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Incomplete lupus erythematosus: results of a multicentre study under the supervision of the EULAR Standing Committee on International Clinical Studies Including Therapeutic Trials (ESCISIT)

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Abstract

Objective. Patients characterized with antinuclear antibodies (ANA) and disease symptoms related to one organ system can be described as having incomplete systemic lupus erythematosus (SLE). The aim of this multicentre study was to describe the outcome of these so-called incomplete SLE patients. Two aspects of the outcome were studied: (i) the disease course, defined

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by the presence or absence of clinical symptoms; and (ii) the number of patients that eventually developed full SLE.

Methods. Outcome parameters were the ACR criteria, the SLE disease Activity Index (SLEDAI), the European Consensus Lupus Activity Measure (ECLAM) and the requirement for treatment. In 10 European rheumatology centres, patients who had been evaluated in the last 3 months of 1994 and had been diagnosed as having incomplete SLE on clinical grounds for at least 1 yr were included in the study. All 122 patients who were included in the study were evaluated annually during 3 yr of follow-up.

Results. Our results are confined to a patient cohort defined by disease duration of at least 1 yr, being under clinical care at the different centres in Europe. These patients showed disease activity that was related mostly to symptoms of the skin and the musculoskeletal system, and leucocytopenia. During the follow-up, low doses of prednisolone were still being prescribed in 43% of the patients. On recruitment to the study, 22 of the 122 incomplete SLE patients already fulfilled the ACR criteria for the diagnosis of SLE. In the 3 yr of follow-up only three patients developed SLE.

Conclusions. A high proportion of patients in our cohort defined on clinical grounds as having incomplete SLE eventually showed disease activity defined by the SLEDAI as well as ECLAM. However, only three cases developed to SLE during the follow-up. This suggests that incomplete SLE forms a subgroup of SLE that has a good prognosis.

KEY WORDS: SLE, Incomplete, Disease activity, Prognosis.

Patients often present with a constellation of disease features suggestive of systemic lupus erythematosus (SLE) but do not fulfil the classification criteria for SLE [1]. In the past, these patients have been described as having latent lupus [2], because only a minority of them eventually develop SLE. In recent studies of patients who do not fulfil the classification criteria for rheumatoid arthritis (RA), SLE, systemic sclerosis (SSC), Sjögren's syndrome (SS), polydermatomyositis (PM) and/or mixed connective tissue disease (MCTD) [3–8], the terms 'undifferentiated connective tissue disease' (UCTD) and 'early undifferentiated connective tissue disease' have been suggested. Also, for patients diagnosed as having UCTD, a benign course of disease has been described with a low incidence of major complications, such as lung fibrosis, renal involvement and/or central nervous system involvement [9–12]. Recently, a study was performed evaluating the disease course of patients who had rheumatic symptoms and who also had antinuclear antibody (ANA) [13]. Only a minority of the patients in this study went on to develop SLE. Diagnosis of SLE is usually not difficult when all the characteristic symptoms are present, but may be difficult when there are only one or a few symptoms. In such cases the diagnosis cannot be made at the onset of the disease, and the patients must be observed for a longer period, until new symptoms appear and the diagnosis can be made with confidence. At present, in daily practice the diagnosis of SLE is confirmed when the patient fulfils the American College of Rheumatology (ACR) criteria [1].

One drawback of the ACR criteria is the possibility that patients with clinical signs related to only one organ system, e.g. the skin (rashes, discoid lesions), together with the presence of ANA and a positive LE cell preparation may fulfil the ACR criteria for SLE. However, it is important to know whether these patients will develop full SLE. Patients with disease symptoms related to one organ system only, together with the presence of ANA, can be said to have incomplete SLE. In order to describe the course of this so-called incomplete SLE, an international follow-up study was started under the supervision of the European League Against Rheumatism (EULAR) Standing Committee on International Clinical Studies Including Therapeutic Trials (ESCISIT). In this prospective follow-up investigation, patients with incomplete SLE were studied to investigate whether they were prone to the development of full SLE and whether they had a stable disease course.

Materials and methods

Ten rheumatology centres in Europe participated in this study. All members of the study group were asked to include in the study those patients who had the diagnosis of incomplete SLE. Incomplete SLE was defined as the presence of symptoms related to one organ system plus the presence of ANA; patients were excluded if they had any other well-known disease. Furthermore, the patient was included in the study only if the clinician suspected that the patient might eventually develop SLE. In total, 122 patients with the diagnosis of incomplete SLE were included. The patients were recruited during the last 3 months of 1994. Characteristics of all 122 patients are shown in Table 1. The clinical data of the patients were recorded in database protocols, with special attention to the disease course in the past and the disease activity present at the time of inclusion in the study. To obtain an impression of disease activity at entry to the study, the SLE disease activity index (SLEDAI) [14] and the European Consensus Lupus Activity Measure (ECLAM) [15] were used. Only those patients who did not fulfil the ACR classification criteria [1] were considered to have an

incomplete form of SLE. In order to standardize the data entries, every item in the protocol was defined according to the Dictionary of Rheumatic Disease prepared by the Glossary Committee of the American College of Rheumatology [16]. Otherwise, definitions were based upon the information given in the most commonly used textbooks of internal medicine and rheumatology. When the recruitment of patients with subclinical SLE was complete, the patients were analysed for their eventual diagnosis of SLE and the number of ACR criteria they fulfilled. In contrast to the revised ARA criteria, the different ANAs were considered as a single criterion.

The disease course was evaluated annually for all patients, changes were recorded, and during the last 3 months of 1995, 1996 and 1997 the disease activity was scored. The physician involved in the study obtained all relevant information from the patients. Each centre recruited at least five patients who fulfilled the defined clinical criteria. The data were entered into a protocol form at the start of the study and annually during the 3 yr of follow-up.

TABLE 1. Patient characteristics

Demographic features		
No. patients		122
Male/female		1:121
Average age at start of study (yr)		40 ± 13
Mean disease duration [yr (range)]		4.5 (1–40)
Geographical distribution	Number of patients	Percentage
Western Europe	27	22
Central Europe	25	20
Southern Europe	22	18
Eastern Europe	48	39

TABLE 2A. Follow-up of patients with incomplete SLE ($n = 122$): number of ACR criteria fulfilled in relation to disease activity score during 1995–1997

Year	Number of ARA criteria fulfilled	ECLAM	SLEDAI
1995	2.8 ± 1.4	2.7 ± 2.46	3.01 ± 3.4
1996	2.4 ± 1.8	2.9 ± 3.2	4.1 ± 6.1
1997	1.8 ± 1.6	2.3 ± 2.4	3.5 ± 5.9

Results

Clinical diagnosis of incomplete SLE versus the ACR criteria

Of the 122 patients recruited in 1994, 22 were found to fulfil the ACR criteria for SLE at their first evaluation in 1995 and were excluded from further follow-up. At the follow-up in 1996, two patients had developed SLE according to the ACR criteria, and at the 1997 follow-up one patient had done so.

Disease course of patients with incomplete SLE

Table 2 shows the follow-up of all 122 patients. The differences in the average number of ACR criteria present illustrate the change in disease activity during the follow-up period, as do also the ECLAM and SLEDAI scores. It is clear that patients who fulfilled four or more ACR criteria had greater disease activity, as measured by both disease activity scoring systems.

Follow-up of skin and musculoskeletal system

The overall disease activity is shown for all 122 patients in Table 2. The table does not indicate which symptoms showed the most change over time. However, changes in specified clinical signs were recorded every year, enabling us to establish which symptom had the most effect on changes in disease activity scores.

Table 3 shows the follow-up data for all specific clinical signs for the 100 patients who did not fulfil the ACR criteria for SLE. As shown in this table, the different symptoms increased, decreased or remained stable during the follow-up period. Most patients had complaints of the joints and fatigue. It is remarkable that at the evaluation in 1995 the prevalence of arthritis was 15%, but in the two subsequent years it was 19 and 13%. Hardly any change was noted in other clinical signs related to the skin and musculoskeletal system (not all are shown in the tables), and the frequencies of these signs were very low.

Follow-up of the cardiovascular and haematopoietic systems

The prevalence of periods of pericarditis declined during the follow-up period from 4 to 0% of the patients. A considerable number of patients had Raynaud's phenomenon (25%); during the follow-up there was very little change in its prevalence (data not shown). Arterial hypertension was noted in a small percentage of patients (5%).

TABLE 2B. Incomplete SLE: disease activity related to the number of ACR criteria fulfilled during the follow-up period

	No. of ACR criteria[a] fulfilled < 4		No. of ACR criteria[a] fulfilled ≥ 4		
Year	ECLAM[b]	SLEDAI[b]	ECLAM[b]	SLEDAI[b]	No. of patients fulfilling ≥ 4 ACR criteria
1995	2.1 ± 2.3	2.6 ± 4.5	4.4 ± 2.3	4.3 ± 4	22
1996	2.1 ± 2	2.0 ± 4.3	6.1 ± 4.5	8.5 ± 9	24
1997	1.7 ± 2	2.4 ± 4.5	5.6 ± 2.2	9.9 ± 8.9	25

[a]Each defined clinical sign present was calculated as a positive criterion.
[b]Values are median ± S.D.

TABLE 3. Changes in occurrence of symptoms in 100 patients with incomplete SLE
(A) Between 1995 and 1996

	Year of follow-up						
		1996					
		Symptom present					Symptom absent
Clinical signs	1995 Symptom present	Total	No change	Decrease in severity	Increase in severity	Newly developed	(complete cessation)
General							
Fever	5	8	1	1	0	6	3
Fatigue	30	20	12	1	2	5	17
Articular							
Arthritis	15	19	7	1	0	11	7
Skin involvement							
Malar rash	4	6	3	0	0	3	1
Generalized rash	1	2	0	0	0	2	1
Discoid rash	4	1	0	0	0	1	4
Pericarditis	4	2	0	1	0	1	3
New psychiatric manifestations							
Seizures	1	2	0	0	0	2	1
Stroke	2	1	0	0	0	1	0
Psychosis	0	1	0	0	0	1	0
Renal manifestations							
Proteinuria	4	4	1	0	0	3	3
Raised serum creat	1	0	0	0	0	0	1
Urinary casts	3	1	0	0	0	1	3
Haematuria	3	1	0	0	0	1	3
	5	5	2	0	0	3	3
Haematological features							
Non-haemolytic anaemia	10	11	4	0	0	7	6
Haemolytic anaemia	2	0	0	0	0	0	2
Leucopenia	36	29	18	1	2	8	15
Thrombocytopenia	8	4	3	0	0	1	5

(B) Between 1996 and 1997

		1997					
		Symptom present					Symptom absent
Clinical signs	1996 Symptom present	Total	No change	Decrease in severity	Increase in severity	Newly developed	(complete cessation)
General							
Fever	8	3	0	2	0	1	8
Fatigue	20	32	13	1	1	17	5
Articular							
Arthritis	19	13	4	0	0	9	15
Skin involvement							
Malar rash	6	10	1	0	0	9	5
Generalized rash	2	1	0	0	0	1	2
Discoid rash	1	4	1	0	0	3	0
Pericarditis	2	0	0	0	0	0	2
New psychiatric manifestations							
Seizures	2	1	0	0	0	1	2
Stroke	3	1	0	0	1	0	2
Psychosis	1	2	0	0	0	2	1
Renal manifestations							
Proteinuria	4	3	2	0	0	1	2
Raised serum creat	1	0	0	0	0	0	1
Urinary casts	5	8	1	0	0	7	4
Haematuria	5	0	0	0	0	0	0
Haematological features							
Non-haemolytic anaemia	11	16	4	0	1	11	0
Haemolytic anaemia	0	0	0	0	0	0	0
Leucopenia	29	20	11	4	0	5	14
Thrombocytopenia	4	5	2	1	1	1	4

Follow-up of the renal and central nervous systems

Only a minority of the patients had symptoms related to renal involvement. Renal involvement was noted in at least 11% of our patients, haematuria in eight and proteinuria in four. As expected, very little involvement of the central nervous system was noted.

Follow-up of haematological features

An episode of haemolytic anaemia was observed in two patients, but non-haemolytic anaemia was seen in 10 patients in 1995 and in 16 in 1997. The most frequently observed symptom was leucocytopenia, the prevalence of which ranged from 36% in 1995 to 20% in 1997.

Change in treatment during follow-up

At the time of recruitment to the study, 38% of the patients were being treated with prednisolone, none of them with a dose higher than 10 mg/day. Corresponding figures for the follow-up evaluations were 38, 43 and 27%. Antimalarials were prescribed in 17% of the patients; during the follow-up this increased to 32%. Azathioprine was prescribed in only 2% of the patients in 1995, and in 3, 5 and 4.5% of patients at the subsequent follow-up evaluations.

Discussion

In daily practice, the diagnosis of SLE is made when the patient fulfils the ACR criteria. When these criteria are used, it can happen that the diagnosis SLE is considered in patients with symptoms related only to skin involvement, such as malar rash and photosensitivity, which are further characterized by a positive LE test result and the presence of ANA. These two sets of clinical features—malar rash and photosensitivity plus a positive LE cell test, combined with positivity for ANA—are closely interrelated. The aim of this study was to investigate the clinical course of patients with incomplete SLE. When the patients were being recruited, the only criterion was that the clinician should have considered the diagnosis SLE but concluded that the criteria for full SLE were not met. It was our intention to analyse the disease course in these patients—in other words to confirm that these patients had a benign disease course—but also to try to define the diagnosis of incomplete SLE as opposed to SLE.

Patients with so-called latent lupus, or incomplete SLE, may represent a cohort of patients who will later develop SLE, or they may form a subset of SLE patients with mild disease. In one of the first studies [2], patients with latent lupus differed from SLE patients in general by the absence of involvement of the renal and central nervous systems. Overall, they were characterized by the presence of ANA, Raynaud's phenomenon and/or arthritis and/or leucocytopenia and/or thrombopenia. These patients were similar to patients described by the term 'undifferentiated', which represents early disease that has not yet evolved into a disease such as SLE, scleroderma, SS or PM–DM. All these cohorts of patients (latent lupus, UCTD, incomplete SLE) are characterized by non-specific symptoms such as arthralgia, Raynaud's phenomenon, fatigue and auto-antibodies to nuclear antigens [10].

In a recent study [13] it was shown that, among patients with both rheumatic complaints and ANA, only 16%—the diagnosis of SLE could be established within 3 yr of disease onset. Similar results have been described in patients not fulfilling the ACR criteria for SLE or other connective tissue disease 2 yr after the onset of disease symptoms [17]. These results suggest that ANA-positive patients with skin and/or musculoskeletal symptoms do not generally develop SLE. Others report similar findings [18, 19]. It remains very difficult to characterize these ANA-positive individuals who do not develop SLE. Only 22 of the 122 patients with incomplete SLE in our study fulfilled the ACR criteria at the first evaluation after recruitment. Of the remaining 100 patients, only three showed a change during follow-up, in that they developed SLE according to the ACR criteria. Table 3 illustrates the differences between the patients who fulfilled three or more ACR criteria. Patients fulfilling four or more ACR criteria were characterized by higher disease activity scores (SLEDAI, ECLAM). By analysing the defined clinical symptoms, two observations can be made. Over the years of follow-up, the disease activity showed a remitting course in individual patients. For example, if a patient had malar rash, the prevalence was 4–10%. These figures suggest that malar rash was observed for the first time in seven patients. However, this conclusion is not correct, because this symptom could have been present in the past but not when the patient was recruited into the study. The clinical signs were recorded only when they were present at the time of recruitment and once a year during follow-up. Attention was only paid to the changes that occurred. The tables show only the disease course, i.e. the changes in symptoms. When the patients were recruited they were characterized only by their history, not by their disease activity. When the prevalences of the clinical symptoms are considered, the discrepancy between the skin-related symptoms in contrast to the haematological aberrations is obvious. Every characteristic symptom of the skin corresponds to a positive ACR criterion, whereas the haematological symptoms are frequently observed together. However, our study still shows that during the 3-yr follow-up our patients showed stable disease in that only a minority (three) of these patients later developed full SLE. At the time of recruitment into the study, one of these patients had skin involvement and two had haematological symptoms. A survey of the literature indicates that 8–13% of patients with so-called UCTD will develop SLE after 3–5 yr [9, 11, 12]. The difference between this figure and our observation of 3% is related to the fact that our patients were known to have had incomplete SLE for between 3½ and 4½ yr, whereas the patients in the studies cited above had disease of more or less recent onset (overall up to 2 yr).

Our study has shown clearly that although patients with so-called incomplete SLE may have periods of disease activity, only a small minority will develop full SLE. At the onset of their disease, the patients who later developed full SLE could not be differentiated from the patients with an incomplete disease course. It is not clear what factors determine whether incomplete SLE remains incomplete or develops into full SLE.

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