Study

Development of the CLASI as a Tool to Measure Disease Severity and Responsiveness to Therapy in Cutaneous Lupus Erythematosus

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Objective: To determine how to use the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) to classify patients according to disease severity (mild, moderate, and severe) and to identify which patients respond to therapy.

Design: Cohort.

Setting: The connective-tissue disease clinic at the Hospital of the University of Pennsylvania, Philadelphia.

Patients: Seventy-five patients with clinical or histopathologic evidence of cutaneous lupus erythematosus or systemic lupus erythematosus were included in the study.

Main Outcome Measures: The CLASI, Skindex-29, and the physician’s subjective assessment of severity and improvement were completed at every visit.

Results: Disease severity was assessed with 45 patient visits. Mild, moderate, and severe disease corresponded with CLASI activity score ranges of 0 to 9, 10 to 20, and 21 to 70, respectively. Improvement in disease activity was assessed in 74 patients. A clinical improvement was associated with a mean 3-point or 18% decrease in the CLASI activity score. However, receiver operating characteristic analysis demonstrated an increased percentage of patients correctly classified when a 4-point (sensitivity, 39%; specificity, 93%; correctly classified, 76%) or 20% (sensitivity, 46%; specificity, 78%; correctly classified, 67%) decrease in the CLASI activity score was used instead to identify improvement.

Conclusion: The CLASI can be used to classify patients into groups according to disease severity and to identify clinically significant improvements in disease activity.

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The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) is a clinical tool that quantifies disease activity and damage in cutaneous lupus erythematosus (CLE). The activity score is based on the degree of erythema, scale, mucous membrane lesions, and nonscarring alopecia. Unlike other outcome measures in dermatology, CLASI scores are not based solely on the area of involved skin; rather, parts of the body that are most visible are weighted more heavily than those that are usually covered. The CLASI has already been shown to have good content validity, addressing the most relevant aspects of CLE as determined by an expert panel of dermatorheumatologists. It also has good interrater and intrarater reliability when used by either dermatologists or rheumatologists. Early small clinical studies have demonstrated responsiveness in all subsets of CLE, including individual lesions, localized and generalized discoid lupus erythematosus (DLE), as well as subacute cutaneous lupus erythematosus (SCLE) and tumid lupus erythematosus.

In 2005, the US Food and Drug Administration (FDA) updated their guidelines regarding the development of new therapeutic agents for the treatment of systemic lupus erythematosus (SLE). They recommended focusing on organ-specific therapies, which may be easier to approve than medications that target multiple organ systems. In order to demonstrate efficacy in 1 organ system, it is important to have an organ-specific index of disease activity and to understand how to use that index to characterize disease severity and define improvement. Therefore, we sought to determine how the CLASI activity score could be used to classify patients into groups according to mild, moderate, and severe disease, as well as the change in the CLASI activity score that corresponds with a clinically significant improvement in disease activity.
METHODS

PATIENT SELECTION

Patients were recruited from our connective tissue disease clinic at the Hospital of the University of Pennsylvania, Philadelphia. Inclusion criteria included a diagnosis of CLE based on the modified Gilliam criteria. All patients were 18 years or older. The study was approved by our institutional review board (IRB), and all patients were enrolled with IRB-approved informed consent and Health Insurance Portability and Accountability Act forms.

OUTCOME MEASURES

Procedures

Several questionnaires were completed at each visit; the principal investigator (V.P.W.) completed the Physician’s Subjective Assessment of Severity, the Physician’s Subjective Assessment of Improvement, and the CLASI. The study participant completed the Skindex-29. These questionnaires are described in detail in the following subsections.

Physician’s Subjective Assessment of Severity

Patients were classified as having mild, moderate, or severe disease by the principle investigator, based on her subjective assessment of disease activity (Physician’s Subjective Assessment of Severity [PSAS]).

Skindex-29

Skin-specific quality of life (QOL) was measured with the previously validated Skindex-29. This questionnaire consists of 29 items, which are used to calculate 3 subscales: symptoms, emotions, and functioning. The symptoms scale measures the physical burden of the disease, such as pain, itch, burning, or sensitivity. The emotions scale measures the psychiatric effects of the disease, such as depression, anxiety, embarrassment, or anger. The functioning subscale focuses on the changes to daily life, such as work, sleep, and relationships with others. Each question ranges from 0 to 100 points, with higher scores indicating worse QOL. Subscale scores were calculated based on the mean scores of the individual questions that comprise the subscale.

Physician’s Subjective Assessment of Improvement

At clinic visits, the principle investigator categorized disease activity in each patient as improved, unchanged, or worse since the last visit. These assignments were based on the physician’s subjective assessment of the patient’s skin disease.

CLASI ACTIVITY SCORE

Disease activity was measured using the CLASI activity score. This score ranges from 0 to 70, with higher scores indicating more severe skin disease (Figure 1).

SEVERITY ANALYSIS

Study patients seen from November 2008 through April 2009 were classified by the principle investigator as having mild, moderate, or severe disease based on the degree of disease activity, as described herein. Corresponding CLASI activity scores were also calculated. The optimal CLASI activity score ranges that corresponded with each severity group were determined by inspection of the CLASI score by PSAS crosstab row percentages and receiver operating characteristic (ROC) analysis. Using the crosstab row percentages, it was determined how frequently a particular CLASI score was associated with each severity group. The CLASI cutoff score for each severity group was determined when 3 consecutive CLASI scores were associated most frequently with the same severity group. Two ROC analyses were used to assess the merits of the CLASI cut points suggested by the crosstab, 1 for mild disease (mild vs moderate and severe) and 1 for severe disease (severe vs moderate and mild). The CLASI scores that fell between the upper limit of mild and the lower limit of severe were designated as indicating moderate disease.

QOL ANALYSIS

Study patients seen between January 2007 and June 2009 were included in the QOL analysis. Quality of life, as indicated by Skindex-29 scores, was then compared between patients in each CLASI severity range using trend analysis, Spearman correlations, and general linear model (GLM) analysis of variance. Quality of life was assessed in terms of mean Skindex-29 scores and the linear relationship between CLASI severity levels and QOL.

RESPONSIVENESS ANALYSIS

In study patients seen between August 2008 and October 2009, disease activity was classified by the principle investigator as improved, unchanged, or worse compared with the previous visit, as described in the subsection titled “Physician’s Subjective Assessment of Improvement” (in this section). Those with disease classified as having improved were considered responders, and those with disease classified as unchanged or worse were considered nonresponders. The CLASI activity score associated with a clinical improvement was estimated by calculating the mean signed change and percentage change in CLASI activity scores for each group. When the baseline CLASI activity score was zero, 0.5 points were added to each score to allow the percentage change to be calculated. In addition, all outlier percentage change scores, defined as more than ±500% in magnitude, were excluded from the analysis. If a patient had more than 1 set of consecutive visits in either the responder or nonresponder group, the mean change in the CLASI activity scores was calculated such that the patient was included only once per category in the final analysis.

An ROC analysis was performed to determine the sensitivity (the likelihood that a patient has a given Δ CLASI given that he or she is a true responder), specificity (the likelihood that a patient does not have a given Δ CLASI given that he or she is not a true responder), and percentage of patients correctly classified for each signed change and percentage change in CLASI activity scores. The final signed change and percentage change CLASI scores associated with a clinical improvement were chosen based on the average signed change and percentage change in CLASI scores derived by responders and then confirmed by assessing the ROC operating characteristics at and around that cutoff, focusing primarily on the classification rate. All analyses were conducted using Stata MP (version 11.0; StataCorp, College Station, Texas) and SAS (version 9.2; SAS Institute Inc, Cary, North Carolina) statistical software.
A total of 187 patients were enrolled in the study; of these, 74 had at least 2 visits recorded and completed the appropriate questionnaires and were included in the responsiveness analysis. A subset of these patients (n=37) was assessed with the PSAS and was included in the severity analysis. Of these, 1 patient did not have consecutive visits recorded and was excluded from the responsiveness analysis. Another subset of these patients (n=65) completed the Skindex-29 and was included in the QOL analysis. In all, 75 patients were included in this analysis. The population was composed mostly of women (89%) and white individuals (64%), with a mean age of 48 years. A number of different CLE subtypes was represented, the most common including generalized discoid lupus erythematosus (DLE) (23%), localized DLE (24%), and subacute cutaneous lupus erythematosus (SCLE) (31%) (Table 1).

**SEVERITY ANALYSIS**

Thirty-seven patients were classified by the principal investigator as having mild, moderate, or severe disease, and corresponding CLASI activity scores were calculated. The number of visits ranged from 1 to 3, for a total of 45 different assessments. Overall, 60% of the patient-visits were mild disease, 29% were moderate disease, and 11% were severe disease. The crosstabs suggested a maximum CLASI activity score of 9 points for mild disease.
A total of 75 patients were included in the analysis. Of these, 1 patient did not have consecutive visits recorded and was therefore included in the severity analysis but not the responsiveness analysis. Patients diagnosed as having more than 1 lupus subtype were counted more than once under “diagnosis.”

Abbreviations: ACLE, acute cutaneous lupus erythematosus; SCLE, subacute cutaneous lupus erythematosus.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Female</td>
<td>67 (89)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
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<tr>
<td>African American</td>
<td>22 (29)</td>
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<tr>
<td>White</td>
<td>48 (64)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (6)</td>
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<tr>
<td>Hispanic/Latino</td>
<td>1 (&lt;1)</td>
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<tr>
<td>Age, mean, y</td>
<td>48</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Discoid, generalized</td>
<td>17 (23)</td>
</tr>
<tr>
<td>Discoid, localized</td>
<td>18 (24)</td>
</tr>
<tr>
<td>Tumid</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Panniculitis</td>
<td>5 (7)</td>
</tr>
<tr>
<td>SCLE</td>
<td>23 (31)</td>
</tr>
<tr>
<td>ACLE</td>
<td>12 (16)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (12)</td>
</tr>
</tbody>
</table>

Figure 2. Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) scores according to disease severity. For a given range of CLASI scores, the percentage of patients within each category of disease severity was calculated.

Figure 3. Quality of life and disease (QOL) severity Skindex-29 scores were calculated for each patient at the initial visit. Patients were divided into severity groups based on Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) scores. Skindex-29 subscores increased with worsening disease severity, indicating moderate convergent validity between the CLASI severity classifications and QOL measures. P < .008; GLM F test = 1.95, P = .15; mild vs severe functioning; rS = 0.35, P < .005; GLM F test = 4.73, P = .04; mild vs severe functioning; rS = 0.35, P < .005; GLM F test = 1.95, P = .15), indicating moderate convergent validity between the CLASI severity classifications and QOL measure (Figure 3).

RESPONSIVENESS ANALYSIS

A total of 74 patients were included in the responsiveness analysis. Of these, there were 59 instances of nonresponsiveness and 28 instances of responsiveness, for a total of 87 assessments. Overall, the prevalence of a clinically significant improvement was 32%.

The mean decreases in the CLASI activity score for responders and nonresponders were 3.2 and −0.3 points, respectively. An ROC analysis indicated that a 3-point change in the CLASI activity score was 50% sensitive and 83% specific for improvement, resulting in 72% of patients being correctly classified as responders or nonresponders. However, a 4-point change in the CLASI activity score had better specificity (93%), resulting in 76% of patients being correctly classified as having improved or not improved (Table 2).

Similarly, the adjusted mean percentage decrease in the CLASI activity score for responders and nonresponders was 18% and −12%, respectively. An ROC analysis indicated that the percentage of patients correctly classified was optimized when using a 20% decrease in the CLASI activity score for responders and nonresponders were 3.2 and −0.3 points, respectively. An ROC analysis indicated that a 3-point change in the CLASI activity score was 50% sensitive and 83% specific for improvement, resulting in 72% of patients being correctly classified as responders or nonresponders. However, a 4-point change in the CLASI activity score had better specificity (93%), resulting in 76% of patients being correctly classified as having improved or not improved (Table 2).

These results indicate that the CLASI can be used to categorize patients into severity groups, with activity scores of 0 to 9 indicating mild disease, scores of 10 to 20 indicating moderate disease, and scores of 21 of 70 indicating severe disease. It is also a useful tool in determin-
ing whether patients responded to treatment, because patients who improved clinically had a mean 3-point or 18% decrease in their CLASI activity scores. However, the ROC analysis suggests that the percentage of patients correctly classified can be optimized by using a 4-point or 20% decrease in the CLASI activity score to identify improvement.

An earlier study3 suggested that the CLASI is responsive to changes in disease activity; members of our group followed 8 patients with CLE (7 DLE, 1 SCLE) for 56 days following the initiation of a new therapy and found that decreases in the CLASI activity score correlated well with improvements in the physician’s global skin assessment, the patient’s global skin assessment, and the pain score. Similarly, Kreuter et al2 have demonstrated that CLASI activity scores decrease significantly in patients with tumid lupus following 3 months of therapy with an antimalarial medication. They have also shown that CLASI activity scores decrease significantly in patients with refractory SCLE after therapy with mycophenolate sodium, which correlates with objective signs of improvement on ultrasonography and colorimetry.6 Finally, Erceg et al7 illustrated a significant decrease in CLASI activity scores in patients with DLE following pulsed dye laser therapy. While these studies imply that the CLASI is sensitive to improvement, to our knowledge this is the first study to systematically determine the minimal change in the CLASI that corresponds to a meaningful clinical improvement.

For both the signed change and percentage change analyses, there was a clear difference in the mean CLASI scores of the responders and nonresponders, indicating that the CLASI is sensitive to improvement. The mean change in the CLASI score for the nonresponders, particularly with respect to percentage change, was negative; this is likely due to the fact that the nonresponder group included patients with both stable and worsening disease activity.

In the responsiveness analysis, the sensitivity was lower than the specificity; sensitivity could have been maximized by using lower CLASI scores, but this would have caused the specificity to decrease. For the purposes of a clinical trial, we felt that it was more important for the CLASI to be specific than sensitive. With high specificity, the degree of false-positive responses decreases, thereby minimizing the inclusion of patients who have not experienced a true clinical improvement.

In addition, the change in the CLASI score that corresponds to a clinical improvement was selected primarily based on the percentage of patients correctly classified rather than by optimizing sensitivity and specificity. This was done because the latter suggested a change in the CLASI activity score of merely 1 point, which is only 69% specific for improvement. As discussed herein, we felt that it was important to have high specificity and therefore based the analysis on the percentage of patients correctly classified instead.

These applications are critical in clinical trials because they provide a standardized technique for quantifying and describing disease activity. Previously, investigators relied on their own individualized, often subjective, methods for describing disease severity and response to treatment in CLE. As such, it can be difficult to know exactly what is meant when a patient is described as having “moderate disease” or as experiencing a “clinical improvement.” It is also difficult to directly compare the results of various trials when different methods are used to determine efficacy of a particular drug. The CLASI addresses these issues by providing a simple, quantitative clinical tool that standardizes the way disease activity is described and provides guidelines for identifying a clinical change.

There are, however, some limitations to this study that should be addressed in the future. First, owing to the small sample size, patients with mild, moderate, and severe disease were analyzed as 1 group. However, it is likely that the patient’s baseline CLASI score influences the magnitude of change seen in a clinical improvement; thus, a patient with mild disease may have a significant improvement even with a small change in the CLASI activity score (>4 points), whereas a patient with severe disease may require a larger change in the CLASI activity score to detect a significant improvement (>4 points). Follow-up studies should therefore be performed in which patients are classified according to disease severity, with separate analyses performed in each group.

Second, also owing to the small sample size, patients with every type of CLE were analyzed as 1 group, including those with localized and generalized disease. The patients with localized disease, by definition, will always have relatively low CLASI scores, even if they have severe disease. It will therefore be more difficult for such patients to demonstrate the changes in CLASI scores that have been associated with a clinical improvement. In these cases, investigators may choose to look at the percentage change in the CLASI activity score rather than signed change. Follow-up studies should include a separate analysis of patients with localized disease to determine how to define the severity groups and how to identify a clinical improvement using signed changes in the CLASI activity score.

The aim of this study was to evaluate responsiveness; the CLASI, however, has other practical applications, such as identifying flares, which will be examined in future studies. Overall, this study provides the framework for

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Table 2. Responsiveness

<table>
<thead>
<tr>
<th>CLASI Change Score</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>% Correctly Classified</th>
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<tbody>
<tr>
<td>Δ 2</td>
<td>57.14</td>
<td>79.66</td>
<td>72.41</td>
</tr>
<tr>
<td>3</td>
<td>50.00</td>
<td>83.05</td>
<td>72.41</td>
</tr>
<tr>
<td>4</td>
<td>39.29</td>
<td>93.22</td>
<td>75.86</td>
</tr>
<tr>
<td>% Δ 10</td>
<td>50.00</td>
<td>70.69</td>
<td>63.95</td>
</tr>
<tr>
<td>17</td>
<td>50.00</td>
<td>72.41</td>
<td>65.12</td>
</tr>
<tr>
<td>20</td>
<td>46.43</td>
<td>77.59</td>
<td>67.44</td>
</tr>
</tbody>
</table>

Abbreviation: CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index.

For each CLASI change score (Δ CLASI) and percentage change score (% Δ CLASI) the sensitivity, specificity, and percentage of patients correctly classified were calculated. The numbers shown are based on the calculated mean Δ CLASI and % Δ CLASI that corresponded with a clinical improvement, as well as the adjacent scores. Within the % Δ CLASI group, there were no patients with an 18- or 19-point change; therefore 10, 17, and 20 are shown instead.
using the CLASI to characterize disease severity and to identify a clinical improvement. While more studies must be done to address specific patient populations, this analysis provides a foundation for the practical use of the CLASI in clinical trials.

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Author Contributions: Dr Werth had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Klein, Moghadam-Kia, Okawa, and Werth. Acquisition of data: Klein, Moghadam-Kia, LoMonico, and Werth. Analysis and interpretation of data: Klein, LoMonico, Coley, Taylor, Troxel, and Werth. Drafting of the manuscript: Klein and LoMonico. Critical revision of the manuscript for important intellectual content: Moghadam-Kia, Okawa, Coley, Taylor, Troxel, and Werth. Statistical analysis: Coley, Taylor, and Troxel. Obtained funding: Klein and Werth. Administrative, technical, and material support: LoMonico, Okawa, and Werth. Study supervision: Moghadam-Kia and Werth.

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REFERENCES