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Cholestatic Disease

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Primary Biliary Cholangitis (PBC)

- Previously known as Primary Biliary Cirrhosis
- PBC is an immune-mediated cholestatic liver disease
- Present in adults. More commonly after age of 40 and predominately females. Mean age at presentation in 52
- Incidence and prevalence is increasing across the globe
- PBC can lead to liver fibrosis, cirrhosis and complications of end-stage liver disease if left untreated

### PBC Phenotype

<table>
<thead>
<tr>
<th><strong>Age</strong></th>
<th>Usually &gt;40 years</th>
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<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>Female &gt; Male (9:1)</td>
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<tr>
<td><strong>Serology</strong></td>
<td>AMA in ~95%; disease-specific ANA in ~30%-50%; ASMA may be present</td>
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<tr>
<td><strong>Immunoglobulin</strong></td>
<td>IgM typically elevated</td>
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<tr>
<td><strong>MRCP</strong></td>
<td>Normal</td>
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<tr>
<td><strong>Liver Histology</strong></td>
<td>Lymphocytic infiltrate; inflammatory duct lesion; granuloma may be present</td>
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<tr>
<td><strong>Coexisting IBD</strong></td>
<td>Not typical</td>
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<tr>
<td><strong>Clinical Symptoms</strong></td>
<td>Itching and fatigue</td>
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Abbreviations: AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti-smooth-muscle antibody; IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiography; PBC, primary biliary cholangitis. Trivedi PJ et al. *Aliment Pharmacol Ther*. 2012;36:517-533.
EASL and AASLD Guidelines for PBC

Abbreviations: AIH, autoimmune hepatitis.
Confirming a PBC Diagnosis According to AASLD

**Suspected PBC**
- Persistent elevated ALP and/or GGT and/or Conjugated Bilirubin
- Pruritus, fatigue, sicca, arthralgia

**Initial Assessment**
- H/P
- Abdominal Ultrasound
- ALP, AST, ALT, Bilirubin
- AMA and/or PBC ANA, ASMA

**Diagnosing PBC**
- Elevated ALP >1.5 x ULN
- AMA Positive

Liver Biopsy: If AST>5xULN, AMA, is absent or if concerning feature of AIH /NAFLD

PBC Diagnostic Criteria

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

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

AASLD 2018.
If Left Inadequately Treated, PBC May Result in Liver Failure, Transplant, or Death

Persistent, toxic exposure to bile acid buildup ultimately leads to end-stage disease

Immune Response → Chronic Cholestasis/Inflammation → Fibrosis → Cirrhosis, End-Stage Liver Disease, Liver Cancer

- Immune Injury to bile ducts
- Bile duct loss and bile acid buildup
- Scarring begins
- Hepatic decompensation

Presence of AMA:
- Elevated alkaline phosphatase
- Elevated bilirubin

First Line Therapy: Ursodeoxycholic Acid (UDCA)

- 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\(^1\)
- Adequate response (60%) of patients = similar survival as the standard population\(^2\)

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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
- 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.


Graphic courtesy of Dr. Cynthia Levy.
Management of PBC According to AASLD

- **START UDCA**
  - UDCA 13-15 mg/kg/day
  - Assess response

- **Stage Disease**
  - Globe Score
  - Fibroscan
  - Cirrhosis (HCC and Variceal screening)

- **Assess and Address**
  - Pruritus
  - Fatigue
  - Osteoporosis
  - Fat-soluble vitamin Deficiencies
  - Sicca Syndrome

- **Extra Hepatic Manifestation**
  - Thyroid disease
  - Renal disease
  - Gallstones
  - Arthritis
Response Criteria Models for UDCA

- **The Paris-II criteria**
  - ALP >1.5x ULN; or
  - AST >1.5x ULN; or
  - Bilirubin >1 mg/dl

- **Globe Score**
  - Free online calculator
  - Uses age, total bilirubin, ALP, albumin, Platelets

- Used to define Adequate response to UDCA
Second Line: Obeticholic Acid (OCA)

- 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
- Can not be used on Child-Pugh B or C or any patients with prior decompensation episodes, nor patients with any evidence of portal hypertension

Abbreviations: BA, bile acid; NF-KB, nuclear factor kappa beta; TNF, tumor necrosis factor; CRP, C-reactive protein.
## Risk Scarification of PBC Patients on Treatment

<table>
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<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
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<tr>
<td>• Mild elevation in ALP and&lt;br&gt;• Normal bilirubin and&lt;br&gt;• Normal albumin and&lt;br&gt;• Early or no fibrosis</td>
<td>• Age at diagnosis &lt;45 years or&lt;br&gt;• ALP &gt;1.5x ULN or&lt;br&gt;• Abnormal bilirubin or&lt;br&gt;• Low albumin or&lt;br&gt;• Child-Pugh A, Advanced fibrosis/early cirrhosis</td>
<td>• Decompensated cirrhosis (Child-Pugh B or C) or&lt;br&gt;• Compensated cirrhosis with evidence of clinically significant portal hypertension or&lt;br&gt;• Bilirubin &gt;2x ULN; or&lt;br&gt;• Severe pruritus</td>
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Symptom Management: Pruritus

- **Cholestaramine up 4G x 4 times a day**
  - Monitor for absorption of other drugs including OCA, UDCA

- **Rifampicin 150 mg to 300 mg a day**
  - Potential hepatotoxicity
  - Drug interactions

- **Naltrexone up to 50 mg per day, Starting at 12.5 mg/day**
  - Monitor for opiate withdrawal-like reactions

- **Sertraline 75 to 100 mg a day**

- **Clinical trails**

- **Liver transplant Intractable Pruritus**

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Symptom Management: Sicca

**Dry Mouth (Xerostomia)**
- Dental cleaning every 6 months
- Sugar free candy or gum
- Rinse with water
- Saliva substitutes
- Pilocarpine or Cevimeline if refractory to above

**Dry Eyes (Keratoconjunctivitis Sicca)**
- Artificial tears
- Referral to ophthalmologist
- Pilocarpine or Cevimeline if refractory to artificial tears

AASLD, PBC:2018 Practice Guidelines.
Osteoporosis

AASLD Recommendations

- Dexa Bone Scan every 2 years
- Vitamin D levels yearly and supplement as needed, 1000 IU a day
- Calcium supplementation if osteopenia is present, 1000 to 1500 mg
- If osteoporosis use Alendronate 70 mg once a week
- TSH annually
- If patients become jaundice routine measurement of Vitamin A, D, E and K is recommended to check for deficiencies
Fatigue

- No approved treatments
- Assess for other causes such as anemia, depression, sleep disorder, hypothyroidism
- Exercise?
  - Single arm, open label trial to assess the feasibility and efficacy of a home-based exercise program (HBEP) to attenuate fatigue associated with PBC
    - In a preliminary analysis of 25 participants:
      - 23/25 reached the primary endpoint
      - 19/25 reached fatigue scores akin to the control population

HBEP is a safe, feasible, and effective in patients with PBC to attenuate fatigue

Freer et al. AASLD 2020.
In the Pipeline…
Peroxisome proliferator-activated receptor (PPARs) agonists

• PPAR are nuclear receptors that occur in three isoforms, α, δ, and γ.

• PPAR’s exert in the liver a transcriptional activity regulating many physiologic functions:
  – bile acid homeostasis
  – lipid and glucose metabolism
  – inflammation

- bezafibrate (pan-PPAR agonist)
- Fenofibrate (PPAR-α agonist)
- Saroglitazar (dual PPAR (α/γ) agonist)
- Seladelpar (selective PPAR-δ agonist)
- Elafibranor (a dual PPAR-α and -δ agonist)
**Elafibranor** Demonstrates Favorable Efficacy and Safety in Patients With PBC and Incomplete Response to UDCA

**Conclusion:**
Elafibranor was generally safe and well tolerated.

Significantly reduced levels of ALP, composite endpoints of bilirubin and ALP, as well as other markers of disease activity in patients with PBC and an incomplete response to UDCA.


**BACKGROUND & AIMS**

- Seladelpar is a potent peroxisome proliferator activated receptor-delta agonist
  - Improved cholestasis markers in PBC
- **AIM**: to evaluate the efficacy, safety, and tolerability of seladelpar during 1 year of treatment in patients with PBC

**METHODS**

- 1-year, Phase 2, open-label, uncontrolled dose-finding study
- PBC patients with an inadequate response or intolerance to UDCA
- **Primary endpoint**: % change in ALP at 1 year
- **Composite endpoint**: ALP <1.67 × ULN; ≥15% decrease in ALP; total bilirubin ≤ULN

**Inclusion criteria**

- ALP ≥1.67 × ULN
- ALT and AST ≤3 × ULN
- Total bilirubin ≤2 mg/dL

**Oral seladelpar**

- 2 mg QD* (n=11)
- 5 mg QD† (n=49)
- 10 mg QD (n=52)

- 112/119 patients evaluated for efficacy
- At 1 year, no patients remained on 2 mg*
- After 1 year, patients could enter a long-term study

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Slide courtesy of Dr. Cynthia Levy.
Levy et al. DILC. 2020.
Durability of Treatment Response After 1 Year of Therapy With Seladelpar in Patients With PBC: Final Results of an International Phase 2 Study

RESULTS

<table>
<thead>
<tr>
<th>Baseline laboratory values</th>
<th>5/10 mg (n=49)</th>
<th>10 mg (n=52)</th>
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<tbody>
<tr>
<td>ALP, U/L</td>
<td>353</td>
<td>301</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>0.76</td>
<td>0.83</td>
</tr>
<tr>
<td>GGT, U/L</td>
<td>244</td>
<td>239</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>46</td>
<td>46</td>
</tr>
</tbody>
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- Seladelpar up to 10 mg appeared safe and well tolerated
- SAEs in 14 patients were unrelated to the drug
- ALP normalized in 14% in 5/10 mg and 33% in 10 mg grps
- 93% with moderate to severe pruritus in the 10 mg grp experienced improvement in itch (VAS decrease ≥20 mm)

CONCLUSION

- Seladelpar resulted in a substantial and sustained biochemical response with a good tolerability and safety profile
Saroglitazar

- PPAR (α/γ) agonist
- Studied on UDCA unresponsive PBC, Phase 2
- Prospective trial to compare efficacy of 2mg and 4 mg
- Conclusion: Saroglitizar at 2 and 4 mg daily resulted in rapid and sustained improvement in ALP
- The study was terminated because of lack of enrollment

Vuppalanchi R et al. AASLD 2020 Abstract.
Budesonide Add-On Therapy in PBC Patients: Phase 3 trial

- Randomized, double-blind, placebo-controlled trial (Completed)
- 62 patients randomized and treated (ITT population) with 36 months of treatment with UDCA (12–16 mg/kg BW/day) with or without BUD (3 mg tid*)

**Improvement in liver histology**
- Did not improve histology

**Improved liver function**
- High drop out rate
- Increased rates of AEs associated with long term steroid use including osteopenia, cataracts and hypertension
- Improvement of liver blood test
OCA and Fibrates

- Comparative Effects in a Multicentric Observational Study
  - 86 patients were treated with OCA
  - 250 with fibrates, 81% bezafibrate and 19% fenofibrate
  - 15 with OCA plus fibrates

- Results:
  - ALP decrease was higher under fibrates
  - Alanine aminotransferase decline was higher under OCA.
  - Adverse events were reported mainly pruritus
  - Discontinuation was more frequent in fenofibrate treatment mainly because of intolerance or adverse events

- Conclusions:
  - Second-line therapy with OCA or fibrates improves hepatic biochemistry and the GLOBE score in PBC patients with suboptimal response to UDCA
  - Simultaneous treatment with OCA and fibrates improved ALP as well
Phase 3 Clinical Trials

Elafibranor

- A dual agonist of PPARα and PPARδ
- Phase 3 clinical trial
- Double-blind (DB), randomized, placebo-controlled study
- To confirm elafibranor 80mg efficacy, based upon changes in biochemical parameters and its potential to improve pruritus, and safety in patients with PBC

*Seladelpar

- Selective PPARδ agonist
- Double-blind (DB), randomized, placebo-controlled study
- To evaluate the treatment effect of seladelpar on composite biochemical improvement in cholestasis markers based on ALP and total bilirubin and to evaluate the safety of seladelpar over 12 months of treatment compared to placebo

*Not for liver cirrhosis or history of hepatic decompensation

Is There a Role for Triple Therapy?

- Retrospective cohort study, 58 eligible patients from 19 centers across seven Western countries
- All patients had failed UDCA or OCA+UDCA or Fibrate therapy +UDCA
- Data suggests that fibrates are more efficient than OCA in reducing ALP level
- OCA could have stronger effects than fibrates on GGT and transaminases
- **Conclusion:** Triple therapy with UDCA, OCA and fibrates has the potential to improve and even normalize the biochemical and clinical features of PBC
- When fibrates were added to OCA and UDCA led to a significant improvement of pruritus

Abstract

In May 2021, the FDA issued a new warning restricting the use of obeticholic acid in patients with advanced cirrhosis. This is defined as cirrhosis with current or prior evidence of liver decompensation (e.g., encephalopathy, coagulopathy) or portal hypertension (e.g., ascites, gastroesophageal varices, or persistent thrombocytopenia).
• **Obeticolic acid:** can not be used in patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event (4) compensated cirrhosis with evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) (4) complete biliary obstruction.

• **Fibrates:** can be considered off label alternative for patients with PBC not responding to UDCA. Discouraged in patients with decompensated disease.
Summary

• PBC Diagnosis can typically be made based on persistent cholestatic liver profile and AMA positivity after other common liver diseases have been excluded

• Risk stratification is important in this patient population

• The use of AASLD/EASL Clinical Practice Guidelines for PBC improves uniform practice

• Is important to assess and manage symptoms of pruritus, sicca, osteoporosis and fatigue

• Promising drugs are in late-stage development