Outcome Measures To Be Used in Clinical Trials in Systemic Lupus Erythematosus

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ABSTRACT. The optimal outcome measures to be employed in clinical trials of systemic lupus erythematosus (SLE) have yet to be determined. Useful instruments should assess disease outcome in terms of all organ system involvement, as well as measures important to the patient. This article reviews those outcome measures that have been utilized in cohort studies in SLE, as well as their limited use in randomized clinical trials (RCT). Six disease activity measures have been developed: British Isles Lupus Assessment Group Scale (BILAG), European Consensus Lupus Activity Measure (ECLAM), Lupus Activity Index (LAI), National Institutes of Health SLE Index Score (SIS), Systemic Lupus Activity Measure (SLAM), and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). They have been validated in cohort studies as reflecting change in disease activity, and against each other. RCT utilizing SLAM, SLEDAI, BILAG, ECLAM, SIS, SLAM, SLEDAI are ongoing. It is recommended that the disease activity index of choice be selected; but simultaneous computer generation of multiple indices will facilitate comparisons across therapeutic interventions. A damage index has been developed and validated as the Systemic Lupus International Cooperating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index or SDI. In several cohort studies it has been shown sensitive to change over time, and to reflect cumulative disease activity. There is no health status or disability instrument specific to SLE. The Medical Outcomes Survey (SF-20) captures health status/health related quality of life (HRQOL) better than the Health Assessment Questionnaire (HAQ) in patients with SLE, but does not adequately reflect fatigue. The SF-36 does assess fatigue, and correlates closely with the SF-20. These data indicate that any individual measure of clinical response to a therapeutic intervention in SLE may reflect only a portion of what might be termed the "true outcome." Based on this work, the way is now paved to attempt to develop consensus on the important domains to be measured in clinical trials in SLE, the most appropriate instruments to use and the minimal clinically important differences in their results. (J Rheumatol 1999;26:490–7)

Key Indexing Terms:

OUTCOME MEASURES   SYSTEMIC LUPUS ERYTHEMATOSUS   CLINICAL TRIALS

The optimal outcome measures to be employed in clinical trials of systemic lupus erythematosus (SLE) have yet to be determined. Patient populations are heterogeneous, the disease course difficult to predict. In contrast to many other autoimmune processes, SLE is characterized both by flares and complete remissions. Although improvement in the face of active disease manifestations may be difficult to define, descriptions of remission are usually agreed upon. A National Institutes of Health (NIH) sponsored consensus conference in September 1993 discussed which outcome measures should be used in clinical trials of SLE. Participants recommended inclusion of a disease activity score, a damage index, and a measure of patient perceived health status, disability, and health related quality of life (HRQOL).

Further discussions during the meeting emphasized the importance of including patient preferences in these assessment instruments, and disease-specific functional measures, as well as generic measures of health status/HRQOL. It was agreed that consensus on a definition of disease "flares" would be useful, to add as a secondary outcome measure, as would definitions of clinically important improvement in disease activity, stabilization of organ system damage, and operational criteria for defining "steroid sparing."

Clinical Endpoints: Use in Clinical Trials

Studies by Balow, Austin and colleagues of the National Institute of Diabetes, Digestive and Kidney Diseases have

explored the use of cytotoxic agents in combination with corticosteroids in SLE nephritis. In this population there was a well defined endpoint of renal failure or endstage renal disease (ESRD). Only when followup extended beyond 5 years were differences in the rate of ESRD evident between therapies. Regimens that included either cyclophosphamide or azathioprine plus prednisone were superior to those of prednisone, methylprednisolone, or azathioprine alone[1–5]. However, these conclusions remain controversial because patient numbers were small at the later time points, and outcome was assessed only in items of ESRD. The renal system is the most objective and therefore easiest to study. The challenge remains to validate instruments that can assess disease outcome in terms of all organ system involvement as well as utilizing measures important to the individual patient.

Clinical Endpoints: Disease Activity Measures

Although consensus does not exist as to which one is preferable, 6 disease activity measures have been validated as reflecting change in disease activity compared to physician global assessment and changes in treatment, and against each other: British Isles Lupus Assessment Group Scale (BILAG), European Consensus Lupus Activity Measure (ECLAM), Lupus Activity Index (LAI), National Institutes of Health SLE Index Score (SIS), Systemic Lupus Activity Measure (SLAM), and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[6–17]. Table 1 summarizes the differences between the 6 indices[18].

Work by Petri, et al, Gladman, et al, and the Systemic Lupus International Cooperating Clinics (SLICC) group have shown the LAI, SLEDAI, SLAM, and BILAG to be sensitive to change in disease activity over time in cohort studies[19–23]. Others have demonstrated the feasibility of use of the SLEDAI by less experienced clinicians and in non-English speaking countries[24,25].

Ward, et al compared the relative validity and sensitivity to change of 5 indices: BILAG, ECLAM, LAI, SLAM, and SLEDAI, in a prospective longitudinal study of 22 patients with SLE. Patients were examined, and indices scored every 2 weeks for up to 40 weeks. Changes over time in each disease activity index correlated with the other indices (0.44–0.73) and with changes in physician global assessment (0.51–0.71)[26].

Bombardieri, et al, and the European League of Associations for Rheumatology Standing Committee on International Clinical Studies including Therapeutic Trials have developed a computerized clinical chart for disease activity in SLE[27]. It allows entry of data for a given patient at 2 observation points and then calculates scores for 5 indices: BILAG, ECLAM, SIS, SLAM, and SLEDAI. It is available free of charge for personal but not commercial use.

Currently, the BILAG, ECLAM, SIS, SLAM, and SLEDAI are being used in clinical trials of a variety of agents. A newer version of the SLAM, the SLAM-R, omits scoring for pneumonitis and truncates several scales[28]. A modified SELENA SLEDAI version has also been developed for a NIH sponsored multicenter study of estrogen/progesterone hormone use in women with SLE[29]. It changes the scoring for rash, alopecia, and mucosal ulcers from "new or recurrent" to "ongoing" and redefines symptoms for pleurisy and pericarditis as "classic and severe."

With the exception of nephritis, few controlled clinical trials have been performed — or published — in SLE. Outcome measures have traditionally included objective measures of renal or hematologic disease, such as thrombocytopenia. The SIS and SLEDAI have been utilized in placebo randomized controlled trials (RCT)[30,31]. Currently, clinical trials employing SLAM, SLEDAI, BILAG, and ECLAM are under way, but data are not yet available. Other than the NIH experience with treatment of lupus nephritis, only 8 RCT have been published in SLE. Four studied plasmapheresis: 2 were negative, one equivocal, and one remains under way[32–35]. A negative report of the use of levamisole was published in 1981[36]. Another trial sponsored by the Cooperative Clinics for the Systematic Study of Rheumatic Diseases compared hydroxychloroquine (HCQ) to placebo for the arthropathy of SLE and evaluated patient assessed joint counts[37]. The Canadian cooperative study of withdrawal of HCQ therapy utilized a preliminary version of the SLEDAI score to evaluate disease activity, but not as a validated outcome measure[38]. The most recent trials, comparing dehydroepiandrosterone to placebo for its steroid sparing effects in patients with mild to moderate SLE, utilized the SLEDAI. Benefit over placebo was observed by this outcome measure as well as patient and physician global assessments and concomitant steroid therapy[39].

Clinical Endpoints: Damage Index

Survival has progressively improved in SLE and now exceeds 95 and 90%, respectively, in patients with 5 and 10 years cumulative disease[40,41]. Longterm outcomes are therefore best defined in terms of irreversible damage to involved organ systems as well as disability and/or loss of health related quality of life (HRQOL), as assessed by the patient.

A damage index was proposed in 1985 and has been developed and validated by the SLICC group, as the Systemic Lupus International Collaborating Clinics/ American College of Rheumatology (SLICC/ACR) Damage Index or SDI[42–45]. It is assessed independently of current disease activity, treatment, or disability. Specific damage variables in 12 organ systems have been defined, and are scored regardless of cause, whether related to SLE, its treatment, or intercurrent illness. To avoid changes that may be due to active inflammation, items are scored only if they have been present for at least 6 months. Since irreversible organ system manifestations are not expected to change rapidly over time, yearly assessment is appropriate. In addi-

Table 1. Comparison of 6 SLE disease activity indices.

	BILAG	ECLAM	LAI	SIS	SLAM	SLEDAI
Where developed	United Kingdom	EU Concerted	UCSF Hopkins	NIH	Boston	Toronto
Development and basis of index	Physician intention-to-treat categorized by organ system	Statistical model based on 704 patients, 29 centers, 14 countries	Clinicians; signs, symptoms, serologies	Clinicians; signs, symptoms, serologies	Clinicians; disease severity as defined by ARA	Delphi: consensus by physician and statistician panel
No. of pages	1 scoring + glossary	1	1	1	3	1
Score	Categories A-E (0–72)	0–10 (max 17.5)	0–3	0-52	0–86 (SLAM-R 81)	0–105
Concomitant steroids weighted?	Yes	No	Yes	No	No	No
Fatigue items	Yes	Yes	Yes	Yes	Yes	No
Weighted	No	Yes	Yes	Yes	Yes	Yes
Laboratory variables	Yes	Yes	Yes	Yes	Yes	Yes
Complement levels	No	Yes	Yes	Yes	No	Yes
Anti-dsDNA	No	No	Yes	Yes	No	Yes
VAS	No	No	Yes	Yes (scored)	Yes (omitted)	No
Time frame considered	Previous month = "new"	1–3 months	2 weeks	2 days	Previous month	10 days or previous month

ARA: American Rheumatism Association; BILAG: British Isles Lupus Assessment Group; ECLAM: European Consensus Lupus Activity Measure; LAI: Lupus Activity Index; SIS: SLE Index Score; SLAM: Systemic Lupus Activity Measure; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

tion, the SDI can be used to stratify patients entered into a clinical trial.

In a cohort of 156 patients with SLE followed over 3 years, Bootsma, *et al* assessed the validity, reliability, and responsiveness of the SDI[46]. In 64 consecutive patients treated, SLAM, SLEDAI, and BILAG were assessed every 3 months, SDI at entry and end of study. Change in SDI was related to cumulative values of SLAM, SLEDAI, and doses of prednisone, and cumulative values of only the renal and hematologic items of the BILAG. They concluded that the SDI was sensitive to change over time, reflected cumulative disease activity, and was feasible to use in clinical trials.

Patient Assessments: Disability, Health Status, Health Related Quality of Life

Outcome in clinical trials is usually defined in terms of mortality and morbidity. Rheumatologists speak of outcomes in terms of death, organ damage, and disability. Disability includes multiple features: physical disability, physical discomfort, psychological discomfort (distress), and psychosocial dysfunction as well as the economic impact of disease. Drug effects (toxicity) must also be assessed. With regard to health status or disability instruments in SLE, most published studies do not address SLE as a distinct disorder, and no instrument has been modified to

be specific to SLE. In contrast to patients with rheumatoid arthritis (RA), patients with SLE have concerns less over pain and loss of mobility and more over fatigue, inability to plan ahead, and appearance.

Hochberg, *et al* administered the Health Assessment Questionnaire (HAQ) to 106 patients with SLE, 50% of whom were married and/or working; 20% were not taking prednisone; 10% were receiving cytotoxic medications[47]. Significant correlations between disability and pain, disability and global assessment, and pain and global assessment were observed. They sampled another 84 patients with SLE and found no correlation between the HAQ and disease activity as measured by the SLEDAI, indicating that health status measures a different domain than disease activity[48]. Callahan, Pincus, and colleagues administered the shortened self-report or modified HAQ (MHAQ) to patients with SLE as one of 5 rheumatic disorders assessed[49,50]. Significant correlations were noted between education status (> high school vs < high school) and disability, dissatisfaction, pain, and global assessment not dissimilar to their work in patients with RA. Milligan, *et al* assessed disability as defined by the HAQ in 120 patients with SLE treated at Case Western Reserve and the Cleveland Clinic[51]. When stratified according to active versus inactive disease, less disability was observed in those with inactive disease.

Krupp, *et al* (1979) developed a 9 item scale for fatigue, the Krupp Fatigue Severity Scale (KFSS), and a more complete fatigue questionnaire[52–54]. In comparing patients with SLE and multiple sclerosis (MS) to healthy controls, they found that the items contributing to fatigue in patients with SLE were different from those in MS, and were not predominantly due to psychologic stress.

Burkhardt, *et al* studied HRQOL in 50 women with SLE and 60 age matched women with RA, using a Swedish version of the Quality of Life Scale (QOLS-S), the Arthritis Impact Measurement Scale (AIMS), a visual analog scale for pain, and a patient version of the SLAM. Patients with SLE focused on fatigue and inability to plan ahead, whereas patients with RA reported issues of mobility[56]. They concluded that the QOLS-S was a reliable and valid measure of HRQOL in SLE. Moderate correlations to the AIMS social, psychological, and global impact scores and patient SLAM supported the hypothesis that it measured a domain distinct from health status and disease activity[56].

Petri, *et al* have studied the HAQ, the KFSS, the Center for Epidemiology Studies Depression Scale (CES-D), and the Rand Medical Outcomes Survey Short Form-20 (SF-20) in their cohort of patients at Johns Hopkins[57,58]. In physical function, patients with SLE differed from controls on all 6 questions in the SF-20 and in the HAQ; in mental health, in all 5 SF-20 questions and 17/20 in the CES-D; in fatigue, for all 9 KFSS questions. Forty-three percent of patients with SLE reported good or better health versus 87% of controls; 61% reported limited work ability versus 6% of controls.

They concluded the following: (1) disability in SLE is global, encompassing all domains of health status; (2) fatigue and depression are markedly increased in SLE versus controls, are quantifiable, and represent important facets of disability in SLE; and (3) damage is not associated with health status.

Studies by other members of the SLICC group showed that the SF-20 captured health status/HRQOL better than the HAQ in patients with SLE, but did not adequately reflect fatigue[59,60]. The SF-36 includes components measuring fatigue, energy, and vitality, and remains as easy for the patient to complete as the SF-20[61,62]. In a preliminary group of 10 patients (Goldsmith, *et al*) and a series of 150 patients with SLE (Gordon, *et al*) the SF-36 was shown to correlate closely with an amended version of the SF-20 (SF-20+), which includes a specific question on fatigue. At the 1995 SLICC Workshop, however, it was decided that the SF-36 should be the measure of choice in SLE. A generic instrument, it would facilitate comparisons to other patient groups, as there are substantial normative data (albeit principally in Caucasian populations) as well as international acceptance of its use in a variety of diseases.

Dobkin, *et al* studied a cohort of 44 patients with SLE, and showed that they perceived their physical health to be quite poor. The global physical health scale scores of the SF-36 were strikingly lower than for healthy women, and lower even than for those with serious medical problems (diabetes, coronary artery disease)[63]. The SELENA trial reported baseline values in all scales of the SF-36 to be low, compared to US norms for women[64]. Postal questionnaires administered to 82 patients with SLE, 82 with RA, and 74 controls in Norway showed that SF-36 scores in the SLE and RA groups were significantly ($p < 0.01$) lower than for controls[65]. Patients with SLE had less pain and disability than patients with RA, but mean MHAQ score was 1.3 compared to 1.1 in the control population.

Gordon, *et al* administered the SF-36 prospectively to 96 patients at 0, 3, and 6 months and showed that SF-36 scores were better in patients with BILAG scores < 4 (indicative of inactive disease) than in those with active disease (BILAG 4–8 and > 8)[66]. Over time, when disease activity decreased, SF-36 scores for physical function, pain, and health perception increased significantly. The SF-36 has also been utilized in several recent clinical trials in SLE, but the data are not yet available. It thus appears that the SF-36 has validity and discrimination and may feasibly be used in longitudinal observational studies and clinical trials in SLE.

Fatigue is an important component of SLE, whether due to the underlying disease or associated fibromyalgia. Fatigue and fibromyalgia may contribute to the health status/HRQOL assessment in SLE[67]. The SLAM-R asks the physician to rate only fatigue they ascribe to the underlying SLE. When Mak, *et al* assessed 81 patients with SLE by SLEDAI, SLAM-R, SLICC, KFSS, and SF-36, they found

a moderate correlation between fatigue and SLAM-R, which was absent once the fatigue question was removed from the SLAM-R[68]. There was no correlation between fatigue and damage, but a strong correlation between fatigue and low scores in all domains of the SF-36. Whether due to active disease or fibromyalgia, it may be important to stratify enrolment of patients with SLE with fatigue and other potential co-morbidities across treatment groups in clinical trials.

Patient and Physician Global Assessments

Patient and physical global assessments have typically been employed in clinical trials of potential therapeutic agents in SLE. Physician global assessments are included as part of the LAI and SLAM, but frequently are used on a stand-alone basis. Patients' assessments of disease activity and/or global health often differ from physicians' evaluations, which are made in the context of measures of disease activity and damage. Wekking showed that patients' perceptions of illness severity were consistently associated with psychosocial stresses, but that no significant relationship was present between patients' perceptions of illness severity and physician related SLE symptoms[69]. Aranow, *et al* repeatedly asked patients and physicians to rate SLE disease activity categorically: remission, stable active, mild/moderate flare, or severe flare; and to indicate disease activity again by visual analog scale[70]. Best agreement occurred when patients believed they had active disease, or the physician considered the SLE to be in remission. Overall agreement was only 51%.

In considering outcomes important to the patient, it appears appropriate to include a patient global assessment of disease activity in clinical trials in SLE.

Responder Analyses

A responder index in SLE would integrate several relatively independent measures of outcome into a single number that would define a patient as either a responder or nonresponder. There needs to be further discussion of the potential place for such a responder index in clinical trials of SLE. There has been increasing consensus on the utility of responder analyses in RA clinical trials (e.g., ACR 20% and DAS), but the issues in SLE require further examination.

Arguments for such an index include:

• The importance of establishing the minimal clinically important difference (MCID) across different components so that clinicians and policymakers can interpret the results. Using a responder index would allow decision analysis and facilitate the use of economic contribution models, where a decision for each "branch" requires the patients to be classified as a responder or nonresponder. Furthermore, presenting results on a per-patient basis makes it easier to present information to patients so they may make informed decisions about treatment choices.

• Unless all investigators can be persuaded to use the same instruments, a responder index that reflects the equivalent MCID across instruments would allow evaluation of conventional and experimental treatments across heterogeneous SLE disease populations.

• Facilitation of comparisons of experimental therapies across disease populations.

• Ease of use and reporting.

There are a number of biostatistical issues that must be addressed before a responder index will be accepted. Empiric data are needed to ensure that the index does not lose statistical power, thus losing the ability to discriminate between placebo and active agents. There are theoretical arguments for responder analyses to both lose power (by transforming results from continuous scales to a categorical outcome of responder/nonresponder) or gain power (by removing the need for adjustments for multiple comparisons; by minimizing ceiling and floor issues that may prevent responses in all variables). If, as in RA, the components of a responder index vary sufficiently independently of each other, in fact power is gained, and sample sizes are decreased[71]. These issues need to be specifically examined in SLE trials.

Liang and Fortin argue for the use of a responder index in SLE clinical trials, based on a definition employing a mathematical formula to evaluate changes in the SLAM and number of organ systems involved[72]. This is a useful proposal, but omits outcomes assessed by the patient, which may reflect disability, health status, and/or HRQOL.

Four recently published observational series have documented relatively weak correlations between disease activity measures, cumulative damage, and health status/HRQOL in SLE. Gladman, *et al* asked 105 clinic patients to complete the SF-20+ during their visit, when SLEDAI and SDI were assessed[73]. There were no correlations between the SLEDAI score and SDI damage index, nor between the SDI and the SF-20+, and statistically significant but clinically insignificant correlations between the SLEDAI and the social functioning and health perception scales of the SF-20. Stoll and colleagues assessed BILAG, SDI, and SF-20 with 2 additional questions (SF-20+) in 141 clinic patients[74]. Weak but significant relationships between the SDI and BILAG components assessing cardiovascular, pulmonary, peripheral vascular/vasculitis, and musculoskeletal items were noted, but not with other organ system manifestations. A similar correlation between the physical function scale of the SF-20+ and musculoskeletal disease was observed, without association with the psychological and social scales.

A subsequent study compared the SF-36 to the SF-20+, BILAG, and SDI in a cross sectional sample of 150 patients with SLE attending 2 specialist clinics in London and Birmingham, UK, between November 1994 and April 1995[75]. SF-36 items correlated significantly with the SF-

20+; the more comprehensive questions of the SF-36 were answered as completely as the shorter questionnaire. Again, (both) SF-20+ and SF-36 reflected that patients with SLE have a significantly lower HRQOL for all domains except "emotional role limitations," when compared to the "normal adults of working age not reporting a longstanding illness." A weak association with the BILAG score was again observed, which correlated more closely than age, SDI, or disease duration. More important, patients with increasing levels of disease activity reflected more impairment in most domains of the SF-36, with the exception of "emotional role limitations" and "general health status change." Fortin, *et al* studied 96 patients with SLE and assessed SLEDAI, SLAM-R, SDI, HAQ, and SF-36 monthly for 4 to 6 months[76]. Within-patient increases in SLE activity over time correlated significantly with simultaneous lowering of SF-36 "physical function," as well as the other 7 scales. In cross sectional analyses, SLAM-R correlated with several aspects of general health measured by SF-36 and HAQ disability index; SLEDAI did not.

Together, these observations support the complementary value of assessing 3 domains in clinical trials or observational studies in SLE: disease activity, damage, and health status/HRQOL; and the potential use of instruments measuring these domains in a composite responder index. Because these domains are not highly correlated it can be expected that taken together, statistical power would be increased and thus sample sizes would decrease.

Many investigators have significantly improved our understanding of the discrepancies between disease activity measures, measures of damage, psychological measures, and patient reported health status/HRQOL. These data indicate that any individual measure of clinical response to a therapeutic intervention in SLE may reflect only a portion of what might be termed the "true outcome." Based on this work, the way is now open to develop consensus on the important domains to be measured, the most appropriate instruments to use, and the minimal clinically important difference in their results. These instruments should include measures of disease activity and damage and patient self-assessment of health status/HRQOL including psychological well being. They may also incorporate patient and/or physician global assessments, unless already included as components of one or more of the other measures employed.

As there is good correlation between each of the individual disease activity measures, it can be assumed (but would require testing to confirm) that each of the measures validated to date could serve as a measure of disease activity. The reliability and validity of a composite responder index across different subsets of SLE will also require investigation and proof. Based on the work discussed above, this should be an achievable goal.

To date there have been few RCT in SLE, but they will be needed to expand our therapeutic approaches to this disease. With new biologic and pharmaceutical agents available, the time is ripe to develop improved assessment tools for clinicians interested in performing clinical trials in SLE and for the patients themselves. This was a topic for discussion at the Outcome Measures in Rheumatology Clinical Trials IV[77].

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