Introduction

- Alagille syndrome (ALGS) is a rare, pediatric cholestatic liver disease that presents with multiple co-morbidities; the most debilitating symptom in children with ALGS is unremitting pruritus.1
- Serum bile acid accumulation due to a paucity of bile ducts is thought to be related to pruritus.2,3
- Cholestatic pruritus in ALGS is among the worst in cholestatic liver diseases, affecting approximately 59–82% of patients.2,3 Patients often have skin lesions and excoriations, and suffer from chronic sleep and mood disturbances.4
- Refractory pruritus is often an indicator for liver transplantation.5
- Although the severity of pruritus in ALGS is well known,4 the within-patient variability of pruritus in this setting has not been fully characterized. Assessments rely on observer- or patient-reported outcome measures.6

To date, there has been a lack of standardized, validated tools to measure cholestatic pruritus.1,3 Kamath et al.6 recently developed two new tools to assess itch in patients with ALGS:
- Itch Reported Outcome Observer (ItchRO(Obs)) for caregivers to report patient pruritus ratings.8
- Itch Reported Outcome Patient (ItchRO(Pt)) for patients ≥ 8 years of age to report their own pruritus ratings.9

ICONIC is a Phase 2, placebo-controlled, randomized study of maralixibat in children with ALGS and cholestatic pruritus (NCT02160782).

Here, the daily natural variability of pruritus in children with ALGS is characterized using ItchRO(Obs) and ItchRO(Pt) scores provided during the 28-day screening period of ICONIC, when no drug was administered.

Aim

- To provide descriptive summaries of responses to the ItchRO(Obs) and ItchRO(Pt) in order to characterize the within-patient natural variability of pruritus in children with ALGS-associated cholestatic pruritus participating in the ICONIC study.

Methods

Study population

- Eligible patients from the intent-to-treat analysis of the ICONIC study were assessed to characterize ALGS-associated cholestatic pruritus.

- Key inclusion criteria included:
  - Males and females aged ≥ 12 months and ≤ 18 years.
  - Diagnosis of ALGS based on criteria outlined in the ICONIC study protocol.
  - Average daily ItchRO score ≥ 2 in the screening period prior to dosing, despite background antipruritic therapy.
  - Consistent caregiver(s) for the duration of the study.

- Completion of ≥ 10 electronic diary (e-diary) reports (morning [AM] and evening [PM]) by the caregiver(s) and age-appropriate subjects during 2 consecutive weeks of the screening period (maximum of two possible ratings per day over the 30 days prior to randomization).

Reported outcomes

- Pruritus severity was reported by caregivers of all patients (regardless of patient age) using the ItchRO(Obs) tool. Patients ≥ 9 years of age also reported their own pruritus ratings using the ItchRO(Pt) tool, and patients 6–8 years of age completed the ItchRO(Pt) with the help of a caregiver.

- Both measures were completed twice daily (AM and PM) in an e-diary; both used a five-point scale, from 0 (none observed or reported) to 4 (very severe) for ItchRO(Obs) and from 0 (I didn’t feel itchy) to 4 (I felt very, very itchy) for ItchRO(Pt).

Data analyses

- Primary objective: to evaluate and establish the natural variability of pruritus based on caregivers’ responses to the ItchRO(Obs) and patients’ responses to the ItchRO(Pt) measures obtained during the screening period.

Statistical methods

- The intra-individual standard deviation (ISD; between-person standard deviations commonly reported) and the intra-individual Gini (G) coefficient (index of inequality [analysis days] among the values of a variable) values were used to assess patients’ variability in pruritus from both the observer- and patient-reported ratings during screening.

- For the G coefficient, 0 = ‘perfect equality’ (scoring data are not variable) and 1 = ‘perfect inequality’ (values closer to 1 indicate scoring data are quite variable).

- Both the ISDs and G coefficient values were averaged across patients and data presented with 95% confidence intervals.

Results

Patient characteristics

- In total, 29 patients with ALGS-associated pruritus were included in the analysis. Of these, 22 patients were aged < 9 years and 7 were ≥ 9 years. Overall, the mean age was 5.7 years and 65.5% of patients were female.

- Observer-reported ratings were available for all 29 patients and patient-reported ratings were available for 14 patients. A median of 28 screening days was reported for each patient, with a total of 1510 observer ratings and 747 patient ratings.

Variability of pruritus

- Pooled (AM and PM) individual patient pruritus ratings did not vary substantially, demonstrating consistency within each patient throughout the 28-day screening period (Table 1).

- The pooled ISD demonstrated that 95% of values were between 0.24 and 1.07 for observer ratings, and between 0.23 and 0.70 for patient ratings, with approximately only 10% of values contributing to the variability (Table 1).

- Similarity, 95% of the G coefficient values were between 0.02 and 0.21 for observer ratings, and between 0.03 and 0.27 for patient ratings, with approximately only 10% of values contributing to the variability (Table 1).

- Observer ratings were available for all 29 patients and patient-reported ratings were available for 14 patients. A median of 28 screening days was reported for each patient, with a total of 1510 observer ratings and 747 patient ratings.

- Despite background antipruritic therapy, pruritus was generally moderate to severe and persistent in nature.

- Supporting these data, colored pruritus heatmaps showed that pruritus as measured by the ItchRO tool remained within a narrow range (i.e. yellow to red, with little to no green) (Figure 1). This indicates that pruritus was persistent and did not fluctuate over time in severity and frequency.

Conclusions

- This is the first cohort study to characterize cholestatic pruritus in children with ALGS using a consistent and validated pruritus tool at both AM and PM time points for 28 days.

- This evaluation shows that pruritus in children with ALGS is persistent over time with minimal fluctuations.

- There is a high unmet need for effective pharmacologic treatment.

- The ICONIC study demonstrated that children with ALGS who were treated with maralixibat exhibited sustained and meaningful reductions in pruritus.1

- Understanding the nature of ALGS-associated cholestatic pruritus is critical for effective patient care and development of new treatment options.1

References


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