Differential expression of bile acid subspecies with maralixibat treatment in pruritus responders with bile salt export pump deficiency

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Introduction

• Progressive familial intrahepatic cholestasis (PFIC) is a genetic disease resulting in the absence of or reduction in bile salt export pump (BSEP) activity. It causes severe pruritus (accumulation of serum bile acids (sBAs)) with subsequent pruritus, delayed growth and development (failure to thrive), liver injury requiring transplantation, and shortened life expectancy.1,2

• Maralixibat (MRX) is a minimally absorbed, selective inhibitor of the ileal apical sodium-dependent bile acid (BA) transporter, interrupting the enterohepatic circulation of BAs, thereby reducing sBAs in both height and weight, as well as reductions in sBAs and pruritus, in children with non-tranfusing BSEP mutations receiving MRX.3

Aim

• To investigate whether changes in the composition of the total sBA pool from baseline (BL) could predict pruritus response in children with non-tranfusing BSEP mutations treated with MRX during the INDIGO study.

Methods

Study population

• Eligible patients were children (1–18 years of age) with BSEP deficiency (biallelic ABCB11 mutations) treated with MRX (280 μg/kg/day initially, increased to 560 μg/kg/day at Week 72).

• This analysis focused on those with mild to moderate non-tranfusing BSEP mutations from BL to Week 72.

Analytical methods: Analysis of C18 bile acids by tandem mass spectrometry

• Quantitative analysis of the 15 major sBAs was carried out by stable-isotope dilution electrospray ionization liquid chromatography-mass spectrometry (MS/MS) using a fully validated proprietary in-house assay that complies with College of American Pathologists/Clinical Laboratory Improvement Amendments certification. Similarly, 7 alpha-hydroxy-4-cholate-3-one (sterol-C4) was measured by tandem mass spectrometry.4

• Total sBA concentrations were calculated from the sum of individual species.

Table 1

<table>
<thead>
<tr>
<th>sBA</th>
<th>hydrophilicity</th>
<th>hydrophobicity</th>
<th>conc. at BL (μM)</th>
<th>conc. at Week 72 (μM)</th>
<th>Δ conc. at Week 72</th>
<th>p-valuea</th>
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<tr>
<td>TCA</td>
<td>hydrophilic</td>
<td>hydrophobic</td>
<td>160.6 ± 108.5</td>
<td>21.8 ± 18.9</td>
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<td>17.1 ± 9.8</td>
<td>167.0 ± 156.9</td>
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<td>12.5%</td>
<td>6.03%</td>
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<td>0.68%</td>
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<td>2.76%</td>
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<td>2.1%</td>
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<td>0%</td>
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</table>

Data analyses

• Primary objective: evaluate changes in sBA subspecies from BL over 72 weeks in children with pruritus response to MRX compared with non-responders.

• Secondary objectives: evaluate the correlation between pruritus (itchRO Observed [itchRO(Obs)]) and sBA subspecies changes over 72 weeks of MRX treatment in pruritus responders vs non-responders, and assess the levels of the BA synthesis marker sterol-C4.

• ItchRO(Obs) ranges on a 5-point scale (0 = no pruritus and 5 = severe pruritus).

• Pruritus response was defined as ≥ 1 point reduction in pruritus score at 1 time point.

Statistical methods

• The two-tailed Student’s t-test was used to compare groups. Pearson’s correlation coefficient was used to analyze itchRO(Obs) and sBA species changes. Statistical computing was conducted with R.2

Results

Patient characteristics

• In total, all patients with mild to moderate non-tranfusing BSEP mutations were induced in this analysis (11 responders and 8 non-responders); all were receiving prior and ongoing concomitant ursodeoxycholic acid (UDCA) therapy.

• Patient demographics: mean age was 4.1 years (± standard deviation [SD] 3.4); males n = 13 (68.4%); mean BL levels ± SD: sBA 373.4 ± 140.6 μM (n = 9); mean BL sterol-C4 levels ± SD: 10.24% ± 6.03% (n = 11).

Changes in sBA levels and composition

• Percentage reductions in total sBA levels were significantly greater in responders vs non-responders (p < 0.01 to 0.005; Figure 1).

Conclusions

• A trend toward increased proportions of unconjugated sBAs was observed in responders (0.84 ± standard error [SE] 0.487%) vs non-responders (0.59 ± SE 0.484%; p = 0.09; Figure 2).

• In pruritus responders, serum sterol-C4 levels increased during treatment, consistent with the biological action of MRX. In non-responders, sterol-C4 levels remained relatively unchanged and were significantly lower vs pruritus responders (p < 0.05; Figure 4).

Figure 1. Change in total serum bile acid levels over 72 weeks of maximal treatment in pruritus responders vs non-responders

Figure 2. Composition of serum bile acid following 72 weeks of maximal treatment in pruritus responders vs non-responders

Figure 3. Correlation between selected conjugated serum bile acid species change from baseline and reduction in the itchRO(Obs) score during 72 weeks of maximal treatment

Figure 4. Serum sterol-C4 levels over 72 weeks of maximal treatment in pruritus responders vs non-responders

References