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# Assessing remission in systemic lupus erythematosus

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## ABSTRACT

*The past few decades have witnessed development and validation of indices to assess activity, damage, and quality of life (QoL) in patients with systemic lupus erythematosus (SLE). These indices are widely used in clinical research and randomised controlled clinical trials, but not in usual clinical care. Definitions of flares and response to therapy have been proposed on the basis of indices. However, criteria for disease remission have not been clearly established for these indices, except for the SLE Disease Activity Index (SLEDAI).*

*Defining remission in SLE in an objective manner depends on reaching agreement on the relative importance of systemic activity, damage, QoL, and laboratory tests, as well as activity and damage of specific organs.*

## Introduction

The clinical picture of systemic lupus erythematosus (SLE) is characterised by extensive variation among patients as well as in the same patient over time. This variation is explained in part by the protean clinical manifestations of SLE and their severity, fluctuation between remission and exacerbation over time, and the coexistence of manifestations related to reversible inflammation and to irreversible damage. The assessment of SLE patients is therefore difficult for the physician in everyday care. These difficulties complicate analysis of patient status and standardisation of a definition of remission in patients with SLE for longitudinal observational studies and randomised controlled clinical trials (1-4).

In view of the complexity of SLE, several different study groups (1-6) have suggested that the assessment of individual patients cannot be accomplished using a single measurement tool but requires the specific and separate evaluation of disease activity, disease damage, patient-related quality of life (QoL), and drug toxicities. Many

studies have documented poor correlations between activity, damage, and patient's perception of the disease, suggesting that these measures assess different aspects of patient status and therefore that all should be evaluated (7-10). Over the past decades, much effort has been made to develop and validate indices to assess activity, damage, and QoL in SLE patients. However, development of a composite index to be used to assess SLE patients is still in its infancy, and different outcomes are being used in different studies (11). The assessment of remission in SLE based on any of these indices, however, is far from developed. Whether remission should be defined on the basis of global disease activity or should be organ-based is as yet unclear. One could envision that a high score on a global index could be obtained, while remission in manifestations at the level of a single organ might be concomitantly observed. Furthermore, no information is yet available on the role of damage and QoL assessment in any definition of remission or response.

## Assessment of remission based on global disease activity indices

Physician global assessment is generally regarded as the gold standard for disease activity. However, physician global assessment is subject to substantial inter-rater variability (5, 12), explained in part by variations among physicians in assigning levels of importance to different organ systems or to serologic activity (13). This variation may lead to difficulties in comparing global activity in clinical research concerning patient status and the efficacy of drugs.

In recent years, many disease activity indices to measure reversible inflammation in SLE have been developed and validated (14). These include the British Isles Lupus Assessment Group (BILAG), the European Consensus Lupus Activity Measurement (ECLAM), the Systemic Lupus Activity Measure (SLAM) and the SLE Disease Activity

Index (SLEDAI), and revised versions as SLEDAI-2K and Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA) SLEDAI (Table I). Each of these indices was designed primarily for longitudinal observational studies rather than for clinical trials (15-18), but the indices have been used in both types of clinical research.

While definition of flares or responses to therapy based on disease activity indices have been proposed, definitions of disease remission have not been clearly established for these indices, with the exception of the SLEDAI. Petri *et al.* have suggested the following definitions of outcomes based on changes in the SLEDAI index: *improvement* – a reduction in SLEDAI of  $> 3$ , *persistently active disease* – a change in SLEDAI  $> 3$ , and *remission* a SLEDAI of 0 (21). This definition, however, raises a question as to the significance to be given to serologic abnormalities, such as low complement levels or elevated anti-dsDNA antibody titers. Clinically significant changes have been observed, which could represent a starting point in the effort of defining remission criteria.

Activity categories have been defined on the basis of SLEDAI scores: no activity (SLEDAI = 0), mild activity (SLEDAI = 1-5), moderate activity (SLEDAI = 6-10), high activity (SLEDAI = 11-19), and very high activity (SLEDAI 20) (21). A flare of SLE has been defined as an increase in SLEDAI  $> 3$ , and a SLEDAI score  $> 5$  is associated with a probability of initiating or changing therapy in more than 50% of instances (19).

In the SELENA trial, a composite definition of flares was proposed, including (1) SELENA SLEDAI instrument; (2) new/worse activity, medication changes, and hospitalisation not recorded in the instrument; and (3) a physician global assessment by visual analog scale. Based on these elements, mild/moderate flares were defined as: a change of SLEDAI  $\geq 3$  points or new/worse skin, stomatitis, serositis, arthritis, fever,  $\geq 1.0$  increase in physician global assessment, or change in therapy—increased prednisolone (PDN)  $< 0.5$

**Table I.** Main characteristics of disease activity indices in systemic lupus erythematosus.

	BILAG	ECLAM	SLAM	SLEDAI
Type of index	Individual organ	Global	Global	Global
Time evaluated, days	28	28	28	10
Number of variables	86	31	31	24
Immunologic variables	No	Yes	No	Yes
Weighted variables	Yes	Yes	No	Yes
Severity assessment	Yes	No	Yes	No
Therapy	No	No	No	No
Retrospective calculation	No	Yes	Yes	Yes
Modified for pregnancy	No	Yes	Yes	Yes
Used in childhood SLE	Yes	Yes	Yes	Yes

BILAG: British Isles Lupus Assessment Group; ECLAM: European Consensus Lupus Activity Measurement; SLAM: Systemic Lupus Activity Measure; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index.

mg/kg or added nonsteroidal anti-inflammatory drug or hydroxychloroquine. Severe flares were defined as either 1) change in SLEDAI  $> 12$ ; or 2) new/worse central nervous system involvement, vasculitis, glomerulonephritis, myositis, platelet counts  $< 60,000$ , haemolytic anemia (haemoglobin  $< 70$  g/L), requiring doubling or  $> 0.5$  PDN or hospitalisation for SLE; or 3) any manifestation requiring PDN  $> 0.5$  mg/kg or new immunosuppressive therapy; or 4) increased physician global assessment  $> 2.5$  (22, 23).

A SLAM score  $> 6$  is considered clinically important, as it is associated with a probability of initiating therapy in more than 50% of instances (19).

Wollaston *et al.* have assessed the responsiveness of the BILAG index and the SLEDAI index in characterising changes in SLE patients (5). The assessment of disease activity was made by expert physicians on a 7-point scale: (i) much improved, (ii) moderately improved, (iii) slightly improved, (iv) unchanged, (v) slightly worse, (vi) moderately worse, (vii) much worse compared to baseline (physician global assessment by visual analog scale). Cut-off points for a clinically significant change were defined using the values of their 25th percentiles in the unimproved group. A high correlation was observed between 3-month changes in BILAG and SLEDAI indices. However, when the physician global assessment on a visual analog scale was taken as the “gold standard,” lower

correlations were found with changes recorded for the two indices.

Recently an American College of Rheumatology Ad Hoc Committee on SLE Response Criteria conducted a study aimed at defining a minimally important clinical difference for six existing disease activity indices in SLE: BILAG, ECLAM, SLAM-R, SLEDAI, SELENA-SLEDAI, and Responder Index for Lupus Erythematosus (RIFLE). The study was based on analysis of vignettes obtained from the medical records of 310 patients. Disease activity indices were calculated for each patient assessment, either prospectively or retrospectively by members of the group. Experts in the treatment of SLE were asked to rate 15 vignettes, judging disease activity as worsened, unchanged, or improved.

Significant agreement was considered to be present when 70% of the responders agreed on the patient's clinical condition. The statistical analysis, integrating the physician's assessment with the disease activity indices, defined a minimally important change as follows: BILAG worsening +8, improvement -7; ECLAM: worsening +4, improvement -3; SLAM-R: worsening +6, improvement -4; SLEDAI: worsening +8, improvement -6; SELENA-SLEDAI: worsening +8, improvement -7; RIFLE: worsening +3, improvement -4 (12). A similar cut point ( $1 \leq -3$ ) was found in juvenile SLE by the Pediatric Rheumatology International Trials Organization (PRINTO) (6), in a study

conducted to define and validate a Disease Activity Core Set. However, no efforts have been made to date to define remission according to any of these indices, other than for the SLEDAI as discussed above.

### Organ-specific assessment of remission

The complexity of SLE could allow disease remission to be considered as a global reduction of disease activity or a reduction relating only to involvement of a single organ. Therefore, organ-specific assessments of activity and response might be desirable to describe remission.

The BILAG index is an organ-specific index, which assesses disease activity in eight systems (version 3): general, mucocutaneous, neurologic, musculoskeletal, cardiorespiratory, vasculitis, renal, and haematologic. Although this index could be used for the organ-specific assessment, some limitations have been observed, particularly a poor association between neurologic A scores and treatment. Furthermore, of all the systems, the mucocutaneous system correlated least well with global assessments of disease by patient and doctor (20). Finally, some systems were not included. Therefore, a new version has been developed in which changes have been made on neuropsychiatric manifestations, and abdominal and ophthalmologic manifestations have been modified. This version is now undergoing validation (14, 24, 25). Based on the BILAG index, a severe flare of lupus has been defined as a new score of A in any system, while a moderate flare has been defined as a score of B in any system that previously scored D or E (20).

The RIFLE is an index designed specifically to assess response to therapy in SLE and can be used to measure the outcome of single organ involvement (12). RIFLE has been designed to assess clinically important changes in SLE. Manifestations can be assessed as not present (0), resolution (1), partial resolution (2), present, no change (3), worsening (4); definitions are given for each item included in the index. Resolution is generally defined as the

absence of the manifestation or normalisation of laboratory abnormality. Many definitions have been proposed regarding renal involvement. However, although renal involvement may appear to be easily assessed, several outcomes and different definitions for the same outcomes have been described in the literature (15-17, 26-29). In 1998, Boumpas and Balow proposed criteria to define remission/response and flares, which, however, have been used only in part in the subsequent literature (29). A specific index to assess cutaneous involvement in lupus erythematosus, the Cutaneous Lupus Erythematosus Disease Activity and Severity Index (CLASI), has been described (30, 31). The CLASI assesses active as well as chronic lesions and scores lesions in different anatomic areas. Disease activity is scored on the basis of erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss, and nonscarring alopecia. Damage is scored on the basis of dyspigmentation and scarring, including scarring alopecia. Furthermore, the extent of itching is assessed on a scale from 0 to 10. The index has been shown to have a high inter-rater and intra-rater reliability (30, 31).

No other organ-specific measures have been developed to date, nor is a definition of remission available.

### Damage assessment

The Systemic Lupus International Collaborating Clinics (SLICC/ACR) damage index has been developed to assess irreversible damage in SLE patients, independently of its cause (SLE activity, therapy, comorbidities), but occurring after disease onset (14, 24). To be recorded, items should have been present for at least 6 months. It has been widely used in longitudinal studies as well as in clinical trials. An early accumulation of damage was related to a poor prognosis and increased mortality. A number of authors have examined longitudinal development of damage in SLE patients during patient follow-up. In their study, Stoll *et al.* have observed, over a period of 5 years, an increase in damage in an average 30% of their patients and a correlation of

damage with disease activity and BILAG A flares. Gladman *et al.* have shown a gradual increase of the SLICC score over a period of 15 years (20, 32-35). Importantly, assessment of changes of SLICC scores requires a minimum follow-up of 6 months and the stratification of patients for damage, as not all patients in a lupus cohort develop damage.

Is it important to include damage in an assessment of remission in SLE? A definition of damage could add information on disease severity and prognostic data; therefore, its assessment covers an important aspect of evaluation of the disease and on the efficacy of a drug. A complete remission of disease activity with high damage scores might be less acceptable than a partial remission of activity with no damage. However, data are not yet available concerning this issue, and therefore an assessment of meaningful changes of damage associated with remission has not been developed (3, 24).

### Quality of life and remission

Patient assessment of disease activity represents an important aspect of assessment of many rheumatic diseases. Data obtained in rheumatoid arthritis (RA) show that patient assessment is correlated very well with disease outcome, treatment effects, and development of disabilities. Therefore, there is no doubt that patient assessment should be considered also when defining remission (36, 37). However, no efforts have yet been made in this field, and discussion is still open regarding how to measure QoL in SLE patients.

Thus far, the most widely used index to assess QoL in SLE patients is the 36-item short form health survey (SF-36). This is a composite index that includes eight subscales: 1) physical function, 2) role physical, 3) bodily pain, 4) general health perception, 5) vitality, 6) social function, 7) role emotional, 8) mental health. Two summary measures are available, a physical component summary (PCS) of #s 1 through 4 and a mental component summary (MCS) of #s 5 through 8. Higher scores indicate better QoL. In SLE patients, SF-36



scores are 30% to 40% lower than in the general population. A low correlation has been observed between SF-36 scores and disease activity or damage, suggesting that these scales address different aspects of the disease. These findings support a need for a composite assessment to evaluate response to therapy and fully describe patient populations (8, 9, 38-44).

In a study assessing changes of QoL over time in different patient cohorts, the annual change in PCS scores ranged between 0.03 and 0.18 and in MCS scores between 0.08 and 0.23, with no substantial differences among countries. Correlation of QoL with poverty, fibromyalgia, fatigue, helplessness, abnormal illness-related behaviours, and less social support has been observed. Although QoL is now widely assessed in longitudinal studies (38, 42) as well as in randomised clinical trials (40), no data on clinically significant changes are available.

Recent studies in RA also suggest that a simple visual analog function scale (VAS-F) has good psychometric properties compared with the Health Assessment Questionnaire and could, therefore, be used in randomised controlled studies (36, 37). Similar data in SLE have not been reported.

### Development of composite response criteria

Composite indices to assess responses in RA have been developed and are extensively used in randomised controlled clinical trials. The use of composite indices has many advantages, such as reduction of sample size requirements in clinical trials (45-47). Although indices to assess activity, damage, and QoL in SLE patients have been developed and validated, a composite response criteria has not yet been developed.

The PRINTO has proposed a core set of measures and definitions of outcomes to be used to assess response to therapy in juvenile SLE. A preliminary core set of measures was proposed, including the physician's global assessment of disease activity, the parent's global assessment of the patient's well-being, anti-double-stranded DNA anti-

bodies, 24-hour proteinuria, serum creatinine level, and a global disease activity index (SLEDAI, SLAM, and ECLAM). This preliminary core set was validated through enrollment of 557 patients from 39 countries. The final core set resulting from this analysis included the physician's global assessment of patient disease activity (scale 0-10), parent's global assessment of patient's overall well-being (scale 1-10), 24-hour proteinuria, ECLAM, and child health questionnaire physical health summary score. This core set was specifically defined to assess pediatric patients, who have different characteristics from adult SLE patients (6).

### Conclusions

Assessment of response in SLE is complex and requires evaluation of disease activity, the patient's assessment of QoL/disease activity, and probably also the evaluation of damage. The significance of serologic findings in addition to clinical status in defining activity and remission remains to be defined. In such a complex disease as SLE, assessing remission in a specific organ system could also be important. Global and organ-specific disease activity indices (the BILAG), as well as organ-specific responder indices, could prove useful for this purpose.

Although validated indices to assess disease activity are available, their use in randomised controlled clinical trials is limited. Recent data suggest that all the most widely used indices are acceptable for use, but few data are available on the minimally important clinical differences for these indices, and only one definition of remission based on global indices (SLEDAI) has been proposed. The CLASI, assessing cutaneous involvement in SLE, is the single organ-specific responder index that has been developed and initially validated. Much work is needed to refine assessment of changes in damage and the patient's perception of the disease.

A composite index that includes disease activity, damage, and QoL appears desirable as in other autoimmune diseases. Further efforts are required to establish a consensus about a definition of remission in SLE.

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