CLINICAL SCIENCE

Remission in systemic lupus erythematosus: testing different definitions in a large multicentre cohort

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ABSTRACT

Objectives Remission in systemic lupus erythematosus (SLE) is defined through a combination of 'clinical SLE Disease Activity Index (cSLEDAI)=0', 'physician's global assessment (PGA) <0.5' and 'prednisone (PDN) ≤5 mg/day'. We investigated the performance of these items, alone or in combination, in defining remission and in predicting SLICC/ACR Damage Index.

Methods We tested seven potential definitions of remission in SLE patients followed-up for ≥5 years: PDN ≤5 mg/day; PGA <0.5; cSLEDAI=0; PGA <0.5 plus PDN ≤5 mg/day; cSLEDAI=0 plus PGA <0.5; cSLEDAI=0 plus PDN ≤5 mg/day; cSLEDAI=0 plus PDN ≤5 mg/day plus PGA <0.5. The effect of these definitions on damage was evaluated by Poisson regression analysis; the best performance was identified as the lowest Akaike and Bayesian information criterion (AIC and BIC). Positive and negative predictive values in identifying no damage increase were calculated.

Results We included 646 patients (mean±SD disease duration 9.2±6.9 years). At multivariate analysis, ≥2 consecutive year remission according to all definitions protected against damage (OR, 95% CI: PGA <0.5 0.631, 0.444 to 0.896; cSLEDAI=0 0.531, 0.371 to 0.759; PGA <0.5 plus PDN ≤5 mg/day 0.554, 0.381 to 0.805; cSLEDAI=0 plus PGA <0.5 0.574, 0.400 to 0.826; cSLEDAI=0 plus PDN ≤5 mg/day 0.543, 0.376 to 0.785; cSLEDAI=0 plus PDN ≤5 mg/day plus PGA <0.5 0.532, 0.363 to 0.781, p<0.01 for all), except PDN ≤5 mg/day, which required four consecutive years (OR 0.534, 95% CI 0.325 to 0.877, p=0.013). Positive and negative predictive values were similar; however, cSLEDAI=0 showed the best performance (AIC 1082.90, BIC 1109.72, p<0.0001). Adding PGA <0.5 and/or PDN ≤5 mg/day to cSLEDAI=0 decreased remission duration (−1.8 and −1.5 year/patient, respectively) without increasing cSLEDAI=0 performance in predicting damage accrual.

Conclusions cSLEDAI=0 is the most attainable definition of remission, while displaying the best performance in predicting damage progression in the short-to-mid-term follow-up.

Key messages

What is already known about this subject?
► Remission is the most desirable target in systemic lupus erythematosus (SLE); however, a universally accepted definition is still missing.

What does this study add?
► A simple definition of remission based on clinical SLE Disease Activity Index (SLEDAI)=0 is easy-to-achieve and protective against damage.
► Adding Physician Global Assessment (<0.5) to clinical SLEDAI=0 decreases the proportion of remitted patients without increasing the performance of clinical SLEDAI in predicting damage accrual.

How might this impact on clinical practice or future developments?
► Clinical SLEDAI=0 could serve as a manageable and meaningful outcome in SLE trials and treat-to-target strategy.

(HRQoL))[1–9]; however, a universally accepted definition of remission combining evidence-based medicine and expert opinion is still missing.[3 10 11] The Definitions Of Remission In SLE (DORIS) international task force defined remission as a sustained state without any symptoms and signs of SLE, assessing disease activity according to the clinical SLE Disease Activity Index 2000 (cSLEDAI),[10] which does not take into account serology,[12] and evaluating the global patient status by Physician Global Assessment (PGA). Addition of PGA was meant to reflect the overall clinician-based evaluation, thereby filling the gaps of cSLEDAI and being also suggested to reflect the patient's perspective.[10]

Since moderate-to-high glucocorticoid dosages contribute to damage accrual in the long term, a prednisone (PDN) dose (or equivalent) ≤5 mg/day was included in the validated definitions of remission.[3 10 13 14]

It should be noted that no clear agreement was reached so far in defining durability in time of any definition of remission, which remains a research priority.

To our knowledge, no head-to-head comparisons were made on the impact of each item or combination

INTRODUCTION

Remission is the most desirable target in the management of systemic lupus erythematosus (SLE), as it leads to a significant improvement across several disease outcome measures (death, organ damage, disease flare-up and health-related quality of life

of items included in the definitions of remission proposed by the DORIS task force (ie, cSLEDAI=0, PGA <0.5, PDN ≤5 mg/day) on disease outcomes in a clinical practice setting. Our aim was to compare the prevalence and duration of different potential definitions of remissions and to evaluate their effect on organ damage in a large, closely monitored cohort of patients with SLE.

PATIENTS AND METHODS
Data source
We carried out a multicentre study enrolling patients with SLE recruited in seven referral lupus centres in Italy: University of Padova, Campus Bio-Medico University (Rome), Sapienza University (Rome), University of Brescia, University Hospital S. Anna (Ferrara), Fondazione Ca' Granda IRCCS Ospedale Maggiore Policlinico (Milano) and University of Pisa. All patients provided an informed consent before the inclusion in the study.

Patients with SLE were enrolled in the study according to the fulfilment of all the following criteria: (1) ≥4 revised American College of Rheumatology (ACR) Classification Criteria for SLE; (2) SLE diagnosis between 1990 and 2013; (3) active disease, that is, at least one clinical manifestation scored in the SLEDAI-2K, or remission lasting no more than 12 months at study entry; (4) at least five consecutive years of follow-up between January 2009 and September 2018; (5) at least three visits per year, no more than 5 months apart. We analysed a period of 5-year for all patients. Data regarding disease manifestations, autoantibody profile, medical history and organ damage were recorded since SLE diagnosis. The cumulative PDN dose taken before baseline was calculated. Clinical and laboratory findings were collected at each visit.

Study variables
At each visit SLE activity was measured by SLEDAI-2K and PGA (scale 0–3). Flares were defined according to SELENA-SLEDAI flare index.[15] Organ damage was assessed by 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 5-year follow-up. Damage was categorised as related to or independent from glucocorticoids, as defined by Gladman et al[16]

We considered the three major items included in the DORIS definition of 'remission on therapy': (1) PGA <0.5; (2) cSLEDAI=0; (3) PDN ≤5 mg/day (or equivalent) daily intake. We also tested their combinations: (4) PGA <0.5 plus PDN ≤5 mg/day; (5) cSLEDAI=0 plus PGA <0.5; (6) cSLEDAI=0 plus PDN ≤5 mg/day; (7) cSLEDAI=0 plus PDN ≤5 mg/day plus PGA <0.5.[10] All seven potential definitions are presented in

table 1. For composite definitions, remission was considered as achieved when the two or three items were concomitantly met. One consecutive year was considered the shortest duration of remission for a clinically meaningful definition. In patients with a relapsing-remitting disease, only the longest period of remission was considered in the analysis.

For all definitions, concomitant lupus medications (antimalarials and/or immunosuppressive drugs and/or biologics) were allowed if on a stable dose. Haemolytic anaemia, myelitis and gastrointestinal lupus involvement prevented the fulfilment of all remission definitions.

We also performed a separate analysis, where the cumulative time spent in remission was evaluated and expressed as proportion of the follow-up in remission, that is, <25%, 25%–49%, 50%–74%, 75%–99% and 100%.

Statistical analysis
T-test was used to compare continuous data with a parametric distribution. Comparison of categorical variables were performed using χ^2 test (Fisher's exact test if necessary). Remission definitions were considered as six-levels categorical variables according to duration (0, 1, 2, 3, 4 and 5 consecutive years). Cohen's kappa coefficient (κ) and 95% CI were used to assess agreement among remission definitions. The patient's demographic and clinical characteristics and remission definitions were tested as predictors of damage accrual by univariate Poisson regression analysis. Those variables with p<0.2 were considered in a multivariate Poisson regression analysis. ORs were estimated with 95% CI. The goodness-of-fit was assessed using Akaike information criterion (AIC) and Bayesian information criterion (BIC): the best performance in predicting damage accrual was identified by the lowest AIC and BIC. Analyses were performed by SAS V.9.4 (SAS Institute) and SPSS (V.25 for Windows), and p<0.05 was considered statistically significant.

This research was done without patient involvement and patients were not invited to comment on the study design or to develop patient outcomes.

RESULTS
Six hundred and forty-six consecutive lupus patients fulfilled inclusion criteria: 621 (96.1%) Caucasian, 585 (90.6%) female, mean±SD age at baseline 40.6±12.1 years, disease duration 9.2±6.9 years. At baseline, 545 patients (84.4%) were taking PDN, 460 (71.2%) antimalarials and 316 (48.8%) immunosuppressants. Demographic and clinical characteristics of patients are reported in table 2.

Table 1 Definitions of remission according to clinical, serological and therapeutic status allowed

| | Disease activity | | | Treatment | |
| | SLEDAI-2K | | | | |
	Clinical	Serological	PGA	PDN	Antimalarials, biologics, immunosuppressants*
PDN ≤5 mg/day	Regardless	Regardless	Regardless	≤5 mg/day	Regardless
PGA <0.5	Regardless	Regardless	<0.5	Regardless	Regardless
cSLEDAI=0	0	Regardless	Regardless	Regardless	Regardless
PDN ≤5 mg/day plus PGA <0.5	Regardless	Regardless	<0.5	≤5 mg/day	Regardless
cSLEDAI=0 plus PGA <0.5	0	Regardless	<0.5	Regardless	Regardless
cSLEDAI=0 plus PDN ≤5 mg/day	0	Regardless	Regardless	≤5 mg/day	Regardless
cSLEDAI=0 plus PDN ≤5 mg/day plus PGA <0.5	0	Regardless	<0.5	≤5 mg/day	Regardless

*Stable well-tolerated doses.
cSLEDAI, clinical systemic lupus erythematosus Disease Activity Index 2000; PDN, prednisone equivalent; PGA, physician global assessment.

Table 2 Demographic and clinical characteristics of lupus patients in the whole cohort and in patients with cSLEDAI=0 for at least 1 year

		cSLEDAI=0 for at least 1 year			
	Whole cohort 646 (100)	Overall 548 (84.8)	PGA <0.5 concordant with cSLEDAI=0 353 (64.4)	PGA <0.5 discordant with cSLEDAI=0 195 (35.6)	P value
Female	585 (90.6)	502 (77.8)	324 (64.5)	178 (35.5)	ns
Age at baseline, years	40.6±12.1	40.7±12.2	39.8±12.3	42.4±12.0	0.015
SLE duration ≤2 years	159 (24.6)	139 (21.5)	107 (77.0)	52 (37.4)	ns
Disease duration, years	9.2±6.7	8.9±6.8	9.1±6.8	8.7±6.9	ns
Damage					
SDI baseline	0.55±0.96	0.52±0.94	0.50±0.96	0.55±0.91	ns
SDI increase during FU	0.43±0.74	0.36±0.67	0.35±0.68	0.37±0.67	ns
SDI increase during FU	206 (31.9)	149 (27.2)	92 (26.1)	57 (29.2)	ns
GC related SDI	88 (13.6)	69 (12.6)	40 (11.3)	29 (14.9)	ns
GC possibly related SDI	43 (6.7)	33 (6.0)	21 (5.9)	12 (6.2)	ns
GC independent SDI	101 (15.6)	64 (11.7)	43 (12.2)	21 (10.8)	ns
Lupus flare during FU					
Muco-cutaneous	243 (37.6)	189 (34.5)	93 (26.3)	44 (22.6)	ns
Musculoskeletal	249 (38.5)	213 (38.9)	97 (27.5)	70 (35.9)	0.040
Serositic	45 (7.0)	37 (6.8)	22 (6.2)	6 (3.1)	ns
Neurological	36 (5.6)	28 (5.1)	12 (3.4)	8 (4.1)	ns
Glomerulonephritis	202 (31.3)	149 (27.2)	76 (21.5)	36 (18.5)	ns
Haematological	166 (25.7)	138 (25.2)	81 (22.9)	39 (20.0)	ns
Therapy during follow-up					
Cumulative PDN, grams	11.25±14.55	9.87±13.45	8.64±11.40	12.10±16.31	0.004
Immunosuppressants	316 (48.9)	250 (45.6)	150 (42.5)	100 (51.3)	0.048
Antimalarials	460 (71.2)	394 (71.9)	248 (70.3)	146 (74.9)	ns
Belimumab	48 (7.4)	32 (4.9)	19 (59.4)	13 (40.6)	ns
Previous treatments					
Immunosuppressant ever	381 (59.0)	306 (55.8)	199 (56.4)	107 (54.9)	ns
Mycophenolate Mofetil	197 (30.5)	150 (27.4)	103 (29.2)	47 (24.1)	ns
Cyclophosphamide	144 (22.3)	111 (20.3)	75 (21.2)	36 (18.5)	ns
Azathioprine	200 (31.0)	158 (28.8)	105 (29.7)	53 (27.2)	ns
Cyclosporine A	110 (17.0)	83 (15.2)	56 (15.9)	27 (13.8)	ns
Methotrexate	90 (13.9)	67 (12.2)	32 (9.1)	35 (17.9)	0.002
Antimalarials	483 (74.8)	409 (74.6)	267 (75.6)	142 (72.8)	ns
Rituximab	31 (4.8)	18 (3.3)	11 (3.1)	7 (3.6)	ns
Belimumab	41 (6.4)	29 (5.3)	15 (4.2)	14 (7.2)	ns
IV Ig	28 (4.3)	19 (3.5)	10 (2.8)	9 (4.6)	ns
Plasmapheresis	26 (4.0)	20 (3.7)	11 (3.1)	9 (4.6)	ns
Previous lupus manifestations, ever					
Muco-cutaneous	412 (63.8)	342 (62.4)	214 (60.6)	128 (65.6)	ns
Musculoskeletal	436 (67.5)	371 (67.7)	230 (65.2)	141 (72.3)	ns
Serosal	125 (19.4)	98 (17.9)	65 (18.4)	33 (16.9)	ns
Neurological	103 (15.9)	82 (15.0)	39 (11.0)	43 (22.1)	0.001
Glomerulonephritis	262 (40.6)	206 (37.6)	148 (41.9)	58 (29.7)	0.005
Haematological	245 (37.9)	211 (38.5)	139 (39.4)	72 (36.9)	ns
Anti-dsDNA antibodies	490 (75.9)	412 (75.2)	259 (73.4)	153 (78.5)	ns
Anti-SSA/SSB antibodies	275 (42.7)	229 (41.9)	145 (41.2)	84 (43.3)	ns
Anti-U1RNP antibodies	135 (20.9)	107 (19.6)	76 (21.6)	31 (15.9)	ns
Anti-Sm antibodies	93 (14.4)	74 (13.5)	45 (12.7)	29 (14.9)	ns
Antiphospholipid antibodies	258 (39.9)	220 (40.1)	140 (39.7)	80 (41.0)	ns
Antiphospholipid syndrome	94 (14.6)	80 (14.6)	51 (14.4)	29 (14.9)	ns

Data are reported as number (%) or mean±SD.
anti-dsDNA, anti double-stranded DNA; anti-U1RNP, anti-(U1) ribonucleoprotein; cSLEDAI, clinical SLE Disease Activity Index 2000; FU, follow-up; GC, glucocorticoids; IV Ig, intravenous immunoglobulines; ns, not significant; PDN, prednisone; PGA, physician global assessment; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE, systemic lupus erythematosus.

Table 3   Number (%) of patients in remission according to different definitions

	PDN ≤5 mg/day	PGA <0.5	cSLEDAI=0	PGA <0.5 plus PDN ≤5 mg/day	cSLEDAI=0 plus PGA <0.5	cSLEDAI=0 plus PDN ≤5 mg/day	cSLEDAI=0 plus PDN ≤5 mg/day plus PGA <0.5
Unremitted patients	73 (11.3)	164 (25.4)	98 (15.2)	194 (30.0)	170 (26.3)	147 (22.8)	199 (30.8)
At least 1 year remission	573 (88.7)	482 (74.6)	548 (84.8)	452 (70.0)	476 (73.7)	499 (77.2)	447 (69.2)
At least 2 years remission	512 (79.3)	377 (58.4)	456 (70.6)	352 (54.5)	369 (57.1)	409 (63.2)	346 (53.6)
At least 3 years remission	425 (65.8)	264 (40.9)	327 (50.6)	248 (38.4)	254 (39.3)	294 (45.5)	243 (37.6)
At least 4 years remission	345 (53.4)	173 (26.8)	250 (38.7)	166 (25.7)	167 (25.9)	220 (34.1)	161 (24.9)
5 years remission	222 (34.4)	84 (13.0)	119 (18.4)	81 (12.5)	82 (12.7)	107 (16.6)	80 (12.4)

cSLEDAI, clinical SLE Disease Activity Index 2000; PDN, prednisone equivalent; PGA, physician global assessment; SLE, systemic lupus erythematosus.

Prevalence of remission using different definitions
According to the seven different definitions, remission lasting at least 1 year was achieved by a proportion of patients ranging between 69.2% and 88.7% and two consecutive year remission by more than 50% of patients (table 3).

Overlapping and agreement among different definitions
The overlapping of the three major items included in the DORIS definitions of remission (cSLEDAI=0, PGA <0.5, PDN ≤5 mg/day) is shown in figure 1.

The agreement was poor between PDN ≤5 mg/day and other definitions except for cSLEDAI=0 plus PDN ≤5 mg/day (κ=0.622) (online supplementary table S1).

The agreement between cSLEDAI=0 and PGA <0.5 was good (κ=0.697). Patients with PGA <0.5 usually had a concomitant cSLEDAI=0, but not vice versa.

When PDN ≤5 mg/day was added to PGA <0.5 or cSLEDAI=0 there was a good agreement with PGA <0.5 alone (κ=0.921) or cSLEDAI=0 alone (κ=0.837), respectively, since patients in remission according to cSLEDAI=0 or PGA <0.5 were often taking a dosage of PDN ≤5 mg/day.

When PGA <0.5 was added to cSLEDAI=0 and/or PDN ≤5 mg/day the prevalence of unremitted patients increased. As it was very uncommon that a patient fulfilled PGA <0.5 and PDN ≤5 mg/day, but not cSLEDAI=0, a very high agreement was observed between PGA <0.5 plus PDN ≤5 mg/day and cSLEDAI=0 plus PDN ≤5 mg/day plus PGA <0.5 (κ=0.981).

Comparison between cSLEDAI=0 and PGA <0.5
The mean time spent in remission was significantly shorter when remission was defined according to PGA <0.5 compared with cSLEDAI=0 (2.1±1.7 vs 2.63±1.7 years, p<0.001).

Figure 1   Venn diagram representing the number of patients fulfilling the three single major remission items (PGA <0.5; cSLEDAI=0; PDN ≤5 mg/day) and their combination, during a 5-year follow-up. (A) Patients achieving at least 1-year remission. (B) Patients with at least two consecutive years in remission. (C) Patients achieving prolonged remission (five consecutive years). cSLEDAI, clinical SLE Disease Activity Index 2000; PGA, physician global assessment; PDN, prednisone-equivalent; SLE, systemic lupus erythematosus.

cSLEDAI=0 was observed in 548/646 patients (84.8%), while concomitant cSLEDAI=0 and PGA ≥0.5 were observed in 195/548 patients (35.6%) (table 2), meaning a loss of remission of 1.8 year/patient when PGA <0.5 was added to cSLEDAI=0.

To understand the reason why some patients had PGA ≥0.5 despite cSLEDAI=0, we compared patients who could not be defined as remitted with those showing no change in remission duration after adding PGA <0.5 to cSLEDAI=0 (table 2). Among patients with cSLEDAI=0, no difference in prevalence, extent or type of damage accrual was observed between those displaying PGA <0.5 or PGA ≥0.5. Patients with PGA ≥0.5 despite cSLEDAI=0 had more frequently musculoskeletal activity/involvement and were more commonly treated with immunosuppressants and/or higher dose of glucocorticoids during follow-up; moreover, they had less frequently previous glomerulonephritis and more commonly previous neurological involvement compared with patients with PGA <0.5 plus cSLEDAI=0 (table 2).

Among patients with musculoskeletal activity, no significant difference was observed in the proportion of patients with PGA ≥0.5 despite cSLEDAI=0 in patients who developed Jaccoud-like arthropathy compared with the overall cohort, confirming that damage was not scored as activity.

Among 195 patients with PGA ≥0.5 and cSLEDAI=0, 126 (64.6%) were on PDN ≤5 mg/day achieving cSLEDAI=0 plus PDN ≤5 mg/day remission; 155/195 (79.5%) were in lupus low disease activity state (LLDAS) according to Franklyn's definition (SLEDAI-2K≤4 and PGA ≤1 and PDN ≤7.5 mg/day).[17] Forty patients did not fulfil LLDAS definition due to a PGA >1 (n=21) and/or PDN intake >7.5 g/day (n=33).

Patients with no residual disease activity (cSLEDAI=0 and/or PGA <0.5) on PDN >5 mg/day
When PDN ≤5 mg/day was added to cSLEDAI=0, 112 (17.3%) patients did not meet remission criteria. This may be due to a longer time needed for glucocorticoid tapering after resolution of the disease manifestations, leading to prolonged PDN intake (>5 mg/day) despite cSLEDAI=0. Accordingly, the difference in the proportion of patients in cSLEDAI=0 and cSLEDAI=0 plus PDN ≤5 mg/day decreased over time, as the longer the remission duration the higher the probability of minimising/withdrawing PDN therapy.

Overall, these patients lost 1.5 year/patient in remission. Among them, patients with renal or serosal involvement lost 2 years/patient in remission, those with haematological manifestations 1.5 year/patient in remission, and patients with articular, cutaneous, constitutional involvement 1.3 year/patient in remission, suggesting that time to reduce PDN ≤5 mg/day after achieving cSLEDAI=0 was different depending on the specific SLE manifestation.
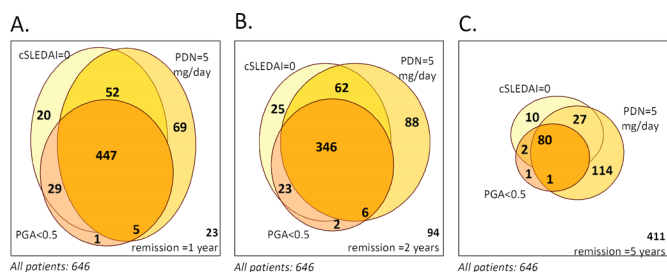
Table 4 ORs (95% CI) and goodness-of-fit of different definitions of remission in predicting damage accrual by Poisson regression*

	PDN ≤5 mg/day	PGA <0.5	cSLEDAI=0	PGA <0.5 plus PDN ≤5 mg/day	cSLEDAI=0 plus PGA <0.5	cSLEDAI=0 plus PDN ≤5 mg/day	cSLEDAI=0 plus PGA <0.5 plus PDN ≤5 mg/day
Five consecutive year remission	0.620 (0.430 to 0.894) *0.010*	0.377 (0.293 to 0.595) *<0.0001*	0.382 (0.260 to 0.561) *<0.0001*	0.363 (0.227 to 0.581) *<0.0001*	0.397 (0.251 to 0.626) *<0.0001*	0.411 (0.275 to 0.614) *0.0001*	0.374 (0.234 to 0.599) *<0.0001*
Four consecutive year remission	0.391 (0.245 to 0.625) *<0.0001*	0.226 (0.130 to 0.394) *<0.0001*	0.173 (0.105 to 0.286) *<0.0001*	0.294 (0.177 to 0.487) *<0.0001*	0.243 (0.140 to 0.424) *<0.0001*	0.251 (0.155 to 0.405) *<0.0001*	0.296 (0.176 to 0.496) *<0.0001*
Three consecutive year remission	0.912 (0.601 to 1.386) *0.668*	0.427 (0.281 to 0.649) *<0.0001*	0.512 (0.342 to 0.767) *0.0001*	0.430 (0.278 to 0.665) *<0.0001*	0.459 (0.302 to 0.698) *<0.0001*	0.548 (0.363 to 0.828) *0.0004*	0.438 (0.284 to 0.676) *<0.0001*
Two consecutive year remission	0.858 (0.566 to 1.300) *0.471*	0.560 (0.396 to 0.793) *0.0001*	0.454 (0.319 to 0.647) *<0.0001*	0.495 (0.341 to 0.718) *<0.0001*	0.514 (0.359 to 0.737) *<0.0001*	0.497 (0.345 to 0.717) *<0.0001*	0.479 (0.327 to 0.702) *<0.0001*
1-year remission	0.952 (0.611 to 1.484) *0.828*	0.808 (0.590 to 1.107) *0.185*	0.766 (0.548 to 1.071) *0.119*	0.764 (0.554 to 1.053) *0.101*	0.857 (0.629 to 1.166) *0.326*	0.888 (0.642 to 1.227) *0.471*	0.800 (0.583 to 1.098) *0.167*
AIC	1132.83	1100.62	1082.90	1105.87	1103.96	1101.13	1106.59
BIC	1159.66	1127.44	1109.72	1132.70	1130.78	1127.96	1133.42
P value	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*

Significant variables are given in grey cells.

Number of patients in the analysis: 646.

*SDI increase during follow-up (range 0–4) was considered the dependent variable in Poisson regression. The best performance in predicting damage accrual was identified with the lowest AIC and BIC.

AIC, Akaike information criterion; BIC, Bayesian information criterion; cSLEDAI, clinical SLE Disease Activity Index 2000; PDN, prednisone; PGA, physician global assessment; SLE, systemic lupus erythematosus.

When PDN ≤5 mg/day was combined with PGA <0.5, 57 (8.8%) patients lost 1.4 year/patient in remission.

Among patients with PGA <0.5 or cSLEDAI=0, no significant difference in the prevalence, extent and type of damage accrual was observed between patients on PDN ≤5 mg/day and those on PDN >5 mg/day (data not shown).

Damage accrual

Over the five consecutive year follow-up, 206 (31.9%) patients developed damage; 280 new damage events were observed, corresponding to 0.43 damage event per 5 years/person.

The prevalence and the extent of damage significantly decreased as the time spent in remission increased with all the definitions (table 4).

In Poisson regression, remission according to cSLEDAI=0 had the best fitness over all other remission models, showing the lowest AIC and BIC (table 4). When PGA was considered (alone or in combination with cSLEDAI=0 and/or PDN ≤5 mg/day) AIC and BIC increased, thereby indicating less fitness.

At the Poisson multivariate analysis, remission lasting at least two consecutive years was an independent negative predictor of damage accrual according to all the definitions of remission, except for PDN ≤5 mg/day that required at least four consecutive years (table 5); age, vasculitis, high glucocorticoid doses and antiphospholipid antibody syndrome were independent predictors of new damage. Due to the possible impact of Centre variability on PGA evaluation, we performed a Poisson regression analysis adjusted for data source, obtaining similar results (data not shown).

Since the different components of remission definitions might have diverse effects depending on whether continuous or cumulative time periods are considered, we also evaluated the cumulative proportion of follow-up spent in remission during the 5-year period. By regression analysis, we found that 50% of the follow-up was the shortest duration of remission which

resulted protective against new damage when remission was defined as PGA <0.5 or cSLEDAI=0, whereas at least 75% of the follow-up was needed when remission was defined as PDN ≤5 mg/day (online supplementary table S2).

When we tested potential definitions of remission that resulted to be protective against damage accrual after at least two consecutive years, we found a similar positive predictive value against damage across all the definitions used (figure 2). In particular, adding PGA <0.5 and/or PDN ≤5 mg/day to cSLEDAI=0 did not improve its positive predictive value, meaning that the ability of cSLEDAI=0 in identifying patients without damage progression is not increased by the concomitant fulfilment of the other items. Addition of PDN ≤5 mg/day to cSLEDAI=0 increased the specificity of cSLEDAI=0 in predicting no damage accrual while maintaining a higher sensitivity compared with the definitions including PGA <0.5 (figure 2 and table 6).

DISCUSSION

Our aim was to explore the performance of the three major items included in the DORIS definition of remission (cSLEDAI=0, PGA <0.5 and PDN ≤5 mg/day) in capturing a remission status and in predicting damage accrual.

First, we showed that adding PGA <0.5 to cSLEDAI=0 led to loss of remission in a relevant proportion of patients, without any significant improvement in its predictive value against damage. Additionally, it did not shorten the time spent in remission required to hinder damage accrual (at least two consecutive years for all remission definitions).

Interestingly, more than one-third of our patients in sustained cSLEDAI=0 spent over 1.7 year with PGA ≥0.5. These patients had more frequently previous neurological involvement, which may imply difficult attribution of neurological events to SLE activity,[18] thereby causing discrepancy between cSLEDAI and PGA. They also showed more frequently musculoskeletal involvement yet not classifiable as arthritis according to

Table 5 Multivariate Poisson regression analysis: predictors of damage accrual over the follow-up (OR, 95% CI, p value)

	PDN ≤5 mg/day	PGA <0.5	cSLEDAI=0	PGA <0.5 plus PDN ≤5 mg/day	cSLEDAI=0 plus PGA <0.5	cSLEDAI=0 plus PDN ≤5 mg/day	cSLEDAI=0 plus PGA <0.5 plus PDN ≤5 mg/day
Five consecutive year remission	0.498 (0.325 to 0.762) 0.0013	0.448 (0.278 to 0.721) 0.001	0.467 (0.311 to 0.702) <0.0001	0.431 (0.264 to 0.705) 0.001	0.470 (0.292 to 0.757) 0.002	0.499 (0.325 to 0.767) 0.002	0.442 (0.270 to 0.722) 0.001
Four consecutive year remission	0.534 (0.325 to 0.877) 0.013	0.322 (0.183 to 0.567) <0.0001	0.230 (0.138 to 0.385) <0.0001	0.400 (0.238 to 0.670) 0.001	0.338 (0.192 to 0.596) <0.0001	0.305 (0.186 to 0.500) <0.0001	0.389 (0.229 to 0.661) <0.0001
Three consecutive year remission	0.885 (0.567 to 1.382) 0.59	0.500 (0.328 to 0.764) 0.001	0.595 (0.393 to 0.900) 0.014	0.485 (0.313 to 0.754) 0.001	0.527 (0.345 to 0.805) 0.003	0.590 (0.387 to 0.899) 0.0014	0.490 (0.315 to 0.760) 0.0019
Two consecutive year remission	0.878 (0.562 to 1.370) 0.56	0.631 (0.444 to 0.896) 0.010	0.531 (0.371 to 0.759) 0.001	0.554 (0.381 to 0.805) 0.002	0.574 (0.400 to 0.826) 0.003	0.543 (0.376 to 0.785) 0.001	0.532 (0.363 to 0.781) 0.001
1-year remission	1.022 (0.642 to 1.627) 0.92	0.868 (0.632 to 1.194) 0.386	0.915 (0.652 to 1.284) 0.606	0.845 (0.610 to 1.171) 0.313	0.913 (0.668 to 1.248) 0.566	1.072 (0.770 to 1.494) 0.679	0.877 (0.636 to 1.208) 0.422
Age at baseline	1.031 (1.019 to 1.042) <0.001	1.029 (1.017 to 1.040) <0.001	1.032 (1.021 to 1.044) <0.001	1.029 (1.017 to 1.041) <0.001	1.029 (1.017 to 1.041) <0.0001	1.033 (1.033 to 1.045) <0.001	1.029 (1.018 to 1.041) <0.001
Previous GC pulses	ns	1.441 (1.100 to 1.888) 0.008	1.369 (1.044 to 1.795) 0.023	1.452 (1.109 to 1.901) 0.007	1.447 (1.105 to 1.895) 0.007	1.457 (1.112 to 1.908) <0.006	1.463 (1.117 to 1.915) 0.006
Previous vasculitis	ns	1.660 (1.175 to 2.346) 0.004	1.689 (1.195 to 2.387) 0.003	1.656 (1.171 to 2.341) 0.004	1.677 (1.187 to 2.370) 0.003	1.666 (1.181 to 2.350) <0.004	1.666 (1.179 to 2.355) 0.004
Cumulative GC dose at baseline	1.008 (1.001 to 1.016) 0.025	ns	1.008 (1.000 to 1.015) 0.036	1.007 (1.000 to 1.014) 0.043	ns	1.008 (1.001 to 1.015) 0.023	1.007 (1.000 to 1.042) 0.046
aPL syndrome	1.377 (1.008 to 1.882) 0.044	ns	1.383 (1.016 to 1.882) 0.039	ns	ns	ns	ns
AIC	1033.68	1031.74	1014.99	1032.56	1032.52	1020.78	1031.48
BIC	1136.52	1107.74	1090.01	1108.56	1108.52	1096.79	1107.49
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Variables with a p<0.2 at the univariate analysis were entered in the multivariate analysis: duration of remission (categorical variable with six levels) and the following characteristics: sex, age, disease duration, baseline SDI, cumulative GC dose at baseline, previous GC pulses, previous cyclophosphamide treatment, previous neurological and renal involvement, previous vasculitis, antiphospholipid syndrome. cSLEDAI, clinical SLE Disease Activity Index 2000. Significant variables are given in grey cells. The table reports only variables with at least one p<0.05 at the multivariate analysis for at least one remission definition.
Goodness-of-fit of different models according to the seven definitions of remission are also reported.
AIC, Akaike Information Criterion; aPL, antiphospholipid antibody; BIC, Bayesian Information Criterion; GC, glucocorticoid; ns, not significant; PDN, prednisone-equivalent; PGA, physician global assessment; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

SLEDAI, leading to higher PDN intake. It should be noted that non specific symptoms (i.e., arthralgias, stiffness, fatigue) are not considered in cSLEDAI, but can increase the PGA without impacting on damage accrual. PGA has a large interobserver and intraobserver variability because it reflects a complex physician-perceived global evaluation not always related to the real disease activity.[19 20] Therefore, patients in cSLEDAI=0 but PGA ≥0.5 should be carefully evaluated in order to distinguish lupus residual activity from other conditions.

Since additional treatment is not always needed in patients with cSLEDAI=0 despite PGA ≥0.5, and since these items showed overlapping sensitivity, specificity, positive and negative predictive value against damage accrual (table 6 and figure 2), adding PGA <0.5 to cSLEDAI=0 could lead to overtreatment in controlled trials as well as in clinical practice when a treat-to-target (T2T) approach is adopted.[21] In fact, T2T should aim at the most reachable target that positively influences patient prognosis. We observed that cSLEDAI=0 was the definition of remission easiest to achieve in real life, being able to predict damage accrual with a consistent degree of accuracy. Note-worthy, cSLEDAI=0 alone or in combination with other items conferred a similar protection against damage accrual, provided remission lasted at least 2 years (table 5), therefore, posing a rationale for the use of cSLEDAI=0 in spite of composite indexes. Importantly, cSLEDAI=0 was already shown to be a feasible target in the BLISS trials, bearing the highest discriminatory capability in capturing remission compared with the DORIS definition, lupus low disease activity state (LLDAS) and D/E in all British Isles Lupus Activity Group (BILAG) domains.[22] Additionally, cSLEDAI=0 had the same performance of the SLE Responder Index-4 (SRI-4) in showing the superiority of belimumab over placebo, while displaying a better correlation with PGA<0.5 than SRI-4 or LLDAS.[22 23] Hence, it could be speculated that adding PGA <0.5 could hamper the results of randomised trials aiming at remission, as patients achieving cSLEDAI=0 at 52 weeks can still have PGA ≥0.5 which will not affect their outcome.

Since definitions of low disease activity (LDA) use the same items included in definitions of remission (cSLEDAI/SLEDAI-2K, PGA, PDN) although with less stringent cut-offs, a patient fulfilling remission definition is often fulfilling LDA status as well.[17 24 25] Notably, in this study, we found that around two thirds of patients with cSLEDAI=0 and PGA ≥0.5 were in LDA and/or in remission according to cSLEDAI=0 and PDN ≤5 mg/day. Since a patient can lose remission definition only due to PGA ≥0.5 while maintaining LDA, adding PGA to definitions including cSLEDAI=0 and/or PDN ≤5 mg/day leads to a consistent overlap between the definitions of LDA and remission.[11 19 24]
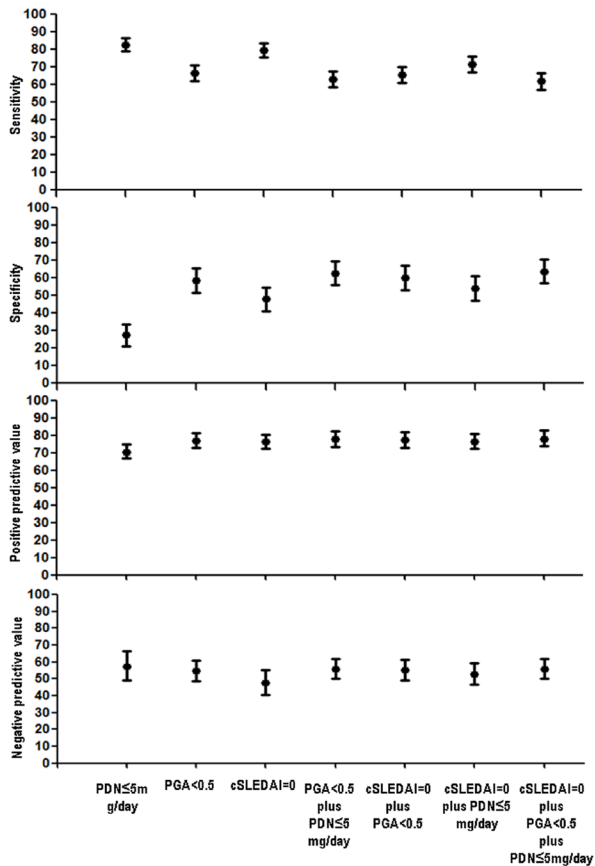
Figure 2 Sensitivity, specificity, positive and negative predictive values of different remission definitions in identifying patients who will not accrue damage throughout the follow-up. Values and their 95% CI are depicted. Remitted is defined as patients with at least two consecutive year remission and unremitted is defined as patients with remission lasting less than 2 years. cSLEDAI, clinical SLE Disease Activity Index; PGA, physician global assessment; PDN, prednisone equivalent; SLE, systemic lupus erythematosus.

On the other hand, 40 out of the 195 patients in cSLEDAI=0 with PGA ≥0.5 did not fulfil LLDAS definition, due to glucocorticoid daily doses and/or PGA over the LLDAS thresholds. This might infer that a significant proportion of patients could have fulfilled simplified remission criteria (cSLEDAI=0), that is, without lupus manifestations, and still not be in a desirable state of remission, due to a suboptimal HRQoL or to a higher glucocorticoid intake. Nevertheless, patients in cSLEDAI=0

irrespective of PDN dosage and PGA accrued significantly less damage than those with cSLEDAI >0 during the follow-up.

A remission lasting at least 50% of the follow-up was protective against damage accrual in our cohort when remission was defined according to PGA <0.5 or c-SLEDAI=0. Notably, this duration corresponds to 2.5 cumulative years in our study where the follow-up was 5 years, in keeping with the results of our analysis of continuous-time periods.

We confirmed a good agreement between cSLEDAI=0 and PGA <0.5 in our real-life cohort. Therefore, a simplified remission definition based on cSLEDAI=0 can be reasonably used in observational studies where complete serological data, PGA and BILAG are not routinely assessed.[21] In the cSLEDAI=0 remission definition, the exclusion of a cut-off for PDN could imply that high dose glucocorticoids may mask disease activity, thus allowing patients not in real remission to be defined as remitted. Nevertheless, we found that adding PDN ≤5 mg/day to cSLEDAI=0 does not increase the performance against damage of cSLEDAI=0 in the short/medium term (5 years), as shown by the high overlap between confidence intervals. Of note, the specificity, sensitivity and predictive values of cSLEDAI=0 were not significantly improved on addition of other items, with a substantially modest prognostic value of all different definitions of remission in predicting damage-free status (table 6). These observations further support cSLEDAI=0 to be considered the first target to achieve in order to prevent damage accrual, while cSLEDAI=0 plus PDN ≤5 mg/day could be considered the best target in the medium/long term, since it has been widely demonstrated that even low dose of PDN lead to damage accrual in the longer run.[4 16 26 27]

We observed that the majority of patients in remission according to cSLEDAI=0 for at least 1 year were on PDN ≤5 mg/day, some being off-steroids (data not shown), while almost half of them were still on immunosuppressive maintenance therapy. This finding reflects the current clinical practice of tapering glucocorticoids before immunosuppressive agents which exert a greater protective effect against flare occurrence in remitted patients.[28] Accordingly, in a recent study by Mathian et al,[29] a relevant proportion of remitted patients who discontinued glucocorticoid therapy experienced a flare during 1-year follow-up, but only 26% of them were on immunosuppressive maintenance therapy at the time of glucocorticoid discontinuation.

There are some limitations in our study that it is a retrospective analysis of prospective collected data, with the majority of patients being Caucasian and follow-up limited to 5 years. Moreover, other relevant outcomes, for example, HRQoL, were not systematically assessed. On the other hand, this is a multicentre real-life

Table 6 Sensitivity, specificity, positive and negative predictive values of different remission definitions in identifying patients without damage accrual throughout the follow-up

	PDN ≤5 mg/day	PGA <0.5	cSLEDAI=0	PGA <0.5 plus PDN ≤5 mg/day	cSLEDAI=0 plus PGA <0.5	cSLEDAI=0 plus PDN ≤5 mg/day	cSLEDAI=0 plus PGA <0.5 plus PDN ≤5 mg/day
Sensitivity	82.4 (78.5 to 85.9)	66.2 (61.6 to 70.6)	79.2 (75.1 to 83.0)	62.6 (57.8 to 67.1)	65.1 (60.4 to 69.5)	71.2 (66.8 to 75.4)	61.6 (56.9 to 66.2)
Specificity	27.4 (21.5 to 34.0)	58.2 (51.2 to 65.0)	47.6 (40.7 to 54.6)	62.5 (55.5 to 69.1)	59.6 (52.6 to 66.3)	53.9 (46.8 to 60.8)	63.5 (56.5 to 70.0)
PPV	70.5 (66.4 to 74.4)	76.9 (72.3 to 81.1)	76.1 (71.9 to 80.0)	77.8 (73.1 to 82.1)	77.2 (72.6 to 81.4)	76.5 (72.1 to 80.5)	78.0 (73.3 to 82.3)
NPV	57.5 (48.6 to 66.0)	55.0 (48.9 to 61.1)	47.9 (40.6 to 55.3)	55.8 (49.9 to 61.6)	55.2 (49.2 to 61.2)	52.9 (46.4 to 59.4)	56.0 (50.2 to 61.7)

Values and their 95% CI are reported.
cSLEDAI, clinical SLE Disease Activity Index; NPV, negative predictive value; PDN, prednisone-equivalent; PGA, physician global assessment; PPV, positive predictive value; SLE, systemic lupus erythematosus.

observational cohort where patients were closely followed-up and homogeneously treated according to current recommendations.

In conclusion, cSLEDAI=0 was the most achievable definition of remission and showed a good performance in terms of damage prediction, while addition of PGA <0.5 to cSLEDAI=0 was not relevant in identifying patients who would develop damage, thus submitting cSLEDAI=0 as the most advisable target in a short-to-mid-term follow-up.

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