Current treatment and management challenges of sclerosing cholangitis

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OUTLINE

- Natural History
- Treatment
- Cancer
Histologic Features of PSC

Liver Transplantation for PBC and PSC

Liver Transplantation for PBC and PSC

PSC Survival in Olmsted County Minnesota

Survival Rates, Elastography and PSC

470 patients with IBD

- 322 screened by MRC (20 years later)
  - 24 patients (7.4%) found to have PSC like lesions
    - Only 7 of these patients (2.2%) were known to have PSC

65% of patients had subclinical PSC associated with progressive IBD and normal liver tests.
Small Duct PSC

- 5% of PSC
- Normal cholangiogram but biopsy showing PSC
- Can progress to classic PSC
Survival in PSC Small Duct vs. Large

Ursodiol in PSC
Small Duct PSC Treated vs. Untreated

## 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


1. Normal alkaline phosphatase is better regardless
2. 35% of placebo developed normal alkaline phosphatase
3. 45% were UDCA treated
Treatments Examined

- Budesonide
- Docosahexaenoic acid
- Bezafibrate
- Minocycline
- Mycophenolate mofetil
- Nicotine
- Pentoxifylline
- Pirfenidone
Emerging Treatments

- Altering the Microbiome
- Vancomycin
- Obeticholic Acid
- Mitomycin C
- BTT1023
- Simtuzumab
- N-acetylcysteine
- Nor ursodeoxycholic acid
Vancomycin & Metronidazole in PSC

Relative Changes in ALP from Baseline to End of Treatment with nor-Urso

Values (%) are means (SD)

- IgG4 elevated in 9% PSC patients
- These patients have more aggressive disease
- These patients may be more steroid responsive.
Natural History “PSC” & IgG4

Elevated immunoglobulin G4 level is associated with reduced colectomy-free survival in patients with primary sclerosing cholangitis and ulcerative colitis. Journal of Crohn’s and Colitis. 2013; 7: e35–e41.

P = 0.026
Percentage Specific IgG4 RNA Molecules of total IgG4

Incidence of Cholangiocarcinoma

Years since PSC diagnosis

Cumulative incidence of Cholangiocarcinoma (%)
Elevated CA 19-9 Values in PSC

* T bars represent interquartile range of the values

Colon Cancer/IBD/PSC

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>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>
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<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>
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<tr>
<td>Pardi 2003</td>
<td>0.146</td>
<td>0.007</td>
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<tr>
<td>Wolf 2005</td>
<td>0.616</td>
<td>0.165</td>
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<tr>
<td>Tung 2001</td>
<td>0.099</td>
<td>0.022</td>
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<tr>
<td>Ullman 2003</td>
<td>0.233</td>
<td>0.038</td>
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</tbody>
</table>

CONCLUSIONS

- 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