Primary biliary cholangitis: Appraising the changing therapeutic landscape

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Patient management in the first line: Treatment goals and risk stratification

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Pre-treatment risk stratification can inform PBC management

UDCA therapy and risk stratification

Baseline evaluations

Patient history

- Age
- Sex
- History of complications of cirrhosis*
- Symptoms: pruritus, fatigue
- Sicca complex

Key investigations

- Blood tests: ALP, bilirubin, AST, ALT, GGT, platelets
- Liver ultrasound
- Liver stiffness measurement
- Bone density

Pre-treatment disease stage and risk stratification

Determine pre-treatment risk of disease progression by utilizing age, gender, biochemical markers and disease stage

Low-risk

- Mild elevation in ALP **AND**
- Normal bilirubin **AND**
- Normal albumin **AND/OR**
- Early or no fibrosis

Intermediate-to-high risk

≥1 of the following:

- Diagnosed aged <45 yr
- ALP >1.5X ULN
- Abnormal bilirubin
- Low albumin
- Advanced fibrosis/early cirrhosis (Child–Pugh A)

Consider further assessment referral

- Decompensated cirrhosis* (Child–Pugh B or C) **OR**
- Bilirubin >2X ULN **OR**
- Severe pruritus

Referral required?

Yes → Further assessment

No → If suitable for local follow-up

Regular follow-up

based on risk profile

*Ascites, variceal bleed or encephalopathy. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; yr, years. Hirschfield GM, et al. *Expert Rev Gastroenterol Hepatol.* 2021;15:929–39.

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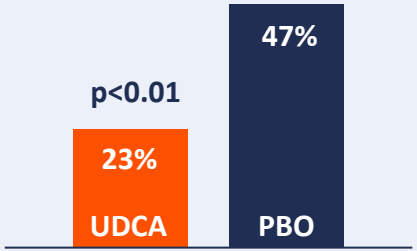
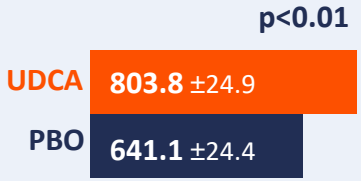
UDCA is an effective first-line therapy, but not all patients respond

Efficacy of UDCA 13–15 mg/kg/day divided into 3 or 4 doses vs PBO in patients with PBC[1]

UDCA, n=86; PBO, n=86



Incidence of treatment failure



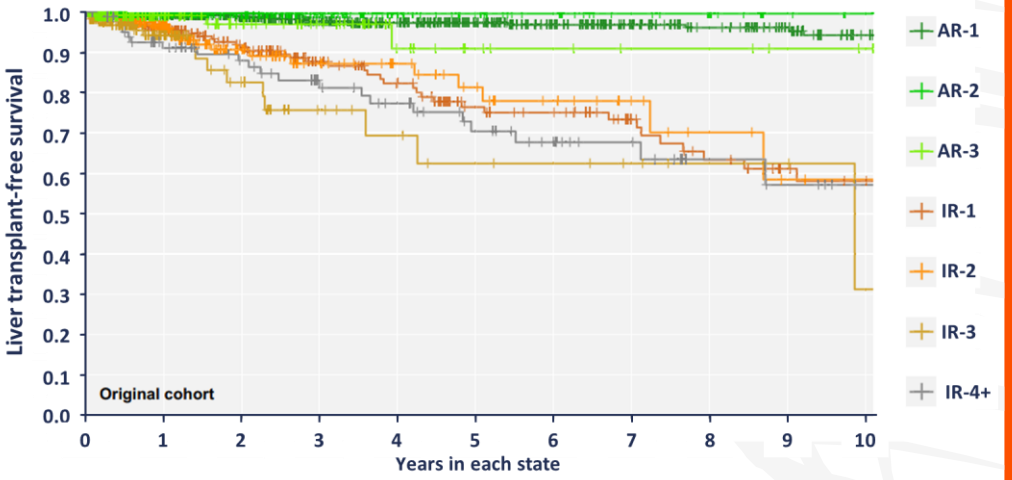
Time to treatment failure* (days)

Incidence of the most common AEs with UDCA in PBO-controlled trials was low (~1–3% of patients):[1]

- Diarrhoea
- ↑ creatinine
- ↑ blood glucose
- Leukopenia
- Peptic ulcer
- Skin rash
- Thrombocytopenia

Loss of biochemical response to UDCA at any time is associated with heightened risk of liver transplant[2]

Liver transplant-free survival from UDCA response states (N=823)†



Over time, adequate response (AR) is always associated with better liver transplant-free survival than inadequate response (IR)[2]

*Excluded doubling of serum bilirubin and voluntary withdrawal, and regardless of either histologic stage or baseline bilirubin levels (>1.8 or ≤1.8 mg/dL). †Figure reproduced under the CC BYNC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). Patients transition to the beginning of the next survival curve upon state change; green curves include patients in their 1st, 2nd, or 3rd states of AR; orange curves include patients in their 1st, 2nd, or 3rd states of IR; grey curve includes patients beyond their 4th state of inadequate response.[2] AE, adverse event; AR, adequate response; IR, inadequate response; PBC, primary biliary cholangitis; PBO, placebo; UDCA, ursodeoxycholic acid.

1. FDA. Ursodeoxycholic acid PI. 2023. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2023/020675s028lbl.pdf (accessed 9 October 2024); 2. Roberts SB, et al. *JHEP Reports*. 2024;6:1–10.

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On-treatment monitoring guides ongoing management of PBC

First-line UDCA
(13–15 mg/kg PO daily)

Assess risk of progression based on response to treatment

Different criteria to score response have been published, e.g. GLOBE; UK-PBC

Assess response within 6–12 months

Blood tests: ALP, bilirubin, AST, ALT, GGT, albumin, platelets

Assess for evidence of fibrosis/ cirrhosis, e.g. elastography

Low-risk

Adequate response to UDCA, e.g.
- ALP ≤1.5X ULN **AND**
- Normal bilirubin **AND**
- Early or no fibrosis

→ Continue UDCA and assess response every 12 months

Intermediate-to-high risk

Intolerance **OR** inadequate response to UDCA, e.g.
- ALP >1.5X ULN **OR**
- Rising bilirubin/levels >ULN **OR**
- Albumin <LLN **OR**
- Progressive/advanced fibrosis or cirrhosis

Consider further assessment referral

- Decompensated cirrhosis*
- Compensated cirrhosis with significant PH
- Bilirubin >2X ULN
- AST or ALT >5X ULN
- Severe pruritus

→ Further assessment to determine risk/benefit of second-line treatment

→ Risk/benefit favours treatment?

→ No

→ Tertiary referral

Disease management

- Pruritus
- Fatigue
- Sicca complex
- Bone density
- CV risk
- Concomitant autoimmune disease
- Metabolic syndrome

*Child–Pugh B or C, ascites, variceal bleed. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CV, cardiovascular; GGT, gamma-glutamyltransferase; LLN, lower limit of normal; PBC, primary biliary cholangitis; PH, portal hypertension; PO, by mouth; UDCA, ursodeoxycholic acid; ULN, upper limit of normal. Hirschfield GM, et al. *Expert Rev Gastroenterol Hepatol.* 2021;15:929-39.

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Treatment sequencing beyond the first-line setting to optimize outcomes in patients with PBC

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Approved agents target different aspects of PBC aetiology

Agent (MoA)	Indication	Contraindications
OCA[1] (FXR agonist)	**Treatment of adults with PBC:** • without cirrhosis or • with compensated cirrhosis, without evidence of portal hypertension either *in combination* with UDCA (if inadequate response to UDCA), or as *monotherapy* in patients unable to tolerate UDCA	• Decompensated cirrhosis (e.g. Child–Pugh class B/C) or a prior decompensation event • Compensated cirrhosis with evidence of portal hypertension • Complete biliary obstruction
Elafibranor[2] (selective PPAR-α/-δ agonist)	**Treatment of adults with PBC:** either *in combination* with UDCA (if inadequate response to UDCA), or as *monotherapy* in patients unable to tolerate UDCA	**None** **Limitations of use:** Not recommended in patients with/who develop decompensated cirrhosis (e.g. ascites, variceal bleeding, hepatic encephalopathy)
Seladelpar[3] (selective PPAR-δ agonist)		

FXR, farnesoid X receptor; MoA, mechanism of action; OCA, obeticholic acid; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; UDCA, ursodeoxycholic acid. 1. FDA. Obeticholic acid PI. 2022; 2. FDA. Elafibranor PI. 2024; 3. FDA. Seladelpar PI. 2024. All PIs are available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (all accessed 9 October 2024).

Approved second-line agents can address different treatment needs

Obeticholic acid (OCA)

N=216

- Patients with PBC who received UDCA for ≥12 months
- 93% received UDCA or PBO plus OCA
- 7% received OCA monotherapy

	OCA 10 mg (n=73)	OCA titration (n=70)	PBO (n=73)
Primary composite endpoint			
Responder rate	48%	46%	10%
Components of primary endpoint			
ALP <1.67X ULN	55%	47%	16%
↓ ALP ≥15%	78%	77%	29%
Total bilirubin ≤ULN	82%	89%	78%

Clinically significant adverse reactions:

- Hepatic decompensation/failure*
- Severe pruritus
- Reduction in HDL-C

*In patients with PBC with cirrhosis.

ALP, alkaline phosphatase; HDL-C, high-density lipoprotein cholesterol; PBC, primary biliary cholangitis; PBO, placebo; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

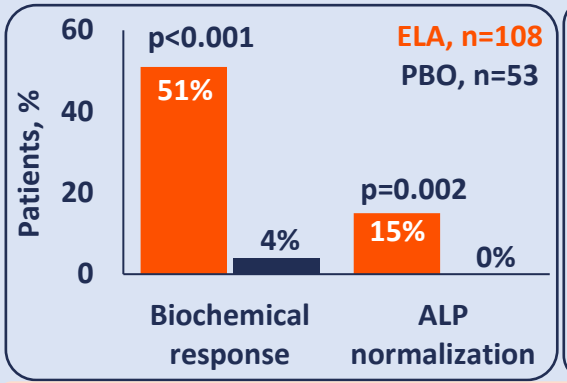
FDA. Ursodeoxycholic acid PI. 2023. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2023/020675s028lbl.pdf (accessed 5 November 2024).

Approved second-line agents can address different treatment needs

Elafibranor[1]

N=161
52-wk study

- Patients with PBC with inadequate response or unable to tolerate UDCA
- 95% received concurrent UDCA therapy



In patients with moderate-to-severe pruritus

Change in WI-NRS* from baseline

-1.93 vs -1.15;

p=0.20

ELA, n=44; PBO, n=22

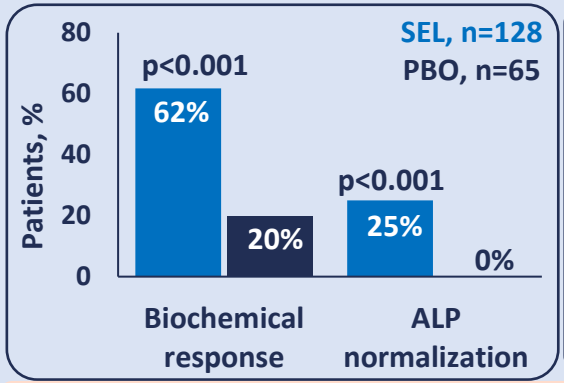
AEs more frequent with **ELA** than **PBO**:

- Abdominal pain (11% vs 6%)
- Diarrhoea (11% vs 9%)
- Nausea (11% vs 6%)
- Vomiting (11% vs 2%)

Seladelpar[2]

N=193
52-wk study

- Patients with PBC with inadequate response or unable to tolerate UDCA
- 94% received UDCA SOC background therapy



In patients with moderate-to-severe pruritus

Change in WI-NRS* from baseline

-3.2 vs -1.7;

p=0.005

SEL, n=49; PBO, n=23

AEs more frequent with **SEL** than **PBO**:

- Headache (8% vs 3%)
- Abdominal pain (7% vs 2%)
- Nausea (6% vs 5%)
- Abdominal distention (6% vs 3%)

NB: Data presented are from separate clinical trials of active agent vs placebo and are not to be directly compared with each other, nor to be interpreted as a substitute for head-to-head trial data.
*LSM change. AE, adverse event; ALP, alkaline phosphatase; ELA, elafibranor; LSM, least-squares mean; PBC, primary biliary cholangitis; PBO, placebo; SEL, seladelpar; SOC, standard of care; UDCA, ursodeoxycholic acid; WI-NRS, Worst Itch Numeric Rating Scale; wk, week.

1. Kowdley KV, et al. *N Engl J Med.* 2024;390:795–805; 2. Hirschfield GM, et al. *N Engl J Med.* 2024;390:783–94.

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Emerging treatments for PBC: A look at the latest data

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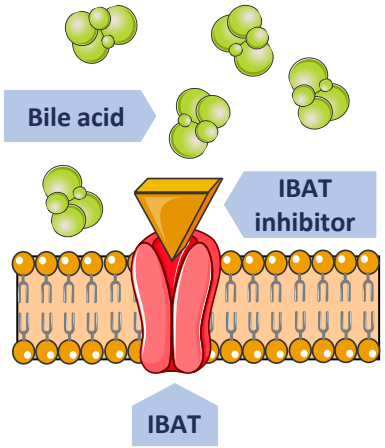
Emerging agents target different facets of PBC pathophysiology

IBAT inhibitors[1]

- Linerixibat
- Volixibat

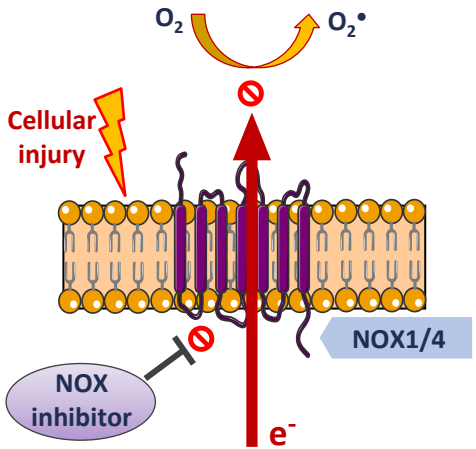
Block bile acid transportation



NOX1/4 inhibitors[2]

- Setanaxib

Reduce ROS formation



Fibrates/PPAR agonists[3,4]

- Bezafibrate
- Pemafibrate
- Saroglitazar

Transcription factor modulation

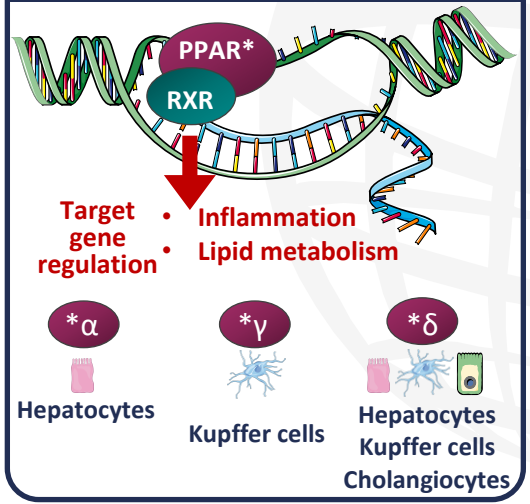


Image source: Servier Medical Art. CC BY 4.0 https://creativecommons.org/licenses/by/4.0/. *PPAR isoforms. IBAT, ileal bile acid transporter; NADPH, nicotinamide adenine dinucleotide phosphate; NOX, NADPH oxidase; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; RXR, retinoid X receptor.

1. Nevens F, et al. *J Hepatol.* 2023;78:430–41; 2. Thannickal VJ, et al. *J Cell Mol Med.* 2023;27:471–81;
3. Colapietro F, et al. *J Transl Autoimm*. 2023;6:100188; 4. Wu J, et al. *Hemato.* 2022;3:422–33.

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Latest data for emerging IBAT inhibitors in PBC

IBATs

Agent (trial/study)	Overview of available data for agent
Linerixibat (Ph IIb GLIMMER; NCT04950127)	**Phase IIb dose-finding GLIMMER trial:**[1] • Significant differences in change in monthly itch score (over 12 weeks) for **PBO vs linerixibat** dosed at: 180 mg once daily **(p=0.04)**, 40 mg twice daily **(p=0.01)**, and 90 mg twice daily **(p=0.04)** • Most frequent AE: **diarrhoea**; incidence increased with dose
Linerixibat (Ph III GLISTEN; NCT04950127)	**Baseline GLISTEN data suggest insufficient control of cholestatic pruritus and need for more effective therapies:**[2] At BL (N=227) **97%** were receiving UDCA; pruritus was moderate **(42%)** or severe **(58%)** • **42%** were receiving concomitant therapy that may reduce pruritus, e.g. antihistamines **(6%)**, bile acid binding resins **(8%)**, fibrates **(22%)**, gabapentin **(4%)**, nalfurafine **(2%)**, naltrexone **(2%)**, pregabalin **(3%)**, rifampin **(3%)** and SSRIs **(10%)** • Reasons for stopping **prior anti-pruritic treatments** included lack of efficacy and lack of tolerability/AEs
Volixibat plus OCA (VLX-602 pilot study)	**Pilot study in six female patients to assess volixibat in combination with OCA:**[3] • Most frequent AE: **diarrhoea (83%)** • TRAEs affecting one participant each: **nausea, fatigue, and vomiting** • Mean AST, ALT, total bilirubin, and ALP were stable (BL vs end of treatment) • Improved patient-reported itch scores achieved with volixibat in three participants

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transferase; BL, baseline; IBAT, ileal bile acid transporter; OCA, obeticholic acid; PBO, placebo; SSRI, selective serotonin reuptake inhibitor; TRAE, treatment related AE; UDCA, ursodeoxycholic acid.

1. Levy C, et al. *Clin Gastroenterol Hepatol.* 2023;21:1902–12; 2. Hirschfield G, et al. *Hepatology.* 2024;80(Suppl. 1):S1–2011. Abstract 2361; 3. Kowdley K, et al. *Hepatology.* 2024;80(Suppl. 1):S1–2011. Abstract 2417.

Latest data for emerging PPAR agonists in PBC

PPAR agonists

Agent (trial/study)	Overview of available data for agent
Bezafibrate plus OCA (NCT04594694)	**Phase II data at 6 months:**[1] **OCA + bezafibrate** (B400 SR) achieved a biochemical remission in **67%** of patients, **65%** reduction in ALP; **61%** of patients **achieved ALP ≤ULN** **Normalization rates:** ALT **(83%)**, AST **(78%)** and GGT **(72%)** **Serious TEAEs**: breast cancer, pruritus, abnormal hepatic function. *Low rate (11%) of new pruritus events*
Pemafibrate (NCT06247735) *Trial ongoing; data pending (phase II)*	***Trial in progress***
Saroglitazar (NCT05133336) *Trial ongoing; data pending (phase II/III)*	**Prior phase II proof-of-concept study at wk 16:**[2] Significant reduction in mean ALP levels from BL in 4 mg (**p<0.001**) and 2 mg (**p<0.001**) saroglitazar cohorts vs PBO

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transferase; BL, baseline; GGT, gamma-glutamyl transferase; OCA, obeticholic acid; PBO, placebo; PPAR, peroxisome proliferator-activated receptor; TEAE, treatment emergent AE; ULN, upper limit of normal; wk, week.

1. Jones DE, et al. *J Hepatol.* 2024;80(Suppl.):S91; 2. Vuppalanchi R, et al. *J Hepatol.* 2022;76:75–85.