Pruritus intensity is associated with cholestasis biomarkers and quality of life measures after maralixibat treatment in children with Alagille syndrome

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Introduction

- Alagille syndrome (ALGS) is a rare, genetic, multisystem disorder that commonly presents in infancy.1
- Patients with ALGS experience severe cholestatic pruritus due to the accumulation of serum bile acids (sBA).1
- ALGS-associated pruritus can be extremely debilitating, resulting in bleeding, scarring, sleep disturbance, fatigue, and decreased quality of life, which can often have a significant impact on the patient and family.1,2
- Maralixibat is an apical sodium-dependent bile acid transporter inhibitor that has been shown to significantly reduce levels of sBA and pruritus via interruption of the enterohepatic circulation.1
- Absolute values of pruritus intensity and cholestasis biomarkers have been shown to poorly correlate.3

Here, we evaluate how change in pruritus intensity correlates with change in cholestasis biomarkers in the ICONIC study (NCT02160782).

Aim

To characterize correlations between pruritus, as measured by the Itch Reported Outcome Observer (ItchRO[Obs]) tool, and multiple parameters, including sBA and sBA subspecies, autotaxin (ATX), and quality of life measures following maralixibat treatment in children with ALGS.

Methods

Study design

- ICONIC is a long-term, Phase 2, double-blind study assessing the effect of maralixibat treatment in children with ALGS, with an initial placebo-controlled, randomized withdrawal period (Figure 1). Participants continue to receive maralixibat in an ongoing rollover study.
  - Participants received doses of 400 µg/kg/day of maralixibat chloride equivalent to 380 µg/kg/day of maralixibat, and hereafter referred to as 380 µg/kg/day maralixibat, for 18 weeks.
  - During the double-blind, randomized withdrawal period, participants were randomized (1:1) to continue with maralixibat or switch to matching placebo for 4 weeks.
  - After the 4-week randomized withdrawal period, all participants received open-label maralixibat to Week 48.
  - Participants were allowed to enter the long-term extension study.
  - Study measurements included, but were not limited to, pruritus, total and subspecies of sBA, ATX, Pediatric Quality of Life Inventory™ (PedsQL™) assessments, Clinician Scratch Scale (CSS) score, and growth. All assessments were collected at Baseline and Week 48 of the study.

Data analysis

- Data collected and reported herein were taken from the first 48 weeks of treatment.
  - Primary objective: to evaluate correlations between multiple parameters associated with pruritus in patients with ALGS:
    - Pruritus intensity was assessed at Baseline and Week 48 using the ItchRO[Obs] tool.
    - sBA, ATX, the CSS score, height z-score, and the PedsQL™ score evaluations were also evaluated.

Statistical methods

- Post-hoc analysis data assessed pairwise correlations between pruritus intensity (defined by the ItchRO[Obs] scale) and cholestasis parameters after Week 48 using Spearman’s rank correlation coefficient (r).
  - A significant correlation coefficient was confirmed by a p-value of < 0.05, which provided evidence to reject the null hypothesis of no pairwise correlation (r = 0).

Results

Baseline characteristics for analysis population

Table 1. Baseline characteristics for analysis population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All participants, N Mean age, years (SD)</th>
<th>Mean CSS score, points (SD)</th>
<th>Mean sBA, mmol/L (SD)</th>
<th>Mean ItchRO(Obs) score, points (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sBA total</td>
<td>25.7 (3.35)</td>
<td>3.0 (0.94)</td>
<td>205 (213.9)</td>
<td>2.9 (1.56)</td>
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<tr>
<td>sBA conjugated</td>
<td>1.7 (0.95)</td>
<td>3.0 (0.94)</td>
<td>85 (75.9)</td>
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Effect of sBA reductions on intensity of pruritus

• Overall average ItchRO(Obs) score reduction was 1.6 points at Week 48.
• Increasing proportional sBA reductions after 50% appeared to be associated with greater ItchRO(Obs) score reductions (Table 3).
• One participant normalized with ItchRO(Obs) score reduction of -3.5 points.

Table 2. Change in pruritus intensity in relation to changes in sBA

<table>
<thead>
<tr>
<th>sBA reduction, %</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
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<tr>
<td>Mean ItchRO(Obs) score, points (SD)</td>
<td>-1.85</td>
<td>-2.12</td>
<td>-2.31</td>
<td>-2.79</td>
<td>-2.71</td>
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Conclusions

- Maralixibat treatment in study participants with ALGS led to significant and clinically meaningful improvements in pruritus, using ItchRO(Obs) and CSS scores.
- sBA reductions correlated with reductions in pruritus intensity, further supporting the causal relationship between the two.
- Significant correlations were also found with ATX and height z-score, with a trend towards significance in the PedsQL™ Impact.
- Pruritus was significantly correlated with PedsQL™ Fatigue when assessing change from Baseline to Week 48, suggesting that improvement in sleep is reduced with increased pruritus.
- Overall, the positive treatment effects of maralixibat in patients with ALGS demonstrate important correlations with multiple clinically relevant parameters at Week 48.

References


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