Emerging Approaches to PBC and PSC

Keith D. Lindor, MD, FACG
Dean, College of Health Solutions
Arizona State University

OUTLINE

PBC
- Epidemiology
- Diagnosis
- Treatment

PSC
- Natural History
- Treatment
- Cancer
PBC Prevalence

PBC Incidence

Predictors of Prognosis

Higher APRI is Associated with Poorer Transplant-Free/Overall Survival in PBC
Survival Rates, Elastography & PBC

Role of Liver Biopsy in PBC

If:
- AMA
- Alk Phos >1.5 times nl
- AST <5 times normal

Then:
- Positive predictive value for PBC >98% 
  (sensitivity 80%, specificity 92%)

Predictors of Esophageal Varices in PBC

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Count</td>
<td>&lt;140,000</td>
</tr>
<tr>
<td>Mayo Risk Score</td>
<td>≥4.5</td>
</tr>
</tbody>
</table>
Medical Approaches to PBC UDCA

Survival Free of Transplantation
Combined Data

Probability of survival %

Survival Free of Transplantation
Combined Data

Survival in PBC

Treated vs. Untreated

Treated vs. Population


Natural History of PBC Effects of UDCA

- Ursodiol Alone
  - Biochemical normalization in ~1/3
  - Risk scores or alkaline phosphatase response predictive*
  - Various drugs tried in combination

Combination Therapy for PBC


Biochemical Endpoints for Predicting Outcomes

- Bezafibrate/Fenofibrate
- Silymarin
- B cell antibodies
- FXR agonists
OCA Treatment in Patients with PBC


Decreases in ALP Values during DB Phase

Change in ALP Values in Completer Population

Decreases in ALP Values during Open-Label Extension

Change in ALP Values during Open-Label Extension

Pruritus Severity in PBC Patients with OCA

**Conclusion Regarding Drug Therapy**

When UDCA is not adequate:
- Doubling dose is not helpful
- No clear, proven choices
- Many promising adjuncts being investigated

**Hepatocellular Cancer Risk in PBC**

- 18 Patients over 25 years
- Multivariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>O.R</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.6</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Male</td>
<td>5.6</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Hx Transfusion</td>
<td>4.7</td>
<td>&lt;.07</td>
</tr>
<tr>
<td>Mayo Risk</td>
<td>1.3</td>
<td>&lt;.02</td>
</tr>
</tbody>
</table>
Conclusions About PBC

- Becoming more common
- Slowly progressive, even if asymptomatic
- Prognostic markers helpful
- UDCA improves natural history
- Cancer risk is present
Histologic Features of PSC
Liver Transplantation for PBC & PSC


PSC Survival in Olmsted County Minnesota

Ursodiol in PSC

High-dose Urso for PSC Results

<table>
<thead>
<tr>
<th>Primary Endpoints</th>
<th>UDCA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Liver Transplant</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Minimal Listing Criteria for Liver Transplant</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Development of Cirrhosis</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Esophageal and/or Gastric Varices</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total Endpoints</strong></td>
<td><strong>52</strong></td>
<td><strong>29</strong></td>
</tr>
</tbody>
</table>
Results

Model Of All Primary Endpoints
Adjusted For Mayo Risk Score, Presence of Varices, and Stage

Kaplan-Meier Analysis of Endpoint Free Survival in all PSC Patients with UDCA Treatment
Immunosuppressive and Other Agents

- Azathioprine
- Budesonide
- Docosahexaenoic acid
- Methotrexate
- Metronidazole
- Minocycline
- Mycophenolate mofetil
- Nicotine
- Pentoxifylline
- Pirfenodone
- Prednisolone
- Tacrolimus
- Vancomycin

Vancomycin & Metronidazole in PSC

Autoimmune Pancreatitis/Cholangitis in PSC

- IgG4 elevated in 9% PSC patients
- These patients have more aggressive disease
- These patients may be more steroid responsive.

Natural History “PSC” & IgG4

Association of IgG4 and Colectomy

Incidence of Cholangiocarcinoma
Elevated CA 19-9 Values in PSC

*7 bars represent interquartile range of the values

Colon Cancer/IBD/PSC
High-Dose Urso in UC & PSC Patients

Eaton J, Silveira MG, Pardi DS, et al. High-dose ursodeoxycholic acid is associated with the development of colorectal neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. Am J Gastroenterol 2011;106(9):1638-45

UDCA and Risk of Colorectal Neoplasia in Patients with PSC - IBD

UDCA and Risk of Advanced Colorectal Neoplasia in Patients with PSC - IBD

<table>
<thead>
<tr>
<th>Study name</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braden 2012</td>
<td>1.420</td>
<td>0.067</td>
<td>30.246</td>
</tr>
<tr>
<td>Eaton 2011</td>
<td>1.261</td>
<td>0.165</td>
<td>9.648</td>
</tr>
<tr>
<td>Lindstrom 2012</td>
<td>0.326</td>
<td>0.033</td>
<td>3.254</td>
</tr>
<tr>
<td>Pardi 2003</td>
<td>0.146</td>
<td>0.007</td>
<td>3.193</td>
</tr>
<tr>
<td>Wolf 2005</td>
<td>0.616</td>
<td>0.165</td>
<td>2.304</td>
</tr>
<tr>
<td>Tung 2001</td>
<td>0.099</td>
<td>0.022</td>
<td>0.442</td>
</tr>
<tr>
<td>Ullman 2003</td>
<td>0.233</td>
<td>0.038</td>
<td>1.429</td>
</tr>
<tr>
<td></td>
<td>0.349</td>
<td>0.167</td>
<td>0.729</td>
</tr>
</tbody>
</table>

Take Home Points

PBC
- Ursodiol is treatment
- Obeticholic acid promising
- Liver cancer risk present

PSC
- No established therapy
- Ursodiol role being defined
- High does UDCA (28 – 30 mg/kg/day) to be avoided
- Risk of bile duct and colon cancer