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Review

Assessment of disease activity in Systemic Lupus Erythematosus: Lights and shadows

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ABSTRACT

The assessment of disease activity in patients affected by Systemic Lupus Erythematosus (SLE) represents an important issue, as recommended by the European League Against Rheumatism (EULAR). Two main types of disease activity measure have been proposed: the global score systems, providing an overall measure of activity, and the individual organ/system assessment scales, assessing disease activity in different organs. All the activity indices included both clinical and laboratory items, related to the disease manifestations.
However, there is no gold standard to measure disease activity in patients affected by SLE. In this review, we will analyze the lights and shadows of the disease activity indices, by means of a critical approach. In particular, we will focus on SLE Disease Activity Index (SLEDAI) and British Isles Lupus Assessment Group (BILAG), the most frequently used in randomized controlled trials and observational studies. The evaluation of data from the literature underlined some limitations of these indices, making their application in clinical practice difficult and suggesting the possible use of specific tools in the different subset of SLE patients, in order to capture all the disease features.

Contents

1. Introduction

Systemic Lupus Erythematosus (SLE) is a multifactorial autoimmune disease, in which genetic and environmental factors interact to determine susceptibility and phenotype [1–4]. A wide range of autoantibodies and clinical manifestations, with a remitting/relapsing course, characterizes SLE [1,4–8]. The better knowledge of disease pathogenic mechanisms and the new therapeutic strategies, available to treat SLE patients, determined the improvement of a five-year survival rate from the 50%, reported in the 1950s, to current over 90% [1,9–13].

In 1996, the Systemic Lupus International Collaborating Clinics (SLICC) suggested the need of a complete assessment in SLE patients, thorough the evaluation of three domains: disease activity, chronic

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damage, and quality of life [14]. More recently, the European League Against Rheumatism (EULAR) recommendations confirmed this concept [15,16]. In particular, the EULAR task force drew a set of recommendations for monitoring SLE patients in routine clinical practice, underlining the need to assess disease activity by using validated indices [16]. More recently, the EULAR suggested new recommendations aiming at improving the management of SLE patients according with the treat-to-target principle, similar to other chronic diseases [17]. The task force stressed the need to control the disease activity in order to prevent the chronic damage development. Moreover, the target of SLE treatment should be the remission of systemic symptoms and organ manifestations or the achievement of the lowest possible disease activity [17]. Considering these overarching principles, an objective measurement of disease activity appears mandatory.

An optimal measure system should reflect both the improvement and the worsening between patients and between different organs in the same patient. Moreover, it should discriminate disease activity from the chronic damage and from the changes related to the other causes, such as infections. The identification of an accurate, valid, reproducible and sensitive to change index could be a critical issue in a disease such as SLE, characterized by a great heterogeneity in terms of clinical and laboratory manifestations [18,19]. The high number of indices proposed and validated by different research groups to assess disease activity in SLE patients confirmed this complexity.

2. How to measure disease activity in Lupus patients? — disease activity indices

Disease activity indices have been applied not only in the longitudinal observational studies, but also in the randomized controlled trials (RCT). In fact, the evaluation of treatment efficacy by assessing disease activity represents the primary outcome in the majority of RCT [16]. Moreover, the application of an index is attractive in routine clinical practice in order to guide therapeutic decisions. Some of the indices proposed in the literature are easy to perform, allowing their use into the routine clinical practice, giving a quick snapshot of the patient's status [20].

The global score systems, providing an overall measure of activity, and the individual organ/system assessment scales, evaluating disease activity in different organs, have been used to assess disease activity. All the activity indices published so far, include both clinical and laboratory items, related to the disease manifestations. In table 1 the main features of the main indices proposed to assess SLE patients are reported. Among these, the most frequently applied in observational studies and RCT are the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the British Isles Lupus Assessment Group (BILAG).

The SLEDAI, first published in 1992, has been subsequently modified in 2002 (SLEDAI-2K), in order to capture ongoing disease activity [21,22]. The latter includes the evaluation of 24 weighted objective variables (16 clinical and 8 laboratory); a manifestation is recorded if it is present over the past 10 days. The sum of the items, identified in a single patient, corresponds to the disease activity [22].

Concerning the laboratory items, the SLEDAI includes the determination of complement levels and of anti-dsDNA antibodies. However, not all the SLE patients showed the presence of anti-dsDNA antibodies, detected around 70%; consequently, SLE patients without anti-dsDNA antibodies may not be fully evaluated using SLEDAI [23].

Data from the literature demonstrated the validity, reliability and sensitivity to change of the original version of SLEDAI; conversely, the SLEDAI-2K version has not been validated. Nevertheless, the revised version correlated with the original, as demonstrated in retrospective study [22]. More recently, Yee and colleagues confirmed the sensitivity to change of SLEDAI-2K; in particular, the changes in the score well correlated with the treatment modifications [24].

However, SLEDAI-2K cannot discriminate an improvement in the descriptors, but can only identify the presence/absence of that item. Thus, Touma and colleagues proposed the SLEDAI-2K Responder Index 50 (SRI-50) for monitoring improvement in disease activity. This index demonstrated its validity and reliability to reflect partial important improvement (equal or superior to 50%) in disease activity between visits. Moreover, it seems to be superior to the SLEDAI-2K in the identification of responders to treatment SLE patients [25,26]. In the SRI-50, an improvement of more than 50% of each descriptor gives as result half of the score assigned for SLEDAI-2K [25,26].

Finally, another version of the SLEDAI was proposed in the Safety of Estrogen in Lupus Erythematosus National Assessment trial (SELENA–SLEDAI) [27].

The main characteristic of SLEDAI-2K is its ability to reflect persistent, active disease in those descriptors that had only considered new or recurrent occurrences in the first version of SLEDAI and in the SELENA–SLEDAI. In particular, in the latter alopecia, mucous membrane lesions, and rash were scored only if new or recurrent; in the SLEDAI-2K any rash, alopecia, or mucosal ulcers have been included. Concerning proteinuria, the SLEDAI and the SELENA–SLEDAI included only the new onset or a recent increase of more than 0.5 g/24 h; conversely, in the SLEDAI-2K all the cases with proteinuria >0.5 g/24 h (new, recurrent, or persistent) were scored [14,22,27]. Moreover, in the SELENA–SLEDAI the definition of flare has been introduced, according with the treatment required to control disease relapse [27].

Table 1
Features of the main indices proposed to assess disease activity in SLE patients.

Disease Activity Index	Referring time	Overall score/range	Items
Global score systems			
Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) SLEDAI-2K SELENA–SLEDAI [14,22,27]	10 days	0–105	24
European Consensus Lupus Activity Measurement (ECLAM) [31].	30 days	0–17.5	15
Systemic Lupus Activity Measure (SLAM) [32]	30 days	0–86	32
Lupus Activity Index (LAI) [20]	10 days	0–3	7
Organ/system assessment scale			
British Isles Lupus Assessment Group Index (BILAG) [28] BILAG-2004 [29]	30 days	A = most active disease B = intermediate activity C = mild, stable disease D = previous involvement, currently inactive E = no previous activity	86 97