Primary Biliary Colangitis (PBC): Screening and Treatment

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Case Presentation

• 55-year-old Caucasian female.
• Presents for evaluation of elevated ALK PHOS (413 U/L).
• What’s your diagnosis?
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

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}

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

Factors possibly associated with onset and perpetuation of bile-duct injury in PBC

PBC is characterized by destruction of the interlobular and septal bile ducts that may lead to cirrhosis

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.

PBC Diagnostic Criteria

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

Two out of these 3 criteria are required for the diagnosis of PBC
AASLD Suggested Diagnostic Algorithm for Patients with Suspected PBC

1. Elevated serum alkaline phosphatase (ALP) activity
2. Exclude other causes of liver disease including alcohol and drugs
3. Imaging of liver to exclude biliary obstruction
4. AMA, ANA (antinuclear antibody), ASMA (anti-smooth muscle antibody)
5. Consider liver biopsy, especially if AST>5x ULN or AMA negative
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
Fatigue Is the Most Common Symptom in PBC

- Fatigue is present in up to 85% of patients with PBC
  - >40% report moderate to severe
- The mechanism of fatigue in PBC is not well understood
- Fatigue in PBC is unrelated to disease activity or stage, and tends to wax and wane throughout the course of illness
- Fatigue in PBC typically is characterized as daytime somnolence, potentially impairing QoL

Despite sparse correlation between fatigue and severity of liver disease, fatigue can be associated with decreased overall survival

Assessed and Alternate Causes of Fatigue Should Be Considered, and Coping Strategies Developed

As an initial step in fatigue management, associated and alternate causes of fatigue should be excluded and, if possible and appropriate, treated \(^1,2\)

### Associated Causes of Fatigue

- Anemia
- Depression
- Sleep disorder
- Hypothyroidism
- Type II diabetes
- Medications, including:
  - Anti-hypertensive therapy
  - Beta-blockers
- Pruritus at night
- Autonomic dysfunction
- Dehydration
- Restless legs syndrome

### EASL Guideline Recommendations: Coping Strategies \(^1\)

- EASL suggests advising patients with fatigue (which in some may be debilitating) on developing coping strategies, including the avoidance of social isolation, which can compound effects of fatigue

**Neither UDCA nor OCA has been proven to improve fatigue in patients with PBC**

Pruritus Is Common Among Patients With PBC and Can Have Negative Effects on QoL

- Pruritus occurs in 20%-70% of patients with PBC
  - Pruritus can range in severity from mild to severe
  - In most patients, pruritus is mild to moderate
- Pruritus severity is variable and not correlated to disease severity or prognosis
- Characteristics of pruritus in PBC
  - Diurnal variation: most intense itch in late evening
  - Typically localized to limbs, soles of feet, and palms of hands
  - Often exacerbated by contact with wool or other fabrics, heat, or pregnancy
- Impact of pruritus should not be underestimated – represents a significant burden for patients living with PBC
- Intractable pruritus can even lead to liver transplant

Current Guidelines Provide Non-Pharmacologic and Pharmacologic Pruritus Management Strategies

### EASL Guideline-Recommended Non-Pharmacologic Strategies

- Use of emollients and oatmeal extract to improve dry and inflamed skin
- Use of cold water for baths or showers to provide some symptom relief of pruritus triggered or exacerbated by heat/warmth (at night)
- Psychologic intervention for addictive scratching/scratch dependence
- Searching for added allergens, especially in patients with associated hypereosinophilia or IgE-mediated allergy

### AASLD and EASL Guideline-Recommended Pharmacologic Strategies

- Cholestyramine is considered first-line pharmacologic treatment for pruritus in PBC
  - 4 g per dose to a maximum of 16 g/day taken 2-4 hours before or after taking UDCA and at least 4 hours before or after taking OCALIVA
- AASLD and EASL practice guidelines provide recommendations on pharmacologic management in patients refractory to cholestyramine or first-line treatment with other bile acid sequestrants
Hyperlipidemia Is Common Among Patients With PBC

- As a result of cholestasis, hyperlipidemia is common in PBC, affecting 75%-95% of patients
- In early disease, elevated very low–density lipoprotein and LDL-C concentrations are reported, as well as significantly elevated HDL-C values
  - As disease progresses, HDL-C decreases while LDL-C may increase further
- Evidence suggests that there is no increased risk of cardiovascular disease in patients with PBC and hyperlipidemia

### AASLD Guideline Recommendations

- UDCA will lower LDL-C levels and is the initial step
- When there is also a family history of lipid abnormalities or cardiovascular disease it may still be considered appropriate, depending on the lipid pattern, to treat with cholesterol-lowering drugs

### EASL Guideline Recommendations

- In the subgroup of patients with PBC and metabolic syndrome (with high cholesterol, low HDL-C and high LDL-C levels), EASL suggests considering a pharmacologic approach with cholesterol-lowering agents on a case-by-case basis; treatment is not contraindicated

## Cholestasis- and/or Cirrhosis-Associated Complications

<table>
<thead>
<tr>
<th>Complications of chronic cholestasis</th>
<th>Patients Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>20%-44%</td>
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<tr>
<td>Vitamin deficiency</td>
<td>8%-33%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complications related to cirrhosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Varices associated with portal hypertension</td>
<td>6% (without cirrhosis)</td>
</tr>
<tr>
<td></td>
<td>~31% (with late-stage disease)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>4% with 10-year risk</td>
</tr>
</tbody>
</table>

*Current AASLD and EASL guidelines provide recommendations for the management of cholestasis- and/or cirrhosis-associated complications*
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

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

Transplant-Free Survival (%)

Time (Years)

Hazard Ratio for LT/Death According to ALP

A

At Baseline*

Thresholds (xULN) for Alkaline Phosphatase Values

Hazard Ratio for Liver Transplantation or Death

0 1 2 3 4 5

At One Year Follow-up*

Thresholds (xULN) for Alkaline Phosphatase Values

Hazard Ratio for Liver Transplantation or Death

0 1 2 3 4 5

*3710/4635 patients were included for this analysis
Risk for Disease Progression Should Be Assessed in All Patients on UDCA

Adequate response to UDCA
- Normal liver function tests

Intermediate Risk
- Intolerance/inadequate response to UDCA

High Risk
- Decompensated cirrhosis* (Child-Pugh B or C)
  - Bilirubin >3x ULN
  - Consider referral to specialist center

Low Risk
- Continue UDCA

“All patients should be evaluated for their risk of developing end-stage complications and, consequently, their potential need for additional treatments” – EASL

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)

Months in Open-Label Phase

0 3 6 9 12 60

OCA 5 mg

OCA 5-10 mg dose adjustment option

Patients Achieving the Primary Composite Endpoint at Month 12*

- Patients taking OCA were 2.5x more likely to achieve a reduction in ALP ≥15%
- 16 patients (7%) who were intolerant did not receive concomitant UDCA.

OCA POISE Trial–Titration Strategy Minimized Pruritus

Abbreviation: OCA, obeticholic acid.


Discontinued Due to Pruritus Regardless of Management Efforts

Abbreviation: OCA, obeticholic acid.

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.
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
- Mathematical models: Globe PBC, UK PBC

Staging: Transient elastography, histology, enhanced liver fibrosis score

GLOBE Score: Online Calculation

- Age at initiation of UDCA
- Total Bilirubin at 1 year
- ALP at 1 year
- Albumin at 1 year
- Platelets at 1 year

Score > 0.30 indicates decreased survival without LT. Predicts 3-, 5- and 10-year survival compared to age-matched population.
## The GLOBE score for patients with Primary Biliary Cholangitis (PBC)

The GLOBE score is an internationally relevant and validated risk assessment tool, able to stratify PBC patients to high and low risk.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Upper limit of normal:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>at initiation of UDCA therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total bilirubin level, µmol/L or mg/dl</strong></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>after one year of UDCA therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alkaline phosphatase level, U/L</strong></td>
<td>260</td>
<td>130</td>
</tr>
<tr>
<td>after one year of UDCA therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Albumin, g/L</strong></td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>after one year of UDCA therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Platelets, x 10⁹/L</strong></td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>after one year of UDCA therapy</td>
<td></td>
<td></td>
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</tbody>
</table>

**GLOBE score:** 0.46

**Liver transplant-free survival**

<table>
<thead>
<tr>
<th></th>
<th>GLOBE score</th>
<th>Mean survival of healthy patients ≤45 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year</td>
<td>94.6%</td>
<td>99.5%</td>
</tr>
<tr>
<td>5-year</td>
<td>90.5%</td>
<td>99.2%</td>
</tr>
<tr>
<td>10-year</td>
<td>76.4%</td>
<td>98.0%</td>
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Recurrent PBC after LT

Recurrent PBC after LT: Preventive UDCA Therapy

![Graph showing cumulative recurrence rate with preventive UDCA vs no preventive UDCA](image)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Preventive UDCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.31 (0.11-0.85)</td>
<td>0.014</td>
</tr>
</tbody>
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# Novel Therapies Under Evaluation for PBC

<table>
<thead>
<tr>
<th>Compound</th>
<th>NCT</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bezafibrate</td>
<td>NCT01654731</td>
<td>Pan PPAR agonist</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>NCT02823353</td>
<td>PPAR alpha agonist</td>
</tr>
<tr>
<td>Genfit</td>
<td></td>
<td>PPAR delta agonist</td>
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<tr>
<td>MBX-8025</td>
<td>NCT02955602</td>
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<tr>
<td>GS9674</td>
<td>NCT02943447</td>
<td>FXR agonist</td>
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<td>LJN452</td>
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<td>NGM 282</td>
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<td>LUM001</td>
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<tr>
<td>FFP104</td>
<td>NCT02193360</td>
<td>CD40 Inhibitor</td>
</tr>
<tr>
<td>Abatacept</td>
<td>NCT02078882</td>
<td>Inhibits T cell activation</td>
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THANK YOU!