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BRIEF REPORT

Definition of Clinically Meaningful Within-Patient Changes in POEM and CDLQI in Children 6 to 11 Years of Age with Severe Atopic Dermatitis

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ABSTRACT

Introduction: The Patient-Oriented Eczema Measure (POEM) assesses patient-reported severity of atopic dermatitis (AD) symptoms, whereas the Children's Dermatology Life Quality Index (CDLQI) measures how AD affects health-related quality of life (HRQoL) in children. Although the POEM and CDLQI have established thresholds for clinically meaningful within-patient change in adolescents (aged 12–17 years), there are no defined within-patient responder thresholds for clinically meaningful change in children aged 6–11 years.

Methods: Data from the LIBERTY AD PEDS phase 3 randomized, double-blind, placebo-controlled trial of dupilumab in children aged 6–11 years with severe AD were used to define the threshold for within-patient meaningful change in POEM and CDLQI scores. Anchor-based methods were applied to estimate mean change in POEM and CDLQI scores from baseline to week 16, with anchors of a 1-point improvement in the Patient Global Impression of Disease (PGID) scale and an improvement in score of ''A little better'' on the Patient Global Impression of Change (PGIC) scale. The distribution-based methods, a one-half standard deviation (SD) at baseline and a standard error mean (SEM) were also used.

Results: The mean POEM change scores associated with the anchors were a change of − 8.40 with the PGID anchor and − 6.30 with the PGIC anchor. Distribution-based estimates for POEM were one-half SD at baseline of 2.76, with a SEM of 3.32. Mean CDLQI change scores corresponding to the PGID and PGIC anchors were − 7.30 and − 6.80, respectively, while distribution-based estimates for CDLQI were a one-half SD at baseline of 3.69, with a SEM of 3.52.

Conclusions: In children with severe AD, an appropriate minimum threshold of clinically meaningful within-patient change was

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estimated as 6 points for both the POEM and CDLQI scores.
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Keywords: Atopic dermatitis; CDLQI; Clinically meaningful; Dupilumab; Pediatric; POEM; Psychometric; Responder threshold; Validation

Key Summary Points

Why carry out this study?

The Patient-Oriented Eczema Measure (POEM) and Children's Dermatology Life Quality Index (CDLQI) questionnaires are widely used but do not have established thresholds for clinically meaningful within-patient change for children aged 6–11 years.

Data from the phase 3 study LIBERTY AD PEDS were used to estimate thresholds of meaningful change in children with severe AD using anchor-based and distribution-based methods.

What was learned from the study?

For children aged 6–11 years with severe AD, an appropriate threshold of clinically meaningful within-patient change was estimated as 6 points for both the POEM and the CDLQI scores.

The data presented herein generally agree with and build upon previous publications that estimated clinically meaningful within-patient change thresholds for POEM and CDLQI scores in patients with similar clinical phenotypes.

DIGITAL FEATURES

This article is published with digital features, including a summary slide and video summary, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14484600.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, lifelong disease with a high patient burden that is under-recognized as a public health concern [1–3]. It is the most common childhood inflammatory skin disease, affecting more than 20% of children in many industrialized countries, with a continually increasing prevalence [4–6].

The Patient-Oriented Eczema Measure (POEM) was developed as a tool for assessing patient-reported severity of AD in clinical practice and clinical trials in adults and children [7]. The instrument has been recommended by Harmonising Outcome Measures for Eczema (HOME), an international initiative formed to establish a set of core outcomes for AD trials, as a core outcome instrument to assess symptom severity in the AD population [8]. The Children's Dermatology Life Quality Index (CDLQI) was developed to measure dermatology-specific health-related quality of life (HRQoL) in children [9]. CDLQI is well established and widely used; from 1995 to 2012, the measure was used in 102 studies across 14 different skin conditions [10]. Both instruments have been validated in the pediatric population, showing good validity and reliability [7, 9, 11–23].

A threshold of 6–8 points for clinically relevant within-patient response or responder definition has been established in adolescents with AD for both the POEM and CDLQI [24] scores. For adults with AD, a responder threshold for clinically meaningful change of 4 points has been established for both POEM [25] and Dermatology Life Quality Index (DLQI) [26]. However, there is currently no validated responder threshold for clinically meaningful change in these instruments for children with AD (aged 6–11 years). This article describes the empirical derivation of within-patient thresholds of clinically meaningful change in POEM and CDLQI scores in children with severe AD.

METHODS

This analysis is based on data from a randomized, double-blind, placebo-controlled trial of dupilumab in children with severe AD. Detailed descriptions of the study population and methodology are reported elsewhere [27] and are briefly summarized here.

The study was conducted in accordance with the provisions of the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice (ICH GCP) guideline, and applicable regulatory requirements; the protocol was reviewed and approved by institutional review boards/ethics committees. For all patients, written informed consent was obtained from a parent or legal guardian and written informed assent was obtained from the patient.

Study Design

The LIBERTY AD PEDS (NCT03345914) phase 3 trial included children (6–11 years of age) with severe AD inadequately controlled with topical medications or for whom topical treatment is medically inadvisable [27]. Patients were randomized in a 1:1:1 ratio to dupilumab administered concomitantly with topical corticosteroids every 2 weeks (100 mg for children < 30 kg or 200 mg for children ≥ 30 kg) or every 4 weeks (300 mg), or placebo for 16 weeks. For the purpose of this analysis all patients were included irrespective of treatment arm.

Patient demographics and background have been reported in detail previously [27]. Briefly, among the 367 patients randomized in the LIBERTY AD PEDS trial, the average age (standard deviation [SD]) was 8.5 (1.72) years, 49.9% were male, 69.2% were White, 16.9% were Black/African American, 7.6% were Asian, and 5.2% were of a race that did not fall into the previous categories.

Patient-Reported Outcome Measures

The POEM comprises seven items that assess the frequency of AD symptoms (itchy, bleeding, weeping or oozing, cracked, flaky, and dry or rough skin) and sleep disturbance over the past week [7]. Items are rated on a 5-point scale ranging from no days (scored 0) to every day (scored 4). The total score ranges from 0 to 28, with higher scores indicating greater frequency of AD symptoms and of sleep disturbance. POEM was completed by caregivers during clinic visits at screening, baseline (week 0), and weeks 2, 4, 8, 12, and 16 (end of treatment).

The CDLQI comprises ten items assessing the impact of skin disease on children's HRQoL over the previous week [9]. The items cover symptoms, leisure activities, school or holiday time, personal relationships, sleep, side effects of treatment, and emotional reactions to having a skin disease. The total score ranges from 0 to 30, with higher scores indicating greater impairment in HRQoL. CDLQI was completed by children at clinic visits at screening, baseline (week 0), and weeks 2, 4, 8, 12, and 16 (end of treatment).

Estimation of Within-Patient Change

Anchor-based and distribution-based methods were applied to estimate the threshold for meaningful within-patient change in POEM and CDLQI scores. For the anchor-based approach, the mean change scores for POEM and CDLQI were calculated based on defined improvement in the selected anchors. In line with recommendations that patient-reported anchors (often global assessments) are the most appropriate [28], a 1-point improvement on the Patient Global Impression of Disease (PGID) scale and "a little better" on the Patient Global Impression of Change (PGIC) scale from baseline to week 16 were selected as the anchors. The PGID questionnaire asked participants about their itching in the last 7 days and was scored on a 5-point scale (not itchy at all, a little itchy, medium itchy, pretty itchy, very itchy). The PGIC questionnaire is designed to measure the perceived change in itching since starting medication and is scored on a 5-point scale (much better, a little better, the same, a little worse, much worse). Distribution-based methods for determining responder thresholds were considered as a supportive approach based on

guidance from the US Food and Drug Administration [29]. The distribution-based methods included one-half SD at baseline and standard error of measurement (SEM) computed as SD $\sqrt{1-r}$, where r is the test–retest intraclass correlation coefficient.

RESULTS

Of the 367 patients randomized in the LIBERTY AD PEDS trial, 357 and 356 caregivers/patients, respectively, completed baseline and week 16 POEM and CDLQI assessments and received at least one dose of dupilumab or placebo.

Both the PGID and PGIC were confirmed to be appropriate anchors, based on the magnitude of change correlations for POEM ($|r|$ = 0.65 with PGID and 0.60 with PGIC) and CDLQI ($|r|$ = 0.58 with PGID and 0.44 with PGIC), which were above the minimum recommended correlation of 0.37 for anchor measures [30–32].

The mean POEM change scores associated with a PGID improvement of 1 point and a PGIC score of "a little better" improvement were − 8.40 and − 6.30, respectively (Table 1). The distribution-based estimates were a one-half SD at baseline of 2.76 and a SEM of 3.32. The mean CDLQI change scores associated with the anchors were − 7.30 with PGID and − 6.80 with PGIC (Table 2). The distribution-based one-half SD was 3.69 at baseline and the SEM was 3.52.

Table 1 Estimates for thresholds for meaningful within-patient change on the Patient-Oriented Eczema Measure using data from the phase 3 randomized, double-blind, placebo-controlled LIBERTY AD PEDS trial

Method	Change in POEM score from baseline to week 16[a] (N = 357)	
	Mean	Median
Anchor based		
PGID improvement of 1 point (n = 93)	− 8.40	− 9.00
PGIC improvement "a little better" (n = 84)	− 6.30	− 5.00
Distribution based		
One-half SD at baseline	2.76	
SEM[b]	3.32	

The analysis sample included 357 randomized patients who received at least one dose of dupilumab or placebo and who had baseline and week 16 POEM assessments

ICC Intraclass correlation coefficient, *PGIC* Patient Global Impression of Change, *PGID* Patient Global Impression of Disease, *POEM* Patient-Oriented Eczema Measure, *SD* standard deviation, *SEM* standardized error of measurement

[a] Negative change scores denote improvement on POEM

[b] Computed as SD $\sqrt{1-r}$, where SD at baseline = 5.51 and r (test–retest ICC) = 0.64 (baseline to week 2 for sample with no change on the PGID)

DISCUSSION

In the absence of thresholds to interpret meaningful within-patient change in POEM and CDLQI scores specifically for children aged 6–11 years with AD, data from the phase 3 LIBERTY AD PEDS were used to define thresholds in POEM and CDLQI scores for the current target population, using anchor-based and distribution-based methods. In a recent paper, Simpson et al. [24] established a within-patient change of 6–8 points in POEM and CDLQI scores as a reasonable responder threshold for clinically meaningful change in each of the two scales in adolescents (aged 12–17 years) with moderate-to-severe AD [24].

The results from the LIBERTY AD PEDS data indicate that a reasonable range of threshold estimates to define meaningful improvement in POEM scores would be − 6.30 to − 8.40 points, equating to a within-patient change in POEM score of 6–8 points. The lower bound of this range is in line with the mean estimate of 6.13 obtained by Howells et al. [33] using a patient-reported (or parent-reported) global assessment (the P/PGA) anchor in a pediatric sample (children aged 1–15 years) with moderate-to-severe AD. Therefore, based on the available evidence,

Table 2 Estimates for thresholds for meaningful within-patient change on the Children's Dermatology Life Quality Index using data from the phase 3 randomized, double-blind, placebo-controlled LIBERTY AD PEDS trial

Method	Change in CDLQI score from baseline to week 16[a] (*N* = 356)	
	Mean	Median
Anchor based		
PGID improvement of 1 point (*n* = 93)	− 7.30	− 6.00
PGIC improvement "A little better" (*n* = 85)	− 6.80	− 7.00
Distribution based		
One-half SD at baseline	3.69	
SEM[b]	3.52	

The analysis sample included 356 randomized patients who received at least one dose of dupilumab or placebo and who had a baseline and week 16 CDLQI assessment

CDLQI Children's Dermatology Life Quality Index

[a] Negative change scores denote improvement on CDLQI

[b] Computed as SD $\sqrt{1-r}$, where SD at baseline = 7.37 and r (test–retest ICC) = 0.77 (baseline to week 2 for sample with no change on the PGID)

a minimum individual patient change score of 6 points in POEM total score is proposed as an appropriate threshold for defining a meaningful within-patient change.

The analyses for CDLQI indicate that a reasonable range of estimates to define meaningful improvement in CDLQI scores would be − 6.80 to − 7.30 points, equating to a within-patient change in CDLQI score of 6–7 points. One study has reported on the interpretation of scores on the CDLQI for children with psoriasis using data reported in the original validation study for the CDLQI [9] and considered that the equivalent one-half SD estimate for children with AD can be estimated as 2.8 [34]. Based on the available evidence and consistent with prior defined clinically meaningful within-patient change for the adolescent population [24], a minimum individual patient change score of 6 points in CDLQI total score is proposed as an appropriate threshold for defining a meaningful within-patient change.

Consistent with published studies [33, 35], POEM distribution estimates based on the trial data (2.76 and 3.32) were considerably lower than the anchor-based estimates. Similarly, CDLQI distribution-based estimates of 3.52 and 3.69 are comparable with the one-half SD of 2.8 based on published CDLQI scores in AD [9] and considerably lower than the anchor-based estimates derived from the LIBERTY AD PEDS data. These findings are in line with earlier literature reporting on lower thresholds for distribution-based methods compared with anchor-based methods [36]. This study primarily used anchor-based methods to define thresholds of meaningful within-patient change in line with guidance from the US Food and Drug Administration on patient-reported outcome measures [29].

A limitation of this analysis is that thresholds were derived using empirically driven data of AD patients aged 6–11 years and may not be appropriate for extrapolation to other age groups or conditions.

CONCLUSION

In children with severe AD, a minimum individual within-patient change of 6 points in POEM and CDLQI scores is proposed as an appropriate threshold for defining a clinically meaningful within-patient change.

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Compliance with ethics guidelines. The study was conducted in accordance with the provisions of the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice (ICH GCP) guideline, and applicable regulatory requirements; the protocol was reviewed and approved by institutional review boards/ethics committees. 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. Requests should be submitted to https://vivli.org/.

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