Development of a Clinical Chart To Compute Different Disease Activity Indices for Systemic Lupus Erythematosus

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ABSTRACT. Between 1990 and 1995 a European Consensus Group carried out a multicenter study to reach agreement of the definition of disease activity in systemic lupus erythematosus (SLE). A new index, the European Consensus Lupus Activity Measurement (ECLAM) index, was developed. In a second phase of the study, a prospective survey aimed at validating ECLAM and 4 other scales as steady-state and transition indices for disease activity in SLE was completed. We present the results of this survey. A standardized clinical chart was developed, together with a computer program that could automatically calculate the ECLAM score, as well as the scores for some of the disease activity scales most widely used at present, i.e., the British Isles Lupus Assessment Group, Systemic Lupus Activity Measure, SLE Disease Activity Index, and the SLE Index Score (SIS). With the participation of 28 centers in 15 different European countries, data from 121 prospectively selected new lupus patients were collected. The validity of the 5 activity scales was assessed by comparing the computed scores for each patient to a gold standard, i.e., the physician's subjective judgment on disease activity measured using a semiquantitative scale. All the indices were found to be valid instruments for measuring disease activity in SLE in both the steady-state and transition phases. The results for the various indices closely correlated with one another. Thus, the computerized chart developed by the European Consensus Group offers a simple and reliable instrument to assess disease activity and could be used to monitor lupus patients both in clinical practice and in clinical trials. (J Rheumatol 1999;26:498–501)

Key Indexing Terms:
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Systemic lupus erythematosus (SLE) is a disease characterized by an often irregular sequence of disease flares and remissions[1]. During periods of active disease, reversible or irreversible damage to various organs or systems may occur. It is important therefore to have instruments that can detect and measure the phases of disease activity before such damage actually occurs[2]. These instruments may be used both for prognostic purposes and to monitor the results of therapy. However, a clear definition of disease activity in SLE is lacking. The state of a patient's disease is usually judged by the physician on the basis of a variety of signs, symptoms, and laboratory data. Since no single variable can be used to measure disease activity in SLE, any proposed activity index must be constructed from a set of well defined, non-redundant variables. It must then be carefully validated and in the absence of a gold standard, the subjective judgment of one or more expert physicians could serve as an acceptable endpoint[3]. In addition, the reliability of the scale must be tested, i.e., its intraobserver and interobserver variability. Finally, such an index must be sensitive, that is, able to detect small changes in disease activity over time[3].

Over the years a large number of activity indices have been developed and used. Although they may be structured differently, there is considerable overlap in the elements included in most of them[3]. Some of the most widely used indices are: Systemic Lupus Activity Measure (SLAM), developed by the Boston group[4], SLE Disease Activity Index (SLEDAI), the result of a multicenter Canadian study[5], British Isles Lupus Assessment Group[6] (BILAG), and SLE Index Score (SIS), the revised version of an index proposed by the National Institutes of Health, Washington, DC[7].

Finally, the European Consensus Lupus Activity Measurement (ECLAM) index was developed as the results of a European Consensus Group Study involving 29 centers from 14 countries and carried out to reach a definitive agreement on the definition of disease activity in SLE. Data from

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704 patients with lupus were collected and for each patient a detailed clinical record was compiled, including clinical and laboratory variables[8]. A subjective grading of the physician perception of disease activity was also elicited in the form of a numerical score from 0 to 10, and was used as the endpoint to select those items representing the main determinants for the clinical judgment. In this way the smallest set of variables providing the best linear model of the numerical score for activity were selected. From these variables and their corresponding weights in the linear model, a new lupus activity index was derived and tentatively called ECLAM[9].

Development of a computerized program to calculate different lupus activity scores

Once the ECLAM index was defined, it had to be validated. For this purpose a standardized clinical chart was developed, in which all the clinical and laboratory items present in the most widely used disease activity scales for SLE (SLAM, SLEDAI, BILAG, and SIS), plus those in the ECLAM, were listed. Every sign and symptom included in the chart was precisely defined in accordance with the American College of Rheumatology glossaries and other standard references. Specific assumptions were made in order to arrive at uniform definitions for those items whose definition varied for the different indices.

A computer program was then developed that could calculate, on the basis of the data gathered from the clinical chart, the scores for all 5 activity indices[10]. A preliminary validation of this computer program was carried out by blindly processing 60 patient charts and calculating 4 of the indices (SLAM, SLEDAI, BILAG, and SIS), once by computer and once by hand. The 60 charts were randomly selected from among the 704 cases collected in the first phase of the study. However, to obtain a homogeneous distribution of disease activity, a range of cases (20 inactive, 20 moderately active, 10 active, and 10 very active disease) as defined qualitatively by the observer who had originally filled in the chart, was included. The results of this evaluation showed a high correlation between the manually and the computer calculated scores, with correlation coefficients ranging from 0.906 for BILAG to 0.927 for SLAM (see Table 1)[10].

Table 1. Comparison [expressed as Pearson's regression coefficient (r)] of the computer versus manually calculated disease activity scores for 60 patients selected from the 704 charts collected in the first phase of the European Consensus Group Study (reproduced with permission[10]).

Instrument	r
SLAM	0.927
SLEDAI	0.918
SIS	0.912
BILAG	0.906

The computerized chart consists of 3 sections. Section I was designed to gather demographic and clinical data (regarding the disease onset and course) on the patient up to the moment of the first observation.

Section II was designed to collect, at the time of the first observation, all the clinical and serological data on the patient that could contribute to the assessment of disease activity. The clinical items have been arranged in 11 subsections, based on the individual organ or system involved. In addition, data on laboratory variables and the therapeutic schedule adopted are elicited. Each item has been carefully defined and, where appropriate, stratified. A given item is selected only if it is present in the patient. Exactly when the feature first became evident or was first noted must also be indicated. This is necessary since disease activity is a time related entity, and indeed most activity indices specify that a given feature must have appeared recently to be considered indicative of active disease.

Section III is analogous to Section II, but is used for the second observation of the patient and any subsequent observations. Once again, every item is recorded only if present. Any variation in the item with respect to the previous observation must also be recorded. Specifically, the observer is asked to specify whether the manifestation is new, or alternatively, if it is a symptom already present, which has worsened, improved, or remained unchanged with respect to the previous observation.

When Section II has been completed, and each time that Section III is completed, the program will automatically calculate the 5 indices (SLAM, BILAG, SLEDAI, SIS, ECLAM) and print out the results, together with a short patient report.

A further validation of the computer program is being carried out on actual patients with lupus recruited at one of the participating centers (Pisa). Twenty-nine consecutive patients with lupus have been enrolled to date, for whom the SLAM, SLEDAI, and ECLAM scores have been calculated, both manually by an observer and automatically using the computerized chart compiled by the same observer. The scores obtained thus far by these 2 procedures are very closely correlated, with a correlation coefficient of 0.93 for ECLAM and 0.99 for SLEDAI (see Table 2). These results confirm that the computer program is highly reliable in calculating the different activity indices.

Table 2. Comparison [expressed as Pearson's regression coefficient (r)] of the computer versus manually calculated disease activity scores for 29 lupus patients prospectively selected at the Clinical Immunology Unit, University of Pisa.

Instrument	r
SLAM	0.934
SLEDAI	0.997
ECLAM	0.929

Validation of the disease activity scales for SLE by computerized computation of the indices

Using the standardized chart and computer program, a prospective study aimed at validating ECLAM and comparing it to the other 4 disease activity scales was prepared. The clinical chart was sent to 41 European lupus centers (15 of which had not taken part in the first phase of the study). The centers were asked to provide data on 3 to 5 newly observed patients with lupus. Each case had to be enrolled at the moment of the first observation, which presumably would have been a phase of moderate to high disease activity. Since it was decided to assess the 5 activity scales both as steady-state and as transition indexes (i.e., their ability to measure disease activity at a single point in time and also to detect any variation in consecutive readings), participants were asked to re-evaluate the enrolled patients after a 3 month period had elapsed, during which time the disease course might have spontaneously changed or been modified by treatment. In addition, the physician was asked to provide a subjective score of the patient's disease activity at each observation time. This was used as the endpoint (gold standard) of disease activity for each patient[10]. By the end of the study 28 centers from 15 countries had provided data on 121 patients with lupus (111 females, 10 males), ranging in age from 11 to 72 years.

Tables 3 and 4 report the Pearson and Spearman correlation coefficients obtained by comparing the physician's score with the scores for the different activity indices. Their steady-state validity was analyzed by comparing the values obtained at the first observation time. The differences in the physician score and in each index score between the first and the second observation were compared to assess the validity of the scales as transition indices. All 5 were shown to work well both as steady-state and transition indices, although ECLAM and BILAG appeared to be slightly more reliable than the others when physician subjective score was used as the endpoint of the comparison. In addition, the indices were very closely correlated to one another, the correlation coefficient ranging from 0.695 (between ECLAM and BILAG) to 0.866 (between SIS and SLAM) when the different scales were evaluated as steady-state indices, and from 0.681 (between ECLAM and SLAM) to 0.874 (between SIS and SLAM) when the validity of the scales as transition indices was tested[11] (manuscript in preparation).

Table 3. Pearson (P) and Spearman (S) correlation coefficients for disease activity scores of 121 patients with lupus recruited in 28 European centers, obtained by comparing the physician scores with the scores derived from each of the different activity indices at the first observation time.

	Pr	Sr
BILAG (0, 1, 4, 9)*	0.651	0.663
SLAM	0.631	0.662
SLEDAI	0.640	0.655
SIS	0.577	0.629
ECLAM	0.706	0.728

*The A, B, C, D classification classes of BILAG were numerically converted to 0, 1, 4, 9.

Table 4. Pearson (P) and Spearman (S) correlation coefficients for disease activity scores of 121 patients with lupus recruited in 28 European centers, obtained by comparing the differences between the first and second observation times in the physician scores with the same differences in the scores derived from each of the different activity indices.

	Pr	Sr
BILAG* (0, 1, 4, 9)	0.694	0.701
SLAM	0.663	0.696
SLEDAI	0.602	0.621
SIS	0.692	0.721
ECLAM	0.766	0.730

*The A, B, C, D classification classes of BILAG were numerically converted to 0, 1, 4, 9.

Comments

The computerized clinical chart described above allows one to reliably calculate SLE disease activity scores based on the BILAG, SLAM, SLEDAI, SIS, and ECLAM indices. Since these are the indices most widely used in the management of patients with lupus, this instrument would allow clinicians to use the index with which they are most familiar, or the one most suitable for a particular type of study or patient group. In addition, it would permit direct comparison of the various clinical studies that have employed any one of these instruments, providing a convenient tool for multicenter studies and therapeutic trials.

In our evaluation of this chart, we have also confirmed by means of a prospective study on a large cohort of patients with lupus that the BILAG, SLAM, SLEDAI, SIS, and ECLAM indices all represent valid and sensitive instruments to assess disease activity in SLE. The 4 older scales have already been cross-validated in international studies, each involving a select group of experts evaluating small groups of patients or patient charts[12–14]. In the present study the comparison of the different activity indices was obtained by analyzing a large population of patients recruited from many European lupus centers, while the different indices were calculated using a uniform database and computer program. It is interesting to note, furthermore, that these results were remarkably similar to those obtained using the standard manual computation of the same indices in a longitudinal followup study of patients with SLE monitored at regular intervals over a long period of time[15].

Thus we are confident that this clinical chart, which requires little time to learn to use and just a few minutes to

compile for each patient, could offer a powerful tool for the exchange of information on a long disputed and complex problem, that of the measurement of disease activity in SLE.

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