Patient-Reported Outcome Measures in Atopic Dermatitis and Chronic Hand Eczema in Adults

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BACKGROUND

- Atopic dermatitis (AD) and chronic hand eczema (CHE) are chronic, relapsing inflammatory skin diseases that often co-occur; having AD is a risk factor for developing CHE.
- AD and CHE often cause intense itching, pain, highly visible symptoms (e.g., redness, flaking, bleeding from scratching), and impaired psychosocial and work functioning.[1,2] AD and CHE are associated with depression and anxiety, even among patients with clinically mild or moderate disease.[3,4]
- Despite the burden associated with AD and CHE, health care providers may underestimate the severity and impact of the symptoms and the stigma of having a visible skin condition.[1]
- Patient-reported outcome measures (PROMs) provide an important complement to clinician-reported outcome (ClinRO) measures in AD and CHE because many of the symptoms (e.g., itch, pain) and impacts cannot be evaluated objectively.

OBJECTIVE

- The aim of this study was to identify PROMs used in studies of AD and CHE and to explore the validation of the available measures in these conditions.

METHODS

- Structured reviews of the following sources were conducted in March 2017:
  - PubMed medical literature database: Clinical studies of drugs approved for AD or CHE indexed from 2006
  - ClinicalTrials.gov database of clinical studies: Interventional clinical studies in AD and CHE indexed from 2012
  - US Food and Drug Administration (FDA) and European Medicines Agency (EMA): Product labeling and regulatory submission packages for noncorticosteroid drugs approved for AD or CHE
- A detailed review of the most commonly used and most relevant PROMs was conducted.

Table 1. FDA PRO Label Language for Noncorticosteroid Products Approved for AD

PRO Measure	Drug/Indication	PRO Label Claim	PRO Data/Additional Description
Peak Pruritus NRS	Dupixent (dupilumab) Moderate-to-severe AD	All three trials assessed… **reduction in itch** as defined by at least a 4-point improvement in the **Peak Pruritus NRS** from baseline to week 16.	**Label** Other endpoints included the…reduction in itch as defined by at least a 4-point improvement in the Peak Pruritus NRS from baseline to week 16. Data were percentages of subjects with improvement in Peak Pruritus NRS ≥ 4 points for each of 3 trials, for dupilumab and placebo groups, with no indication of statistical significance
Pruritus (VAS based on DAP)	Protopic (tacrolimus) Moderate-to-severe AD	In both Protopic ointment treatment groups in adults and in the Protopic ointment 0.03% treatment group in pediatric patients, a **significantly greater improvement** compared to vehicle ($P < 0.001$) was observed in the secondary efficacy endpoints of percent body surface area involved, **patient evaluation of pruritus**, erythema, edema, excoriation, oozing, scaling, and lichenification.	**Label** No further results on pruritus improvement in label **DAP, medical review** "The amount and intensity of pruritus experienced during the previous 24-hour period was assessed using a 10-cm VAS where 0 cm = 'no itch' and 10 cm = 'worst itch imaginable'"
Pruritus (assessment not described)	Elidel (pimecrolimus) Moderate-to-severe AD	The **improvement in pruritus** occurred in conjunction with the improvement of the patients' AD.	**Label** More Elidel patients (57%) had mild or no pruritus at 6 weeks compared with vehicle patients (34%). *[Means of assessing this outcome not reported]*

Table 2. EMA PRO Label Language for Noncorticosteroid Products Approved for AD

PRO Measure	Drug/Indication	PRO Label Claim	PRO Data/Additional Description
Pruritus NRS **POEM** **DLQI** **HADS**	Dupixent (dupilumab) Moderate-to-severe AD	Relative to placebo, dupilumab **significantly improved patient-reported symptoms** (as indicated by a **Pruritus NRS**) and **improved sleep and health-related quality of life** as indicated by **POEM** and **DLQI** total scores. **Anxiety and depression symptoms** as indicated by the **HADS** total score **were significantly reduced** with dupilumab relative to placebo.	**SmPC** A significantly larger proportion of patients administered dupilumab had clinically meaningful reductions in POEM and DLQI total score (each defined as ≥ 4 points improvement) from baseline to week 16 compared to placebo group. **EPAR, Scientific Discussion** 58.8% of patients achieved a reduction of ≥ 4 points from baseline in weekly average of peak daily Pruritus NRS score at week 16 in dupilumab 300 mg Q2W + TCS, 50.8% in dupilumab 300 mg QW + TCS, and 19.7% in the placebo + TCS group.
DLQI **CDLQI**	Protopic (tacrolimus) Moderate-to-severe AD	None	**EPAR, Scientific Discussion** "Both the IGA score and **DLQI** were superior for tacrolimus versus placebo." All five phase 3 comparative studies showed improvements in QOL as determined using **DLQI** and Children's Dermatology Life Quality Index. In general, treatment differences paralleled the results for the efficacy endpoints.

Q2W = every 2 weeks; QW = weekly; TCS = topical corticosteroids.

Table 3. Summary of Key Characteristics of PROMs of Interest[a]

Characteristic	DLQI	Pruritus NRS	POEM	QOLHEQ[b]
Type of measure	Dermatology-specific HRQOL	Single item assessing itch/pruritus with an NRS	AD-specific symptoms and sleep interference	Hand eczema–specific HRQOL
Assessments	Dermatology-related HRQOL over the previous week (10 items); total score and 6 subscores: • Symptoms and feelings • Daily activities • Leisure • Work and school • Personal relationships • Side effects of treatment	Single item, 0-10 NRS with anchors 0 = no itch and 10 = worst imaginable itch; assessed related to the past 24 hours Multiple item wording possibilities; e.g., itch severity, itch frequency, itch intensity	Frequency of AD symptoms and sleep interference during the past week (7 items): • Dryness • Itching • Flaking • Cracking • Sleep disturbance • Bleeding • Weeping/oozing	CHE-related HRQOL during the past 7 days 4 domains (30 items) • Symptoms • Emotions • Functioning • Treatment and prevention
Responsiveness in clinical trials	**AD:** DLQI was used in 33 efficacy studies between 1994 and 2007 and detected change in patients before and after treatment in moderate-to-severe AD[5] **CHE:** Not responsive in 1 clinical trial of alitretinoin	Was included in 2 dupilumab AD trials in adults and found statistically significant between-group differences in each study	Was included in 3 dupilumab AD trials in adults and found statistically significant between-group differences in each study	None identified
Interpretation of change in scores	Anchor-based methods were used to estimate a threshold for meaningful change in a sample of 192 patients with skin diseases, including 12.5% with eczema. A change of 2-3 points on a 15-point patient global rating of change was associated with a mean DLQI change score of 3.3.[6] The authors recommended a threshold of 4 points as a meaningful change in DLQI scores over time.	The dupilumab phase 3 studies used a responder analysis such that patients with a reduction of 4 or more points in the weekly average of the daily NRS score were considered responders. A change of 4 points has been identified as the minimum change demonstrating clinically meaningful improvement in a psoriasis population.[7]	4-point change represents a clinically meaningful difference.[8]	Developers calculated the SRD as 13.3, indicating that a change of 11.2% of the scale would result in a statistically significant improvement. For the subscales, SRD values were 3.2 for Symptoms, 4.2 for Emotions, 4.1 for Functioning, and 3.4 for Treatment and prevention.

SRD = smallest real difference.
[a] These 4 PROMs were selected for in-depth review based on the findings of the structured reviews.
[b] No clinical studies using the QOLHEQ were identified.

RESULTS

- Among the 213 potentially relevant PubMed abstracts identified in the structured literature review, 33 studies using PROMs or describing the development or validation of a PROM in AD or CHE were gathered for full-text review.
  - See Figure 1 for a summary of PROMs identified in clinical studies.
- Among the 64 ClinicalTrials.gov entries reviewed, 29 contained a PROM.
  - See Figure 2 for a summary of PROMs identified.
- FDA and EMA submissions and product labeling were reviewed for 4 noncorticosteroid AD products: dupilumab, tacrolimus, pimecrolimus, and crisaborole.
- No CHE drugs had been approved by the FDA or the EMA at the time the review was conducted; however, alitretinoin was approved for CHE in a number of countries through a decentralized process, and a Patient Global Assessment item was used as a secondary endpoint.

Table 4. Summary of Psychometric Properties Reported in the Literature for PROMs Reviewed

	DLQI		Pruritus NRS	POEM	QOLHEQ
Psychometric Property	AD	CHE	Pruritic Conditions	AD	CHE
Internal consistency[a]	✓	✓	NA	✓	✓
Test-retest reliability[b]	✓	✓	✓	✓	✓
Content validity[c]	✓	NR	NR[h]	✓	✓
Construct validity, convergent[d]	✓	✓	✓	✓	✓
Construct validity, divergent[d]	NR	NR	NR	NR	✓
Discriminant validity[e]	✓	✓	NR	NR	✓
Responsiveness, longitudinal validation study[f]	✓	NR	NR	✓	✓
Responsiveness, RCT[g]	✓	—	✓	✓	NR

NA = not applicable; ICC = intraclass correlation coefficient; NR = not reported; RCT = randomized clinical trial.
✓ = Instrument achieved or exceeded the established psychometric standard or the standard set by the authors of this review (see notes for the specific standard for each property).
— = Instrument did not meet the established psychometric standard or the standard set by the authors of this review (see notes for the specific standard for each property).
[a] Range for acceptable Cronbach's alpha: above 0.70 but not higher than 0.95.[9]
[b] Threshold for acceptable test-retest reliability: ICC of 0.75 or greater.[10]
[c] Target population (e.g., patients with AD or CHE) provided input in the development of the instrument in one or more of the following areas: generation of item concept and wording, evaluation of completeness of item coverage, or assessment of item clarity and readability.
[d] At least one Pearson's correlation coefficient (r) value was categorized as moderate (0.10-0.50) or strong (> 0.50).[11]
[e] Discriminant validity demonstrated by statistically significant ($P < 0.05$) difference in at least one comparison of patient subgroups with differing clinical features.
[f] Responsiveness demonstrated by statistically significant ($P < 0.05$) results in at least one longitudinal validation study.
[g] Responsiveness demonstrated by statistically significant ($P < 0.05$) results in at least one randomized controlled trial.
[h] It is not uncommon for single-item symptom assessments to have limited published information on development history and psychometric evaluation.

Figure 1. PROMs Used in Published Clinical Studies in AD

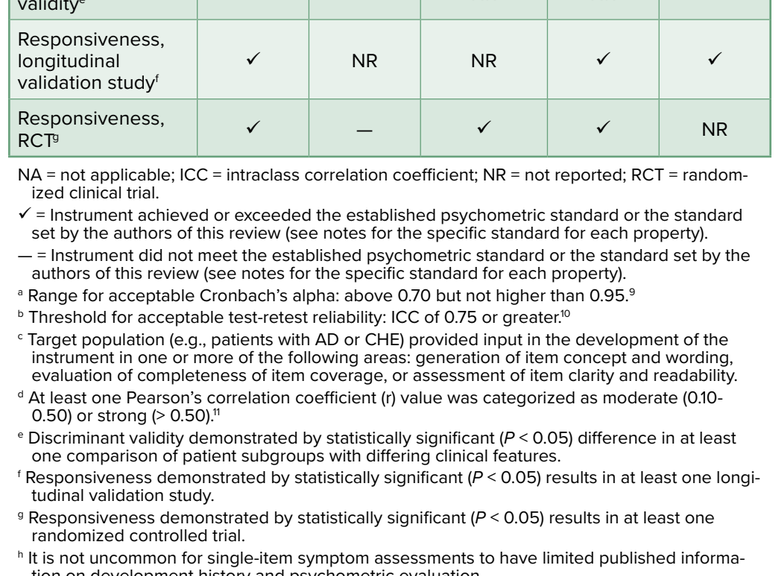

Figure 2. PROMs Used in AD Studies Indexed in ClinicalTrials.gov

CONCLUSIONS

- Symptoms of AD and CHE are being assessed with PROMs in increasing numbers of clinical trials. Available PROMs (including single-item symptom assessments) appear to cover the key symptoms of these conditions, as well as their functional and HRQOL impacts.
- The use of PRO assessments in dermatologic conditions appears to be part of a broader trend of more consistent assessment of symptoms using PROMs alongside clinician-assessed signs in clinical trials.
- Regulatory agencies have adopted a more patient-focused view of treatment benefit.[12,13] However, recent FDA PRO label claims in AD are limited to pruritis severity. EMA label claims include treatment-related improvement in impacts of AD such as HRQOL and sleep disturbance.
- Preliminary research suggests that the key symptoms and impacts of AD and CHE differ, and the need for disease-specific PROMs for hand eczema should be based on further exploration of the experience of patients with site-specific eczema.

REFERENCES

See handout for references.

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