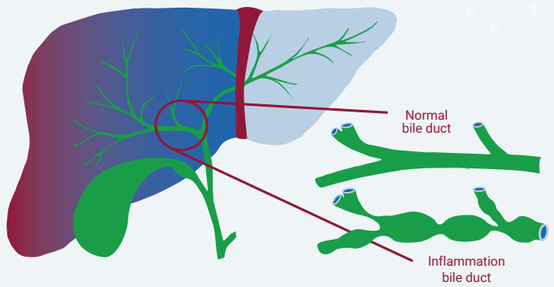
Improving **PBC** outcomes by prioritizing patients' needs

BREAKING DOWN PBC
A COMPREHENSIVE GUIDE

Springer Healthcare IME

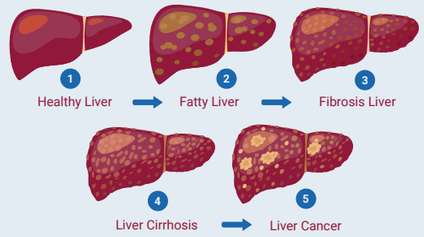
1 Understanding PBC[1-3]

PBC is a chronic autoimmune liver disease characterized by inflammation and fibrosis caused by the destruction of small intrahepatic bile ducts.

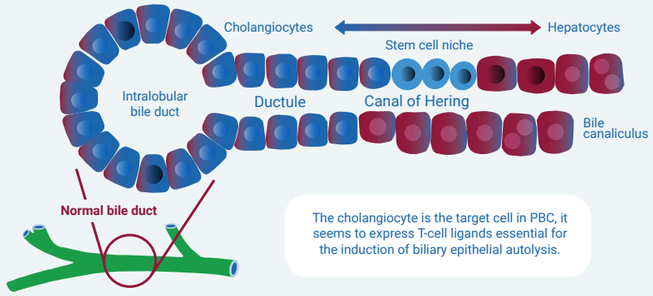


- Predominantly diagnosed in women
- Global incidence: 1.76 per 100,000 persons
- Global prevalence: 14.60 per 100,000 persons

Without treatment, it can lead to cirrhosis and liver failure, resulting in liver-related death.

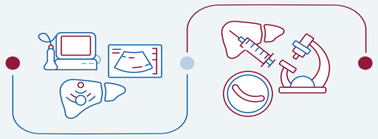


2 Pathogenesis[3-6]



The cholangiocyte is the target cell in PBC, it seems to express T-cell ligands essential for the induction of biliary epithelial autolysis.

Growing evidence indicates that the apoptosis of cholangiocytes, also known as BECs, could be a primary mechanism in the development of PBC. The pathogenic mechanism is thought to originate from an impairment in immune tolerance, leading to the proliferation and activation of T and B lymphocyte clones specific to self-antigens. This, in turn, triggers the generation of circulating autoantibodies alongside various cytokines and inflammatory agents.



The loss of the canals of Hering (pictured, left) appears to be the earliest histologic change associated with PBC, with characteristic diagnostic findings becoming evident subsequently.

3 Diagnosis[3,4,7,8]

The diagnosis of PBC is made when **2 of the 3** following items are met

- Consistent elevation of liver tests in a cholestatic pattern
- Detection of AMA
- PBC histopathology

Baseline assessment of PBC

- Measurement of liver tests including bilirubin
- The presence of PBC-specific symptoms
- Physical examination to identify hepatomegaly, splenomegaly, and/or extrahepatic signs of advanced liver disease

The serological hallmark of PBC is the presence of AMA, highly disease-specific antibodies identified in about 95% of PBC patients.

A positive AMA in a patient with raised ALP is diagnostic of PBC, after the exclusion of other intrahepatic and extrahepatic causes of cholestasis.

Other auto-Abs are often identified in PBC patients, particularly ANAs. IgM levels are often high, and this is useful in the differential diagnosis with AIH.

Liver biopsy has historically been the gold standard for staging the disease, but non-invasive methods to assess hepatic fibrosis are currently being developed and used.

Imaging-based NIT for PBC include:

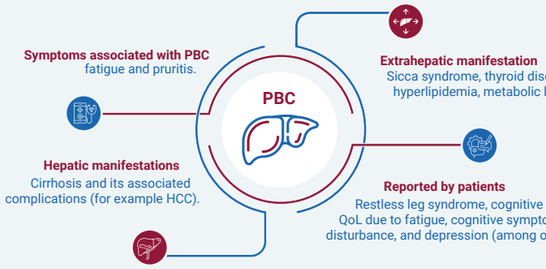
- VCTE
- Ultrasound elastography
- MRE

It has been recommended that these NIT should be used in staging the disease.

4 Symptoms[3,4]

The most common symptoms are fatigue and pruritus. They often have a significant negative impact on QoL.

Symptoms of PBC may encompass more than just liver-related manifestations.



5 Management Approach[1,3,4,7-10]

Goals

- Target greater reductions in ALP and bilirubin
- Achieve the lowest ALP level possible after adding a second-line therapy for PBC
- Prevention of end-stage liver disease and the improvement of associated symptoms

Current approach

- Diagnosis
  - First-line treatment with UDCA
- At 12 months
  - UDCA response assessment
- For UDCA non-responders
  - Second-line therapy and symptoms management

Towards personalized care

- Tailor addition of second-line treatment to patient risk and individual profile including assessment of
  - fibrosis stage
  - symptoms burden
  - risk factors for rapid progression
- Treatment aims
  - Achieve excellent QoL
  - Achieve normalization of liver serum test
  - Avoid liver transplant
  - Resolve ductopenia and liver fibrosis

Treatment options[1,4,7-12]

First-line treatment — UDCA 13–15 mg/kg daily

Second-line therapy

FXR agonists

OCA is approved as a second-line therapy in patients who have failed treatment or are unable to tolerate UDCA.

Remaining challenges:

- ~50% response rate
- often leads to pruritus
- contrainated in patients with advanced disease / clinically significant portal HTN

PPAR agonists

They exhibit a range of beneficial properties: anti-cholestatic, anti-inflammatory, and anti-fibrotic effects, making them attractive targets, and have been gaining importance as promising therapeutics.

PPARs exist in three isotypes (PPAR-α, PPAR-γ, PPAR-β/δ), each encoded by distinct genes and exhibiting specific tissue distribution and functions.

Fibrates

Such as bezafibrate and fenofibrate are the most evaluated fibrates assessed in PBC patients.

- Guidelines suggest they might be used off-label for patients with inadequate response to UDCA but should not be used in patients with decompensated liver disease
- Using fibrates in combination with UDCA in PBC has demonstrated improvements in biochemical measures and symptom relief

Other PPAR agonists: such as seladelpar, elafibranor, saroglitazar

- Elafibranor (dual PPAR-α/δ agonist) is now FDA approved and seladelpar (PPAR-δ agonist) is in late stage development with a potential approval fast approaching
- Saroglitazar is currently undergoing phase 2b/3 investigations

Triple combination

People with inadequate treatment responses might benefit from the combination of on-label and off-label therapies.

Other options

Under investigation: agents targeting the FGF19 pathway, agents targeting the NADPH oxidase enzymes, agents with immunomodulatory properties, antiretroviral therapy.

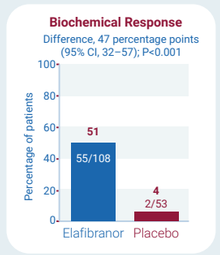
6 Latest clinical data[5,8,13]

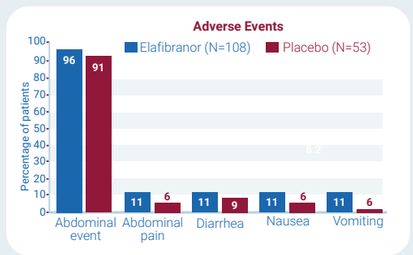
OCA and bezafibrate

Two phase 2 clinical trials have assessed a range of doses and formulations of this combination in PBC patients with inadequate response to or were unable to tolerate UDCA.

Their latest data have shown that OCA-bezafibrate led to biochemical remission including normalized ALP, total bilirubin, GGT, ALT, and AST in 40-44% of patients after 12 weeks.

In particular, OCA-bezafibrate 400 mg showed a higher than 60% reduction in ALP and a higher than 20% reduction in total bilirubin in both studies.





Elafibranor

The latest phase 3 trial was a double-blind, placebo-controlled study where patients with PBC who had an inadequate response to or unacceptable side effects with UDCA were randomly assigned to receive elafibranor, once a day at a dose of 80 mg, or placebo.

Primary endpoint: Biochemical response, defined as an ALP level <1.67 times the upper limit of the normal range, with a reduction of ≥15% from baseline, and normal total bilirubin levels. A biochemical response was observed in 51% of the elafibranor-treated patients vs 4% in placebo-treated patients. At week 52, ALP level normalization was achieved in 15% of elafibranor-treated patients vs 0% in placebo-treated patients.

Safety: Incidence of AEs was similar in both groups, those that occurred more frequently with elafibranor than with placebo included abdominal pain, diarrhea, nausea, and vomiting.

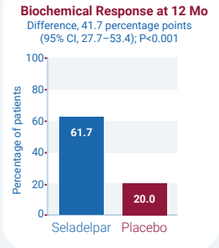
Seladelpar

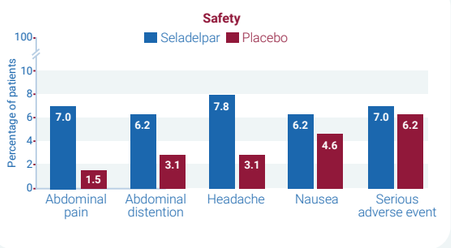
The latest phase 3 trial was a double-blind, placebo-controlled study where patients with PBC who had an inadequate response to or unacceptable side effects with UDCA were randomly assigned to receive seladelpar 10mg once per day or placebo.

Primary endpoint: Biochemical response, defined as an ALP level <1.67 times the upper limit of the normal range, with a decrease of 15% or more from baseline, and normal total bilirubin levels at 12 months.

A biochemical response was observed in 61.7% of the seladelpar-treated patients vs 20.0% in placebo-treated patients. ALP level normalization was achieved in 25% of seladelpar-treated patients vs 0% in placebo-treated patients.

Safety: AEs were reported in 86.7% of the patients in the seladelpar group and 84.6% in the placebo group, and serious AEs in 7.0% and 6.2%, respectively.





Abbreviation list: Ab, antibody; AE, adverse event; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine transaminase; AMA, antimitochondrial antibody; ANA, anti-nuclear antibody; AST, aspartate aminotransferase; BEC, biliary epithelial cells; FGF, fibroblast growth factors; GGT, gamma-glutamyl transpeptidase; HCC, hepatocellular carcinoma; MRE, magnetic resonance elastography; NADPH, nicotinamide adenine dinucleotide phosphate; NIT, non-invasive techniques; OCA, obeticholic acid; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptors; QoL, quality of life; UDCA, ursodeoxycholic acid; VCTE, vibration-controlled transient elastography.

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