Editorial

# Measuring Disease Activity in Systemic Lupus: Progress and Problems

There are a number of exciting new drugs in development for the treatment of systemic lupus erythematosus (SLE). However, serious issues have arisen in the design and interpretation of early, multicenter clinical trials for these agents, in particular the tendency for these studies to demonstrate high placebo effects[1-3]. One problem is that instruments designed to measure disease activity do not automatically lend themselves to the kind of "before and after" analysis required in a drug study.

The SLE Disease Activity Index (SLEDAI) is an index that measures disease activity by weighting the importance of each organ system involved. This instrument has been shown to be reliable and reproducible when used by various investigators, and sensitive to change in a patient's condition[4-10]. However, it does not measure worsening of an already existing sign or symptom, nor does it detect partial improvement if some degree of residual symptom remains. Both of these limits might contribute to narrowing the gap between the observed effects of placebo treatment and that of a potentially useful medication. The SLEDAI also does not account for subjective symptoms such as fatigue, dysphoria, arthralgia, or myalgia, which might genuinely reflect lupus activity, and may be of high importance to patients[9,10]. However, separate, quality of life instruments can be used for that purpose.

The revised Systemic Lupus Activity Measure (SLAM-R) has also been fully validated as generally reliable in measuring lupus activity and sensitive to change[9-12]. It seems to be more effective than the SLEDAI in measuring either partial improvement or worsening of pre-existing lupus signs and symptoms, but, unlike the SLEDAI, it gives almost equal weight to mild and serious organ manifestations. This can be a major problem in some clinical situations. For example there might be only a one point difference in final scores on the SLAM-R between a person with florid central nervous system lupus who improves and a person with moderate fatigue who improves. The first might have required an effective medication, the second might occur with placebo treatment. Further, the inclusion of subjective symptoms in the SLAM could induce serious artifact, depending on the care with which the instrument is scored. It would be possible to score 7-8 points on the SLAM for symptoms that are not attributable to lupus and are common among middle aged people. Although physicians are supposed to score only those symptoms (including patient-reported symptoms) that are due to SLE, it is sometimes extremely difficult to distinguish reactive complaints from mild lupus flare manifestations. It is also difficult to ensure consistency in the scoring of subjective complaints in multicenter clinical trials. The SLEDAI, on the other hand, appears to work far more reliably as a specific measure for stricter lupus manifestations.

The costs of clinical trials are rising at a time when regulatory issues have posed serious additional impediments to drug testing. Complicated diseases such as lupus increase the financial risk of Phase II and III trials without providing a large potential market to drive the development process. There would appear to be little economic incentive to invest in drugs for a relatively rare disease such as lupus. However, lupus is a fascinating disease to study, not only for the insights it provides into the normal functioning of the immune system, but also for clues it provides to disorders with similar, but more subtle inflammatory vascular manifestations, such as chronic viral diseases and atherosclerosis. A pharmaceutical developer with foresight might find an attractive opportunity in the study of lupus to establish a relatively rapid, relatively small scale proof of concept for a novel immune-modulating agent that might later be applied to the prevention of chronic disease in a wider, aging population. This will never be the case, however, if lupus drug trials continue to fail because of high placebo responses causing difficulties in determining clear outcomes in our patients.

Understandably, there is significant pressure for rheumatologists to reach a consensus about which tools for measur-

*See* Organ manifestations influence differently the responsiveness of 2 lupus disease activity measures, *page 2350*

ing activity and flare in this problematic disease should be applied in the growing number of lupus trials that are imminent. Although it is hard to imagine that a "one size fits all" solution would be even remotely appropriate in selecting the best instrument for use in all trials of all designs for all drugs in lupus, it may be that in the near future, limited numbers of measurements can be uniformly applied to various standard study designs in lupus trials. The clear advantage to this approach would be a greater interstudy reliability by which to compare the outcomes of various trials. The potential disadvantage is that the legislation of homogeneity, attractive as this might be to ensure some immediate standardization, may not be an acceptable scientific approach to a disease as heterogenous as lupus. The greatest risk is that we will lose the opportunity to properly evaluate potentially helpful new medications that might work best "outside the box," either because of their organ-specific effects or due to their limited but very important effects. Diversity in instruments is a major asset that should be carefully protected.

In either case, the optimization and best use of disease activity indices is an important and timely problem. A better understanding of what each instrument measures best will help in selecting appropriate patients for studies (drug trials or not) and in the use, timing, and application of each index. In this issue of *The Journal*, Chang, *et al*[13] report objective confirmation of differences between SLEDAI and SLAM-R so that some widely-held investigator opinions about their strengths and weaknesses can be replaced with well organized, objective, tabulated data. The statistical approaches used are quite valuable, in particular the structured handling of organ system weighting in SLEDAI in order to compare it to the more limited increments available in the patient and physician global assessments. The decision to eliminate all incomplete instrument scores also improves the reliability of conclusions that can be drawn from the data.

The information presented in their article should find useful application in creating models and structures for clinical research. It cannot be over-stressed, however, that more thoughtful studies such as this one are greatly needed. Such studies should be sure to include the British Isles Lupus Assessment Group[14], which is more complicated to apply, but more versatile than either the SLEDAI or SLAM-R, in that it incorporates weighting by organ involvement as well as worsening/improvement in one assessment.

In particular it can be hoped that new clinical experiments will specifically address the problem of high placebo responses, an issue that has plagued all 3 of these instruments in multicenter drug studies. This problem should be addressed before consensus groups move forward to recommend the optimal use of standardized instruments for lupus trials.

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## REFERENCES

1. Petri M, Lahita R, van Vollenhoven RF, et al. Effects of prasterone on corticosteroid requirements of women with SLE Arthritis Rheum 2002;46:1820-9.
2. Kalunian K, Davis J, Merrill JT, et al. Treatment of systemic lupus erythematosus by inhibition of T cell costimulation [abstract]. Arthritis Rheum 2000;43 Suppl:S271.
3. Mease P, Merrill JT, Lahita RG, et al. GL701 (prasterone, dehydroepiandrosterone) improves systemic lupus erythematosus [abstract]. Arthritis Rheum 2000;43 Suppl:S271.
4. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992;35:630-40.
5. Petri M, Hellman D, Hochberg M. Validity and reliability of lupus activity measures in the routine clinical setting. J Rheumatol 1992;19:53-9.
6. Gladman DD, Goldsmith CH, Urowitz MB, et al. Sensitivity to change of 3 systemic lupus erythematosus disease activity indices: international validation. J Rheumatol 1994;21:1468-71.
7. Gladman DD, Goldsmith CH, Urowitz MB, et al. Crosscultural validation and reliability of 3 disease activity indices in systemic lupus erythematosus. J Rheumatol 1992;19:608-11.
8. Ward MM, Marx AS, Barry NN. Comparison of the validity and sensitivity to change of 5 activity indices in systemic lupus erythematosus. J Rheumatol 2000;27:664-70.
9. Fortin PR, Abrahamowicz M, Clarke AE, et al. Do lupus disease activity measures detect clinically important change? J Rheumatol 2000;27:1421-8.
10. Chang E, Abrahamowicz M, Ferland D, Fortin PR. CaNIOS Investigators. Comparison of the responsiveness of lupus disease activity measures to changes in systemic lupus erythematosus activity relevant to patients and physicians. J Clin Epidemiol 2002;55:488-97.
11. Neville C, Clarke AE, Joseph L, Belisle P, Ferland D, Fortin PR. Learning from discordance in patient and physician global assessments of systemic lupus erythematosus disease activity. J Rheumatol 2000;27:675-9.
12. Bae SC, Koh HK, Chang DK, Kim MH, Park JK, Kim SY. Reliability and validity of systemic lupus activity measure-revised (SLAM-R) for measuring clinical disease activity in systemic lupus erythematosus. Lupus 2001;10:405-9.
13. Chang ER, Abrahamowicz M, Ferland D, Fortin PR. Organ manifestations influence differently the responsiveness of 2 lupus disease activity measures, according to patients' or physicians' evaluations of recent lupus activity. J Rheumatol 2002;29:xxxx.
14. Symmons DP, Coppock JS, Bacon PA, et al. Development and assessment of a computerized index of clinical disease activity in systemic lupus erythematosus. Members of the British Isles Lupus Assessment Group (BILAG). Q J Med 1988;69:927-37.