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Primary biliary cholangitis: Appraising the changing therapeutic landscape

Practice aid for the management of patients with primary biliary cholangitis

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Early diagnosis and pre-treatment risk stratification in PBC are important

Symptoms[1]

Early stages may be asymptomatic

Common initial symptoms:

- Fatigue and pruritus
- Abdominal pain
- Xanthomas or xanthelasmas
- Dry mouth and eyes

Symptoms of cirrhosis as disease progresses:

- Jaundice
- Oedema
- Ascites
- Variceal bleeds

Index of suspicion[2]

- Chronic cholestasis after excluding other liver disease
- Particularly in middle-aged females with unexplained serum ALP elevation

Diagnosis[2]

- Largely confirmed by AMA testing
- Liver biopsy may substantiate diagnosis but is rarely needed

UDCA therapy and risk stratification[3]

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[3]

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[3]

based on risk profile

*Ascites, variceal bleed or encephalopathy.

Ongoing monitoring to assess response to first-line UDCA is needed in patients with PBC

Frontline UDCA is effective, but 25–50% of patients do not respond, and not all can tolerate treatment[4–6]

Loss of biochemical response to UDCA at any time is associated with heightened risk of liver transplant[4]

Over time, adequate response is always associated with better liver transplant-free survival vs inadequate response[4]

Incidence of the most common AEs with UDCA in placebo-controlled trials was low (~1–3% of patients):[5]

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

First-line UDCA[3]
(13–15 mg/kg PO daily)

Assess risk of progression based on response to treatment[3]

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
- Cardiovascular risk
- Concomitant autoimmune disease
- Metabolic syndrome

*Child–Pugh B or C, ascites, variceal bleed. .

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The established treatment landscape is expanding with four treatments now approved for PBC

UDCA[5]

Treatment of patients with PBC

CONTRAINDICATIONS: Patients with complete biliary obstruction and known hypersensitivity or intolerance to ursodiol, or any components of the formulation

OCA[7]

Treatment of adults with PBC without cirrhosis or with compensated cirrhosis, without evidence of PH, either *in combination* with UDCA (if inadequate response to UDCA), or as *monotherapy* in patients unable to tolerate UDCA

CONTRAINDICATIONS: Decompensated cirrhosis (e.g. Child–Pugh Class B/C) or a prior decompensation event; compensated cirrhosis with evidence of PH; complete biliary obstruction

Elafibranor[8]

Seladelpar[9]

Treatment of adults with PBC either *in combination* with UDCA (if inadequate response to UDCA), or as *monotherapy* in patients unable to tolerate UDCA

CONTRAINDICATIONS: None

Limitations of use:

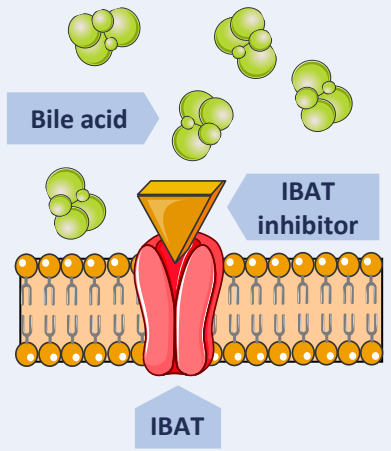
Not recommended in patients with/who develop decompensated cirrhosis (e.g. ascites, variceal bleeding, hepatic encephalopathy)

Novel treatments for PBC are in development[10–13]

IBAT inhibitors[10]

- Linerixibat
- Volixibat

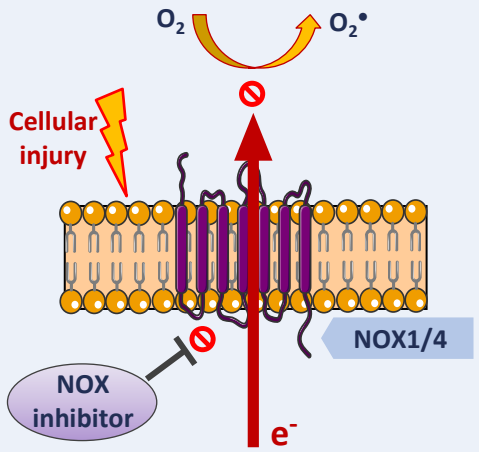
Block bile acid transportation



NOX1/4 inhibitors[11]

- Setanaxib

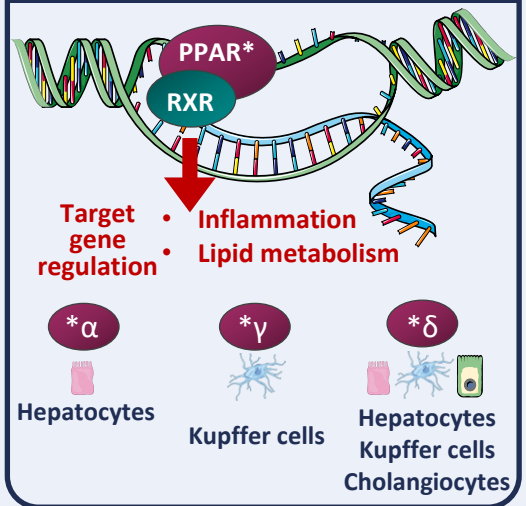
Reduce ROS formation



Fibrates/PPAR agonists[12,13]

- Bezafibrate
- Pemafibrate
- Saroglitazar

Transcription factor modulation



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Abbreviations and references

Abbreviations

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibody; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; IBAT, ileal bile acid transporter; LLN, lower limit of normal; NOX, nicotinamide adenine dinucleotide phosphate (NAPDH) oxidase; OCA, obeticholic acid; PBC, primary biliary cholangitis; PH, portal hypertension; PO, per os (by mouth); PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; RXR, retinoid X receptor; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; yr, years.

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