RESEARCH LETTER

Patient-reported Itch Outcome Measures for Chronic Pruritus in Dystrophic Epidermolysis Bullosa: Exploratory Analysis of a Phase 2 Randomized Controlled Trial

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To the Editor,

Epidermolysis bullosa (EB) is a group of genodermatoses characterized by skin fragility and blistering. Pruritus is one of the most burdensome EB symptoms that provokes a need to scratch, resulting in new wounds (1, 2). This itch-scratch-blister cycle results in patient guilt, frustration and anxiety (1). The most appropriate approaches for measuring itch in EB remain under investigation. Prior clinical studies investigating pruritus in EB used severity scales, most commonly the Numeric Rating Scale (NRS) or Visual Analogue Scale (3). Multidimensional pruritus assessment tools such as Patient-Reported Outcome Measurement Information System (PROMIS) (4) or Leuven Itch Scale (LIS) (5) and the itch-specific quality-of-life instrument (ItchyQoL) (6) were used in EB studies (3). However, these itch instruments have not been content-validated in EB, and severe dystrophic epidermolysis bullosa (DEB) may reduce item applicability due to profound activity restriction (7).

In this study, we examined how existing instruments (PROMIS itch questionnaires (4), LIS (5), and ItchyQoL (6)) correspond to NRS ratings of itch in DEB.

We used data from a randomized, double-blind, placebo-controlled phase 2 trial of oral serlopitant for EB-related itch (NCT03836001; Stanford Institutional Review Board (IRB) #49084) (8). Participants were aged ≥13 years, reported ≥6 weeks of itch and had a screening average-itch NRS≥5. At baseline, month 1 and month 2, participants completed the 24 h average-itch, worst-itch and dressing-itch NRS (0–10; higher score indicates worse itch); dressing-itch refers to pruritus during dressing changes or bathing. Simultaneously, participants answered 3 multidimensional instruments: PROMIS itch questionnaires (interference, mood and sleep, scratching behaviour, activity and clothing), LIS (severity, consequences, distress), and ItchyQoL (**Table I**). Linear mixed models estimated the change in instrument scores per 1-point increase in each NRS item across visits, with two-sided $\alpha<0.05$. Models included a participant-level random intercept and were fit using maximum likelihood with all available observations, without imputation. For instrument correspondence, treatment assignment was disregarded, and all DEB participants were analysed together.

Twenty participants with DEB (recessive DEB=17, dominant DEB=3) were included (Table I). Five participants were aged <18 years (13 years, n=2; 14 years, n=3).

All 4 PROMIS itch domains showed significant positive associations with the 3 itch NRS measures (all $\beta>0$; $p<0.05$; **Table II**). For average-itch NRS, the largest estimated T-score increase per 1-point rise in NRS was observed for scratching behaviour ($\beta=3.0$; 95% confidence interval [CI] 1.4–4.6). For worst-itch and dressing-itch NRS, mood and sleep showed the largest estimated changes (worst-itch: $\beta=3.9$; 2.3–5.4; dressing-itch: $\beta=4.4$; 3.1–5.8), followed by scratching behaviour, with smaller effects for activity and clothing and interference.

Across LIS domains, associations were strongest with worst-itch NRS (Table II); effects were smaller yet concordant for dressing-itch, and estimates for average-itch were less precise, especially for distress, for which the 95% CI narrowly included zero (Table II). Overall, LIS may preferentially reflect peak itch burden.

Table I. Baseline data of 20 participants with DEB

	Median	(Range)
Age (years)	31	(13 to 73)
Average-itch NRS	7	(3 to 9)
Worst-itch NRS	7.7	(2.0 to 9.1)
Dressing-itch NRS	7	(2 to 10)
PROMIS itch questionnaires[a]		
Interference	49.6	(47.1 to 51.6)
Mood and sleep	49.2	(40.9 to 53.3)
Scratching behaviour	56.4	(54.0 to 69.0)
Activity and clothing	44.4	(42.0 to 54.0)
Leuven Itch Scale[b]		
Severity	65	(30 to 100)
Consequences	32.9	(4.5 to 72.7)
Distress	60	(2 to 100)
ItchyQoL[c]	46	(22 to 74)

[a]T-score of each domain was calculated using the HealthMeasures Scoring Service. A T-score of 50 is the average score for the general population having itch. Higher scores reflect worse impairment. [b]Each domain ranges from 0 to 100. Higher scores reflect worse condition. [c] Each item is scored from 1 to 5, with a sum of 22 items ranging from 22 to 110. Higher scores reflect worse itch-specific health-related quality of life impairment.
Dressing-itch:Dressing change-related itch NRS; NRS:Numeric Rating Scale; PROMIS:Patient-Reported Outcomes Measurement Information System.

Table II. Predicted change in each outcome for a 1-point increase in itch NRS items

Outcome variables (range)[a]		**Covariate (itch NRS items)**		
		Average-itch NRS	Worst-itch NRS	Dressing-itch NRS
		Predicted change (95% CI)		
PROMIS itch instruments (T-score)				
	Interference	1.4 (0.06–2.8)*	2.0 (1.1–2.9)**	1.6 (0.4–2.8)*
	Mood and sleep	2.0 (0.2–3.8)*	3.9 (2.3–5.4)***	4.4 (3.1–5.8)***
	Scratching behaviour	3.0 (1.4–4.6)**	3.2 (1.5–4.8)**	2.2 (0.6–3.9)*
	Activity and clothing	1.9 (0.1–3.7)*	2.5 (1.0–4.0)**	1.9 (0.5–3.3)*
Leuven Itch Scale (0–100)				
	Severity	6.8 (4.7–8.9)***	6.4 (4.3–8.6)***	3.4 (1.4–5.3)**
	Consequences	3.4 (0.06–6.7)*	4.4 (1.0–7.9)*	2.6 (0.3–4.8)*
	Distress	4.4 (-0.1–8.9)	6.0 (1.8–10.2)**	3.7 (1.0–6.4)*
ItchyQoL				
	Total (22–110)	3.1 (0.6–5.6)*	4.2 (1.8–6.6)**	2.1 (0.3–3.9)*
	Symptoms (6–30)	1.1 (0.4–1.9)**	1.3 (0.6–2.0)***	0.9 (0.4–1.4)**
	Functional limitations (7–35)	0.9 (-0.07–1.8)	1.4 (0.6–2.2)**	0.5 (-0.1–1.2)
	Emotions (9–45)	1.2 (-0.04–2.4)	1.4 (0.1–2.7)*	0.7 (-0.2–1.6)

*** = $p<0.001$, ** = $p<0.01$, * $p<0.05$. [a]The range shows the score range in each domain.
CI:Confidence Interval; Dressing-Itch:Dressing change-related Itch NRS; NRS:Numeric Rating Scale; PROMIS:Patient-Reported Outcomes Measurement Information System.

ItchyQoL total score showed significant positive associations with all 3 itch NRS measures. Among subscales, symptoms were consistently significant, whereas functional limitations and emotions showed the clearest associations with worst-itch NRS, with smaller or less precise effects for average- and dressing-itch (Table II). Overall, this pattern suggests that ItchyQoL may preferentially reflect QoL burden at peak itch.

In this DEB-focused analysis, all PROMIS itch domains showed significant positive associations with NRS-measured itch intensity; scratching behaviour exhibited the largest slope for average-itch, whereas mood and sleep predominated for worst- and dressing-itch. These findings are clinically coherent in EB, where scratching can exacerbate skin damage and itch-related sleep disturbance is common (1, 2), supporting PROMIS scratching behaviour and mood and sleep as candidate endpoints for future trials.

LIS domains likewise tracked with NRS – they were strongest for worst-itch, with attenuation for dressing-itch and less precise estimates for average-itch (especially distress) – supporting their applicability in DEB. While the ItchyQoL total score was associated with NRS, subscale heterogeneity (with symptoms most consistent) suggests that some items may be less relevant to DEB, echoing prior observations that general dermatology QoL tools under-represent EB-specific concerns (7).

Primary limitations include the small DEB sample size, which may yield imprecise estimates and chance findings, and the post hoc nature of this subgroup analysis. The age range included adolescents, and responses to several instruments, which have primarily been validated in adults, may not be fully comparable across age groups. Larger, prospectively designed cohorts are needed to confirm these findings across EB subtypes, evaluate adolescents and adults separately, and further evaluate responsiveness, minimal clinically important differences and test–retest reliability.

In DEB, PROMIS itch domains – particularly scratching behaviour and mood and sleep – and LIS positively correspond with NRS-measured itch intensity, supporting their use as complementary multidimensional endpoints in future DEB trials. These findings may help prioritize pruritus measures and harmonize outcome assessment across studies.

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Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

IRB approval status: Reviewed and approved by Stanford IRB; approval #49084.

Conflicts of interest: Dr. Gorell, Dr. Tang and Dr. Chiou have been clinical investigators for Abeona Therapeutics, Inc. and Phoenix Tissue Repair. Dr. Gorell has been a consultant for Abeona Therapeutics, Krystal Biotech and Amryt Pharma. Dr. Gorell has been a clinical investigator for Krystal Biotech. Dr. Tang is a consultant for Sol-gel. Dr. Chiou also serves as a clinical investigator for Biomendics, LLC, a consultant for AbbVie, Trevi Therapeutics and a Medical Advisory Board member for Pfizer and Abeona. Other authors have no conflicts of interest to declare.

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