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Original article

A novel lupus activity index accounting for glucocorticoids: SLEDAI-2K glucocorticoid index

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Abstract

Objective. To develop and validate a modification of SLEDAI-2K to accurately describe disease activity while accounting for glucocorticoid (GC) doses.

Methods. The first two phases focused on the development of the index. Phase 1: identification of scenarios of real patients seen prospectively in a longitudinal cohort. Phase 2: derivation of an equation that explains the association between SLEDAI-2K and GC doses using physician global assessment as the external construct. Phase 3: comparison of SLEDAI-2K and SLEDAI-2K GC (SLEDAI-2KG), using different cut-off points (4–7), in identifying responders in response to therapy.

Results. In phase 1, 150 scenarios with different organ involvement and a range of GC doses were identified. In phase 2, three rheumatologists ranked disease activity using physician global assessment. A quadratic linear regression model relating GC doses and SLEDAI-2K resulted in the following equation: SLEDAI-2KG score = SLEDAI-2K score + [0.32 × GC − 0.0031 × GC^2]. The weighted score of different GC doses was derived. In phase 3, SLEDAI-2KG identified more responders in a total of 111 patients at 6 months (84 *vs* 93%) and at 12 months (76 *vs* 92%) compared with SLEDAI-2K. SLEDAI-2KG performances were superior to SLEDAI-2K with all cut-off points (5–7).

Conclusion. We developed a modification of SLEDAI-2K, SLEDAI-2KG, that describes disease activity while accounting for GC dose category. SLEDAI-2KG identifies more responders compared with SLEDAI-2K.

Key words: SLEDAI, lupus, SLEDAI-2KG, disease activity, glucocorticoids

CLINICAL SCIENCE

Rheumatology key messages

- This study describes the development and validation of a novel index, SLEDAI-2K Glucocorticoid Index (SLEDAI-2KG).
- SLEDAI-2KG describes lupus disease activity while accounting for glucocorticoid doses.
- SLEDAI-2KG enhance the differentiation between responders on different doses of glucocorticoid.

Introduction

The SLEDAI is a global disease activity measure that was initially developed in 1985 [1], with an updated version, SLEDAI-2000 (SLEDAI-2K), introduced in 2002 [2]. SLEDAI-2K's good psychometric properties and low burden of administration and scoring have made it one of the most commonly used disease activity indices in research [2–4] and clinical trials [5]. However, SLEDAI-2K does not account for the severity within each descriptor, nor for glucocorticoid (GC) dose, and GC is always an important factor to account for in observational studies and the majority of lupus trials [5–7] evaluating new drugs in the context of standard of care (SoC) therapy, which includes GC. Thus, there is an unmet need to develop a disease activity instrument that incorporates GC dose into the disease activity measure.

In this study we describe the development of a modification of SLEDAI-2K, SLEDAI-2K GC (SLEDAI-2KG), to accurately describe disease activity while accounting for GC doses. We further compared the performance of SLEDAI-2K and SLEDAI-2KG in identifying responders in response to standard of care therapy.

Methods

Phase 1 focused on the identification of scenarios of real patients to derive weighted scores for GC dose. Phase 2 focused on the development of SLEDAI-2KG (derivation of

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an equation to explain the link between SLEDAI-2K and GC doses), and phase 3 focused on SLEDAI-2KG validation.

Phase 1: identification of scenarios with a spectrum of organ involvement taking different GC doses

The scenarios were of real patients followed prospectively at the University of Toronto Lupus Clinic in the past 20 years (1400 patients and 29 577 visits). Adult patients at the lupus clinic are >18 years of age with a diagnosis of SLE based on four or more ACR criteria or three ACR criteria plus a typical histological lesion of SLE on renal or skin biopsy [8]. The standard protocol at each visit includes: complete history, including demographics and therapy, physical examination and laboratory evaluation. Patients attend the lupus clinic at 2–6 month intervals regardless of the state of activity of their lupus. Disease activity is measured at each visit by SLEDAI-2K 30 days [2, 9].

The collection, storage and use of the clinical and laboratory data on the patients at the Centre are conducted in accordance with the Declaration of Helsinki and are approved by the Research Ethics Board of the University Health Network, Toronto, Canada. All patients sign an informed consent (REB#11-0397-AE).

To ensure that scenarios include a spectrum of organ systems manifestation and a full range of GC doses, two data sampling approaches were utilized as follows.

The 15 most common organ involvement combinations in the database were identified (SLEDAI-2K includes nine organ systems and 24 descriptors). We identified the median and 25th and 75th quartile of GC (mg/day) doses in each combination and randomly selected two scenarios at median and one each at the 25th and 75th quartile from the 13 most common combinations of SLEDAI-2K organ involvements. An additional seven scenarios with low complement or anti-ds DNA antibodies alone and scenarios with SLEDAI-2K of 0 were added. This resulted in 59 scenarios, exceeding the minimum sample size calculation required according to the formulas for reliability analysis presented by Streiner *et al.* [10].

Patients from the entire database were grouped into eight categories based on a range of GC doses (5, 10, 15, 20, 30, 40, 50 and 60 mg/day) and 10 patients (10 most common SLEDAI-2K organ combinations) were selected randomly from each GC dose level. This approach generated an additional 80 scenarios. An additional 11 scenarios were added with a SLEDAI-2K score of 0 and low complement or anti-ds DNA, which resulted in a total of 91 scenarios. Thus from the two sampling approaches 150 scenarios were generated. Scenarios included information on patient SLEDAI-2K scores, organ involvement by SLEDAI-2K and GC doses.

Phase 2: derivation of an equation for the new index (SLEDAI-2KG) based on phase 1 scenarios

In this phase, the physician global assessment (PGA) was used to discern the relationship between an increasing GC dose and the SLEDAI-2K score. First, three rheumatologists (Z.T., D.D.G. and M.B.U.) ranked disease activity of patient scenarios using PGA (Likert scale 0: not active; scale 7: most active) [11] which was considered the gold standard. Raters were provided with the SLEDAI-2K total score, individual organ involvement and GC dose. Raters were instructed to account for GC dose while rating disease activity on the PGA. Second, an equation that explained the association between SLEDAI-2K and GC doses was derived.

Phase 3: comparison of SLEDAI-2KG and SLEDAI-2K in identifying responders

Patients seen between January 2011 and 2014, at the University of Toronto Lupus Clinic, with active disease (SLEDAI-2K $\geqslant$ 6) and on prednisone $\geqslant$10 mg/day, and with follow-up visits within 5–24 months were studied. SoC treatment was determined based on the judgement of the treating rheumatologist. Response to SoC therapy, at first follow-up visit, was assessed by SLEDAI-2K and SLEDAI-2KG. Responders were defined based on the decrease in SLEDAI-2K and SLEDAI-2KG score by $\geqslant$4. The performance of SLEDAI-2K and SLEDAI-2KG was also compared using different cut-off points: 5, 6 and 7.

Analysis

Phase 1. The sample size calculation of needed scenarios was based on the assumption of reliability [intra-class correlation coefficient (ICC)] $\geqslant$0.80 with a standard error of 0.05 and three raters. The required minimum was 46 scenarios.

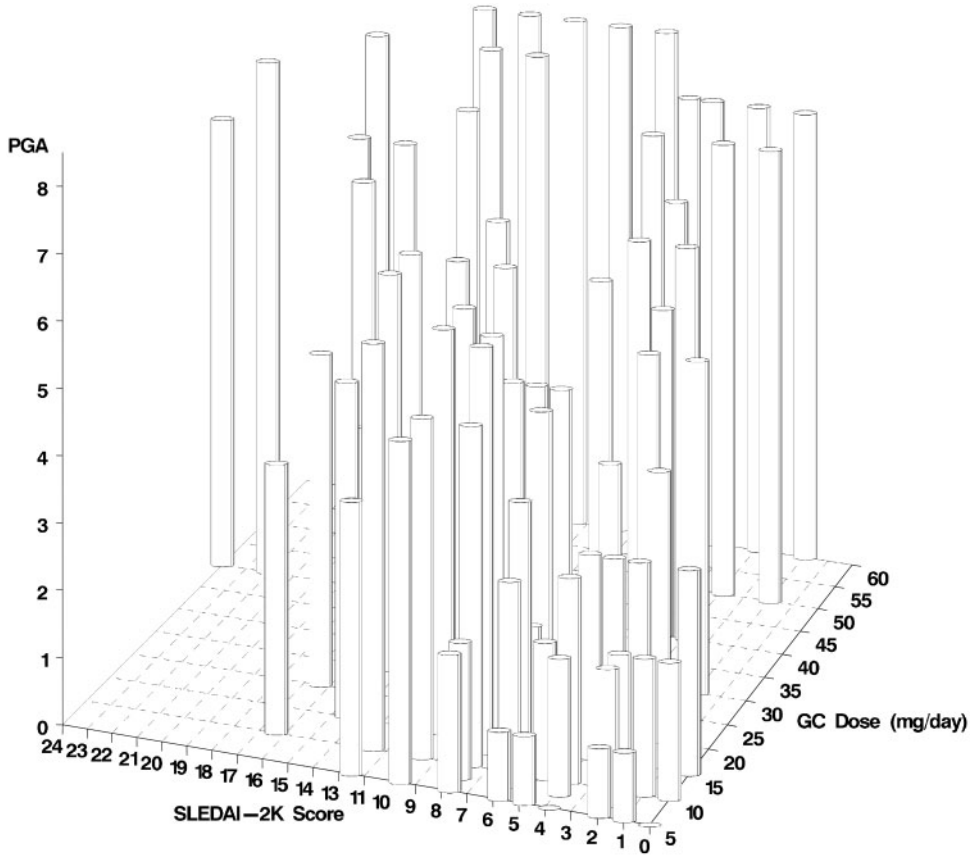
Phase 2. The Shrout and Fleiss [12] ICC (2, *k*) was calculated to examine the agreement among three raters. The ICC and the 95% CI calculation was based on the bootstrap method by re-sampling 1000 times with replacement; an ICC >0.85 reflects good agreement [10, 12, 13].

Derivation of the equation for the new index (SLEDAI-2KG). In preparation for the derivation of the equation, it was important to study the association between GC doses and disease activity score by SLEDAI-2K. First, we evaluated the relationship between GC doses and PGA for different individual SLEDAI-2K levels, and second, we combined all SLEDAI-2K levels in one plot. This allowed us to conclude that the relationship between GC doses and PGA is quadratic (plots are not shown). The relationship among the three components (SLEDAI-2K, PGA and GC doses) is illustrated in a three dimensional histogram (Fig. 1). A quadratic linear regression model was created (model 1) to describe the relationship between PGA and GC doses. We also tried a cubic term of GC doses but the regression coefficient of that term was minimal and thus it was neglected. The final model encompassed the linear and the quadratic terms.

$$\text{PGA} = \text{intercept} + \beta_1 \times \text{GC dose} + \beta_2 \times \text{GC dose}^2$$

The relationship between PGA and SLEDAI-2K was linear and therefore a linear model was created between PGA and SLEDAI-2K (model 2). The last step was to replace the independent parameter of PGA in model 2 with the

Fig. 1 Relationships among SLEDAI-2K, PGA and GC doses



GC: glucocorticoid; PGA: physician global assessment; SLEDAI-2K: SLE Disease Activity Index 2000.

relationship we obtained in model 1. The final predicted weighted GC dose score is:

$$\text{Weighted GC dose score} = \text{intercept} + \beta_1 \times \text{GC dose} + \beta_2 \text{GC dose}^2$$

Phase 3. Descriptive statistics were used in the analysis.

Results

Phase 1: identification of scenarios

Both approaches yielded 150 visits with different organ involvement (Table 1) on a range of GC doses (Table 2).

Phase 2: derivation of equation based on phase 1 scenarios

One hundred and fifty scenarios were summarized and ranked by three rheumatologists leading to 450 records. An excellent agreement in PGA was achieved with an ICC (2, *k*) of 0.89 (95% CI: 0.83, 0.89).

A three-dimensional histogram that was plotted to illustrate the relation between SLEDAI-2K score (*x*-axis), GC dose (*y*-axis) and Likert scale (*z*-axis) (Fig. 1) demonstrated that PGA was at a high level (active disease reflected by the height of bars) with high SLEDAI-2K scores or with higher doses of GC (Fig. 1).

The weighted scores of GC doses were derived from equations above. The derived equation between GC and the new SLEDAI-2KG score is as follows:

$$\text{SLEDAI-2KG score} = \text{SLEDAI-2K score} + (0.32 \times \text{GC dose} - 0.0031 \times \text{GC dose}^2)$$

A simplified table was created to dispay the weighted scores for different GC doses. All SLEDAI-2KG scores were rounded to the nearest integer. For instance, SLEDAI-2K of 6 in a patient on 10 mg/day of GC results in SLEDAI-2KG of 9 (Table 3). The weighted GC dose score plateaued when the GC dose reached $\geqslant$37.5 mg/day. Therefore, a score of 8 was assigned to GC doses $\geqslant$37.5 mg/day (supplementary Fig. S1, available at *Rheumatology* online). Table 4 shows the newly developed index, SLEDAI-2KG, which includes the same 24 descriptors of SLEDAI-2K, in addition to the new descriptor, GC, and its scoring approach.

Phase 3: comparison of SLEDAI-2KG and SLEDAI-2K in identifying responders

One hundred and eleven patients met the inclusion criteria of the study and were further analysed. Patients' characteristics

Table 1 Organ involvement in 150 scenarios

Organ systems	CNS	VAS	MSK	REN	DER	SER	IMM	CONS	HEM
Percentage of patients with organ involvement	9.9	3.8	25.9	33.6	45.8	2.3	62.6	0.8	13.7

CNS: central nervous system; VAS: vasculitis; MSK: musculoskeletal; REN: renal; DER: dermal; SER: serosal; IMM: immunological; CONS: constitutional; HEM: haematological.

Table 2 GC distribution in 150 scenarios

GC dose, mg/day	5	7.5	10	12.5	15	20	25	30	40	50	60
Percentage of patients with organ involvement	18.3	4.6	22.1	2.3	11.4	9.9	0.8	7.6	7.6	7.6	7.6

GC: glucocorticoid.

Table 3 SLEDAI-2KG scores based on the weighted score of different GC doses

GC weighted score corresponding to different GC doses		Example of the application of SLEDAI-2KG to a patient with SLEDAI-2K of 6	
GC dose, mg/day	GC weighted score	SLEDAI-2K	SLEDAI-2KG = SLEDAI-2K + GC weighted score
<5	0	6	6 + 0 = 6
5	2	6	6 + 2 = 8
7.5	2	6	6 + 2 = 8
10	3	6	6 + 3 = 9
12.5–15	4	6	6 + 4 = 10
17.5–20	5	6	6 + 5 = 11
22.5–27.5	6	6	6 + 6 = 12
30–35	7	6	6 + 7 = 13
⩾37.5	8	6	6 + 8 = 14

GC: glucocorticoid; SLEDAI-2KG: SLE Disease Activity Index Glucocorticosteroid Index.

are represented in supplementary Table S1, available at *Rheumatology* online. SLEDAI-2KG identified more responders at 6 months (93% *vs* 84%) and at 12 months (92% *vs* 76%) compared with SLEDAI-2K by cut-off of 4. SLEDAI-2KG also identified more responders with cut-off points 5, 6 and 7 (Table 5).

Discussion

In this study, we presented the development of a modification of SLEDAI-2K, SLEDAI-2KG, able to describe disease activity while accounting for GC doses. Phase 1 resulted in the identification of 150 case scenarios of real patients, with a spectrum of organ systems manifestations and a wide range of GC doses, which were scored by rheumatologists and resulted in the derivation of weighted scores of different GC doses. Phase 2 resulted in the derivation of an equation for SLEDAI-2KG that accounts for SLEDAI-2K score and the weighted score of different GC doses. The weighted score of GC doses was further simplified in a Table 3 (First and second columns) that summarizes the GC dose weighted scores for different cut-offs of GC doses. The newly developed index, SLEDAI-2KG, was superior to SLEDAI-2K in identifying responders at 6 and 12 months.

The assessment of lupus disease activity can be very challenging and SLEDAI-2K standardized this assessment and quantified disease activity [2, 9]. The wide use of SLEDAI-2K was a result of its good psychometric properties [2, 9, 14], acceptable administration burden and simple scoring [15]. While a complete history, physical examination and laboratory results are required, the scoring of SLEDAI-2K is simple and additive. We also ensured that the new index, SLEDAI-2KG, conveys a low administration burden and a simple scoring system. Table 3 demonstrated the simple and intuitive steps required for the derivation of SLEDAI-2KG scores. Indeed, it requires only the SLEDAI-2K scores and the dose of GC, which becomes the final descriptor in the activity index as reflected in Table 4.

Table 4 Newly developed index SLEDAI-2KG

Weight	Descriptor	Definition
8	Seizure	Recent onset, exclude metabolic, infectious or drug causes
8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized or catatonic behavior. Exclude uraemia and drug causes
8	Organic brain syndrome	Altered mental function with impaired orientation, memory or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes
8	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal haemorrhages, serous exudate or haemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection or drug causes
8	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves
8	Lupus headache	Severe, persistent headache; may be migrainous, but must be unresponsive to narcotic analgesia
8	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis
8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter haemorrhages, or biopsy or angiogram proof of vasculitis
4	Arthritis	Two or more joints with pain and signs of inflammation (i.e. tenderness, swelling or effusion)
4	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis
4	Urinary casts	Haem-granular or red blood cell casts
4	Haematuria	More than five red blood cells/high power field. Exclude stone, infection or other cause
4	Proteinuria	$>$0.5 g/24 h
2	Pyuria	More than five white blood cells/high power field. Exclude infection
2	Rash	Inflammatory type rash
2	Alopecia	Abnormal, patchy or diffuse loss of hair
2	Mucosal ulcers	Oral or nasal ulcerations
2	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening
2	Pericarditis	Pericardial pain with at least one of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation
2	Low complement	Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory
2	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory
1	Fever	$>$38°C. Exclude infectious cause
1	Thrombocytopenia	$<$100 000 platelets$\times 10^9$/L, exclude drug causes
1	Leukopenia	$<$3000 white blood cells$\times 10^9$/L, exclude drug causes
0–8	Weighted glucocorticoid dose[a]	Based on current visit dose: 0 for $<$5 mg/day; 2 for 5–7.5 mg/day; 3 for 10 mg/day; 4 for 12.5–15 mg/day; 5 for 17.5–20 mg/day; 6 for 22.5–27.5 mg/day; 7 for 30–35 mg/day; 8 for $\geqslant$37.5 mg/day

SLEDAI-2KG descriptor if present at the time of the visit or in the preceding 30 days. [a]Glucocorticoid weighted score is derived only if glucocorticoid is used to treat lupus. If the patient is on glucocorticoid for asthma, in the context of renal transplant, etc. the weighted GC score should be 0. SLEDAI-2KG: SLE Disease Activity Index Glucocorticosteroid Index; CVA: cerebrovascular accident; CH 50: hemolytic complement; (C3) and C4: complement.

Table 5 Responders by SLEDAI-2K and SLEDAI-2KG in 111 patients

Indices	Percentage of responders at 6 months using different cut-off points					Percentage of responders at 12 months using different cut-off points				
	$\geqslant$3	$\geqslant$4	$\geqslant$5	$\geqslant$6	$\geqslant$7	$\geqslant$3	$\geqslant$4	$\geqslant$5	$\geqslant$6	$\geqslant$7
SLEDAI-2K, %	84	84	68	68	59	77	76	57	55	44
SLEDAI-2KG, %	95	93	88	83	79	93	92	80	70	62
Additional responders, %	11	9	20	15	20	16	16	23	15	18

SLEDAI-2K: SLE Disease Activity Index 2000; SLEDAI2KG: SLE Disease Activity Index Glucocorticosteroid Index.

The new modification (SLEDAI-2KG) adds another variable (weighted score for GC dose), which will allow the physician to more accurately gauge the severity of activity within a descriptor of SLEDAI-2K. For example a patient with thrombocytopenia of 80 000 and another at 10 000 will both be scored as 1 on SLEDAI-2K, but will be treated with different doses of prednisone. This will be accounted for with the new GC dose descriptor. This concept is applicable to all 24 descriptors of SLEDAI-2KG. The management of nephrotic proteinuria in lupus nephritis (e.g. proteinuria of 4 g/day) often requires a larger dose of prednisone compared with the management of subnephrotic proteinuria (e.g. proteinuria of 1 g/day) where a lower dose of prednisone might be sufficient. SLEDAI-2KG accounts for prednisone dose and differentiates between these scenarios [e.g. proteinuria (weighted score of 4) and prednisone 40 mg/day (weighted score of 7) will result in a total score of 11 compared with proteinuria (weighted score of 4) and prednisone 15 mg/day (weighted score of 4) that will result in a total score of 8]. In this example, a higher total score of 11 was achieved in the patient with nephrotic proteinuria compared with a total score of 8 in the patient with subnephrotic proteinuria. Clearly SLEDAI-2KG helps to reflect the severity of disease activity, within each descriptor, while accounting for GC doses, rather than describing the descriptor as present or absent as with SLEDAI-2K. Thus a reduction in GC dose signifies a response or a signal of decrease in the severity of the clinical manifestation or its complete resolution. The level required to achieve disease improvement as opposed to disease quiescence based on the new index will be determined in future studies.

SLEDAI-2K is widely utilized in research settings, clinical trials and to a lesser extent in clinics. The use of SLEDAI-2KG will enable researchers to study the effect of disease activity combined with GC dose in long term observational studies looking at outcomes in SLE and at organ damage where GC dose may be an important factor to account for in patients with different demographics and in patients from different cohorts. In the past decade we have witnessed a plethora of clinical trials for potential new drugs in lupus. The concept of SLEDAI-2KG is novel and it might enhance the analyses in clinical trials to differentiate between responders on minimal and large doses of GC. In clinical trials where GC doses are fixed, the role of this new index, SLEDAI-2KG, might be limited and future analyses will further elaborate on this hypothesis.

In our scenarios we only chose patients taking up to a maximum of 60 mg/day of prednisone. However, in the derivation of this new index, it was clear that the GC dose weighted score plateaued when GC dose reached $\geqslant$37.5 mg/day. Thus, the quadratic relationship between GC doses and equivalent SLEDAI-2K scores resulted in the assignment of a score of 8 to GC doses $\geqslant$37.5 mg/day. Furthermore, in our clinic $<$8% of patients received GC treatment higher than 60 mg/day. Similarly, in drug trials patients taking GC doses of 60 mg/day or more are usually excluded. This also ensured that GC dose was not assigned a value greater than any other SLEDAI-2K descriptor.

In conclusion, we developed a novel modification of SLEDAI-2K, SLEDAI-2KG, that describes disease activity while accounting for GC dose. Furthermore, we showed that SLEDAI-2KG improves the ability to identify responders compared with SLEDAI-2K in outcome studies. Ongoing prospective data collection at the University of Toronto Lupus Clinic is being conducted to further validate SLEDAI-2KG compared with different constructs including PGA on a visual analogue scale and Likert scale. In addition, an international external validation phase will be conducted on SLEDAI-2KG.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992;35:630–40.

2 Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29:288–91.

3 Touma Z, Urowitz MB, Gladman DD. SLEDAI-2K for a 30-day window. Lupus 2010;19:49–51.

4 Touma Z, Gladman DD, Su J, Ibañez D, Urowitz MB. SLEDAI-2K does not conceal worsening in a particular system when there is overall improvement. J Rheumatol 2015;42:1401–5.

5 Medina-Rosas J, Al-Rayes H, Moustafa AT, Touma Z. Recent advances in the biologic therapy of lupus: the 10 most important areas to look for common pitfalls in clinical trials. Expert Opin Biol Ther 2016;16:1225–38.

6 Al Rayes H, Touma Z. Profile of epratuzumab and its potential in the treatment of systemic lupus erythematosus. Drug Des Devel Ther 2014;8:2303–10.

7 Narain S, Furie R. Update on clinical trials in systemic lupus erythematosus. Curr Opin Rheumatol 2016;28:477–87.

8 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.

9 Touma Z, Urowitz MB, Ibañez D, Gladman DD. SLEDAI-2K 10 days versus SLEDAI-2K 30 days in a longitudinal evaluation. Lupus 2011;20:67–70.

10 Streiner DL, Norman GR. Health measurement scales: a practical guide to their development and use. In: Streiner DL, Norman GR, eds. Reliability, Generalizability Theory and Validity. New York: Oxford University Press; 2008, 167–276.

11 Touma Z, Gladman DD, Ibañez D, Urowitz MB. Development and initial validation of the systemic lupus erythematosus disease activity index 2000 responder index 50. J Rheumatol 2011;38:275–84.

12 Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull 1979;86:420–8.

13 Winer BJ. Statistical Principles in Experimental Design. New York: McGraw Hill, 1971.

14 Ward MM, Marx AS, Barry NN. Comparison of the validity and sensitivity to change of 5 activity indices in systemic lupus erythematosus. J Rheumatol 2000;27:664–70.

15 Romero-Diaz J, Isenberg D, Ramsey-Goldman R. Measures of adult systemic lupus erythematosus: updated version of British Isles Lupus Assessment Group (BILAG 2004), European Consensus Lupus Activity Measurements (ECLAM), Systemic Lupus Activity Measure, Revised (SLAM-R), Systemic Lupus Activity Questionnaire for Population Studies (SLAQ), Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). Arthritis Care Res 2011;63(Suppl 11):S37–46.