Development and Initial Validation of the Systemic Lupus Erythematosus Disease Activity Index 2000 Responder Index 50

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ABSTRACT. ***Objective.*** To describe the development and validation of the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) Responder Index 50 (SRI-50), an index to measure improvement in disease manifestations on followup visits.

Methods. We proposed 50% improvement of SLEDAI-2K scores as this was felt by clinicians to reflect a clinically important improvement. We determined the best definitions of 50% improvement in each of the SLEDAI-2K descriptors. The SRI-50 data retrieval form was developed to standardize the documentation of the descriptors. The new assigned scores for the descriptors of SRI-50 were derived by dividing the score of SLEDAI-2K by 2. To evaluate the construct validity of SRI-50, all patients attending the Lupus Clinic from September 2009 to December 2009 were studied. Patients were assessed initially and on a followup visit according to both SLEDAI-2K and SRI-50 along with physician response assessment on a Likert scale (LS), which was considered the external construct.

Results. SRI-50 is a 2-page document comprising 24 descriptors. The scoring method is simple, intuitive, and cumulative, and can be derived during the patient visit. Of the 298 patients enrolled in this study, 141 had a followup visit and were studied further. SRI-50 scores decreased more in patients with LS ≥ 50% compared to LS < 50% with a decrease of > 3. The decrease in SRI-50 scores was statistically and clinically more significant than the decrease in SLEDAI-2K scores. SRI-50 detected incomplete improvement, which would not have been discerned using SLEDAI-2K.

Conclusion. SRI-50 has construct validity and is able to demonstrate incomplete, but clinically significant, improvement in disease activity between visits in patients with lupus. (First Release Dec 1 2010; J Rheumatol 2011;38:275–84; doi:10.3899/jrheum.100724)

Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX 2000
SLEDAI-2K SRI-50 RESPONDER INDEX DISEASE ACTIVITY
SYSTEMIC LUPUS ERYTHEMATOSUS OUTCOME MEASURES

Systemic lupus erythematosus (SLE) is a complex disease characterized by various clinical manifestations that can be related to acute disease activity or to chronic damage, which makes the disease difficult to monitor. In 1998, Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) 4 recommended that 5 domains be assessed in all SLE clinical trials and longitudinal observational cohort studies: disease activity, damage resulting from lupus activity or its therapy, health related quality of life, adverse events, and economic costs including health utilities[1,2].

Disease activity is defined as a reversible manifestation of the underlying inflammatory process and is a reflection of the type and severity of organ involvement at each point in time[3]. The assessment of disease activity depends on the use of standardized, reliable, and validated indices. For this purpose several indices for scoring disease activity in SLE are currently used[3,4,5,6,7,8,9,10,11,12,13,14,15]. Of those that have been validated, 2 indices, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and British Isles Lupus Assessment Group Index (BILAG), have been used most in clinical trials and have undergone changes to assure optimal performance in clinical and research settings[3,8].

SLEDAI is a global index that was developed and validated and introduced in 1985 as a clinical index for disease activity. This index was modeled on clinicians' global judgment. It was developed with a panel of experienced rheuma-

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Dr. Touma is a recipient of the Geoff Carr Award provided by Lupus Ontario and the Arthritis Centre of Excellence Fellowship provided by the University of Toronto.

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Accepted for publication September 27, 2010.

tologists with expertise in SLE, using well established group techniques and index development methods. SLEDAI is based on the presence of 24 features in 9 organ systems and measures disease activity in SLE patients in the previous 10 days[3]. SLEDAI has been used successfully by both expert clinicians and trainees, and has been adopted in both research and clinical settings[16,17,18,19]. SLEDAI is sensitive to change in disease activity over time[20]. In 2002 a revised version of SLEDAI, SLEDAI-2000 (SLEDAI-2K), was introduced, in which the persistent ongoing active disease in the items rash, alopecia, mucosal ulcers, and proteinuria would be scored, as opposed to only new occurrences as in the original SLEDAI[4]. SLEDAI-2K was validated against the original SLEDAI and was shown to describe disease activity at various activity levels in a manner comparable to the original SLEDAI[4]. However, both SLEDAI and SLEDAI-2K document findings in the past 10 days prior to the visit[4]. Since patients in drug trials are followed at 30-day window intervals the SLEDAI-2K was validated for a 30-day window both in a cross-sectional study and longitudinally over 1 year[6,7].

SLEDAI-2K records features of disease activity in lupus as present or absent[2,3,4]. Thus its utility in clinical trials is limited as it cannot reflect partial improvement in a disease manifestation. This led us to develop the SLEDAI-2K Responder Index-50 (SRI-50), which could document a minimum 50% improvement in disease manifestations among lupus patients.

Our aims were: (1) to describe the development of SRI-50, an index derived from SLEDAI-2K to measure at least 50% improvement in disease activity; (2) to describe the development of the SRI-50 data retrieval form that would standardize the method of scoring of the descriptors; and (3) to test the construct validity of SRI-50 as a responder index measuring global disease activity improvement.

MATERIALS AND METHODS

Derivation of SRI-50 definitions, SRI-50 data retrieval form, and SRI-50 scores. We used SLEDAI-2K to develop the new responder index, SRI-50[3]. A minimum of 50% improvement was felt by clinicians to reflect a significant improvement.

SRI-50 definitions. We searched the literature and generated definitions to identify 50% improvement in each of the 24 descriptors of SLEDAI-2K. The agreed-upon descriptor definitions of SRI-50 and the SRI-50 data retrieval form were evaluated first by 3 rheumatologists (ZT, DDG, and MBU) on several occasions. These definitions were then discussed with and refined by other lupologists and rheumatologists at a series of interdivisional meetings to establish areas for improvement, mostly concerning the wording of the index. Where appropriate, changes were made in accord with the suggestions.

Rules for ascertainment were provided for each of the descriptors, whether they were physical findings, laboratory findings, patient self-evaluation, physician evaluation of variables such as cognitive dysfunction, laboratory results, or diagnostic tools (Table 1). Each descriptor refers to the preceding 30 days as in the SLEDAI-2K 30 days and descriptors are measured in a generally accepted way (Table 2)[6,7].

The SRI-50 data retrieval form was developed to standardize the recording of SLEDAI-2K descriptors in an efficient way to allow calculation of SRI-50 scores (Table 3).

SRI-50 score is evaluated at the followup visit and corresponds to the sum of each of the 24 descriptors' scores found on the SRI-50 data retrieval form. For patients with multiple followup visits, we recommend determining the score of the SRI-50 using the baseline visit scores. For patients who become worse after a period of improvement in a specific manifestation, or if a new manifestation develops in a followup visit, a subgroup analysis can be conducted to include that visit in the determination of SRI-50.

Assessment of construct validity. Construct validity of the SRI-50 definitions and the SRI-50 data retrieval form was assessed.

Patient selection. We conducted a cross-sectional study on all patients who attended the Lupus Clinic from September 2009 to December 2009. Of the 298 patients enrolled, 141 had a followup visit and were studied further.

Patient assessment. Patients were assessed initially (at an anchor visit) and then reassessed, after treatment was initiated or adjusted, in 1 to 3 months. SLEDAI-2K 0 (anchor visit) was determined on the baseline visit and the SRI-50 data retrieval form was completed. SLEDAI-2K 1 (followup visit) and SRI-50 scores were determined on a followup visit at 1 to 3 months. During the first visit a physician global assessment was determined on visual analog scale (VAS) line of 100 mm, with anchors of 0 "no disease activity" and 10 for "very active disease." During the followup visit a physician response assessment was determined on a 7-point Likert scale (LS); 7 = much improved, 6 = moderately improved, 5 = slightly improved, 4 = unchanged, 3 = slightly worse, 2 = moderately worse, and 1 = much worse. We defined a 50% improvement as LS score ≥ 6.

Clinician scoring of disease activity. A clinician who did not know the patients and who was not aware of the SLEDAI-2K scores evaluated each patient's record and assigned a clinical activity score for each assessment according to the following scale: improved, same, and worse, using standardized predefined definitions. "Improved," defined as one of the follow-

Table 1. Approaches to measuring disease activity.

Physical Findings	Patient Self-evaluation	Laboratory Results	Diagnostic Tools
Psychosis	Seizure	Myositis	Cranial nerve disorder
Organic brain syndrome	Cranial nerve disorder	Urinary casts	Cerebrovascular accident
Visual disturbance	Lupus headache	Hematuria	Pleurisy
Cranial nerve disorder	Alopecia	Proteinuria	Pericarditis
Cerebrovascular accident	Mucosal ulcers	Pyuria	
Vasculitis	Pleurisy	Low complements	
Arthritis	Pericarditis	Increased anti-DNA antibodies	
Myositis	Fever	Thrombocytopenia	
Rash		Leukopenia	
Alopecia			

Table 2. SLEDAI-2K Responder Index 50 (SRI-50)© — Definitions. Descriptors are present at the time of the visit or in the preceding 30 days and attributed to lupus.

DESCRIPTOR	SLEDAI-2K DEFINTION	DEFINITION OF SRI-50 IMPROVEMENT
Seizure	Recent onset. Exclude metabolic, infectious or drug causes.	≥50% reduction in frequency of baseline seizure days/month.
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 uremia and drug causes.	≥50% improvement of the psychotic manifestations judged by physician.
Organic brain syndrome*	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.	≥50% improvement of the organic brain manifestations judged by physician.
Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.	≥50% improvement of the retinal exam assessed by physician.
Cranial Nerve disorder§	New onset of sensory or motor neuropathy involving cranial nerves.	≥50% recovery of motor or sensory function in affected nerve within 1 month from the event on the basis of decrease in lupus disease activity or ≥50% decrease of the severity of pain within 1 month from the event on the basis of decrease in lupus disease activity as determined by patient on numerical scale of 1-10 if applicable with no worsening in either.
Lupus headache#	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.	≥50% decrease of the severity of pain as determined by patient on numerical scale of 1-10.
CVA§	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.	≥50% recovery of motor or sensory function related to CVA within 1 month from the event on the basis of decrease in lupus disease activity as determined by physician without worsening in either.
Vasculitis†	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.	≥50% improvement of the vasculitis lesions present with no new lesion or worsening in either. A ≥50% improvement for ulceration or gangrene is defined as ≥50% decrease in the body surface area; for periungual infarction, splinter hemorrhages or tender finger nodules a ≥50% improvement is defined as ≥50% decrease in the total number of involved digits with periungual infarction, splinter hemorrhages and tender finger nodules. Multiple lesions in a single digit, count only one.

Numerical scale: 1is mild and 10 is most severe

To determine body surface area use Rule of Nines for skin scoring: Head 9%, chest 9%, abdomen 9%, back 18%, legs 36%, arms/hands 18% and mucous membrane 1%; physician's palm for 1%.

* Overlap of symptoms will count for only one descriptor either Psychosis or Organic Brain Syndrome.

\# Lupus headache improvement will count regardless of whether patient is using narcotic analgesia or not though it has to be part of the baseline lupus headache.

§ CVA and Cranial Nerve improvement will count if it occurs within 1 month from the event on the basis of decrease in lupus disease activity as this more likely on the basis of decrease disease activity.

† Vasculitis, Rash and Alopecia; if the total BSA ≤1%, a ≥50% improvement is defined by ≥50% decrease in the activity of the most active lesion by decreasing by 2 grades or ≥50% decrease in the number of lesions or decrease in the size of the biggest lesion with no worsening in either.

Table 2 Continued. SLEDAI-2K Responder Index 50 (SRI-50)© — Definitions.

DESCRIPTOR	SLEDAI-2K DEFINITION	DEFINITION OF SRI-50 IMPROVEMENT
Arthritis	≥2 joints with pain and signs of inflammation (i.e. tenderness, swelling or effusion).	≥50% reduction in the number of joints with pain and signs of inflammation (i.e. tenderness, swelling or effusion).
Myositis	Proximal muscle aching/weakness, associated with elevated creatinine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.	≥50% increase in muscles power judged by physician or increase by or 1 grade upon a scale of zero to five or ≥50% decrease in the level of creatinine phosphokinase/aldolase level comparing to previous visit with no worsening in either.
Urinary casts	Heme-granular or red blood cell casts.	Decrease by ≥50% in the total number of casts (heme-granular and red blood cell casts).
Hematuria	>5 red blood cells/high power field. Exclude stone, infection, or other cause.	Decrease by ≥50% in the number of red blood cell /high power field at this visit.
Proteinuria	New onset, recurrent, or persistent proteinuria of more than > 0.5 gram/24 hours.	Decrease by ≥50% in the range of proteinuria.
Pyuria	>5 white blood cells/ high power field. Exclude infection.	Decrease by ≥50% in the number of white blood cells/ high power field.
Rash†	New onset, recurrent, or persistent inflammatory lupus rash. *Activity of skin lesions should be based on the evaluation of the most active lesion.*	Decrease by ≥50% of involved body surface area and/or activity of most active lesion with no worsening in either. Activity of the lesion should be determined by the color of the lesions: 0 –absent 1 – pink, faint erythema 2 – red 3 – dark red/purple/violaceous/crusted/hemorrhagic A ≥50% decrease in the activity of the lesion is defined by decreasing by 2 grades. Dyspigmentation, scarring and atrophy are not active lesions.
Alopecia†	New onset, recurrent, or persistent abnormal, patchy or diffuse loss of hair. *Size of patchy alopecic lesion should be determined based on involved total scalp surface. Total scalp surface is 4.5%.* *Diffuse alopecia is determined* by patient on numerical scale of 1-10. *Activity of alopecia should be based on the evaluation of the most active lesion.*	Decrease by ≥50% of total scalp involved area for patchy alopecic lesion or ≥50% reduction in the diffuse alopecia as determined by patient on numerical scale of 1-10, and/or activity of the most active alopecic lesions with no worsening in either. Activity of the alopecic lesion should be determined by the color of the most active lesion: 0 –absent 1 – pink, faint erythema 2 – red 3 – dark red/purple/violaceous/crusted/hemorrhagic A ≥50% decrease in the activity of the lesion is defined by decreasing by 2 grades.
Mucosal Ulcers	New onset, recurrent, or persistent oral or nasal ulcerations.	Decrease by ≥50% in the number of ulcers at this visit.
Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.	≥50% reduction in the pain severity as determined by patient on numerical scale of 1-10 and/or ≥50% reduction in the amount of fluid (on imaging) with no worsening in either.
Pericarditis	Pericardial pain with at least one of the following: Rub, effusion, electrocardiogram or echocardiogram confirmation.	≥50% reduction in the pain severity as determined by patient on numerical scale of 1-10 and/or ≥50% reduction in the amount of fluid (on imaging) with no worsening in either.
Low Complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.	≥50% increase in the level of any complement or normalization of one of them without a drop in either.
Increased anti-DNA antibodies levels	Increase in the level of anti-DNA antibodies above normal range for testing laboratory.	≥50% reduction in the level of anti-DNA antibodies.
Fever	>38° C. Exclude infectious causes.	≥50% reduction in the degree of fever above normal.
Thrombocytopenia	<100,000 platelets/ x 10^9/L. Exclude drug causes.	≥50% increase in the level of platelets but <100,000 platelets/mm^3.
Leukopenia	<3,000 white blood cells/x 10^9/L. Exclude drug causes.	≥50% increase in the level of white blood cells but <3,000/mm^3.

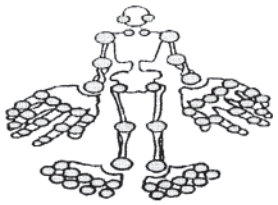
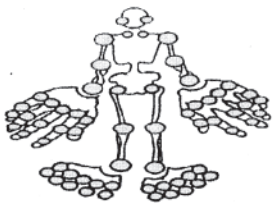
ing: (1) stopping treatment in the presence of improvement of an already active system or in response to complete remission of an active system; (2) a decrease in medication dosage for the above reason; (3) indication of improvement in SLE disease activity in the physician's notes; (4) use of the term improvement in the physician's notes. "Worse," defined as one of the following: (1) introduction of new treatment in the presence of worsening of an already active system, or in response to activation of a new system; (2) increase in medication dosage for the above reasons; (3) indication of concern regarding SLE disease activity in the physician's notes — arrangement for an earlier appointment/investigation to assess SLE disease activity; (4) the

Table 3. Data retrieval form of SLEDAI-2K Responder Index-50 (SRI-50)©.

Descriptors are present at the time of the visit or in the preceding 30 days **Patient ID:**_____

BASELINE VISIT **Visit Date:** _____/_____/_____	**Score** (Circle)	**FOLLOW-UP VISIT** **Visit Date:** _____/_____/_____	**Score** (Circle) **Improvement** **< 50%**	**≥ 50%**	**100%**
Seizure ☐ Partial (focal, local) seizures ☐ simple partial seizures (consciousness not impaired) ☐ complex partial (with impairment of consciousness) ☐ partial seizures (simple or complex) evolving to secondarily generalized seizures ☐ Generalized seizures ☐ nonconvulsive (absence) ☐ convulsive **Days per month**_____	8	**Seizure** ☐ Partial (focal, local) seizures ☐ simple partial seizures (consciousness not impaired) ☐ complex partial (with impairment of consciousness) ☐ partial seizures (simple or complex) evolving to secondarily generalized seizures ☐ Generalized seizures ☐ nonconvulsive (absence) ☐ convulsive **Days per month**_____	8	4	0
Psychosis ☐ Altered ability to function in normal activity due to: ☐ hallucinations ☐ incoherence ☐ marked loose associations ☐ impoverished thought content ☐ marked illogical thinking ☐ bizarre, disorganized or catatonic behavior	8	**Psychosis** ☐ Altered ability to function in normal activity due to: ☐ hallucinations ☐ incoherence ☐ marked loose associations ☐ impoverished thought content ☐ marked illogical thinking ☐ bizarre, disorganized or catatonic behavior **Percentage of improvement of the acute event** _____%	8	4	0
Organic brain syndrome ☐ Altered mental function (with rapid onset and fluctuating clinical features) with impaired: ☐ orientation ☐ memory ☐ other intellectual function ☐ clouding of consciousness with reduced capacity to focus and inability to sustain attention to environment ☐ perceptual disturbance ☐ incoherent speech ☐ insomnia or daytime drowsiness ☐ increased or decreased psychomotor activity	8	**Organic brain syndrome** ☐ Altered mental function (with rapid onset and fluctuating clinical features) with impaired: ☐ orientation ☐ memory ☐ other intellectual function clinical features ☐ clouding of consciousness with reduced capacity to focus and inability to sustain attention to environment ☐ perceptual disturbance ☐ incoherent speech ☐ insomnia or daytime drowsiness ☐ increased or decreased psychomotor activity **Percentage of improvement of the acute event** _____%	8	4	0
Visual disturbance ☐ cytoid bodies ☐ retinal hemorrhage ☐ serous exudates in the choroid ☐ hemorrhage in the choroid ☐ optic neuritis	8	**Visual disturbance** ☐ cytoid bodies ☐ retinal hemorrhage ☐ serous exudates in the choroid ☐ hemorrhage in the choroid ☐ optic neuritis **Percentage of improvement of the retinal exam** _____%	8	4	0
Cranial nerve disorder Nerves involved _____ ☐ motor power _____ ☐ sensory deficit _____ ☐ pain as determined by patient on numerical scale of 1-10_____	8	**Cranial nerve disorder** Nerves involved _____ ☐ motor power _____ **Percentage of improvement of the acute event** _____% ☐ sensory deficit _____ **Percentage of improvement of the acute event** _____% ☐ **pain as determined by patient on numerical scale of 1-10**_____	8	4	0
Lupus headache ☐ pain as determined by patient on numerical scale of 1-10_____	8	**Lupus headache** ☐ **pain as determined by patient on numerical scale of 1-10**_____	8	4	0
CVA Clinical diagnosis:_____ Date of CVA (yyyy/mm/dd) _____ ☐ face ☐ upper extremities ☐ lower extremities ☐ motor power _____ ☐ sensory deficit location: _____	8	**CVA** Clinical diagnosis:_____ Date of CVA (yyyy/mm/dd) _____ ☐ face ☐ upper extremities ☐ lower extremities ☐ motor power _____ ☐ sensory deficit location: _____ **Percentage of improvement of the acute event** _____%	8	4	0
Vasculitis ☐ ulceration of _____ ☐ gangrene of _____ Body Surface Area _____% Number of lesions:_____ Size of biggest lesion: _____ ☐ periungual infarction # of involved digits _____ ☐ splinter hemorrhages # of involved digits _____ ☐ tender finger nodules # of involved digits _____	8	**Vasculitis** ☐ ulceration of _____ ☐ gangrene of _____ **Body Surface Area** _____**%** **Number of lesions:**_____ **Size of biggest lesion:** _____ ☐ periungual infarction **# of involved digits** _____ ☐ splinter hemorrhages **# of involved digits** _____ ☐ tender finger nodules **# of involved digits** _____	8	4	0

Table 3 Continued. Data retrieval form of SLEDAI-2K Responder Index-50 (SRI-50)©.

BASELINE VISIT	Score (Circle)	FOLLOW-UP VISIT	Score (Circle) Improvement		
			< 50%	≥ 50%	100%
Arthritis  Number of joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion) #.....	4	**Arthritis**  Number of joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion) #.....	4	2	0
Myositis Motor power ..... creatinine phosphokinase level..... or aldolase.....	4	**Myositis** Motor power ..... creatinine phosphokinase level..... or aldolase..... **Percentage of improvement in muscles power .....%**	4	2	0
Urinary casts Number of heme-granular casts ..... or red blood cells casts	4	**Urinary casts** Number of heme-granular casts ..... or red blood cells casts	4	2	0
Hematuria: Number of red blood cells/high power field.....	4	**Hematuria**: Number of red blood cells/high power field.....	4	2	0
Proteinuria : Level of proteinuria	4	**Proteinuria** Level of proteinuria	4	2	0
Pyuria: Number of white blood cells/high power field.....	4	**Pyuria:** Number of white blood cells/high power field	4	2	0
Rash ☐ head ☐ chest ☐ abdomen ☐ back ☐ legs ☐arms/hands ☐ mucous membrane Body Surface Area .....% Number of lesions:..... Size of biggest lesion: ..... Activity of most active skin lesion by color: ☐ absent ☐ pink, faint erythema ☐ red ☐ dark/purple/violaceous/crusted/hemorrhagic dyspigmentation, scarring and atrophy are not active lesions	2	**Rash** ☐ head ☐ chest ☐ abdomen ☐ back ☐ legs ☐ arms/hands ☐ mucous membrane **Body Surface Area .....% Number of lesions:..... Size of biggest lesion: ..... Activity of most active skin lesion by color:** ☐ absent☐ pink, faint erythema ☐ red ☐ dark/purple/violaceous/crusted/hemorrhagic dyspigmentation, scarring and atrophy are not active lesions	2	1	0
Alopecia ☐ patchy total scalp area involved: .....% number of lesions:..... size of biggest lesion: ..... ☐ diffuse alopecia as determined by patient on numerical scale of 1-10..... Activity of alopecia by color based on most active lesion: ☐ absent ☐ pink, faint erythema ☐ red ☐ dark/purple / violaceous/ crusted / hemorrhagic	2	**Alopecia** ☐ patchy **total scalp area involved: .....% number of lesions:..... size of biggest lesion: .....** ☐ **diffuse alopecia as determined by patient on numerical scale of 1-10..... Activity of alopecia by color based on most active lesion:** ☐ absent ☐ pink, faint erythema ☐ red ☐ dark/purple / violaceous/ crusted / hemorrhagic	2	1	0
Mucosal ulcers Number of ulcers per month	2	**Mucosal ulcers** Number of ulcers per month	2	1	0
Pleurisy ☐ pain as determined by patient on numerical scale of 1-10..... Amount of effusion if determined radiologically	2	**Pleurisy** ☐ **pain as determined by patient on numerical scale of 1-10..... Amount of effusion if determined radiologically .....**	2	1	0
Pericarditis ☐ pain as determined by patient on numerical scale of 1-10..... Amount of effusion if determined radiologically	2	**Pericarditis** ☐ **pain as determined by patient on numerical scale of 1-10..... Amount of effusion if determined radiologically .....**	2	1	0
Low complement C3 ..... C4	2	**Low complement** C3 ..... C4	2	1	0
Anti-DNA antibodies level.....	2	**Anti-DNA antibodies level**.....	2	1	0
Fever T ° C (mean)	1	**Fever** T ° C (mean)	1	0.5	0
Thrombocytopenia Platelet count	1	**Thrombocytopenia** Platelet count	1	0.5	0
Leucopenia WBC count	1	**Leucopenia** WBC count	1	0.5	0
TOTAL SCORE		**TOTAL SCORE**			

Numerical scale: 1 is minimal and 10 is most severe

use of the term flare/worsening in the physician's notes; (5) new diagnosis of SLE (new presentation, not just the accumulation of American College of Rheumatology criteria[21])[22]. "Same", defined as no change in disease activity in patients who did not qualify for the definitions of improved or worse.

Method and analysis. Descriptive statistics were used to describe the characteristics of the patients. We determined the mean change of SRI-50 scores (Δ SRI-50 = SLEDAI-2K 0 – SRI-50) and the mean change of SLEDAI-2K scores (Δ SLEDAI-2K = SLEDAI-2K 0 – SLEDAI-2K 1) among patients who improved, got worse, and remained unchanged as determined by the external physician.

External construct. The external construct was the LS. We further divided into 4 groups the group of patients who improved as determined by the external physician; that is, LS 4 (unchanged), LS 5 (mildly improved), LS 6 (moderately improved; ≥ 50%), and LS 7 (much improved; ≥ 50%). We determined the mean change of SRI-50 (Δ SRI-50) scores and mean change of SLEDAI-2K (Δ SLEDAI-2K) in each of the 4 groups. Spearman correlation coefficient was determined between Δ SRI-50 and Δ SLEDAI-2K, with LS 4, LS 5, LS 6, and LS 7. The paired t test was used to compare the mean Δ SRI-50 and the mean Δ SLEDAI-2K scores in patients with LS ≥ 6 to those with LS 4–5. We hypothesized that patients who had ≥ 50% improvement (LS ≥ 6–7) would be identified better by SRI-50 than by SLEDAI-2K, and the change in their SRI-50 scores would meet the definition of improvement by SLEDAI-2K (decrease > 3).

Written consent was obtained from all patients and the study was approved by the Institutional Review Board at the University of Toronto, Toronto Western Hospital.

RESULTS

Derivation of SRI-50 definitions, SRI-50 data retrieval form, and SRI-50 score

The SRI-50 definitions were developed as a 2-page document including 24 definitions for the descriptors of SLEDAI-2K to define ≥ 50% improvement (Table 2).

The SRI-50 data retrieval form is a 2-page document to standardize the recording of descriptors to allow the calculation of SRI-50 (Table 3). The assigned scores for the descriptors of SRI-50 were derived by dividing the score of the corresponding SLEDAI-2K descriptor by 2.

For the individual descriptors, separate approaches are utilized by both physician and patient to evaluate improvement between visits. The physician analyzes the results of physical findings and laboratory and diagnostic results (radiological, electrocardiogram, and others), all based on hard, well defined outcomes, to complete the SRI-50 data retrieval form (Table 1). For the descriptors, which are more subjective and require patient self-evaluation (namely cranial nerve disorder, headache, the pain of pleurisy and pericarditis, and diffuse alopecia), the SRI-50 data retrieval form records the patient self-evaluation based on a numerical scale ranging from 1 to 10 (1 is mild and 10 is most severe). For descriptors requiring a health professional's evaluation, e.g., ≥ 50% improvement in cognitive dysfunction, the percentage improvement discerned by the professional is recorded on the data retrieval form. The physician collects and records the patients' information on the SRI-50 data retrieval form (Table 3).

For the descriptors related to neurolupus, and more specifically psychosis and organic brain syndrome, we left it to the rheumatologist to determine if there is ≥ 50% improvement or not. Presumably the rheumatologist will confer/consult with other healthcare providers with expertise in this area, e.g., neuropsychologists or psychiatrists, to help judge percentage improvement. In trials looking specifically at these outcomes such expertise could be included in the design. As an example, in a trial of therapy for the treatment of acute cognitive dysfunction, evaluation by a neurocognitive expert would be included.

Practical applicability, administration, scoring

Administration. The SRI-50 data retrieval form is completed by the physician during the visit based on the history and clinical and laboratory findings. A complete history and physical examination are required in addition to the laboratory results related to the index. Similarly to SLEDAI-2K, for most patients it takes a couple of minutes to complete the form.

Scoring. The method of scoring is simple, cumulative, and intuitive as in the original SLEDAI-2K. In general, if required, one session of training is enough to become familiar with the definitions of SRI-50.

When a descriptor is recorded as present at the initial visit, one of 3 situations can follow: (1) the descriptor achieves complete remission at followup, in which case the score would be "0"; (2) the descriptor does not achieve a minimum of 50% improvement at followup, in which case the score would be identical to its corresponding SLEDAI-2K value; or (3) the descriptor improves by ≥ 50% (according to the SRI-50 definition) but has not achieved complete remission, in which case the score is evaluated as one-half the score that would be assigned for SLEDAI-2K. If a descriptor was not present at the initial visit, the value for SRI-50 at the followup visit will be the same as that for SLEDAI-2K. This process is repeated for each of the 24 descriptors. Finally, the SRI-50 score at followup is evaluated as the sum of the 24 individual descriptor scores.

SRI-50 score is evaluated at the followup visit and corresponds to the sum of each of the 24 descriptor scores found on the SRI-50 data retrieval form.

As recommended by the US Food and Drug Administration (FDA) in clinical trials, landmark analyses are important for comparing current patient scores versus scores recorded at their baseline visit. These landmark comparisons can be made at a series of intervals, e.g., at 2, 4, and 6 months (vs anchor visit), even though the primary outcome may be 6 months. Any deterioration in SRI-50 at 2 or 4 months would indicate a worsening in the original disease manifestation or the development of a new disease manifestation. Such occurrences could be secondary outcomes. In clinical practice, the physician is interested in how the patient is today compared to the last visit and here the comparison to the last visit may be appropriate.

Table 4. Characteristics of patients.

Characteristic	
Female/male, %	89.4/10.6
Ethnicity, %	
Caucasian	57.4
Black	16.3
Asian	9.9
Other	16.3
Age at diagnosis, yrs	29.1 ± 11.4
Age at 1st visit in study, yrs	44.5 ± 12.8
Disease duration at 1st visit in study, yrs	15.3 ± 11.2
Time between baseline and followup visits, mo	3.2 ± 1.4
SLEDAI-2K score at 1st visit in study	4.79 ± 4.67

Testing of concurrent construct validity

Between September 2009 and December 2009, of the 298 patients enrolled, 141 patients had followup visits and were studied further. The majority of the 141 patients were female (89.4%). The patients' ethnic distribution was Caucasian 57.4%, Black 16.3%, Asian 9.9%, and other 16.3%. The mean age at diagnosis of SLE was 29.1 ± 11.4 years and age at first visit in this study was 44.5 ± 12.8 years. Patient characteristics are presented in Table 4.

Change in SLEDAI-2K and SRI-50 scores in patients as determined by external physician. The external physician rated patients as follows: 14 patients were worse, 65 the same, and 62 improved. SRI-50 scores did not decrease significantly below their presenting SLEDAI-2K score in patients who remained stable or worsened. In patients who improved as determined by the external physician, the SRI-50 score decreased by a mean of 2.40 ± 3.11, while SLEDAI-2K scores decreased by 1.65 ± 2.91 (Table 5). This decrease in the score of SRI-50 reflects partial improvement in the descriptors that was not determined by SLEDAI-2K on followup visit.

Change in SLEDAI-2K and SRI-50 scores in patients who improved in association with the external construct. The correlation between the external construct, LS, was moderate with the SLEDAI-2K ($r_1 = 0.39$; $p = 0.02$) and with the SRI-50 ($r_2 = 0.48$; $p < 0.0001$). It is not surprising that SLEDAI-2K detected improvement when there was complete resolution of a feature, which could happen with LS improvement ≥ 6. Moreover, SLEDAI-2K scores decreased with LS 4–5 (0.69 ± 2.40) and to a greater extent with LS ≥ 6 (2.89 ± 3.09) ($p = 0.03$). However, SRI-50 scores decreased to a greater extent with both LS 4–5 (1.06 ± 2.48) and with LS ≥ 6 (4.15 ± 3.01) ($p < 0.0001$). Importantly, the decrease in SRI-50 scores compared to the decrease in SLEDAI-2K scores on followup visit in patients with LS ≥ 6 was statistically and clinically more significant, meeting the definition of improvement by SLEDAI-2K, with a reduction > 3 (Table 6).

DISCUSSION

In the development of SLEDAI and its updated version, SLEDAI-2K, investigators were focused on describing disease activity and documenting descriptors as present or absent[3,4,5]. In clinical trials and observational studies it is very important to identify improvement related to treatment between visits. The improvement need not be total resolution to suggest that a therapeutic agent is useful. Recognition that SLEDAI-2K and other disease activity measures adopted in clinical trials have limited ability to identify partial improvement led us to consider developing alternative measures for monitoring disease activity of lupus patients[23]. The development of a new measurement based on a simple known index is an important advance.

We describe development and initial validation of a novel clinical index measuring improvement of SLE disease activity between visits, the SRI-50. SLEDAI-2K is a reliable and valid index that has been adopted in clinical trials and observational studies[3,24]. Our goal was to modify SLEDAI-2K to allow it to record partial improvement in disease activity, which would be useful to detect response to treatment in both clinical trials and observational studies. A minimum 50% improvement was felt by clinicians to reflect a clinically important improvement. The SRI-50 comprises the same 24 descriptors and covers the 9 organ systems found in the original SLEDAI-2K. SRI-50 reflects disease activity over the previous 30 days. The SRI-50 data retrieval form, which standardizes the documentation of the descriptors, performed extremely well in all descriptors; this is especially relevant for multicenter studies that form the backbone of any therapeutic evaluation for SLE.

As a first effort toward validating SRI-50, we assessed its content validity, face validity, practical applicability including administration and scoring, and concurrent construct

Table 5. Statistical results in patients in whom disease activity changed.

Measure	Worse, n = 14	Same, n = 65	Improved, n = 62
SLEDAI-2K 0	4.43 ± 3.32	3.15 ± 4.16	6.58 ± 4.84
SLEDAI-2K 1	7.29 ± 4.55	2.97 ± 4.03	4.94 ± 4.47
SRI-50	7.21 ± 4.61	2.76 ± 3.86	4.18 ± 4.06
Δ SLEDAI-2K	2.86 ± 3.76	–0.18 ± 2.64	–1.65 ± 2.91
Δ SRI-50	2.79 ± 3.79	–0.39 ± 2.74	–2.40 ± 3.11

Δ SLEDAI-2K: (SLEDAI-2K 0) – (SLEDAI-2K 1). Δ SRI-50: (SLEDAI-2K 0) – (SRI-50).

Table 6. Change in SLEDAI-2K and SRI-50 scores in patients who improved in association with the external construct, the Likert scale (LS) score.

Likert Scale	Δ SLEDAI-2K	Δ SRI-50
LS 4, n = 15	–0.33 ± 1.99	–0.47 ± 2.07
LS 5, n = 20	–0.95 ± 2.68	–1.50 ± 2.72
LS 6, n = 20	–2.40 ± 2.60	–3.80 ± 2.95
LS 7, n = 7	–4.29 ± 4.07	–5.14 ± 3.18
r_1 and r_2	0.39	0.48
p	0.02	< 0.0001
Improvement (n = 62)		
LS 4–5	–0.69 ± 2.40	–1.06 ± 2.48
LS ≥ 6	–2.89 ± 3.09	–4.15 ± 3.01
t test	0.003	< 0.0001

LS 4: unchanged; LS 5: mildly improved; LS 6: moderately improved, i.e., ≥ 50%; LS7: much improved, i.e., ≥ 50%.

validity. Content and face validity are qualitative assessments of a measure that rely on understanding how the items or individual questions in a measure were derived. Since the SRI-50 is derived from the SLEDAI-2K, face and content validity related to selection of the 24 descriptors to study disease activity were assumed to be present[3,4]. Moreover, content validity and face validity of the SRI-50 definitions and the SRI-50 data retrieval form were confirmed according to the methodology adopted in the development of the SRI-50. The agreed-on descriptor definitions of the SRI-50 definitions and the SRI-50 data retrieval form were thoroughly revised as described in Materials and Methods.

The traditional way to validate a new measure is to determine its correlation with some other measure of the trait, ideally, a "gold standard," concurrent criterion validity. In the absence of a gold standard measure, correlation is conducted on the most commonly adopted measure in the field. In our initial validation we studied the concurrent construct validity of SRI-50 and the physician response assessment, as determined by LS, both obtained at the same time[25,26]. A moderate correlation (0.30–0.70) and preferably strong correlation (> 0.70) is desirable in this step[25,27,28]. We evaluated the performance of SRI-50 on 141 patients seen in our lupus clinic and determined its correlation with physician response assessment determined by LS. We showed that the SLEDAI-2K and SRI-50 scores on followup visit correlated with LS score ≥ 6. Importantly, the decreases in SRI-50 scores were clinically significant, meeting the accepted definition of improvement of a decrease in SLEDAI-2K of > 3, but this was not achieved with the SLEDAI-2K followup visit. Indeed, this reflected the ability of the SRI-50 to determine partial improvement between visits in patients who improved, while the SLEDAI-2K did not discern this improvement. This confirmed the SRI-50 concurrent construct validity.

In the early stage of the development of SLEDAI in 1985, the authors retained the 24 "most important" descriptors along with their corresponding weighted scores to constitute what we know today as SLEDAI. In the SRI-50, descriptors are scored as present, absent, or improved by ≥ 50%. Similar to SLEDAI-2K, the weighted scores of the descriptors in SRI-50 are not affected by their severity but are weighted by their status. A 50% improvement in certain severe features might not have a great influence on the score when compared to a 50% improvement in certain milder features. However, in a moderate to large size study, the effect of such instances is likely to be relatively small.

A number of new agents have been introduced and are in various phases of drug development in lupus; nevertheless, none have to date been approved by the FDA, and few achieved their primary outcomes in clinical trials. Although the results of these studies were disappointing, it would be premature to conclude that these therapeutic strategies cannot be effective in SLE. Several aspects of clinical design could have affected the outcomes of these trials, namely, inclusion criteria and difficulty ensuring the enrollment only of patients with active disease, the choice of primary outcomes, and use of concomitant drugs. More importantly, the lack of a robust responder index for global disease activity in SLE patients is a serious limitation when designing clinical trials. The use of the SRI-50 has the potential to overcome these problems.

In the initial validation of the SRI-50, we have used the data available at baseline and at one followup visit. We are currently analyzing our data on a larger sample size and multiple followup visits for each patient. This will allow us to evaluate the situations when comparing the scores to the baseline visit in contrast to last visit or the visit with worsening. Nevertheless, we recommend determining the score of the SRI-50 by using the baseline visit scores, whereas in a subgroup analysis, the visit that includes the worsening can be used.

Additional validation for the SRI-50 will be necessary. The minimal clinically important difference of the SRI-50 and responsiveness in clinical trials have yet to be determined. Studies are currently under way to evaluate these aspects. This validation of the SRI-50 enables it to be used as an outcome measure in clinical trials.

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