URSODEOXYCHOLIC ACID FOR THE TREATMENT OF PSC

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OUTLINE

- Survival
- PBC vs. PSC
- IgG4 and Small-duct PSC
- Urso for PSC
- Other Therapy
- High Dose Trial
Natural History of PSC

PSC SURVIVAL IN OLMSTED COUNTY MINNESOTA

LIVER TRANSPLANTATION FOR PBC & PSC

AUTOIMMUNE PANCREATITIS/CHOLANGITIS IN PSC

- IgG4 elevated in 9% PSC patients
- These patients may be more steroid responsive.
NATURAL HISTORY “PSC” & IgG4

CLINICAL PRESENTATION

- Laboratory – liver tests

SURVIVAL IN PSC – SMALL DUCT VS. LARGE

SMAL-DUCT PSC
TREATED VS. UNTREATED

UDCA FOR PSC

- Liver tests
- Survival
- Cancer
UDCA IMPROVES LIVER TESTS IN PSC

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

High-dose URSO in PSC

UDCA MAY IMPROVE SURVIVAL

Lindor K, et al NEJM 1997;336:691-95
UDCA MAY IMPROVE SURVIVAL

High-dose URSO in PSC

P = 0.002

CAUSES OF MORTALITY

FIVE YEAR TREATMENT WITH HIGH DOSE UDCA IN PSC

- 219 Scandinavian patients
- 17-23 mg/kg/d UDCA vs. placebo
  
  Death or Transplant
  
  UDCA          Placebo
  
  7.2%            10.9%     (p=0.37)

- Symptoms and quality of life not different
- Initially had estimated 396 patients needed

UDCA MAY IMPROVE SURVIVAL

Differences not significant

UCDA MAY IMPROVE HISTOLOGY

P<0.05

UDCA MAY IMPROVE CHOLANGIOGRAM

ERCP CHANGES OVER 2 YEARS OF HIGH DOSE UDCA TRIAL

- DETERIORATED
- UNCHANGED
- IMPROVED

No. of Patients

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>
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</thead>
<tbody>
<tr>
<td>Ursodiol use</td>
<td>0.14 (0.03-0.64)</td>
<td>0.01</td>
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<tr>
<td>Age at onset of colitis†</td>
<td>0.49 (0.25-0.95)</td>
<td>0.04</td>
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<tr>
<td>Duration of ulcerative colitis‡</td>
<td>0.86 (0.38-2.0)</td>
<td>&gt;0.2</td>
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*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

COLORECTAL CANCER OR DYSPLASIA IN UDCA


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

Lindor K. et al. NEJM 1997;336:691-95
PSC FOLLOWING LIVER TRANSPLANTATION

- Risks for recurrence
  - Rejection
  - Steroids
- Role of UDCA undefined
SURVIVAL AFTER RECURRENT PSC

Specific Therapy

- Medical therapy tested to date
  - Penicillamine
  - Colchicine
  - Mycophenolate Mofetil
  - Cyclosporine
  - Methotrexate
  - Silymarin
  - Pentoxifylline
  - Budesonide
  - Tacrolimus
  - Nicotine
  - Pirfenidone
  - Ursodeoxycholic acid
  - Azathioprine
  - Etanercept

_____ = possible benefit
INFLIXIMAB IN PSC

MORTALITY IN CHOLESTATIC LIVER DISEASE

CONCLUSIONS

- UDCA is reasonable for PSC
- Improves liver tests, histology, cholangiogram
- Reduces risk of dysplasia on colon biopsy
- May improve disease course
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