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REVIEW

Endpoints: consensus recommendations from OMERACT IV

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The goal of the 'Outcome Measures in Rheumatology' (OMERACT) process is to select domains and/or outcome measures for clinical trials in each defined disease category according to truth, discrimination and feasibility. OMERACT IV, held in Cancun, Mexico, April 1998, included the module 'Systemic Lupus Erythematosus (SLE)', designed to define a preliminary core set of outcome domains for randomized controlled trials and longitudinal observational studies (LOS). Although specific measures to be used in clinical trials of SLE have yet to be determined, both randomized controlled trials and longitudinal observation studies groups recommended that outcome be assessed in terms of disease activity and damage in all organ systems involved, as well as by health related quality of life, meaningful to patients, and adverse events. These recommendations were ratified by the majority of participants. In a heterogeneous patient population such as SLE, it is recognized that any individual measure of clinical response may reflect only a portion of what might be termed the 'true outcome'. A responder index could integrate such relatively independent measures of outcome into a single assessment, potentially increasing statistical power and decreasing sample size. Results from randomized controlled trials currently underway assessing these outcome domains are eagerly awaited, and are expected to rapidly advance the field.
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Introduction

The first conference on 'Outcome Measures in Rheumatoid Arthritis Clinical Trials' (OMERACT) was held in Maastricht, The Netherlands in 1992. Three consensus conferences have followed (1994–98), and a fourth is planned (2000).[1,2] The title has been changed to 'Outcome Measures in Rheumatology' to reflect inclusion of clinical trials in osteoarthritis, osteoporosis, ankylongitudinal observation studies on spondylitis and systemic lupus erythematosus.[3] Following each biyearly meeting, topics are proposed, and the organizing committee polls opinion leaders and experts in the field regarding their interest in the topics and applicability to clinical trials. Specific topic 'modules' and module committees are then organized. They are charged to develop data driven reviews of currently available methodology, to propose an agenda and select domains of outcome. These domains and applicable measures to assess their outcome are presented to all attendees at the conference. Small group discussions follow the plenary presentations to facilitate discussion and expression of preferences. Consensus evolves through anonymous polling in small group sessions and electronic voting in plenary sessions of the entire participant audience. Votes are then presented to the final plenary session for discussion and ratification and/or decision regarding formulation of a research agenda. The emphasis is to select domains and/or outcome measures for clinical trials in each defined disease category according to truth, discrimination and feasibility, based on guidelines originally proposed by Tugwell and Bombardier.[4] OMERACT IV,

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held in Cancun, Mexico, in April 1998, included a module on Systemic Lupus Erythematosus (SLE).

Background: outcome measures used in clinical trials in SLE

With the exception of nephritis, few controlled clinical trials have been performed in SLE (or published). Outcome measures have traditionally included objective measures of renal or hematologic disease, such as thrombocytopenia. Studies performed at the National Institutes of Health, Institute of Diabetes, Digestive and Kidney Diseases (NIH, NIDDK) compared the use of cytotoxic agents in SLE nephritis, using the well defined endpoint of renal failure or end stage renal disease.[5–9] Only when follow-up extended beyond five years were differences in the rate of end stage renal disease evident between therapies. However, these conclusions remain controversial because patient numbers were small at the later time points and outcome was assessed only in terms of end stage renal disease. The hydroxychloroquine withdrawal trial was the first to assess outcome in terms of multiorgan system involvement in SLE.[10] The challenge remains to validate instruments which can assess disease outcome in terms of all organ system involvement as well as to utilize measures of outcomes important to the individual patient.

An NIH sponsored consensus conference in September 1993 discussed which outcome measures should be used in clinical trials of SLE. Participants recommended inclusion of the following:

- a disease activity score,
- a damage index,
- a patient assessed measure of health status, disability, and health related quality of life.

Disease activity indices

Although there is no consensus as to which one is preferable, six disease activity measures have been validated compared to physician global assessment and change in treatment decisions, 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).[11–22] The SIS and SLEDAI have been utilized in randomized placebo controlled trials.[23,24] Currently, clinical trials employing SLAM, SLEDAI, BILAG and ECLAM are ongoing, but data regarding their use are not yet available. A newer version of the SLAM, the SLAM-R, omits scoring for pneumonitis and truncates several scales.[25] A modified SELENA SLEDAI version has also been developed for a NIH sponsored multicenter study of estrogen/progesterone hormone use in women with SLE, and is described elsewhere in this issue.[26]

The European League of Associations of Rheumatology (EULAR) Standing Committee on International Clinical Studies including Therapeutic Trials (ESCISIT) has developed a computerized clinical chart for disease activity in SLE.[27] Data for a given patient is entered at two observation points and scores for five indices are then calculated: BILAG, ECLAM, SIS, SLAM and SLEDAI. It is available free of charge for personal, but not commercial, use.

Damage index

As survival has progressively improved in SLE, long term outcomes are better defined in terms of irreversible damage to involved organ systems as well as by disability and/or longitudinal observation studies of health related quality of life.

A damage index was proposed in 1985 and has been developed and validated by the SLICC group, as the SLICC/ACR Damage Index or SDI.[28–31] Specific 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 which may reverse when disease activity improves, items are scored only if present for at least 6 months. Yearly assessment is appropriate, or at the initiation and completion of a clinical trial, and the SDI can be used to stratify patients at entry into a protocol.

Health related quality of life measures

In comparison to patients with rheumatoid arthritis (RA), patients with SLE have less concerns over pain and longitudinal observation studies of mobility, and moreover fatigue, inability to plan ahead and appearance. In terms of disability and health related quality of life, most published studies have not addressed SLE as a distinct disorder; and no instrument has been modified to be specific to SLE.

Hochberg *et al* administered the Health Assessment Questionnaire (HAQ) to SLE patients, and showed significant correlations between disability, pain and patient global assessments, but that health status

measures a different domain than disease activity.[32,33] Burckhardt *et al* studied 50 women with SLE and 50 age-matched women with RA in Sweden. Patients with SLE focused on fatigue and inability to plan ahead whereas patients with RA reported issues of mobility.[34] Again, health related quality of life appeared distinct from disease activity.[35]

Petri *et al* administered the HAQ, the Center for Epidemiologic Studies Depression Scale (CES-D) and the Rand Medical Outcomes Survey Short Form-20 (SF-20) in their patient cohort.[36,37] SLE patients differed from controls in physical functioning, in mental health as well as in questions regarding depression. Compared with 87% of controls, only 43% of SLE patients reported good or better health; 61% reported limited work ability *vs* 6% of controls. They concluded that disability in SLE encompases all domains of health related quality of life; that fatigue and depression represent important aspects of disability in SLE and that damage is not associated with health related quality of life. Further work by other members of the SLICC group demonstrated that the SF-20 captured health related quality of life better than the HAQ in SLE patients, but did not adequately reflect fatigue.[38,39] Because the SF-36 includes questions measuring fatigue, energy and vitality, and remains as easy to complete as the SF-20, it was decided at the 1995 SLICC workshop that the SF-36 should be the measure of choice in SLE.[40,41] As it is a generic instrument, translated and validated into other languages and cultures, its use may facilitate comparisons with other patient populations.

Although the SF-36 has been utilized in several recent clinical trials in SLE, data regarding its validity in randomized controlled trials are not yet available. Published results from cohort studies in SLE indicate it to have truth and discrimination. Several studies have reported low baseline values in all domains of the SF-36 compared with US norms for women.[42–44] 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).[45] Over time, when disease activity decreased, SF-36 scores for physical function, pain and health perception increased significantly.

Fatigue and fibromyalgia may contribute to the assessment of health related quality of life in SLE.[46] When Mak *et al* assessed 81 SLE patients by SLEDAI, SLAM-R, SLICC 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.[47] 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, in clinical trials it may be important to stratify enrollment of SLE patients with fatigue across treatment groups.

Four recently published observational series have demonstrated that disease activity measures, cumulative damage and health related quality of life measure different domains of outcome in patients with SLE. Stoll *et al*, assessed BILAG, SDI and SF-20 with two additional questions (SF-20+) in 141 clinic patients and reported weak correlations between SDI and BILAG components.[48] Gladman *et al* showed no correlation between SLEDAI score and SDI; nor between SDI and the SF-20+.[49] A subsequent study by Stoll *et al* compared SF-36 to SF-20+, BILAG and SDI in a cross-sectional sample of 150 patients with SLE.[50] SF-36 items correlated significantly with the SF-20+; both indicated that patients with SLE have a significantly lower health related quality of life in all domains except 'emotional role limitations' and patients with increasing levels of disease activity reported more impairment. Fortin *et al* assessed SLEDAI, SLAM-R, SDI, HAQ, and SF-36 monthly for 4–6 months in 96 SLE patients.[51] Within-patient increases in disease activity over time correlated significantly with simultaneous lower domains of SF-36.

Patient and physician global assessments

Physician global assessments are included as part of the LAI and SLAM, but frequently are used on a stand-alone basis. Patients' assessment of disease activity and/or global health often differ from physicians' evaluations. Wekking showed that patients' perception of illness severity was consistently related to psychosocial stresses and poorly related to physician rated SLE symptoms.[52] Aranow *et al* repeatedly asked patients and physicians to rate SLE disease activity categorically and by visual analog scale.[53] Overall agreement between patients and physicians was only 51%, with best agreement when patients thought they had active disease, or the physician considered the SLE to be in remission.

Materials and methods

Development of consensus

OMERACT IV, held in Cancun, Mexico, in April 1998, included a module on SLE. A discussion document was prepared by members of the OMERACT SLE Steering Committee, reviewing outcome measures

utilized in published cohort studies in SLE, as well as their limited use in randomized controlled trials.[54]

The SLE Steering Committee presented the information discussed above regarding the development and use of disease activity measures, SDI and measures of health related quality of life in SLE. A list of 21 domains for discussion was presented and the committee recommended the following be included in SLE clinical trials: disease activity, damage, health related quality of life and, consistent with previous OMERACT initiatives, adverse events and economic costs (Figure 1).[55] Participants were assigned to one of six discussion groups, three to define core outcome domains for randomized controlled trials, and three for longitudinal observational studies in SLE. The groups were asked independently to judge the items listed, add additional domains deemed important, and define those items which should be included in a core set for randomized controlled trials or longitudinal observation studies in SLE. To facilitate nominal group technique, after much discussion, each member was asked to anonymously rank their choice of domains by assigning a total of 100 points in order of preference. All member votes were then tallied and divided by total votes to rank domains by mean scores within each group. Then votes from the randomized controlled trials and longitudinal observation studies groups, respectively, were tallied and meaned to derive overall ranking.

Results

The randomized controlled trials discussion groups recommended that disease activity, health related quality of life, adverse events and damage be included as core outcome domains, in that order of preference. This was presented to the plenary session of more than 60 participants who, using electronic ballots, ratified this recommendation by a vote of 85% yes, 13% no and 2% abstaining.

The longitudinal observation studies discussion groups recommended that disease activity, damage, health related quality of life and adverse events be included, assigning more importance to damage than the randomized controlled trials group; health related quality of life was ranked equally important in both randomized controlled trials and longitudinal observation studies groups. This recommendation was presented to the plenary session and ratified by a vote of 83% yes, 15% no and 2% abstaining.

Other domains were considered important by the groups but were not included for a variety of reasons. It was felt that economic costs were important, but that the measurement instruments required further refinement and should not be recommended for all trials. Measurement of disability was considered to require further research, but would also be included to at least some degree in a health related quality of life measure. Similarly, global assessments and fatigue were considered redundant as they would be included in measures of health related quality of life or disease activity scores. Fibromyalgia was reported to occur variably in different geographic regions, and that further research regarding cultural, social and racial differences was necessary. It was agreed that the following domains be included on the research agenda, for future work: economic costs, serologies not currently included in the disease activity indices, fatigue, physical disability and psychosocial measures.

—domains selected as necessary for RCTs and LOS may overlap; even be identical;
—domains may vary by the duration of trials (RCTs: ≤ 12 *vs* > 12 months; LOS: ≤ 5 *vs* > 5 y)

Suggested as a minimum by the SLE Steering Committee:
- Disease activity
- Damage
- Health status/HRQOL
- Consistent with previous OMERACT initiatives should also include:
  - economic costs including health utilities
  - adverse events

Domains to be considered:
- Death
- Disability
- Disease severity, as distinct from disease activity and damage
- Fatigue
- Fibromyalgia
- Global assessment by patient
- Global assessment by physician
- Hypertension
- Psychosocial measures
- Serologies
- Working status

Figure 1 Domains to be considered for inclusion in RCTs or LOS of SLE.

Discussion

It was recognized by all participants that much progress has occurred regarding outcome assessment in SLE. However, the majority of the work has been conducted in cohort or longitudinal observational studies, thereby limiting the validation of currently available outcome measures. Nonetheless, an increasing number of randomized controlled trials are being conducted in SLE, in indications other than nephritis, and their results can be expected to advance the field considerably in the next several years.

Because of the existing limitations regarding the validation of current outcome measures in SLE, the OMERACT SLE Steering Committee elected to emphasize discussion and ratification regarding

appropriate domains to be assessed in randomized controlled trials and longitudinal observation studies instead of specific outcome measures. In a heterogeneous patient population such as SLE, it is recognized that any individual measure of clinical response in SLE may reflect only a portion of what might be termed the 'true outcome'. A responder index could integrate such relatively independent measures of outcome into a single assessment which would define a patient as either a responder or non-responder. Arguments for such an index include:

- Use of a responder index would allow decision analysis and facilitate the use of economic contribution models, where a decision for each 'branch' requires the patient to be classified as a responder or non-responder. Presenting results on a 'per patient' basis makes it easier to discuss with patients and other care-givers 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 equivalent minimum clinically important differences (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.

Because changes within these domains are not highly correlated it can be expected that, taken together, statistical power would be increased and sample sizes would thus decrease.

Subsequent to the OMERACT IV meeting held in April 1998, the FDA Arthritis Advisory Panel held an open meeting in February 1999 to discuss outcome measures in SLE clinical trials, with a plan to draft guidelines for the development of new products for the treatment of SLE. It is expected that the SLE OMERACT module will be reconvened when more information regarding the use of these instruments in randomized controlled trials and longitudinal observation studies in SLE become available in the public domain. Results from randomized controlled trials currently underway are expected to rapidly advance this field.

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