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PAPER

Early Lupus Project – A multicentre Italian study on systemic lupus erythematosus of recent onset

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Background: Systemic lupus erythematosus (SLE) is an autoimmune disease with a high degree of variability at onset that is problematic for a correct and prompt diagnosis. We undertook this project with the purpose of collecting an inception cohort of Italian patients with recent-onset SLE, in order to obtain information on the main clinical and serological characteristics at the beginning of the disease. In this first report we describe the characteristics of this cohort at study entry. **Methods:** All patients with a diagnosis of SLE (1997 ACR criteria) and a disease duration less than 12 months were consecutively enrolled between 1 January 2012 and 31 December 2013 in a multicentre prospective study. Information on clinical and serological characteristics at study entry and then every six months was collected into a specific electronic database. Statistical analysis was performed by means of the Openstat program. **Results:** Among 122 patients enrolled (103 F) 94.3% were Caucasians. Mean age (SD) of patients at study entry was 37.3 (14.3) years, mean age at disease onset was 34.8 (14.3) years, mean age at diagnosis was 36.9 (14.3) years, and mean disease duration was 2.9 (3.9) months. The frequency of the manifestations included in the 1997 ACR criteria was as follows: ANA 97.5%, immunologic disorders (anti-dsDNA, anti-Sm, antiphospholipid antibodies) 85.2%, arthritis 61.8%, haematologic disorders 55.7%, malar rash 31.1%, photosensitivity 29.5%, serositis 27%, renal disorders 27%, oral/nasal ulcers 11.5%, neurologic disorders 8.2%, and discoid rash 5.7%. The cumulative frequency of mucocutaneous symptoms was 77.8%. At enrolment, autoantibody frequency was: ANA 100%, anti-dsDNA 83.6%, anti-SSA 28%, anticardiolipin 24.5%, anti-nRNP 20.4%, anti-beta2GPI 17.2%, lupus anticoagulant 16.3%, anti-Sm 16%, and anti-SSB 13.1%. **Conclusions:** In this paper we describe the main clinical and serological characteristics of an Italian inception cohort of patients with recent-onset SLE. At disease onset, mucocutaneous manifestations, arthritis and haematologic manifestations were the most frequent symptoms; ANA, anti-dsDNA and complement reduction were the most frequent laboratory findings. Our data confirm that the diagnosis of SLE is a challenging one, and that SLE is a severe disease even at onset, since the majority of patients require at least a hospitalization before the diagnosis. *Lupus* (2015) **0,** 1–7.

Key words: Systemic lupus erythematosus; recent-onset SLE; early SLE; autoantibodies; anti-DNA antibodies; anticardiolipin antibodies

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease mostly affecting women during their 30s and 40s. Its nature of 'multisystemic disease' is associated to a high degree of variability at onset, from more specific symptoms such as the typical malar rash, nephropathy and anti-double-stranded DNA antibodies (anti-dsDNA), to very nonspecific findings such as fever, anaemia, arthritis and antinuclear antibodies (ANA). Thus, especially at the onset the diagnosis of SLE can be challenging, in some cases even for experienced physicians, and this can result in dangerous

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diagnostic delay. A prompt diagnosis is usually followed by the adoption of the appropriate therapy, with important impact on the patient's prognosis. In addition, the natural history of SLE is characterized by episodes of relapses or flares intercalated with remissions, and the outcome is highly variable, ranging from sustained remission to death. In recent decades, both morbidity and mortality have been modified for a number of possible reasons, including a better knowledge of the pathogenetic mechanisms and prognostic factors of SLE, the reduction of the time elapsing from disease onset and diagnosis, and the use of immunosuppressive regimens.[1–3]

For these reasons, and because of the importance of assessing the clinical and serological profile of SLE patients at the start of their disease, we focused our attention on an inception cohort of lupus patients with short disease duration (less than 12 months), coming from eight Italian centres.

Our objective was to prospectively collect the demographic, clinical and serological characteristics of this Italian population of SLE patients with recent disease onset, for the purpose of obtaining information on the relative impact of these characteristics on disease course and prognosis.

In this first report we describe the population and disease characteristics at the study entry of the patients as yet enrolled.

Patients and methods

This is a multicentre prospective study. Eight Italian centres with longstanding experience in lupus management are involved. All patients with a diagnosis of SLE according to the 1997 American College of Rheumatology (ACR) Classification Criteria[4] and disease duration (from diagnosis until study entry) less than 12 months were consecutively enrolled in the study. The study started on 1 January 2012; in this paper we report the data of those patients enrolled until the end of December 2013.

This study received the approval of the local ethics committee. Informed consent was sought and signed by the patients in order to participate in the study.

Information on demographic characteristics, medical history, clinical symptoms, physical examinations, laboratory results, disease activity, disease damage, patient quality of life, at entry into the study and then every six months, was collected on a specific form and subsequently transferred into a specific electronic database. Global SLE disease activity was measured by the European Consensus Lupus Activity Measurement (ECLAM), a validated measure of disease activity in SLE.[5,6] Cumulative damage was scored according to the Systemic Lupus International Collaborating Clinics (SLICC) Damage Index, a validated measure to assess damage in SLE.[7] Patient quality of life was estimated by means of a visual analogue scale (VAS).

Autoantibody assessments

Autoantibodies were detected locally in each participating centre. The following autoantibodies were considered in this study: ANA, anti-dsDNA, anti-SSA (Ro), anti-SSB (La), anti-Sm, anti-RNP, anticardiolipin (aCL), anti-beta2 glycoprotein I (anti-beta2GPI), and lupus anticoagulant (LA). ANA were detected by indirect immunofluorescence using Hep2 cells as substrate. Anti-dsDNA were detected either by indirect immunofluorescence using *Crithidia luciliae* or Farr assay. Anti-SSA, anti-SSB, anti-Sm, and anti-RNP were detected by immunoblot technique. aCL antibodies and anti-beta2GPI were measured by enzyme-linked immunosorbent assay (ELISA).[8,9] LA was measured by coagulometric assay.[10] Importantly, in each centre the same technique was used throughout the study.

Statistical analysis

Statistical analysis was performed by means of the Openstat program using the information stored in the database program. Conventional chi-square and Fisher exact test were used for analysing qualitative differences. A p value less than 0.05 was taken to indicate statistical significance. Continuous variables are indicated as mean $\pm$ standard deviation (SD) or median and range, as appropriate.

Results

During a two-year period, we enrolled 122 patients with recent-onset SLE (103 female (F), 84.4%, 19 male (M), 15.6%). There were 115 (94.3%) Caucasian patients and seven (5.7%) of other ethnicities. Mean age (SD) of patients at study entry was 37.3 (14.3) years, mean age at disease onset (first symptom of SLE) was 34.8 (14.3) years, and mean age at diagnosis was 36.9 (14.3) years. Mean

disease duration (from diagnosis until study entry) was 2.9 (3.9) months. Demographic features of this cohort are more extensively depicted in Table 1.

The frequency (from onset until enrolment) of the manifestations included in the classification criteria is reported in Table 2. The cumulative frequency of the mucocutaneous classification criteria was 77.8%, confirming that they are among the most common clinical manifestations included in the ACR classification criteria at SLE onset. ANA were present in all but three patients at disease onset. Two of these three ANA-negative patients had anti-Ro antibodies, and one patient had antiphospholipid antibodies only (aCL anti-beta2GPI at medium-high titre). All the three patients reported to be ANA negative at disease onset were found to be ANA positive at the enrolment visit.

The frequency of the clinical and serological features of this cohort of patients as detected at the enrolment visit is reported in Table 3. With respect to neuropsychiatric manifestations, five patients presented lupus headache, four cerebrovascular disease, three organic brain syndrome, two cerebral vasculitis, two polyneuropathy, one with psychosis and one with seizure disorders. Of the gastrointestinal manifestations, five patients presented peritonitis, two lupus hepatitis, two protein-losing enteropathy, and one patient acute lupus pancreatitis. Of the renal manifestations, 35 patients presented proteinuria (seven with nephrotic syndrome), 19 had biopsy-proven nephritis (class iii or iv in 15 cases, class v in four cases), and six had serum creatinine level above the normal limit. Among cardiorespiratory problems, 13 patients had pericarditis, 12 pleurisy, six pleural effusion with dyspnea, three interstitial alveolitis/

Table 1 Demographics of the 122 patients with recent-onset SLE

Women, no. (%)	103 (84.4)
Ethnicity, no. (%)	
White	115 (94.3)
Black	4 (3.3)
Asian	3 (2.4)
Age at onset (first symptom/s of SLE), mean (SD) years	34.8 (14.3)
Age at diagnosis (fulfilment of ACR criteria), mean (SD) years	36.9 (14.3)
Age at enrolment, mean (SD) years	37.3 (14.3)
Disease duration (from diagnosis until enrolment), mean (SD) mo	2.9 (3.9)
Marital status %	
Married	46.8
Single	34.5
Widowed	1.8
Divorced	–
Separated	1.8
Partner	14.7
Years of school education	
<8, no. (%)	2
8–13	69
>13 no. (%)	29
Smoking	
Ever smoked, no. (%)	47.4
Actually smoking, no. (%)	31

SLE: systemic lupus erythematosus; ACR: American College of Rheumatology.

Table 2 Frequency (from onset until enrolment) of the manifestations (%) included in the ACR classification criteria in the cohort of 122 patients with recent-onset SLE

ANA	97.5
Immunologic disorders[a]	85.2
Arthritis	61.8
Haematologic manifestations	55.7
Malar rash	31.1
Photosensitivity	29.5
Serositis	27
Nephropathy	27
Mucosal ulcers	11.5
Neurologic disorders	8.2
Discoid rash	5.7

[a]Anti-double-stranded DNA (anti-dsDNA), anti-Sm, antiphospholipid antibodies.
ACR: American College of Rheumatology; SLE: systemic lupus erythematosus; ANA: antinuclear antibodies.

Table 3 Frequency (%) of clinical symptoms and immunological features at study entry in the cohort of 122 patients with recent-onset SLE

Musculoskeletal	57.1
Constitutional	50
Mucocutaneous	50
Haematological	38.9
Renal	28.6
Cardiorespiratory	17.8
Neuropsychiatric	14.3
Gastrointestinal	5.4
Ophthalmic	1.8
ANA	100
Anti-dsDNA	83.6
Low C4	51.8
Low C3	49.5
Anti-SSA (Ro)	28
aCL	24.5
Anti-nRNP	20.4
Anti-beta2GPI	17.2
Lupus anticoagulant	16.3
Anti-Sm	16
Anti-SSB (La)	13.1

SLE: systemic lupus erythematosus; ANA: antinuclear antibodies; aCL: anticardiolipin antibodies; anti-beta2GPI: anti-beta2 glycoprotein I antibodies.

pneumonitis, and two lupus endocarditis. Ophthalmic problems were very rare; one patient had keratitis and another one orbital inflammation.

Drug therapy at study entry is reported in Table 4. Widespread use of glucocorticoids in lupus patients (85.1%) at study entry is evident compared with other immunosuppressive drugs. Hydroxychloroquine is given to a high proportion of patients too (63.6%).

The frequency of the clinical and serological characteristics at study entry in female patients compared with males is reported in Table 5. Even though the numbers are too small, it appears that male patients are more often affected by neuropsychiatric and musculoskeletal symptoms, whereas female patients have more haematological problems and anti-Ro antibodies.

At the enrolment visit, median (range) disease activity (ECLAM) was 4 (0–10), median damage (SLICC) was 0 (0–3), and median patient quality of life (VAS) was 53 (0–100).

Eighty-three patients had at least one hospitalization in the period from diagnosis until study entry. The mean (SD) hospitalization number was 1.54 (1.58), and median (interquartile range) was 1 (1–2); the mean number of days of hospitalization was 14.4 (14.5), and median was 12 (0.5–20.5).

Table 4 Drug therapy (%) at study entry in the cohort of 122 patients with recent-onset SLE

Drug	
Prednisone	85.1
Hydroxychloroquine	63.6
Azathioprine	10.7
Cyclophosphamide	9.1
Cyclosporine A	0
Methotrexate	10.7
Mycophenolate	7.4
Rituximab	0.8
Belimumab	0.8
Epratuzumab	0.8
Abatacept	0
Other DMARD[a]	5

[a]DMARD: disease-modifying antirheumatic drug.
SLE: systemic lupus erythematosus.

Table 5 Clinical symptoms and serological features (%) at study entry in 103 female and 19 male patients

	Female	*Male*
Constitutional	47.2	52.9
Mucocutaneous	46.7	50
Neuropsychiatric	9.9	16.6
Musculoskeletal	56	77.7
Cardiorespiratory	16.5	23.5
Gastrointestinal	6.6	0
Ophthalmic	3.3	0
Renal	31.5	27.8
Anaemia	20.6	9.1
Leucopenia	28.9	22.2
Thrombocytopenia	4.3	0
Low C3	50.5	44.4
Low C4	52.2	50
ANA	100	100
Anti-dsDNA	84	80
Anti-SSA (Ro)	38.6	26.3
Anti-SSB (La)	15.8	15.8
Anti-Sm	14.3	16.7
Anti-nRNP	21.7	16.7
aCL	30.4	37.5
Anti-beta2GPI	24.3	20
Lupus anticoagulant	20.8	18.7
ECLAM (mean)	3.1	3

ANA: antinuclear antibodies; Anti-dsDNA: anti-double-stranded DNA antibodies; aCL: anticardiolipin antibodies; anti-beta2GPI: anti-beta2 glycoprotein I antibodies; ECLAM: European Consensus Lupus Activity Measurement.

Discussion

In the present study we analysed the prevalence of the most relevant clinical and serological features in a cohort of SLE patients with recent disease onset. Our data confirm a previous observation that SLE onset is during the fourth decade of life in the majority of patients. We observed a slightly higher representation of men compared with previous studies.

In our cohort, only 31.1% of patients presented with the typical malar rash at onset. Conversely, a greater proportion of patients presented with non-specific symptoms, such as arthritis and constitutional symptoms such as fever (about 50%). This could make the early diagnosis of SLE more difficult. On the other hand, the relatively high proportion of musculoskeletal manifestations at SLE onset suggests that a prompt referral of such patients to the rheumatologist could significantly reduce the delay of the correct diagnosis.

Recently, Nossent et al. described the early disease course in a European multinational inception cohort of 200 SLE patients. Similarly to us, they showed that arthritis was a predominant symptom at SLE onset, but in their patients leucopenia (54%) and malar rash (53%) were also more prevalent (in our study they are 27.9% and 31.1%, respectively), suggesting that SLE phenotypes are susceptible to genetic and geographic influences.[11]

Mean age at onset of symptoms in our patients was about 35 years; at the fulfilment of four or

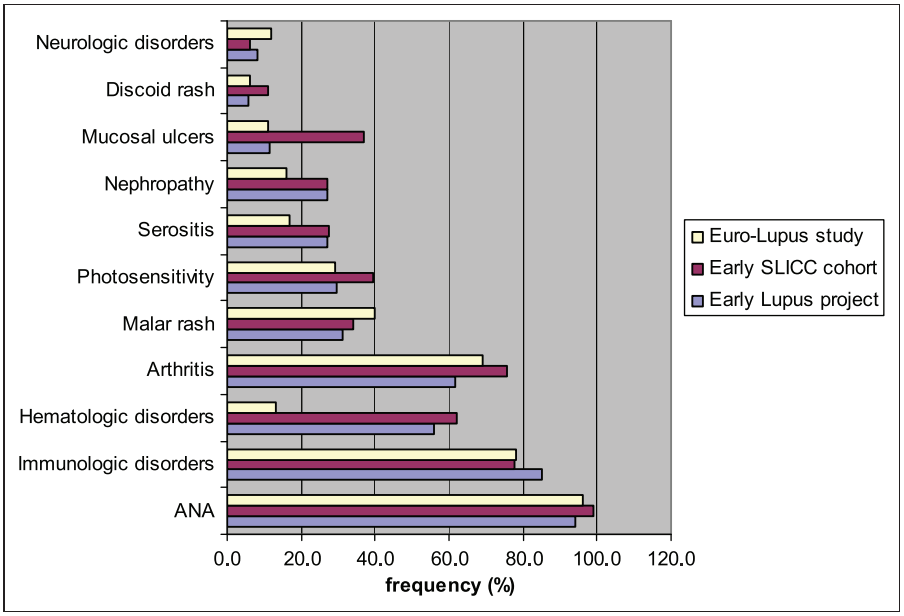

Figure 1 Prevalence of the manifestations included in the 1997 ACR classification criteria at the onset of the disease in the present cohort (Early-Lupus project) compared with the Early SLICC cohort and the Euro-Lupus study.
ACR: American College of Rheumatology; SLICC: Systemic Lupus International Collaborating Clinics.

more of the ACR criteria of SLE, the mean age was about 37 years. Therefore, the mean time between the first manifestations and the final classification of SLE was about two years. The lag time between the onset and the diagnosis of SLE reported in major cohort studies was approximately 50 months before 1980[12] and approximately 25–26 months after 1980.[13] The progressive decrease in the time elapsed between disease onset and diagnosis is one of the major contributors to the improvement of survival[14] and quality of life[15] in SLE patients over time. However, additional efforts should be made in order to further improve the diagnostic procedures which could help with earlier diagnosis of SLE.

Anti-dsDNA antibodies, the hallmark antibody for SLE diagnosis, were present at baseline in the large majority of patients (78%) and resulted in the most frequent SLE-specific classification criterion. A similar high prevalence of anti-dsDNA antibodies was also seen in the Euro-Lupus study (78%) and greatly exceeds the 21% prevalence in the Caucasian patients in the LUpus in MInorities: NAture vs. nurture (LUMINA) cohort.[16] Whether this reflects differences in testing strategies or type of anti-DNA assays or a true difference in disease characteristics remains to be determined. The second most important serological feature was hypocomplementaemia in about 50% of patients. Low complement levels are much more prevalent in SLE than in other connective tissue and inflammatory joint diseases, and, when combined with the presence of anti-dsDNA, will probably also be highly specific for SLE, strongly suggesting the diagnosis.

In Figure 1, the prevalence of the major clinical features as well as of the major immunologic features at onset of the disease in the present cohort is compared to that reported in two large previous studies, the Early SLICC cohort[17] and the Euro-Lupus project.[18] When looking at these data in comparison, it appears that haematologic manifestations, serositis and nephritis are much less represented in the Euro-Lupus study than in our cohort and in the SLICC one, whereas mucosal ulcers are more frequent in the Early SLICC cohort. It is hard to explain these discrepancies, probably related to different enrolment criteria or to the different ethnic composition of the cohorts. Furthermore, whereas our study and the SLICC cohort included patients with recent disease onset, the Euro-Lupus study included consecutive lupus patients with no regard to disease onset, and was performed during the last decade of the 1990s, 20 years previously compared with the present study. It is possible that the higher frequency of nephropathy and haematologic disorders in our cohort reflect a better awareness of the disease and related problems at the present time than in the past.

Another debate is whether lupus among males has a particular clinical phenotype. Opinions have varied. Some authors have seemed more convinced

that lupus in males may take a more severe course,[19] in particular with an increased incidence of renal disease, serositis, thromboses and discoid skin disease. However, the reports have been inconsistent and, like many studies of SLE, are complicated by disparities in ethnicity, duration of follow-up and selection bias.[20] The greater awareness of SLE as a potential diagnosis particularly in fertile females as compared with the concept of the relative rarity of the disease in males, may lead to a greater delay in diagnosis in men with similar symptoms. Alternatively, if men displayed an atypical phenotype at presentation, a delay in diagnosis, and thus treatment, might result. The consequence would be a greater burden of inflammation and subsequent damage over time. Complicated by low patient numbers, studies that fail to apply corrections for differences in disease duration, ethnicity, comorbidities or other potential selection bias may lead to a skewed representation of the clinical phenotype in men.

Nonetheless, there are suggestions that a number of clinical characteristics may be differentially expressed. There is consistent evidence for a reduced incidence of Raynaud's phenomenon, alopecia, malar rash and arthralgia/arthritis in men at presentation and in the subsequent disease course. In contrast, it cannot be reliably said that there is a definite increased incidence of nephropathy, thrombotic episodes, damage or, most importantly, a greater mortality risk. In the present cohort, composed of Italian patients, men presented more often with neuropsychiatric problems and musculoskeletal symptoms, whereas women presented with haematological manifestations and anti-Ro antibodies.

Our preliminary results show that the disease activity is quite moderate in SLE patients at disease onset, and the damage is low, suggesting that a prompt diagnosis followed by early treatment could impact favourably on the prognosis.

However, much has to be done concerning the therapy, given that almost all patients are treated by corticosteroids, and this may negatively influence long-term morbidity and mortality.[21–23] Indeed, in addition to their common and well-known side effects, in SLE more than in other conditions, prolonged corticosteroid therapy is associated with an increased risk of infection.[24–28]

About two-thirds of our patients had at least a hospitalization during the short period between diagnosis and study entry, thus confirming that SLE is a severe disease even at onset, with impact both on patient quality of life and on the burden of costs for the community.

In conclusion, in this paper we have shown the preliminary results of a multicentre prospective study of a cohort of Italian patients affected by SLE at disease onset, describing the demographic and clinical characteristics obtained at patient enrolment and making comparison with other reports of similar patients.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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