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]

Silent
AMA+, normal biochemistries

↓

Asymptomatic
Abnormal biochemistries

↓

Symptomatic
Fatigue/pruritus
portal hypertension

↓

Liver failure
Death

Treatment/unmet need

Licensed first line: UDCA[2]

- 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. Lleo 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/yeyndzw3 (accessed 24 November 2022).

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Diagnosing and managing PBC: Guidelines[1–4]

Diagnostic pathway

- AASLD and APASL recommend diagnosing PBC based on patients meeting ≥2 criteria
  - 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)*

Liver biopsy?

Risk stratification

- 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

How to stratify?

Treatment response

- Surrogate serum biochemical responses are used for treatment decision-making[5]
- 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

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.

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Understanding the evolving treatment landscape for primary biliary cholangitis

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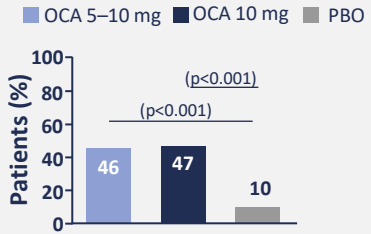
PBC: Evidence for OCA as a second-line therapy

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%



Real-world data: OCA following 12 months' treatment

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.

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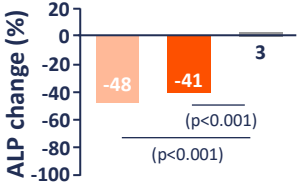
Efficacy and safety of PPAR agonists to treat PBC as a second line

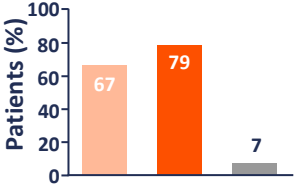
Elafibranor (PPAR α/δ)[1]

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

Primary endpoint



Composite endpoint*



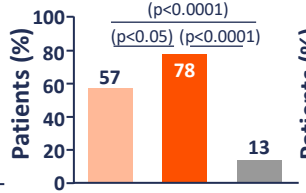
TRAEs
7% (PBO); 13% (Ela 80 mg); 33% (Ela 120 mg)

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

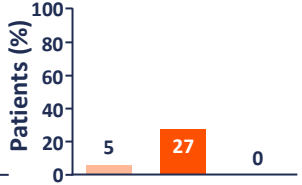
Seladelpar (PPAR δ)[2]

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



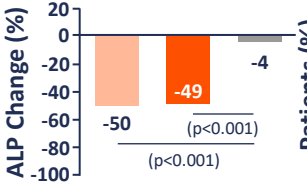
AEs
Mild to moderate

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

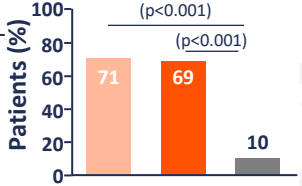
Saroglitazar (PPAR α/γ)[3]

EPICS; phase II‡; N=37
PBO vs Sar 2 mg vs Sar 4 mg (≈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.

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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

Diagnostic[1–5]

Biological[1,2]

Liver biochemistry
e.g. varying levels of ALP, ALT, gGT

Stage of liver fibrosis

Positive AMA + normal biochemistry

Non-cirrhotic portal hypertension

Varying levels of ALT/AST elevation

Disease stage

Risk stratification

Patient characteristics[1,2,6]

Age at presentation

Gender

Symptomatic presentation

Presence of comorbidities e.g. coexisting NAFLD, systemic/extrahepatic

Use of concomitant medications
e.g. immunosuppressants, biologics, fibrates, corticosteroids

Compliance with treatment

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.

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