CURRENT AND FUTURE THERAPY FOR PRIMARY SCLEROSING CHOLANGITIS

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Rochester, MN
OVERVIEW

- Review of Pathogenetic Mechanics
- Potential Targets for Therapy
- Review of Experiences
LIVER TRANSPLANTATION FOR PBC & PSC

REVIEW OF PATHOGENETIC MECHANICS (NIH CONFERENCE)

- Genetic
- Transporter Defects
- Autoimmunity
- Infection Agents
- Innate Immunity
- Cholestasis and Cell Injury
POTENTIAL TARGETS

- Bacterial Infection
- Receptor Function
- Apoptosis
- Immunologic Abnormalities
- Fibrosis
INITIAL EXPERIENCES

- Bacterial Links
Animal Model of Small Bowel Bacterial Overgrowth (blind jejunal loop)

1) Hepatic Inflammation in Rats with Experimental Small Intestinal Bacterial Overgrowth. (Gastroenterology 1990;98:414-23)

2) Biliary Tract Disease in Rats with Experimental Small Bowel Bacterial Overgrowth. (Hepatology 1991;13:766-72)

3) Evidence of Peptidoglycan Absorption in Rats with Experimental Small Bowel Bacterial Overgrowth. (Infection and Immunity 1991;59:555-62)
Animal Model of Small Bowel Bacterial Overgrowth (blind jejunal loop)

4) Hepatic Injury Associated with Small Bowel Bacterial Overgrowth in Rats is Prevented by Metronidazole and Tetracycline. (Gastroenterology 1992;100:513-19)

5) Hepatic Injury Associated with Small Bowel Bacterial Overgrowth in Rats is Prevented by Metronidazole and Tetracycline. (Gastroenterology 1992;100:513-19)

6) Inhibition of Endogenous TNF Formation by Pentoxifylline. (Immunobiology 1993;187:447-63)
PENTOXIFYLLINE IN PSC

ANTIBACTERIAL AGENTS

- Metronidazole and UDCA for PSC
  - A randomized trial
    - 80 patients
    - UDCA (15 mg/kg/d)
    - UDCA and Metronidazole (600-800 mg/d)
    - 3 years
METRONIDAZOLE AND UDCA FOR PSC

# Other Antibiotics in PSC

<table>
<thead>
<tr>
<th>Drug</th>
<th># Months</th>
<th>ALP</th>
<th>AST</th>
<th>ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline (n=5)</td>
<td>1-10</td>
<td>-45</td>
<td>-60</td>
<td>-45</td>
</tr>
<tr>
<td>Vancomycin (short term) (n=3)</td>
<td>Mean 9</td>
<td>--</td>
<td>--</td>
<td>-89</td>
</tr>
<tr>
<td>Vancomycin (long term) (n=14)</td>
<td>54±43</td>
<td>--</td>
<td>--</td>
<td>-78</td>
</tr>
<tr>
<td>Azithromycin (n=1)</td>
<td>5</td>
<td>-72</td>
<td>-31</td>
<td>-33</td>
</tr>
</tbody>
</table>

TRANSPORTER DEFECTS/
RECEPTOR FUNCTION IN PSC
IS PSC ASSOCIATED WITH DEFECTS IN CFTR?

- Etiology of PSC is unknown
  - 5% of IBD patients develop PSC
  - 80% of PSC patients have IBD
- Exaggerated fibroinflammatory response
- PSC has similar cholangiographic and histologic appearances as seen in cystic fibrosis liver disease

Courtesy of S. Freedman, Boston, MA
HYPOTHESIS

- PSC
  - Defect in the innate immune system
  - Liver exposed to pathogenic bacteria secondary to colitis

- CFTR dysfunction
  - Defect in the innate immune system
  - Decreased PPAR α and γ involving epithelial cells and monocytes
  - Pathogenic bacteria

Courtesy of S. Freedman, Boston, MA
CFTR FUNCTION IS ABNORMAL IN ADULT PATIENTS WITH PSC: NASAL PD MEASUREMENTS

 Courtesy of S. Freedman, Boston, MA
STUDY DESIGN

- Pilot open label trial of DHA in adults with PSC
- 28 subjects will be given 2.4 gm of DHA (four 200mg DHA capsules tid) for 48 weeks
- PSC confirmed by liver biopsy and/or cholangiography
- Assessed every 4 wks for the first 3 months, then every 8 wks until study completion

Courtesy of S. Freedman, Boston, MA
DOCOSAHEXAENOIC ACID (DHA) FOR PSC

12 months, 28 patients

Fatigue improved ≤ 70%

Baseline
9 months of DHA

p < 0.01
NUCLEAR RECEPTORS (FXR, CXR, PXR)

- Involved in multiple steps in bile acid and bilirubin metabolism
  - Uptake
  - Synthesis
  - Conjugation
  - Export
APOPTOSIS AND PSC

- Less work than in PBC
- Evidence not strong
# APOPTOSIS OF BILIARY EPITHELIAL CELLS WITH PBC AND PSC

<table>
<thead>
<tr>
<th></th>
<th>TUNEL Staining Score (TSS)</th>
<th>P-value (compared to PBC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBC (n=13)</td>
<td>22.2</td>
<td>-</td>
</tr>
<tr>
<td>PSC (n=12)</td>
<td>12.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Normal (n=10)</td>
<td>14.5</td>
<td>0.01</td>
</tr>
</tbody>
</table>

# APOPTOSIS OF BILIARY EPITHELIAL CELLS IN PBC AND PSC

<table>
<thead>
<tr>
<th></th>
<th>TSS in Inflamed Ducts (grades 1-3)</th>
<th>TSS in Non-Inflamed Ducts (grade 0)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBC (n=12)</td>
<td>23.4</td>
<td>16.8</td>
<td>0.03</td>
</tr>
<tr>
<td>PSC (n=11)</td>
<td>10.2</td>
<td>12.3</td>
<td>0.13</td>
</tr>
<tr>
<td>Normal (n=8)</td>
<td>14.1</td>
<td>12.4</td>
<td>0.30</td>
</tr>
</tbody>
</table>

MINOCYCLINE IN PSC

- Reduces iNOS
  - NO implicated in carcinogen
  - Inhibits DNA repair
  - Promotes angiogenesis
  - Inhibits apoptosis
IMMUNOLOGIC ABNORMALITIES

- Mycophenolate Mofetil (Cellcept)
- Tacrolimus
- Budesonide
- IgG4
### MYCOPHENOLATE MOFETIL FOR THE TREATMENT OF PSC

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post-Rx</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alk. phos. (IU/L)</td>
<td>1135±581</td>
<td>912±463</td>
<td>0.02</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>102±48</td>
<td>97±64</td>
<td>0.4</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>1.1±0.6</td>
<td>1.3±1.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.9±0.3</td>
<td>3.8±0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Mayo risk score</td>
<td>0.57±0.76</td>
<td>0.66±1.1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Baseline and 1-yr posttreatment serum liver biochemistry values in patients with PSC

MYCOPHENOLATE MOFETIL FOR THE TREATMENT OF PSC

Nausea/abdominal pain (2 patients)
Diarrhea (1 patient)
Sore throat (1 patient)
Noncompliance (1 patient)

Potential drug-related adverse events from MMF resulting in study withdrawal

MYCOPHENOLATE MOFETIL IN PSC: LIVER BIOCHEMISTRY VALUES

MYCOPHENOLATE MOFETIL IN PSC: LIVER BIOCHEMISTRY VALUES

TACROLIMUS IN PSC

15 patients, one year, 0.05 mg/kg bid (3-7 mg/wk)

p < .0001

AST unchanged
7/15 required dose reduction
8/15 dropped out

Alkaline Phosphatase

Talwalkar J. Gastroenterology 2005;128(4):A775
TACROLIMUS IN PSC

10 patients, 1 year, serum FK 506 level of 0.6 to 1.0 ng/ml

BUDESONIDE IN PSC

BUDESONIDE IN PSC

AUTOIMMUNE PANCREATITIS/CHOLANGITIS IN PSC

- IgG4 elevated in 9% PSC patients
- These patients may be more steroid responsive.
ANTI-TNF AGENTS

- Silymarin
- Pentoxifylline
- Etanercept
- Adalimumab
- Thalidomide
SILYMARIN IN PSC

30 patients, 23 completed one year, 140 mg tid,

P=0.007

P=0.01
PENTOXIFYLLINE IN PSC

MEDICAL THERAPY IN PSC - ETANERCEPT

10 patient pilot, 6 months duration

<table>
<thead>
<tr>
<th></th>
<th>Alk Phos (IU)</th>
<th>Total Bilirubin (mg/dl)</th>
<th>ALT (U/L)</th>
<th>Albumin (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>310</td>
<td>2.0</td>
<td>89</td>
<td>3.6</td>
</tr>
<tr>
<td>After</td>
<td>401</td>
<td>3.6</td>
<td>139</td>
<td>3.6</td>
</tr>
<tr>
<td>Mean</td>
<td>310</td>
<td>2.0</td>
<td>89</td>
<td>3.6</td>
</tr>
<tr>
<td>P Value</td>
<td>0.171</td>
<td>0.026</td>
<td>0.076</td>
<td>0.718</td>
</tr>
</tbody>
</table>

Conclusion: Etanercept not effective

CYTOKINES THAT PROMOTE FIBROGENESIS

- Monocyte chemotactic protein type 1
- TGF B1
- PDGF
- Norepinephrine
- Angiotensin II
- NADPH oxidase
- Endothelin-1
- Adipokines
- Leptin
ANTIFIBROTIC THERAPY

- Pirfenidone
- Angiotensin system
  - Moexipril
  - Genetic Model
  - Other Inhibitors (ACE)
- Sirolimus/rapamycin
PIRFENIDONE IN PSC

PIRFENIDONE IN PSC

PIRFENIDONE IN PSC

ACE INHIBITORS

■ Antioxidant

■ Antifibrotic
  – Reduces stellate cell proliferation
  – Reduces TGFβ expression

■ Effective in reducing fibrosis in animal models of cholestasis (Gastroenterology 2001;121:148-55)
ACE INHIBITORS/ARB IN HUMAN DISEASE

- Short term
- Usually small
- Retrospective reviews of HTN treatment
- Promising effects on liver and fibrosis markers
SIROLIMUS (RAPAMYCIN)

- Inhibits T cell activation
- Inhibits antibody production
- Promotes apoptosis
- Induces TGFβ production
- May be antifibrotic

UDCA IS A LOGICAL THERAPY FOR PSC

- Improves liver tests
- Improves histology
- Improves cholangiogram
- Reduces cancer risk
- May improve survival
UDCA IMPROVES LIVER TESTS IN PSC

Lindor K, et al NEJM 1997;336:691-95
UCDA IMPROVES HISTOLOGY

P<0.05

UDCA IMPROVES CHOLANGIOGRAM


P<0.015
### UDCA IMPROVES CANCER RISK

**Multivariate Analysis of Risk Factors for Dysplasia***

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted Odds Ratio for Risk of Dysplasia (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ursodiol use</td>
<td>0.14 (0.03-0.64)</td>
<td>0.01</td>
</tr>
<tr>
<td>Age at onset of colitis†</td>
<td>0.49 (0.25-0.95)</td>
<td>0.04</td>
</tr>
<tr>
<td>Duration of ulcerative colitis‡‡</td>
<td>0.86 (0.38-2.0)</td>
<td>&gt;0.2</td>
</tr>
</tbody>
</table>

*Adjusted for sex, age at onset of colitis, duration of colitis, duration of PSC, Child-Pugh, class, use of ursodiol, and use of sulfasalazine.

†Odds ratio for a 10-year increase in age at onset of ulcerative colitis
‡Odds ratio for a 10-year increase in duration of ulcerative colitis

UDCA IMPROVES CANCER RISK COLON


P<0.034
**UDCA MAY IMPROVE CANCER RISK**

**BILE DUCT**

<table>
<thead>
<tr>
<th>Trial</th>
<th># pts.</th>
<th>Average follow-up</th>
<th>UDCA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindor</td>
<td>105</td>
<td>2.2 yr</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Olsson</td>
<td>229</td>
<td>5 yr</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Olsson RG, et al. J Hepatol 2004;40(1)161
Lindor K, et al. NEJM 1997;336:691-95
UDCA MAY IMPROVE SURVIVAL

Lindor K, et al NEJM 1997;336:691-95
PRIMARY SCLEROSING CHOLANGITIS

High-dose URSO in PSC

UDCA MAY IMPROVE SURVIVAL

High-dose URSO in PSC

P = 0.002

FIVE YEAR TREATMENT WITH HIGH DOSE UDCA IN PSC

- 219 Scandinavian patients
- 17-23 mg/kg/d UDCA vs. placebo
  - Death or Transplant
  - UDCA: 7.2%  
  - Placebo: 10.9%  
    (p=0.37)
- Symptoms and quality of life not different
- Initially had estimated 396 patients needed

Olsson RG, et al. J Hepatol 2004;40(1)161
UDCA MAY IMPROVE SURVIVAL

Differences not significant

Olsson RG, et al. J Hepatol 2004;40(1)161
SHOULD UDCA BE USED TO TREAT PSC?

Need well designed clinical trial to truly answer

- NIH Sponsored
- High dose (28-30 mg/kg/day) UDCA in PSC
- 150 patients, minimum 5 year follow-up
- Endpoints: cirrhosis, varices, cancer, OLT, death
NIH SPONSORED STUDY FOR UDCA IN PSC

150 patients from the following sites:

- Mayo Clinic; Rochester, MN
- Mayo Clinic; Jacksonville, FL
- Mayo Clinic; Scottsdale, AZ
- Medical College of Virginia; Richmond; VA
- St. Louis University; St. Louis, MO
- University of Nebraska Med. Ctr; Omaha, NE
- University of Washington; Seattle, WA
## RESULTS

### Primary Endpoints

<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>Total Endpoints</td>
<td>52</td>
<td>29</td>
</tr>
</tbody>
</table>

RESULTS

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

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>Time to Event (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UDCA</td>
<td>76  73  60  51  34  18  9  0</td>
</tr>
<tr>
<td>PLACEBO</td>
<td>74  65  60  58  41  24  7  0</td>
</tr>
</tbody>
</table>

p = 0.008

CONCLUSION

- Various potential mechanisms
- Many agents to test
- Need pilot studies initially
- Followed by large scale randomized trial with clinically relevant endpoints