Disease activity patterns in a monocentric cohort of SLE patients: a seven-year follow-up study

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Abstract

Objectives

To evaluate disease activity patterns and flare occurrence in a cohort of systemic lupus erythematosus (SLE) patients.

Methods

Patients registered in our lupus Database, diagnosed with SLE between 1991 and 2004 and followed up quarterly from 2004 to 2010 were considered in the study. Disease activity patterns were defined using SLE Disease Activity Index-2000 (SLEDAI-2K), excluding serology, as follows: clinical quiescent disease (CQD), SLEDAI-2K=0 in the three annual visits; minimal disease activity (MDA), SLEDAI-2K=1 in one or more annual visits; chronic active disease (CAD), SLEDAI-2K≥2 in at least two annual visits; relapsing-remitting disease (RRD), SLEDAI-2K≥2 in one out of 3 annual visits. Flare was defined as an increase in SLEDAI-2K≥4 from the previous visit, according to SELENA-SLEDAI flare index.

Results

One hundred and sixty-five patients fulfilled the inclusion criteria. During the 7 year follow-up, 109 (66%) patients experienced at least one period of active disease (CAD, RRD and MDA), whereas 56 patients (34%) had a persistent CQD. The mean±SD number of patients in each pattern per year was: CAD 52.4±5.8 (31.7%), RRD 16.1±6.8 (9.7%), MDA 9.7±1.7, (5.9%), CQD 87±10.5 (52.6%). Annual flare-rate was 0.19 flare per patient/year and mean±SD number of flares was higher in CAD compared with RRD patients ($p<0.01$). At the multivariate analysis positive anti-dsDNA antibodies, low C3 or C4, male sex, longer lag time between SLE onset and diagnosis, higher number of flares, and use of immunosuppressant were independently associated with active disease including CAD and RRD patterns.

Conclusion

Two-thirds of our patients developed at least one period of active disease during the 7-year follow-up despite tight monitoring and standard treatment.

Key words

systemic lupus erythematosus, disease activity patterns, SLEDAI-2K, SLE activity index, lupus flares, lupus follow-up.

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease characterised by a variety of clinical manifestations and organ involvement (1, 2). Disease activity often fluctuates over time and flare can occur even in patients with a previously inactive disease, which makes these flares often unpredictable.

Recent randomised controlled trials (RCTs) confirmed the heterogeneity of SLE course and highlighted the difficulties in defining clinically relevant outcomes (3-5).

Some indices have been developed in order to identify disease activity in SLE patients; the most used in clinical trials are Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (6), the SLEDAI 2000 (SLEDAI-2K) (7), the Modified SLEDAI (M-SLEDAI) (8), and British Isles Assessment Group index (BILAG) (9) and currently there is no consensus on which of them is the most suitable index to describe SLE activity (10).

However, looking at the variation of disease activity score over time, three major patterns of disease activity have been identified in previous studies (8, 11-13): chronic active, defined as persistent disease activity over time; relapsing-remitting, characterised by periods of disease activity interspersed with periods of disease inactivity; long quiescent, defined as absence of disease activity. However, the definitions of patterns used in these studies (8, 11-13) are different, which makes the comparison of the results difficult. Moreover, in these studies patients with minimal disease activity were considered in the same group of those with chronic disease activity although the therapeutic approach to these patients is different.

The evaluation of SLE course is crucial in estimating the number of patients who could benefit from the introduction of the new targeted therapies.

The aim of our study was to examine disease activity patterns and flare occurrence in a monocentric cohort of SLE patients monitored during a 7-year follow-up.

Patients and methods

We used our Lupus Database which included patients recruited between 1970 and 2010. Patients attending our outpatient clinic, diagnosed with SLE after 1990 and before 2004 and seen at least every four months between January 2004 and December 2010 were included in the study.

All patients met at least four of the revised American College of Rheumatology Classification criteria for SLE (14). Clinical and laboratory findings were recorded at each visit according to standardised protocol and were stored in a dedicated database.

Definitions of disease activity patterns

Disease activity was monitored using the SLEDAI-2K index which was calculated at each visit. Disease activity patterns were evaluated at each year of observation in order to obtain their annual incidence.

Annual disease activity patterns were defined using SLEDAI-2K, excluding serology, as follows: clinical quiescent disease (CQD), a SLEDAI-2K=0 in the three annual visits; minimal disease activity (MDA), a SLEDAI-2K=1 in one or more annual visits; chronic active disease (CAD), a SLEDAI-2K≥2 in at least two out of the three annual visits; relapsing-remitting disease (RRD), a SLEDAI-2K≥2 in one out of 3 annual visits. We excluded serology in order to focus our study on clinical activity.

The CQD pattern describes disease characterised by absence of activity for at least 1 year. This minimal time interval was selected to be consistent with criteria for remission (10, 15).

The CAD pattern reflects a disease which continues to be active for at least 8 months per year. The interval of eight months was chosen because it was considered to be clinically meaningful. The RRD pattern describe a fluctuating disease activity over one year, with periods of activity interspersed with periods of silent disease. We have introduced the pattern of MDA characterised by periods of minimal disease activity which are variable in length. The therapeutic approach to patients with MDA differs from that used in patients with CAD or RRD.

Laboratory testing

Antinuclear antibodies (ANAs) were determined by indirect immunofluorescence on Hep-2 cell monolayers. A cut-off at 1:160 was considered as clinically significant. Anti-double stranded DNA (anti-dsDNA) antibodies were measured by an enzyme linked immunosorbent assay ELISA (16). Standard laboratory tests were used to determine haemoglobin, white cell count, platelet count, blood urea nitrogen, creatinine and creatinine clearance, C-reactive protein, erythrocyte sedimentation rate, protein profile, transaminases, C3, C4, and urinalysis.

Definition of flare

Flare was defined according to SELENA-SLEDAI definitions of flare (17) and as an increase of SLEDAI-2K≥4 from the previous visit.

We registered the organ systems involved at the time of flare or during a period of disease activity, including renal, musculoskeletal, cutaneous, haematological, serositic, neuropsychiatric, and vasculitic flares. Clinical manifestations were defined using ACR definitions (18, 19).

Statistical analysis

Statistics were performed by the SPSS software for Windows (version 18.0, SPSS, Chicago, IL); chi-square test (Pearson test), one-way analysis of variance (ANOVA), and multivariate analysis (logistic regression analysis) were calculated; a p-value <0.05 was considered significant.

The following variables were considered in the univariate analysis: sex, age, age at the onset of the disease, disease duration, lag-time between SLE onset and diagnosis, SLEDAI-2K score, anti-dsDNA antibodies, low C3 or C4, organ involvement, number and type of flares, therapy including immunosuppressants, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and hydroxychloroquine.

The association between patterns of disease activity and demographic and clinical variables (age, sex, age at the onset of the disease, lag time onset-diagnosis, anti-dsDNA positivity, low C3 or C4, immunosuppressive treatment) was tested by logistic regression analysis: odds ratios (OR) and their 95% confidence intervals (CI) were determined.

Results

Clinical findings

Among 258 consecutive patients who were evaluated, 165 (64%) patients fulfilled inclusion criteria. Thirty-one (12%) patients were excluded from the study because SLE was diagnosed before 1990, 19 patients (7.4%) were excluded because of less than 3 visits per year during the 7-year follow-up, 16 (6.2%) due to incomplete data records, and 27 (10.5%) due to lost-to-follow-up for more than 6 months. One-hundred and sixty-five patients contributed to a 1155 person-years of follow-up.

Demographic and clinical characteristics of patients are summarised in Table I.

Our patient group consisted of 144 (87.3%) women and 21 (12.7%) men; mean±SD age at the time of the study entry was 37.5±12.4 years, the mean±SD lag-time between disease onset and diagnosis 20.1±19.7 months, and the mean±SD disease duration 10.7±8.0 years.

Table I. Demographic and clinical findings overall in 165 patients included in the cohort and in 1155 patient/years of follow-up according to each disease activity pattern.

	Overall	Pattern of SLE activity (n. of patients/years of follow-up)			
Characteristics		CQD (611)	MDA (68)	CAD (361)	RRD (115)
Age, years, mean ± SD	37.5 ± 12.4	39 ± 13	36 ± 8.6	34.9 ± 11.4	37.7 ± 12.5
Female, n. (%)	144 (87.3)	550 (90)	67 (98)	292 (80.9)	98 (85.2)
Caucasian, n. (%)	165 (100)	611 (100)	68 (100)	361 (100)	115 (100)
Age at the onset, years, mean ± SD	27.1 ± 10.2	28.8 ± 7.2	27.7 ± 4.2	25 ± 9.7	24.9 ± 9.1
SLE duration, years, mean ± SD	10.7 ± 8	11.3 ± 7.8	10.6 ± 6.5	9.7 ± 7.3	10.2 ± 7.8
Lagtime onset-diagnosis, months, mean ± SD	20.1 ± 19.7	18.4 ± 18	17 ± 12.2	21.8 ± 20.5	19.8 ± 14
ANA positivity, n. (%)	165 (100)	611 (100)	68 (100)	361 (100)	115 (100)
Anti-dsDNA Ab, n. (%)	104 (63)	237 (38.8)	45 (66.2)	297 (82.5)*	75 (65.2)
Low C3 or C4 serum levels, n. (%)	127 (76.9)	81 (69.4)	51 (75.1)	322 (89.2)‡	91 (79.1)
Clinical manifestations					
Skin, n. (%)	38 (23.3)	0	0	130 (36.1)	35 (30.4)
Arthritis, n. (%)	25 (15.2)	0	0	61 (16.8)	22 (19.1)
Pleurisy - pericarditis, n. (%)	13 (8.1)	0	0	10 (2.7)	9 (7.8)
Renal, n. (%)	56 (34.4)	0	0	237 (65.6)	60 (52.2)
Neuropsychiatric, n. (%)	4 (2.5)	0	0	3 (0.8)	2 (1.7)
Haematological, n. (%)	27 (16.6)	0	68 (100)	14 (0.38)	8 (6.9)
Vasculitis, n. (%)	7 (4.3)	0	0	7 (1.9)	4 (3.4)
Immunosuppressive therapy (CYF, MMF, Aza, Cy, MTX)	66 (39.9)	110 (18)	38 (55.8)	261 (72.2)§	52 (45.2)

CQD: clinical quiescent disease; MDA: minimal disease activity; CAD: chronic active disease; RRD: relapsing-remitting disease; SD: standard deviation; SLE: systemic lupus erythematosus; ANA: anti-nuclear antibodies; Anti-dsDNA Ab: anti double-stranded DNA antibodies; C3/C4: complement fractions; CYF: cyclophosphamide; MMF: mycophenolate mophetil; Aza: azathioprine; Cy: cyclosporine; MTX: methotrexate.

* CAD *vs*. CQD, p<0.001; CAD *vs*. MDA, p=0.008; CAD *vs*. RRD, p=0.015; ‡ MDA+CAD+RRD *vs*. CQD, p<0.001; CAD *vs*. RRD, p=0.007;

§ MDA+CAD+RRD *vs*. CQD, p<0.001; CAD *vs*. MDA, p<0.001; CAD *vs*. RRD, p<0.001.

Table II. Number (%) of patients with different disease activity patterns according to the year of observation.

	2004	2005	2006	2007	2008	2009	2010
Clinical quiescent disease	72 (43.6)	88 (53.3)	100 (61)	76 (46)	87 (52.7)	88 (53.3)	99 (60)
Minimal activity disease	10 (6.1)	10 (6.1)	8 (4.9)	10 (6.1)	8 (4.9)	13 (7.8)	9 (5.2)
Chronic active disease	64 (39)	55 (33.3)	47 (28.4)	50 (30.5)	51 (30.9)	48 (29.1)	47 (28.4)
Relapsing-remitting disease	19 (11.5)	12 (7.2)	10 (6.1)	29 (17.6)	19 (11.5)	16 (9.8)	10 (6.1)

Annual incidence of CQD, MDA, CAD and RRD is summarised in Table II. The mean±SD number of patients per year of observation was 87±10.5 (52.6%) for CQD, 52.4±5.8 (31.7%) for CAD, 16.1±6.8 (9.7%) for RRD, and 9.7±1.7 (5.9%) for MDA (Fig. 1a). Pooling CAD and RRD patterns and CDQ and MDA patterns, the mean±SD number of patients per year of observation was 68.1±10 (41.3%) for CAD/RRD and 96.8±10.1 (58.7%) for CQD/MDA (Fig. 1b).

Some patients developed more than one pattern of disease activity during the follow-up. The most common switch was between the RRD and CAD pattern, which was observed in eighty-two patients (49.6%). The duration of CAD pattern ranged between 1 and 7 years, with a mean±SD duration of 2.5±1.6 years.

Analysing the whole period of follow-up (7 years), 56 patients (34%) had a persistent CQD, whereas 109 (66%) experienced at least one period of active disease, including CAD, RRD or MDA. In fact, 95 patients (57.5%) experienced *at least* one period of CAD, 69 patients (41.8%) *at least* one period of RRD, and 18 patients (11%) *at least* one period of MDA.

Sixty-two patients (37.5%) experienced an active disease at least for half of the follow-up (3.5 years), including periods of CAD or RRD; 47 patients (28.4%) experienced periods of active disease lasting less than 3.5 years.

Sex, age, age at SLE onset, disease duration and lag-time between disease onset and diagnosis were similar among patients with different patterns of disease activity (Table I).

During the 7-year follow-up, renal involvement was the most prevalent clinical manifestation (34.4%), followed by skin involvement (23.3%), haematological abnormalities (16.6%), arthritis/myositis (15.3%), pleurisy/pericarditis (8.1%), vasculitis (4.3%), and active neuropsychiatric involvement (seizure in 2 cases, mood disorders and psychosis in 1 case, respectively) (Table I). A part from haematologic abnormalities, which occurred in 100% of MDA patients, all other SLE manifestations were absent in CQD and MDA patients and were observed in a similar percentage between CAD and RRD patients (Table I).

The proportion of patients treated with immunosuppressants was higher in patients with active disease (MDA, CAD, RRD) compared with patients with CQD (64.5% *vs*. 18%, $p<0.001$); moreover, patients with CAD were more frequently treated with immunosuppressants compared with those with RRD (72.2% *vs*. 45.2%, $p<0.001$) or MDA (72.2% *vs*. 55.8%, $p<0.001$).

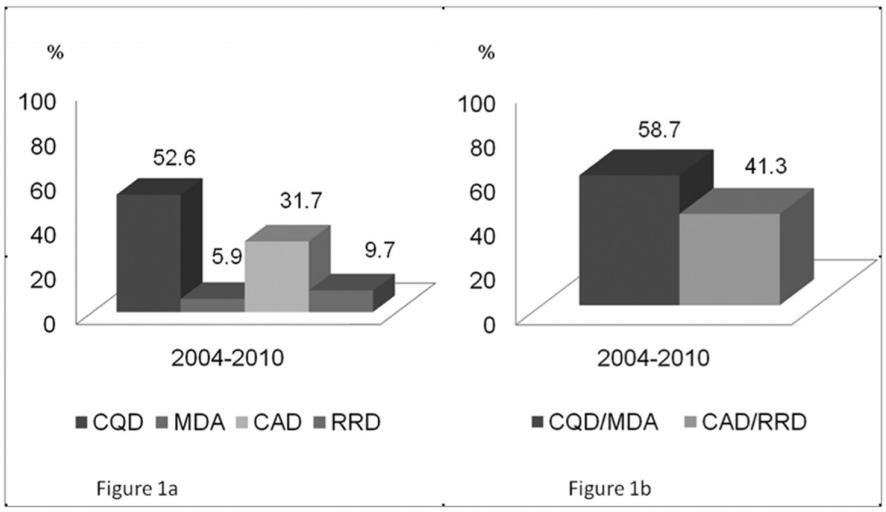

Fig. 1. Mean annual incidence of disease activity patterns in the 165 SLE patients. **Fig. 1a**: Mean annual incidence of CQD, MDA, CAD, and RRD. **Fig. 1b**: Mean annual incidence of CQD/MDA *vs*. CAD/RRD.
CQD: clinical quiescent disease; MDA: minimal disease activity; CAD: chronic active disease; RRD: relapsing-remitting disease; SD: standard deviation; SLE: systemic lupus erythematosus.

Serology

All patients were positive for ANAs and 104 (63%) for anti-dsDNA antibodies. In 49 patients (29.6%) anti-dsDNA antibody levels fluctuated over time. Patients with CAD were more frequently positive for anti-dsDNA antibodies compared to those with other disease patterns (Table I). Notably, among patients who were anti-dsDNA antibody negative, a CQD pattern was more common than CAD, MDA and RRD patterns (73.1% *vs*.26.9%, $p<0.001$).

Hypocomplementaemia (low C3 and/or C4 serum levels) was observed in 76.9% of patients; half of these patients were also positive for anti-dsDNA antibodies (49.5%). Hypocomplementaemia was more frequent in patients with active disease, including MDA, RRD and CAD, compared to those with CQD (Table I, $p<0.001$). Comparing CAD and RRD group, patients with CAD had more frequently low C3 and/or C4 serum levels ($p=0.007$).

Flares

One or more lupus flares occurred during follow-up in 102 patients (61.8%),

whereas 63 patients (38.2%) had no flares; 68 (40.9%) patients experienced more than one flare. Patients who experienced at least one flare were younger compared with those with CQD (35.4±11.5 *vs*. 41.5±14.0, p=0.024).

A total of 221 flares were observed: 120 (54.7%) were mild flares, and 101 (45.3%) severe flares. Among the 221 flares, 153 (69.1%) were observed in patients with CAD, 45 (20.3%) in patients with RRD, and 23 (10.4%) in patients with MDA. The mean±SD number of flares was higher in patients with CAD compared with those with RRD (2.59±1.54 *vs*. 1.86±1.04, p<0.01). In both CAD and RRD patients flares were more frequently due to renal and cutaneous involvement.

Comparing men and women, the proportion of patients with renal flares was higher in male patients compared with female (52.4% *vs*. 31.7%, p<0.001); no other differences in flare incidence (types and number of flares) between male and female subjects were observed. No other differences in terms of demographic and clinical characteristics were observed between patients with and without flares.

Annual incidence of any flares in the whole cohort was 0.19 per patient/year, whereas the annual incidence of mild flares was 0.10 per patient/year, and that of severe flares was 0.09 per patient/year. In patients with CAD, annual rate of severe flares was 0.21 per patient/year, and that of mild flares was 0.22 per patient/year; in patients with RRD and MDA annual rate of severe flares was 0.16 and 0.11 and that of mild flares 0.22 and 0.23, respectively.

Multivariate analysis

Results of multivariate analysis are reported in Table III. Positive anti-dsDNA antibodies, the use of immunosuppressants, and a higher number of SLE flares were independently associated with CAD pattern. In contrast, we did not find any association between the presence of low C3 or C4 serum levels and CAD, probably due to the fact that hypocomplementaemia was considered as a dichotomic variable (present or absent) and thus differences in C3 and/or C4 serum levels were not accountable.

Table III. Multiple logistic regression analysis of factors associated with active patterns of disease activity in the 165 SLE patients.

Variables	Odds ratio	95% CI	p-value
Dependent variable: chronic active disease			
Independent variables:			
Immunosuppressive therapy	3.18	2.26-4.49	<0.001
n. of SLE flares	2.29	1.99-2.64	<0.001
Positive anti-dsDNA	1.68	1.22-2.32	0.002
Dependent variable: active disease patterns (CAD/RRD)			
Independent variables:			
Immunosuppressive therapy	3.01	2.12-4.29	<0.001
n. of SLE flares	2.25	1.95-2.60	<0.001
Positive anti-dsDNA	1.86	1.32-2.61	<0.001
Male sex	1.82	1.14-2.91	0.011
Low C3 and/or C4	1.58	1.01-2.47	0.043
Lag-time onset-diagnosis	1.13	1.04-1.22	0.002

SLE: Systemic lupus erythematosus; Anti-dsDNA: anti double-stranded DNA antibodies; CAD/RRD: chronic active disease and relapsing-remitting disease; C3 and C4: complement fractions C3 and C4; OD: odd ratios; CI: confidence intervals.

No clinical or demographic data were associated with MDA and RRD patterns (data not shown). Moreover, we pooled the data of RRD and CAD patients (CAD/RRD) and evaluated the factors associated with this combined pattern which included the most active patients. Male sex, a longer lag time between SLE onset and diagnosis, immunosuppressants use, low C3 or C4 serum levels, positive anti-dsDNA antibodies, and a higher number of flares were independently associated with combined CAD/RRD pattern.

As expected, male sex, positive anti-dsDNA antibodies and low C3 or C4 serum levels were negatively associated with CQD (male sex OR 0.60, p=0.006, positive anti-dsDNA antibody OR 0.37, p<0.001; low C3 or C4 levels OR 0.47, p<0.001).

Discussion

The variability of disease activity over time is a well known finding in SLE patients. However, controversial data on the prevalence of activity patterns in SLE patients were reported in previous studies (8, 11-13, 15, 20-24) (Table IV).

Seven studies evaluated the prevalence of disease patterns in SLE patients. Unfortunately, different SLE activity indices as well as different definitions of flare and of patterns of disease activity were used in these studies, with the definition of disease activity patterns not clearly reported in some of them (Table IV). In addition, the definitions of disease activity pattern used in some of these studies do not seem to appropriately depict the profile of disease activity observed in clinical practice.

In 1999 Barr *et al*. (8) reported the prevalence of disease activity patterns in a SLE cohort of 204 patients followed for a mean period of 4.5 years; they introduced the concept of RRD defined as a period of disease activity interspersed with periods of clinical quiescent disease. Disease activity was measured by M-SLEDAI score. This might explain the high percentage of RRD found in their cohort, since the M-SLEDAI does not count chronic ongoing manifestations; thus, some patients with CAD might have been classified as RRD.

In 2005 Urowitz *et al*. (12) analysed a cohort of 703 SLE patient and identified two patterns of disease activity: active disease, in patients with SLEDAI>0, which was the more prevalent pattern (75.5% in the first year of observation), and a long quiescent disease in patients with SLEDAI = 0. In this study chronic active and relapsing-remitting disease patterns were not separately evaluated. Notably, in this study serological activity alone was sufficient to classify a patient as having an active disease; this might explain the higher proportion of patients with active disease compared with that observed in our as well as in other cohorts.

Table IV. Observational studies of SLE activity patterns.

Authors	Country	n. of pts	Follow-up	Activity score	Definition of flare	Flare rate	Definition of SLE activity patterns	Outcome	Notes
Nossent 2010	Europe	200	4 years (mean)	PGA	PGA>0 and presence of disease manifestations that required changes in therapy.	0.23 patient/ year interspersed	Differences between RRD and CAD not clearly reported. (i.e. RRD: periods of disease activity with periods of inactivity).	31% QD 27% CAD 42% RRD	New-onset SLE patients (1999-2005).
Laustrup 2010	Europe	94	8 years	M-SLEDAI	M-SLEDAI≥4 from previous visit	0.21 patient/ year	Activity defined as presence of flares (M-SLEDAI≥4). Differences between RRD and CAD not clearly reported.	43% SACQD 57% AD	1995-2003
Otten 2010	Europe	35 JSLE	2.8 years (mean)	SLEDAI	SLEDAI>0 and need for change in therapy	0.45 patient/ year	Activity defined as presence of flares. CAD: chronic activity with need for therapy (PDN>0.3 mg/kg); RRD: periods of flares followed by periods of inactive disease.	37% SACQD 49% CAD 14% RRD	Patients with recent onset of JSLE (2007-2008). Therapy used to define patterns.
Nikpour 2009	Canada	417	2 year	SLEDAI-2K	SLEDAI-2K≥4 from previous visit	0.52 patient/ year	CAD: SLEDAI-2K≥4, excluding serology alone on ≥2 consecutive visits; RRD: presence of flares without achieving CAD definition.	38.3%-44.3%* CQD 52.3%-46.1%* CAD 9.3%-9.6%* RRD	*Pattern proportions refer to 2004 and 2005
Urowitz 2005	Canada	703	1 year	SLEDAI	–	–	SLEDAI>0 Differences between RRD and CAD not clearly reported.	24.5% CQD 75.5% AD	Serological activity alone was considered as AD
Urowitz 2005	Canada	703	5 years	SLEDAI	–	–	SLEDAI>0 at least one time in 5 years. Differences between RRD and CAD not clearly reported.	4.7% CQD 95.3% AD	Also serological activity alone was considered as AD
Barr 1999	USA	204	4.5 years (mean)	M-SLEDAI	M-SLEDAI>0	–	RRD: periods of M-SLEDAI>0 interspersed with M-SLEDAI=0 in at least two annual visits; CAD: M-SLEDAI>0 for at least one year	25% SACQD 40% CAD 35% RRD	Mean annual prevalence of the three patterns was considered
Formiga 1999	Spain	100	6 years	M-SLEDAI	–	–	M-SLEDAI>0	24% SACQD	
Drenkard 1996	USA	667	1 year	M-SLEDAI	–	–	M-SLEDAI>0	23% SACQD without therapy	
Heller 1985	USA	305	At least 6 months	Clinical and serological evalutation	–	–	Inactive disease: clinical inactivity and seroconversion from positive to negative ANA.	4% QD	
Dubois 1964	USA	520	1 year	Clinical evalutation	–	–	Presence of clinical activity	35% CQD	Clinical definition of active/inactive disease, without a score definition

SLE: systemic lupus erythematosus; JSLE: juvenile systemic lupus erythematosus; SACQD: serological active, clinical quiescent disease; CAD: chronic active disease; RRD: relapsing-remitting disease; CQD: clinical quiescent disease; QD: quiescent disease; AD: active disease.

More recently, Laustrup *et al*. (13) published an 8-year follow-up study on disease activity patterns in a cohort of 94 European patients, without providing a clear distinction between CAD and RRD. The disease was considered active in patients who experienced SLE flares, defined as M-SLEDAI≥4 from the previous visit. This definition of active disease prevents the identification of patients with CAD, who might have a stable but increased M-SLEDAI score. In addition, Laustrup's cohort included patients followed from 1995 to 2003, therefore earlier than in our study (2004-2010).

Nossent *et al*. (23) studied a group of 200 new-onset SLE patients diagnosed between 1999 and 2005. A comparison of their results with the previously mentioned studies and with our study is difficult for three reasons: first, Physicians Global Assessment (PGA) instead of SLEDAI/M-SLEDAI/SLEDAI-2K for defining disease activity was used; second, flare was defined as the occurrence of disease manifestations which required a treatment change; third, only new-onset SLE patients were considered.

Otten *et al*. (24) analysed 35 patients with a recent diagnosis of juvenile SLE. The results of this study can not be compared with other studies due to the small sample size and the exclusive inclusion of juvenile SLE patients.

We used the SLEDAI-2K score for measuring disease activity because it describes chronicity better than SLEDAI; in fact, in the SLEDAI score only new onset or recurrence of cutaneous and renal manifestations are considered, whereas in SLEDAI-2K also stable and ongoing involvements are counted. Notably, skin and renal manifestations were the most common manifestations during the 7-year follow-up in our study. Moreover, we defined disease activity patterns using a modified SLEDAI-2K obtained excluding serological descriptors (hypocomplemen-

taemia and anti-dsDNA antibodies) in order to focus our study on clinical activity which represents the main factor which guides our therapeutic decision.

Interestingly, in 2009 Nikpour *et al*. (11) evaluated disease activity patterns in a group of 417 Canadian SLE patients followed for 2 years (2004-2005) and defined CAD as the presence of a SLEDAI-2K≥4, excluding serology alone, on two or more consecutive visits, performed from 2 to 4 months apart, and RRD as presence of disease flares (defined as SLEDAI-2K≥4 from previous visit) without achieving the definition of CAD.

These definitions are in part similar to those used by us. However, in the Canadian study serological descriptors were excluded only when they were concomitantly present without haematological and clinical manifestations otherwise they were counted for defining CAD and RRD.

We have also introduced the MDA pattern which identified a small group of patients with mild manifestations, mostly haematological, which were not captured using Nikpour definition of CAD and, thus, were included among patients with quiescent disease.

In addition, in the Nikpour study the visits were performed at intervals ranging between two and four months, which means that the minimal period of disease activity in the definition of CAD was 4 months, whereas in our study it was eight months.

These differences and, in addition, the different ethnicity of the two cohorts (100% caucasian patients in our study) can account for the higher proportion of active patients in the Nikpour study compared to that observed in our cohort.

A critical aspect in the definition of disease activity patterns is whether or not to consider lupus treatment, particularly in the definition of CQD. Indeed, it is clear that CQD in patients on treatment is much more frequent than in those free of therapy (25). In this cohort we included patients on medications in the CQD group in order to be consistent with the daily clinical practice, since treatment is usually discontinued only after a long period of time from the achievement of clinical remission. Thus, our definition of CQD led us to classify patients as inactive as soon as disease remission was achieved. This definition could also explain the higher proportion of inactive patients observed in our cohort compared with that reported by others (Table 4).

Interestingly, a longer lag-time between onset and diagnosis (meaning a longer period of disease activity without treatment) was associated with the occurrence of CAD/RRD pattern, suggesting that early diagnosis and treatment remain an unmet-need in SLE patients (25-27).

In our study we observed an association between positive anti-dsDNA antibodies and CAD and combined CAD/RRD patterns. Notably, among patients who were anti-dsDNA antibody negative, a CQD was more common than CAD, MDA and RRD, which means that negative anti-dsDNA antibodies have a high negative predictive value for active disease patterns (CAD, RRD, MDA).

In conclusion, in our study the annual prevalence of disease activity patterns was similar through the period 2004-2010. Using a definition of disease activity patterns which was as adherent as possible to the clinical profile of SLE patients, we demonstrated that two-third of patients experienced at least one period of CAD, RRD, or MDA during the entire follow-up, despite a tight monitoring and a standard treatment. Thus, the identification of new predictive biomarkers and the development of new molecules is still needed in order to abrogate disease activity and decrease recurrences, increasing disease survival and quality of life of SLE patients (28-30).

Recently a new biological agent, belimumab (31), has been approved for SLE by the Food and Drug Administration (FDA) in United States (32) and by the European Medicines Agency (EMA) in Europe (33), and this was after a wait of several years in which no new drug has been approved for the treatment of SLE (34, 35). Other new drugs are currently under investigation and, thus, our study may represent a useful tool to estimate the number of SLE patients who might benefit from the availability of these new targeted therapies.

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