Diagnosis and Management of PBC

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Primary Biliary Cholangitis (PBC)

- Chronic cholestatic liver disease
- Autoimmune in nature
- Inflammation and destruction of small interlobular bile ducts
- Affects predominantly middle-aged females
- Rising incidence and prevalence

PBC Diagnosis

- Unexplained Elevation of ALP $\geq 1.5 \times$ ULN
- Positive anti-mitochondrial antibody
- Non-suppurative destructive cholangitis on histology

Two out of these 3 criteria are required for the diagnosis of PBC
Variant Syndromes

AMA-negative PBC
- 50% will have antinuclear antibodies (ANA)
- PBC-specific ANA – anti gp210, anti sp100
- Same clinical presentation

Overlap syndrome with autoimmune hepatitis
- Consider when ALP: transaminase ratio <1.5, IgG is elevated and smooth muscle antibodies are present with titer >1:80

Premature Ductopenic Variant
- 5-10%
- Very rapid onset of ductopenia, severe icteric cholestasis and fast progression towards cirrhosis
Clinical Features Vary Greatly Between Patients

- Fatigue\textsuperscript{1,2}
- Pruritus\textsuperscript{1,2}
- Concurrent autoimmune diseases\textsuperscript{1,2}
- Reduced bone density\textsuperscript{1,2}
- Hypercholesterolemia\textsuperscript{1,2}
- Xanthoma and Xanthelasma\textsuperscript{2,3}

PBC can range from asymptomatic and slowly progressive to symptomatic and rapidly evolving.\textsuperscript{1}

First Line Therapy: Ursodeoxycholic Acid

- Orally administered, naturally occurring, hydrophilic secondary bile acid
- Dose: 13-15 mg/kg/day
- Improvement in liver tests may be seen within a few weeks and 90% of the improvement usually occurs within 6-9 months

Therapeutic Effects UDCA

UDCA 13-15 mg/kg/day

Improves TB, ALP, GGT, AST and ALT

Improves cholesterol, IgM

Improves survival free of liver transplantation

UDCA 13-15 mg/kg/day

Delays development of esophageal varices

Delays histological progression

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; IgM, immunoglobulin M; TB, total bilirubin; UDCA, ursodeoxycholic acid.
Combined Effect of TB and ALP on Transplant-Free Survival

ALP and TB at 1 Year Follow-up

- **Normal bilirubin and ALP ≤ 2.0 x ULN**
- **Normal bilirubin and ALP > 2.0 x ULN**
- **Abnormal bilirubin and ALP ≤ 2.0 x ULN**
- **Abnormal bilirubin and ALP > 2.0 x ULN**

Transplant-Free Survival (%)

<table>
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<th>Time (Years)</th>
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<th>10</th>
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<td>1482</td>
<td>887</td>
<td>504</td>
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<td>b</td>
<td>681</td>
<td>489</td>
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<tr>
<td>d</td>
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<td>345</td>
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</table>

Hazard Ratio for LT/Death According to ALP

*3710/4635 patients were included for this analysis
New Targets for Treatment of Cholestatic Diseases

OCA in Patients with PBC: POISE Study Design

- Placebo (n=73)
- OCA 10 mg (n=73)
- Titrate to OCA 10 mg (n=33)
- Remain at OCA 5 mg (n=36)
- OCA 5 mg

Months in Open-Label Phase:
- 0
- 3
- 6
- 9
- 12
- 60

Primary Endpoint in the Double-Blind and Open-Label Extension Phases

Other Effects of OCA During POISE Trial

- Significant drop in ALP, AST, ALT, GGT, TB
- Significant reduction in inflammatory markers
- Reduction in HDL-cholesterol (20% in 10mg/day, 9% in 5-10 mg/day)
- No change in liver stiffness scores (50% had LS measured)
- Significant reduction in serum bile acid levels and increase in FGF 19 levels
- Main side effect: Pruritus mitigated by starting at 5 mg/day and only titrating up IF well tolerated

Obeticholic Acid Is Approved:

- In combination with UDCA for patients with PBC who have been treated with UDCA for > 1 year and have incomplete response

- As monotherapy for patients with PBC who are intolerant to UDCA

Improvement in survival free of liver transplantation has not yet been demonstrated. Conditional approval granted
In patients with inadequate response to UDCA, **OCA** decreased 15-yr cumulative incidences of:

- **Decompensated cirrhosis** from 12.2% to 4.5%
- **HCC** from 9.1% to 4%
- **OLT** from 4.5% to 1.2%
- **Liver-related deaths** from 16.2% to 5.7%
Cost-Effectiveness Study of OCA in PBC

- Treating 10,000 patients would prevent: 770 cases of decompensated cirrhosis, 510 cases of HCC, 330 OLTs and 1050 liver-related deaths

- Lifetime treatment cost of PBC increased from $63,100 to $902,200 (1,330%) with addition of OCA to UDCA

- ICER: $473,400/QALY → NOT cost-effective

- Recommended price reduction: 73%

WHO SHOULD RECEIVE ADJUVANT THERAPY?

WHO IS AT RISK FOR PROGRESSION?
PBC - Risk Stratification

**Pre-Treatment**
- Age, gender, ethnicity
- Anti gp 210, anti-centromere
- Variant syndromes

**After 1 year of treatment with UDCA**
- Response to UDCA
  - ALP, TB

Staging: Transient elastography, histology, enhanced liver fibrosis score

Mathematical models:
- Globe PBC, UK PBC

- **LS > 9.6 at baseline** associated with 5x increase in risk of adverse outcomes
- **LS increase >2.1 kPa/year** associated with 8x increase in risk of adverse outcomes

# Novel Therapies Under Evaluation for PBC

<table>
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<th>Compound</th>
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<td>Phase 3, Europe – has results</td>
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<td>Phase 2, China</td>
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<td>NCT02193360</td>
<td>CD40 Inhibitor</td>
<td>Phase 1/2 - Europe</td>
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<td>ASBT inhibitor</td>
<td>Phase 2, complete; primary endpoint: itching</td>
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<tr>
<td>Genfit</td>
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<td>PPAR delta agonist</td>
<td>Phase 2, not yet recruiting</td>
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</table>
Bezafibrate+UDCA vs. Placebo+UDCA

- 100 patients with incomplete response to UDCA
- Randomized to BZF 400 mg/day or placebo, for 2 years
- Primary endpoint* at 2 years: 30% BZF vs. 0% Placebo
- Itch score, LSM and ELF all improved in BZF group

Summary: Updated Management Strategy

New Diagnosis

Baseline Evaluation
- Imaging & Labs
- Assess symptoms
- Staging*
- DEXA

Initiate PBC-specific therapy
- UDCA 13-15 mg/kg/day

Long-term monitoring
- Clinical evaluation
- Biochemistries
- Transient elastography

Pruritus
- Fatigue
- Sicca Syndrome

Cirrhosis? MRS > 4.1?
- Thrombocytopenia
- EGD; HCC surveillance

Risk stratification after 1 year of therapy
- Evaluate need for adjuvant therapy

Approved: Ocaliva
Off label: Fibrates, budesonide