Clinical and Experimental Rheumatology 2007; 25: 666-671.

# Response criteria for cutaneous SLE in clincal trials

Ad hoc committee on response criteria for cutaneous SLE

*Members of the Ad Hoc Committee on Response Criteria for Cutaneous SLE are: Marta Mosca, MD (Co-Chair); Michael Lockshin, MD, MPH (Co-Chair); Matthias Schneider (Co-Chair); Matthew H. Liang, MD, MPH; Joerg Albrecht, MD; Martin Aringer, MD; Stefano Bombardieri, MD; Jill Buyon, MD; Richard Cervera, MD; PhD, Paola dePablo, MD, MPH; Barri J. Fessler, MD; Rebecca Fischer-Betz, MD; Victoria Gall, MEd, Dafna Gladman, MD; Nicolas Hunzelman, MD; Joachim R. Kalden, MD; Thomas Krieg, MD; Annegret Kuhn, MD, PhD; Lela Lee, MD; David Norris, MD; Jutta Richter, MD; Animesh Sinha, MD; Josef Smolen, MD; Richard Sontheimer, MD, PhD; Cristof Specker, MD; Victoria P. Werth, MD.*

*Supported by grants from the American College of Rheumatology, a Kirkland Scholar Award, the SLE Foundation of New York, The Lupus Erythematodes Selbsthilfegemeinschaft e. V. Germany, NIH Grant number AR47782, R13 AR47584-01, Robert B. Brigham Arthritis and Musculoskeletal Diseases Clinical Research Center, the Heinrich-Heine-University in Düsseldorf, the Arthritis Research Centre of Canada, the Massachusetts Veterans Epidemiology Research and Information Center, and the Center for Advanced Methodological Support for Innovative SLE Clinical Trials (ASSIST).*

*Please address correspondence and reprint requests to: Matthew H. Liang, MD, MPH, Brigham and Women's Hospital, 75 Francis Street, PBB3, Boston, MA 02115, USA.*
*E-mail: mliang@partners.org*

*Received on November 23, 2006; accepted on February 26, 2007.*

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**Key words***:* SLE, clinical trials, cutaneous lupus, response criteria, severity.

*Competing interests: none declared.*

**ABSTRACT**

*Systemic lupus erythematosus (SLE) is a complex phenotype characterized by a wide variety of clinical manifestations but the skin is involved in 70-80% of patients. Acute cutaneous lupus erythematosus lesions, like other organ manifestations of SLE wax and wane with other manifestations of active disease and quantifying it is a useful a "signal" to screen new therapies in SLE and pre- and post-treatment biopsies can be additionally informative. The ACR has recommended a priori response criteria for SLE Activity Measures (2) and that these be used along with organ specific response criteria in clinical trials. We review the literature on evaluation of skin manifestations in lupus erythematosus (LE) and propose the parameters of evaluating responsiveness and criteria for minimal clinically important changes in skin manifestations. The Committee presents two options for grading skin manifestations. These recommendations add to the tools of SLE trials.*

## Introduction

Systemic lupus erythematosus (SLE) is a complex phenotype characterized by a wide variety of clinical manifestations. The skin is involved in 70-80% of patients with SLE. (Table I). Lupus involvement of the skin without systemic manifestations or cutaneous lupus erythematosus (CLE) may be 2 to 3 times more frequent than SLE itself (1). Some cutaneous lesions are present in SLE and are markers of disease activity while other lesions may be present in patients without systemic disease. Acute cutaneous lupus erythematosus lesions, like other organ manifestations of SLE do not always fluctuate with other manifestations of active disease. Nevertheless, quantifying it may be a useful "signal" to screen new therapies in SLE; pre- and post-treatment biopsies can be also be informative from a disease mechanism point of view. In addition, the U.S. Food and Drug Administration has endorsed the concept that drugs may be approved based on the demonstration of efficacy in single-organ disease activity.

The ACR has recommended *a priori* response criteria for SLE Activity Measures (2) and that these be used along with organ specific response criteria in clinical trials. The first of the latter for renal disease has been published (3). Recommendations for criteria for steroid sparing have also been put forth (4). In this paper, we review the existing literature on evaluation of skin manifestations in lupus erythematosus (LE) and propose the parameters of skin disease which should be evaluated in assessing the activity of cutaneous lesions, and recommend the quantitative criteria for defininig minimal clinically important changes in skin manifestations. The latter is necessary to estimate the sample size required for a trial where the skin is a primary endpoint.

## Methods

A MEDLINE search covering the period 1975-2004 was conducted using the following search terms to identify published classification systems for all types of skin diseases and for SLE skin manifestations (2, 5-9): disease activity, scoring, index, response criteria, clinical trials, lupus erythematosus, autoimmune diseases, systemic sclerosis, Raynaud's phenomenon, psoriasis, burns, skin cancers/melanoma, wounds, vitiligo, atopic dermatitis, acne, rosacea, alopecia, hypo-hyper-pigmentation, scars, telangectasias. Additional studies were identified through the bibliographies in retrieved articles.

Cutaneous manifestations included in the British Isles Lupus Activity Group (BILAG) index (5), the European Consensus Lupus Activity Measurement (ECLAM) (2, 10, 11), the revised Systemic Lupus Activity Measure (SLAM-R) (12), the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (13) and its revised version, SLEDAI-2K (14) the SELENA (Safety of Estrogen in Lupus Erythematosus National assessment)-SLEDAI (15) and the Responder Index for Lupus Erythematosus (RIFLE) (16), were also scrutinized.

To determine whether response criteria for skin manifestation might be based on existing scoring systems designed for other skin diseases these were also

**Table I.** Classification of skin lesions in SLE.

**SLE–specific skin lesions**

*Chronic cutaneous lupus erythematosus (CCLE)*
- Localized DLE
- Generalized DLE
- Lupus profundus (lupus panniculitis)

*Subacute cutaneous lupus erythematosus (SCLE)*
- Papulosquamous (psoriasiform) SCLE
- Annular polycyclic SCLE

*Acute cutaneous lupus erythematosus (ACLE)*
- Localized ACLE (malar rash)
- Generalized ACLE:
  - widespread erythema of face, scalp, neck, upper chest, shoulder, extensor arms, back of hands;
  - bullous or toxic epidermal necrolysis-like lesions.

**Non-SLE specific skin lesions**

*Vascular lesions*
- Telangectatic lesions
- Dermal vasculitis
- Thrombophlebitis
- Raynaud's phenomenon
- Livaedo reticularis
- Chronic ulcers
- Rheumatoid nodules
- Peripheral gangrene

*Alopecia*
- Frontal (lupus hair)
- Diffuse (non-scarring)

*Mucous membrane lesions*
*Urticaria*
*Sclerodactyly*
*Pigmentary abnormalities*
*Calcinosis cutis*
*Bullous lesions*
*Papulonodular mucinosis*

**Table II.** Coverage of skin manifestations in current SLE activity indices.

| Manifestation | SLEDAI | SLEDAI-2K | SELENA-SLEDAI | SLAM-R | BILAG | ECLAM | RIFLE |
|---|---|---|---|---|---|---|---|
| Malar rash | + | + | + | + | + | + | + |
| Maculopapular Eruption | + | + | + | + | + | + | – |
| Discoid lesions | + | + | – | + | + | + | + |
| Lupus profundus | – | | – | + | + | | – |
| Panniculitis | – | – | – | + | + | – | + |
| Bullous eruption | + | + | + | + | + | + | + |
| Cutaneous vasculitis | + | + | + | + | – | + | + |
| Mucosal ulceration | + | + | + | + | + | + | + |
| Photosensitivity | – | – | – | | | – | + |
| Alopecia | + | + | + | + | + | – | + |
| Angioedema | – | – | – | – | + | – | + |

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index;
SLEDAI-2K: revised Systemic Lupus Erythematosus Disease Activity Index;
SELENA-SLEDAI: Safety of Estrogen in Lupus Erythematosus National Assessment;
SLAM-R: Systemic Lupus Activity Measure – Revised;
BILAG: British Isles Lupus Activity Group;
ECLAM: European Consensus Lupus Activity Measure;
RIFLE: Responder Index for Lupus Erythematosus.

reviewed for their suitability. These included clinical evaluation criteria and scoring systems designed for other skin diseases which were selected on the basis of similarities to lupus manifestations relative to basic lesions, configuration and distribution of lesions and body areas involved (example, face: acne, rosacea) (2, 17-48).

A subcommittee met in Heinrich-Heine-University's Schloss Mickeln in May 2001 to review measurement systems and to define a clinically important change in these systems. Additional subcommittee members, 12 dermatologists at the 1st International Conference on Cutaneous Lupus Erythematosus in 2004, also at the Schloss Mickeln, reviewed the resultant draft and literature. Additional comments were solicited from experts (see Acknowledgements).

## Results

The skin manifestations of relevance to SLE can be divided into specific and non-specific lesions. Disease specific findings for cutaneous lupus erythematosus are chronic cutaneous LE (CCLE), subacute cutaneous LE (SCLE) and acute cutaneous LE (ACLE). All of these have characteristic cutaneous manifestations and distinct histopathology specific for LE and the diagnosis of LE can be confirmed regardless of whether the subject meets other ACR criteria. In addition there are lesions, which are clearly associated with SLE whose histology is not distinct for LE and can be seen in other diseases (49, 50). Table I, summarizing these, is a classification based on one originally devised by the late Dr. James Gilliam and revised by Dr. Richard Sontheimer (2, 51, 52). Versions appear in major textbooks on SLE.

The review of the existent literature shows no standardized validated evaluation system for cutaneous lupus, but there were examples from other skin disorders. Many have not been evaluated for their measurement properties, i.e. reliability, validity, sensitivity. Major skin disorders such as psoriasis, atopic dermatitis, and acne have validated scoring systems and are widely used.

The generic scoring system, the Dermatology Index of Disease Severity (DIDS) (18), is validated in psoriasis but not in cutaneous lupus. Its measure of body surface and involvement appears too crude for use in LE, which has a different distribution and surface area involvement than psoriasis.

Photographs of lesions sometimes with computer-based systems have been used to document progression or improvement of lesions, to provide visual standards of degrees of severity (examples include the Samuelson nine point scale for acne grading is used with nine photographic standards and the Leeds Grading System for acne), to anchor a scoring system (e.g. reference Atlas for the SCORAD index), and to validate and to test reliability. A limitation to photography is the need to standardize the procurement of images.

Measuring the extent of skin lesions over the entire body surface area (BSA) with the rule of nines has intraobserver consistency, showing differences of 1-2% over 1-day intervals in untrained observers, but high interobserver variability, mostly for patients with inflammatory lesions of moderate intensity (25-33, 38, 42). One cause of this variability may be the difficulty in delineating the areas involved due to ill-defined

**Table III.** Definition of elements used in response criteria.

| Brief Option | |
|---|---|
| Variable | Definition |
| Malar rash (butterfly) | Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds. |
| Maculopapular rash | Non-indurated psoriasiform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telengectasias, seen SCLE. Non-indurated erythematosus macules or papules, often in photodistribution, in SLE. |
| Discoid lupus | An erythematosus raised, indurated plaque or nodule confirmed by biopsy to have SLE-specific skin changes that may also have one or more of the following features: adherent, keratotic scale (with or without carpet tack sign), follicular plugging, telangectasias. Atrophic scarring and hyper-/hypopigmentation may be seen in older lesions. |
| Panniculitis | Firm, deep subcutaneous nodules with biopsy consistent with LE panniculitis/profundus associated with atrophic scarring. May have changes at the overlying skin surface that are typical of DLE. May be associated with dystrophic calcification and ulceration. |
| Bullous lesions | Vesicles and bullae arising on, but not limited to, sun-exposed skin. Routine histopathologic findings consistent with dermatitis herpetiformis, and a direct immunofluorescence revealing IgG and/or IgM and often IgA and C3 at the dermal-epidermal junction. |
| Vasculitis | Palpable purpura, including digital ulcers not due to Raynaud's phenomenon or urticaria-like lesions |
| Mucosal ulcers | Oral or nasopharyngeal ulcerations, usually painless felt to be from SLE. |
| Alopecia | Attributable to SLE, with diffuse, nonscarring pattern. Not due to inflammatory lesions like discoid or subacute cutaneous LE. |

borders of lesions in patients with low-intensity inflammation, but significant body surface involvement (> 10-20%). Evaluation of BSA based on schematic figures has low agreement between observers (interclass correlation coefficient, ICC: 0.637) and a low level of precision. Different shading techniques and the difficulty in deriving a numerical percentage from a manikin repres-ent the main problems using these for BSA in LE. Furthermore, definition of the method to calculate BSA will be required (25).

The committee also inspected the available measures of SLE activity (Table II) for their suitability in clinical trials of cutaneous lupus. All include skin manifestations but differ slightly in which ones they cover. Most rate absence or presence and do not permit assessment of change, which would be necessary in a clinical trial. Parodi (53) felt SLAM was the best available tool for cutaneous SLE. However, it could be usefully revised to distinguish scarring and non-scarring alopecia, increase the categories for surface area involvement to make it more sensitive, and distinguish or change the period of time covered by the rating to reflect acute disease.

Finally, the Committee reviewed the new lupus-specific measure, the Cutaneous LE Disease Activity and Severity Index (CLAS1) (47, 52). The CLASI is calculated by summing the extent of erythema, scale, dyspigmentation, scarring, alopecia, and mucous membrane involvement. Patients report whether dyspigmentation due to CLE lesions usually last more than 12 months; this is defined as permanent. If the lesions last more than 12 months, the dyspigmentation score is doubled. The extent of involvement for each skin symptom is based on the scores from specific anatomic regions of the whole integument, which are scored according to the worst affected lesion within each area. Activity of the skin lesion is scored on erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss and non-scarring alopecia. Damage is scored in terms of dyspigmentation and scarring including scarring alopecia. Patients also indicate the extent of itching, pain and fatigue on a 1-10 visual analogue scale.

The CLASI has high inter-rater and intra-rater reliability. The intraclass correlation coefficient (ICC) for inter-rater reliability was 0.86 (95% confidence interval 0.73 to 0.99) for the activity scale and 0.92 (95% confidence interval 0.85 to 1.00) for the damage scale. The ICC for intra-rater reliability was 0.96 for activity (95% confidence interval 0.89 to 1.00) and 0.99 (95% confidence interval 0.97 to 1.00) for the damage scale (54). In patients with DLE, SCLE and with combined DLE and SCLE has shown sensitivity to aspects of skin health such as itching, pain, and global assessment and correlates with patient's self assessment and physician assessment. (55).

Uncontrolled skin disease can cause pigmentary change, alopecia, scarring and ulceration, and psychological stress, occupational disability and impaired quality of life. There are no validated health related quality of life measures specifically for cutaneous LE.

In defining a minimal clinically important difference, the Committee has taken a conventional approach of asking clinicians. It is arbitrary and presupposes that the lesions can be measured reliably. This is an important starting point since the assessment of a clinically important difference should be studied and any measure should be tested for its reliability and sensitivity.

**Table IV.** Rating schemes.

| Erythema | Scale/Hypertrophy | Discomfort |
|---|---|---|
| 0 Absent | 0 Absent | 0 Absent |
| 1 Pink; faint erythema | 1 Scale | 1 Mild discomfort or pruritus |
| 2 Red | 2 Verrucous/hypertrophic | 2 Moderate discomfort or pruritus |
| 3 Dark red; purple/violaceous/ crusted/hemorrhagic | | 3 Severe discomfort/nocturnal symptoms |

**Table V.** Cutaneous LE Disease Area and Severity Index (CLASI) (with permission from the Publisher).

## Cutaneous LE Disease Area and Severity Index (CLASI)

**Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion**

**activity** ⟷ **damage**

| Anatomical Location | Erythema | Scale/ Hypertrophy | Dyspigmentation | Scarring/ Atrophy/ Panniculitis | Anatomical Location |
|---|---|---|---|---|---|
| | 0-absent<br>1-pink; faint erythema<br>2- red;<br>3-dark red;<br>purple/violaceous/ crusted/ hemorrhagic | 0-absent;<br>1-scale<br>2-verrucous/ hypertrophic | 0-absent,<br>1-dyspigmentaton | 0 – absent<br>1 – scarring<br>2 – severely atrophic scarring or panniculitis | |
| Scalp | | | | See below | Scalp |
| Ears | | | | | Ears |
| Nose (incl. malar area) | | | | | Nose (incl. malar area) |
| Rest of the face | | | | | Rest of the face |
| V-area neck (frontal) | | | | | V-area neck (frontal) |
| Post. Neck &/or shoulders | | | | | Post. Neck &/or shoulders |
| Chest | | | | | Chest |
| Abdomen | | | | | Abdomen |
| Back, buttocks | | | | | Back, buttocks |
| Arms | | | | | Arms |
| Hands | | | | | Hands |
| Legs | | | | | Legs |
| Feet | | | | | Feet |

### Mucous membrane

| Mucous membrane lesions (examine if patient confirms involvement) | |
|---|---|
| 0-absent;<br>1-lesion or ulceration | |

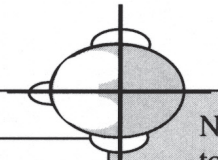
### Dyspigmentation

Report duration of dyspigmentation after active lesions have resolved (verbal report by patient – tick appropriate box)

☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)

☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

### Alopecia



| Recent Hair loss<br>(within the last 30 days / as reported by patient) | |
|---|---|
| 1-Yes<br>0-No | |

NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

| Alopecia (clinically not obviously scarred) | | Scarring of the scalp (judged clinically) | |
|---|---|---|---|
| 0-absent<br>1-diffuse; non-inflammatory<br>2-focal or patchy in one quadrant;<br>3-focal or patchy in more than one quadrant | | 0- absent<br>3- in one quadrant<br>4- two quadrants<br>5- three quadrants<br>6- affects the whole skull | |

**Total Activity Score**
(For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)

**Total Damage Score**
(For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)

The parameters by which cutaneous LE disease activity can be assessed are surface area involved; erythema (rubor, calor); scale/hypertrophy (tumor) and discomfort (or pruritis) (dolor). Scarred skin is, by definition, an irreversible lesion and represents end-organ damage and is not a surrogate for active skin disease or overall disease activity.

The Committee presents two options for grading skin manifestations. These recognize that the precision and the sensitivity of the measure needed will be greater in a clinical trial where the primary endpoint is the skin than when it is one of the group of target organs so involved or where the clinical picture is dominated by other organ involvement.

*The Brief Option*

We suggest that a brief assessment be done when skin involvement is neither the dominant phenotype nor the primary endpoint of the trial. It would be used in a rating of overall disease activity. The types of skin lesions rated are defined in Table III. Some lesions are rated only as a present or absent. Diffuse (or generalized) lesions are distinguished from single lesions.

The following were defined as clinical meaningful changes:

- Presence/absence: malar rash, alopecia, mucosal ulcers, bullous lesions, panniculitis;
- Improvement: at least 50% reduction in number of lesions (for diffuse conditions) or in extension of lesion (in single lesions);
- Worsening: more than 50% increase in number of lesions (for diffuse conditions) or in extension of lesion (for single lesions).

  The parameters of these assessments can be semiquantitated and a rating scale is suggested (Table IV).

*The Complete Option*

In the complete option, the CLASI is recommended. All LE-specific and non-specific skin lesions present in an individual (Table V) contribute to the overall assessment of improved or worsened in judging lesional surface area, erythema, and hypertrophic/scaling. Based on the standard errors for the mean inter-rater and intra-rater reliability (55) a difference between two CLASI ratings of more than 3 points for the Activity Score and 4 points for the Damage Score would exceed the difference expected between raters. Based on the same calculation a difference of more than 1 point for damage and activity would exceed the difference expected to occur by chance when a rating is repeated by the same rater. Therefore differences exceeding these thresholds could be construed to be statistically valid and beyond rater error. However, there is no data or an estimate of a clinically meaningful change but a study in progress which correlates the CLASI with changes of the patient and physician's general impression and with Quality of Life measures. Photographic documentation of the patients can be used to develop a consensus amongst professionals which threshold can be used to define clinical meaningful changes. Based on this consensus, power estimates for clinical trials can be calculated.

## Discussion

This interdisciplinary committee of clinical trialists, rheumatologists, and dermatologists specializing in immune-mediated cutaneous diseases has reviewed the existing systems for quantitating skin involvement in routine assessment and for the special demands of controlled clinical trials. Assessment of skin involvement that is so common in SLE, has inherent face validity but their appearance is often pleomorphic and their attribution to SLE may not always be certain. These recommendations add to the tools of SLE trials and apply to patients where active skin lesions are present and also when it is the primary target of therapy. In either case the cutaneous disease should be measured as objectively, quantitatively, and as sensitively as possible. To facilitate the comparison of individual trials with qualitative and quantitative synthesis, using standardized measures have enormous advantages even if they are not completely validated. In rating cutaneous manifestations photographs of skin lesions with examples of grades and of simple, confluent, and numerous lesions would aid standardization and improve reliability. Our definitions for a clinically meaningful improvement or worsening of skin lesions are from the professional's perspective but there is evidence that these are meaningful to affected patients as well (54, 55). Nevertheless, future studies should validate these criteria.

## Acknowledgements

We are grateful for the thoughtful comments of Drs. Filippa Nyberg, Daniel Wallace and the expert assistance of Ms. Angela Strickland.

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