SLEDAI-2K Does Not Conceal Worsening in a Particular System When There Is Overall Improvement

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ABSTRACT. ***Objective.*** To determine whether the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) is valid in identifying patients who had a clinically important overall improvement with no worsening in other descriptors/systems.

Methods. Consecutive patients with systemic lupus erythematosus with active disease who attended the Lupus Clinic between 2000 and 2012 were studied. Based on the change in the total SLEDAI-2K scores on last visit, patients were grouped as improved, flared/worsened, and unchanged. Patients showing improvement were evaluated for the presence of new active descriptors at last visit compared with baseline visit.

Results. Of the 158 patients studied, 109 patients had improved, 38 remained unchanged, and 11 flared/worsened at last visit. In the improved group, 11 patients had a new laboratory descriptor that was not present at baseline visit. In those 11 patients, this new laboratory descriptor was not clinically significant and did not require a change in disease management.

Conclusion. The SLEDAI-2K identifies improvement in disease activity overall without concealing clinically important worsening. (First Release June 15 2015; J Rheumatol 2015;42:1401–5; doi:10.3899/jrheum.141088)

Key Indexing Terms:
SLEDAI-2K SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY

The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) is a global disease activity index that was initially developed in 1985[1]. It has demonstrated reliability among expert rheumatologists and trainees and has shown sensitivity to change[2,3,4]. The original SLEDAI has descriptors that are scored as active only if they are new. The SLEDAI-2000 (SLEDAI-2K) was introduced and validated against the original SLEDAI to allow the inclusion of ongoing disease activity in the selected descriptors: rash, alopecia, mucosal ulcers, and proteinuria > 0.5 g/day[5]. Both SLEDAI and SLEDAI-2K consist of 24 descriptors covering 9 organ systems[1,2,6]. As in the original SLEDAI, all the descriptors in SLEDAI-2K must be attributed to systemic lupus erythematosus (SLE) activity. While initially the time frame for the descriptors was a 10-day period prior to the assessment, SLEDAI-2K has been shown to be valid to measure disease activity occurring in the preceding 30 days[7,8].

It has been suggested that a global score such as SLEDAI-2K may conceal deterioration in 1 system while describing overall improvement. This has led researchers in clinical trials of biologic therapies to develop composite indices in which global (SLEDAI-2K) and organ-specific indices [British Isles Lupus Assessment Group index (BILAG)] were combined, such as the SLE Responder Index (SRI) and the BILAG-Based Composite Lupus Assessment[9,10].

Whether in a research setting or a drug trial, the use of multiple measures is time-consuming and physicians favor 1 measure, as long as the results are robust and valid. In our study, we aimed to determine whether patients who show a clinically important overall improvement in SLEDAI-2K conceal deterioration in 1 or more individual descriptors/systems.

MATERIALS AND METHODS

Patients' setting, clinical, and laboratory assessment. Patients with adult SLE [> 18 yrs, 4 or more of the American College of Rheumatology (ACR) criteria or 3 ACR criteria plus a typical histological lesion of SLE on renal or skin biopsy] were followed prospectively at the University of Toronto

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The University of Toronto Lupus Clinic is funded by the University Health Network, the Toronto General and Western Hospital Foundation and the Arthritis Research Foundation.

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Accepted for publication April 27, 2015.

Lupus Clinic[11]. Collection, storage, and use of clinical and laboratory data on patients followed at the Lupus Clinic were conducted in accordance with the Declaration of Helsinki and were approved by the Research Ethics Board of the University Health Network, Toronto, Ontario, Canada. Signed informed consent for the collection and use of clinical and laboratory data were obtained from all patients included in the Lupus Clinic. The standard protocol at each visit included complete history, including demographics, physical examination, and laboratory evaluation. Patients attended the Lupus Clinic at 2- to 6-month intervals, regardless of the state of activity of their SLE.

Disease activity was measured at each visit by SLEDAI-2K 30 days[5,7]. SLEDAI-2K consists of 24 descriptors covering 9 organ systems: 6 clinical and 3 laboratory (Table 1)[5]. All patients received standard of care treatment by the treating rheumatologist.

Patient selection. Consecutive patients with active SLE with SLEDAI-2K ≥ 6 at baseline visit (first visit in our study) who attended the clinic between 2000 and 2012 were studied. Patients were included if they had at least 1 of the following 6 SLEDAI-2K clinical organ systems active: central nervous system (CNS), vascular, renal, musculoskeletal (MSK), serosal, or dermal. For the renal system, the presence of proteinuria was mandatory. Patients also need to have started or increased prednisone therapy to be included. All patients had to have at least 1 followup visit at 9–12 months (defined as the last visit). If 2 visits were available within this period, the last visit was selected.

Study design and analysis. Based on the change in the total SLEDAI-2K score (baseline to last visit), patients at last visit were grouped as (1) improved (SLEDAI-2K decreased by ≥ 4), (2) flared/worsened (SLEDAI-2K increased by ≥ 4), and (3) unchanged[5,12]. Descriptive statistics were used to describe the characteristics of the patients and the results of the analysis (proportions and percentages) at 6, 12, and 9–12 months.

Determination of new descriptors at last visit (9–12 mos), but absent at baseline in patients with overall improvement. The analysis was focused on the group of patients who were defined as improved by SLEDAI-2K. The SLE protocol for each patient from this group was assessed individually to determine whether there was a new active descriptor at last visit that was not present at baseline visit.

Determination of SLE manifestations at last visit (9–12 mos) that were not included in SLEDAI-2K in the group of patients with improvement. Additional analyses were performed to document possible SLE clinical manifestations warranting change in treatment at followup visits. Although SLEDAI-2K includes only 24 descriptors, the presence of all possible SLE disease activity manifestations was assessed in the group of patients with improvement. The protocol at the Toronto Lupus Clinic identifies all possible SLE manifestations including those that are not part of the SLEDAI-2K, e.g., peritonitis, enteritis/colitis, pancreatitis, interstitial pneumonitis, pulmonary hemorrhage and pulmonary hypertension, shrinking lung syndrome, episcleritis, uveitis, papilledema, retinal detachment, and myocarditis/endocarditis, and assessment for valvular lesions, aseptic meningitis, chorea, benign intracranial hypertension, myelitis, mono/polyneuropathies, tendinitis, and others. For the hemolysis assessment, we identified all patients with anemia (hemoglobin < 120 g/l) and positive Coombs test (direct/indirect), and reviewed their medical charts to ensure attribution to active SLE.

Determination of SLE manifestations warranting change in treatment between visits in the group of patients with improvement. Data available from followup visits at 2- to 6-month intervals were reviewed. All new SLEDAI-2K descriptors present on followup visits but absent at baseline visit were identified, and all SLE manifestations that required change in treatment (based on the review of the database and the medical charts) were also identified.

Table 1. SLEDAI-2K organ systems, their descriptors, and scores[5].

Types	Organ Systems	Descriptors	Descriptors' Weighted Scores
Clinical	Central nervous system	Seizure	8
		Psychosis	8
		Organic brain syndrome	8
		Visual	8
		Cranial nerve disorder	8
		Lupus headache	8
		Cerebrovascular accident	8
	Vascular	Vasculitis	8
	Musculoskeletal	Arthritis	4
		Myositis	4
	Serosal	Pleurisy	2
		Pericarditis	2
	Dermal	Rash	2
		Alopecia	2
		Mucosal ulcers	2
	Constitutional	Fever	1
Laboratory	Renal	Urinary casts	4
		Hematuria	4
		Proteinuria	4
		Pyuria	4
	Immunological	Low complement	2
		DNA	2
	Hematological	Thrombocytopenia	1
		Leukopenia	1

SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000.

RESULTS

There were 158 patients who fulfilled the inclusion criteria and were further studied. SLEDAI-2K was 12 ± 5.2 at baseline visit and 6.4 ± 4.9 at last visit. Of the 158 patients, at the last visit (9–12 mos), 109 (69%) showed overall improvement, 38 (24%) were unchanged, and 11 (7%) flared/worsened. At 9–12 months, of the 109 patients, 20 (18.3%) had a remission (SLEDAI-2K = 0); 45 (41.3%) had a clinical remission but were serologically active [either positive anti-dsDNA antibodies and/or low complements, SLEDAI-2K including SLE serology (anti-dsDNA antibodies and/or low complements) = 2 or 4]; and 44 (40.4%) had clinically active disease [SLEDAI-2K > 0, serology: anti-dsDNA antibodies and/or low complements; e.g., 24 patients had proteinuria, 6 had arthritis, 13 patients had mucocutaneous manifestations (alopecia and rash)].

At 6 months, 128 patients had SLEDAI-2K performed. Of the 128 patients, 85 showed overall improvement, 29 were unchanged, and 14 worsened. At 12 months, 116 patients had SLEDAI-2K performed. Of the 116 patients, 88 showed overall improvement, 23 were unchanged, and 5 worsened.

The characteristics of 109 patients with overall improvement (decreasing their total score by ≥ 4) are presented in Table 2. In this group of patients, SLEDAI-2K was 13.1 ± 5.7 at baseline visit and 4.8 ± 4.4 at last visit. At study start, CNS descriptors were present in 15 patients, vascular in 18, MSK in 50, renal in 54, dermal in 48, serosal in 4, immunological in 85, constitutional (fever) in 7, and hematological in 8.

Table 2. Characteristics of patients who improved. Values are n (%) or mean ± SD.

Characteristics	n = 109
Female	97 (89)
Age at diagnosis, yrs	26 ± 11
Age at first visit in the study, yrs	39 ± 13
Disease duration at first visit in the study, yrs	12 ± 9
Race	
White	67 (61)
Black	13 (12)
Asian	14 (13)
Others	15 (14)
Medications at first visit in the study	
Steroids	109 (100)
Antimalarial	82 (75)
Immunosuppressants	69 (63)

For the MSK system, in particular arthritis, 50% of the patients improved by 3 months (95% CI 3–6 mos). For the mucocutaneous system, in particular mucosal ulcers, rash, and alopecia, 50% of the patients improved by 6 months (95% CI 3–12 mos). For proteinuria, 50% of the patients improved by 9 months (95% CI 3–9 mos).

Determination of new descriptors at last visit, but absent at baseline in patients with overall improvement. There were 109 patients who showed overall improvement with SLEDAI-2K by decreasing their total score by ≥ 4. In this group of patients, 11 developed a new active descriptor at the last visit that was not present at the baseline visit, as follows:

(1) The first patient had vasculitis and active lupus nephritis (proteinuria, casts, and hematuria) in the context of positive serology at the baseline visit. At the last visit, the vasculitis resolved completely and the renal system continued to be active with the presence of proteinuria, hematuria, and casts. Pyuria was absent at the first visit, but present at the last visit. In this case, the addition of pyuria did not require a change in the clinical diagnosis or the management since the renal system continued to be active with the presence of proteinuria and nephritis was already treated.

(2) Four patients developed activity in the immunological descriptors with the occurrence of low complement in addition to an existing positive anti-DNA. The first patient improved in the vasculitis system, the second in the MSK and dermal systems, and 2 patients improved in their CNS and MSK systems at the last visit. The dose of corticosteroids was tapered in all 4 patients.

(3) Four patients developed low complement at the last visit that was not present at baseline visit. Their anti-DNA continued to be negative at the last visit. The first patient improved in the MSK and dermal systems; the second in the MSK, dermal, and constitutional systems; the third in the vasculitis and MSK systems; and the fourth in the renal at the last visit.

(4) Two additional patients had new low complements at the last visit while anti-DNA became negative leading to no change in therapy.

In all 11 patients, this resulted from abnormal laboratory results. More importantly, this new activity in the laboratory descriptors (in the renal system and in the immunological system) was not considered to be clinically significant and did not result in a change in treatment or management.

Determination of SLE manifestations that were not included in SLEDAI-2K in the group of patients with improvement. The results confirmed that in the group of patients who improved, there was no evidence of SLE clinical activity related to a specific SLE manifestation or a specific system that was not included in the SLEDAI-2K.

For the hemolysis assessment, we identified all patients with anemia (hemoglobin < 120 g/l) and positive Coombs test (direct/indirect), and reviewed their medical charts. In the group of 109 patients with improvement, there was no evidence of SLE activity in the manifestations listed above, including hemolysis.

Determination of SLE manifestations warranting change in treatment between visits in the group of patients with improvement. In the group of 109 patients with improvement, 6 patients had new SLEDAI-2K descriptors at 3 and 6 months, but did not require change in treatment as follows: (1) Patient 1: new casts were documented on followup visits 3 months after the baseline visit in the context of active lupus nephritis; (2) Patients 2 and 3: new hematuria was documented on followup visits 3 months after the baseline visit in the first patient and 6 months after the baseline visit in the second patient in the context of active lupus nephritis; (3) Patient 4: new pyuria was documented on followup visits 3 months after the baseline visit in the context of active lupus nephritis; (4) Patient 5: new alopecia was documented at 6 months and this resolved 2.5 months later with no change in treatment; and (5) Patient 6: oral mucous membrane ulcers were documented as new at 3 months and disappeared at 6 months with no change in therapy.

DISCUSSION

In our study, we have shown that patients who improved in the SLEDAI-2K on the last visit of the study, by decreasing the total score by ≥ 4, did not have deterioration in SLEDAI-2K clinical descriptors. While a very small number of patients in our study showed activity in new laboratory descriptors, this was not considered to be clinically significant and did not result in a change in treatment or management. Although these changes were not clinically significant, the activity in any new descriptors can be of concern in clinical trials of a new treatment. Thus, it is important to compare the presence of clinical and laboratory descriptors of the SLEDAI-2K at last visit but absent at baseline in patients with overall improvement. In our study, we compared SLEDAI-2K descriptors at baseline and at last

visit and showed that it is unlikely to have new descriptors at last visit if there is an improvement in disease activity overall.

Researchers and clinicians seek reliable and valid indices to measure disease activity. Nevertheless, other attributes of measurement outcomes, such as administrative burden, must be considered. The administrative burden of a specific instrument is defined as "the time to administration, energy and demands placed on those who administer the instrument"[13]. One should also consider the practical applicability and the method of scoring[13]. The scoring of the SLEDAI-2K is simple, additive, and is derived by adding the weighted score of all descriptors, and the administrative burden is the number of minutes leading to an immediate answer.

In the original derivation of the SLEDAI, 37 variables that had been used to describe disease activity in SLE based on literature review were considered[1,2]. Using the nominal group process approach, participants rated descriptors based on the importance of the descriptors for measuring disease activity. Only 24 descriptors, rated as most important, were retained and constituted the original SLEDAI and its current validated derivation, SLEDAI-2K. The list of the excluded descriptors includes Coombs test, fatigue, enteritis, pulmonary embolus, Raynaud phenomenon, and others. If these items are deemed important in a specific clinical trial, they need to be assessed individually. The methodological approach adopted in the current study confirmed that in the group of patients with improvement, there were no SLE manifestations present that could have been missed by the SLEDAI-2K. Indeed, the protocol completed in the Toronto Lupus Clinic on every visit allows the identification of all SLE manifestations, including the less common ones (e.g., myelitis, enteritis, and others that are not included in the SLEDAI-2K).

In the trials of biologics, we have witnessed the development of composite indices where global and organ-specific indices were combined. This approach was triggered by the assumption that an improvement identified by a global index such as SLEDAI-2K may conceal deterioration in descriptors in another organ system. This dichotomy of response could be reflected by an organ system index such as BILAG. The composite SRI incorporates a modification of the SLEDAI, the Safety of Estrogens in Lupus Erythematosus National Assessment trial (SELENA-SLEDAI), BILAG, and the physician's global assessment. The SELENA-SLEDAI was used to measure disease improvement overall and the BILAG ensured that no new organ systems (no new A or 2B) have occurred[9]. In the Phase III belimumab trial in Latin America, Asia-Pacific, and Eastern Europe, the percentage of responders as determined by SRI was 58% and the percentage of patients who had ≥ 4 decrease in the total score of SELENA-SLEDAI was 58% in the 10 mg/kg group[14]. In the Phase III belimumab trial (BLISS-76) in Europe and North/Central America, 43% of patients achieved the definition of SRI and 46.5% improved by SELENA-SLEDAI in the 10 mg/kg group. At 76 weeks, 38.5% were deemed responders by SRI and 41.4% improved by SELENA-SLEDAI[15]. The interpretation of these results brings into question the additional information gained in these trials because the percentage of responders was dictated by the SELENA-SLEDAI. The results of these trials confirm that it is unusual to have disease activity improving overall as determined by the SLEDAI-2K or its derivation SELENA-SLEDAI total score, and significantly worsening in another system[16].

Our current study clearly highlights the multifaceted use of the global index SLEDAI-2K. Although global indices describe disease activity overall as reflected in their total score, the individual analysis of the 9 organ systems of the SLEDAI-2K can also provide important clinical data. As we have shown in our study, SLEDAI-2K can be used to evaluate overall improvement in disease activity while not concealing deterioration in other descriptors/systems. The posthoc analysis of pooled data from the BLISS-52 (n = 865) and BLISS-76 (n = 819) showed that the findings regarding the improvement in organ systems with BILAG and SELENA-SLEDAI were consistent across the 2 indices. Both SELENA-SLEDAI and BILAG allowed the documentation of improvement in the mucocutaneous and MSK domains, the most common manifestations assessed[17].

If disease activity improves significantly in 1 system with treatment, it is unusual to have clinically important worsening in another system. The SLEDAI-2K can be used as a single measure in the assessment of disease activity.

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