

Achieving best practice management of primary biliary cholangitis now and in the future

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Current practice and recommendations for the treatment of primary biliary cholangitis

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PBC: Disease overview, treatment and unmet need



PBC^{1,2}

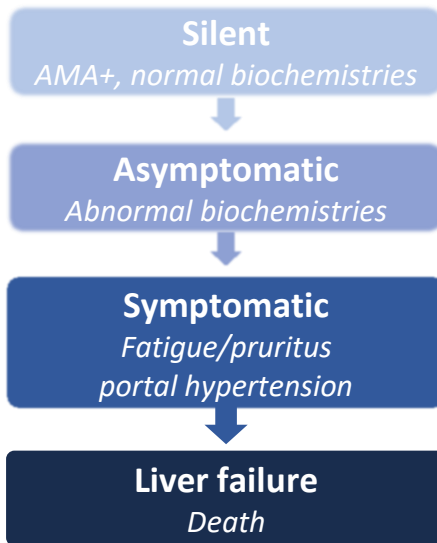
- Cholestatic liver disease
- Characterized by circulating AMAs and the destruction of intrahepatic cholangiocytes
- Highly heterogeneous presentation, symptomatology, clinical course and response to therapy



Aetiology/epidemiology^{1–4}

- Genetic predisposition with microbial/environmental triggers
- Primarily affects middle-aged women (female:male up to 10:1)
- Global annual incidence and prevalence rates range from 0.84–2.75 and 1.9–40.2/100,000 individuals, respectively

Natural history of PBC^{2,5}



Treatment/unmet need

Licensed first line: UDCA²

- Reduces serum biochemical parameters
- Slows disease progression
- Prolongs transplant-free survival

25–40% of patients do not experience an adequate biochemical response

Licensed second line: OCA^{6,7}




- Farnesoid X receptor agonist
- + UDCA in inadequate responders to first-line UDCA
- Monotherapy in patients intolerant to UDCA

OCA is contraindicated in patients with decompensated cirrhosis

AMA, antimitochondrial antibody; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

1. Onofrio FQ, et al. *Gastroenterol Hepatol*. 2019;15:145–54; 2. Alvaro D, et al. *Liver Int*. 2020;40:2590–601; 3. Uleo A, et al. *Sci Rep*. 2016;6:25906; 4. Trivedi P, Hirschfield G. *Gut*. 2021;70:1989–2003; 5. Al-Harthy N, Kumagi T. *Hepat Med*. 2012;4:61–71; 6. EMA. Obeticholic acid SmPC. Available at: www.ema.europa.eu (accessed 24 November 2022); 7. FDA. Obeticholic acid PI. Available at: tinyurl.com/yevndzw3 (accessed 24 November 2022).

Diagnosing and managing PBC: Guidelines¹⁻⁴

 Diagnostic pathway	 Risk stratification	 Treatment response
<ul style="list-style-type: none">• AASLD and APASL recommend diagnosing PBC based on patients meeting ≥ 2 criteria<ul style="list-style-type: none">◦ Biochemical evidence of cholestasis; AMA or PBC-specific ANAs; histological evidence*• EASL and UK-PBC/BSG recommend diagnosis based on evidence of cholestasis, elevated ALP and AMA (titre $>1:40$)*	<ul style="list-style-type: none">• Risk stratification is used to ensure all patients receive a personalized approach to their care• EASL and UK-PBC/BSG recommend stratifying patients for risk on diagnosis (elastography, risk scores, age and gender)• All four guidelines agree on risk stratification when assessing response to UDCA	<ul style="list-style-type: none">• Surrogate serum biochemical responses are used for treatment decision-making⁵• All guidelines recommend assessing response to UDCA after 12 months• There are multiple UDCA response criteria and two risk scoring systems, which include additional criteria• None of the guidelines specify which scoring system should be used
Liver biopsy?	How to stratify?	UDCA response: criteria, timing?

*The guidelines note that liver biopsy is only necessary in specific circumstances.

AASLD, American Association for the Study of Liver Diseases; ALP, alkaline phosphatase; AMA, antimitochondrial antibody; ANA, antinuclear antibodies; APASL, Asian Pacific Association for the Study of the Liver; BSG, British Society of Gastroenterology; EASL, European Association for the Study of the Liver; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

1. European Association for the Study of the Liver. *J Hepatol*. 2017;67:145–72; 2. Lindor KD, et al. *Hepatology*. 2019;69:394–419; 3. You H, et al. *Hepatol Int*. 2022;16:1–23; 4. Hirschfield GM, et al. *Gut*. 2018;67:1568–94; 5. Jones DE, et al. *eBioMedicine*. 2022;80:104068.

Understanding the evolving treatment landscape for primary biliary cholangitis

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PBC: Evidence for OCA as a second-line therapy



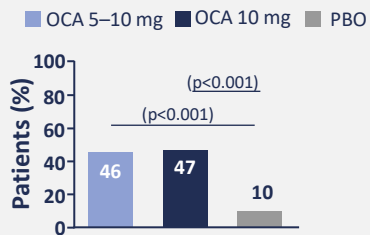
Real-world data: OCA following 12 months' treatment



OCA (FXR agonist)¹

POISE (NCT01473524); phase III; N=216
PBO vs OCA 5–10 mg vs OCA 10 mg (1:1:1);
12 months

- Patients**
Inadequate response to UDCA or intolerant
- Primary endpoint**
ALP <1.67xULN + tbil ≤ULN +
ALP reduction ≥15%



Country	OCA (N)	Fibrates (N)	Principal findings
Canada ²	64	—	Bioch. response (POISE): 18%; mean ALP: ↓20%; mean gGT: ↓59%; mean ALT: ↓26%; tbil: stable
Spain/Portugal ³	120	—	Bioch. response (POISE): 30%; mean ALP: ↓26%; mean ALT: ↓37%; mean tbil: ↓14%
Italy ⁴	191	—	Bioch. response (POISE): 43%; median ALP: ↓32%; median ALT: ↓31%; median tbil: ↓11%
UK ⁵	259	80	Bioch. response: 71% (OCA); 80% (fibrates); ALP: OCA, ↓30%; fibrates, ↓57% normalized ALT: OCA, 56%; fibrates, 33%; tbil: stable
Spain ⁶	86	250	↓ALP, gGT and ALT; normalized ALP: OCA, 4%; fibrates, 45% normalized ALT: OCA, 79%; fibrates, 62%

Pruritus is a commonly reported AE, which can lead to treatment discontinuation^{2–4,6}

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine transaminase; Bioch, biochemical; FXR, farnesoid X receptor; gGT, gamma-glutamyl transferase; OCA, obeticholic acid; PBC, primary biliary cholangitis; PBO, placebo; tbil, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

1. Nevens F, et al. *N Engl J Med* 2016;375:631–43; 2. Roberts SB, et al. *Hepatol Commun*. 2020;4:1332–45; 3. Gomez E, et al. *Aliment Pharmacol Ther*. 2021;53:519–30;

4. D'Amato D, et al. *JHEP Rep*. 2021;3:100248; 5. Abbas N, et al. *Clin Gastroenterol Hepatol*. 2022. doi: 10.1016/j.cgh.2022.07.038;

6. Reig A, et al. *Am J Gastroenterol*. 2021;116:2250–7.

Efficacy and safety of PPAR agonists to treat PBC as a second line

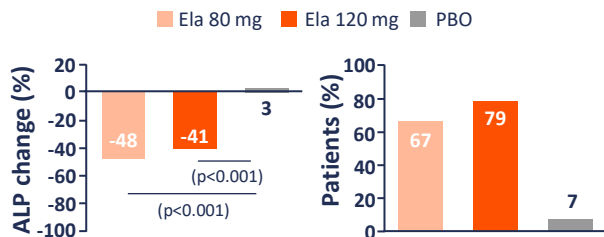


Elafibranor (PPAR α/δ)¹

NCT03124108; phase II; N=45
PBO vs Ela 120 mg vs Ela 80 mg (1:1:1); 12 weeks

Primary endpoint

Composite endpoint*



TRAEs

7% (PBO); 13% (Ela 80 mg); 33% (Ela 120 mg)

Severe pruritus

2 pts (PBO); 0 pts (Ela 80 or 120 mg)

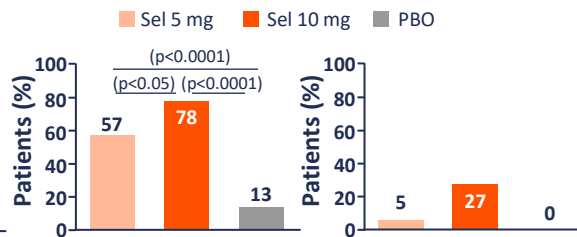


Seladelpar (PPAR δ)²

ENHANCE; phase III; N=240
PBO vs Sel 5 mg vs Sel 10 mg (1:1:1); 52 weeks

Primary endpoint:
Composite[†] at 3 mo

Secondary endpoint:
Normalized ALP at 3 mo



AEs

Mild to moderate

Pruritus

13% (PBO); 3% (Sel 5 mg); 11% (Sel 10 mg)

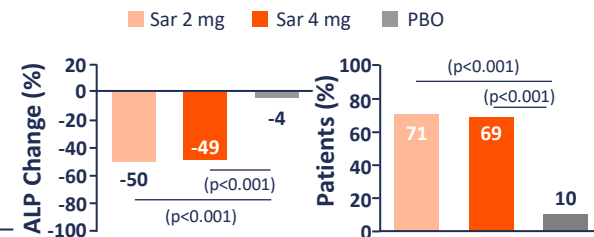


Saroglitazar (PPAR α/γ)³

EPICS; phase II[‡]; N=37
PBO vs Sar 2 mg vs Sar 4 mg (\approx 1:1:1); 16 weeks

Primary endpoint

Composite endpoint[†]
(post hoc)



TRAEs

30% (PBO); 29% (Sar 2 mg); 54% (Sar 4 mg)

Pruritus

No worsening of pruritus was observed

*Composite endpoint: ALP <1.67xULN + tbil <ULN + ALP reduction >15%; †Composite endpoint: ALP <1.67xULN + tbil ≤ULN + ALP reduction ≥15%;

[‡]95% of patients took UDCA at baseline and throughout the trial. AE, adverse event; ALP, alkaline phosphatase; Ela, elafibranor; mo, month; PBC, primary biliary cholangitis; PBO, placebo; PPAR, peroxisome proliferator-activated receptor; pt, patient; Sar, saroglitazar; Sel, seladelpar; tbil, total bilirubin;

TRAe, treatment-related AE; UDCA, ursodeoxycholic acid; ULN, upper limit of normal. 1. Schattenberg JM, et al. *J Hepatol.* 2021;74:1344–54;

2. Hirschfield GM, et al. *Hepatology.* 2020;72(Suppl. 1):LO11; 3. Vuppalanchi R, et al. *J Hepatol.* 2022;76:75–85.

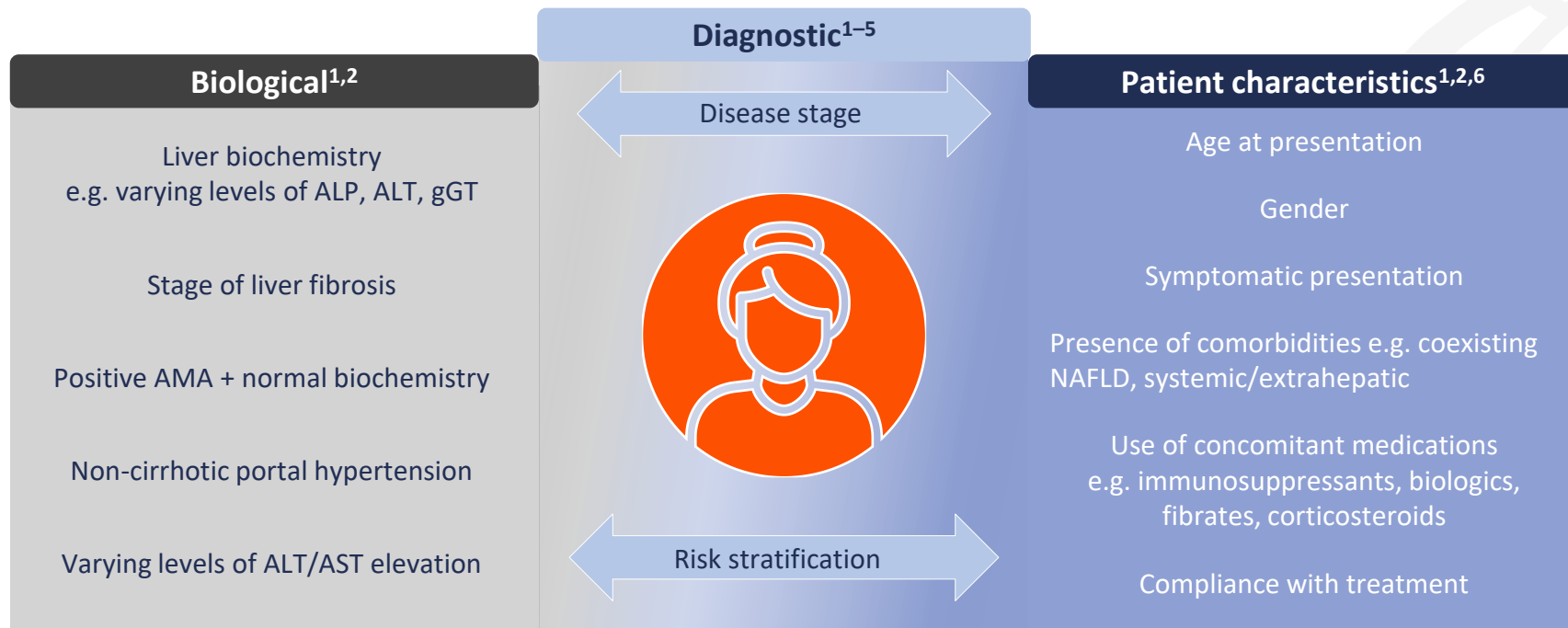
Individualizing treatment of PBC to optimize outcomes and patient quality of life

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Dimensions of individual variation contributing heterogeneity in disease presentation



ALP, alkaline phosphatase; ALT, alanine transaminase; AMA, antimitochondrial antibody; AST, aspartate aminotransferase; gGT, gamma-glutamyl transferase; NAFLD, non-alcoholic fatty liver disease.

1. Alvaro D, et al. *Liver Int.* 2020;40:2590–601; 2. Hirschfield GM, et al. *Expert Rev Gastroenterol Hepatol.* 2021;15:929–39;
3. European Association for the Study of the Liver. *J Hepatol.* 2017;67:145–72; 4. Lindor KD, et al. *Hepatology.* 2019;69:394–419;
5. You H, et al. *Hepatol Int.* 2022;16:1–23; 6. Levy C, et al. *Hepatol Commun.* 2018;2:484–491.