Department of Dermatology, Johns Hopkins University School of Medicine, Baltimore, Maryland[b]*; and Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, Ohio.*[c]

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Correspondence to: Angela H. Wei, BS, Department of Dermatology, University Hospitals Cleveland Medical Center, Case Western Reserve University, 11100 Euclid Ave, Cleveland, OH 44106

E-mail: ahw52@case.edu

Conflicts of interest

None disclosed.

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Development and validation of a caregiver-reported Numeric Rating Scale for measuring worst scratch/itch in patients aged 6 months to younger than 6 years with atopic dermatitis

To the Editor: In patients with atopic dermatitis (AD), reduction of itch is a key therapeutic goal and a marker of treatment benefit.[1] Worst Itch Scale is a validated scale for self-evaluation of itch in children aged 6-11 with AD.[2] For patients without the cognitive capacity to self-report itch, such as younger children, the US Food and Drug Administration (FDA) supports observer-reported outcome measures.[3]

The aim of this study was to develop and validate a caregiver-reported worst scratch/itch Numeric Rating Scale (WSI-NRS) and empirically derive a meaningful within-patient change threshold for patients with AD aged 6 months to <6 years (Supplementary Material, available via Mendeley at https://data.mendeley.com/datasets/fzz446rngc/1).

The single-item caregiver-reported WSI-NRS wording was adapted from the Peak Pruritus NRS.[4] Psychometric evaluation used data from part B of LIBERTY AD PRESCHOOL (NCT03346434; RD668-AD-1539), a 16-week, randomized, double-blind, parallel-group, placebo-controlled phase 3 study of dupilumab plus topical corticosteroids in patients aged 6 months to <6 years with moderate-to-severe AD.[5]

Interviews were conducted with 24 caregivers (mean age 34 years). Among their children, 21% were aged 6 months to <2 years, 46% 2 to <4 years, and 33% 4 to <6 years. During concept elicitation, all caregivers described observing their child "scratch" or "itch" the AD-affected area. During cognitive debriefing, all caregivers reported the WSI-NRS clear and easy to understand, consistently interpreted the 24-hour recall period used, and found it easy to recall their child's worst scratching/itching, without difficulty distinguishing between the numeric response options (0 [no scratching/itching] to 10 [worst scratching/itching]).

The test−retest reliability intraclass correlation coefficient for the weekly WSI-NRS scores during the last 2 weeks of the treatment period was 0.94 (95% CI 0.89, 0.96; $n = 58$), well above the accepted 0.70 threshold for reliability.

Convergent/discriminant validity results for WSI-NRS scores (Table I; Supplementary Material; Table I, available via Mendeley at https://data.mendeley.com/datasets/fzz446rngc/1) showed strong correlations at study week 16 ($r \geq 0.7$) with skin pain NRS, SCORing AD (SCORAD) itch Visual Analog Scales (VAS), Infant Dermatology Quality of Life itching/scratching, and Caregiver Global Impression of Disease, and moderate correlations ($r = 0.3$ to <0.7) with Children's Dermatology Life Quality Index itch/scratch/pain, Patient-Oriented Eczema Measure itch, and sleep quality NRS, providing evidence of convergent validity. Correlations between WSI-NRS and the clinician-reported outcome measures (SCORAD objective, Eczema Area and Severity Index, and

Table I. Convergent/discriminant validity and responsiveness correlations

	Correlation coefficient* (95% CI)		
	Convergent/discriminant validity		Responsiveness
	Baseline	Week 16	Change from baseline to week 16
Caregiver-reported outcomes			
Skin pain NRS	0.70† (0.61, 0.77) (*n* = 158)	0.89† (0.85, 0.92) (*n* = 136)	0.91† (0.87, 0.93) (*n* = 135)
Sleep quality NRS	−0.34† (−0.47, −0.19) (*n* = 159)	−0.54† (−0.65, −0.41) (*n* = 131)	−0.44† (−0.56, −0.28) (*n* = 131)
CGID	0.40† (0.26, 0.52) (*n* = 161)	0.72† (0.63, 0.79) (*n* = 137)	0.66† (0.55, 0.74) (*n* = 137)
CGIC	NA‡	NA‡	0.60† (0.48, 0.70) (*n* = 137)
SCORAD itch VAS	0.50† (0.38, 0.61) (*n* = 161)	0.81† (0.75, 0.86) (*n* = 136)	0.72† (0.63, 0.79) (*n* = 136)
SCORAD sleeplessness VAS	0.19† (0.04, 0.34) (*n* = 161)	0.67† (0.57, 0.75) (*n* = 136)	0.59† (0.46, 0.69) (*n* = 136)
POEM itch	0.10 (−0.06, 0.25) (*n* = 161)	0.65† (0.54, 0.74) (*n* = 137)	0.58† (0.45, 0.68) (*n* = 137)
POEM total	0.22† (0.07, 0.36) (*n* = 161)	0.67† (0.57, 0.76) (*n* = 137)	0.63† (0.52, 0.72) (*n* = 137)
Clinician-reported outcomes			
SCORAD objective	0.14 (−0.01, 0.29) (*n* = 161)	0.63† (0.51, 0.72) (*n* = 136)	0.55† (0.41, 0.65) (*n* = 136)
EASI total	0.12 (−0.03, 0.27) (*n* = 161)	0.55† (0.42, 0.66) (*n* = 137)	0.41† (0.25, 0.54) (*n* = 137)
IGA	NA§	0.53† (0.40, 0.64) (*n* = 137)	0.43† (0.28, 0.56) (*n* = 137)

CGIC, Caregiver Global Assessment of Change; *CGID*, Caregiver Global Assessment of Disease; *EASI*, Eczema Area and Severity Index; *IGA*, Investigator's Global Assessment; *NA*, not applicable; *NRS*, Numeric Rating Scale; *POEM*, Patient-Oriented Eczema Measure; *SCORAD*, SCORing Atopic Dermatitis; *VAS*, Visual Analog Scale.

*Correlations of <0.3 were considered small, 0.3 to <0.7 moderate, 0.7 to <0.9 strong, and ≥0.9 very strong.

†$P < .05$ (Pearson correlation).

‡Due to CGIC being change from baseline to week 16.

§Correlational analysis was not appropriate because of the baseline requirement (i.e., IGA ≥ 3).

Table II. Meaningful within-patient change threshold characterizing improvement

Anchor-based estimates: mean change from baseline to week 16 in WSI-NRS for anchor group		
	Median	Mean
CGID		
1-point improvement* (*n* = 44)	−1.9	−2.1
2-pointimprovement† (*n* = 45)	−4.4	−4.1
CGIC at week 16		
A little better† (*n* = 21)	−1.7	−2.3
Moderately better† (*n* = 33)	−2.3	−3.0
EASI response at week 16		
EASI 50-74% improvement† (*n* = 27)	−3.0	−3.4
EASI 75-89% improvement† (*n* = 37)	−3.3	−3.3
IGA response at week 16		
IGA = 1† (*n* = 21)	−4.9	−4.4
1-point improvement† (*n* = 55)	−2.3	−2.8
2-point improvement† (*n* = 37)	−4.3	−4.0
Distribution-based estimate		
Half-SD at baseline‡	−0.70	
Standardized error of measurement	−0.36, −0.99	

CGIC, Caregiver Global Impression of Change; *CGID*, Caregiver Global Impression of Disease; *EASI*, Eczema Area and Severity Index; *IGA*, Investigator's Global Assessment; *NRS*, Numeric Rating Scale; *SD*, standard deviation; *WSI*, worst scratch/itch.

*Primary anchor-based.

†Supplementary anchor-based.

‡Computed using SD at baseline = 1.40 using intraclass correlation coefficients 0.935 and 0.498.

Investigator Global Assessment) tended to be lower (r = 0.53-0.63), providing evidence of discriminant validity of the WSI-NRS at week 16 (Table I).

The consistent score patterns and significant differences between patients at the known group levels tested at week 16 provide strong support for

the discriminating ability of the WSI-NRS (Supplementary Material; Table II, available via Mendeley at https://data.mendeley.com/datasets/fzz446rngc/1). The moderate-to-strong correlations of change and large standardized overall effect sizes of change (−2.16 and −1.21) from baseline to week 16 between WSI-NRS and supporting measures support the responsiveness of the WSI-NRS (Supplementary Material; Table III, available via Mendeley at https://data.mendeley.com/datasets/fzz446rngc/1).

The meaningful within-patient change threshold was estimated to be 3-4 points (Table II).

In conclusion, the WSI-NRS is a well-defined, reliable, sensitive, and valid scale for caregiver evaluation of pruritus in children aged 6 months to <6 years with moderate-to-severe AD.

Amy S. Paller, MD,[a,b] Elaine Siegfried, MD,[c,d] Servando E. Marron, MD,[e,f] Marci Clark, PharmD,[g] Dana DiBenedetti, PhD,[b] Lauren Nelson, PhD,[b] Jingdong Chao, PhD,[i] Ashish Bansal, MD,[j] Chien-Chia Chuang, PhD,[k] and Zhixiao Wang, PhD[i]

From the Departments of Dermatology and Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois[a]; Division of Dermatology, Ann and Robert H. Lurie Children's Hospital, Chicago, Illinois[b]; Department of Pediatrics, Saint Louis University, St. Louis, Missouri[c]; Department of Pediatric Dematology, Cardinal Glennon Children's Hospital, St. Louis, Missouri[d]; Department of Dermatology, Aragon Psychodermatology Research Group (GAI + PD), partnered with Aragon Health Sciences Institute (IACS), University Hospital Miguel Servet, Zaragoza, Spain[e]; Department of Medicine, Department of Medicine, Psychiatry and Dermatology, University of Zaragoza, Zaragoza, Spain[f]; Department of Patient-Centered Outcomes Assessment, RTI Health Solutions, Ann Arbor, Michigan[g]; Department of Patient-Centered Outcomes Assessment, RTI Health Solutions, Research Triangle Park, North Carolina[b]; Department of Health Economics and Outcomes Research, Regeneron Pharmaceuticals Inc., Tarrytown, New York[i]; Department of Immunology and Inflammation Clinical Development, Regeneron Pharmaceuticals Inc., Tarrytown, New York[j]; and Department of Health Economics and Value Assessment, Sanofi, Cambridge, Massachusetts.[k]

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Correspondence to: Amy S. Paller, MD, Departments of Dermatology and Pediatrics, 676 N. St. Clair, Suite 1600, Chicago, IL 60611

E-mail: apaller@northwestern.edu

Conflicts of interest

Dr Paller has been an investigator for AbbVie, Dermavant, Eli Lilly, Incyte, Janssen, Krystal Biotech, and UCB; a consultant for Aegerion Pharma, Azitra, BioCryst, Boehringer Ingelheim, Bristol Myers Squibb, Castle Creek Biosciences, Eli Lilly, Janssen, Krystal Biotech, LEO Pharma, Novartis, Regeneron Pharmaceuticals Inc., Sanofi, Seanergy, TWi Biotechnology, and UCB, on the data and safety monitoring board for AbbVie, Abeona Therapeutics, Catawba Research, Galderma, and InMed. Dr Siegfried is a consultant for Dermavant, Eli Lilly, Pfizer, Regeneron Pharmaceuticals Inc., and Verrica Pharmaceuticals; reports data and safety monitoring board membership for GSK, LEO Pharma, and Novan; and is a principal investigator in clinical trials for Eli Lilly, Janssen, Regeneron Pharmaceuticals Inc., Stiefel, and Verrica Pharmaceuticals. Dr Marron is an advisory board member for and has received honoraria and research support from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, Sanofi, Regeneron Pharmaceuticals Inc., and Roche. Dr Clark, Dr DiBenedetti, and Dr Nelson are employees of RTI Health Solutions, which received funding from Regeneron

Pharmaceuticals Inc. Dr Chao, Dr Bansal, and Dr Wang are employees and shareholders of Regeneron Pharmaceuticals Inc. Dr Chuang is a Sanofi employee, and may hold stock and/or stock options in the company.

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Anti-SS-A antibody is a potential predictor of severe Stevens-Johnson syndrome and toxic epidermal necrolysis: A retrospective cohort study

To the Editor: Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) is a life-threatening mucocutaneous adverse reaction for which biomarkers are required to predict their severity and outcomes. In our clinical experience, patients with severe SJS/TEN frequently test positive for anti-SS-A antibody. This study aimed to investigate whether anti-SS-A positivity predicts disease severity and mortality in patients with SJS/TEN.

This retrospective cohort study included 64 patients with SJS ($n = 37$), SJS/TEN overlap ($n = 5$) or TEN ($n = 22$). Assessments and analyses are detailed in Supplementary Methods, available via Mendeley at https://doi.org/10.17632/83mxb7ydpw.1. Only 4 patients had a history of autoimmune diseases associated with anti-SS-A or antinuclear antibody production prior to SJS/TEN onset. Thirteen patients tested positive for anti-SS-A at SJS/TEN onset (Supplementary Table I, available via Mendeley at https://doi.org/10.17632/83mxb7ydpw.1). Anti-SS-A positivity and titers were significantly higher in patients with SJS/TEN overlap and TEN than in those with SJS. No autoantibody production-related drugs[1] were included among anti-SS-A-positive patients in whom the culprit drug was identified (Supplementary Table I and II, available via Mendeley at https://doi.org/10.17632/83mxb7ydpw.1). Patients with extensive maximum detachment, prolonged hospitalization, and severe mucosal involvement had significantly higher anti-SS-A, with extensive maximum detachment and prolonged hospitalization showing a positive correlation with anti-SS-A titers (Fig 1, Supplementary Figs 1 and 2, available via Mendeley at https://doi.org/10.17632/83mxb7ydpw.1). Notably, severe ocular involvement was significantly associated with anti-SS-A (Supplementary Fig 3, available via Mendeley at https://doi.org/10.17632/83mxb7ydpw.1).

Sequential samples obtained from 9 patients after recovery were analyzed to determine whether the anti-SS-A levels were episodic or persistent. All patients, except for one with SJS accompanied by systemic lupus erythematosus, exhibited significantly decreased anti-SS-A levels after recovery (Supplementary Fig 4, available via Mendeley at https://doi.org/10.17632/83mxb7ydpw.1). Furthermore, poor outcomes, defined as death or severe sequelae, was significantly associated with anti-SS-A (Supplementary Fig 5, available via Mendeley at https://doi.org/10.17632/83mxb7ydpw.1).

Finally, risk ratios were calculated for disease severity and outcomes in anti-SS-A-positive patients (Table I). The risk ratios for maximum detachment area >30%, prolonged hospitalization >30 days and >60 days, and severe ocular involvement were higher in the anti-SS-A-positive group than in the anti-SS-A-negative group, suggesting that anti-SS-A was a significant predictor of severity. Additionally, anti-SS-A positivity was identified as a predictor of poor outcomes.

Anti-SS-A has 2 target proteins—namely, Ro52 and Ro60.[2] The anti-SS-A detected in this study was anti-Ro60. Ro60, a component of cytoplasmic ribonucleoprotein complexes, has been implicated in autoantibody production and possibly plays important roles in the immunopathology of autoimmune diseases.[3,4] Currently, it remains unclear whether anti-SS-A elevation is attributable to the abnormal immune status of SJS/TEN or whether the presence of anti-SS-A is an aggravating factor for SJS/TEN. Anti-SS-A significantly decreased after recovery, and only a few anti-SS-A-positive patients with SJS/TEN had a history of autoimmune