Itch Reported Outcome tool for caregivers of pediatric patients with cholestatic liver disease: an analysis of validation and scoring from the ICONIC maralixibat study

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Introduction

- Cholestatic liver disease associated with Alagille syndrome (ALGS) commonly presents with unrelenting cholestatic pruritus in childhood,[1,2] and often results in skin lesions, as well as sleep and mood disturbances.[3]
- Assessments to quantify the physiological, psychosocial, and behavioral aspects of cholestatic pruritus need to rely on observer- or patient-reported outcome measures.[4]
- Due to the lack of standardized pediatric assessments for childhood cholestatic pruritus, Kamath *et al.*[4] recently developed a new tool to assess the severity and frequency of itch-related symptoms in children with cholestatic disease, including in patients with ALGS: the Itch Reported Outcome Observer (ItchRO[Obs]) for caregivers.[4]
- Here, the psychometric performance of the ItchRO(Obs) in children with ALGS is evaluated using data from the intent-to-treat (ITT) analysis set of a phase 2, placebo-controlled, randomized withdrawal study with maralixibat (ICONIC; NCT02160782).

Objectives

- To assess and validate the scoring and psychometric performance of the ItchRO(Obs) tool in patients of the ICONIC study with ALGS-associated cholestatic pruritus.
- To compare the psychometric properties of the ItchRO(Obs) between patients of the ICONIC study < 9 and ≥ 9 years of age.

Methods

Study population

- The ITT data set (N = 29) of the ICONIC study, from patients with ALGS-associated cholestatic pruritus, was analyzed.
- Key inclusion criteria were:
  - Male or female between 12 months and 18 years of age, inclusive.
  - Diagnosis of ALGS based on the diagnostic criteria outlined in the ICONIC study protocol.
  - Biological and clinical evidence of cholestasis.
  - Patients were expected to have a consistent caregiver(s) for the duration of the study.
  - Average daily ItchRO(Obs) scores > 2 in the screening period prior to dosing.

ItchRO(Obs) administration and scoring

- Cholestatic pruritus severity was reported by caregivers of all patients (regardless of patient age) using the ItchRO(Obs) tool.[4]
- The ItchRO(Obs) was completed twice daily (morning [AM] and evening [PM]) using electronic diaries, as follows:
  - Caregivers were asked to rate the severity of the patient's itch-related symptoms from the time the child went to bed until waking up (AM diary), and from waking up until the time of diary completion in the evening (PM diary), using a five-point scale (0 = none observed or reported, 4 = very severe).[4]
  - AM and PM 7-day average scores were calculated as the average of either the daily AM or PM scores over each defined study week, which consisted of the 7 days before the scheduled visit (Baseline [Day 0], Weeks 3, 6, 12, 18, 22, 28, 38, and 48).
  - AM and PM 28-day average scores were calculated as the average of either the daily AM or PM scores over each defined 28-day period, which consisted of the 28 days before select scheduled visits (Baseline [Day 0], Weeks 3, 6, 12, 18, 22, 28, 38, and 48).

Scales used to validate ItchRO(Obs) for ALGS

- Covalidators for the ItchRO(Obs) included the Pediatric Quality of Life Inventory (PedsQL),[5] Clinician Scratch Scale (CSS) score,[6,7] and the Caregiver Impression of Change-Itch Related Symptoms (CIC-Itch; a global measure for change).

Psychometric validation

Assessment of score quality

- Convergent validity: examined by estimating Pearson correlations between the ItchRO(Obs) score and the CSS score ($r \geq 0.40$ considered acceptable validity).
- Divergent validity: examined by estimating Pearson correlations between the ItchRO(Obs) score and the PedsQL Total (Child and Parent), PedsQL Family Impact Total, and PedsQL Fatigue (Child and Parent) scores ($r \leq -0.40$ considered acceptable validity).
- Known groups validity: examined by calculating mean ItchRO(Obs) scores within strata defined by caregivers' CSS ratings (validity established if average ItchRO[Obs] scores showed monotonic increases within corresponding CSS strata for pruritus severity).
- Test-retest reliability: the intraclass correlation coefficient (ICC[2,1]) was calculated using data from screening and Baseline (ICC[2,1] ≥ 0.70 was considered satisfactory).

Examination of meaningful change

- Score variability: standard error of measurement (SEM) was estimated for the 7-day and 28-day ItchRO(Obs) scores for AM and PM within stratifications for age (i.e. < 9 and ≥ 9 years of age) and calculated as $SEM = s\sqrt{(1-r_{xx})}$, where s was the Week 12 age-group specific standard deviation of the ItchRO(Obs) scores; r_{xx} was the reliability of the scores, which is the ICC(2,1) for the score.[8] Due to limited sample sizes, the r_{xx} term in the present analyses is equivalent to the sample-level ICC(2,1) statistic for each ItchRO(Obs) score. Differences in the magnitude of the SEM between age groups were compared for all scores.
- Distribution-based method: the SEM was used in conjunction with the distribution of ItchRO(Obs) change scores to assess whether patients experienced true change from Week 18 to Week 22. To assess the number of patients who likely experienced change, the number of patients with change scores exceeding 2 SEMs was calculated (ItchRO[Obs] change scores exceeding 2 SEMs were considered to exceed the measurement error).
- Anchor-based method: an attempt was made to characterize a range of plausible estimates for meaningful change; empirical cumulative density function of both Week 18 to 22 and Baseline to Week 48 change scores were generated within strata of the CIC-Itch to characterize the proportions of the sample falling into the range of all possible differences in ItchRO(Obs) scores and help interpret the minimally clinically important change.

Results

Assessment of score quality

- Positive correlations between ItchRO(Obs) and CSS scores indicated convergent validity ($r = 0.63$ to 0.78; Table 1).
- Negative correlations between ItchRO(Obs) and PedsQL scores indicated divergent validity ($r = -0.08$ to -0.96; Table 1).

Table 1. Convergent and divergent correlations with ItchRO(Obs) scores stratified by age

Age (years)	Measures	7-day scores		28-day scores	
		AM	PM	AM	PM
< 9	Multidimensional Fatigue Scale (Children)	–0.643	–0.716	–0.797	–0.708
	Physical Health Summary (Children)	–0.422	–0.152	–0.432	–0.173
	Psychosocial Health Summary (Children)	–0.082	–0.508	–0.379	–0.471
	PedsQL Total Scale (Children)	–0.276	–0.506	–0.533	–0.485
	Family Impact Total Scale	–0.239	–0.217	–0.330	–0.343
	Parent Functioning Summary	–0.225	–0.203	–0.318	–0.305
	Multidimensional Fatigue Scale (Parent)	–0.430	–0.368	–0.539	–0.504
	Physical Health Summary (Parent)	–0.117	–0.083	–0.188	–0.135
	Psychosocial Health Summary (Parent)	–0.427	–0.352	–0.515	–0.462
	PedsQL Total Scale (Parent)	–0.307	–0.250	–0.404	–0.348
	CSS	0.673	0.784	0.633	0.693
≥ 9	Multidimensional Fatigue Scale (Children)	–0.629	–0.702	–0.688	–0.760
	Physical Health Summary (Children)	–0.383	–0.362	–0.478	–0.415
	Psychosocial Health Summary (Children)	–0.601	–0.790	–0.716	–0.816
	PedsQL Total Scale (Children)	–0.582	–0.703	–0.702	–0.744
	Family Impact Total Scale	–0.881	–0.961	–0.865	–0.959
	Parent Functioning Summary	–0.939	–0.955	–0.915	–0.956
	Multidimensional Fatigue Scale (Parent)	–0.958	–0.923	–0.952	–0.945
	Physical Health Summary (Parent)	–0.613	–0.384	–0.493	–0.423
	Psychosocial Health Summary (Parent)	–0.457	–0.454	–0.437	–0.509
	PedsQL Total Scale (Parent)	–0.543	–0.466	–0.489	–0.520
	CSS	0.647	0.775	0.767	0.756

Convergent correlations in the range of $r \geq 0.40$ and divergent correlations in the range of $r \leq -0.40$ were general thresholds for demonstrating validity

AM, morning; CSS, Clinician Scratch Scale; ItchRO(Obs), Itch Reported Outcome Observer; PedsQL, Pediatric Quality of Life Inventory; PM, evening

- Analysis of known groups validity indicated that worse ItchRO(Obs) scores were associated with more pruritus-associated skin damage, as measured by the CSS. Patterns were consistent for 7-day and 28-day summaries and results considered robust given the limited sample sizes within each of the strata examined (Table 2).

Table 2. Known groups validity for ItchRO(Obs) scores stratified by age within strata of the CSS

ItchRO	CSS	7-day AM		7-day PM		28-day AM		28-day PM	
		≥ 9 years	< 9 years	≥ 9 years	< 9 years	≥ 9 years	< 9 years	≥ 9 years	< 9 years
ItchRO (Obs)	No evidence	0.21 (0.30), 2	0.45 (0.51), 6	0.07 (0.10), 2	0.43 (0.50), 6	0.29 (0.41), 2	0.59 (0.59), 6	0.19 (0.27), 2	0.59 (0.53), 6
	Rubbing	1.43 (0.81), 2	1 (0.82), 7	0.71 (0.40), 2	1.04 (0.79), 7	1.45 (0.43), 2	1.1 (0.81), 7	0.79 (0.40), 2	1.12 (0.86), 7
	Scratching	1.9 (1.08), 2	– (–), 1	1.64 (1.11), 2	– (–), 1	1.86 (0.90), 2	– (–), 1	1.8 (1.04), 2	– (–), 1
	Abrasion	NA	2 (0.44), 7	NA	2.08 (0.41), 7	NA	2.1 (0.53), 7	NA	2.11 (0.52), 7
	Scarring	– (–), 1	– (–), 1	– (–), 1	– (–), 1	– (–), 1	– (–), 1	– (–), 1	– (–), 1

Data are mean (SD), N
Dashes represent cases where the mean and SD were not meaningful with N = 1

AM, morning; CSS, Clinician Scratch Scale; ItchRO, Itch Reported Outcome; ItchRO(Obs), Itch Reported Outcome Observer; NA, not available; PM, evening; SD, standard deviation

Meaningful change

- For the ItchRO(Obs), the estimated SEMs ranged from 0.28 to 0.32, indicating that 7-day and 28-day AM and PM change scores of –0.56 to –0.64 were indicative of experienced changes (Table 3).

Table 3. Average and SEM for ItchRO(Obs) scores calculated within strata of age groups

ItchRO	Average score	Age (years)	N	Mean	SD	SEM[a]
ItchRO (Obs)	28-day PM	≥ 9	7	1.34	0.78	0.305
	28-day AM	≥ 9	7	1.54	0.78	0.302
	7-day PM	≥ 9	7	1.10	0.78	0.281
	7-day AM	≥ 9	7	1.34	0.82	0.300
	28-day PM	< 9	22	1.41	0.78	0.306
	28-day AM	< 9	22	1.44	0.78	0.301
	7-day PM	< 9	22	1.37	0.85	0.308
	7-day AM	< 9	22	1.36	0.88	0.322

[a]SEM calculations are based on the Week 12 scores and utilize the intraclass correlation for Weeks 12–18 for the entire analytic sample

AM, morning; ItchRO, Itch Reported Outcome; ItchRO(Obs), Itch Reported Outcome Observer; PM, evening; SD, standard deviation; SEM, standard error of measurement

- Distribution-based analysis using SEMs showed that more than half of patients had change scores that exceeded 2 SEMs (Table 4). This indicates that the ItchRO(Obs) was capable of detecting change that exceeded the error of measurement; differences between age groups were not found.

Table 4. Number of patients whose Weeks 18–22 ItchRO(Obs) change scores exceeded 2 SEMs

ItchRO	Category	7-day AM		28-day AM		7-day PM		28-day PM	
		≥ 9 years	< 9 years	≥ 9 years	< 9 years	≥ 9 years	< 9 years	≥ 9 years	< 9 years
ItchRO (Obs)	Change did not exceed 2 SEMs	4	6	4	8	4	10	4	14
	Change exceeded 2 SEMs	3	15	3	14	3	12	3	8
	Total	**7**	**21**	**7**	**22**	**7**	**22**	**7**	**22**

AM, morning; ItchRO, Itch Reported Outcome; ItchRO(Obs), Itch Reported Outcome Observer; PM, evening; SEM, standard error of measurement

- Anchor-based analysis showed that results were of little interpretative value due to the small sample size.

Conclusions

- The ItchRO(Obs) is a reliable and valid tool that is capable of detecting small, clinically meaningful changes in cholestatic pruritus-related symptoms in children with ALGS across all ages.
- Change scores as small as –0.56 were likely indicative of experienced change on the ItchRO(Obs) scale.
- Similarity between AM and PM scores suggests that the ItchRO(Obs) tool may be used once a day, instead of twice a day, for future studies.

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References
1. Bergasa NV. Pruritus of cholestasis. In: Carstens E, Akiyama T, eds. *Itch: Mechanisms and Treatment.* Boca Raton, FL: CRC Press/Taylor & Francis; 2014; 2. Emerick KM, Rand EB, Goldmuntz E, *et al.* Features of Alagille syndrome in 92 patients: frequency and relation to prognosis. *Hepatology* 1999;29(3):822–829; 3. Elisofon SA, Emerick KM, Sinacore JM, Alonso EM. Health status of patients with Alagille syndrome. *J Pediatr Gastroenterol Nutr* 2010;51(6):759–765; 4. Kamath BM, Abetz-Webb L, Kennedy C, *et al.* Development of a novel tool to assess the impact of itching in pediatric cholestasis. *Patient* 2018;11(1):69–82; 5. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory Version 4.0 generic core scales in healthy and patient populations. *Med Care* 2001;39(8):800–812; 6. Shneider BL, Spino C, Kamath BM, *et al.* Placebo-controlled randomized trial of an intestinal bile salt transport inhibitor for pruritus in Alagille syndrome. *Hepatol Commun* 2018;2(10):1184–1198; 7. Whitington PF, Whitington GL. Partial external diversion of bile for the treatment of intractable pruritus associated with intrahepatic cholestasis. *Gastroenterology* 1988;95(1):130–136; 8. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 1979;86(2):420–428

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