Current Perspectives in the Treatment of PSC
Defining Targets for Treatment
Pathology of Primary Sclerosing Cholangitis
Fibrous Obliterative Cholangitis of Medium to Large Caliber Ducts
Pathology Primary Sclerosing Cholangitis

Small Ducts

Medium Ducts
Pathogenesis of Primary Sclerosing Cholangitis

Adaptive Immunity + Innate Immunity

Bacterial Molecules Into Portal Vein

Ulcerative or Crohn’s Colitis

Cytokines, Chemokines, Fibrosing Inflammation

Bile Regurgitation

Abnormal Cholangiocyte Functions

Displacement Of Arterial Vessels

Atrophy of Cholangiocytes

Immune and Other Genetic Susceptibilities

Atrophy of Cholangiocytes
Types of PSC
How many clinical types of PSC are now included in its diagnostic classification?

1. 1
2. 2
3. 3
4. 4
5. 5
6. 6
How many clinical types of PSC are now included in its diagnostic classification?

1. 1
2. 2
3. 3
4. 4
Clinical Categories of PSC

1. Typical PSC
2. Small duct PSC
3. AIH – PSC
4. IAC – Immunoglobulin G4 – associated cholangitis
The Cholangiography (ERCP) of PSC

1. Typical PSC: Intra- and extra-hepatic strictures
2. Small duct PSC: Normal
3. AIH – PSC: same as typical PSC
4. IAC – Immunoglobulin G4 – associated cholangitis: same as typical PSC, pancreatic involvement
The Pathology of PSC

1. Typical PSC: Concentric ductal fibrosis

2. Small duct PSC: Same as typical PSC

3. AIH – PSC: lymphoplasmacytic infiltration, interface hepatitis

4. IAC – Immunoglobulin G4 – associated cholangitis: lymphoplasmacytic infiltration with >10 IgG4-positive cells per hpf
The Diagnosis of PSC

1. Typical PSC: MRCP

2. Small duct PSC: Liver Biopsy

3. AIH – PSC: Liver Biopsy

4. IAC – Immunoglobulin G4 – associated cholangitis: MRCP; Liver Biopsy
The Medical Treatment of PSC
What medical therapies have been shown to prevent progression of typical PSC?

1. Low dose UDCA
2. High dose UDCA
3. Corticosteroids
4. Azathioprine
5. Cyclosporine, Tacrolimus
6. Methotrexate
7. Anti-TNF-α drugs
No obvious or Consistent Clinical Benefit.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Treatment</th>
<th>N (treat/placebo)</th>
<th>Study duration</th>
<th>Lab</th>
<th>Histology</th>
<th>OLT-free survival</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>La Russo et al.</td>
<td>1988</td>
<td>Penicillamine</td>
<td>70 (39/31)</td>
<td>3 years</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>No effect on liver tests, histology or survival</td>
</tr>
<tr>
<td>Knox et al.</td>
<td>1994</td>
<td>Methotrexate</td>
<td>24 (12/12)</td>
<td>2 years</td>
<td>+ (ALP only)</td>
<td>—</td>
<td>—</td>
<td>Improved ALP. No effect on histology, cholangiography or outcome</td>
</tr>
<tr>
<td>Olsson et al.</td>
<td>1995</td>
<td>Colchicine</td>
<td>84 (44/40)</td>
<td>3 years</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>No effect on liver tests, histology or survival</td>
</tr>
<tr>
<td>Sterling et al.</td>
<td>2004</td>
<td>Mycophenolate mofetil/UDCA vs. UDCA</td>
<td>25 (12/13)</td>
<td>2 years</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>No effect on liver tests, histology, cholangiography or Mayo Risk Score</td>
</tr>
<tr>
<td>Farkkila et al.</td>
<td>2004</td>
<td>Metronidazole/UDCA</td>
<td>80 (39/41)</td>
<td>36 months</td>
<td>+</td>
<td>(+)</td>
<td>—</td>
<td>Improved liver tests and Mayo Risk Score, but no improvement in histology or cholangiography</td>
</tr>
<tr>
<td>Hommes et al.</td>
<td>2008</td>
<td>Infliximab</td>
<td>10 (6/4)</td>
<td>12 months</td>
<td>—</td>
<td>—</td>
<td>ND</td>
<td>Patient enrolment was prematurely stopped when interim analysis showed no treatment benefit. No effect on liver tests, histology</td>
</tr>
</tbody>
</table>
Current Treatment for PSC: UDCA?
By Clinical Category of PSC

1. Typical PSC: UDCA?; Stricture management; CCA screening

2. Small duct PSC: UDCA?; Rarely need Stricture management; CCA screening

3. AIH – PSC: UDCA?; Stricture management; Corticosteroids/Azathioprine for AIH component

4. IAC – Immunoglobulin G4 – associated cholangitis: UDCA?; Stricture management; Corticosteroids/Azathioprine
Ursodeoxycholate
Standard Doses (15 mg/kg/d)
UDCA may reduce risk for Colon Cancer in PSC

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Odds ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>Lower limit</td>
</tr>
<tr>
<td>Braden 2012</td>
<td>1.420</td>
<td>0.067</td>
</tr>
<tr>
<td>Eaton 2011</td>
<td>1.261</td>
<td>0.165</td>
</tr>
<tr>
<td>Lindstrom 2012</td>
<td>0.326</td>
<td>0.033</td>
</tr>
<tr>
<td>Pardi 2003</td>
<td>0.146</td>
<td>0.007</td>
</tr>
<tr>
<td>Wolf 2005</td>
<td>0.616</td>
<td>0.165</td>
</tr>
<tr>
<td>Tung 2001</td>
<td>0.099</td>
<td>0.022</td>
</tr>
<tr>
<td>Ullman 2003</td>
<td>0.233</td>
<td>0.038</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Dose (mg/kg bw/day)</th>
<th>N (treat/control)</th>
<th>Study duration</th>
<th>Lab</th>
<th>Histology</th>
<th>CCA</th>
<th>OLT-free survival</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>O'Brien et al.</td>
<td>1991</td>
<td>10</td>
<td>12*</td>
<td>2.5 years</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Improvement of liver tests in treatment periods and worsening in nontreatment periods</td>
</tr>
<tr>
<td>Beuers et al.</td>
<td>1992</td>
<td>13–15</td>
<td>14 (6/8)</td>
<td>1 year</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>Significant improvement in liver biochemistry</td>
</tr>
<tr>
<td>Stiehl et al.</td>
<td>1994</td>
<td>750/day†</td>
<td>20 (10/10)</td>
<td>3 months</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Significant improvement in liver tests</td>
</tr>
<tr>
<td>De Maria et al.</td>
<td>1996</td>
<td>300 b.d.†</td>
<td>40 (20/20)</td>
<td>2 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No effect on liver tests or cholangiography</td>
</tr>
<tr>
<td>Lindor et al.</td>
<td>1997</td>
<td>13–15</td>
<td>102 (51/51)</td>
<td>2.2 years</td>
<td>+</td>
<td>−</td>
<td>ND</td>
<td>−</td>
<td>No significant effect on primary end-points (death, OLT, histology, lab)</td>
</tr>
<tr>
<td>Mitchell et al.</td>
<td>2001</td>
<td>20</td>
<td>26 (13/13)</td>
<td>2 years</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>UDCA group had improved liver test results, histology and cholangiography</td>
</tr>
<tr>
<td>Harnois et al.</td>
<td>2001</td>
<td>25–30</td>
<td>30‡</td>
<td>1 year</td>
<td>+</td>
<td></td>
<td>ND</td>
<td>ND</td>
<td>Improved Mayo Risk Score for UDCA vs. placebo and for high-dose vs. low-dose UDCA</td>
</tr>
<tr>
<td>Olsson et al.</td>
<td>2005</td>
<td>17–23</td>
<td>198 (97/101)</td>
<td>5 years</td>
<td>(+)</td>
<td>ND</td>
<td>−</td>
<td>−</td>
<td>No effect on death, OLT, CCA or liver tests</td>
</tr>
<tr>
<td>Lindor et al.</td>
<td>2009</td>
<td>28–30</td>
<td>149 (76/73)</td>
<td>6 years</td>
<td>+</td>
<td></td>
<td>ND</td>
<td>−</td>
<td>Terminated at 6 years as worse outcome in treatment group for death or OLT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Improved liver tests in UDCA group</td>
</tr>
</tbody>
</table>
Ursodeoxycholate
High Doses (28 to 30 mg/kg/d)
Endpoints: Death, Liver Transplantation, Meeting Minimal Listing Criteria, Varices, CCA, Progress to Cirrhosis

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

p = 0.008

High Dose UDCA Increases Risk for Complications?

High Dose UDCA Increases Mortality in Early PSC?

UDCA, What’s the Verdict? Friend or Foe?

1. Certainly UDCA does not benefit all patients
2. Low or normal Alkaline Phosphatase is associated with better prognosis
3. Trial of UDCA, 15 mg/kd/d, in divided doses – check Alk Phos over 3 – 6 months
4. Responders (nl Alk Phos, or >50% reduction in Alk Phos) – stay on UDCA
Emerging Treatments
What are the novel emerging treatments?

1. Vancomycin, microbiota therapy
2. Tumor Necrosis Factor (TNF-α) antagonists
3. Interleukin blockade
4. α-Integrin antagonists
5. FXR Agonists
6. Anti-fibrotic drugs
Oral Vancomycin
Case Report Suggesting Benefit of Vancomycin
15 yo with PSC recurrence after liver transplantation

Prior to Vancomycin

During Vancomycin, 500 tid po

Long-Term Vancomycin: Non-cirrhotic Patients

Long-Term Vancomycin: Cirrhotic Patients

Randomized Controlled Trial

Vancomycin: low vs high dose
Metronidazole: low vs high dose
Vancomycin Arms
Low dose (125 mg po q6h) Vs
High Dose (250 mg po q6h)

Metronidazole Arms
Low dose (250 mg po tid) Vs
High Dose (250 mg po tid)

Vancomycin, What’s the Verdict? Friend or Foe?

1. Certainly Vancomycin does not benefit all patients

2. Unique safety consideration – emergence of vancomycin-resistant organisms

3. Not recommended for routine use – until there are more clinical trial data to support benefit and determine long-term risk
Antibiotic Treatment to Modify the Microbiota
### Past Experience with Antibiotics for PSC

**Table 1** | Previously reported results of antibacterial treatment in primary sclerosing cholangitis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year</th>
<th>n</th>
<th>Antibiotic dose</th>
<th>Months of therapy</th>
<th>ALK</th>
<th>AST</th>
<th>ALT</th>
<th>GGT</th>
<th>% change from baseline post-therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline&lt;sup&gt;32,†&lt;/sup&gt;</td>
<td>1959</td>
<td>5</td>
<td>500 mg/day</td>
<td>1–10</td>
<td>-45</td>
<td>-60</td>
<td>-45</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Tetracycline&lt;sup&gt;36,‡&lt;/sup&gt;</td>
<td>1965</td>
<td>5</td>
<td>500 mg/day</td>
<td>48 (mean)</td>
<td>+21</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Sulphasalazine (+UDCA)&lt;sup&gt;34,§&lt;/sup&gt;</td>
<td>1998</td>
<td>2*</td>
<td>-</td>
<td>30</td>
<td>-79</td>
<td>-38</td>
<td>-70</td>
<td>-26</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45</td>
<td>-35</td>
<td>-87</td>
<td>-95</td>
<td>-94</td>
</tr>
<tr>
<td>Vancomycin&lt;sup&gt;28&lt;/sup&gt;</td>
<td>1998</td>
<td>3*</td>
<td>375–1000 mg/day</td>
<td>9 (mean)</td>
<td>-</td>
<td>-</td>
<td>-89</td>
<td>-93</td>
<td></td>
</tr>
<tr>
<td>Sulphasalazine (+UDCA)&lt;sup&gt;35&lt;/sup&gt;</td>
<td>2002</td>
<td>1</td>
<td>50 mg/kg/day</td>
<td>37</td>
<td>-</td>
<td>-</td>
<td>-92</td>
<td>-83</td>
<td></td>
</tr>
<tr>
<td>Metronidazole (+UDCA)&lt;sup&gt;38&lt;/sup&gt;</td>
<td>2004</td>
<td>39</td>
<td>600–800 mg/day</td>
<td>36</td>
<td>-52.4</td>
<td>-41.0</td>
<td>-67.9</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Sulphasalazine&lt;sup&gt;29&lt;/sup&gt;</td>
<td>2006</td>
<td>1</td>
<td>2–4.5 g/day</td>
<td>24</td>
<td>-74</td>
<td>-</td>
<td>-84</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Azithromycin (+UDCA)&lt;sup&gt;33&lt;/sup&gt;</td>
<td>2007</td>
<td>1</td>
<td>500 mg/day, 3 days/week</td>
<td>5</td>
<td>-72</td>
<td>-31</td>
<td>-33</td>
<td>-54</td>
<td></td>
</tr>
<tr>
<td>Vancomycin&lt;sup&gt;27&lt;/sup&gt;</td>
<td>2008</td>
<td>14*</td>
<td>50 mg/kg/day</td>
<td>54 ± 43</td>
<td>-</td>
<td>-</td>
<td>-78</td>
<td>-89</td>
<td></td>
</tr>
<tr>
<td>Minocycline&lt;sup&gt;39&lt;/sup&gt;</td>
<td>2009</td>
<td>16</td>
<td>200 mg/day</td>
<td>12</td>
<td>-19.7</td>
<td>-2.8</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

ALK, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, \( \gamma \)-glutamyl transpeptidase; q.d., four times a day; UDCA, ursodeoxycholic acid.

Months of treatment and follow-up are absolute unless otherwise indicated.

Table adapted from Elfaki and Lindor.<sup>37</sup>

* Paediatric patients.

† Includes one patient who also received prednisone but was not separable from the other four patients.

‡ Does not include two patients who received prednisone.

§ Does not include a third patient who also received prednisolone and mizoribine.

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Inhibiting Inflammatory Responses
CUC at Colonoscopy
PSC at Cholangioscopy

Normal

PSC Stricture
TNF-α Antagonists
Could this work for patients with PSC? One small study stopped early – no effect.

Interleukin Blockade
Ustekinimab Mechanism of Action

**IL-12**
- p-40
- p-35
- Ustekinumab

**IL-23**
- p-40
- p-19
- Ustekinumab

**Cell Membrane**
- IL-12Rβ1
- IL-12Rβ2

- No Th 1 Signaling
  - (TNF-α, IFN-γ, IL-2)

- IL-23R
- IL-12Rβ1

- No Th 17 Signaling
  - (IL-6, -17, -21, -22, TNF-α, IFN-γ)
Ustekinimab for Psoriasis

Before

After
α-Integrin Antagonists
FXR Agonists
Figure 1  Graphic representation of a bile-acid molecule (taurocholate).
Enterohepatic Circulation of Bile Acids
Figure 3  Diagrammatic representation of the cellular adaptive response to cholestasis.
Obeticholic Acid

1. **PBC Trial, Phase 3**: Placebo 73 pts, OCA 5 mg 70 pts, OCA 10 mg 73 pts. Met endpoints for Alk Phos and Bili. But, pruritus in 68% in 10 mg/d arm – only 6% withdrew for pruritus. ?Will FDA approve for PBC?

2. **NAFLD Trial**: Beneficial biochemical effects. Question of dyslipidemia?
Anti-fibrotics
LOX-L2 inhibitor

Galectin inhibitor

Others
Conclusion about Treatment

The Future looks promising –

Hopefully the options for treatment will Expand and improve!!