Indices to assess patients with systemic lupus erythematosus in clinical trials, long-term observational studies, and clinical care

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ABSTRACT

This review summarises most currently used indices to assess and monitor patients with systemic lupus erythematosus (SLE) in clinical trials, long-term observational studies, and clinical care. Six SLE disease activity indices include the British Isles Lupus Assessment Group Index (BILAG), European Consensus Lupus Activity Measurement (ECLAM), Systemic Lupus Activity Measure (SLAM), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Lupus Activity Index (LAI), and Systemic Lupus Erythematosus Activity Questionnaire (SLAQ). Three SLE responder indices include Responder Index for Lupus Erythematosus (RIFLE), SLE Responder Index (SRI), and BILAG Based Combined Lupus Assessment (BICLA). Three SLE damage indices include the Systemic Lupus International Collaborating Clinics/American College of Rheumatology-Damage Index (SLICC/ACE-DI), Lupus Damage Index Questionnaire (LDIQ), and Brief Index of Lupus Damage (BILD). The SLAQ, LDIQ and the BILD are patient self-report questionnaires, which appear to give similar information to physician-completed indices, but are pragmatically more easily completed as patients do almost all the work. Additional self-report indices which have been used to assess and monitor patients with in SLE include a generic general health short form 36 (SF36), a SLE-specific Lupus Patient Reported Outcome (LupusPRO), and a generic rheumatology index, Routine Assessment of Patient Index Data 3 (RAPID3). These activity, response, damage and patient self-report indices have been validated at different levels with no consensus about what it is the most appropriate for every setting. Sensitive and feasible assessment of SLE in clinical trials, observational studies, and busy clinical settings remains a challenge to the rheumatology community.

Introduction

Quantitative assessment of patients with systemic lupus erythematosus (SLE) presents many challenges. First, although many measures are useful in *groups* of patients, a single *gold standard* biomarker such as blood pressure or haemoglobin A1C to assess each *individual* patient is not available, leaving a need for a pooled index of multiple measures (1). Second, multisystem involvement presents complexities in measurement, as similar scores in different patients may result from involvement of different organs.Third, global estimates by the physician (DOCGL), which often serve as a measure to validate complex indices and compare patients, may differ among different physicians on the basis of clinical perspectives and experience (2). Fourth, it may be difficult to distinguish between disease manifestations resulting from reversible inflammation *versus* irreversible damage, which introduces uncertainty into accurate estimation of inflammatory activity.

Quantitative assessment in SLE is needed for optimal information to recognise improvement or worsening in clinical trials for analysing possible new therapies, and to guide optimal control of disease activity and prevent organ damage in usual care. Many measures which indicate high or persistent disease activity are associated with a higher accrual of damage, lower probability of later remission, and need for higher corticosteroid doses (3).

This review presents a summary of various indices used to measure disease activity, responsiveness, damage, and quality of life in patients with SLE in clinical trials, long-term observational studies, and clinical care. The reader is referred to other recent review articles for further details (4, 5).

Disease activity indexes

Six indices of SLE disease activity have been described: BILAG, ECLAM,

SLAM, SLEDAI, LAI, and SLAQ. Different aspects of validation have been explored in each of these indices (Table I) to be used in clinical trials and observational studies (5). The ECLAM, SLAM, SLEDAI, LAI, and SLAQ provide a single summary score for activity, while the BILAG provides assessment scales for individual organs and systems. Summary scores provide a single disease activity score to monitor individual patients from one visit to the next and to compare patient cohorts with different disease manifestations. However, overall summary scores are limited as the same score may be associated with different types of disease severity, *e.g.* multiple mild manifestations *versus* a single severe manifestation. Furthermore, improvement in one organ may be accompanied by worsening in another organ, while the summary score may remain unchanged, *e.g.* arthritis is resolved but skin is worse. By contrast, individual organ/system scores capture the disease variability, but are complex and limited to provide stratification of patients with different organ involvement.

British Isles Lupus Assessment Group (BILAG)

The British Isles lupus assessment group (BILAG) began to gather regularly in 1984, and reported an index to measure disease activity in patients with SLE in 1988 (6). An updated version of the BILAG has been published in 2005 in an attempt to improve the characteristics of this index (7) (Fig. 1).

The BILAG was developed by this group of experts based on physician's intent to treat. It evaluates specific manifestations over the previous four weeks in a total of 8 organs systems, 9 in the revised Index: constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal, and haematological (8). Activity in each organ system is scored as: A=most active disease; B=intermediate activity; C=mild, stable disease; D=previous involvement, currently inactive; E=no previous activity. The BILAG is correlated moderately with physician global estimate (rho = 0.43) and with patient global assessment (rho =0.50) (9).

The BILAG also is used to evaluate the occurrence of flares in patients with SLE. A severe flare is defined as a score of A, new appearance and a moderate flare is defined with a score of B, and a reoccurrence is defined with a score of D or E. Agreement between BILAG flare and intensification of treatment by the physician in routine care was seen in 92% of patients with a severe flare and 41% of patients with a moderate flare (10).

The BILAG can be calculated manually although there is a computerised method known as BLIPS (British Lupus Integrated Prospective System), which also includes demographic variables and the SLAM, SLEDAI, SLICC/ACR Damage Index and the SF-36 patient Health Questionnaire (11).

European Consensus Lupus Activity Measurement (ECLAM)

The ECLAM was described by a European Consensus Study group in 1992 (Fig. 2) (12). It was developed from the study of 704 actual SLE patients, selecting the clinical and laboratory measures better correlated with the

Table I. Quick guide for interpreting the results on aspects of validation.

Term	Aspects	Analysis technique
FEASIBILITY Measure of how beneficial or practical the instrument will be to a group of patients	Time required Clarity of elements (simple) Accepted by patients and users	Pilot Study (30 patients)
RELIABILITY Degree with which the instrument precisely measures without error. Reliable, precise and error-free (systematic error / bias and random error)	Internal consistency: assesses whether the items that measure a same attribute present homogeneity among them. It depends on the number of items and their correlation among them.	Cronbach's alpha (0-1): it is interpreted as a correlation coefficient
	Intra-rater reliability or test-retest: It measures the stability of the scores awarded by the same reviewer in the same subjects. Inter-rater reliability or measurement error: degree of agreement between 2 or more evaluators.	ICC (Intraclass Correlation Coefficient): quantitative Cohen kappa: qualitative Standard Error of Measurement (SEM), Minimum Detectable Change (MDC), Limits of Agreement (Bland-Altman plot)
VALIDITY The ability to measure that which it is designed to	Face validity: truthfully reflect what it is supposed to measure Content Validity: Representative sample of the items. Construct Validity: the degree to which a test measures what it claims, or purports, to be measuring	Experts' opinion about the relevance and compressibility of items Expert panel Structural: Factorial Analysis Test of Ho: correlations Cross-Cultural Validation
	Criterion Validity: the degree to which the scores of an instrument are an adequate reflection of "the truth" in the form of a *gold standard* (GS) or compared to an already validated instrument.	Continuous variables: correlations with the GS or ROC curves Dichotomous variables: Sensitivity and Specificity
RESPONSIVENESS	Reflects the ability of an instrument to detect change over time in the construct to be measured	Multiple statistical parameters have been proposed with no consensus about the best one; *e.g.* the standardised response mean (mean change score/SD change score)

BILAG2004 INDEX Centre: UCLH Date: PATIENT LABEL:

Only record items due to SLE Disease Activity & assessment refers to manifestations occurring in the last 4 weeks (compared with the previous 4 weeks).

♦♦TO BE USED WITH THE GLOSSARY♦♦

Scoring: ND Not Done
1 Improving
2 Same
3 Worse
4 New
Yes/No OR Value (where indicated)
□ Indicate if not due to SLE activity (default is 0 = not present)

CONSTITUTIONAL
1. Pyrexia – documented > 37.5°C ( )
2. Weight loss – unintentional >5% ( )
3. Lymphadenopathy/splenomegaly ( )
4. Anorexia ( )

MUCOCUTANEOUS
5. Skin eruption – severe ( )
6. Skin eruption – mild ( )
7. Angio-oedema – severe ( )
8. Angio-oedema – mild ( )
9. Mucosal ulceration – severe ( )
10. Mucosal ulceration – mild ( )
11. Panniculitis/Bullous lupus – severe ( )
12. Panniculitis/Bullous lupus – mild ( )
13. Major cutaneous vasculitis/thrombosis ( )
14. Digital infarcts or nodular vasculitis ( )
15. Alopecia – severe ( )
16. Alopecia – mild ( )
17. Peri-ungual erythema/chilblains ( )
18. Splinter haemorrhages ( )

NEUROPSYCHIATRIC
19. Aseptic meningitis ( )
20. Cerebral vasculitis ( )
21. Demyelinating syndrome ( )
22. Myelopathy ( )
23. Acute confusional state ( )
24. Psychosis ( )
25. Acute inflammatory demyelinating polyradiculoneuropathy ( )
26. Mononeuropathy (single/multiplex) ( )
27. Cranial neuropathy ( )
28. Plexopathy ( )
29. Polyneuropathy ( )
30. Seizure disorder ( )
31. Status epilepticus ( )
32. Cerebrovascular disease (not due to vasculitis) ( )
33. Cognitive dysfunction ( )
34. Movement disorder ( )
35. Autonomic disorder ( )
36. Cerebellar ataxia (isolated) ( )
37. Lupus headache – severe unremitting ( )
38. Headache from IC hypertension ( )

MUSCULOSKELETAL
39. Myositis – severe ( )
40. Myositis – mild ( )
41. Arthritis (severe) ( )
42. Arthritis (moderate)/Tendonitis/Tenosynovitis ( )
43. Arthritis (mild)/Arthralgia/Myalgia ( )

Weight (kg):	Serum Urea (mmol/l):
African ancestry: Yes/No	Serum Albumin (g/l):

VAS(Patient) 0----------10cm

BLOOD RESULTS: ESR DNA C3 C4 CR-P

CARDIORESPIRATORY
44. Myocarditis – mild ( )
45. Myocarditis/Endocarditis + Cardiac failure ( )
46. Arrhythmia ( )
47. New valvular dysfunction ( )
48. Pleurisy/Pericarditis ( )
49. Cardiac tamponade ( )
50. Pleural effusion with dyspnoea ( )
51. Pulmonary haemorrhage/vasculitis ( )
52. Interstitial alveolitis/pheumonitis ( )
53. Shrinking lung syndrome ( )
54. Aortitis ( )
55. Coronary vasculitis ( )

GASTROINTESTINAL
56. Lupus peritonitis ( )
57. Abdomial serositis or ascites ( )
58. Lupus enteritis/colitis ( )
59. Malabsorption ( )
60. Protein losing enteropathy ( )
61. Intestinal pseudo-obstruction ( )
62. Lupus hepatitis ( )
63. Acute lupus cholecystitis ( )
64. Acute lupus pancreatitis ( )

OPHTHALMIC
65.Orbital inflammation/myositis/proptosis ( )
66. Keratitis – severe ( )
67. Keratitis – mild ( )
68. Anterior uveitis ( )
69. Posterior uveitis/retinal vasculitis – severe ( )
70. Posterior uveitis/retinal vasculitis – mild ( )
71. Episcleritis ( )
72. Scleritis – severe ( )
73. Scleritis – mild ( )
74. Retinal/choroidal vaso-occlusive disease ( )
75. Isolated cotton-wool spots (cytoid bodies) ( )
76. Optic neuritis ( )
77. Anterior ischaemic optic neuropathy ( )

RENAL
78. Systolic blood pressure (mmHg) value ( )
79. Diastolic blood pressure (mmHg) value ( )
80. Accelerated hyptention Yes/No ( )
81. Urine dipstick protein (+=1. ++=2. +++=3) ( )
82. Urine albumin-creatinine ratio mg/mmol ( )
83. Urine protein-creatinine ratio mg/mmol ( )
84. 24 hour urine protein (g) value ( )
85. Nephrotic syndrome Yes/No ( )
86. Creatinine (plasma/serum) µmol/l ( )
87. GFR (calculated) ml/min/1.73 m² ( )
88. Active urinary sediment Yes/No ( )
89. Active nephritis Yes/No ( )

HAEMATOLOGICAL
90. Haemoglobin (g/dl) value ( )
91. Total white cell count (x 10^9/l) value ( )
92. Neutrophils (x 10^9/l) value ( )
93. Lymphocytes (x 10^9/l) value ( )
94. Platelets (x 10^9/l) value ( )
95. TTP ( )
96. Evidence of active haemolysis Yes/No ( )
97. Coombs' test positive (isolated) Yes/No ( )

VAS(Dr)0----------10cm

Fig. 1. British Isles Lupus Assessment Group Index 2004 version.

1. Generalized manifestations	Any of the following:	0.5
Fever	Documented basal morning temperature of 37.5°C not due to an infective process	
Fatigue	A subjective feeling of extraordinary tiredness	
2. Articular manifestations	Any of the following:	1
Arthritis	Non-erosive arthritis involving at least 2 peripheral joints (wrist, metacarpophalangeal or proximal, interphalangeal joints).	
Evolving arthalgia	New onset or worsening of specific localized pain without objective symptoms in at least two peripheral joints	
3a. Active muco-cutaneous manifestations	Any of the following:	0.5
Malar rash	Fixed erythema, flat or raised over the malar eminences, and tending to spare the naso-labial folds.	
Generalised rash	Amaculo-papular rash not induced by drugs, that may be located anywhere on the body, and that is not strictly dependent on sun exposure.	
Discoid rash	Erythmatosus, raised patches with adherent keratotic scaling and follicular plugging.	
Skin vasculitis	Including digital ulcers, purpura, urticaria, bullous lesions.	
Oral ulcers	Oral or naso-phayngeal ulcers, usually painless, observed by a physician.	
3b. Evolving mucocutanteous manifestations	If any of the above mucocutaneuous manifestations are new or have worsened since the last observation, add 1 point.	1
4. Myositis*	Confirmed by raised muscle enzymes and/or EMG examination and/or histology.	2
5. Pericarditis	Documented by ECC or rub or evidence of pericardial effusion on ultrasound.	1
6. Intestinal manifestations	Any of the following:	2
Intestinal vasculitis	Evidence of acute intestinal vasculitis.	
Sterile peritonitis	Evidence of abdominal effusion in the absence of infective processes.	
7. Pulmonary manifestations	Any of the following:	1
Pleurisy	Clinical or radiological evidence of pleural effusion in the absence of infective processes.	
Pneumonitis	Single or multiple lung opacities on chest X-ray thought to reflect active disease not due to an infective process.	
Ingravescent dyspnoea	Due to an evolving interstitial involvement.	
8. Evolving neuropsychiatric manifest.*	New appearance or worsening of any of the following:	2
Headache/migrane	Recently developed, persistent or recurrent/ Poorly responsive to the most commonly used drugs, but partially or totally responsive to corticosteroids.	
Seizures	Grand mal or petit mal seizures, Jacksonian fits, temporal lobe seizures, or choreic syndrome, in the absence of offending drugs or known metabolic derangements (e.g. uremia, ketoacidosis, or electrolyte imbalance).	
Stroke	Cerebral infarction or haemorrphage, instrumentally confirmed.	
Organic brain disease	Impairment of memory orientation, perception, and ability to calculate.	
Psychosis	Dissociative features in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis, or electrolye imbalance.	
9a. Renal manifestations*+	Any of the following:	0.5
Proteinuria	At least 500 mg/day.	
Urinary casts	Red cells, haemoglobin, granular, tubular, or mixed casts.	
Haematuria	Microscopic or macroscopic.	
Raised serum creatinine or reduced creatinine clearance		
9b. Evolving renal manifestations	If any of the above renal manifestations are new and have worsened since the last two observations, add 2 points.	
10. Haematologic features	Any of the following:	1
Non-haemolytic anaemia	A Coombs-negative normocytic hypochromic or normochromic anaemia without reticulocytosis.	
Haemolytic anaemia*	A Coombs-positive haemolytic anaemia, with reticulocytosis and elevated LDH, in the absence of offending drugs.	
Leukopenia (or lymphopenia)	Less than 3,500/mm^3 WBC (or 1,500/mm^3 lymphocytes) in the absence of offending drugs.	
Thromocytopenia	Less than 100,000/mm^3 in the absence of offending drugs.	
11. Erythrocyte sedimentation rate		
Raised ESR	>25 mm/h by Westergren or comparable methods, not due to other concomitant pathological process.	1
12a. Hypocomplementaemia	Reduced plasma level of any of the following:	1
C3	By radial immunodiffusion or laser nephelometer.	
CH50	By standardized haemolytic methods.	
12b. Evolving hypocomplementaemia	Significantly reduced level of any of the items mentioned above (plus C4) with respect to the last observation.	1
FINAL SCORE #		

*If this system (or manifestations) is the only involvement present from among items 1-10, add 2 more points. + Excluding patients with end-stage chronic renal disease. #If the final total score is not an integer number, round off to the lower integer for values <6 and to the higher integer for values >6.
If the final total score is >10, round off to 10.

Fig. 2. European Consensus Lupus Activity Measurement (ECLAM) Reproduced with developers' permission.

physician global assessment as a reference *gold standard*. ECLAM was also compared with other composite indices with a good correlation with SLAM, BILAG and SLEDAI (rho=0.72) (13), and these four indices also were correlated at similar levels with the physician global estimate.

The ECLAM includes 10 organ systems and two laboratory measures, ESR and serum complement, for a total of 33 items that are scored from 0.5 to 2; the overall score ranges from 0 to 15.5. The ECLAM can be used in retrospective studies, as a strong correlation (rho=0.87) has been found between the ECLAM calculated immediately *versus* calculated from data collected from a medical record (14). In addition, it can be calculated using a computerised system with excellent correlation with manual calculation (r=0.90–0.92) (15).

Systemic Lupus Activity Index (SLAM)

The SLAM was first published in 1986 (16) and revised as the SLAM-R to improve clarity and reproducibility. In 2001, the feasibility and construct validity of this new version was explored (17), and the correlation with physician global assessment was rho=0.87.

The SLAM-R evaluates specific manifestations in 9 organ systems and 7 laboratory measures; some items are scored 0–3, depending on severity, and others 0–1. Total scores range from 0–84, with a maximum laboratory score of 21 points. A score of 7 or more was associated with a change in treatment in 50% of patients.

The SLAM is regarded by some experts as less desirable than other indices, since it includes subjective measures such as fatigue and arthralgias. However, scores on these variables often reflect SLE activity (18). Training is needed in its use, particularly for multicenter studies (4).

Systemic Lupus Erythematosus Disease Activity Measure (SLEDAI)

The SLEDAI is a global index that was developed in Toronto in 1986 and described in detail by Bombardier and collaborators in 1992 (19). It was amended by the SELENA Group (Safety of Estrogen in Lupus Erythematosus National Assessment Group) during a study to evaluate the use of estrogen and progesterone in women (20), and it was later updated by Gladman *et al*. in 2002 as the SLEDAI-2K (21). In addition, a version was developed by Mexican researchers that excluded some laboratory tests to reduce cost (22). Therefore, currently there are 4 versions: SLEDAI, SELENA-SLEDAI, SLEDAI-2K, and MEX-SLEDAI.

The SLEDAI is a global index that evaluates disease activity over the previous 10 days and includes 24 items collecting specific manifestations in 9 organ systems: neurological, musculoskeletal, renal, mucocutaneous, general, heart, respiratory, vascular, and haematological. The maximum score is 105.

The SLEDAI appears sensitive to change in disease activity over time (23), although when SLAM-R and SLEDAI were compared for responsiveness, both were responsive to changes in SLE disease activity important to physicians, but only SLAM-R was responsive to changes important to patients. These differences likely result from inclusion of SLE manifestations found in a patient history in SLAM-R (24).

The SLEDAI-2K scores persistent and not merely emerging rash, alopecia, oral ulcers, and proteinuria, and it presents a high correlation *versus* the original SLEDAI (rho=0.97) (25, 26). Both versions predict mortality in a similar way (21). The SLEDAI-2K collects disease aspects as present or absent and may not reflect partial improvement, which limits its use in clinical trials. A 50% response rate (SRI-50) for improvement in SLEDAI was reported in 2011 (27).

SLEDAI scores above 5 are associated with a probability of initiating therapy higher than 50% (4). Activity categories have been defined on the basis of SLEDAI scores: no activity (SLEDAI= 0), mild activity (SLEDAI 1-5), moderate activity (SLEDAI 6-10), high activity (SLEDAI 11-19), very high activity (SLEDAI ≥20) (28).

UCSF/JHU Lupus Activity Index (LAI)

The LAI is a global activity score to assess activity over the previous 2 weeks, and is completed by the physician in 1 minute (29-31). The LAI includes the evaluation of 4 organs neurological, renal, pulmonary, and hematology, as well as 3 laboratory measures - anti-double stranded DNA antibodies, proteinuria and complement levels. It also includes a physician global estimate from 0 to 3 on a visual analogue scale, and the possibile need for treatment with immunosuppressive agents.

Changes in the LAI of 0.26 points are observed at the time of a flare in disease activity, defined as a change ≥1 in the physician global estimate of activity. The LAI showed greater inter-observer reliability than SLEDAI, (32) and is much simpler to calculate.

Systemic Lupus Activity questionnaire (SLAQ)

The SLAQ is the only index of SLE activity designed as a self-report questionnaire for use in epidemiological studies and large cohorts of patients (33). The SLAQ was developed in a clinical cohort of 93 patients and found to have a good correlation with the SLAM excluding laboratory data (r=0.62, p=<0.001) (34). The SLAQ was further validated in a large observational cohort showing a good correlation with the physician global estimate assessment (rho=0.73) and the patient self report SF-36 (rho=0.66) (34).

Responder indices for SLE

Responder indices have been developed to improve sensitivity to detect a response to therapy. One responder Index for Lupus Erythematosus (RIFLE) is a newly-developed index (35), while 2 responder indices, the SLE Responder Index (SRI) (36) and BILAG Based Combined Lupus Assessment (BICLA) (37) include scores from available indices.

Responder Index for Lupus Erythematosus (RIFLE)

The RIFLE is a consensus instrument that was developed for an anti-CD40 ligand clinical trial to improve lupus nephritis. It was first published as an abstract in 2000 (35) and has subsequently been used in clinical trials and evaluated with simulated patients based

Table II. Variables included in BILAG, ECLAM, SLAM, SLAQ and SLEDAI.

	Items included in each index	BILAG	ECLAM	SLAM	SLAQ	SLEDAI
GENERAL	Pyrexia/Fever (documented)	✓	✓	✓	✓	✓
	Weight loss – unintentional >5%	✓		✓	✓	
	Lymphadenopathy (Swollen glands neck)/Splenomegaly	✓		✓	✓	
	Fatigue/Malaise/Lethargy	✓	✓	✓	✓	
	Anorexia/Nausea/Vomiting	✓				
MUCOCUTANEOUS	Maculopapular eruption/ Generalised rash	✓	✓		✓	✓
	Active discoid lesions/rash	✓	✓	✓	✓	
	Alopecia/Bald patches on scalp or clumps of hair on pillow	✓		✓	✓	✓
	Panniculitis/Angioedema	✓				
	Mucosal ulcers (oral or nasal)/sores in mouth or nose	✓	✓	✓	✓	✓
	Malar erythema/rash on cheeks	✓	✓	✓	✓	
	Subcutaneous nodules/Perniotic skin lesions	✓				
	Swollen fingers/Sclerodactyly	✓				
	Calcinosis/Telangiectasia	✓				
	Rash or feeling sick after going out in the sun			✓	✓	
NEUROLOGICAL	Deteriorating level of consciousness/Coma	✓		✓		
	Acute psychosis, delirium, confusion	✓	✓	✓		✓
	Seizures	✓	✓	✓	✓	✓
	Stroke or stroke syndrome/CVA	✓	✓	✓	✓	✓
	Aseptic meningitis/ Ascending or transverse myelitis	✓				
	Mononeuritis multiplex/ Numbness or tingling in arms or legs	✓		✓	✓	
	Peripheral or cranial neuropathy	✓				✓
	Disc swelling/cytoid bodies (eye)/Retinal haemorrhages or Episcleritis	✓		✓		
	chorea/ Cerebellar ataxia	✓				
	Headache/migranous severe, episodic or unremitting/Unusual headache	✓	✓	✓	✓	✓
	Organic depressive illness/Personality disorder/Cognitive deficit/Forgetfulness	✓		✓	✓	
	Papillitis/ organic brain syndrome including Pseudotumour cerebri	✓	✓	✓		✓
MS	Definite myositis (Bohan & Peter)	✓		✓		
	Severe Polyarthritis with loss of function/Arthritis/Joint swelling	✓	✓		✓	✓
	Tendonitis/Contractures/Deformity	✓				
	Mild chronic myositis	✓	✓			✓
	Arthralgia/Joint pain	✓	✓	✓	✓	
	Myalgia/Muscle pain/Weakness	✓		✓	✓	
	Aseptic necrosis	✓				
CARDIOPULMONAR	Pleuropericardial Pain/Chest pain	✓			✓	
	Dyspnea/Shortness of breath	✓			✓	
	Cardiac failure/ Cardiac dysrhythmias (Tachycardia >100 in absence of fever)	✓				
	Friction Rub/Effusion (pericardial or pleural)/Pleurisy	✓	✓	✓		✓
	Progressive x-ray changes – Lung fields OR Heart size	✓				
	ECG Evidence of Pericarditis or Myocarditis	✓	✓	✓		✓
	Pulmonary function fall of 20%	✓				
	Cytohistological evidence of inflammatory lung disease/Pneumonitis	✓	✓	✓		
VASCULAR	Cutaneous vasculitis/ Dark blue or purple spots you could feel on skin	✓	✓	✓	✓	✓
	Major abdominal crisis due to vasculitis/Abdominal pain/Stomach pain	✓		✓		✓
	Thromboembolism excluding strokes (first episode or recurrent)	✓				
	Raynaud's/Fingers or toes turning white in the cold	✓		✓	✓	
	Livido Reticularis/Superficial phlebitis	✓				
RENAL	Hypertension (Systolic/Diastolic Blood Pressure values)	✓		✓		
	Urinary Protein (urine dipstick)/Proteinuria or Nephrotic Syndrome	✓	✓			✓
	Serum creatinine or Creatinine clearance	✓	✓	✓		
	Active urinary sediment/Urinary casts/ Pyuria/Haematuria	✓	✓	✓		✓
	Histological evidence of active nephritis – within 3 months	✓				
LABORATORY	Haemoglobin/Haematocrit/ Non-haemolytic Anaemia	✓	✓	✓		
	Total White cell count/ Leukopenia/Lymphopenia	✓	✓	✓		✓
	Platelets/Thrombocytopenia	✓	✓	✓		✓
	Evidence of active haemolysis/ Coombs test positive/ Haemolytic anaemia	✓	✓			
	Erythrocye sedimentation rate	✓	✓			
	Hypocomplementaemia		✓			✓
	Increased DNA binding					✓

on medical records (38, 39). For each renal manifestation in each organ system, definitions are provided for "not present," "partial response," "complete response," or "worsening."

SLE Responder Index (SRI). This composite index combines the SELENA-SLEDAI and BILAG indices and the physician global assessment. A responder is defined as (i) 4 point or greater improvement of SELENA SLEDAI score from baseline; (ii) no worsening of the physician global estimate; (iii) no new BILAG A or two BILAG B scores. This index is driven primarily by the SELENA-SLEDAI, and was used as the primary end point in the phase 2 and 3 trials with belimumab (BLISS-52 and BLISS-76) (40, 41).

BILAG Based Combined Lupus Assessment (BICLA). The BICLA combines BILAG, SLEDAI and physician global assessment with requirement for a response as (i) improvement of BILAG A to BILAG B/C/D or of BILAG B to C/D, (ii) no worsening: no single new BILAG A or two new BILAG B scores and no worsening of baseline SLEDAI total score and no worsening in physician global estimate (<10% worsening relative to baseline); (iii) no treatment failure. This index is driven primarily by the BILAG, and has been used in the phase 2 (EMBLEM) and phase 3 epratuzumab studies (37).

Comparison between disease activity indices

Although each of these composite indices has been developed to evaluate disease activity in SLE, each includes different items to evaluate organ systems and different laboratory measures (Table II). All this composite measures have greater or lesser degree of validation, and none has been accepted as the single one or standard measure of choice. The selection of the most appropriate disease activity assessment tool will critically depend on the context in which it is used, and the question to be answered. Knowing the measurement properties for each index may help an investigator or clinician to decide which one would be more useful in a specific scenario (Table III).

The first study that compared different SLE indices in 1989 (16) indicated correlations between the SLAM, SLEDAI, and BILAG which ranged from r=0.81-0.97, and correlations of each with a physician global estimate on a visual analog scale of r=0.76-0.96. Evaluation of the sensitivity to change of the 3 indices according to 3 visits of 8 patients evaluated by 8 rheumatologists, indicated correlations of 0.35 to 0.61 (23). In this study, only the SLEDAI differentiated between visits. In a later study, each of the 3 indices were sensitive to change, using as external criteria the evaluation of change on a 5-point Likert scale by the physician global estimate, with slightly better results for SLAM (42).

In another study comparing indices the SLAM captured patient perceptions more than SLEDAI, LAI, BILAG and ECLAM, as might be expected (43). The correlation between change in each index and physician global estimate was in descending order: LAI r=0.75; ECLAM r=0.65; BILAG r=0.61; SLAM r=0.54 and the SLEDAI r=0.52 (all p<0,0001). LAI showed greatest and SLEDAI least sensitivity to change *versus* physician global assessment (43).

The BILAG and SLEDAI were found comparable for sensitivity to change using as reference the physician's global estimate on a 7-point Likert scale (2). In this study, 20 SLE experts evaluated eighty paper patients. Considerable variability was seen in the assessments of this group of doctors, even among those with extensive experience with SLE.

Table III. Summary of validity aspects for each disease activity and damage instrument.

	Feasibility (Minutes to complete)	Internal Consistency (α Cronbach)	Test-retest	Construct Validity	Responsiveness
Measures of disease activity					
BILAG	5-20	α=0.35	ICC=0.48	+++	SRM=0.68
ECLAM	5-10	-	-	+++	SRM=0.75
SLAM	10-15	-	ANOVA=0.78	+++	SRM=0.62
SLEDAI	10-20	-	ICC=0.79	+++	SRM=0.48
LAI	1	-	ICC=0.81	+++	-
SLAQ	Self-reported	α=0.87	-	+++	SRM=0.12
Measures of damage					
SDI	15	α=0.41	ICC=0.55	+++	-
LDIQ	Self-reported	-	-	+++	-
BILD	Self-reported	-	-	+++	-

Indices to assess damage in SLE

Three indices have been developed to assess damage in SLE, the SLIICC/ACE-DI (SDI), LDIQ and BILD.

Systemic Lupus International Collaborating Clinics/American College of Rheumatology-Damage Index: SLICC/ACR-DI (SDI)

The SLIICC/ACE-DI (SDI) was developed in 1996 by an international collaboration (Group SLICC) and adopted by the American College of Rheumatology (ACR) (44). This index includes 42 items in 12 domains, with a maximum score of 46. Each item is rated as present or absent, with the possibility to rate it a 2 or 3 in the case of recurring events, such as a stroke.

The SDI scores irreversible damage regardless of cause. The definition of damage is an irreversible change in an organ or system that has occurred since the onset of SLE and is present for at least 6 months. The SDI shows good reliability when completed by a different physician, based on retrospective medical history of the patient (45). SDI values increase with disease progression similarly in patients from different countries, and predict mortality in patients with SLE (46, 47).

Lupus Damage Index Questionnaire (LDIQ)

The LDIQ was reported in 2010 as a patient self-report questionnaire concerning irreversible damage, based on the SDI. The LDIQ includes 56 items, incorporating each domain from the

SDI in a self-report format. The correlation between SDI and LDIQ is r=0.48 (48, 49).

Brief Index of Lupus Damage (BILD)
The BILD is a shorter version self-report damage questionnaire, including only 28 items (50). It is correlated with SDI (r=0.54). Patients who had higher values for the BILD were older, with longer disease duration and higher activity.

Using disease activity indices in randomised clinical trials
Although no SLE activity index indices were designed specifically for use in randomised controlled clinical trials, one of these indices usually provides the primary outcome in trials to evaluate candidate new therapies for SLE. The American College of Rheumatology (ACR) Ad Hoc Committee on SLE Response Criteria conducted a study aimed at defining the minimally important clinical difference for 6 existing disease activity indices in SLE: BILAG, ECLAM, SLAM-R, SLEDAI, SELENA-SLEDAI, and RIFLE, with results as follows: BILAG worsening +8, improvement -7; ECLAM: worsening +4, improvement -3; SLAM-R: worsening +6, improvement -4; SLEDAI: worsening +8, improvement –6; SELENA-SLEDAI: worsening +8, improvement -7; RIFLE: worsening +3, improvement -4 (38).
Some SLE experts have suggested that the failure of some important clinical trials in SLE may be attributed in part to the insensitivity of available indices to detect a response to therapy. This consideration has led to development of response indices such as the RIFLE(35), SRI (36) and the BICLA (37). Nonetheless, concerns remain about the sensitivity to change of available quantitative measures in SLE clinical trials.

Using disease activity indices in observational studies
One of the activity indices described above has been included in almost all reported observational studies of SLE patients over the last 2 decades. A PubMed search with key words "SLE" and "disease activity" identified 497 records, of which 28 were longitudinal observational studies in the English language. A validated disease activity score was applied to 26 of 28 study cohorts, including SLEDAI-2K or SELENA-SLEDAI in 22 reports, ECLAM in 2, and SLAM and SLAQ in one report, respectively. The 2 reports that did not include any activity index were a study only of renal involvement and a 20-year retrospective study with substantial data loss (51, 52). This literature snapshot appears to reflect current practice in specialised SLE clinics in the United States and Europe.

Using disease activity indices in routine clinical care
EULAR recommendations for monitoring disease activity in SLE patients in routine clinical care suggest inclusion of a validated index (53). However, SLE indices are not feasible in busy clinical settings and rarely are incorporated into most routine care. Indeed, often the only quantitative clinical data in the medical records of many SLE patients are laboratory tests, which are limited as the rationale for the indices. This is unfortunate, as most information for clinical decisions in SLE and most rheumatic diseases is derived from the patient history and physical examination, as documented in a survey concerning rheumatoid arthritis (54). A patient self-report questionnaire records components of the patient history as quantitative data rather than traditional narrative descriptions, to better compare visits over time in individual patients and clinical status in different patients.
Patient questionnaires have become more prominent in rheumatology in general over the last 3 decades. They present pragmatic advantages of cost effectiveness, as the patient does much of the work, which can save time for the doctor, particularly when a questionnaire is reviewed by the doctor before engaging in conversation with the patient (pragmatic advantages are reduced considerably when this practice is not followed). Patient questionnaires also present scientific advantages, as the patient perspective is recognised to be of great importance in the prognosis of rheumatic diseases and results of therapy. As noted, the SLAQ, LDIQ, and BILD are SLE specific self-report questionnaires to assess activity or damage. Patient self-report questionnaires are sensitive to quality of life beyond strict disease activity and damage. In patients with SLE (and most chronic diseases), a high correlation is seen between disease activity and quality of life. In clinical trials, responses of measures of disease activity to therapy are almost always accompanied by similar improvements in measures of quality of life. In general, 3 types of questionnaires have been studied in SLE, including generic general health patient questionnaires, such as the prototype short form 36 or SF 36 (55), generic rheumatology questionnaires such as a multidimensional health assessment questionnaire/ Routine Assessment of Patient Index Data (MDHAQ/RAPID3),(56) and an SLE disease-specific questionnaire such as (LupusPRO) (57). Each of these 3 self-report questionnaires requires 5–10 minutes for patients to complete and is feasible in busy clinical settings.

SF-36
The SF-36 is a generic survey instrument initially designed to assess quality of life in general population studies rather than clinical settings (55). The SF-36 includes 8 domains: 4 to assess physical health - physical function, role-physical, bodily pain, and general health; 4 to assess mental health - vitality, social function, role-emotional, and mental health. A major advantage of the SF 36 is that it can be used to compare quality of life in all diseases, although only a few such comparisons have been made for rheumatic diseases, including SLE (58). One limitation is that the SF 36 cannot be scored without a computer program, so it is of lesser pragmatic value in a busy clinical setting.

MDHAQ/RAPID3
The MDHAQ includes RAPID3, a simple index, which is informative in patients with all rheumatic diseases. One advantage of MDHAQ/RAPID3 is that it can be presented to all patients by a clinic receptionist to be completed in the waiting area before seeing the rheumatologist, without a need to present different questionnaires to patients with

different diagnoses, which generally is not feasible in busy clinical settings.

In one study, RAPID3 scores were correlated significantly with SLAQ scores in 50 SLE patients, and were significantly higher in patients with SLEDAI, BILAG, and SLAM scores above median levels in patients scored by the rheumatologist as having few noninflammatory symptoms. RAPID3 and SLAQ both were elevated significantly in 16 patients scored by the physician as having many noninflammatory symptoms (generally fibromyalgia) (59). In another study, RAPID3 scores fell similarly with clinical improvement in SLE patients as in patients with rheumatoid arthritis or ankylosing spondylitis over a 2-month period, and therefore appear sensitive to change in clinical status (60). Collection of MDHAQ/RAPID3 patient self-report scores before the clinical encounter scores in no way excludes a clinician from collection of SLE specific indices, although that is not commonly accomplished in routine care.

Lupus PRO

LupusPRO is a patient reported quality of life questionnaire (57) developed specifically for SLE patients. Development of LupusPRO included feedback from SLE patients of varying gender, ethnicity and race concerning possible effects of SLE or its treatment on their daily lives. Cognitive interviews were conducted to develop the item pool, as patients did not find all the health concerns pertinent to SLE well represented in generic patient reported tools.

LupusPRO was designed conceptually to include both health and non-health related quality of life constructs (HRQOL and non-HRQOL). Forty-three items identify the following domains within each of these two constructs: HRQOL – lupus symptoms, lupus medication, physical health, emotional health, pain, vitality, procreation, cognition, and body image; non-HRQOL – desires-goals, coping, social support, and satisfaction with care. Domain scores range from 0–100, and an overall total HRQOL and non-HRQOL score can also be obtained. LupusPRO has been shown to have reliability and validity (57). It is responsive to change in health status, and maintains its measurement properties in varied language and cultural settings (61).

Conclusions

Many indices to assess disease activity in SLE have been developed; all the available indices have been validated over time, although all appear limited to varying degrees, to provide optimal sensitivity to change in clinical status. Most SLE-specific indices are used only in clinical trials and observational studies in centers which specialise in studies of SLE patients, but not in usual care. Therefore, significant limitations exist to monitoring clinical care quantitatively. Quantitative monitoring in routine care may be most pragmatically and accurately accomplished using patient self-report questionnaires that are completed by patients in 5–10 minutes, and do not interfere with work flow in busy clinic settings.

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