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Why and how should we measure disease activity and damage in lupus?

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Summary

The assessment of disease activity and flare and differentiating them from permanent damage in patients with SLE is challenging. The SLEDAI, SLEDAI-2K and SELENA-SLEDAI measure global disease activity. The BILAG measures organ-specific activity. The BILAG better captures the change in the different organs at the expense of complexity. The SRI is a composite index incorporating both BILAG and SLEDAI indices and a physician's global assessment. It has been used in the most recent clinical trials. Damage correlates with prognosis; it is assessed by the SLICC/SDI index. This index scores damage whatever the cause, disease or treatment related, or the consequence of concomitant disease. The disease activity and damage indices do not correlate well with the patient's health related quality of life (HRQoL), the degree of disability or the impact of disease. The impact of the patients' joint disease on their HRQoL is assessed via the HAQ questionnaire and the global health status via the SF-36 index, or one of the more recently described lupus specific quality of life indices [Lupus QoL]. The global assessment instruments and the BILAG index can also be used in children and adolescents with SLE. However, a modified paediatric version of the SLICC/SDI damage index is advised. Many advances have been achieved in disease activity and damage measurement in the past 20 years but the problem of how best to capture flare accurately remains.

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease which is heterogeneous in its presentation, course and outcome. The disease can present with diverse manifestations and severity. When active and flaring, it can cause life threatening manifestations and, in some, irreversible permanent end organ scaring referred to as damage. The differentiation between disease activity and damage is crucial for patient management and treatment strategies.

Accurate assessment of disease activity and damage in SLE is needed to: assess the disease longitudinally in observational and clinical trials, differentiate patterns of disease involvement, evaluate responses to new drugs and evaluate outcome. Several validated, in two cases updated,

activity assessment instruments have been available since the 1980s. More recent studies (described later on in this review) have focussed on ascertaining reliability and validity for classifying and monitoring groups of patients in both the clinic and research setting.

For the purpose of this review, we have selected those indices that have shown the strongest evidence of validity when used by investigators from different countries in large studies of patients with SLE.

Assessing disease activity

Assessment of disease activity is crucial for forming the basis of treatment decisions in routine clinical practice and research. Therefore, it is necessary to be able to quantify the change in disease activity in a way that includes all the possible manifestations.

Two cardinal features of SLE have challenged investigators when assessing disease activity:

- the complex multi-system nature of this disease with levels of disease activity which may fluctuate in different body systems, varying between patients and within the same patient over time;
- the absence of a ''gold standard'' for comparing the instruments with an objective measure.

Several assessment systems have been developed and validated, including: the British Isles Lupus Assessment Group (BILAG) [1,2], Systemic Lupus Activity Measure (SLAM) [3], European Community Lupus Activity Measure (ECLAM) [4,5], and the SLE Disease Activity Index (SLEDAI) [6,7]. These systems have been developed to capture disease activity at a given time. Clearly patients may have no active disease, or if they are active this may be persistent, improving or deteriorating.

The SLEDAI, SLAM and ECLAM are global indices providing an overall measure of activity. In contrast, the classic BILAG [1,2], established on the principle of the physician's intention to treat, provides a more comprehensive ''at a glance'' overview of activity in eight organs/systems. In all activity indices, the recorded clinical data should only be entered if the physician is sure that the feature is due to SLE. Assessment in the BILAG index distinguishes clinical features that are improving from those that are getting worse, staying the same, or are new or recurrent. Instead of giving a single score covering all systems, the BILAG index gives individual scores (from A to E, where A represents the highest disease activity) for eight different systems. There were problems, however, with the classic BILAG index, which incorporated a small number of items that were more clearly due to damage rather than to disease activity and failed to capture adequately disease activity in the gastrointestinal or ophthalmic systems. The substantially revised version, the BILAG 2004 index [2], has now been validated [8], shown to be reliable [9] and sensitive to change [10].

The SLEDAI, SLAM, and BILAG have performed in an effective and reliable manner in many studies and have been shown to correlate well with one another, despite their different origins [11–13]. The BILAG assessment tool takes longer to complete than SLEDAI or SLAM, but all of the indices work optimally with training.

The global indices have the advantage of simplicity, in that the clinical features in each organ/system are assigned numerical scores that are summated to give a total score for disease activity. The main problem with these scoring systems is that points are awarded for clinical features if present, but do not distinguish those features that are improving from those that are deteriorating or those that are unchanged. The original SLEDAI version was introduced in 1985; it was revised in 2002 [6,7,14] to reflect persistent active disease in those descriptors that had previously considered new or recurrent occurrences (SLEDAI-2K). The SLEDAI-2K measures only complete recovery in active descriptors on follow-up visits. For this reason the SLEDAI-2K Responder Index-50 (S2K RI-50) was developed [15]. This index is able to capture partial improvement $\geq$ 50%, in each of the active descriptors at subsequent visits. However, although this index captures partial improvement, it does not capture deterioration in SLE symptoms [16].

There is ongoing debate about how best to capture flare in patients with lupus. This clearly represents disease which is becoming more active. However, in SLE the accurate and uniform acceptance of flare definition has been challenging. For example, can a patient with increasing disease activity in just the kidney be judged to be suffering a worse flare than a patient with increasing disease activity in the skin, lung or joints? Should flare be determined by the treatments likely to be offered to a patient?

A ''flare'' of disease activity has been utilised in previous and ongoing studies. The critical question of how best to define a flare of SLE remains problematic. Using the BILAG 2004 index, a flare can be defined in terms of the number of systems scoring A or B based on items recorded as new or worse. On this basis, one might define a severe flare as occurring in a patient with an A score in any system, or a moderate flare as B score in at least two systems. In the global score indices the presence of a flare is defined according to a pre-specified increase in this total score. Therefore, if a patient was to increase her\his score by, say, 4 points; a flare might be deemed to have occurred.

The SELENA-SLEDAI flare index was developed for use in clinical trials by the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) group with the intention of distinguishing severe flares from those that are only mild or moderate [17,18]. The SELENA group has recently devised a more comprehensive instrument that distinguished mild from moderate flares. It provides separate analysis of flares in different organ systems, and collects treatment data as part of the evaluation. The revised SELENA flare index is organ-system based, and is not linked to the