Moving from early to moderate or advanced biochemical disease stage during follow-up is associated with an increasing risk of clinical events in PBC patients.


on behalf of the Global PBC Study Group
Background

• Primary biliary cholangitis (PBC) is a slowly progressive cholestatic liver disease characterized by destruction of small and medium size intrahepatic bile ducts.

• This destruction may lead to cirrhosis and eventually liver failure requiring liver transplantation.

• Ursodeoxycholic acid (UDCA) is the only approved first line therapy, but new therapies are becoming available.

Background

- **Age at diagnosis** increased incrementally from the 1970’s (mean 46.9) to 2010 (mean 57.3) years.

- The proportion of patients with an **early biochemical disease stage** in the 1970’s and after 2010 was 41% and 69.9%, respectively.

Murillo Perez, Hepatology 2017.
Background

• 482 patients
• Age at diagnosis: 56.3 ± 13.7 years
• Prevalence: 582 cases / million
• **At diagnosis:**
  - 43.6% asymptomatic
  - 16.2% cirrhotic
  - 82.6% biopsy stage 0-I-II
Aim

Transition rates? Predictive factors?

EARLY
ALB & BILI: normal

MODERATE
ALB or BILI: abnormal

ADVANCED
ALB and BILI: abnormal

NATURAL HISTORY

Kuiper, Gastroenterology 2009.
Methods

• Retrospective patient data were obtained from the prospectively collected GLOBAL PBC Study Group database

  - 19 liver centres from 12 European and North American countries

• Patients with an early biochemical stage (normal ALB & BILI) were included

• Endpoints

  - 1\textsuperscript{st}: At every visit, patients who transited to moderate (abnormal ALB or BILI) or advanced (abnormal ALB & BILI) were identified

  - 2\textsuperscript{nd}: A composite clinical event defined by either liver transplantation, ascites, variceal bleeding, hepatic encephalopathy, or development of HCC
Results

Baseline study population characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=2039</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>54.1 (11.8)</td>
</tr>
<tr>
<td>Age at entry (years)</td>
<td>55.7 (11.8)</td>
</tr>
<tr>
<td>Year of diagnosis, range</td>
<td>1961-2014</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>1865 (91.5%)</td>
</tr>
<tr>
<td>AMA+, n (%)</td>
<td>1847 (90.6%)</td>
</tr>
<tr>
<td>UDCA treated</td>
<td>1721 (84.4%)</td>
</tr>
<tr>
<td>Biopsy stage^a</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>508 (46.1%)</td>
</tr>
<tr>
<td>II</td>
<td>344 (31.2%)</td>
</tr>
<tr>
<td>III</td>
<td>174 (15.8%)</td>
</tr>
<tr>
<td>IV</td>
<td>75 (6.8%)</td>
</tr>
<tr>
<td>Serum total bilirubin ×ULN</td>
<td>0.53 (0.40-0.70)</td>
</tr>
<tr>
<td>Serum albumin ×LLN</td>
<td>1.17 (1.11-1.26)</td>
</tr>
<tr>
<td>Serum ALP ×ULN</td>
<td>1.77 (1.15-2.84)</td>
</tr>
<tr>
<td>Serum AST ×ULN</td>
<td>1.15 (0.80-1.73)</td>
</tr>
<tr>
<td>Serum ALT ×ULN</td>
<td>1.48 (0.93-2.30)</td>
</tr>
<tr>
<td>Serum platelets ×10^3/mm^3</td>
<td>253 (203-303)</td>
</tr>
</tbody>
</table>
Results

median (IQR) total follow-up period: 7.7 (4.0-11.9) years
Results

Transitions in biochemical disease stages

**Early to Moderate**

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>No. at risk UDCA</th>
<th>No. at risk Non-UDCA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>804</td>
<td>109</td>
</tr>
<tr>
<td></td>
<td>695</td>
<td>23</td>
</tr>
<tr>
<td>Median (years)</td>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>No. at risk UDCA</th>
<th>No. at risk Non-UDCA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>254</td>
<td>23</td>
</tr>
<tr>
<td>Median (years)</td>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>

**Moderate to Advanced**

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>No. at risk UDCA</th>
<th>No. at risk Non-UDCA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>78</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>No. at risk UDCA</th>
<th>No. at risk Non-UDCA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>72</td>
<td>7</td>
</tr>
</tbody>
</table>

Median time for transitions: 30 (6-180) months

18 (6-138) months
# Results

Covariates associated with transition from biochemical early - to moderate disease stage

<table>
<thead>
<tr>
<th>Covariate</th>
<th>N</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>2039</td>
<td>1.288</td>
<td>1.048</td>
<td>1.582</td>
<td>0.016</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age at entry, per 10 years</td>
<td>2039</td>
<td>1.062</td>
<td>1.003</td>
<td>1.121</td>
<td>0.022</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Year of diagnosis, per 10 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1996</td>
<td>0.827</td>
<td>0.749</td>
<td>0.905</td>
<td>&lt;0.001</td>
<td>0.905</td>
<td>0.826</td>
</tr>
<tr>
<td>UDCA usage</td>
<td>2039</td>
<td>0.882</td>
<td>0.745</td>
<td>1.044</td>
<td>0.143</td>
<td>0.762</td>
<td>0.642</td>
</tr>
<tr>
<td>Bilirubin (&gt;0.5xULN)</td>
<td>2039</td>
<td>1.874</td>
<td>1.656</td>
<td>2.122</td>
<td>&lt;0.001</td>
<td>1.675</td>
<td>1.469</td>
</tr>
<tr>
<td>Albumin (≤1.2xLLN)</td>
<td>2039</td>
<td>1.597</td>
<td>1.406</td>
<td>1.814</td>
<td>&lt;0.001</td>
<td>1.574</td>
<td>1.381</td>
</tr>
<tr>
<td>ALP xULN&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2039</td>
<td>2.253</td>
<td>1.830</td>
<td>2.774</td>
<td>&lt;0.001</td>
<td>2.104</td>
<td>1.674</td>
</tr>
<tr>
<td>AST/ALT ratio</td>
<td>2039</td>
<td>1.293</td>
<td>1.032</td>
<td>1.619</td>
<td>0.025</td>
<td>1.292</td>
<td>1.135</td>
</tr>
<tr>
<td>Platelets, per 10 units (x10³/mm³) increase</td>
<td>2039</td>
<td>0.980</td>
<td>0.973</td>
<td>0.988</td>
<td>&lt;0.001</td>
<td>0.990</td>
<td>0.931</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adjusted for baseline characteristics (age, sex, race, body mass index, and baseline laboratory values).

<sup>b</sup> ALP activity in units per minute per milliliter.
Results

Survival free of biochemical transition from early- to moderate biochemical disease stage according to Platelets and ALP.
Results

Covariates associated with transition from biochemical moderate to advanced disease stage

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Univariate analysis</th>
<th>Multivariable analysis</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1.137</td>
<td>0.551</td>
<td>1.734</td>
</tr>
<tr>
<td>Age, per 10 years^a</td>
<td>1.041</td>
<td>&lt;0.001</td>
<td>0.943</td>
</tr>
<tr>
<td>Year of diagnosis, per 10 years^b</td>
<td>0.887</td>
<td>0.163</td>
<td>1.044</td>
</tr>
<tr>
<td>UDCA usage</td>
<td>0.506</td>
<td>&lt;0.001</td>
<td>0.364</td>
</tr>
<tr>
<td>Bilirubin (&gt;1xULN)</td>
<td>2.088</td>
<td>&lt;0.001</td>
<td>1.591</td>
</tr>
<tr>
<td>Albumin (&lt;1xLLN)</td>
<td>1.109</td>
<td>0.426</td>
<td>0.860</td>
</tr>
<tr>
<td>ALP xULN^d</td>
<td>4.853</td>
<td>&lt;0.001</td>
<td>3.168</td>
</tr>
<tr>
<td>AST/ALT ratio^d</td>
<td>8.168</td>
<td>&lt;0.001</td>
<td>4.128</td>
</tr>
<tr>
<td>Platelets, per 10 units (x10^9/mm3) increase</td>
<td>0.961</td>
<td>&lt;0.001</td>
<td>0.941</td>
</tr>
</tbody>
</table>

^a Calculated as years from diagnosis to analysis date
^b Year of diagnosis
^c ULN = upper limit of normal
^d LLN = lower limit of normal
Results

MILD
(normal albumin and bilirubin)
N=2039

MODERATE
(albumin or bilirubin abnormal)
N=1084a

SEVERE
(albumin and bilirubin abnormal)
N=238a
Results
The impact of biochemical transition on events (Time-dependent analyses)

- 98% (HR 3.3, moderate vs. early, 95% CI: 2.4-4.6)
- 94% (HR advanced vs. early, 15.7, 95% CI: 11.1-22.2)
- 73% (HR advanced vs. moderate, 4.7, 95% CI: 3.7-6.1)

Event-free survival (%) over time (years):
- A: 2039, 1460, 951, 663, 413, 254
- B: 1084, 771, 559, 426, 303, 196
- C: 238, 163, 101, 68, 36, 17

Legend:
- Patients without transition from biochemical early to moderate or advanced stage
- Patients that transited from biochemically early to moderate stage
- Patients that transited from biochemically moderate to advanced disease
Summary

• Our internationally study provides a comprehensive overview of the natural history of PBC patients with early disease stage

• Almost one out of two patients with early biochemical disease will transit to moderate disease and, approximately one fourth of them to the advanced disease stage

• These transitions are associated with an increased risk of a clinical event

• ALP ≥1.67xULN and Platelets < 200 x10^3 /mm^3 could be used as surrogate predictive markers

• UDCA treatment was associated with lower rates of biochemical transitions and clinical events during follow up
Conclusion

Our findings underline the importance of clinical surveillance and UDCA treatment even in early stage PBC patients.
Acknowledgments