Primary Biliary Colangitis (PBC): Deciding Which Patients are Ursodiol Nonresponders

Fred Poordad, MD
Case Study

- 57-year-old white female presents to you for routine annual exam
- Reports fatigue and intermittent itching
- Only medication is Synthroid; no OTC products
- BMI = 28; no metabolic syndrome

- ALP 300 IU/mL, AST 60 IU/mL, ALT 73 IU/mL, total bilirubin 0.7 mg/dL, hemoglobin 12.3 mg/dL, platelets 185K
- Viral hepatitis serologies negative
- Abdominal ultrasound shows normal liver/spleen morphology, no bile duct dilatation and normal gall bladder.
PBC is a Chronic, Progressive Autoimmune Disease

- PBC is characterized by destruction of the interlobular and septal bile ducts that may lead to cirrhosis
- Factors possibly associated with onset and perpetuation of bile duct injury in PBC

PBC Phenotype

<table>
<thead>
<tr>
<th></th>
<th>Details</th>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Usually &gt;45 years</td>
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<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>
</tr>
<tr>
<td><strong>Liver Histology</strong></td>
<td>Lymphocytic infiltrate; inflammatory duct lesion; granuloma may be present</td>
</tr>
<tr>
<td><strong>Coexisting IBD</strong></td>
<td>Not typical</td>
</tr>
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</table>

Abbreviations: AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti-smooth-muscle antibody; IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiography; PBC, primary biliary cirrhosis.

PBC Prevalence

Clinical Features Vary Greatly Between Patients

- Fatigue\(^1,2\)
- Pruritus\(^1,2\)
- Concurrent autoimmune diseases\(^1,2\)
- Reduced bone density\(^1,2\)
- Hypercholesterolemia\(^1,2\)
- Xanthoma and Xanthelasma\(^2,3\)

PBC can range from asymptomatic and slowly progressive to symptomatic and rapidly evolving.\(^1\)

## Diagnostic Considerations

### Spectrum of Autoimmune Liver Injuries

- Autoimmune hepatitis\(^1\)
- Primary biliary cholangitis\(^1\)
- Primary sclerosing cholangitis\(^1\)
- IgG4-related disease\(^2\)

### Differential for Cholestatic Liver Biochemistry

- Drug-induced liver injury
- Inherited cholestasis
- Idiopathic ductopenia
- Malignant infiltration
- Nonalcoholic fatty liver disease
- Obstructive biliary lesion
- Primary biliary cholangitis
- Primary sclerosing cholangitis
- Sarcoidosis

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Elevated serum alkaline phosphatase (ALP) activity

Exclude other causes of liver disease including alcohol and drugs

Cross sectional imaging of liver to exclude biliary obstruction

AMA (Antimitochondrial antibody), ANA (antinuclear antibody), ASMA (anti-smooth muscle antibody)

Consider liver biopsy, especially if AST>5x ULN or AMA negative
Higher APRI and Elastography Associated with Poor Survival

Disease Management
Assessing and Managing Fatigue

• Though fatigue caused by PBC may not be reversible, associated causes of fatigue should be actively excluded—or identified and managed\(^1,2\)

<table>
<thead>
<tr>
<th>Rule Out:</th>
<th>Consider Fatigue Management Strategies:</th>
</tr>
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<tbody>
<tr>
<td><strong>Associated causes of fatigue (disease or medication):</strong></td>
<td><strong>Fatigue may be improved by:</strong></td>
</tr>
<tr>
<td>• Anemia(^2)</td>
<td>• Maintaining regular physical activity(^4,5)</td>
</tr>
<tr>
<td>• Depression(^2)</td>
<td>• Modafinil (100-200 mg)(^6,7)</td>
</tr>
<tr>
<td>• Sleep disorder(^2)</td>
<td>• Methotrexate for patients with severe fatigue(^8)</td>
</tr>
<tr>
<td>• Hypothyroidism(^1-3)</td>
<td></td>
</tr>
<tr>
<td>• Medications that can cause or contribute to fatigue (eg, excessive antihypertensive medication)(^1)</td>
<td></td>
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Pruritus Is Common Among PBC Patients

- Prevalence reported as high as 69%\(^1\)
- Unknown etiology\(^1,2\)
  - Bile salts, endogenous opioids, histamine, serotonin, progesterone/estrogen, and autotaxin/lysophosphatidic acid are suspected pruritogens\(^2\)
- Diurnal variation – most intense itch in the late evening\(^2\)
- Localization reported at limbs – soles of feet, palms of hands\(^2\)
- Exacerbated by contact with wool, heat, or pregnancy\(^3\)

### General Recommendations

- Skin moisturizer
- Wet, cooling, or moist wraps
- Topical agents with symptomatic relief (e.g., camphor, menthol)
- Relaxation techniques
- Training to stop the cycle of itch, scratch, itch

### First-line

- Bile acid sequestrants:
  - Cholestyramine
  - Colestipol, colesvelam

**The following agents may be used for pruritus that is refractory to bile acid sequestrants:**

#### Second-line

- Rifampicin

#### Third-line

- Oral opioid antagonists:
  - Naltrexone
  - Nalmefene

#### Fourth-line

- Selective serotonin reuptake inhibitors:
  - Sertraline

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Long Term Management

- Liver chemistry tests every 3-6 months
- Thyroid status (TSH) annually
- Bone mineral densitometry every 2-4 years
- Vitamins A, D, K annually if bilirubin >2.0
- Upper endoscopy every 1-3 years if cirrhotic or Mayo risk score >4.1
- Ultrasound ± AFP every 6 months in patients with known or suspected cirrhosis
Ursodeoxycholic Acid (UDCA) and Treatment Response
First Line: Ursodeoxycholic Acid (UDCA)

- UDCA is the only FDA-approved first-line PBC therapy
- Recommended adult dosage is 13–15 mg/kg/day
- Orally administered, naturally occurring, hydrophilic secondary bile acid
- Typically administered in 2 divided doses

UDCA: Bilirubin and Alkaline Phosphatase at 1 Year Follow-up

UDCA: Overall Survival

**UDCA Treated vs. Untreated**

- Treated patients
- Untreated patients
- Mayo model

**UDCA Treated vs. Healthy Control**

- French control group

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UDCA Treatment Failure: Depends on Definition

<table>
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<tr>
<th>Study</th>
<th>Treatment Failure (%)</th>
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| Pells et al, 2013¹ (UK-PBC group) | • 60% of patients presenting at age <40 years  
                               | • 10% of patients presenting at age >70 years          |
| Corpechot et al, 2011²       | • 13%–37%*                                                |
| Kuiper et al, 2009³          | • 34%–38%*                                                |
| Corpechot et al, 2008⁴       | • 35%–39%*                                                |

*Depending on criteria used.
Established Response Criteria Models (2006-2010)

<table>
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<tr>
<th>Location</th>
<th>Criteria</th>
</tr>
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<tbody>
<tr>
<td>Barcelona(^1) (2006)</td>
<td>ALP decreased by &gt;40% from baseline or normalized after 1 year UDCA</td>
</tr>
<tr>
<td>Paris-I(^2) (2008)</td>
<td>All 3 of the following: ALP $\leq 3 \times$ ULN; AST $\leq 2 \times$ ULN; and bilirubin $\leq 1 \text{ mg/dL}$ after 1 year UDCA</td>
</tr>
<tr>
<td>Rotterdam(^3) (2009)</td>
<td>Albumin and bilirubin normalization when 1 or both were abnormal at baseline; albumin OR bilirubin normalization when both were abnormal at baseline after 1 year UDCA</td>
</tr>
<tr>
<td>Toronto(^4) (2010)</td>
<td>ALP $&lt;1.67 \times$ ULN after 2 years UDCA</td>
</tr>
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Modifications of Biochemical Response Criteria Models (2011-2013)

**Paris-II**

All 3 of the following: ALP ≤1.5 x ULN; AST ≤1.5 x ULN; and bilirubin ≤1 mg/dL after 1 year UDCA

**Early Biochemical Response**

Barcelona, Paris-I, or Toronto criteria met at 6 months UDCA

**Abbreviations:** ALP, alkaline phosphatase; AST, aspartate aminotransferase; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.


<table>
<thead>
<tr>
<th>Criteria/Model</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Biochemical response (Barcelona, Paris-I/II, or Toronto) and APRI ≤0.54 after 1 year UDCA</td>
<td>Biochemical + APRI&lt;sup&gt;1&lt;/sup&gt; (2014)</td>
</tr>
<tr>
<td>Prognostic index comprising baseline albumin and platelet count, plus bilirubin, ALT or AST, and ALP after 1 year UDCA</td>
<td>UK-PBC Risk Score&lt;sup&gt;2&lt;/sup&gt; (2015)</td>
</tr>
<tr>
<td>Prognostic index comprising baseline age, and bilirubin, ALP, albumin, and platelet count after 1 year UDCA</td>
<td>GLOBE Score&lt;sup&gt;3&lt;/sup&gt; (2015)</td>
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Treating Those with an Inadequate Response to UDCA
Farnesoid X Receptor Signaling

FXR (Hepatocytes, biliary epithelium, small bowel enterocytes, renal tubular cells, adrenal cells, adipocytes, beta cells)

Binding

↑ Gene Expression
(BSEP, MDR3, MRP 2/3/4, OST α/β)

↓ Gene Expression
(CYP7A1, NTCP, OATP)

↑ Bile Acid Efflux

↓ Bile Acid Synthesis and Uptake

Bile Acids
(Primary ligands for FXR)

Direct Effects

Indirect Effects

Abbreviations: BSEP, bile salt export pump; FXR, farnesoid X receptor; MRP 2/3/4, multidrug resistant protein 2/3/4; NTCP, sodium/taurocholate cotransporting polypeptide; OATP, organic anion transporting polypeptide; OST α/β, organic soluble transporter α/β.

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
- OCA 5-10 mg dose adjustment option

- If patients were on UDCA at baseline, they were allowed to continue throughout the course of therapy.

Positive response at 12 months defined as:
- ALP <1.67 x ULN and
- bilirubin WNL and
- ≥15% ALP reduction

Both OCA 10 mg and OCA 5-10 mg titration arm significantly better than placebo arm (p<0.0001)
# Adverse Events in POISE and Open-Label Extension

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo N=73 n (%)</th>
<th>OCA 5-10 mg N=70 n (%)</th>
<th>OCA 10 mg N=73 n (%)</th>
<th>Open Label N=193 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>28 (38)</td>
<td>39 (56)</td>
<td>50 (68)</td>
<td>138 (72)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>13 (18)</td>
<td>17 (24)</td>
<td>13 (18)</td>
<td>45 (23)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (18)</td>
<td>12 (17)</td>
<td>6 (8)</td>
<td>36 (19)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (14)</td>
<td>11 (16)</td>
<td>17 (23)</td>
<td>50 (26)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (12)</td>
<td>4 (6)</td>
<td>8 (11)</td>
<td>28 (15)</td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td>3 (4)</td>
<td>11 (16)</td>
<td>8 (11)</td>
<td>27 (14)</td>
</tr>
</tbody>
</table>

Conclusions

• PBC is a slowly progressive disease that is associated with morbidity and mortality
• Fatigue and pruritus limit health-related quality of life
• UDCA has been a mainstay of therapy
• Definition of UDCA nonresponse still not standardized
• OCA given to those with an inadequate response to or unable to tolerate UDCA produced a significant clinically meaningful improvement in liver biochemistry, which have been shown to correlate strongly with clinical benefit.