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Systemic lupus erythematosus: clinical features in patients with a disease duration of over 10 years, first evaluation[1]

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Abstract

Objective. Most information available about the disease course of patients with systemic lupus erythematosus (SLE) is restricted to the first 5 yr after disease onset. Data about the disease course 10 yr after disease onset are rare. The aim of this multicentre study was to describe the outcome of SLE patients with a disease duration of >10 yr.

Methods. Outcome parameters were the SLE Disease Activity Index (SLEDAI), the European Consensus Lupus Activity Measure (ECLAM), the Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SLICC/ACR), a global damage index (DI) and required treatment. In 10 different European rheumatology centres, all SLE patients who were evaluated in the last 3 months of 1994, and who had been diagnosed with SLE at least 10 yr ago, were included in the study.

Results. It should be stressed that our results are confined to a patient cohort, defined by a disease duration of at least 10 yr, and who are still under clinical care at the different centres in Europe. These SLE patients still showed some disease activity, related to symptoms of the skin and musculoskeletal systems, next to the presence of renal involvement. A total of 72% of the patients needed treatment with prednisolone (⩽7.5 mg). The cumulative damage was overall related to clinical features of the central nervous system (14%) and renal involvement (14%), next to deforming arthritis (14%), osteoporosis (15%) and hypertension (40%). The prevalences of obesity, Cushing appearance and diabetes are highly suggestive that the ongoing treatment and that in the past might have had an impact on the total sum of end-organ damage.

Conclusions. After 10 yr, a high proportion of patients in our cohort continued to show evidence of active disease, defined by the SLEDAI as well as ECLAM. The DI was related to the involvement of the central nervous system, renal involvement and the presence of hypertension.

KEY WORDS: SLE, Disease activity, SLEDAI, ECLAM, Damage Index.

Systemic lupus erythematosus (SLE) still has the reputation of a fatal condition, with no cure, although it is the main goal of treatment to achieve remission. In the past, different studies have investigated the occurrence of remissions. Remission of the disease was already described by Dubois in 1956 [1] to occur in 35% of 520 patients and some of the remissions lasted for 10–20 yr. The observation that long periods could be observed in which patients did not need any treatment was already made before 1953, as well as thereafter, when treatment with corticosteroids and immunosuppressive drugs became available [2–4].

In a recent study [5], a number of patients were described with a disease-free period of >18 yr, in some cases lasting as long as 30 yr. This study demonstrated that there is a continuous increase in the likelihood of having a remission of the disease, with increasing disease

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duration; at a disease duration of 20 yr, 50% of the patients had entered into remission. In this study, remission was defined as at least a 1 yr lack of clinical disease activity, with withdrawal of all treatment. Importantly, the occurrence of remission was not limited to patients with a mild disease course. On the other hand, the longer the time interval between the initial manifestations and the diagnosis of SLE, the less likely it was for a patient to enter remission.

For estimating the prognosis of the disease, the chance of having a remission is important, but also the end-organ damage. In the assessment of damage, two factors are important to consider: possible adverse effects of treatment and the end-organ damage as a result of the disease process. A number of validated disease activity and damage indices have been described [6], including the SLE Disease Activity Index (SLEDAI) [7] and the Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SLICC/ACR) [8] for the assessment of accumulated damage.

From previous studies [9, 10], it is highly suggestive that prognosis, assessed by the remission rate of disease activity and end-organ damage or damage index will be determined by the first years after disease onset. In fact, many SLE patients either die or have end-organ failure within the first decade of their disease. On the other hand, little is known about the characteristics of patients with long-standing disease with respect to their clinical features and general disease activity [9, 10].

The study was designed to establish disease activity damage indices and treatment requirements in lupus patients who had been diagnosed with SLE at least 10 yr ago. These variables were then compared with historical details collected at the time of diagnosis/onset of the disease, as well as obtained retrospectively.

Materials and methods

Ten different European rheumatological centres participated in this cooperative study. A total of 187 SLE patients were included. All SLE patients fulfilled the revised ARA classification criteria [11]; they have been followed for at least 10 yr at the departments which included them in the study. The inclusion of all patients took place during the last 3 months of 1994. In all participating centres, all consecutive patients were included who were seen during that time period and had a disease duration of at least 10 yr. Demographic features of all 187 SLE patients are shown in Table 1.

Age at diagnosis was defined by the age of the patients when they fulfilled the ARA criteria. Age at onset was obtained, in a retrospective way, as the time the patient showed clinical signs of SLE for the first time. Disease duration was defined by the time interval between age at diagnosis and at study entry. If clinical data were not available, like the ANA determination at onset, the results were expressed as a percentage of the number of patients in which these parameters were known.

Clinical data of the patients were then registered in database protocols, with special attention to the disease course in the past, the disease activity at the time of inclusion and the extent of organ damage. A standardized history chart containing relevant clinical symptoms at the time of onset and diagnosis (defined by the time of fulfilling the 1982 ARA criteria) was filled in. These data were obtained using the patients' medical charts. To obtain an impression of disease activity at entry, the SLEDAI [7, 12] and European Consensus Lupus Activity Measure (ECLAM) [13] were used. Also, a global damage index (DI), describing the total sum of all the damage that has occurred, was obtained by using the DI as described by Urowitz [14] and recently validated [8]. If data were not available, the prevalences were corrected for the number of patients. In order to standardize the data entries, every item in the protocols was defined according to the Dictionary of Rheumatic Disease prepared by the Glossary Committee of the American College of Rheumatology [11]. Otherwise, definitions were based on the most commonly used textbooks of internal medicine or rheumatology.

TABLE 1. 1A. Demographic data of 187 SLE patients with a disease duration[a] of ⩾10 yr

	Mean	S.D.
Age at onset	29	12
Age at diagnosis	31	12
Age at study entry	46	12
Disease duration	16	9
Male/female	21/166	

[a]Disease duration from the time of diagnosis (⩾4 ARA criteria until the start of the study).

TABLE 1B. Geographical distribution

	Number of patients	Percentage
Western Europe	55	29
Central Europe	57	30
Southern Europe	41	22
Eastern Europe	34	18

Results

Clinical manifestations at onset and diagnosis

The frequency of the different clinical features related to the ARA criteria at the time of disease onset and at diagnosis, and the cumulative prevalences of the different clinical manifestations during the follow-up study, are shown in Table 2. The low prevalence of anti-Sm in these patients was remarkable. At the time of diagnosis, anti-Sm was reported to be positive only in 3% and during follow-up in 11% of the patients. After diagnosis, the prevalence of symptoms such as butterfly rash, arthritis and haematological abnormalities remained stable, whereas the prevalence of central nervous manifestations increased from 6 to 65%, renal involvement up to 47% and serositis from 36 to 67%.

In Table 2, prevalences of clinical signs and laboratory

TABLE 2. Clinical manifestations and laboratory test based on the ARA criteria at onset and diagnosis and during follow-up

	At onset[a] (%)[b]	At diagnosis[a] (%)[b]	During follow-up[c] (%)[b]
Butterfly rash	29	47	47
Discoid rash	11	18	21
Oral ulcers	3	6	ni
Photosensitivity	30	45	58
Arthritis	76	85	85
Serositis	15	36	67
Renal disorder	12	26	47
Neurological disorder	6	6	65
Haematological disorders	32	62	62
LE-cell test	27	78	78
Anti-Sm	1	3	11
ANA	35	89	89

ni, not investigated.
[a]Clinical manifestations at onset, diagnosis and follow-up are obtained in a retrospective way.
[b]Percentage of the number of patients positive for the defined clinical manifestations.
[c]Cumulative percentage calculated at the time the patient was taken into the study.

tests related to the ARA criteria are summarized. Apart from these symptoms, attention was also paid to other SLE-related symptoms during follow-up, as shown in Table 3. The table illustrates other frequently occurring manifestations during the disease course. Examples of frequently observed skin manifestations were livedo reticularis (17%) and digital skin vasculitis (13%); other clinical signs such as urticaria (6%), panniculitis (1%) and periorbital oedema were relatively rare. Regarding the cardiovascular and pulmonary system, the most frequent clinical signs were Raynaud's phenomenon (46%), hypertension (40%), pleuritis (35%) and pericarditis (22%), whereas myocarditis was only observed in 5% of the patients. Anaemia was diagnosed at least once during the disease course in 33% of the patients. In 5% of the cases, the anaemia was haemolytic, in 27% of the cases it was an anaemia of chronic disease. Leucocytopenia was observed in 42% and thrombocytopenia in 17% of the patients. The most frequent clinical signs related to abdominal abnormalities were the findings of hepatomegaly (17%) and splenomegaly (8%). Other symptoms, such as pancreatitis (3%) and intestinal vasculitis (1%), were only registered in a minority of the patients.

TABLE 3. The prevalence of frequent clinical manifestations in patients with systemic lupus erythematosus during their disease course

Organ system	Clinical manifestations	Percentage of patients
Skin	Alopecia	16
	Chronic urticaria	6
Vascular system	Livedo reticularis	17
	Raynaud's phenomenon	46
	Digital skin vasculitis	13
	Periungual erythema	2
Cardiopulmonary system	Arterial hypertension	40
	Valve involvement	10
	Pulmonary hypertension	9
	Interstitial pneumonitis	13
	Myocarditis	5
Musculoskeletal system	Deforming arthritis	14
	Myalgia	29
	Muscle weakness	24

TABLE 4. Kind of treatment in patients with systemic lupus erythematosus with a disease duration longer than 10 yr at entry

Treatment	Percentage of patients (%)
Non-steroidal anti-inflammatory drugs	20
Corticosteroids	72
Antimalarials	11
Azathioprine	17
Cyclophosphamide	7

As shown in Table 2, renal involvement was found in 47% of the patients; the most reported abnormalities were proteinuria (32%), a decreased creatinine clearance (27%), haematuria (20%) and casts (17%). In 12% of the patients, renal involvement coincided with the presence of hypertension. Central nervous involvement was found in 65% of the patients. In these patients, a diversity of clinical signs were reported during follow-up, e.g. depression (14%), seizures (9%), organic brain syndrome (9%), peripheral neuropathy (6%), cranial nerve palsy (5%), impaired consciousness (4%), psychosis (4%), aseptic meningitis (2%) and cerebellar ataxia (2%). At the time of this investigation, 72% of the patients were still being treated with corticosteroids and 24% with an immunosuppressive and/or cytotoxic drugs (Table 4).

Disease activity in relation to damage index and disease duration

The data obtained on the patients for the different scores of disease activity (SLEDAI and ECLAM and DI) are shown in Table 5. DI correlated very well with the two disease activity scores, but not with disease duration. Both disease activity scores were related to one another. The prevalence of symptoms with the greatest impact on the disease activity scoring systems are summarized in Table 6, showing, for example, that 26% of the patients still had an active arthritis, and at least 20% signs of active skin disease like skin rashes and vasculitis. Regarding the central nervous system, the most frequently reported clinical signs, $\geqslant 10$ yr after disease onset, were headache and/or migraine. The most frequently reported clinical signs related to the SLICC/ACR DI are shown in Table 7. In 14% of the patients, renal impairment was described, defined by a creatinine clearance of <50 ml/min and in 2% of the patients of <10 ml/min (dialysis patients). Clinical signs related to the cardiovascular system could be divided into myocardial infarction (5%), coronary artery disease (coronary insufficiency, angina) (8%), congestive heart failure (8%) and constrictive pericarditis (1%). At the time of inclusion, 21% of the patients had a Cushingoid appearance, 7% had diabetes and obesity was noted in 10% of the patients.

TABLE 5. Disease activity and damage index in patients with systemic lupus erythematosus with a disease duration longer than 10 yr and the correlation between disease activity, damage and total disease duration

	Mean	S.D.
Disease activity		
SLEDAI	7.5	9.2
ECLAM	5.3	5.0
Damage index		
DI + co-morbidity[a]	3.7	4.5
DI − co-morbidity	2.8	3.4

Relationship disease activity and damage index

	Disease activity		Disease duration	
	SLEDAI	ECLAM	Onset[b]	Diagnosis[c]
DI +	<0.0001****	<0.0001	ns	ns
DI −	<0.0001	<0.0001	ns	ns
SLEDAI		<0.0001	ns	ns
ECLAM			0.04	ns

DI +, damage index combined with co-morbidity; DI −, damage index without co-morbidity.

[a]Co-morbidity is defined by the presence of obesity, Cushingoid appearances and diabetes.

[b]Disease duration onset: total disease duration from onset until evaluation (1994).

[c]Disease duration diagnosis: total disease duration from the time of diagnosis until evaluation (1994).

****Significant, $P < 0.0001$; ns, not significant.

TABLE 6. The disease course defined by the most frequently observed symptoms at the time the patients were included in the study

	Percentage of patients in whom the symptoms were present or had worsened[a]	
Symptoms	Present	Worsened
Arthritis	21	5
Malar rash	17	3
Skin vasculitis	9	2
Headache/migraine	14	2
Proteinuria	17	7
Urinary casts	9	3
Haematuria	15	2
Raised serum creatinine	11	2
Reduced creatinine clearance	16	3
Non-haemolytic anaemia	12	5
Leucocytopenia	14	5

[a]The disease activity was scored depending on the disease course preceding a 3 month period when they were included in the study.

Discussion

In this study, the prevalence of the most relevant clinical features in a large cohort of SLE patients with a disease duration of at least 10 yr is described, with special attention to disease activity and the total end-organ failure (damage index).

The old view of SLE as a relatively unremitting disease course, ending in death of the patients within a few years, has gradually been replaced by a new one, in which remission to some degree is achievable in most patients. At present, patients with SLE have a far better prognosis than 40 yr ago. The prognosis increased from a 50% cumulative survival rate after diagnosis to 95% [15–10]; the 10 yr survival is now estimated to be 80–90% [10]. Coinciding with this improved survival, other outcome measures were developed. Gladmann and Urowitz [16, 17] proposed a damage index composed of disease-related morbidity outcomes such as renal failure, coronary artery disease, avascular necrosis and cognitive neurophysiological dysfunction.

TABLE 7. The prevalence of the most frequently reported clinical signs related to the Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SLICC/ACR) in patients with systemic lupus erythematosus with a disease duration longer than 10 yr

Clinical signs	Prevalence (%)
Avascular necrosis	8
Deforming arthritis	14
Osteoporosis	15
Central nervous system	14
Organic brain syndrome	9
Renal impairment	14
Hypertension	40
Cardiovascular diseases	15

In previous studies, different factors such as age at disease onset, sex, race, socio-economic status and disease activity at onset and diagnosis were investigated with regard to their impact on survival [15, 18], but data about the disease activity and end-organ damage in patients who survived the first 10 yr of their disease are rather scarce. This international study is, to our knowledge, the first report describing a multicentre cohort of SLE patients with a disease duration of at least 10 yr. Disease activity in this cohort was expressed by the SLEDAI and ECLAM, the end-organ damage by the SLICC scoring system.

A major drawback of our study was that our patients were included during three consecutive months in 1994. This may have an effect on the results; however, dividing our patients into Western and Eastern Europe origin, or looking at the separate centres, the different patient populations were comparable. The results are also biased by the fact that they are derived from patients who still require follow-up. Patients in long-term remission are presumably discharged. In other words, perhaps an overrepresentation is seen in patients with a more active disease, caused by the fact that these patients are more frequently observed than SLE patients with a mild disease who are attending the department just for their annual review.

To overcome the mentioned drawbacks of our study, a prospective study is needed in which patients are followed from the time of disease onset. In that way, insight is obtained about the real figures related to the number of patients going into remission and the number of patients lost to follow-up, caused by death or by the fact that they developed an end-stage renal failure and

were transferred to the care of a renal physician. It should, therefore, be stressed that our study will only give an insight into that population of patients that is followed at the different centres in Europe which are involved in lupus research.

A remission of disease can best be defined by the absence of disease-related signs without the need for any treatment. None of the patients who were included in our collaborative study fulfilled these criteria. All the included patients were still under continuing care and needed some form of treatment; 72% of them still needed treatment with prednisolone.

Following this cohort in a prospective way, which is the intention, may allow us to obtain more insight into the disease course regarding mortality, disease activity and changes in treatment. Overall, the end-organ damage, expressed as DI, was low in this patient group with a disease duration of >10 yr. That the patients followed were not in a remission of their disease is shown in Table 6, which clearly shows that by using the ECLAM disease activity was present in quite a number of patients, like arthritis, rashes, vasculitis etc., but also that in quite a number of patients these symptoms were worsened 2 weeks prior to study inclusion.

The most striking observation in our study is hypertension in 40% of the patients. A deforming arthritis was found in 14% of the patients. Possible adverse effects of treatment consisted of signs of obesity and Cushingoid appearance. Apart from disease- and treatment-related symptoms, we observed avascular necrosis in 7% and serious osteoporosis in 6% of the patients.

Recently, the first data obtained by the European Working Party on Systemic Lupus Erythematosus (Eurolupus project) were published. The aim of this group was to analyse the incidence and characteristics of the main clinical and immunological manifestations of SLE during the evolution of the disease [19]. These data were also derived by a multicentre study with a prospective design. When the data of this Eurolupus project are compared with those of our study, the similarity is striking. Mean age at onset and at diagnosis was 29 and 31 yr in both studies, with the same range, but also the prevalences of most clinical features at onset of the disease were similar to those of our study, indicating that the group of patients presented here are a good representation of SLE patients in general.

Nevertheless, one should consider that the assessment of features at disease onset is obtained in a retrospective way, which means that the number and severity may be underestimations.

The number of our patients is too small to analyse separately the effect of age at onset or gender on the ECLAM and DI as outcome measure at the start of this study. In a recently published study by Gladman *et al.* [20], a cohort of 155 SLE patients was described, defined by a mean disease duration of 12.9 yr, ranging from 0.82 to 44.9 yr. In this cohort, a mean SLEDAI of 4.2 is described and a SLICC/ACR DI of 1.2. However, it is not possible to compare these results with those of our study, because our patients overall had a longer disease duration. Yet, the study of Gladman *et al.* revealed that after a mean disease duration of 12.9 yr, patients still have complaints and need treatment. However, the extent of end-organ damage was rather limited at longer disease duration, as is the case in our patients. In their study, no correlation between SLEDAI and SLICC/ACR DI was shown, in contrast to our study. This may be explained by the wider range of disease duration in their study. That both disease activity scoring systems (SLEDAI and ECLAM) are strongly correlated with each other was already shown in previous studies.

In one of the first studies related to the course of the disease over time, it was shown that major events, e.g. exacerbations of disease, will develop mainly in the first few years following onset of disease [21]; an observation recently confirmed by Drenkard *et al.* [22]. By following our patients, more reliable data will be obtained about the incidence of exacerbations in a patient cohort with a disease duration of >10 yr.

In conclusion, our multicentre study of SLE patients defined by a disease duration of >10 yr showed that these patients still needed some form of treatment. Seventy-two per cent of the patients were treated with corticosteroids, maintained because of the presence of some disease activity. The overall accumulated end-organ damage in our patient group was comparable with previous studies [19]. Clinical features with the greatest impact on the DI were deforming arthritis and renal involvement, as well as the central nervous system. The most striking and unexpected feature was the high prevalence of hypertension. The latter, however, may also be related to therapy.

Note

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