Evaluating change in disease activity needed to reflect meaningful improvement in quality of life for clinical trials in cutaneous lupus erythematosus

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Background: Outcome measures of clinical trials in cutaneous lupus erythematosus (CLE) should reflect clinically meaningful improvement in disease activity, as measured by the Cutaneous Lupus Disease Area and Severity Index activity score (CLASI-A).

Objective: We aimed to define the degree of improvement in disease activity meaningful to a patient's quality of life.

Methods: The change in the CLASI-A in 126 patients needed to predict meaningful change in QoL, as defined by the Emotions and Symptoms subscales of the Skindex-29, was evaluated by linear regression models.

Results: In patients with an initial CLASI-A of ≥8, a 42.1% or ≥7-point and a 31.0% or ≥5-point decrease in CLASI-A predicts meaningful improvement in the Emotions and the Symptoms subscales, respectively.

Limitations: This is a retrospective study of prospectively collected data at a single site.

Conclusions: A CLASI-A score of ≥8 for trial entry allows for inclusion of patients with milder disease where CLASI-A improvement by ≥50% is clinically significant and meaningful. (J Am Acad Dermatol 2021;84:1562-7.)

Key words: autoimmune skin disease; clinical trials; cutaneous lupus erythematosus; efficacy measures; patient-reported outcomes; quality of life.

Cutaneous lupus erythematosus (CLE) can occur with or without other features of systemic lupus erythematosus (SLE).[1] The disease can impose a significant burden on patients' lives, compromising mental and psychological health and impairing quality of life (QoL).[2] Furthermore, it has been established that an improvement in disease activity, as defined by the Cutaneous Lupus Disease Area and Severity Index (CLASI) score for activity (CLASI-A), is correlated to an improvement in QoL, as measured by Skindex-29.[3,4]

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The impact of CLE on QoL is severe when compared to the impact of several other skin conditions and particularly affects the Emotions (Skindex-E) and Symptoms (Skindex-S) subscales of Skindex-29.[3] In the past 50 years, there have been no new medications approved for the treatment of CLE.[5] SLE trials face many obstacles, including complex trial endpoints, efficacy measures, heterogeneity of the disease, and prevalence of background medications.[5,6] The US Food and Drug Administration has recommended endpoints for lupus that are organ specific,[7] and a goal is that implementation of the skin-specific endpoint may lead to US Food and Drug Administration–approved treatments for CLE.[5,7] From a regulatory standpoint, it is important to determine a meaningful change in the CLASI-A score that reflects the patient's perspective.

CAPSULE SUMMARY

- We aimed to define the degree of change in CLASI activity scores that correlates with meaningful improvement in quality of life in patients with cutaneous lupus.
- Analysis of clinical trials can include patients with milder disease and use endpoints that are meaningful to patients to advance new treatments.

Although minimal clinically significant improvement in disease activity has been determined,[3,4,8] there has been no quantification of the amount of change in the CLASI-A needed to predict a meaningful change in QoL, as determined by the changes in the Skindex-E and Skindex-S subscales. Clinical trials using the CLASI currently use endpoints that have been discriminatory between effective treatments and placebo (eg, the percentage of patients with ≥50% improvement in CLASI-A in patients with a CLASI-A of ≥10).[9-11] The goal of our project was to define the degree of change in the CLASI-A score correlating with a meaningful improvement in QoL. This meaningful improvement in CLASI-A score is an important variable in the design and interpretation of future clinical trials.[12,13]

METHODS

Patients

This study included 126 patients seen at the Autoimmune Skin Disease Clinic at the Hospital of the University of Pennsylvania who had elected to participate in a research database from 2006 to 2019. The diagnosis of CLE was based on clinical, laboratory, and histopathologic evidence and determined by an expert physician trained in immunodermatology. This prospective CLE database, established to monitor disease progression and changes in QoL during routine clinical visits, was approved by University of Pennsylvania's institutional review board. Patients were not required to have a research visit after their clinical evaluation. We used physician-collected CLASI-A scores and patient-reported Skindex-29 scores for this study. Individuals were excluded if questionnaires were incomplete or if there was only one visit. Individuals with an initial CLASI-A of ≤3 were also excluded because a previous study[14] has shown that there is no additional improvement in the Skindex-E and Skindex-S with further improvement in the CLASI scores in this low range. Patients were included if all responses to Skindex-29 and CLASI scores were completely recorded and if they had at least 2 research visits.

CLASI

The CLASI is a validated scoring system developed to provide an accurate way to measure clinical outcomes for therapeutic trials.[15] The scoring system takes into consideration the activity of the disease and damage caused by the disease, with each scored separately. The scores are based on anatomic locations and the most severe lesion located in that location. Activity is measured by erythema, scale/hypertrophy, mucous membrane involvement, and nonscarring alopecia or hair loss in the past 30 days, with a maximum of 70 points, and is evaluated by the CLASI-A score. Damage is scored by dyspigmentation or scarring and includes the extent of scarring alopecia in the scalp, with a maximum of 80 points. Higher activity scores indicate more severe disease, with a score of 0 to 9 indicating mild disease, 10 to 20 indicating moderate disease, and 21 to 70 indicating severe disease.[16] CLASI-A scores have been shown to have higher correlations with Skindex-29 subscales than CLASI damage scores.[17]

Skindex-29

The Skindex-29 was developed as a QoL measurement tool specific to dermatology. It includes 29 questions that are categorized into 3 subscales: the Skindex-E, Skindex-S, and Functioning (Skindex-F). Each question is scored from 0 to 4 and then normalized to a 100-point scale, with higher scores indicating worse QoL. Subscale scores are calculated as the mean score of the questions specific for the individual subscale. Patients with CLE have particularly high scores on the Skindex-E and Skindex-S, much more so than on

Abbreviations used:

CLASI:	Cutaneous Lupus Disease Area and Severity Index
CLASI-A:	Cutaneous Lupus Disease Area and Severity Index activity score
CLE:	cutaneous lupus erythematosus
DLQI:	Dermatology Life Quality Index
DM:	dermatomyositis
QoL:	quality of life
Skindex-E:	Emotions subscale of Skindex-29
Skindex-F:	Functioning subscale of Skindex-29
Skindex-S:	Symptoms subscale of Skindex-29
SLE:	systemic lupus erythematosus

the Skindex-F.[3] Although the Skindex-F responds to changes in CLASI-A scores, it was found to have poor correlation with disease activity at all CLASI scores.[4,14] Because of poor correlation between the Skindex-F and CLASI-A scores, this study considered only the Skindex-E and Skindex-S.[14]

Before this study the values of meaningful change in Skindex-29 subscales had not been established, and to do so, we used a prospective database of patients with dermatomyositis (DM) that collected the Dermatology Life Quality Index (DLQI) in addition to the Skindex-29 to determine meaningful change in the Skindex-E and Skindex-S. Using the known value of meaningful improvement in the DLQI, which is a score decrease of 5 points,[18,19] we found that a 9.38-point change in Skindex-E and a 7.37-point change in Skindex-S indicate a meaningful change in QoL in patients with a Cutaneous Dermatomyositis Disease Area and Severity Index score of ≥10, a point of disease activity that correlates well with the DLQI, Skindex-E, and Skindex-S. Both CLE and DM are inflammatory skin conditions that can have a similar magnitude and symptomology of the clinical presentation, with the potential for multisystem manifestations.[20] The shared symptomology between the two conditions includes photosensitivity, pruritus, inflammatory rash, and alopecia, among others, all of which have the potential to have a significant negative impact on a patient's QoL.[3,21-24] Given these similarities, we applied results from previous studies of meaningful change in the Skindex in dermatomyositis to CLE.

Analysis

Analysis was performed with GraphPad Prism, version 5 (GraphPad Software, San Diego, CA) with a significance level of .05. Our patient population was characterized by using descriptive statistics. All patients were evaluated together to confirm correlations between CLASI-A scores and Skindex-29 subscales by using a Pearson correlation. Subsequently, patients with mild, moderate, or severe initial CLASI-A scores were analyzed separately, with severity levels categorized as scores of 4 to 9, 10t o 20, and greater than 20, respectively. Patients with mild initial activity were stratified further by analyzing all patients with initial CLASI score of less than 4, CLASI score of less than 5, and at further increments of 1-point increases. By using parametric correlations, change in CLASI-A scores was also correlated to changes in the Skindex-E and Skindex-S scores for patients with mild initial disease activity (CLASI-A, 4-9) in 2 different subdivisions: CLASI-A of 4 to 7 and CLASI-A of 8 to 9. The percent change and difference between the CLASI-A scores of the first 2 visits were estimated and compared with the difference between each of the Skindex-29 subscale scores between the 2 visits by using a linear regression analysis.

Meaningful change in each Skindex-29 subscale, which is the independent variable in the linear regression models and defined as a 9.38-point change in Skindex-E and a 7.37-point change in Skindex-S, was divided by each of the

Table I. Patient characteristics

Characteristics	n	%
Sex		
Female	106	84.1
Male	20	15.9
Race		
White	81	64.2
African American	31	24.6
Asian	7	5.6
Other	7	5.6
CLE/SLE (n = 46)		
Generalized DLE	15	32.6
Localized DLE	9	19.6
Tumid	1	2.17
Panniculitis	0	0.00
SCLE	10	21.7
ACLE	6	13.0
Multiple subtypes	5	10.9
CLE (n = 80)		
Generalized DLE	15	18.8
Localized DLE	19	23.8
Hypertrophic	2	2.50
Chilblains	1	1.25
Tumid	8	10.0
Panniculitis	1	1.25
SCLE	26	32.5
ACLE	0	0.00
Multiple subtypes	8	10.0

ACLE, Acute cutaneous lupus erythematosus; *CLE,* cutaneous lupus erythematosus; *DLE,* discoid lupus erythematosus; *SCLE,* systemic cutaneous lupus erythematosus; *SLE,* systemic lupus erythematosus.

Table II. Percent change and difference needed in CLASI-A* scores to predict meaningful improvement in Skindex-29 subscales (Emotions and Symptoms)† in patients with a range of initial CLASI-A scores

Severity of disease activity	Percent change in CLASI-A	Slope (95% CI)	*P* value
Mild disease activity (CLASI-A, 8-9) (n = 13)			
Skindex-29 Emotions	48.85	0.192 (0.053-0.332)	.0114
Skindex-29 Symptoms	38.19	0.193 (0.010-0.376)	.0403
Moderate disease activity (CLASI-A, 10-20) (n = 46)			
Skindex-29 Emotions	49.11	0.191 (0.062-0.321)	.0050
Skindex-29 Symptoms	33.96	0.217 (0.130-0.303)	<.0001
Severe disease activity (CLASI-A, >20) (n = 31)			
Skindex-29 Emotions	25.42	0.369 (0.165-0.573)	.0010
Skindex-29 Symptoms	18.90	0.390 (0.111-0.669)	.0080
	Change in CLASI-A‡	**Slope (95% CI)**	***P* value**
Mild disease activity (CLASI-A, 8-9) (n = 13)			
Skindex-29 Emotions	4.265	2.199 (0.583-3.816)	.0122
Skindex-29 Symptoms	3.277	2.249 (0.149-4.349)	.0380
Moderate disease activity (CLASI-A, 10-20) (n = 46)			
Skindex-29 Emotions	7.415	1.265 (0.369-2.161)	.0067
Skindex-29 Symptoms	5.051	1.459 (0.861-2.058)	<.0001
Severe disease activity (CLASI-A, >20) (n = 31)			
Skindex-29 Emotions	6.541	1.434 (0.734-2.135)	.0002
Skindex-29 Symptoms	4.426	1.665 (0.728-2.601)	.0011

CLASI-A, Cutaneous Lupus Disease Area and Severity Index activity score; *CI,* confidence interval.
*Higher scores in CLASI-A indicate more severe disease, with scores of 0 to 9 indicating mild disease, 10 to 20 indicating moderate disease, and 21 to 70 indicating severe disease.
†Questions in the survey are normalized to 100 points, with higher scores indicating worse quality of life.
‡Change in CLASI-A is defined as the difference between 2 CLASI-A scores needed to result in a meaningful improvement in a patient's quality of life, measured by Skindex-29.

slopes of the linear equation to estimate the percent change and difference in CLASI that was associated with a meaningful change in the Skindex-E and Skindex-S.

RESULTS

Patient characteristics, including sex, ethnicity, SLE prevalence, and CLE subtype are summarized in Table I. The median time between the initial visit and the first follow-up visit was 4.0 months (interquartile range [IQR], 2.0-9.0) for all patients. In this study, 49 patients had an initial CLASI-A score in the mild category (CLASI-A, 4-9), 46 patients were in the moderate category (CLASI-A, 10-20) and 31 patients were in the severe category (CLASI-A, >20). The median change in CLASI-A score was a decrease of 3.0 points (IQR, -8.0 to 1.0), and the median change in Skindex-29 subscales was a decrease of 10.0 points (IQR, -22.5 to 2.5) in the Skindex-E and a decrease of 7.1 points (IQR, -17.9 to 3.6) in the Skindex-S. For all patients, change in the CLASI-A score was correlated with changes in both Skindex-29 subscales using a Pearson correlation: $r = 0.498$ ($P < .0001$) for the Skindex-E and $r = 0.475$ ($P < .0001$) for the Skindex-S. Pearson correlations were also established between change in disease activity and change in Skindex-E ($r^2 = 0.143$; $P = .0229$) and change in Skindex-S ($r^2 = 0.027$; $P = .3400$) for patients in the lower range of mild initial disease activity (CLASI-A, 4-7) and between the change in disease activity and change in Skindex-E ($r^2 = 0.449$; $P = .0122$) and Skindex-S ($r^2 = 0.336$; $P = .0380$) for patients in the upper range of mild initial disease activity (CLASI-A, 8-9).

For both subscales, patients with severe initial disease required a smaller percent change in CLASI-A to achieve a meaningful change in QoL (Skindex-E, 25.42%; Skindex-S, 18.90%) than patients with moderate initial disease (Skindex-E, 49.11%; Skindex-S, 33.96%) (Table II). When looking at the differences in CLASI-A, a smaller reduction in the CLASI-A score was needed to predict meaningful change in the Skindex-E and Skindex S in patients with an initial CLASI-A score of 8 to 9 (Table II). In patients with an initial CLASI-A score of 8 or greater, an improvement of 42.1% in disease activity was associated with a meaningful improvement in the Skindex-E and an improvement of 31.0% for the

Table III. Percent change and the difference needed in CLASI-A scores to predict meaningful improvement in Skindex-29 subscales (Emotions and Symptoms) in patients with a CLASI-A of ≥8

Severity of disease activity	Percent change in CLASI-A	Slope (95% CI)	*P* value
Initial CLASI-A of ≥8 (n = 90)			
Skindex-29 Emotions	42.06	0.223 (0.136-0.310)	<.0001
Skindex-29 Symptoms	30.97	0.238 (0.153-0.322)	<.0001
	Change in CLASI-A	**Slope (95% CI)**	***P* value**
Initial CLASI-A of ≥8 (n = 90)			
Skindex-29 Emotions	6.871	1.365 (0.872-1.858)	<.0001
Skindex-29 Symptoms	5.107	1.443 (0.965-1.921)	<.0001

CLASI-A, Cutaneous Lupus Disease Area and Severity Index activity score; *CI,* confidence interval.

Skindex-S (Table III). When looking for the difference in CLASI-A associated with meaningful impact on QoL in patients with an initial CLASI-A score of 8 or greater, a decrease in CLASI-A by 7 or more and 5 or more points predicts meaningful change for the Skindex-E and Skindex-S, respectively (Table III).

DISCUSSION

Currently, clinical trials for lupus erythematosus use an efficacy measure of at least 50% improvement in the CLASI-A score in patients with an initial CLASI-A score of 10 or greater.[9-11] However, many trials enroll only a subset of patients with that degree of skin severity. Our study confirms that in patients with an initial CLASI-A score of 8 or greater, an improvement in CLASI-A by at least 42.1% and 31.0% is associated with a meaningful change in the Skindex-E and Skindex-S, respectively (Table III), which would allow for patients with milder disease to be included in trials that use an efficacy measure of 50% or greater improvement in the CLASI-A score. A minimum CLASI-A score of 8 used at trial entry would allow for the inclusion of patients with milder disease who might have been excluded from skin-specific endpoints. Whether this would discriminate optimally between effective treatments and placebo remains to be determined, but the clinical significance of cutaneous improvement defined here is supported by patient data.

We found that correlation between change in disease activity and change in the 2 Skindex subscales was much lower for patients on the low end of mild initial disease activity (CLASI-A, 4-7) than for patients on the higher end of the spectrum (CLASI-A, 8-9). This suggests that in patients with CLASI-A scores 7 or less, it would be difficult to show meaningful improvement in QoL because of floor effects, whereas those in the more severe range of mild initial disease activity (CLASI-A scores of 8-9) can have meaningful improvement in their QoL without complete clearance of their disease.

Klein et al[16] identified a 4-point, or 20%, decrease in CLASI-A as the minimal clinically significant improvement in the CLASI-A score.[16] For patients with an initial CLASI-A score of 8 or greater, a decrease in activity by at least 7 and 5 points is not only a clinically significant improvement but also is associated with a meaningful impact on the Skindex-E and Skindex-S, respectively (Table III). A lower magnitude of improvement in disease activity is needed to predict meaningful change in the Skindex-S compared to the Skindex-E; if the CLASI score decreases enough to meaningfully affect the Skindex-E, then there is also an associated meaningful improvement in the Skindex-S.

For patients with initial disease activity in the severe range of mild disease (patients with a CLASI-A score of 8-9), accomplishing an actual score improvement of 7 points, or nearly total clearance of disease activity, would require complete resolution of the skin lesions. For these patients, using a percent improvement of 50% as a marker for meaningful improvement in the Skindex-E correlates with a meaningful improvement in QoL without disease clearance. Ultimately, the choice of using percent improvement or absolute decrease in the CLASI-A score for trials would come down to preference and feasibility.

CLE has a widely variable clinical presentation across multiple subtypes, some with a higher potential to be a scarring process. In this article, a variety of subtypes are represented by our patient population, but future research will evaluate meaningful change in disease activity among subtypes. In addition, a database of patients with dermatomyositis was used to determine meaningful change in the Skindex-29 subscales. Although both CLE and DM are inflammatory skin conditions that can have a similar magnitude and symptomology of the clinical presentation with the potential for multisystem manifestations, there is potential for differences in meaningful change in the Skindex-29 subscales.[3,20-24] For the purposes of this study, we

believe that using patients with DM to evaluate meaningful change in Skindex-29 for patients with CLE is reasonable; however, future studies should evaluate meaningful changes in Skindex-29 using patients with CLE.

We find that currently established efficacy measures of at least a 50% improvement in disease activity is predictive of meaningful change in patients with an initial CLASI-A score of 8 or greater. Using a CLASI-A score of 8 or greater for trial entry allows for the inclusion of patients with milder disease for whom improvement of disease activity by 50% or greater can result in a meaningful impact on QoL, as determined by the Skindex-E and Skindex-S. Our findings begin to establish appropriate trial endpoints by determining the clinically significant change in disease activity associated with meaningful changes in patients' QoL.

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