BIOCHEMICAL PROFILE IN 68 PRIMARY BILIARY CHOLANGITIS (PBC) SUBJECTS HAVING AN INADEQUATE RESPONSE TO URSODEOXYCHOLIC ACID

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Introduction

Primary biliary cholangitis (PBC) is a rare, chronic and progressive liver disease caused by autoimmune destruction of hepatobiliary ducts. Consequently, bile and other toxins build up in the liver (cholestasis). This can lead to fibrosis, cirrhosis and liver failure. The prevalence of PBC is estimated to 2 to 4 per 100,000 people and the incidence is estimated to be between 0.3 to 6 per 100,000 people per year. PBC is predominantly seen in females (~90%) and is typically diagnosed in its early stage by consistently elevated levels of alkaline phosphatase (ALP), a marker of cholestasis, on routine blood tests. Ursodeoxycholic acid (UDCA), a natural, non-cytotoxic bile acid has been the first-line PBC therapy for more than 20 years. However, approximately 40% of PBC patients treated with UDCA have persistent elevation of ALP and are considered inadequate responders.

The efficacy and safety of the anti-cholestatic PPAR-α agonist, seladelpar (MBX-8025), was evaluated in PBC subjects with an inadequate response to UDCA (NCT02609048/ EudraCT2015-002984-39). The study provided an opportunity to evaluate an extensive biochemical profile among the 68 PBC subjects that were screened in this study.

Methods

This was a multi-center, randomized, double blind study in PBC subjects. Sixty-eight subjects with a confirmed diagnosis of PBC and an elevated ALP (≥1.5xULN) despite treatment with a stable dose of UDCA for at least one year were screened for a phase 2 intervention study. PBC subjects were 65 females and 3 males whose age ranged from 33 to 73 years old.

For biochemical and hematological parameters, the percentage of subjects with abnormal biochemical values and mean elevation relative to the upper limit of normal (ULN) were calculated. The presence of IgG4related X (IgG4-X) in serum was evaluated. Multiple correlation analyses were performed using Pearson’s method. Correlations between ALP and biochemical parameters are presented in order of significance. Platelet and white blood cell counts were not measured in this study.

Bile acids and their glycine/taurine conjugates were measured in serum samples from 35 subjects: cholixic acid (CA), chenodeoxycholic acid (CDCA), deoxycholic acid (DCA), lithocholic acid (LCA), ursodeoxycholic acid (UDCA), glycocholic acid (G-CA), glycochenodeoxycholic acid (G-CDCA), glycocholic acid (G-CA), glycochenodeoxycholic acid (G-CDCA), glycocholic acid (G-CA), glycochenodeoxycholic acid (G-CDCA), glycocholic acid (G-CA), glycochenodeoxycholic acid (G-CDCA), glycocholic acid (G-CA), glycochenodeoxycholic acid (G-CDCA), taurocholic acid (T-CA), taurochenodeoxycholic acid (T-CDCA), taurocholic acid (T-CA), and tauroursodeoxycholic acid (T-UDCA).

Results

PBC History and UDCA Dosage

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>150</td>
</tr>
<tr>
<td>UK</td>
<td>10</td>
</tr>
<tr>
<td>Canada</td>
<td>10</td>
</tr>
<tr>
<td>Germany</td>
<td>2</td>
</tr>
<tr>
<td>Poland</td>
<td>4</td>
</tr>
</tbody>
</table>

Subjects (n) Race (%) Weight (kg) BMI (kg/m²)

<table>
<thead>
<tr>
<th>ALP (U/L)</th>
<th>8 (0.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GGT (U/L)</td>
<td>15 (3)</td>
</tr>
</tbody>
</table>

Biochemical Profile

<table>
<thead>
<tr>
<th>Biochemical Parameters</th>
<th>Normal Range (ULN-ULN)</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP</td>
<td>70-118 U/L</td>
<td>87 (61)</td>
<td>84</td>
<td>71</td>
</tr>
<tr>
<td>GGT</td>
<td>8-30 U/L</td>
<td>16 (7)</td>
<td>14</td>
<td>13</td>
</tr>
</tbody>
</table>

Correlations with ALP

- r = 0.3214, p < 0.05
- r = 0.6958, p < 0.0001
- r = 0.7806, p < 0.0001
- r = 0.2726, p < 0.05
- r = 0.7906, p < 0.0001
- r = 0.6241, p < 0.0001
- r = 0.4963, p < 0.0001

Discussion

- In addition to ALP elevation, PBC subjects with an inadequate response to UDCA have multiple biochemical abnormalities.
- The elevation of GGT is quantitatively (fold over UNL) higher than the elevation of ALP. This fact is currently unexplained.
- Direct bilirubin is more frequently elevated than total bilirubin and, thus, is a more specific marker of cholestasis.
- The frequent elevation of bone-specific ALP (90%) has not been described previously and needs to be further explored.
- More than 50% of patients have an elevation of transaminases which points, in addition to the damage of cholangiocytes, to a dysfunction of hepatocytes.
- The abnormalities of lipid parameters are frequent, particularly the elevation of HDL-C. The high HDL-C levels are striking as extreme levels are rarely seen in other diseases.
- While this elevation has classically been linked to cholestasis, the absence of correlation with ALP and the absence of Lp-X in serum both go against this explanation. A dysfunction of the hepatocytes could constitute another explanation (e.g. down-regulation of HLD-receptors) and needs to be further explored.
- The frequent elevation of total protein, probably explained by the polyclonal activation of immunoglobulins, could potentially be associated with an increased plasma viscosity. This needs to be further explored as an increase of viscosity could contribute to the frequent asthenia seen in PBC subjects.

Conclusions

- The frequency of bone-specific ALP elevation and its strong correlation with ALP were unexpected and could indicate that osteopenia may be prevalent in this population.
- The elevation of direct bilirubin was twice more frequent than the elevation of total bilirubin and could constitute a more sensitive prognostic marker.
- GGT was quantitatively more elevated than ALP.
- The HDL-C elevation, which is known in PBC, can however reach unusual levels that are rarely seen in other conditions. The HDL-C increase did not correlate with the other markers of cholestasis, and its mechanism is unclear.
- Lp-X was not detected in any patients’ samples.
- The frequent increase in total protein is probably a consequence of the polyclonal activation of immunoglobulins.

References