EXTENDED REPORT

Lupus low disease activity state is associated with a decrease in damage progression in Caucasian patients with SLE, but overlaps with remission

Margherita Zen, Luca Iaccarino, Mariele Gatto, Francesca Saccon, Maddalena Larosa, Anna Ghirardello, Leonardo Punzi, Andrea Doria

Handling editor Tore K Kvien

Department of Medicine, University of Padova, Division of Rheumatology, Padova, Italy

Correspondence to
Professor Andrea Doria, Division of Rheumatology, Department of Medicine,University of Padova, Padova 35128, Italy; adoria@unipd.it

Received 7 April 2017
Revised 4 August 2017
Accepted 15 September 2017
Published Online First 26 September 2017

ABSTRACT

Objective To evaluate the prevalence, duration and effect on damage accrual of the 'Lupus Low Disease Activity State' (LLDAS) in a monocentric cohort of patients with systemic lupus erythematosus (SLE).

Methods We studied 293 Caucasian patients with SLE during a 7-year follow-up period. Disease activity was assessed by SLE Disease Activity Index 2000 (SLEDAI-2K) and SELENA-SLEDAI physician global assessment (PGA), and damage by Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). We considered the following definition of LLDAS: SLEDAI-2K ≤4 without major organ activity, no new disease activity, PGA (0–3)≤1, prednisone ≤7.5 mg/day and well-tolerated immunosuppressant dosages. The effect of LLDAS on SDI was evaluated by multivariate regression analysis. We also evaluated remission defined as clinical SLEDAI-2K=0 and prednisone ≤5 mg/day in patients treated with/without stable immunosuppressants and/or antimalarials.

Results LLDAS lasting 1, 2, 3, 4 or ≥5 consecutive years was achieved by 33 (11.3%), 43 (14.7%), 39 (13.3%), 31 (10.6%) and 109 (37.2%) patients, respectively. Patients who spent at least two consecutive years in LLDAS had significantly less damage accrual compared with patients never in LLDAS (p=0.001), and they were significantly less likely to have an increase in SDI (OR 0.160, 95% CI 0.060 to 0.426, p<0.001). On average, 84% of patients in LLDAS also fulfilled the criteria for remission.

Conclusions LLDAS was associated with a decrease in damage progression in Caucasian patients with SLE. The majority of patients in LLDAS were in remission, which can largely contribute to the protective effect of LLDAS on damage accrual.

INTRODUCTION

Despite the improvement in the diagnosis and treatment of the disease, patients with systemic lupus erythematosus (SLE) continue to be at high risk of morbidity and mortality.[1]

The efficacy of the treat-to-target approach in improving disease outcomes has recently been demonstrated in rheumatoid arthritis (RA) and other rheumatic diseases.[2–6]

Indeed, remission and low disease activity (LDA) are currently used as clinical targets in the management of patients with RA.[7] Unfortunately, the concept of remission in SLE is less clear than in RA, and a widely accepted definition of remission to be used as therapeutic target in SLE does not exist yet.[8] In 2016, an international panel of experts and patient representatives (DORIS—Definition Of Remission In SLE) achieved a consensus, providing a framework for testing different definitions of remission against long-term outcomes, including death and irreversible organ damage.[9] In line with these suggestions, we have tested a definition of remission in our cohort of Caucasian patients with SLE.[10 11] We demonstrated that remission, defined using clinical, serological and therapeutic criteria, was not rare, and remission lasting at least two consecutive years was associated with a decrease in damage progression.[11]

Recently, Franklyn *et al*[12] suggested a definition of LDA in SLE (the lupus low disease activity state, LLDAS), and they tested this definition in their single-centre SLE cohort. They showed that patients followed up for a mean period of 3.9 years (range 0.06–6.9 years) who spent more than 50% of their follow-up time in LLDAS accrued significantly less organ damage than other patients.

The aim of our study was to assess the prevalence of LLDAS, to evaluate its protective effect against damage in our Caucasian SLE cohort and to identify the shortest duration of LLDAS associated with less damage progression in SLE.

PATIENTS AND METHODS

Caucasian patients with lupus prospectively followed at our lupus clinic were eligible for inclusion in the study if they met the SLE American College of Rheumatology (ACR) classification criteria,[13] were diagnosed with SLE between January 1990 and December 2008, and had at least three visits per year, no more than 5 months apart, in the 7-year period from January 2009 to December 2015 (an incomplete follow-up due to death did not exclude patients from the study). All patients provided an informed consent before the inclusion in the study.

Information collected at baseline included demographics (age, gender, year of first symptom, year of diagnosis), disease manifestations at baseline and over patients' disease course, current and previous therapies, complement (C3 and C4) serum levels, antinuclear antibody, antiextractable nuclear antigen antibodies, antidouble-stranded DNA (anti-dsDNA) and antiphospholipid antibodies. The cumulative prednisone dose (g) taken by patients before baseline was calculated.

To cite: Zen M, Iaccarino L, Gatto M, *et al*. *Ann Rheum Dis* 2018;**77**:104–110.

Clinical and laboratory findings (complete blood cell count, urea and electrolytes, liver function tests, complement and anti-dsDNA serum levels, urinary sediment and 24-hour proteinuria) and data regarding therapy were recorded at each visit.

SLE activity was measured by the SLE Disease Activity Index 2000 (SLEDAI-2K) and Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA)-SLEDAI physician global assessment (PGA, scale 0–3) at each visit. Organ damage was assessed by the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI), which was calculated at baseline and annually thereafter. SDI increase was defined as the difference between SDI at the end and at the beginning of the follow-up ('SDI increase'='SDI at the end of 2015' – 'SDI at the beginning of 2009'). Antiphospholipid antibody syndrome (APS) was defined according to the revised Sapporo criteria.[14]

LLDAS was defined as recently reported by Franklyn *et al*[12]: (1) SLEDAI-2K ≤4, with no activity in major organ systems (renal, central nervous system, cardiopulmonary, vasculitis, fever), and no haemolytic anaemia or gastrointestinal active involvement; (2) no new lupus disease activity compared with the previous assessment; (3) a PGA ≤1; (4) a current prednisone (or equivalent) dose ≤7.5 mg/day; and (5) well-tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents. Achievement of LLDAS was determined at each visit.

We evaluated the effect on damage of different durations of LLDAS: 1, 2, 3, 4 and ≥5 consecutive years. In patients who experienced a relapsing-remitting disease, only the longest period of LLDAS was considered in the analysis.

Remission was assessed according to the definitions previously published by Zen *et al*[11]: complete remission was defined as SLEDAI-2K=0 in corticosteroid-free and immunosuppressant-free patients (antimalarials allowed); clinical remission off corticosteroids as serological active clinical quiescent disease (SACQD) according to SLEDAI-2K in corticosteroid-free patients (stable immunosuppressive therapy and antimalarials allowed); and clinical remission on corticosteroids as SACQD in patients on prednisone 1–5 mg/day (stable immunosuppressants and antimalarials allowed).

In this study we classified patients as being in remission or not, irrespective of the level of remission achieved, that is, patients fulfilling any of the three levels of remission were categorised as remitted. Accordingly, remission was overall defined as clinical SLEDAI-2K=0 and prednisone ≤5 mg/day in patients who could be on a stable immunosuppressive and/or antimalarial therapy.

Statistical analysis

A retrospective analysis of the prospectively collected data was performed. Comparison of continuous data with parametric and non-parametric distribution was performed using t-test and one-way analysis of variance with Bonferroni's post-hoc analysis or by the Wilcoxon's test and the Kruskal-Wallis test, respectively. Comparison of categorical variables was performed using χ^2 test (Fisher's exact test). Factors with a $p<0.2$ at univariate analysis were entered into the multivariate model. Backward stepwise multivariate logistic regression was performed with damage accrual considered as a dichotomous dependent variable (ie, SDI increased or not increased during the follow-up), with significance set at 5%. Spearman's correlation was used to assess the relationship between the duration of LLDAS and damage accrual. Analyses were performed by the SPSS V.23.0 software for Windows.

RESULTS

Two-hundred ninety-three patients were considered in the study. One hundred sixty-nine patients were excluded and the reasons for exclusion were previously detailed.[11]

During the 7-year follow-up, 33 patients (11.3%) achieved 1 consecutive year LLDAS, 43 (14.7%) achieved 2 consecutive year LLDAS, 39 (13.3%) achieved 3 consecutive year LLDAS, 31 (10.6%) achieved 4 consecutive year LLDAS and 109 (37.2%) ≥5 consecutive year LLDAS. Conversely, 38 patients (13.3%) had never been in LLDAS. Demographic characteristics and damage in our cohort, according to the duration of LLDAS achieved, are reported in table 1, and clinical features and treatment in online supplementary table S1 and supplementary table S2.

Damage more frequently occurred in ocular (17%), neuropsychiatric (16.4%), musculoskeletal (14%) and renal (11.3%) domains, followed by cutaneous (9.5%) and cardiovascular (6.9%) domains; damage in other organs and malignancies were more rarely observed.

Table 1 Demographic features and damage increase according to the durations of LLDAS achieved during the follow-up

	Never in LLDAS	1-Year LLDAS	2-Year LLDAS	3-Year LLDAS	4-Year LLDAS	≥5-Year LLDAS	p
Number of patients (%)	38 (13.3)	33 (11.3)	43 (14.7)	39 (13.3)	31 (10.6)	109 (37.2)	
Age at recruitment, mean±SD years	39.9±13	36.6±16.4	40.0±13.0	42.4±11.7	41.9±11.2	39.8±12.5	n.s.
Female, n (%)	31 (83.7)	27 (81.8)	39 (90.7)	31 (79.5)	25 (80.6)	100 (91.7)	n.s.
SLE duration at recruitment, mean±SD years	10.8±7.2	10.2±7.1	11.8±6.7	11.4±6.1	10.2±6.3	12.0±5.4	n.s.
SDI at recruitment, mean±SD	0.87±1.53	0.68±0.90	0.97±1.14	0.75±0.94	0.48±0.85	0.42±0.88	n.s.
SDI increase, mean±SD	1.67±1.35	1.20±0.90	0.91±0.89	0.90±0.87	0.45±0.69	0.27±0.49	<0.05*
Increase in SDI≥1, number of patients (%)	32 (84.2)	26 (78.8)	27 (62.8)	23 (58.9)	13 (41.9)	30 (27.5)	<0.05†
Increase in SDI≥2, number of patients (%)	17 (44.7)	9 (27.3)	11 (25.6)	10 (25.6)	2 (8.0)	2 (1.8)	<0.05‡

p Values refer to the analysis of variance with 5 df.

*Never in LLDAS vs 1-year LLDAS, p=n.s.; never in LLDAS vs 2-year LLDAS, p=0.001; never in LLDAS vs 3-year LLDAS, p=0.001; never in LLDAS vs 4-year LLDAS, p<0.001; never in LLDAS vs ≥5-year LLDAS, p<0.001.

†Never in LLDAS vs 1-year LLDAS, p=n.s.; never in LLDAS vs 2-year LLDAS, p=0.02; never in LLDAS vs 3-year LLDAS, p=0.01; never in LLDAS vs 4-year LLDAS, p<0.001; never in LLDAS vs ≥5-year LLDAS, p<0.001.

‡Never in LLDAS vs 1-year LLDAS, p=n.s.; never in LLDAS vs 2-year LLDAS, p=n.s.; never in LLDAS vs 3-year LLDAS, p=n.s.; never in LLDAS vs 4-year LLDAS, p<0.001; never in LLDAS vs ≥5-year LLDAS, p<0.001.

LLDAS, lupus low disease activity state; n.s., not significant; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE, systemic lupus erythematosus.

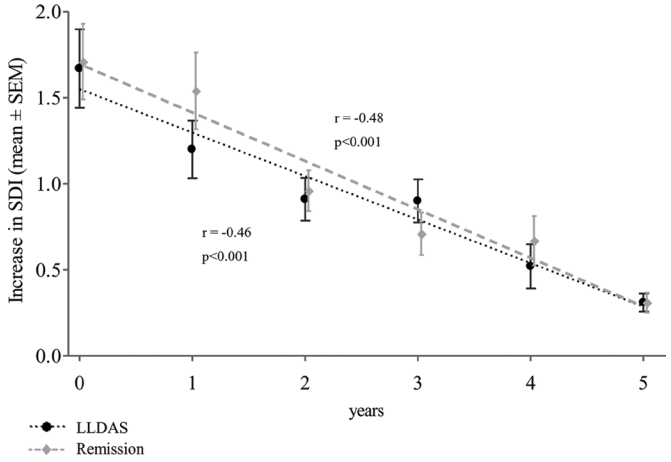

Figure 1 Correlation between duration of LLDAS or remission and damage accrual during the 7-year follow-up. LLDAS, lupus low disease activity state; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

The mean SDI increase was lower in patients achieving LLDAS for at least two consecutive years compared with patients never in LLDAS (p<0.001), whereas it was similar in patients with 1-year LLDAS and in those who had never been in LLDAS.

The proportion of patients with damage accrual progressively decreased as the duration of LLDAS increased, both in terms of SDI increase ≥1 or ≥2 (high damage accrual) (table 1).

Moreover, the higher the duration of LLDAS, the lower the increase in SDI (figure 1).

Table 2 reports the characteristics of patients with or without damage accrual during the 7-year follow-up.

In a multivariate logistic regression model including LLDAS and baseline characteristics, an LLDAS lasting 2, 3, 4 and 5 or more consecutive years was protective against damage, whereas age, the use of mycophenolate, a higher cumulative prednisone dose and APS were independent predictors of damage accrual (table 3A). Similar findings were obtained by including in the multivariate model lupus therapies and manifestations ever occurred during the follow-up (see online supplementary table S3).

We also performed a second multivariate analysis, including among the potential predictors of damage a remission lasting at least two consecutive years in addition to LLDAS, since we previously demonstrated its protective effect against damage progression.[11] In this model, LLDAS was not independently associated to damage, whereas remission was, meaning LLDAS did not have any additional protective effect over remission (table 3B).

In table 4 the characteristics of patients who achieved or not the LLDAS for at least two consecutive years are reported. As baseline predictors are concerned, patients with a higher SLEDAI-2K, PGA >1, joint and skin involvement, and those treated with methotrexate, ciclosporin and a higher prednisone dose were less likely to achieve an LLDAS lasting two or more consecutive years (table 4).

The multivariate logistic regression model including baseline characteristics showed that a higher cumulative prednisone dose, skin involvement and PGA higher than 1 were the three most significant negative predictors of LLDAS attainment (OR 0.302, 95% CI 0.151 to 0.605, p=0.001; OR 0.333, 95% CI 0.148 to 0.748, p=0.008; OR 0.093, 95% CI 0.151 to 0.605, p<0.001, respectively).

As disease manifestations and treatment over the disease course are concerned, patients with joint involvement, serositis,

Table 2 Characteristics of patients with or without damage increase during the 7-year follow-up

	Patients with no increase in SDI during follow-up (142)	Patients with increase in SDI during follow-up (151)	p
Gender (female), n (%)	123 (86.6)	130 (86.1)	n.s.
Age at recruitment, mean±SD years	37.3±13.41	40.8±12.2	n.s.
SLE duration at recruitment, mean±SD years	10.7±7.0	13.48±8.34	0.013
Low C3 or C4 serum levels, n (%)	126 (89.4)	131 (86.8)	n.s.
Anti-dsDNA Ab, n (%)	121 (85.2)	125 (82.8)	n.s.
ANA, n (%)	142 (100)	151 (100)	n.s.
Antiphospholipid Ab, n (%)	33 (23.2)	63 (41.7)	0.001
SDI in 2008, mean±SD	0.42±0.84	0.85±1.16	0.007
Lupus manifestations at baseline			
SLEDAI-2K, mean±SD	3.90±3.76	4.98±4.59	0.032
PGA >1, n (%)	32 (23.5)	39 (26.9)	n.s.
Skin rashes, n (%)	12 (9.8)	35 (23.2)	<0.001
Arthritis, n (%)	13 (9.2)	17 (11.3)	n.s.
Serositis, n (%)	1 (0.7)	3 (2.0)	n.s.
Glomerulonephritis, n (%)	32 (22.5)	27 (17.9)	n.s.
NP manifestations, n (%)	1 (0.7)	1 (0.7)	n.s.
Vasculitis, n (%)	2 (1.4)	8 (5.3)	n.s.
Haematological involvement, n (%)	10 (7.0)	11 (7.1)	n.s.
Lupus therapy at baseline			
Mycophenolate, n (%)	19 (13.6)	38 (25.5)	0.011
Azathioprine, n (%)	22 (15.7)	21 (14.1)	n.s.
Ciclosporin A, n (%)	3 (2.1)	3 (2.0)	n.s.
Methotrexate, n (%)	5 (3.6)	9 (6.0)	n.s.
Antimalarials, n (%)	113 (80.7)	100 (67.1)	0.009
Cyclophosphamide, n (%)	3 (2.1)	1 (0.7)	n.s.
Rituximab, n (%)	2 (1.4)	1 (0.7)	n.s.
Prednisone dose, mean±SD, mg	5.41±7.85	7.28±9.85	n.s.
Cumulative average prednisone dose ≥180 mg/month	24 (16.8)	54 (36.5)	<0.001
Lupus manifestations ever			
Skin rashes, n (%)	81 (57.4)	100 (66.8)	0.05
Arthritis, n (%)	98 (69.5)	120 (79.5)	0.05
Serositis, n (%)	26 (18.4)	50 (33.1)	0.004
Glomerulonephritis, n (%)	76 (53.9)	92 (60.9)	n.s.
NP manifestations, n (%)	14 (9.9)	25 (16.6)	n.s.
Vasculitis, n (%)	6 (4.3)	28 (18.5)	0.001
Haematological involvement, n (%)	46 (32.4)	65 (43.0)	n.s.
Antiphospholipid Ab syndrome, n (%)	10 (7.0)	30 (19.9)	0.001
Lupus therapy ever			
Methylprednisolone, intravenous, n (%)	70 (5.0)	99 (56.1)	n.s.
Mycophenolate, n (%)	49 (34.5)	78 (51.7)	0.003
Azathioprine, n (%)	40 (28.2)	57 (37.7)	n.s.
Ciclosporin A, n (%)	15 (10.6)	39 (25.8)	0.001
Methotrexate, n (%)	16 (11.3)	31 (20.5)	0.031
Antimalarials, n (%)	131 (92.7)	135 (89.4)	n.s.
Cyclophosphamide, n (%)	31 (21.8)	50 (33.1)	0.031

Continued

Table 2 Continued

	Patients with no increase in SDI during follow-up (142)	Patients with increase in SDI during follow-up (151)	p
Rituximab, n (%)	4 (2.8)	18 (11.9)	0.003
Belimumab, n (%)	10 (7.0)	20 (13.1)	n.s.
Intravenous immunoglobulins, n (%)	2 (1.4)	10 (6.6)	0.03

Ab, antibodies; ANA, antinuclear antibodies; anti-dsDNA, antidouble-stranded DNA; C3/C4, complement fractions; NP, neuropsychiatric; n.s., not significant; PGA, physician global assessment; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000.

vasculitis and those treated with immunosuppressive drugs were less likely to achieve an LLDAS for 2 consecutive years. Notably, the majority of patients treated with belimumab achieved LLDAS for at least 2 years (25/30 patients, 83.3%).

We also evaluated the proportion of patients attaining the LLDAS who concomitantly fulfilled the criteria for remission.[10 11] Among the 255 patients achieving the definition of LLDAS for at least 1 year during the follow-up, 246 patients (96.5%) satisfied the definition of remission for the same length of time.

Hence, in order to quantify the overlap between the definitions of LLDAS and remission, the proportion of patients achieving LLDAS and meanwhile a remission of the same duration was calculated (figure 2).

Overall, 214 patients (83.9%) experienced a remission being as long as their LLDAS, suggesting a high overlap exists between the two conditions.

Interestingly, remitted patients accrued significantly less damage than did other LLDAS patients (0.59±0.78 vs 0.90±0.89, p=0.021).

Only one death was observed during follow-up; thus, the evaluation of the relationship between LLDAS achievement and mortality was not possible.

Table 3 Multivariate analysis: protective factors and risk factors for damage accrual over the follow-up

	OR	95% CI	p Value
(A) Baseline predictors and LLDAS			
≥5 Consecutive year LLDAS	**0.071**	**0.023 to 0.217**	**<0.001**
4 Consecutive year LLDAS	**0.122**	**0.034 to 0.443**	**0.001**
3 Consecutive year LLDAS	**0.252**	**0.075 to 0.842**	**0.025**
2 Consecutive year LLDAS	**0.279**	**0.085 to 0.920**	**0.036**
1-Year LLDAS	0.899	0.232 to 3.480	0.877
Age	**1.038**	**1.015 to 1.062**	**0.001**
Mycophenolate	**2.173**	**1.062 to 4.446**	**0.034**
Antiphospholipid antibody syndrome	**4.008**	**1.648 to 9.749**	**0.002**
Cumulative PDN dose, g	**1.016**	**1.003 to 1.033**	**0.049**
(B) Baseline predictors, LLDAS and remission			
≥2 consecutive year remission	**0.076**	**0.023 to 0.250**	**<0.001**
Age	**1.045**	**1.021 to 1.069**	**0.001**
Skin involvement	**2.303**	**0.961 to 5.516**	**0.061**
Mycophenolate	**2.160**	**1.044 to 4.470**	**0.038**
Antiphospholipid antibody syndrome	**2.928**	**1.205 to 7.114**	**0.018**
Cumulative PDN dose, g	**1.021**	**1.005 to 1.037**	**0.011**

Variables entered in the multivariate analysis A were duration of LLDAS (categorical variable with six levels) and the following baseline characteristics: age, disease duration, SDI, mean SLEDAI-2K, skin involvement, vasculitis, use of mycophenolate and antimalarials, mean prednisone dose, APS and cumulative prednisone dose.
Variables entered in the multivariate analysis B were remission (considered as a dichotomous variable with two levels: remission lasting ≥2 consecutive years vs remission lasting <2 years), LLDAS (considered as a dichotomous variable with two levels: LLDAS lasting ≥2 consecutive years vs LLDAS lasting <2 years), and the following variables at baseline: age, disease duration, cumulative prednisone dose, SDI, APS, mean SLEDAI-2K, skin involvement and vasculitis, use of mycophenolate, cyclophosphamide and antimalarials, and mean prednisone dose.
Significant variables are given in bold.
LLDAS, lupus low disease activity state; PDN, prednisone.

DISCUSSION

In the last few years, the beneficial effect of remission on organ damage accrual in patients with SLE has been proven.[10 11 15] We demonstrated that prolonged remission, defined as 5 or more consecutive years of no clinical disease activity (SLEDAI-2K=0) in patients treated with antimalarials and/or stable dose of immunosuppressive drugs and/or prednisone ≤5 mg/day, was associated with a decrease in damage progression.[10] This finding was confirmed by Tsang-A-Sjoe *et al* in a multiethnic cohort in the Netherlands.[15] In a further study,[11] we found that a remission lasting at least 2 years had still a protective effect against new damage.

No shared definition of remission is currently accepted for SLE; thus, the frequency of remission in SLE varies among different cohorts, ranging from 1.2% to 45%.[10 11 15–19] This discrepancy led to the search for other measures of outcome, as in other autoimmune diseases, including the so-called LLDAS.

The effect of LLDAS on damage was first evaluated by Franklyn *et al*[12] who found that among patients followed for an average time of 3.9 years, those who spent more than 50% of their follow-up in LLDAS accrued significantly less organ damage than other patients. This finding was confirmed in the study by Tsang-A-Sjoe *et al*.[15]

However, the protective effect on damage of different durations of LLDAS, the shortest duration of LLDAS resulting in decreased damage progression as well as the overlap between LLDAS and remission have not been evaluated yet.

We demonstrated that 2 consecutive years was the shortest duration of LLDAS associated with a decrease in damage progression. Interestingly, since the mean follow-up of patients in Franklyn *et al*'s study was 3.9 years,[12] the 50% of their follow-up time corresponds approximately to 2 years.

Patients who had a higher SLEDAI-2K or PGA, skin and joint involvements, and those treated with a higher cumulative prednisone dose and a higher prednisone dose at baseline were less likely to achieve an LLDAS lasting 2 consecutive years. Similarly, vasculitis, immunosuppressants and high prednisone dose were associated with lack of LLDAS maintenance for at least 50% of follow-up in Franklyn *et al*'s study.[12] In a multinational cross-sectional study, disease duration ≤1 year, history of discoid rash or renal disease, and current elevated anti-dsDNA or hypocomplementaemia emerged as negative predictors of LLDAS achievement at a single point in time.[20]

Our results are in keeping with the daily clinical practice, since high cumulative doses of prednisone are usually employed in patients with more active and/or refractory disease, who might less likely achieve LLDAS or remission. Skin and joint involvements are usually relapsing-remitting manifestations, which are characterised by a rapid fluctuation of activity over time, and

Table 4 Characteristics of patients with or without two consecutive years of LLDAS

	LLDAS <2 years (71 pts)	LLDAS ≥2 years (222 pts)	OR	95% CI	p
Gender (female), n (%)	58 (81.7)	194 (87.8)			n.s.
Age at recruitment, mean±SD years	38.7±13.41	40.6±12.2			n.s.
SLE duration at recruitment, mean±SD years	10.6±7.1	11.5±6.1			n.s.
Low C3 or C4 serum levels, n (%)	62 (87.3)	194 (88.2)			n.s.
Anti-dsDNA Ab, n (%)	63 (88.7)	182 (82.4)			n.s.
ANA, (%)	71 (100)	222 (100)			n.s.
Anti-SSA/SSB Ab, n (%)	29 (40.8)	85 (38.5)			n.s.
Anti-U1RNP Ab, n (%)	27 (38.0)	54 (24.4)	1.556	1.068 to 2.268	0.026
Antiphospholipid Ab, n (%)	25 (35.2)	71 (32.1)			n.s.
Lupus manifestation at baseline					
SLEDAI-2K, mean±SD	6.52±4.55	3.94±3.99	2.686	1.563 to 3.808	0.001
PGA>, n (%)	47 (66.2)	25 (11.3)	5.854	3.904 to 8.772	<0.001
Skin rashes, n (%)	23 (32.4)	22 (10.0)	3.254	1.935 to 5.472	<0.001
Arthritis, n (%)	13 (18.3)	17 (7.7)	2.380	1.217 to 4.655	0.010
Serositis, n (%)	0 (0)	4 (1.8)			n.s.
Glomerulonephritis, n (%)	13 (18.3)	46 (20.8)			n.s.
NP manifestations, n (%)	1 (1.4)	1 (0.5)			n.s.
Vasculitis, n (%)	4 (5.6)	6 (2.7)			n.s.
Haematological involvement, n (%)	8 (11.3)	13 (5.9)			n.s.
Lupus therapy at baseline					n.s.
Mycophenolate, n (%)	12 (17.4)	45 (20.5)			n.s.
Azathioprine, n (%)	13 (18.3)	30 (13.7)			n.s.
Ciclosporin A, n (%)	4 (5.8)	2 (0.9)	6.348	1.188 to 33.913	0.013
Methotrexate, n (%)	7 (10.1)	7 (3.2)	3.174	1.154 to 8.733	0.019
Antimalarials, n (%)	48 (69.6)	164 (74.9)			n.s.
Cyclophosphamide, n (%)	0 (0)	4 (1.8)			n.s.
Rituximab, n (%)	1 (1.4)	2 (0.9)			n.s.
Prednisone dose, mean±SD, mg	9.24±11.3	5.49±7.8	3.746	1.380 to 6.128	0.002
Cumulative average prednisone dose ≥180 mg/month	38 (53.5)	40 (18.1)	2.957	2.075 to 4.215	<0.001
Lupus manifestations (ever)					
Skin rashes, n (%)	50 (70.4)	128 (58.2)			n.s.
Arthritis, n (%)	61 (85.9)	157 (71.4)	1.204	1.061 to 1.366	0.018
Serositis, n (%)	25 (35.2)	51 (23.2)	1.519	1.021 to 2.259	0.045
Glomerulonephritis, n (%)	44 (62.0)	124 (56.4)			n.s.
NP manifestations, n (%)	12 (16.9)	27 (12.3)			n.s.
Vasculitis, n (%)	13 (18.3)	21 (9.5)	1.918	1.014 to 3.630	0.046
Haematological involvement, n (%)	31 (43.7)	80 (36.0)			n.s.
Antiphospholipid Ab syndrome, n (%)	11 (15.5)	29 (13.1)			n.s.
Lupus therapy (ever)					
Methylprednisolone, intravenous, n (%)	45 (63.4)	124 (56.1)			n.s.
Mycophenolate, n (%)	39 (54.9)	88 (39.8)	1.379	1.057 to 1.800	0.025
Azathioprine, n (%)	32 (45.1)	65 (29.4)	1.532	1.104 to 2.127	0.025
Ciclosporin A, n (%)	18 (25.4)	36 (16.3)			n.s.
Methotrexate, n (%)	25 (35.2)	22 (10.0)	3.537	2.131 to 5.871	<0.001
Antimalarials, n (%)	65 (90.1)	201 (91.0)			n.s.
Cyclophosphamide, n (%)	26 (36.6)	55 (24.9)	1.471	1.004 to 2.156	0.050
Rituximab, n (%)	14 (19.7)	8 (3.6)	5.447	2.384 to 12.448	<0.001
Belimumab, n (%)	5 (7.4)	25 (11.2)			n.s.
Intravenous immunoglobulins, n (%)	7 (9.9)	5 (2.3)	4.358	1.427 to 13.303	0.005

For significant variables, OR and 95% CI are reported.
Ab, antibodies; ANA, antinuclear antibodies; anti-dsDNA, antidouble-stranded DNA; C3/C4, complement fractions; LLDAS, lupus low disease activity state; NP, neuropsychiatric; n.s., not significant; pts, patients; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000.

flares can occur shortly after remission is achieved. In addition, although those manifestations are usually considered as mild, it is likely that patients with such organ involvement are treated with less aggressive treatment regimens compared with patients with severe manifestations and are those who more rapidly decrease the prednisone dosage or discontinue induction therapy, being thus at higher risk of early disease flares.

In our study, we considered different periods of time (1, 2, 3, 4, 5 or more consecutive years) instead of the proportion of follow-up spent in LLDAS because such an analysis has more

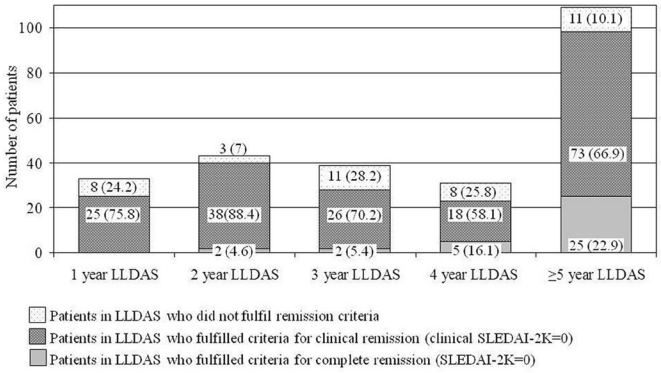

Figure 2 Proportion of patients with different durations of LLDAS who fulfilled or not the definitions of a remission lasting at least the same number of consecutive year(s). Number of patients (%) are reported. LLDAS, lupus low disease activity state; SLEDAI-2K, SLE Disease Activity Index 2000.

practical implications and can be used in clinical practice to identify patients at higher/lower risk of developing new organ damage.

We evaluated the consecutive time spent in LLDAS and not the sum of separate periods of LLDAS since we previously demonstrated that a shorter consecutive period of remission was as good as a longer cumulative period (3 vs 2 years) in hindering damage accrual over time.[11] In fact, it is likely that patients with a relapsing-remitting disease pattern, in whom LLDAS is achieved for short periods and is interspersed by episodes of active disease, require a longer cumulative time of LLDAS to be protected against damage progression.

In addition, we assessed the proportion of patients in LLDAS fulfilling the criteria of remission. In fact, the definition of LLDAS used in the study by Franklyn *et al*[12] Tsang-A-Sjoe *et al*[15] as well as in our study included patients who were in LDA but also patients in true remission. This is different from what was defined for RA and other rheumatic diseases,[21 22] where the definitions of LDA and remission do not overlap (eg, disease activity score (DAS)-28 in RA identifies remitted patients when DAS-28 is lower than 2.6, while patients in LDA have a DAS-28 between 2.6 and 3.2).

In our cohort we found that the great majority of patients in LLDAS were, actually, in remission. This result is relevant since it is likely that the protective effect of remission on new organ damage significantly contributed to the lower damage accrual observed in the LLDAS group. The finding that remitted patients accrued less damage than other LLDAS patients supports this hypothesis. Moreover, in the multivariate analysis we found that LLDAS did not show any additional protective effect against damage progression over remission.

Unfortunately, the number of patients included in our cohort does not allow an explorative analysis on the effect of LLDAS after exclusion of patients in remission.

Recently, Polachek *et al*[23] performed a study, in a monocentric cohort of 620 patients, using a definition of LDA different from the Franklyn *et al*'s definition, namely a clinical SLEDAI-2K <3 (excluding serology), in corticosteroids-free and immunosuppressant-free patients, and a different definition of remission compared with ours, that is, clinical SLEDAI-2K=0 (excluding serology) in corticosteroids-free and immunosuppressant-free patients. They found that the accrual of organ damage in LDA patients was similar to that of patients in remission. However, the definitions of LDA and remission used by Polachek *et al* are very close to each other, as they both exclude the use of corticosteroids, which are indeed a major determinant of organ damage.

Conversely, the Franklyn *et al*'s definition of LLDAS and our definition of remission greatly differ in clinical and therapeutic criteria; thus, whether damage accrual is similar in LLDAS and remitted patients is less predictable.

The great overlap between LLDAS and remission observed in our study is not surprising. Indeed, SLE is predominantly a relapsing-remitting disease, which means that its clinical course is characterised by periods of clinical remission intermixed with periods of disease activity. Thus, the disease can be either active or in remission. Accordingly, the LLDAS should be more conveniently applied to patients with a chronic active disease, which is a pattern of SLE activity accounting for a minority of patients with lupus.[24]

In the multivariate analysis, the protective effect of LLDAS lasting 2, 3, 4 and 5 years on damage accrual was similar, as shown by the overlap in the 95% CIs. This might be due to the relatively short duration of the follow-up in our study. Studies with a longer follow-up could elucidate whether the attainment of prolonged periods of LLDAS has a higher protective effect on damage progression in the long term.

Our study has a number of strengths: we studied a large cohort of patients prospectively and regularly followed for a long period by the same team; we evaluated a range of durations of LLDAS; and we used a validated definition of LLDAS. Moreover, our cohort includes patients treated with biological disease-modifying antirheumatic drugs.

However, our study has also some limitations: we studied only Caucasian patients and we retrospectively analysed data prospectively collected in a single centre. Moreover, this is not an inception cohort and we did not specifically analyse patients with an early disease. Indeed, the purpose of our study was to identify potential predictors of good outcome in a cohort of patients representative of what can be observed in a 'real life' lupus clinic.

In conclusion, LLDAS was frequently observed in our SLE cohort and 2 years was the shortest LLDAS duration predictive of better outcome in terms of damage progression. Since a very high proportion of patients in the LLDAS group was also in remission, the remission state could have greatly contributed to the protective effect of LLDAS on damage accrual. A more stringent definition of LLDAS, which does not include the remission state, should be the objective of future studies.

Contributors MZ contributed to the conception and design of the work, the follow-up of patients, acquisition, analysis and interpretation of data, and she drafted the work; LI followed up patients and gave his contribution in revising the work; MG followed up patients and helped in drafting the work; FS contributed to the acquisition of data; ML followed up patients; AG helped in the analysis of data; LP critically revised the final work; AD led the team who followed up patients, designed the work, interpreted the data, and drafted and revised the manuscript for important intellectual content. All the authors approved the final version of the manuscript and gave their agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests None declared.

Ethics approval The Ethics Committee of the 'Azienda Ospedaliera-Università degli Studi di Padova', Padova, Italy.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Doria A, Gatto M, Zen M, *et al*. Optimizing outcome in SLE: treating-to-target and definition of treatment goals. *Autoimmun Rev* 2014;13:770–7.
2 Verstappen SM, Jacobs JW, van der Veen MJ, *et al*. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis* 2007;66:1443–9.
3 Balduzzi S, Scirè CA, Sakellariou G, *et al*. In early inflammatory polyarthritis more intensive management according to the 2010 ACR/EULAR criteria leads to higher rates of clinical remission: comparison of two cohorts treated according to different treat-to-target protocols. *Clin Exp Rheumatol* 2017;35.
4 Coates LC, Helliwell PS. Treating to target in psoriatic arthritis: how to implement in clinical practice. *Ann Rheum Dis* 2016;75:640–3.
5 Mandl P, Navarro-Compán V, Terslev L, *et al*. EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. *Ann Rheum Dis* 2015;74:1327–39.
6 Doria A, Gershwin ME, Selmi C. From old concerns to new advances and personalized medicine in lupus: The end of the tunnel is approaching. *J Autoimmun* 2016;74:1–5.
7 Smolen JS, Landewé R, Bijlsma J, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017;76:960–77.
8 van Vollenhoven RF, Mosca M, Bertsias G, *et al*. Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. *Ann Rheum Dis* 2014;73:958–67.
9 van Vollenhoven R, Voskuyl A, Bertsias G, *et al*. A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS). *Ann Rheum Dis* 2017;76:554–61.
10 Zen M, Iaccarino L, Gatto M, *et al*. Prolonged remission in caucasian patients with SLE: prevalence and outcomes. *Ann Rheum Dis* 2015;74:2117–22.
11 Zen M, Iaccarino L, Gatto M, *et al*. The effect of different durations of remission on damage accrual: results from a prospective monocentric cohort of caucasian patients. *Ann Rheum Dis* 2017;76:562–5.
12 Franklyn K, Lau CS, Navarra SV, *et al*. Definition and initial validation of a lupus low disease activity state (LLDAS). *Ann Rheum Dis* 2016;75:1615–21.
13 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. *Arthritis Rheum* 1725;1997:40.
14 Miyakis S, Lockshin MD, Atsumi T, *et al*. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;4:295–306.
15 Tsang-A-Sjoe MW, Bultink IE, Heslinga M, *et al*. Both prolonged remission and Lupus Low Disease Activity State are associated with reduced damage accrual in systemic lupus erythematosus. *Rheumatology* 2017;56:121–8.
16 Wilhelm TR, Magder LS, Petri M. Remission in systemic lupus erythematosus: durable remission is rare. *Ann Rheum Dis* 2017;76:547–53.
17 Steiman AJ, Gladman DD, Ibañez D, *et al*. Outcomes in patients with systemic lupus erythematosus with and without a prolonged serologically active clinically quiescent period. *Arthritis Care Res* 2012;64:511–8.
18 Medina-Quiñones CV, Ramos-Merino L, Ruiz-Sada P, *et al*. Analysis of complete remission in lupus patients over a period of 32 years. *Arthritis Care Res* 2016;68:981–7.
19 Moroni G, Raffiotta F, Ponticelli C. Remission and withdrawal of therapy in lupus nephritis. *J Nephrol* 2016;29:559–65.
20 Golder V, Kandane-Rathnayake R, Hoi AY, *et al*. Frequency and predictors of the lupus low disease activity state in a multi-national and multi-ethnic cohort. *Arthritis Res Ther* 2016;18:260.
21 Wells G, Boers M, Shea B, *et al*. MCID/Low disease activity state workshop: low disease activity state in rheumatoid arthritis. *J Rheumatol* 2003;30:1110–1.
22 Helliwell PS, FitzGerald O, Fransen J, *et al*. The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). *Ann Rheum Dis* 2013;72:986–91.
23 Polachek A, Gladman DD, Su J, *et al*. Defining low disease activity in systemic lupus erythematosus. *Arthritis Care Res* 2016 (Epub ahead of print).
24 Zen M, Bassi N, Nalotto L, *et al*. Disease activity patterns in a monocentric cohort of SLE patients: a seven-year follow-up study. *Clin Exp Rheumatol* 2012;30:856–63.