due to their shared PPAR-mediated hepatic effects, and with insulin or insulin secretagogues such as sulfonylureas, given the potential increased risk of hypoglycaemia related to improved insulin sensitivity.

5. Unmet clinical needs in PBC

Despite the recent expansion of the therapeutic landscape for PBC, several unmet clinical needs continue to limit optimal patient management in routine clinical practice. These include heterogeneity of treatment response, persistent symptom burden, limited long-term outcome data for newly approved therapies, and uncertainties regarding optimal treatment sequencing and real-world applicability.

5.1. Challenges in second-line treatment selection

In the absence of head-to-head comparative studies, the optimal selection of second-line therapy remains uncertain. Differences in efficacy, safety, and impact on symptoms between seladelpar and elafibranor cannot be directly assessed, and treatment decisions are therefore largely based on indirect considerations such as tolerability profile, comorbidities, and centre-specific experience. This evidence gap limits the implementation of personalized treatment strategies and hampers the development of structured, evidence-based therapeutic algorithms, particularly for patients with more complex disease phenotypes. Hopefully, the profiles of the two drugs will be further clarified by real-world experience.

5.2. Patients previously treated with OCA

The recent market withdrawal of OCA has highlighted an additional area of clinical uncertainty related to the management of patients who had previously achieved biochemical improvement while receiving OCA. This population, often characterized by prior non-response to UDCA and an intermediate-to-high prognostic risk, currently lacks specific evidence-based guidance to inform

therapeutic transition strategies. Uncertainty remains regarding the optimal timing and choice of alternative second-line therapies in these patients, underscoring the need for dedicated studies and expert consensus.

5.3. Limitations of surrogate endpoints and lack of long-term outcome data

Despite encouraging biochemical responses, a major unmet need in PBC remains the limited availability of long-term data on hard clinical outcomes for newly approved therapies. Current evidence largely relies on surrogate endpoints such as ALP and bilirubin, which, although validated as prognostic markers, do not fully substitute for clinically meaningful outcomes including hepatic decompensation, liver transplantation, or survival [25,46]. The experience with OCA has emphasized the challenges associated with relying predominantly on surrogate biochemical endpoints for accelerated or conditional drug approval in PBC. The results of the COBALT confirmatory trial, which included both placebo and external control arms, illustrated the difficulty of demonstrating long-term clinical benefit despite sustained biochemical effects and contributed to subsequent regulatory reassessment [14]. The cumulative experience with second-line therapies has prompted international scientific societies to re-evaluate trial design and regulatory pathways. In this context, EASL and AASLD have jointly promoted a global, multi-stakeholder consensus process aimed at defining the scientific, clinical, and regulatory requirements for surrogate endpoint qualification and at clarifying the role of real-world evidence in confirmatory trial design, with the goal of strengthening future drug development strategies in PBC [145–148].

5.4. Patients not responding to new therapies

Another insufficiently explored unmet need concerns patients who are intolerant or do not respond, or respond only partially, to PPAR agonists. For this subgroup, no validated strategies for treatment sequencing or combination currently exist. As mentioned in the treatment section, switching from one PPAR agonist to the other appears reasonable in cases of intolerance or inadequate efficacy. However, to date, it is not known whether intolerance to one of the two drugs is associated with a higher risk of intolerance to the other, nor whether patients with an inadequate response to one of the two agents may derive greater benefit from the other. Moreover, an important unmet need is the current inability to combine molecules targeting different pharmacological pathways, with the potential for additive or even synergistic activity, as suggested by the preliminary results obtained with the OCA plus bezafibrate combination [149–151].

5.5. Refractory pruritus and fatigue

Symptom control, particularly pruritus and fatigue, remains a major unmet clinical need in PBC. Symptom burden is often dissociated from biochemical response and disease stage [1]. Even with newer therapies, the impact on symptoms is variable, and fatigue in particular remains largely refractory to available treatments.

The 2017 EASL Clinical Practice Guidelines recommended a stepwise approach for the management of pruritus in PBC patients, with the sequential introduction of cholestyramine (4 g, 1–4 times daily), rifampicin (150–300 mg daily), naltrexone (starting at 12.5 mg daily and gradually increasing up to 50 mg daily if well tolerated), and sertraline (50–100 mg daily) [1]. Subsequently, the management strategy for cholestatic pruritus was further refined in the previous AISF guidelines on PBC [2], also incorporating evidence on the beneficial effects of bezafibrate on pruritus emerging from the Fitch study [152]. Indeed, bezafibrate was suggested as the first-line option for patients with PBC and moderate-to-severe pruritus, except in cases of decompensated cirrhosis or other contraindications [2]. More recently, in its pivotal registration trial, seladelpar demonstrated a significant reduction in pruritus among patients with moderate-to-severe baseline pruritus [17], an effect that was maintained during the open-label extension phase of the study [74,75]. Similarly, although the antipruritic effect of elafibranor did not reach statistical significance in the registration trial [16], sustained improvement in pruritus was also observed in patients presenting with moderate-to-severe pruritus at baseline and receiving medium-to-long term elafibranor treatment [76]. Therefore, at present, in patients with pruritus who do not achieve a complete biochemical response, it is reasonable to prioritize treatment with one of the two new PPAR agonists, the evidence being currently clearer for seladelpar, in order to assess whether biochemical improvement is accompanied by a parallel benefit in pruritus.

Notably, regarding elafibranor and seladelpar, an unresolved issue concerns the appropriateness of initiating second-line disease-modifying therapies primarily for symptom control in patients who achieve a complete biochemical response to UDCA. This question is particularly relevant given that the registrational trials of elafibranor and seladelpar were designed and powered on biochemical endpoints and enrolled patients based on incomplete biochemical response [16,17]. Consequently, evidence supporting the use of these agents solely for symptom management in UDCA responders is currently limited, highlighting an important gap between clinical need and available data and reinforcing the importance of incorporating PROs into future trials. In this context, bezafibrate may still be considered as an off-label treatment for pruritus in patients who have already achieved a complete biochemical response to UDCA.

IBAT-i have recently emerged as a promising therapeutic option for cholestatic pruritus in PBC. Maralixibat was evaluated in a phase 2 placebo-controlled trial, showing reductions in serum bile acids but no significant improvement in pruritus compared with placebo, likely due to a marked placebo response [153]. More robust evidence has been generated for linerixibat, which demonstrated improvement in cholestatic pruritus and reduction in serum bile acid levels in phase II studies [108,154].

In the phase III GLISTEN trial, linerixibat significantly improved worst-itch numerical rating scale scores and increased the proportion of patients achieving clinically meaningful pruritus reduction *versus* placebo [109], supporting its FDA approval on 17 March 2026. Gastrointestinal adverse events, particularly diarrhoea, were the most common side effects across studies and appear to represent a class effect of IBAT inhibitors [108,109,154].

Volixibat has shown promising preliminary antipruritic activity in the phase II b VANTAGE study in patients with PBC [155], with some additional signal of benefit on fatigue and sleep [156], although further confirmation is required. Overall, although IBAT inhibitors represent a potentially effective antipruritic strategy, their long-term clinical role in PBC remains to be fully established. Of particular interest is the hypothesis that combining IBAT inhibitors with PPAR agonists may provide improved control of pruritus in patients who continue to experience clinically significant itching despite treatment with PPAR agonists.

Notably, severe refractory pruritus represents a less frequent but clinically relevant indication for LT in selected patients with PBC [1]. In cases where symptoms remain disabling despite optimized medical therapy, transplantation may be considered because of the profound impact of pruritus on quality of life and daily functioning. Indeed, unlike fatigue, pruritus dramatically resolves after LT, often within the first 24 h [157]. However, evidence guiding transplant referral and prioritization in this setting is limited, and

decisions should therefore be individualized and discussed within a multidisciplinary transplant framework.

Fatigue remains a major therapeutic challenge in PBC, as no pharmacological treatment is currently approved specifically for its management. Accordingly, current recommendations emphasize a comprehensive diagnostic assessment to identify and treat reversible contributors and comorbid conditions that may cause or exacerbate fatigue, together with supportive measures, including the development of practical coping strategies and the maintenance of social engagement, since social withdrawal may amplify the burden of fatigue [1,2]. Regular, individually tailored physical activity, including graded aerobic and resistance exercise, may also help reduce fatigue and improve physical, social, and emotional functioning [158–161]. Finally, signals of a direct beneficial effect on fatigue have emerged with elafibranor [81,82] and, in the case of seladelpar [83], likely as a consequence of its antipruritic effect; however, more robust evidence is required to confirm these findings.

6. Conclusions and future directions

PBC has undergone a profound transformation over the past two decades, evolving from a rare cholestatic disease with a single therapeutic option into a paradigmatic model of chronic autoimmune liver disease with different potential treatment strategies. The increasing prevalence of PBC, largely driven by improved case identification and prolonged survival, has reshaped its epidemiological profile and progressively shifted the clinical focus from end-stage complications to long-term disease control, quality of life, and disease-related comorbidities. In this context, the AISF position articulated in this document reflects a necessary reappraisal of both therapeutic goals and clinical strategies in contemporary PBC management.

A further evolution emerging from recent developments concerns how prognostic assessment is used to guide therapeutic decisions. Continuous prognostic models have been available for the last decade and have already moved the field beyond purely dichotomous response categories. What is changing, however, is the feasibility of translating these risk estimates into more granular, bedside treatment stratification in routine practice. The increasing integration of biochemical variables with demographic factors and, importantly, non-invasive liver stiffness assessment makes risk evaluation more immediate and clinically actionable, supporting a more precise and rapid identification of patients who may benefit from closer monitoring and earlier treatment step-up.

In this setting, the expanding availability of effective second-line therapies makes earlier response assessment increasingly relevant, particularly for patients at higher risk of progression. This has renewed interest in evaluating treatment response at six months. Remain of interest the question whether we should push the boundaries and assess the likelihood of UDCA response as early as at the diagnosis using existing prognostic scores (*i.e.* UDCA response score).

The expanding therapeutic armamentarium has been instrumental in driving this conceptual shift. Beyond UDCA, the availability of OCA and, more recently, PPAR agonists has provided effective second-line options for patients with an inadequate biochemical response or with features of higher disease activity. Importantly, PPAR agonists appear uniquely positioned to address a long-standing therapeutic gap in PBC treatment by coupling biochemical efficacy with clinically meaningful improvements in PROs, including pruritus and fatigue. This dual impact challenges the traditional separation between disease-modifying therapies and symptomatic treatments, suggesting that treatment indication should explicitly consider both dimensions.

Looking forward, several priorities emerge. Clinically, there is a clear need to validate treatment strategies based on early risk stratification and treatment escalation, as well as to generate long-term real-world data on the impact of newer agents on hard clinical endpoints. From a research perspective, future studies should increasingly incorporate PROs as co-primary or key secondary endpoints, recognizing their central role in defining therapeutic success in a chronic disease with prolonged survival.

In conclusion, PBC has entered a new therapeutic era characterized by improved prognostic stratification, expanding treatment options, and a growing emphasis on patient-centred outcomes. The challenge ahead lies in translating these advances into coherent, personalized, and equitable care pathways. By embracing a holistic definition of response and integrating prognostic tools into everyday practice, clinicians can move beyond disease stabilization toward truly optimized long-term management. Continued clinical, translational, and regulatory efforts will be essential to ensure that the full potential of emerging therapies is realized for all patients with PBC.

Declaration of competing interest

The authors declare the following competing interests

AAg: Abbvie, Ipsen, Gilead, Madrigal, Sobi, Novo Nordisk, Boerhinger Advisory boards. **VC**: speaking, teaching and advisory board for Abbvie, Advanz, Alfa-Sigma, Gilead Science, GSK, Ipsen, Mirum, Roche. **MC**: advisor board member/consultat/speaker for: Advanz, Albireo, Alentis, Alfasigma, Echosens, Falk, Gilead, GSK, Intercept, Ipsen, Kowa, Malesci, Mayoly, Mirum, Zydus, Signant health, Calliditas. **NC**: Consultant Ipsen, Gilead, GSK, Advanz, Dr Falk; Speaker Orphalan, Ipsen, Albireo, Advanz; Travel Grant Orphalan, Ipsen; Research Grant Orphalan, Gilead. **LC**: advisor board member/consultat/speaker for: Advanz Pharma, Dr.Falk, Gilead, Ipsen, Mirum, Signant health, Calliditas. **DD**: no COI. **RD**: speaking, teaching and advisory board for Gilead Science and AbbVie; consultant and advisory board for Madrigal. **FF**: travel grant from Ipsen and Mirum; **GG:** speaking, consulting fee fees and/or travel fees for Chiesi, Alfasigma, Ipsen, Biotest, Novartis. **EGG:** Speaking and Teaching: AbbVie, AstraZeneca, Dompé, Gilead, Ipsen, Mirum, Roche; Advisory Board participation: Gilead, Ipsen, Mirum; Consulting: GSK. **SG:** speaking and/or advisory board for Gilead. **PI**: Consultant for Advanz, Zydus, GSK, Cymabay, Ipsen, Gilead, Calliditas, Mirum; Grant supports: Ipsen, Gilead. **SL**: Advisory board Ipsen, Gilead (commercial). **AL:** consulting fees from Advanz Pharma, Ipsen, GSK, Dr. Falk, Gilead, Mirum, speaker fees fromGilead, Advanz Pharma, GSK, Incyte, Gore, AstraZeneca, and Ipsen. She has received travel support from Ipsen and Falk Foundation and grant support from EU COST Action (CA22125), Italian Ministry of Health, Italian Association for Cancer Research (AIRC), EU JTC 2024-TRASCAN-3, Gilead Sciences, and Regione Lombardia (FRRB); she has support for sponsored clinical studies (to Humanitas Research Hospital) from Dr. Falk, Intercept Pharma, Gilead, GSK, Mirum, Ipsen, Umacrine. **GM:** speaking for MSD-Eisai, Chiesi, Kedrion, Ipsen, Alfasigma. **MM**: Speaker/Advisor for Ipsen, Gilead, Gsk, Advanz. **GP**: Speaking, consulting, teaching and advisory board for Echosense, Madrigal, Novo Nordisk, Advanz. **FRP:** consultant for Ipsen, Gilead, Abbvie, Roche, AstraZeneca. **CR**: Speaking and teaching and Consulting: Gilead, Ipsen, Echosens, ABBvie. Research Grant: Gilead. **VR:** Speaking and teaching and Consulting: Ipsen. Research Grant: Gilead. **FTe:** advisor board member/consultant/speaker for Ipsen, Gilead, Echosens. **FTo:** consultant for Astrazeneca, Roche, Eisai, BMS, Ipsen; **AV**: no COI**. UVG:** advisor board member/consultant/speaker for Ipsen, Gilead, Advanz, AstraZeneca, Madrigal, Echosens, Mirum**. MV**: Speaking and teaching and Consulting: Gilead, Mirum, Ipsen. Research Grant: Gilead.

Appendix A

Associazione Italiana per lo Studio del Fegato (AISF).

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On behalf of Rare Diseases Committee, Innovative Drugs Committee and AISF Scientific Board

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