

The Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD): The development and reliability testing of a novel clinical outcome measurement instrument for the severity of atopic dermatitis

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Background: An Investigator Global Assessment (IGA) is recommended by health agencies for drug registration in atopic dermatitis (AD). Current IGA scales lack standardization.

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Objectives: To develop an IGA scale, training module, and clinical certification examination for use in AD trials; establish content validity; and assess reliability.

Methods: Expert dermatologists participated in the development of the validated IGA for AD (vIGA-AD™). Reliability (interrater and intrarater) was assessed by 2 web-based surveys. Clinical certification for investigators consisted of a training module and examination.

Results: Expert consensus was achieved around a 5-point IGA scale including morphologic descriptions, and content validity was established. Survey 1 showed strong interrater reliability (Kendall's coefficient of concordance W [Kendall's W], 0.809; intraclass correlation [ICC], 0.817) and excellent agreement (weighted kappa, 0.857). Survey 2, completed 5 months after training of dermatologists, showed improvements in scale reliability (Kendall's W , 0.819; ICC, 0.852; weighted kappa, 0.889). In this study, 627 investigators completed vIGA-AD training and certification.

Limitations: Ratings were assessed on photographs.

Conclusion: A validated IGA scale and training module were developed with the intent of harmonizing assessment of disease severity in AD trials. Strong reliability and excellent agreement between assessments were observed. (J Am Acad Dermatol <https://doi.org/10.1016/j.jaad.2020.04.104>.)

Key words: atopic dermatitis; atopic eczema; clinical outcome measure; Investigator Global Assessment; severity; validated.

Atopic dermatitis (AD) is a common chronic, heterogeneous, relapsing pruritic, inflammatory skin disease associated with unpredictable flares or exacerbations that has significant unmet medical need.¹ Multiple novel treatments, including topical and systemic therapies, are under development.² The robustness of clinical trials depends on the validity of key study endpoints, and systematic reviews indicate that many of the published AD outcome

CAPSULE SUMMARY

- Global severity measures provide a clinical snapshot of disease severity; no standardized Investigator Global Assessment scale for atopic dermatitis exists.
- This study developed a validated Investigator Global Assessment scale for atopic dermatitis to harmonize outcome assessments in clinical trials. The scale is freely available to dermatologists, investigators, and sponsors.

measures lack adequate validation.^{3,4} In a recent systematic review,⁴ 16 eligible outcome measures for the assessment of AD clinical signs were identified. Only the Eczema Area and Severity Index (EASI)⁵ and the Scoring Atopic Dermatitis (SCORAD) index⁶ were classified as being adequately validated and were recommended to assess the clinical signs of AD. However, these measures are not accepted by US regulators without an

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Abbreviations used:

AD:	atopic dermatitis
BSA:	body surface area
EASI:	Eczema Area and Severity Index
FDA:	US Food and Drug Administration
ICC:	intra-class correlation
IGA:	Investigator Global Assessment
SCORAD:	Scoring Atopic Dermatitis Index
vIGA-AD:	Validated Investigator Global Assessment for Atopic Dermatitis

Investigator Global Assessment (IGA) as at least a coprimary endpoint.

An IGA scale uses clinical characteristics to assess overall disease severity at any given timepoint.⁷ Currently, IGAs for AD vary in the number of response options, definitions of severity levels, and morphologic descriptors, making it difficult

for treating physicians to compare across trials and interpret results. The US Food and Drug Administration (FDA) and other health agencies recommend that an IGA be included as a primary endpoint for trials supporting new drug applications in AD⁸; however, IGA scales used previously lack standardization and validation. To date, no IGA has shown sufficient intra- and interrater reliability to harmonize AD clinical research across different programs.⁹

The objective of this study was to develop and perform initial validation of an IGA for AD. We report the development, content validation, and reliability testing of the IGA-AD scale and the development of a training and certification examination for the use of the validated IGA to ensure harmonization in the assessment of AD in clinical trials.

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MATERIALS AND METHODS

Development of the Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-ADTM), training module, and clinical certification examination

An advisory group of 24 global dermatology experts on AD (20 adult dermatologists and 4 pediatric dermatologists) was formed to develop a validated IGA scale for AD (vIGA-ADTM). Nineteen academic and 5 industry dermatologists from the European Union, Japan, Canada, and the United States were identified through the International Eczema Council, the American Academy of Dermatology Atopic Dermatitis Expert Resource Group, and publications. A consensus decision-making process was used to obtain expert opinion to define scale content. Between October 2016 and August 2017, advisors met via teleconference. The 24 experts were divided in 2 groups: a core team with 7 advisors (ES, EG, BK, LE, JS, RB, and AP) who conducted initial scale development and a review group composed of the remaining experts. The scale was developed to measure improvement in clinical signs, the priority domain for regulatory agencies in drug registration trials. The FDA recommended that the scale's morphologic descriptors articulate clear, nonoverlapping, noncomparative categories, with *clear skin* representing the absence of disease, and that focus should be given to having clearly distinct categories for mild (IGA score of 2) versus almost clear (IGA score of 1). An investigator training video and certification examination were subsequently created.

Reliability testing of the vIGA-AD scale and survey content

Web-based surveys were developed to assess the reliability of the vIGA-AD. The 24 global dermatologists participated in 2 surveys conducted approximately 5 months apart. Survey 1 contained 35 photographs of patients, including 5 duplicates that were modified slightly on repeat assessment by cropping, flipping, etc. Survey 2 contained 25 photographs and a training video. The dermatologists were required to watch the training video with instructions on proper implementation of the vIGA-AD before rating the lesions in survey 2. Because computer screen resolution and color profile can vary significantly, a hardcopy booklet with high-resolution photographs of the lesions was mailed to each survey participant. To ensure ratings were conducted using the high-resolution color images, online images for both surveys were black and white.

vIGA-AD scale training and clinical certification examination

To facilitate correct use of the vIGA-AD, a training video on best practices for using the scale to rate disease severity was developed to train and certify clinical trial investigators. To participate, investigators must have been actively involved in phase 3 clinical trials in AD and had previous experience in dermatology clinical research, including rating with the EASI and SCORAD. The video provided an overview of the scale, guidelines for its use, and examples for the different ratings. Investigators were required to complete the training module before accessing the certification examination, which included 20 photographs of patients with AD. The investigator's vIGA-AD score for each photograph was compared to the corresponding score assigned by an expert rater (ES). For most photographs (18/20), there was only 1 correct score out of 5 possible options. Two photographs had 2 possible correct answers because of screen resolution variability for these specific images. An investigator was required to rate at least 14 (70%) photographs correctly to pass.

Photographs

Photographs of AD cases were obtained from a commercial vendor (DermNetNz.org). All photographs were reviewed and selected by 2 AD clinical experts (ES and AP). Photographs were selected if the image was a confirmed case of AD, of high quality (eg, in focus, well lit, and lacking obstructions of the affected area), and included no comorbid conditions that could interfere with the vIGA-AD assessment (eg, bacterial or viral skin infections). Photographs in the surveys and clinical examination were selected to represent a full spectrum of severity levels (including *clear*) and were included only if agreed on by the 2 raters. Photographs included pediatric and adult patients with different skin tones and consisted of a mix of images such as whole chest or whole leg, with insets of higher magnification of individual lesions, as well as some target lesion (or regional) images. To allow investigators to consider a global assessment of disease severity, each photograph was accompanied by a general descriptor of disease extent, such as "bilateral symmetric lesions," "no other areas involved," or "similar lesions involving back and lower extremities." Descriptors did not include values for specific body surface area (BSA) involved.

Statistical analysis

Interrater reliability. Overall interrater reliability was evaluated with survey 1 and survey 2 by

using the intraclass correlation (ICC) metrics, weighted kappa (quadratic), and Kendall's coefficient of concordance W (Kendall's W).

Intrarater reliability. For each pair of duplicated photographs within survey 1 from the same patient, the consistency between the 2 ratings by the same physician was evaluated by using a linear mixed-effects model. Although repeated photos from survey 1 were included in survey 2 with the initial intent of assessing intrarater reliability, the implementation of the training video before survey 2 may affect reliability analyses.

vIGA-AD scale reliability. Reliability of the vIGA-AD was evaluated using the ICC metrics, weighted kappa (quadratic), and Kendall's W .

RESULTS

vIGA-AD scale content validation

Expert consensus was achieved around a 5-point scale (0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe) with morphologic descriptors for each score (Fig 1). The FDA reviewed the final scale and indicated that the vIGA-AD was adequate to assess the efficacy of a product being developed for AD treatment.

Reliability of the vIGA-AD

Interrater reliability. The images used in each online validation survey are summarized in Table I. Survey 1 ($n = 21$) showed that the scale had strong interrater reliability and excellent agreement (Table II). Survey 2 ($n = 20$) showed additional improvements in scale reliability and agreement after training of the dermatologists.

Intrarater reliability. Assessment of the duplicated photographs in survey 1 showed high intrarater reliability as measured by an ICC(2,1) of 0.879. Similar results were seen with the repeated photographs between survey 1 and survey 2 (ICC[2,1] of 0.881).

vIGA-AD scale training and certification examination

A total of 627 investigators completed both the training module and clinical certification examination, with 79% (497/627) passing the examination on their first attempt (Fig 2). Approximately 25% of investigators rated at least 90% of the photographs ($\geq 18/20$ photographs) correctly on their first attempt (Fig 2). Clinical certification examination data showed that the vIGA-AD scale continued to show good reliability in a larger population of investigators (ICC[2,1], 0.849; Kendall's W , 0.813) with strong agreement among all investigators ($N = 627$; weighted kappa, 0.869). Results were

further improved when restricting the analysis to investigators who passed the certification examination on their first attempt ($n = 497$; ICC[2,1], 0.878; Kendall's W , 0.838; weighted kappa, 0.893).

DISCUSSION

We developed a validated, standardized IGA scale (vIGA-AD) and training module for the assessment of disease severity in future AD clinical trials. FDA feedback reinforced the importance of distinct categories, particularly between the descriptors of vIGA 1 or 2, to properly categorize responders. Reliability testing of the vIGA-AD was performed by 2 web-based surveys and indicated strong interrater reliability and excellent agreement among physicians. Intrarater reliability was evaluated by the duplication of photographs and was robust. Both intra- and interrater reliability improved after physicians completed the vIGA-AD training video. A clinical certification examination was developed to ensure appropriate use of the scale, and its results confirmed that the vIGA-AD is reliable with strong agreement when performed by a population of more than 600 investigators. Investigator training on the assessment of primary or key secondary endpoints, such as an IGA assessment in AD, is usually a regulatory requirement for drug registration; therefore, the availability of a standardized training module on how to best implement the vIGA-AD was necessary.

IGAs represent a holistic measure of disease severity, are relatively easy to complete, and measure clinical signs at a single timepoint.⁸ Currently, IGAs serve as primary endpoint measures for AD in randomized clinical trials and drug registration trials, in which improvement in clinical signs remains the priority domain for regulatory agencies but for which there are no standardized and validated scales available for use.⁸ We envision that the vIGA-AD will become the standardized IGA to be implemented in future AD clinical trials.

To enhance the objectivity and reliability needed for drug registration trials, the vIGA-AD uses clinical signs, including erythema, lichenification, induration/papulation, and oozing/crusting. Although the content of the scale was not developed by using patients, the clinical signs used in the scale are consistent with those rated as the most important by patients and providers.^{8,10} Although the experts involved in the scale development agreed that excoriation is an important component of AD, the intensity of excoriation can vary significantly in AD based on whether a patient scratches using the nails, with a tool (such as a brush), or by rubbing. The presence or severity of excoriation does not necessarily reflect disease severity. Thus, excoriation was

Validated Investigator Global Assessment scale for Atopic Dermatitis

vIGA-AD™

Instructions:

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

Score	Morphological Description
0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 – Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 – Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Notes:

1. In indeterminate cases, please use extent to differentiate between scores.

For example:

- Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered “3 – Moderate”.

2. Excoriations should not be considered when assessing disease severity.

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Fig 1. The Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD™). Expert consensus was achieved around a 5-point scale with morphologic descriptors for each score.

Table I. Cases of atopic dermatitis depicted in each survey, n

Image Characteristics	Survey 1	Survey 2
Total cases	35	25
Cases represented using more than 1 photograph	2	5
Duplicate cases	5	—
Repeat cases from survey 1	—	8
Age		
Pediatric	3	0
Adult	17	10
Indeterminate*	15	15
Body area		
Head/neck	10	1
Trunk [†]	2	4
Upper extremities	12	12
Lower extremities	10	7
Multiple [‡]	1	1

*Localized images could be perceived as adolescents or adults.
[†]Body areas represent the primary region assessed in the images; however, images of the trunk often included multiple areas, including the trunk, neck, and arms.
[‡]In survey 1, images of the trunk and legs were displayed in 1 case. In survey 2, images of the trunk and arms were displayed in 1 case.

Table II. Interrater reliability of the vIGA-AD scale

Measure	Survey 1	Survey 2
Number of physicians	21	20
Number of photographs in survey	35	25
ICC(2,1)	0.817	0.852
Weighted kappa* (quadratic)	0.857	0.889
Kendall's <i>W</i>	0.809	0.819

ICC, Intraclass correlation; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis; Kendall's *W*, Kendall's coefficient of concordance *W*.

*Kappa values indicate the level of agreement between the physicians: 0.1 to 0.2, slight agreement; 0.21 to 0.4, fair agreement; 0.4 to 0.6, moderate agreement; 0.6 to 0.8, substantial agreement; 0.81 to 1.0, almost perfect agreement. Kendall's *W*: <0.3, low correlation; 0.3 to 0.5, moderate correlation; >0.5, large correlation.

excluded from the morphologic descriptors of the vIGA-AD.

Disease extent is an important component of AD disease severity.¹⁰ In clinical trials, changes in BSA involvement are often used to show improvement with treatment, as well as a requirement for defining disease severity (eg, $\geq 10\%$ BSA involvement is often used for trials in moderate to severe AD).¹¹ Although BSA is included as an important component of both the EASI⁵ and SCORAD,⁶ IGAs have not often listed the area of involvement as a component of the morphologic descriptors. In the vIGA-AD, extent is used in 2 ways. First, disease must be widespread to

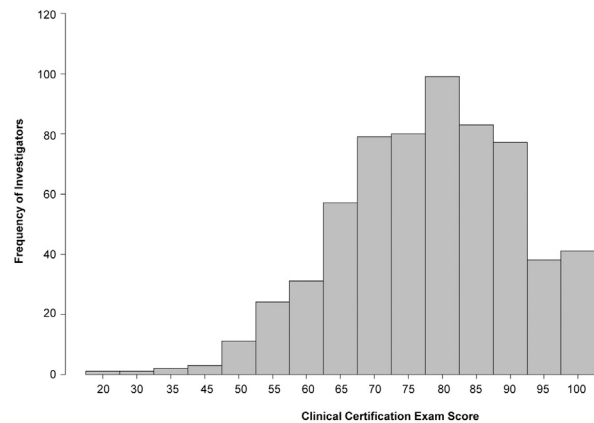


Fig 2. Histogram of investigators' certification examination results. Investigators completed the Validated Investigator Global Assessment for Atopic Dermatitis clinical certification examination after completing the training module. The certification examination consisted of 20 photographs of atopic dermatitis lesions; each photograph was rated by the investigators (N = 627). If an investigator scored fewer than 70% of the photographs correctly in the examination, this was considered a fail (n = 130).

be considered severe. Although a specific BSA cutoff to meet the definition of *widespread* is not defined on the scale, experts agree that approximately 10% or greater BSA involvement should be required for the disease to be considered severe, assuming that the morphologic descriptors also match severe disease (ie, marked erythema, marked induration/papulation, and/or marked lichenification). Patients with severe lesions affecting less than 10% BSA should be classified as having moderate disease according to the vIGA-AD. Second, although disease extent alone is not sufficient to define disease severity (ie, a patient with clearly mild-appearing lesions affecting a large BSA should still be rated as having mild disease), the vIGA-AD allows for the use of disease extent when rating indeterminate cases. For example, if a clinician struggles to decide between a mild versus moderate rating based on the appearance of skin lesions, the clinician can use disease extent to assist in the rating. Thus, a patient with lesions that are indeterminate in appearance, ranging between mild and moderate based on morphologic descriptors, but who has extensive disease would be classified as having moderate disease, whereas the same patient would be rated as having mild disease if the disease were limited in extent.

Dermatologists agree that a standardized validated IGA is required to harmonize AD clinical trials to enable the comparison of AD treatments. To ensure harmonization across trials and correct use of the vIGA-AD, a training video and certification

examination were developed. The benefits of a training video were suggested by the improvement in interrater reliability observed in survey 2. Given the ease of completion of the vIGA-AD clinical certification training and examination by more than 600 investigators, with most (79%) passing certification on their first attempt, it is envisioned that the vIGA-AD could be used in the routine clinical setting. For this goal, however, further testing is needed, in particular for responsiveness and cross-cultural validity.

A high degree of agreement existed between raters and investigators using the vIGA-AD; however, ratings were assessed from photographs, which limit the raters' ability to fully assess the physical characteristics as compared to a physical examination. In addition, assessments were often restricted to 1 body region. To help minimize these limitations, photographs were accompanied by a general descriptor of disease extent. Although a variety of skin tones were represented in the surveys and certification examination, most photographs were of white skin types. The assessment of disease severity in patients with dark skin types can represent a challenge, and further data from trials in other races or ethnicities are required.

Additional psychometric validation of the vIGA-AD against existing clinician-reported AD severity assessment instruments such as the EASI and SCORAD, as well as patient-reported global assessment of disease severity, has been conducted using data from 2 global phase 3 trials in AD (NCT03334396, NCT03334422). Results from these additional psychometric analyses (eg, assessment of reliability, validity, and responsiveness) will be reported separately. In addition, further validation with onsite patient evaluation by AD experts would provide evidence of the scale's performance in clinical practice. For example, a recent study¹² showed the vIGA-AD's utility in pediatric patients with mild to severe AD. Investigators found that the vIGA-AD provided a rapid, accurate, and easily interpretable practice-based measurement of disease severity and correlated well with the EASI, further supporting the scale's use in clinical settings and the potential for widespread adoption.

The vIGA-AD provides a simple yet efficient scale for assessing AD severity. Investigators benefitted from the addition of a training video that provided an overview of the scale and guidelines for its use. To enable the harmonization of clinical efficacy results of new AD drugs, the vIGA-AD and associated training module are available to investigators and

sponsors through the International Eczema Council (www.eczemacouncil.org/research/investigator-global-assessment-scale/) and Eli Lilly and Company. As of January 2020, 4623 investigators in 48 countries had completed the vIGA-AD training and certification examination, and the vIGA-AD had been adopted by 13 sponsors in 38 clinical trials.

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