BRIEF REPORT

Responder Threshold for Patient-Oriented Eczema Measure (POEM) and Children's Dermatology Life Quality Index (CDLQI) in Adolescents with Atopic Dermatitis

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ABSTRACT

Introduction: The Patient-Oriented Eczema Measure (POEM) assesses patient-reported frequency of atopic dermatitis (AD) symptoms, while the Children's Dermatology Life Quality Index (CDLQI) measures the impact of skin disease on health-related quality of life (HRQoL) in children. There is currently no threshold for clinically meaningful within-person change in POEM or CDLQI scores in adolescents. Here we empirically derive within-person thresholds of meaningful within-person change in POEM and CDLQI scores in adolescents with moderate-to-severe AD.

Methods: Data were used from a phase 3, randomized, double-blind, placebo-controlled trial of dupilumab in adolescents (aged ≥ 12 to < 18 years) with moderate-to-severe AD. Anchor-based methods were employed using the mean change in POEM and CDLQI scores from baseline to week 16 linked with a 1-point improvement in Patient Global Assessment of Disease (PGAD), a score of "a little better" on the Patient Global Assessment of Treatment effect (PGAT), a 50–74% improvement from baseline in the Eczema Area and Severity Index (EASI-50–74), and a 1-point improvement in Investigator's Global Assessment (IGA) score.

Results: A mean change of $- 7.8$ and $- 5.6$ in the POEM score was associated with PGAD and

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PGAT anchors, respectively. EASI-50–74 was associated with a mean change in POEM score of − 8.2, while the IGA anchor was associated with a mean change of − 7.9 in POEM score. The mean changes in CDLQI score associated with PGAD and PGAT anchors were − 6.4 and − 6.6, respectively, while CDLQI mean scores changed by − 8.3 and − 8.0 for the EASI and IGA anchors, respectively.

Conclusion: In adolescents (aged ≥ 12 to < 18 years) with moderate-to-severe AD, a within-person change of 6–8 points in POEM and CDLQI scores, independently, can be considered a reasonable responder threshold for clinically meaningful change in each of the two scales, respectively.

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INTRODUCTION

It is important to understand patient-reported symptoms and impact of atopic dermatitis (AD) to comprehend the burden of living with AD and interpret purported treatment benefits. These burdens and benefits may be different in adolescents with AD compared with adults with AD.

The Patient-Oriented Eczema Measure (POEM) assesses patient-reported frequency of AD symptoms in adults and children [1]. Gerbens et al. evaluated the measurement properties of the POEM and recommended the use of the tool in clinical trials [2]. Furthermore, the Harmonising Outcome Measures for Eczema (HOME) initiative also recommended the POEM as the core outcome instrument for assessing patient-reported AD symptoms in clinical trials [3]. The Dermatology Life Quality Index (DLQI) is frequently used to assess dermatology-specific health-related quality of life (HRQoL) in adult patients [4] but is not appropriate for pediatric patients. A version for pediatric patients, the

Children's Dermatology Life Quality Index (CDLQI), has been developed for patients aged 3–16 years [5]. The CDLQI is a well-established and widely used tool that was used in 102 studies across 14 different skin conditions between 1995 and 2012 [6].

For adults with AD, a within-person responder threshold for clinically meaningful change of four points has been established for both POEM [7] and DLQI [8]. However, currently, there is no validated within-person responder threshold for clinically meaningful within-person change in POEM or CDLQI scores in adolescents. The objective of this study was to empirically derive within-person responder thresholds of clinically meaningful change in POEM and CDLQI scores, independently, in adolescents with moderate-to-severe AD.[1]

METHODS

This analysis is based on data from a randomized, double-blind, placebo-controlled trial of dupilumab in adolescents with moderate-to-severe AD. Detailed descriptions of the study population, methodology, and efficacy and safety were previously reported [9]. The LIBERTY AD ADOL phase 3 trial included adolescent patients (aged 12 to < 18 years) with moderate-to-severe AD inadequately controlled with topical therapies, who were randomized (1:1:1) to dupilumab every 2 weeks (200 mg if baseline body weight < 60 kg, 300 mg if ≥ 60 kg), 300 mg dupilumab every 4 weeks , or placebo, for 16 weeks. The POEM and CDLQI were administered to patients in this trial at screening, baseline, and at weeks 2, 4, 8, 12, and 16. Of the 251 patients randomized in the LIBERTY AD ADOL trial, 250 (99.6%) received ≥ 1 dose of dupilumab or placebo and had ≥ 1 post-baseline POEM or CDLQI assessment during the treatment period and were therefore included in the present analysis.

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[1] Since only a within-person response is being considered, the term "minimal clinically important difference" (MCID) is not used, as the MCID can define a clinically meaningful difference for either a within-patient change or a cross-population mean change in score.

Instruments

The POEM [1] is a 7-item questionnaire inquiring about AD-specific symptoms in the preceding week; each item is scored 0–4, for a total score of 0–28. A decrease in POEM score indicates a reduction (improvement) in the frequency of symptoms of AD. The CDLQI [5] is a 10-item questionnaire measuring the effect of skin disease on patient HRQoL in the preceding week. Each CDLQI item is scored 0–3, for a total score of 0–30; lower scores indicate lesser impairment in HRQoL.

Estimation of Within-Person Change

Anchor-based approaches were primarily used to define responder thresholds per the patient-reported outcomes guidance from the US Food and Drug Administration [10], with distribution-based methods used as a secondary approach.

For anchor-based methods, the mean change in POEM score and, separately, the mean change in CDLQI score from baseline to week 16 were calculated for adolescents with a defined improvement in two patient-reported outcome (PRO) anchors, namely, a 1-point improvement in the Patient Global Assessment of Disease (PGAD) score and a score of "a little better" on the Patient Global Assessment of Treatment effect (PGAT), and in two clinician-reported outcome (ClinRO) anchors, namely, a 50–74% improvement from baseline in the Eczema Area and Severity Index (EASI) (EASI-50–74), and a 1-point improvement in the Investigator's Global Assessment (IGA) score.

Distribution-based methods included one-half of standard deviation (SD) at baseline and the standard error of measurement (SEM) at baseline (assessed as SEM = SD $\sqrt{1 - r}$, where r is the test–retest reliability). All analyses were performed using SAS software version 9.4 (SAS Institute Inc.; Cary, NC, USA).

The study was conducted in accordance with the provisions of the Declaration of Helsinki 1964, as revised in 2013, the International Council on Harmonization Good Clinical Practice (ICH GCP) guideline, and applicable regulatory requirements; the protocol was reviewed and approved by institutional review boards/ethics committees at all study sites (Electronic Supplementary Material Table). For all patients, written informed consent was obtained from a parent or legal guardian, and written informed assent was obtained from the patient.

RESULTS

The within-person responder thresholds for clinically meaningful change for POEM and CDLQI are shown in Table 1.

POEM

For the PRO anchors, a mean change of − 7.8 and − 5.6 in the POEM score was associated with improvement in the PGAD and PGAT, respectively. For the ClinRO anchors, a mean change of − 8.2 and − 7.9 in the POEM score was associated with improvement in EASI and IGA, respectively.

The distribution-based one-half of SD at baseline was 2.6 and the SEM was 2.3.

CDLQI

For the PRO anchors, a mean change of − 6.4 and − 6.6 in the CDLQI score was associated with improvement in the PGAD and PGAT, respectively. For the ClinRO anchors, a mean change of − 8.3 and − 8.0 in the CDLQI score was associated with improvement in the EASI and IGA, respectively.

The distribution-based one-half of SD at baseline was 3.4 and the SEM was 2.8.

DISCUSSION

To the best of our knowledge, there are no previous reports that clearly define a responder threshold for POEM and CDLQI in this target population of adolescents with moderate-to-severe AD.

Table 1 Estimated thresholds for clinically meaningful change for the Patient-Oriented Eczema Measure and Children's Dermatology Life Quality Index scales in adolescents with moderate-to-severe atopic dermatitis

Estimation methods	POEM		CDLQI	
	Mean change from baseline to Week 16	Median change from baseline to Week 16	Mean change from baseline to Week 16	Median change from baseline to Week 16
Anchor-based estimates				
PGAD improvement of 1 point (*n* = 95)	− 7.8	− 8.0	− 6.4	− 6.0
PGAT score of "a little better" (*n* = 75)	− 5.6	− 4.0	− 6.6	− 6.0
EASI-50–74 (*n* = 55)	− 8.2	− 8.0	− 8.3	− 8.0
IGA improvement of 1 point (*n* = 92)	− 7.9	− 8.0	− 8.0	− 8.0
Distribution-based estimates				
One-half of SD at baseline	2.6		3.4	
SEM	2.3		2.8	

CDLQI Children's Dermatology Life Quality Index, *EASI-50–74* 50–74% improvement from baseline in Eczema Area and Severity Index, *IGA* Investigator's Global Assessment, *PGAD* Patient Global Assessment of Disease, *PGAT* Patient Global Assessment of Treatment, *POEM* Patient-Oriented Eczema Measure, *SD* standard deviation, *SEM* standard error of the mean

Using anchor-based methods in adults, Schram et al. estimated a within-person responder definition for POEM as 3.4 [7]. This equates to a change in POEM score of 4 points in an individual patient as POEM is scored in integers. The COMET randomized feasibility study estimated the mean within-person change threshold for POEM as 4.27 using parent-reported data of children with AD aged between 1 month and 5 years to derive a responder threshold [11]. The estimated threshold from receiver operating characteristic (ROC) curve analysis was 3, whereas the distribution-based estimates were 2.5 (effect size) and 2.9 (one-half of SD). More recently, Howells et al. evaluated data from the randomized, controlled CLOTHES trial that included 300 children aged 1–15 years (mean age 5 years) with moderate-to-severe AD [12]. A change of 1 point on a 6-point Patient/Parent Global Assessment (P/PGA) or on a 6-point IGA were used as predefined anchors of clinically relevant

change, from which the mean within-person meaningful change in POEM was 6.13 and 5.25, respectively. Other anchor-based estimates of meaningful change using the P/PGA and IGA were 4.75 and 5.38 based on ROC curve analysis, and 4.52 and 4.43 based on logistic regression models, respectively. The distribution-based one-half of SD was 2.68. Howells et al. [12] combined the findings from other studies along with their own results and recommended that changes in POEM of < 3 points were unlikely to be clinically important, changes of 3.0–3.9 points were probably clinically important, and changes of ≥ 4 points were very likely to be clinically important. Distribution-based estimates based on our trial data (2.6 and 2.3) were considerably lower than the anchor-based estimates, but similar to estimates provided in the literature [11, 12]. Although the CLOTHES trial also included adolescent patients [12], the responder definition is not provided separately for adolescents and the results do not directly

apply to a population of adolescents (12 to < 18 years) with moderate-to-severe AD.

No previous publications have estimated a meaningful within-person change threshold for the CDLQI score in adolescent patients with moderate-to-severe AD. Our results presented here suggest that a reasonable clinically meaningful change in CDLQI would range between 6.4 and 8.3 points, equivalent to a within-person score change of 6–8 points, given that CDLQI is only scored in integers.

The distribution estimates of 3.4 and 2.8 are comparable with the one-half of-SD of 2.8 based on published CDLQI scores in AD [5] but, similar to POEM results, are considerably lower than the anchor-based estimates derived from our trial data. Further work is warranted to estimate an appropriate within-person responder definition in children aged < 12.

A limitation of this analysis is that the EASI score, although containing a component measuring lesions on the head region, is not correlated with quality of life assessed by CDLQI. However, we have mitigated this limitation by using other instruments, such as PGAD and PGAT, in our anchor-based methods for determining appropriate within-person responder definitions.

CONCLUSION

In adolescents with moderate-to-severe AD, a within-person change of 6–8 points in the POEM and CDLQI scores, independently, can be considered to be a reasonable responder threshold for clinically meaningful change in each of the two scales, respectively.

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Compliance with Ethics Guidelines. The study was conducted in accordance with the provisions of the Declaration of Helsinki 1964, as revised in 2013, the ICH GCP guideline, and applicable regulatory requirements; the protocol was reviewed and approved by institutional review boards/ethics committees at all study sites (Electronic Supplementary Material Table). For all patients, written informed consent was obtained from a parent or legal guardian, and written informed assent was obtained from the patient.

Data Availability. Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing once the indication has been approved by a regulatory body, if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Submit requests to https://errs.regeneron.com/external.

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