PBC features and management in the era of UDCA and Budesonide

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Université P&M Curie, AP-Hôpitaux de Paris, Inserm, Paris, France
The changing pattern of PBC

Over the last 2 decades:

- More patients are being recognized with early disease
- Most of the patients are given UDCA therapy
- The natural history is improving
- The requirement for liver transplantation is falling
Decrease in liver transplantation burden of PBC

Lee et al. Clin Gastroenterol Hepatology 2007
Corpechot et al. Hepatology 2007
Putative explanations for the improved natural history

- Change in intrinsic severity of PBC
- Routine use of UDCA
- Early recognition and treatment of the PBC-AIH overlap syndrome
Natural history of PBC in the era of UDCA

Corpechot et al. Hepatology 2000, Gastroenterology 2005
Predictors of suboptimal response to UDCA and long-term liver failure
Time Profile of Cirrhosis Development

from stage I

from stage II

from stage III

Incidence of cirrhosis [%]

Years

0 5 10

0 5 10

0 5 10

Corpechot et al. gastroenterology 2002
Time Profile of Cirrhosis Development

from Stage II

- With bilirubin $\leq 17$ M and albumin $\geq 38$ g/l, severe PMN.
- With bilirubin $\leq 17$ M and albumin $\geq 38$ g/l, moderate PMN.
- With bilirubin $\leq 17$ M and a moderate PMN, mild PMN.
- With albumin $\geq 38$ g/l and a moderate PMN, severe PMN.

Corpechot et al. gastroenterology 2002
Barcelona criteria of response to UDCA

Decrease in ALP > 40% or normal ALP after 1 year of UDCA therapy

Transplantation-free survival

Years

0 5 10 15

YES

NO

RR: 5.5 (1.7-16.0), P<.01

Standardized population

Parés et al. Gastroenterology 2006
Objectives

- To determine the biochemical criteria of response which allow to predict long-term efficacy of UDCA in patients with PBC.
- To assess the prognostic value of the Barcelona criteria from a large independent cohort of patients with PBC.
- To determine whether liver histological examination may be avoided by using biochemical criteria of response to UDCA for assessing prognosis in PBC.
Studied population

- Eligibility criteria:
  - Histologically proven PBC.
  - Treatment with UDCA at 13-15 mg/kg/day.
  - Available biochemical data at T0 and 1 year.

- Ineligibility criteria:
  - Overlap syndrome.
  - Immunosuppressive therapy.
  - Follow-up < 1 year.
Response criteria

- Barcelona criteria.
- Biochemical liver tests at 1 year:

1. Bilirubin $\leq 1$ mg/dl + ALP $\leq 1.5N$ + AST $\leq 1N$
2. Bilirubin $\leq 1$ mg/dl + ALP $\leq 1.5N$ + AST $\leq 1.5N$
3. Bilirubin $\leq 1$ mg/dl + ALP $\leq 2N$ + AST $\leq 1N$
4. Bilirubin $\leq 1$ mg/dl + ALP $\leq 2N$ + AST $\leq 1.5N$
5. Bilirubin $\leq 1$ mg/dl + ALP $\leq 2N$ + AST $\leq 2N$
6. Bilirubin $\leq 1$ mg/dl + ALP $\leq 3N$ + AST $\leq 2N$
7. Bilirubin $\leq 1$ mg/dl

N: upper limit of normal.
Survival

Mean follow-up = 6.1±4.3 yrs [1 - 21 yrs]

- Survival - RR: 1.6 (P=0.15)
- Survival without OLT - RR: 2.8 (P<.0001)
- Control population

Years
## Selection of the most discriminative biochemical response

<table>
<thead>
<tr>
<th>Response at 1 year</th>
<th>Yes</th>
<th>No</th>
<th>Likelihood ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in ALP&gt;40% or ALP ≤ N</td>
<td>65%</td>
<td>35%</td>
<td>8.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bilirubin N, ALP ≤1.5N, AST ≤N</td>
<td>32%</td>
<td>68%</td>
<td>17.4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Bilirubin N, ALP ≤2N, AST ≤N</td>
<td>39%</td>
<td>61%</td>
<td>21.5</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Bilirubin N, ALP ≤1.5N, AST ≤1.5N</td>
<td>37%</td>
<td>63%</td>
<td>22.6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Bilirubin N. ALP ≤2N, AST ≤1.5N</td>
<td>48%</td>
<td>52%</td>
<td>34.4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Bilirubin N, ALP ≤2N, AST ≤2N</td>
<td>52%</td>
<td>48%</td>
<td>40.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Bilirubin N, ALP ≤3N, AST ≤2N</td>
<td>61%</td>
<td>39%</td>
<td>48.9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Bilirubin N</td>
<td>80%</td>
<td>20%</td>
<td>70.6</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Number of patients = 292
Response at 1 year (whole cohort)

Decrease in ALP > 40% or normal ALP

- YES (65%)
- NO (35%)

RR: 0.7 (0.5-0.9), P<.01*

Bilirubin ≤ 1 mg/DL, ALP ≤ 3N and AST ≤ 2N

- YES (61%)
- NO (39%)

RR: 0.4 (0.3-0.5), P<.0001***

Number of patients = 292
## Multivariate analysis

<table>
<thead>
<tr>
<th>Predictive factors of death or LT</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin &gt; 1 mg/dl *</td>
<td>1.7 (1.1 - 2.6)</td>
</tr>
<tr>
<td>Histological stage 3-4 *</td>
<td>1.5 (1.0 - 2.2)</td>
</tr>
<tr>
<td>Interface hepatitis *</td>
<td>1.9 (1.2 - 2.9)</td>
</tr>
<tr>
<td>Lack of biochemical response at 1 year **</td>
<td>2.3 (1.5 - 3.7)</td>
</tr>
</tbody>
</table>

* Before treatment.
** i.e. bilirubin >1 mg/dL or ALP >3N or AST >2N.
Rationale for the use of UDCA-glucocorticoids combination

- **Clinical trials:**
  - better efficacy of the combination vs UDCA alone

- **Biological basis**
  - reversal of cytokine-induced inhibition of canalicular and ductal choleresis
  - PXR agonist activity
  - UDCA-glucocorticoids potentiation on:
    - AE2 expression and activity
    - Inflammation
    - MHC expression
    - Apoptosis inhibition
Objective

To assess the long-term effect of glucocorticoids-UDCA combination on the risk of development of cirrhosis and liver failure in patients with severe PBC and suboptimal response to UDCA alone.
Studied population

- **Eligibility criteria:**
  - PBC treated with UDCA (13-15 mg/kg/day)
  - PBC with suboptimal response to UDCA (ALP > 3N or AST > 2N or S.bilirubin > 1mg/dL) or with moderate or severe lymphocytic piecemeal necrosis or with several lobular septa (F3)

- **Ineligibility criteria**
  - Cirrhosis
  - Hyperbilirubinemia (> 3 mg/dL)
  - Autoimmune hepatitis (score > 15)
  - Contraindication to glucocorticoids
Maintenance therapy

- 1995-2000
  Glucocorticoids (Prednisone) (10-15 mg/day)
  ± Azathioprine (50-100 mg/day)

- 2000-2006
  Budesonide (3-6 mg/day)
  ± Mycophenolate mofetil (1-1.5 g/day)
End-point for treatment efficacy

- Cirrhosis
- S. bilirubin > 3 mg/dL
- Liver transplantation
Methods

- The survival without treatment failure was estimated by the Kaplan-Meier method.
- Survival rates were compared to those expected according to our 4-stage Markov model (Gastroenterology, 2002) in a control population matched for age, serum bilirubin and albumin, histological stage, severity of interface hepatitis and duration of follow-up.
- The 95% confidence intervals were estimated using a bootstrap method with 1000 replicates.
- The survival rates of the controls were averaged to obtain a cirrhosis-free survival curve.
**Baseline characteristics**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>45</td>
<td>[18–66]</td>
</tr>
<tr>
<td><strong>Female gender</strong></td>
<td>41</td>
<td>(97.6%)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>22.2</td>
<td>[18.5–29.8]</td>
</tr>
<tr>
<td><strong>Pruritus</strong></td>
<td>26</td>
<td>(65.0%)</td>
</tr>
<tr>
<td><strong>S. bilirubin</strong></td>
<td>.85</td>
<td>[.24–2.57]</td>
</tr>
<tr>
<td><strong>AST</strong></td>
<td>82</td>
<td>[24–296]</td>
</tr>
<tr>
<td><strong>ALP</strong></td>
<td>400</td>
<td>[99–2351]</td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td>40.7</td>
<td>[34.0–47.7]</td>
</tr>
<tr>
<td><strong>Prothrombin time</strong></td>
<td>100</td>
<td>[82–120]</td>
</tr>
</tbody>
</table>

Number of patients: 42
Baseline characteristics

<table>
<thead>
<tr>
<th>Stage</th>
<th>I</th>
<th>9 (21.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>II</td>
<td>19 (45.2%)</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>14 (33.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prednisolone – AZT</th>
<th>32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide – MMF</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of treatment (years)</th>
<th>5 [5–15]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of follow-up (years)</td>
<td>6 [1–17]</td>
</tr>
</tbody>
</table>

Number of patients: 42
Observed and predicted time to treatment failure

Verification of survival with time. The red line represents the observed survival, and the blue lines represent the predicted survival with 95% confidence intervals. The relative risk (RR) is 0.29 (0.12-0.72), with a p-value of 0.008.
Baseline characteristics and biochemical response according to the long-term outcome

<table>
<thead>
<tr>
<th></th>
<th>Cirrhosis - OLT</th>
<th>Good outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n=5</strong></td>
<td></td>
<td><strong>n=37</strong></td>
</tr>
<tr>
<td><strong>Age</strong> (years)</td>
<td>34</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>[29–50]</td>
<td>[18–66]</td>
</tr>
<tr>
<td><strong>Female gender</strong></td>
<td>5</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>(100%)</td>
<td>(97 %)</td>
</tr>
<tr>
<td><strong>Budesonide+MMF+UDCA</strong></td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td><strong>Prednisolone+AZT+UDCA</strong></td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td><strong>Albumine</strong> (g/L)</td>
<td><strong>40.5</strong></td>
<td><strong>40.8</strong></td>
</tr>
<tr>
<td></td>
<td>[37.0–46.9]</td>
<td>[34.0–47.7]</td>
</tr>
<tr>
<td><strong>Prothrombin time</strong> (%)</td>
<td>86</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>[82–100]</td>
<td>[85–120]</td>
</tr>
<tr>
<td><strong>S. bilirubin</strong> (mg/dL)</td>
<td><strong>13</strong></td>
<td><strong>15</strong></td>
</tr>
<tr>
<td></td>
<td>[8–28]</td>
<td>[4–40]</td>
</tr>
<tr>
<td><strong>AST</strong> (IU)</td>
<td><strong>45</strong></td>
<td><strong>82</strong></td>
</tr>
<tr>
<td></td>
<td>[32–204]</td>
<td>[24–96]</td>
</tr>
<tr>
<td><strong>ALP</strong> (IU)</td>
<td><strong>309</strong></td>
<td><strong>402</strong></td>
</tr>
<tr>
<td></td>
<td>[153–466]</td>
<td>[99–2351]</td>
</tr>
<tr>
<td><strong>Optimal response</strong></td>
<td>0</td>
<td>27</td>
</tr>
</tbody>
</table>

*median [range]*
Summary

- The biochemical response to UDCA is a potent surrogate marker of long-term prognosis.
- Liver biopsy and quantitative assessment of severity of interface hepatitis and fibrosis are mandatory for a full assessment of prognosis.
- Glucorticoids-UDCA combination improves long-term prognosis of patients with features of poor outcome.
Survival Compared with that of an Age- and Sex-matched French Population

Corpechot et al. Gastroenterology 2005
Long-term prognosis of primary biliary cirrhosis (PBC) in Japan and analysis of the factors of stage progression in asymptomatic PBC (a-PBC)

Toshiaki Nakano, Kyoichi Inoue, Junko Hirohara, Seizaburou Arita, Kiyohiro Higuchi, Masao Omatada and Gotaro Toda

Hepatology Research, Volume 22, Issue 4, April 2002, Pages 241-249
Survival without transplantation according to the 1-year biochemical response to UDCA

- Control population
- Responders (n=171)
- No responders (n=121)
- Mayo score
## Univariate analysis

<table>
<thead>
<tr>
<th>Predictive factors of death or LT</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 55 yrs</td>
<td>1.3 (1.0 - 1.6)</td>
</tr>
<tr>
<td>Bilirubin &gt; 1 mg/dL*</td>
<td>2.7 (2.0 - 3.7)</td>
</tr>
<tr>
<td>ALP &gt; 3N *</td>
<td>1.6 (1.2 - 2.0)</td>
</tr>
<tr>
<td>AST &gt; 2N *</td>
<td>1.6 (1.3 - 2.1)</td>
</tr>
<tr>
<td>Albumin &lt; 38 g/L*</td>
<td>2.0 (1.6 - 2.7)</td>
</tr>
<tr>
<td>Prothrombin index &lt; 80%*</td>
<td>2.2 (1.7 - 2.9)</td>
</tr>
<tr>
<td>Histological stage 3-4*</td>
<td>2.5 (1.9 - 3.2)</td>
</tr>
<tr>
<td>Interface hepatitis*</td>
<td>2.0 (1.5 - 2.7)</td>
</tr>
<tr>
<td>Ductopenia*</td>
<td>1.8 (1.3 - 2.7)</td>
</tr>
</tbody>
</table>

Lack of biochemical response at 1 year:
- according to Barcelona criteria 1.5 (1.2 - 2.0)
- according to the present study criteria** 2.9 (2.1 - 4.2)

* Before treatment.
** i.e. bilirubin >1 mg/dL or ALP >3N or AST >2N.
Rationale for the use of UDCA-glucocorticoids combination

• Clinical trials:
  – better efficacy of the combination vs UDCA alone

  Leuschner 1996, 1999
  Wolfhagen 1998
  Angulo 2000
  Rautiainen 2005
 UDCA / Budesonide for PBC

Leuschner et al. Gastroenterology 1999
UDCA / Budesonide for PBC

Leuschner et al. Gastroenterology 1999
Glucocorticoids and cholestasis
<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Albumine</strong></td>
<td>(g/L) 40.8</td>
<td>[34.0–47.7]</td>
<td>41.9 [32.2–58.3]</td>
</tr>
<tr>
<td><strong>Prothrombin time</strong></td>
<td>(%) 100</td>
<td>[85–120]</td>
<td>100 [80–124]</td>
</tr>
<tr>
<td><strong>S. bilirubin</strong></td>
<td>(mg/dL) .85</td>
<td>[.24–2.57]</td>
<td>.70 [.24–5.85]</td>
</tr>
<tr>
<td><strong>ALP</strong></td>
<td>(IU) 402</td>
<td>[99–2351]</td>
<td>176 [60–498]</td>
</tr>
</tbody>
</table>

*Wilcoxon Signed Ranks Test*
### Predicted and observe cirrhosis-free survival

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>A0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>A1</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>A2</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>A3</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>F2</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>F3</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>F4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Number of patients: 35
“Double-blind, randomised, placebo-controlled, multi-centre phase III clinical study comparing the combination of ursodeoxycholic acid capsules plus budesonide capsules to ursodeoxycholic acid capsules plus placebo in the treatment of primary biliary cirrhosis”
Study Design

- Multicentric
- Double Blind
- Randomized
- Placebo-controlled
- Phase III
Trial Treatment

A
9 mg budesonide,
6 mg budesonide are allowed if ALT values are normalized
plus
12-16 mg/kg BW/d ursodeoxycholic acid

B
Placebo to budesonide
plus
12-16 mg/kg BW/d ursodeoxycholic acid
## Treatment Duration

- **Treatment period:** 3 years
- **Inclusion Period:** 3Q. 2008 – 3Q. 2009
- **No. of visits:** 11

<table>
<thead>
<tr>
<th>Baseline visit</th>
<th>Interim visits</th>
<th>Final visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>week 0 (day -14 to 0)</td>
<td>week 2, week 4</td>
<td>months 3, 6, 9, 12, 18, 24, 30</td>
</tr>
<tr>
<td>V1</td>
<td>V2 and V3</td>
<td>V4 – V10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>V11</td>
</tr>
</tbody>
</table>

- Months: 3, 6, 9, 12, 18, 24, 30
- Week: 0 (day -14 to 0)
- V11: withdrawal visit
Sample Size

- 183 patients
- currently 12 countries
- 30 sites planned
Agenda

1. Welcome (M. Pröls)
2. Rationale & Background of the Trial (R. Poupon)
3. Protocol & Procedures (A. Meyer)
4. Histology (D. Wendum)
5. Status of the Trial (A. Meyer)
6. Discussion (All)
7. Conclusion (M. Pröls)
Response at 1 year  
(normal bilirubin before treatment)  

(Number of patients = 186)

A) Decrease in ALP > 40% or normal ALP  
B) Bilirubin ≤ 1 mg/dl, ALP ≤ 3N and AST≤ 2N

RR: 0.3 (0.1- 0.5), p=.0001***  
RR: 0.6 (0.3 - 1.2), p=.15

B) Bilirubin ≤ 1 mg/dl, ALP ≤ 3N and AST≤ 2N