High dose UDCA in the Treatment of Primary Sclerosing Cholangitis

Falk Meeting, Freiberg 2006
Dr RW Chapman
John Radcliffe Hospital
Oxford, UK
Specific Medical Therapy for PSC

- **Immunosuppressants**
  - prednisolone
  - budesonide
  - azathioprine
  - ciclosporine
  - tacrolimus
  - methotrexate

- **Antifibrotics**
  - colchicine

- **Miscellaneous**
  - nicotine
  - pentoxyphylline

- **Ursodeoxycholic acid** *conventional dose 10-15mg/kg*

Summary: results of trials disappointing!
Novel Approaches to Treatment

- **High dose Urso**
- Novel drugs eg *silymarin; perfenidone; entercept*
- Endoscopic therapy eg *balloon dilatation*
- Combination therapy
  - endoscopic & drug therapy
  - drug combinations
The Optimum dose of Urso in Cholestatic Liver Diseases (PBC/PSC)?

Original dosages in PBC derived from gallstone dissolution data viz 10mg/kg body wt
## DB controlled trials of low dose UDCA (10-15mg/kg) in PSC

<table>
<thead>
<tr>
<th>Author</th>
<th>Pt No</th>
<th>Study durat</th>
<th>Alk phos</th>
<th>Sympt improv</th>
<th>Liver histol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beuers 1992</td>
<td>14</td>
<td>12 mo</td>
<td>imp</td>
<td>no</td>
<td>imp</td>
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<tr>
<td>Stiehl 1994</td>
<td>20</td>
<td>24 mo</td>
<td>imp</td>
<td>no</td>
<td>imp</td>
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<td>Van Hoo 1998</td>
<td>48</td>
<td>24 mo</td>
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<tr>
<td>Lindor 1997</td>
<td>105</td>
<td>36 mo</td>
<td>imp</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>
Rationale for High Dose UDCA in treatment of PSC

- Low dose doesn’t work!

- In advanced cholestasis in PSC the enrichment of the bile acid pool is diminished cp cystic fibrosis
  
  *Stiehl et al, J Hepatol 1995*,
  *Rost et al, Hepatol 2004*

- Biliary enrichment with UDCA is proportional to administered dose
  
  *Roda et al, Europ J Gastro 2002*
  *Rost et al, Hepatol 2004*
High-dose UDCA on biliary enrichment in PSC

Biliary enrichment of UDCA
2 doses 10-13 mg/kg; <22 mg/kg
Higher dose increased enrichment

Biliary enrichment at various doses; plateau effect at 22-25 mg/kg
High dose UDCA in PSC*

- DBCT 26 PSC pts
- Randomised to placebo or UDCA (20 – 25mg /day)
- Repeat liver biopsy/ERCP at 2 yrs
- 22/26 completed the trial
- Serum bile acids (HPLC) 0,1,2 yrs

*Mitchell S et al, Gastro 2001
High Dose Urso in PSC

*Histological Disease stage over 2 yrs*

Histological stage worsened in placebo group cp UDCA
High Dose Urso in PSC

ERCP changes over 2 years

ERCP worsened in placebo group cp UDCA
### High Dose Urso in PSC

**Serum bile acids (by HPLC)**

<table>
<thead>
<tr>
<th>% of UDCA fraction of bile acid pool</th>
<th>Placebo group</th>
<th>at 0 year</th>
<th>at 1 years</th>
<th>at 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo group</td>
<td>3%</td>
<td>7.8%</td>
<td>7.3%</td>
</tr>
<tr>
<td>High dose UDCA</td>
<td></td>
<td>6%</td>
<td>78%</td>
<td>73%</td>
</tr>
</tbody>
</table>
High Dose Urso in PSC

Summary of results

- Well tolerated
- No effect on colitis activity
- Significant improvements in alkaline phosphatase/GGT
- No improvements in symptoms
- Majority of treated group had improved inflam/fibrosis scores
  - 4/10 had regression disease stage – not seen in placebo group
High dose Urso as a therapy for patients with PSC*

patients / methods

- 30 PSC pts
- treated with 25-30 mg/kg/daily for one year –open study
- compared with historical PSC controls
  *viz placebo (52 pts) and mod dose urso 13-15mg/kg/daily (53 pts)*

*Harnois et al; Am J Gastro 2001*
High dose UDCA as a therapy for patients with PSC*

Results at one year

- Marked improvement in LFT’s
- Changes in Mayo Risk Score were significantly different at one year between 3 groups

Expected survival at 4 years
- High dose improved vs placebo (p=0.04)
- Mod dose vs placebo - no difference (p=0.4)

Harnois et al; Am J Gastro 2001
FIVE-YEAR TREATMENT WITH HIGH-DOSE UDCA IN PSC

R.G. Olsson\(^1\), K.M. Boberg\(^2\), O. Schaffalitzky de Muckadel\(^3\),
S. Lindgren\(^1\), R. Hultcrantz\(^1\), G. Folvik\(^4\), H. Bell\(^5\), G. Kristiansen\(^6\),
J. Matre\(^7\), A. Rydning\(^8\), O. Wikman\(^9\), A. Danielsson\(^1\),
H. Sandberg-Gertzen\(^1\), K.A. Ung\(^10\), A. Eriksson\(^1\), L. Loof\(^1\), H. Prytz\(^1\),
U. Broome\(^1\). \(^1\)SILK (Swedish Internal Medicine Liver Club),
\(^2\)Department of Medicine, Rikshospitalet, Oslo, Norway; \(^3\)Department of

- 97 pts high dose UDCA (17-23 mg/kg) for 5 years
- 101 pts placebo
Scandanian trial high dose UDCA: changes in serum biochemistry

- Alk phos
- ALT
- Bilirubin

Red = placebo
High dose Scandanavian Trial

Death / Transplantation:

7.2% UDCA vs 10.9% placebo (ns)
High dose UDCA
Scandanavian study: potential problems

- Study underpowered *(only 10% placebo pts reached endpoint)*
- High dropout rate
- Dose too low! *(15 -20mg/kg)*
- Study period too short *(even at 5 yrs!)*
- Strong possibility of type II error
Low dose UDCA    High dose UDCA

5 yr Survival


Olsson et al: J Hepatol 2004
High dose UDCA

Glass half empty!

Current status?

Glass half full!
UDCA+?
What about even Higher Dose UDCA in PSC?*

- 2 year DBRCT pilot study in 33 PSC pts
- Munich & Oxford
- Pts randomised to UDCA either 10mg/kg; 20 or 30 mg/kg
- Liver biopsy 0 and 2 years assessed using Ludwig Score

# High dose UDCA

**Improvement in liver function Tests**

<table>
<thead>
<tr>
<th></th>
<th>T-test (within treatment group)</th>
<th>10mg</th>
<th>20mg</th>
<th>30 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td></td>
<td>p=0.77</td>
<td>p=0.71</td>
<td>p=0.57</td>
</tr>
<tr>
<td>Alk Phos</td>
<td></td>
<td>p=0.01</td>
<td>p=0.01</td>
<td>p=0.03</td>
</tr>
<tr>
<td>AST</td>
<td></td>
<td>p=0.08</td>
<td>p=0.03</td>
<td>p=0.09</td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td>p=0.05</td>
<td>p=0.02</td>
<td>p=0.06</td>
</tr>
<tr>
<td>GGT</td>
<td></td>
<td>p=0.01</td>
<td>p=0.01</td>
<td>p=0.01</td>
</tr>
</tbody>
</table>
High Dose UDCA in PSC
Mayo Risk Scores;
difference in survival probabilities from
baseline to end of the study

Survival probabilities

Time (years)

1 year 2 years 3 years 4 years

All 10mg/ kg 20mg/ kg 30mg/ kg
# High dose UDCA in PSC

<table>
<thead>
<tr>
<th>Change in Ludwig score</th>
<th>All patients n=31</th>
<th>Low dose UDCA (10mg/kg) n=11</th>
<th>Standard dose UDCA (20mg/kg) n=11</th>
<th>High dose UDCA (30mg/kg) n=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>No change</td>
<td>17</td>
<td>7</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Worsening</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No biopsy</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>
High Dose UDCA in PSC*

- Very high dose (ie 30mg/kgm) well tolerated
- Cholestatic LFT’s - improved in all groups
- Trend towards improvement in the Ludwig score in standard and high dose groups
- Significantly increased survival (using Mayo Risk score) in 30mg/kg group
- However SMALL pilot study!

*Cullen S et al; EASL 2006*
UDCA treatment for PSC
UDCA anticancer role

- Evidence in favour of reduction of colon cancer risk in PSC/IBD
- Tentative evidence for reduction in risk of cholangiocarcinoma: not proven
- Effect of UDCA dose is unknown in chemoprotection
High dose UDCA in PSC

- Data still suggestive that UDCA indicated in high dose

- Large US study in progress

- New studies are unlikely to occur

  *viz* cancer protective effect

  *on colon & ? bile ducts*
High Dose Urso in PSC
- combination therapy: the future?

Studies of combination therapy with UDCA (low dose)
- antibiotics
  (metronidazole) - Pos [DBCT]
- immunomodulatory
  (mycophenolate mofetil) - Neg (DBCT)
- immunosuppressant
  (pred 1mg/kg; Azathioprine 1mg daily) - Pos (Uncont)
- rifampicin (no trial)
High Dose Urso in PSC
- combination therapy

Studies of combination therapy with UDCA

- antibiotics
  (metronidazole) - Positive [DBCT]

- immunomodulatory
  (mycophenolate mofetil) - Negative [DBCT]

- immunosuppressant ( undocumented )
High dose UDCA in PSC

- Data still suggestive that UDCA indicated in high dose
- Large US study in progress
- New studies are unlikely to occur

viz cancer protective effect

on colon & ? bile ducts
# Cochrane Review

**Review:** Bile acids for primary sclerosing cholangitis (for peer rev. 17.06.02)

**Comparison:** 01 UDCA versus control (placebo or no treatment)

**Outcome:** 01 Number of deaths at the end of treatment (RR)

<table>
<thead>
<tr>
<th>Study</th>
<th>UDCA n/N</th>
<th>Control n/N</th>
<th>RR (95% CI Fixed)</th>
<th>Weight %</th>
<th>RR (95% CI Fixed)</th>
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</thead>
<tbody>
<tr>
<td>Beuers 1992</td>
<td>0/6</td>
<td>1/8</td>
<td></td>
<td>46.7</td>
<td>0.43[0.02,9.00]</td>
</tr>
<tr>
<td>x Lindor 1997</td>
<td>0/53</td>
<td>0/52</td>
<td></td>
<td>0.0</td>
<td>Not Estimable</td>
</tr>
<tr>
<td>x Lo 1992</td>
<td>0/8</td>
<td>0/10</td>
<td></td>
<td>0.0</td>
<td>Not Estimable</td>
</tr>
<tr>
<td>Mitchell 2001</td>
<td>0/13</td>
<td>1/13</td>
<td></td>
<td>53.3</td>
<td>0.35[0.01,7.50]</td>
</tr>
<tr>
<td>x Stehl 1994</td>
<td>0/10</td>
<td>0/10</td>
<td></td>
<td>0.0</td>
<td>Not Estimable</td>
</tr>
<tr>
<td>x de Maria 1996</td>
<td>0/20</td>
<td>0/20</td>
<td></td>
<td>0.0</td>
<td>Not Estimable</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>0/110</strong></td>
<td><strong>2/113</strong></td>
<td></td>
<td><strong>100.0</strong></td>
<td><strong>0.35[0.04,3.32]</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=0.01 df=1  p=0.91  
Test for overall effect z=0.88  p=0.4

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*Gluud & Chen 2002*
Potential Benefits of Ursodeoxycholic acid in Colon Cancer*

- Toxic bile acids viz deoxycholic acid induce cell proliferation -induces dysplasia and colon cancer [in vitro model] NB Effects reversed by UDCA

- In vivo – reduced prevalence of Colon Polyps/cancer in PBC treated with UDCA

- Colonic dysplasia / cancer increased in PSC/UC compared with UC alone

*Martinez et al; Nutr Cancer 1998;31:111-8
Proportion of PSC/UC pts free of colonic cancer / dysplasia*

*Pardi et al, Gastro 2003; 124:889-3

NB Similar results in Oxford
Novel treatment for PSC

UDCA anticancer role

- Strong evidence in favour of reduction of colon cancer risk in PSC/IBD
- Tentative evidence for reduction in risk of cholangioca: not proven
- Effect of UDCA dose is unknown
Novel Approaches to Treatment

- Novel drugs
- High dose Urso
- Endoscopic therapy
- **Combination therapy**
  - endoscopic & drug therapy
  - drug combinations
High Dose Urso in PSC

- combination therapy

Studies of combination therapy with UDCA

- antibiotics (metronidazole) Positive [DBCT]

- immunomodulatory
  (mycophenolate mofetil) Negative [DBCT]

- immunosuppressant
  (pred 1mg/kg; Azathioprine 1mg daily)
  Positive [Unc]
Novel Treatments of PSC

Conclusion

- UDCA indicated in PSC/UC pts because of reduced risk of colonic neoplasia
  
- Further trials required of combination studies of UDCA with other agents
  
  - antibiotics eg metronidazole
  
  - endoscopic therapies
Novel drug therapies for PSC

- **Etanercept** (anti TNF antibody)
- Pilot study: 25 mg twice weekly s/c [10 PSC pts] treated for 1 year*
  - No improvement in LFT’s (bilirubin 2x!)
  - 2 /5 pts improved itch

- NB: PSC pts refractory: all had failed UDCA and /or MTX
- NO trials of infliximab (etanercept no good in IBD)

*Epstein MP, Kaplan MM
Dig Dis Sci 2004
Novel Approaches to Treatment

- **Novel drugs**
- High dose Urso
- Endoscopic therapy
- Combination therapy
  - endoscopic & drug therapy
  - drug combinations
Novel drug therapies for PSC

- **Silymarin** (antioxidant) aka milk thistle
  - Pilot study: 140 mg tds 1 year [22 PSC pts]
  - No effect
  
  Angulo et al, 2003

- **Perfenidone** (antifibrotic)
  - Pilot study: 2400mg daily 1 year [24 PSC pts]
  - No benefit; adverse effects 23/24

Low Dose UDCA in PSC
Survival free of treatment failure*

High Dose Urso in PSC

HIGH DOSE URSODEOXYCHOLIC ACID IN PRIMARY SCLEROSING CHOLANGITIS: RESULTS AFTER TWO YEARS OF A RANDOMISED DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL.

Department of Gastroenterology and Nuffield Department of Pathology*, Oxford Radcliffe Hospital, Oxford, UK.

Mitchell et al: Gastroenterology 2001
High Dose Urso in PSC
Aims of the Study

- Randomised placebo controlled pilot study using high dose UDCA (20mg/kg/day) in order to:
  - Determine effect of high dose UDCA on clinical, biochemical, cholangiographic, histological features of PSC over 2yr
  - Assess side effect profile and effect on activity of colitis
High Dose Urso in PSC
Patients / Methods

- 26 pts with PSC randomised to UDCA or placebo
- Full assessment at entry
  (clinical; biochem; liver biopsy; ERCP)
- Repeat liver biopsy/ERCP at 2 yrs
- Serum bile acids at 0; 1yr; 2yr
  - measured by HPLC
High Dose Urso in PSC

Results - Clinical

- 22 of 26 pts completed the trial:
- 3 pts withdrawn:
  - One pt in UDCA group – main duct stricture/transplant
  - One pt in placebo group – variceal haemorrhage
  - One pt died unrelated cause
High Dose UDCA in PSC

Results - Clinical

- No improvement in symptoms ie fatigue/malaise/pruritis – despite improvement in biochemistry

- No adverse events/side effects- in particular no diarrhoea/worsening of activity of inflammatory bowel disease
Scandanavian trial high dose UDCA: changes in serum biochemistry

Alk phos

Red = placebo

ALT

bilirubin
# High dose Urso in PSC

## Serum Biochemistry

<table>
<thead>
<tr>
<th>Mean</th>
<th>Plac 0 yr</th>
<th>Plac 2yr</th>
<th>UDCA 0yr</th>
<th>UDCA 2yr</th>
<th>P value</th>
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<tbody>
<tr>
<td>bilirubin</td>
<td>19</td>
<td>24</td>
<td>16</td>
<td>16</td>
<td>p=.08</td>
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<tr>
<td>Alk phos</td>
<td>791</td>
<td>875</td>
<td>834</td>
<td>455</td>
<td>p=.03</td>
</tr>
<tr>
<td>Ast</td>
<td>61</td>
<td>80</td>
<td>87</td>
<td>47</td>
<td>p=0.1</td>
</tr>
<tr>
<td>Ggt</td>
<td>560</td>
<td>595</td>
<td>476</td>
<td>178</td>
<td>p=.01</td>
</tr>
<tr>
<td>Albumin</td>
<td>41</td>
<td>41</td>
<td>44</td>
<td>43</td>
<td>p=.93</td>
</tr>
</tbody>
</table>
High Dose Urso in PSC

Liver Histology

Portal inflammation scores over 2 yrs
Comparison of 3 doses of UDCA on duodenal bile acid enrichment at 1 yr
Low Dose UDCA in PSC*
Survival Free of Treatment Failure
Stage 1 or 2 disease

Patients with Stage I or II Disease

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>B</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tbody>
<tr>
<td>Placebo</td>
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<td>17</td>
<td>11</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ursodiol</td>
<td></td>
<td>24</td>
<td>18</td>
<td>10</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*Lindor et al; N Engl J Med 1997*
Low dose UDCA*  High dose in PSC**
Survival Free of Liver Transplantation


**Olsson et al; J Hepatol 2004
Low dose UDCA in PSC
Survival Free of Liver Transplantation

Management of PSC

- Management of chronic cholestasis
- Management of end stage liver disease
- Management of complications spec to PSC
  - dominant stricture
  - biliary sludge
  - cholangiocarcinoma

- Specific Medical Therapy – to prevent disease progression
- Liver Transplantation
Comparison of 3 doses of UDCA in PBC – randomized trial*

Effect on Mayo Risk Score

Low dose 5-7mg/kg; standard 13-15; high 23-25mg/’kg/daily

*Angulo et al; J Hepatol 1999
Review: Bile acids for primary sclerosing cholangitis (for peer rev. 17.06.02)
Comparison: 01 UDCA versus control (placebo or no treatment)
Outcome: 07 Serum bilirubin level (μmol/l) at the end of treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>UDCA n</th>
<th>mean(sd)</th>
<th>Control n</th>
<th>mean(sd)</th>
<th>WMD (95%CI Fixed)</th>
<th>Weight %</th>
<th>WMD (95%CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindor 1997</td>
<td>37</td>
<td>25.50(35.70)</td>
<td>29</td>
<td>44.20(62.90)</td>
<td></td>
<td>2.5</td>
<td>-18.70[-44.32,6.92]</td>
</tr>
<tr>
<td>Mitchell 2001</td>
<td>11</td>
<td>16.00(10.00)</td>
<td>11</td>
<td>24.00(19.00)</td>
<td></td>
<td>10.2</td>
<td>-8.00[-20.69,4.69]</td>
</tr>
<tr>
<td>Stiehl 1994</td>
<td>10</td>
<td>10.20(1.70)</td>
<td>10</td>
<td>25.50(6.80)</td>
<td></td>
<td>87.3</td>
<td>-15.30[-19.64,-10.96]</td>
</tr>
<tr>
<td>Total(55%CI)</td>
<td>53</td>
<td></td>
<td>50</td>
<td></td>
<td>100.0</td>
<td></td>
<td>-14.64[-18.70,-10.56]</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=1.24  df=2  p=0.54
Test for overall effect z=7.07 p<0.00001
**Review:** Bile acids for primary sclerosing cholangitis (for peer rev. 17.06.02)
**Comparison:** 01 UDCA versus control (placebo or no treatment)
**Outcome:** 05 Number of patients with cholangiography deterioration at the end of treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>UDCA n/N</th>
<th>Control n/N</th>
<th>RR (95%CI Fixed)</th>
<th>Weight %</th>
<th>RR (95%CI Fixed)</th>
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</thead>
<tbody>
<tr>
<td>Mitchell 2001</td>
<td>4 / 13</td>
<td>9 / 13</td>
<td></td>
<td>85.7</td>
<td>0.44 [0.18, 1.08]</td>
</tr>
<tr>
<td>Stiehl 1994</td>
<td>0 / 10</td>
<td>1 / 10</td>
<td></td>
<td>14.3</td>
<td>0.33 [0.02, 7.32]</td>
</tr>
<tr>
<td>de Mars 1996</td>
<td>0 / 20</td>
<td>0 / 20</td>
<td></td>
<td>0.0</td>
<td>Not Estimable</td>
</tr>
<tr>
<td><strong>Total (95%CI)</strong></td>
<td><strong>4 / 43</strong></td>
<td><strong>10 / 43</strong></td>
<td></td>
<td><strong>100.0</strong></td>
<td><strong>0.43 [0.18, 1.02]</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square = 0.03 df = 1 p = 0.86
Test for overall effect z = -1.91 p = 0.06
Primary Sclerosing Cholangitis

- Chronic cholestatic liver disease
- Stricturing and dilatation of biliary tree
- Progresses to cirrhosis/liver failure
- Predisposes to cancer (bile duct; colon; panc)
Comparison of 3 doses of UDCA in PBC – randomized trial*

Effect on Alkaline Phosphatase

*Angulo et al; J Hepatol 1999
Comparison of 3 doses of UDCA in PBC – Conclusions*

- Ursodeoxycholic Acid in doses of 5-25 mg/kg/day is well tolerated
- Dose of 13-15 mg/kg/day is the preferred dose in the treatment of PBC

*Angulo et al: JHepatol 1999