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SHORT REPORT

Clinically meaningful change threshold in health-related quality of life among patients aged 6 months to 5 years with atopic dermatitis and their caregiver(s)/family

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Abstract

Background: Atopic dermatitis (AD) significantly impacts health-related quality of life (HRQoL) in children and their caregiver(s)/family. Measures to assess HRQoL include the Children's Dermatology Life Quality Index (CDLQI), Infants' Dermatitis Quality of Life Index (IDQoL) and Dermatitis Family Impact (DFI) questionnaire. Currently, there are no established clinically meaningful within-person change thresholds for these measures in young children (6 months to 5 years) and their caregiver(s)/family.

Objectives: To determine the clinically meaningful within-person change thresholds for CDLQI (4–5 years), IDQoL (<4 years) and DFI scores in children aged 6 months to 5 years with moderate-to-severe AD and their caregiver(s)/family.

Methods: Data from the 16-week, randomised, double-blind, placebo-controlled, phase 3 LIBERTY AD PRESCHOOL part B study in children aged 6 months to 5 years were used. The anchor-based method was used to assess meaningful change thresholds for the three instruments, using the Caregiver Global Impression of Disease (CGID; range: 'no symptoms' to 'very severe') as the primary anchor, and Caregiver Global Impression of Change (CGIC; range: 'much better' to 'much worse') as a supportive anchor.

Results: The mean CDLQI change scores were −6.3 and −9.5 based on CGID 1-point improvement and CGIC improvement of 'a little better', respectively. The mean IDQoL change scores were −5.6 and −3.4 based on the CGID and CGIC anchors. The mean DFI change scores were −7.0 and −6.7 based on the CGID and CGIC anchors.

Conclusions: Based on primary anchor findings, improvements of ≥6 points on the CDLQI total score for children aged 4–5 years and on the IDQoL total score for children aged <4 years were recommended as the clinically

meaningful within-person change thresholds in children with moderate-to-severe AD. A 7-point improvement on the DFI total score may be considered as the meaningful threshold for the caregiver(s)/family of children aged 6 months to 5 years with moderate-to-severe AD.

KEYWORDS
Children's Dermatology Life Quality Index, Dermatitis Family Impact, Infants' Dermatitis Quality of Life Index, within-person change threshold

INTRODUCTION

Atopic dermatitis (AD) is a chronic, inflammatory skin disease with a high disease burden.[1,2] The prevalence of diagnosed AD has been estimated to be 12.1% in children aged 6 months to <6 years.[3] AD has a profoundly negative impact on health-related quality of life (HRQoL), further exacerbated in children with severe AD.[4] The condition also negatively impacts the HRQoL of caregiver(s) and families of these young patients.[5] Assessment of HRQoL is essential in young patients (aged 6 months to 5 years) with AD, and is estimated using the Children's Dermatology Life Quality Index (CDLQI) in children aged 4 to <6 years and the Infants' Dermatitis Quality of Life Index (IDQoL) in children aged 6 months to <4 years.[6–8] Furthermore, assessment of the impact of AD on the wider family is important in these young patients; the Dermatitis Family Impact (DFI) questionnaire has been widely used for this purpose.[8,9]

A threshold of ≥6, ≥6–8 and ≥4 points for clinically relevant within-patient change has been established in children aged 6–11 years, adolescents and adults with AD, respectively, for the CDLQI/DLQI scores.[10–12] Currently, there are no established clinically meaningful within-person change thresholds for the CDLQI (in 4- to 5-year-olds), IDQoL (in 6-month- to <4-year-olds) or DFI to help interpret scores in children aged 6 months to 5 years of age and their caregiver(s)/family. The purpose of the current study was to determine the clinically meaningful within-person change in scores on the CDLQI, IDQoL and DFI for children aged 6 months to 5 years with moderate-to-severe AD and their caregiver(s)/family.

MATERIALS AND METHODS

Study design

The LIBERTY AD PRESCHOOL study (NCT03346434, part B) was a phase 3, randomised trial including children aged 6 months to 5 years with moderate-to-severe AD whose disease was inadequately controlled with topical medications or for whom topical treatment was medically inadvisable.[13] Patients were randomised 1:1 to receive either subcutaneous dupilumab every 4 weeks ($n = 83$) or matching placebo ($n = 79$) for 16 weeks. Dupilumab dosing was weight-tiered, and patients who weighed between 5 and <15 kg received 200 mg, while patients weighing between 15 and <30 kg received 300 mg. All children received concomitant low-potency topical corticosteroids (hydrocortisone acetate 1% cream). Data from both treatment arms were pooled for the purpose of this analysis.

Instruments

The 10-item CDLQI (score range 0–30) covers symptoms, leisure activities, school or holiday time, personal relationships, sleep, treatment side effects and emotional reactions to having a skin disease.[6] The 10-item IDQoL (score range 0–30) covers symptoms, mood, sleep, play, family activities, mealtimes, treatments, and dressing and bathing.[8] The DFI questionnaire (score range 0–30) assesses the impact of AD on caregiver(s)/family of children affected by AD and comprises 10 questions examining domains that may be impacted by AD (housework, food preparation, sleep, family leisure activity, shopping, expenditure, tiredness, emotional distress, relationships and the impact of helping with treatment).[9]

Estimation of within-person change

Within-person change in CDLQI, IDQoL and DFI scores was evaluated from baseline to week 16. The primary anchor measure was a Caregiver Global Impression of Disease (CGID) scale, on which caregivers rated their child's AD symptoms during the past 7 days on a 5-point scale ('no symptoms', 'mild', 'moderate', 'severe' or 'very severe'). Two sets of results are presented using this anchor measure: 1-point and

2-point improvement from baseline to week 16. A 7-point Caregiver Global Impression of Change (CGIC; ranging from 'much better' to 'much worse') scale was used as a supportive anchor measure. Two sets of results are presented using this anchor measure: 'a little better' and 'moderately better' at week 16. Investigator's Global Assessment (IGA) and Eczema Area and Severity Index were also evaluated as candidate clinical anchors for this study, but they showed lower associations with the target measures than CGID and CGIC, thus confirming CGID and CGIC as the more appropriate anchors to use. The distribution-based method was based on a one-half standard deviation (SD) at baseline and the standard error of measurement (SEM).

RESULTS

Baseline characteristics from the LIBERTY AD PRESCHOOL study have been published previously.[13] Briefly, a large proportion (77%) had severe disease (IGA score of 4) at baseline and one-third (29%) of patients had previously used systemic medications for AD. Most patients (81%) had ≥1 concurrent type 2 inflammatory disease, suggesting a high disease burden in this population.[13]

Overall, the primary anchor CGID had a high magnitude of change correlation across all three instruments. Both CGID change and CGIC were confirmed to have acceptable levels of association (minimum recommended correlation of 0.371) with the changes in CDLQI total scores ($r = 0.64$ and 0.57, respectively), IDQoL total scores ($r = 0.76$ and 0.64, respectively) and DFI total scores (0.67 and 0.55, respectively), confirming CGID and CGIC as acceptable anchor measures.[14–16]

In total, 84 and 66 patients were included in the CDLQI and IDQoL analyses, respectively. Mean change in CDLQI scores ranged from −6.3 to −12.2 based on CGID 1- and 2-point improvement from baseline to week 16, respectively. Mean change in CDLQI scores ranged from −9.5 to −8.3 based on CGIC improvement of 'a little better' and 'moderately better', respectively. For CDLQI, the half SD at baseline was 2.9, and the SEM ranged from 2.4 to 3.3 (Table 1). Mean change in IDQoL scores ranged from −5.6 based on a CGID 1-point improvement to −12.2 based on a CGID 2-point improvement from baseline to week 16. Mean change in IDQoL scores ranged from −3.4 based on a CGIC improvement of 'a little better' to −8.8 based on a CGIC improvement of 'moderately better'. For IDQoL, the half SD at baseline was 2.7, and the SEM ranged from 2.2 to 3.7 (Table 1).

A total of 158 patients and their caregiver(s)/families were included in the DFI analyses. Mean change in DFI

TABLE 1 Within-person change thresholds for CDLQI, IDQoL and DFI.

Method	Total score threshold characterising improvement		
	CDLQI ($N = 84$)	IDQoL ($N = 66$)	DFI ($N = 158$)
CGID change from baseline at week 16			
1-point improvement: mean (median), *n*	−6.3 (−5.5), 24	−5.6 (−4.5), 26	−7.0 (−6.0), 52
2-point improvement: mean (median), *n*	−12.2 (−12.0), 33	−12.2 (−11.0), 17	−12.2 (−12.5), 50
CGIC at week 16			
A little better: mean (median), *n*	−9.5 (−10.5), 10	−3.4 (−4.0), 11	−6.7 (−5.0), 26
Moderately better: mean (median), *n*	−8.3 (−8.0), 23	−8.8 (−10.0), 10	−7.9 (−6.5), 34
Distribution-based			
Half-SD at baseline	−2.9	−2.7	−3.3
SEM[a]	−3.3 to −2.4	−3.7 to −2.2	−3.1 to −2.7

Abbreviations: CDLQI, Children's Dermatology Life Quality Index; CGIC, Caregiver Global Impression of Change; CGID, Caregiver Global Impression of Disease; DFI, Dermatitis Family Impact; ICC, intraclass correlation coefficient; IDQoL, Infants' Dermatitis Quality of Life Index; SD, standard deviation; SEM, standard error of measurement.

[a]$\text{SEM} = \text{SD}_{\text{baseline}} \times \sqrt{(1 - \text{ICC})}$.

scores ranged from −7.0 based on a CGID 1-point improvement to −12.2 based on a CGID 2-point improvement from baseline to week 16. Mean change in DFI scores ranged from −6.7 based on a CGIC improvement of 'a little better' to −7.9 based on a CGIC improvement of 'moderately better'. The half SD at baseline was 3.3, and the SEM ranged from 2.7 to 3.1 (Table 1).

DISCUSSION

There are currently no thresholds to interpret clinically meaningful within-person change in CDLQI, IDQoL and DFI scores specifically for children aged 6 months to 5 years with moderate-to-severe AD and their caregiver(s)/families. Establishing meaningful thresholds for within-person change in clinical measures can help healthcare decision-makers interpret and implement results during their evidence-based evaluation of the effectiveness of therapies. We used data from the phase 3 LIBERTY AD PRESCHOOL study to define thresholds in CDLQI, IDQoL and DFI scores using anchor-based and distribution-based methods.

The anchor-based method is preferred by the US Food and Drug Administration (FDA)[17] and has been recommended in the literature as a primary method for estimating minimally important differences for HRQoL measures.[14–16] The distribution-based method provided lower thresholds than the anchor-based threshold estimates and was considered a supportive approach based on guidance from the FDA.[17]

A limitation of this study is that thresholds were derived using empirically driven data from patients aged 6 months to 5 years with moderate-to-severe AD and their caregivers, and may not be appropriate for extrapolation to other age groups or conditions.

In conclusion, based on a post hoc analysis of data from the R668-AD-1539 (part B) LIBERTY AD PRESCHOOL study, an individual score improvement of ≥6 points on the CDLQI total score is an appropriate meaningful within-person change threshold for children aged 4 to 5 years with moderate-to-severe AD, consistent with the threshold for the CDLQI previously identified for patients with AD aged ≥6 to <12 years. An individual score improvement of ≥6 points on the IDQoL total score is an appropriate meaningful within-person change threshold for children aged up to 4 years with moderate-to-severe AD. Finally, an individual score improvement of ≥7 points on the DFI is an appropriate threshold to define meaningful within-person change for caregiver(s)/families of children aged 6 months to 5 years with moderate-to-severe AD. These instruments are used in different dermatology conditions; further research is required to evaluate these thresholds in other conditions.

AUTHOR CONTRIBUTIONS

Diane Whalley, Lauren Nelson, Shanshan Qin, Jingdong Chao, Ashish Bansal, Chien-Chia Chuang and Zhixiao Wang contributed to the study concept and design. Amy S. Paller, Ashish Bansal and Zhixiao Wang acquired data. Diane Whalley, Lauren Nelson and Shanshan Qin conducted the statistical analyses on the data. All authors (Amy S. Paller, Servando E. Marron, Diane Whalley, Lauren Nelson, Shanshan Qin, Jingdong Chao, Ashish Bansal, Chien-Chia Chuang and Zhixiao Wang) interpreted the data, provided critical feedback on the manuscript, approved the final manuscript for submission and were accountable for the accuracy and integrity of the manuscript.

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CONFLICTS OF INTEREST STATEMENT

Amy S. Paller: AbbVie, Dermavant, Incyte, Janssen, Krystal Biotech, LEO Pharma, Lilly, UCB—investigator; Aegerion Pharma, Azitra, BioCryst, Boehringer Ingelheim, Bristol Myers Squibb, Castle Creek Biosciences, Janssen, Krystal Biotech, LEO Pharma, Lilly, Novartis, Regeneron Pharmaceuticals Inc., Sanofi, Seanergy, TWi Biotechnology, UCB—consultant; AbbVie, Abeona Therapeutics, Catawba Research, Galderma, InMed Pharmaceuticals—data and safety monitoring board. Servando E. Marron: AbbVie, Almirall, Amgen, Boehringer Ingelheim, Galderma, Janssen, LEO Pharma, Lilly, Novartis, Regeneron Pharmaceuticals Inc., Roche, Sanofi—advisory board, consultant, research support, honoraria. Diane Whalley, Lauren Nelson and Shanshan Qin: Employees of RTI Health Solutions, which received funding from Regeneron Pharmaceuticals Inc. Jingdong Chao, Ashish Bansal, Zhixiao Wang: Regeneron Pharmaceuticals Inc.—employees and shareholders. Chien-Chia Chuang: Sanofi—employee, may hold stock and/or stock options in the company.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to patient-level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan and data set specifications. Patient-level data will be anonymised, and study documents will be redacted to protect the privacy

of our trial participants. Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form and statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymised 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 reidentification. Submit requests to https://vivli.org/.

ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. The local institutional review board (IRB) or Ethics Committee at each study centre oversaw trial conduct and documentation. All patients, or their parents/guardians, provided written informed consent before participating in the trial. Paediatric patients provided assent according to the Ethics Committee (IRB/Independent Ethics Committee)-approved standard practice for paediatric patients at each participating centre.

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REFERENCES

1. Bieber T. Atopic dermatitis. Ann Dermatol. 2010;22:125–37.
2. Laughter MR, Maymone MBC, Mashayekhi S, Arents BWM, Karimkhani C, Langan SM, et al. The global burden of atopic dermatitis: lessons from the Global Burden of Disease Study 1990–2017. Br J Dermatol. 2021;184:304–9.
3. Silverberg JI, Barbarot S, Gadkari A, Simpson EL, Weidinger S, Mina-Osorio P, et al. Atopic dermatitis in the pediatric population: a cross-sectional, international epidemiologic study. Ann Allergy Asthma Immunol. 2021;126:417–28.
4. Sánchez-Pérez J, Daudén-Tello E, Mora AM, Lara Surinyac N. Impacto de la calidad de vida relacionada con la salud en población pediátrica y adulta española con dermatitis atópica. Estudio PSEDA. Actas Dermosifiliogr. 2013;104:44–52.
5. Na CH, Chung J, Simpson EL. Quality of life and disease impact of atopic dermatitis and psoriasis on children and their families. Children (Basel). 2019;6:133.
6. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. Br J Dermatol. 1995;132:942–9.
7. Heinl D, Prinsen CAC, Sach T, Drucker AM, Ofenloch R, Flohr C, et al. Measurement properties of quality-of-life measurement instruments for infants, children and adolescents with eczema: a systematic review. Br J Dermatol. 2017;176:878–89.
8. Lewis-Jones MS, Finlay AY, Dykes PJ. The Infants' Dermatitis Quality of Life Index. Br J Dermatol. 2001;144:104–10.
9. Dodington SR, Basra MKA, Finlay AY, Salek MS. The Dermatitis Family Impact questionnaire: a review of its measurement properties and clinical application. Br J Dermatol. 2013;169:31–46.
10. Simpson EL, de Bruin-Weller M, Bansal A, Chen Z, Nelson L, Whalley D, et al. Definition of clinically meaningful within-patient changes in POEM and CDLQI in children 6 to 11 years of age with severe atopic dermatitis. Dermatol Ther (Heidelb). 2021;11:1415–22.
11. Simpson EL, de Bruin-Weller M, Eckert L, Whalley D, Guillemin I, Reaney M, et al. Responder threshold for Patient-Oriented Eczema Measure (POEM) and Children's Dermatology Life Quality Index (CDLQI) in adolescents with atopic dermatitis. Dermatol Ther (Heidelb). 2019;9:799–805.
12. Basra MKA, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. Dermatology. 2015;230:27–33.
13. Paller AS, Simpson EL, Siegfried EC, Cork MJ, Wollenberg A, Arkwright PD, et al. Dupilumab in children aged 6 months to younger than 6 years with uncontrolled atopic dermatitis: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2022;400:908–19.
14. Fayers PM, Hays RD. Don't middle your MIDs: regression to the mean shrinks estimates of minimally important differences. Qual Life Res. 2014;23:1–4.
15. Hays RD, Farivar SS, Liu H. Approaches and recommendations for estimating minimally important differences for health-related quality of life measures. J Chronic Obstruct Pulm Dis. 2005;2:63–7.
16. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol. 2008;61:102–9.
17. US Food and Drug Administration. Guidance for industry. Patient-reported outcome measures: use in medical product development to support labeling claims. https://www.fda.gov/media/77832/download (2009). Accessed 12 Oct 2023.

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