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Achieving remission or low disease activity is associated with better outcomes in patients with systemic lupus erythematosus: a systematic literature review

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ABSTRACT

Background Remission and low disease activity (LDA) have been proposed as the treatment goals for patients with systemic lupus erythematosus (SLE). Several definitions for each have been proposed in the literature.

Objective To assess the impact of remission/LDA according to various definitions on relevant outcomes in patients with SLE.

Methods This systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses using PubMed (1946–week 2, April 2021), Cochrane library (1985–week 2, week 2, April 2021) and EMBASE (1974–week 2, April 2021). We included longitudinal and cross-sectional studies in patients with SLE reporting the impact of remission and LDA (regardless their definition) on mortality, damage accrual, flares, health-related quality of life and other outcomes (cardiovascular risk, hospitalisation and direct costs). The quality of evidence was evaluated using the Newcastle-Ottawa Scale.

Results We identified 7497 articles; of them, 31 studies met the inclusion criteria and were evaluated. Some articles reported a positive association with survival, although this was not confirmed in all of them. Organ damage accrual was the most frequently reported outcome, and remission and LDA were reported as protective of this outcome (risk measures varying from 0.04 to 0.95 depending on the definition). Similarly, both states were associated with a lower probability of SLE flares, hospitalisations and a better health-related quality of life, in particular the physical domain.

Conclusion Remission and LDA are associated with improvement in multiple outcomes in patients with SLE, thus reinforcing their relevance in clinical practice.

PROSPERO registration number CRD42020162724.

Key messages

What is already known about this subject?

- Remission and low disease activity (LDA) have been reported as potential targets in the systemic lupus erythematosus (SLE) treatment.

What does this study add?

- Remission and LDA (regardless of the definitions used) are associated with better outcomes.

How might this impact on clinical practice or future developments?

- Remission and LDA should be considered as the target for the management of patients with SLE.
- However, it is important to have a uniform definition of both.

INTRODUCTION

A treat-to-target (T2T) strategy has been proposed for several chronic diseases in order to improve the affected patients' treatment, and thus, their outcome; in systemic lupus erythematosus (SLE), however, a uniform definition of treatment goals is lacking.

The ideal goal is remission, which was defined in 2015 and modified in 2021 by the DORIS (Definition Of Remission In SLE) group as the absence of clinical disease activity (Clinical Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)=0 and Physician Global Assessment (PGA) <0.5), with no or minimal intake of glucocorticoids (prednisone daily dose not higher than 5 mg/day) and/or immunosuppressive drugs on stable maintenance dose.[1 2] However, some modifications of this definition have been reported in the literature.

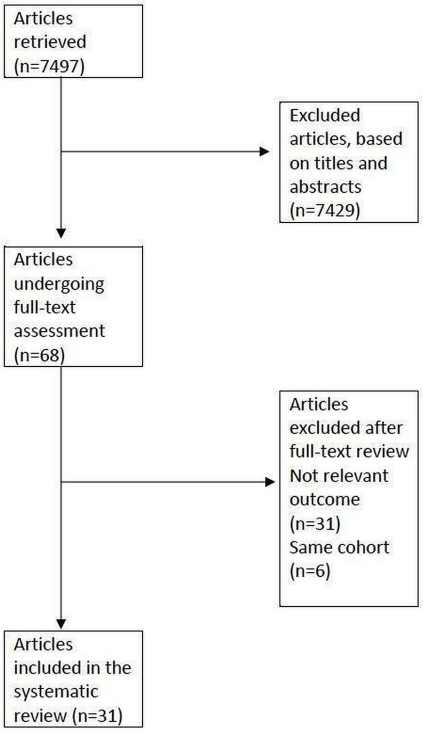
Nevertheless, as remission state is not achieved frequently,[3–5] low disease activity (LDA) has been proposed as an alternative target. To this end, there are several

definitions about LDA in the literature; for example, the Asia Pacific Lupus Consortium (APLC) has introduced the lupus low disease activity state (LLDAS): SLEDAI ≤4, which allows a low level of disease activity, without activity in major organ systems or new disease activity, PGA ≤1, prednisone daily dose not higher than 7.5 mg/day and/or immunosuppressive drugs on maintenance dose.[6] The Toronto Lupus Cohort investigators have proposed using the term low disease activity (LDA by Toronto Lupus Cohort): SLEDAI (excluding serology)≤2, without prednisone and immunosuppressive drugs.[7]

All these definitions allow the use of antimalarials.

The probability of patients achieving these states seems to vary according to a number of factors including race/ethnicity, in particular African ancestry,[8 9] age at diagnosis,[10] previous disease activity,[8 10 11] major organ involvement[10 12] and treatment.[8–10] Furthermore, the clinical impact of achieving such states in several clinical outcomes has been examined.[13] The outcome most frequently evaluated has been organ damage accrual; in fact, in several cohorts, remission and/or LDA have been found to prevent damage, but the exact definitions used for these states have not been uniform.[3 6 7 11 14–20]

One of the main challenges is to validate whether all these definitions are indeed predictive of outcomes such as organ damage, death, recurrent flares, number of hospitalisations and quality of life (QoL), and which of them would be the better option. Therefore, our aim was to perform a systematic review of the current literature to assess the impact of the existing definitions of remission/LDA on relevant outcomes of patients with SLE.



*No additional articles were retrieved by reviewing the references of the selected articles.

Figure 1 PRISMA flowchart.

METHODS

Search strategies

A systematic review according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines[21] was carried out. The protocol was registered with PROSPERO (CRD42020162724).

We used the electronic databases PubMed (1946-week 2, April 2021), Cochrane library (1985-week 2, week 2, April 2021) and EMBASE (1974-week 2, April 2021) were searched. We used the Medical Subject Heading (MeSH) terms and Key words in all possible combinations using Boolean operators with the following search strategy: 'systemic lupus erythematosus', 'lupus', 'SLE', 'remission', 'low disease activity status', 'low lupus disease activity status', 'minimal disease activity'. References of all included full-text articles were handsearched in order to find additional references from the articles that seem to be relevant for the review. Details of the full search strategy are listed in online supplemental table 1.

These articles were downloaded into EndNote software (V.9.3.2); duplicates were deleted. Two independent teams examined each selected article and performed data extraction independently (MFU-G and CR-S or CM-P and GP-E). In case of disagreement, a third investigator was consulted. Discrepancies were resolved by consensus. The literature review team also made every effort to identify multiple publications from a single cohort.

Criteria for the selection of studies

We included both observational studies (case–control, cross-sectional or cohort) and clinical trials on adults or children with SLE in LDA (using a validated definition) or remission (as defined by available criteria) and reporting different disease outcomes in the follow-up (mortality, damage, flare, health-related QoL (HRQoL), risk of cardiovascular disease, hospitalisations and direct healthcare cost). A minimum sample size of 100 patients was required for an article to be included. Patients needed to have similar duration of follow-up in studies that reported flare rates (using a validated definition) as percentages; alternatively, reported flares per person-years was used in cases where patients had unequal follow-up duration. Damage data, as assessed by the validated instrument (the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)), were considered.

Studies published only as abstracts were excluded.

Articles written in English or Spanish were included. Case reports, case series, editorials, comments, letters and reviews were excluded.

Data extraction

Two reviewers independently screened all articles and applied the eligibility criteria to identify appropriate

Table 1 Characteristics of the articles included in this systematic review

Authors	Country/ region	Year of publication	Patients	Remission							
				Ethnicity, %					Cross-sectional or longitudinal	Follow-up years	NOS
				Caucasian	Asian	Mestizo/ Hispanic	African descent	Others			
Drenkard *et al*[4]	Mexico	1996	667	NR	NR	NR	NR	NR	Longitudinal	11.6	5
Medina-Quiñones *et al*[5]	UK	2016	532	55.3	18.0	NR	10.9	6.8	Longitudinal	12.0	7
Polachek *et al*[7]*	Canada	2017	620	NR	NR	NR	NR	NR	Longitudinal	4.0	7
Zen *et al*[16]	Italy	2017	293	100.0	0.0	0.0	0.0	0.0	Longitudinal	7.0	7
Ugarte-Gil *et al*[14]*	Latin America	2017	1350	41.8	NR	42.7	11.7	3.8	Longitudinal	2.4	8
Tsang-A-Sjoe *et al*[15]*	The Netherlands	2017	183	68.3	NR	NR	NR	31.7	Longitudinal	5.0	8
Mok *et al*[3]	Hong Kong	2017	769	0.0	100.0	0.0	0.0	0.0	Longitudinal	≥5.0	7
Petri *et al*[18]*	USA	2018	1356	55.0	NR	NR	38.0	7.0	Longitudinal	3.8	7
Tani *et al*[11]*	Italy	2018	115	NR	NR	NR	NR	NR	Longitudinal	≥5.0	8
Poomsalood *et al*[24]*	Thailand	2019	237	NR	NR	NR	NR	NR	Cross-sectional	NR	7
Alarcon *et al*[20]*	USA	2019	558	28.0	0.0	35.0	37.0	0.0	Longitudinal	NR	8
Ugarte-Gil *et al*[25]	USA	2019	483	NR	NR	NR	NR	NR	Longitudinal	NR	7
Mathian *et al*[26]*	France	2019	407	NR	NR	NR	NR	NR	Longitudinal	1.0	7
Golder *et al*[27]	Asia Pacific	2019	1707	10.1	87.7	NR	NR	2.2	Longitudinal	2.2	6
Reátegui-Sokolova *et al*[28]*	Peru	2019	315	NR	NR	NR	NR	NR	Longitudinal	NR	9
Margiotta *et al*[29]	Italy	2019	136	NR	NR	NR	NR	NR	Cross-sectional	NR	7
Fasano *et al*[30]	Italy	2019	294	NR	NR	NR	NR	NR	Longitudinal	9.0	7
Goswami *et al*[31]	India	2019	126	NR	NR	NR	NR	NR	Longitudinal	0.5	7
Tsang-A-Sjoe *et al*[15]	The Netherlands	2019	154	69.5	NR	NR	NR	30.5	Longitudinal	2.0	7
Ugarte-Gil *et al*[33]*	Peru	2020	208	NR	NR	NR	NR	NR	Longitudinal	2.2	9
Floris *et al*[34] *	Italy	2020	116	100.0	0.0	0.0	0.0	0.0	Longitudinal	1.5	8
Saccon *et al*[35]	Italy	2020	646	NR	NR	NR	NR	NR	Longitudinal	5.0	9
Jakez-Ocampo *et al*[36]	Mexico	2020	132	NR	NR	NR	NR	NR	Cross-sectional	NR	6
Nikfar *et al*[37]	Iran	2021	193	NR	NR	NR	NR	NR	Longitudinal	8.0	8

Continued

Table 1 Continued

Authors	Country/ region	Year of publication	Patients	LDA					Cross-sectional or longitudinal	Follow-up years	NOS
				Ethnicity, %							
				Caucasian	Asian	Mestizo/ Hispanic	African descent	Others			
Polachek *et al*[7]*	Canada	2017	620	NR	NR	NR	NR	NR	Longitudinal	4.0	7
Ugarte-Gil *et al*[14]*	Latin America	2017	1350	41.8	NR	42.7	11.7	3.8	Longitudinal	2.4	8
Tsang-A-Sjoe *et al*[15]*	The Netherlands	2017	183	68.3	NR	NR	NR	31.7	Longitudinal	5.0	8
Golder *et al*[39]	Asia Pacific	2017	1422	8.0	90.0	NR	NR	2.0	Cross-sectional	NR	7
Tani *et al*[11]*	Italy	2018	115	NR	NR	NR	NR	NR	Longitudinal	≥5	8
Zen *et al*[17]	Italy	2018	293	100.0	0.0	0.0	0.0	0.0	Longitudinal	7.0	9
Petri *et al*[18]*	USA	2018	1356	55.0	NR	NR	38.0	7.0	Longitudinal	NR	7
Poomsalood *et al*[24]*	Thailand	2019	237	NR	NR	NR	NR	NR	Cross-sectional	NR	7
Alarcon *et al*[20] *	USA	2019	558	28.0	0.0	35.0	37.0	0.0	Longitudinal	NR	8
Ugarte.Gil *et al*[25]*	USA	2019	483	NR	NR	NR	NR	NR	Longitudinal	NR	7
Mathian *et al*[26]*	France	2019	407	NR	NR	NR	NR	NR	Longitudinal	1.0	7
Golder *et al*[38]	Asia Pacific	2019	1707	10.1	87.7	NR	NR	2.2	Longitudinal	2.2	6
Reategui-Sokolova *et al*[28]*	Peru	2019	315	NR	NR	NR	NR	NR	Longitudinal	NR	9
Ugarte-Gil *et al*[33]*	Peru	2020	243	NR	NR	NR	NR	NR	Longitudinal	2.2	7
Sharma *et al*[40]	Norway	2020	206	100.0	0.0	0.0	0.0	0.0	Longitudinal	10.0	6
Yeo *et al*[41]	Australia	2020	200	52.0	39.5	NR	NR	8.5	Longitudinal	2.1	9
Floris *et al*[34]*	Italy	2020	116	100.0	0.0	0.0	0.0	0.0	Longitudinal	1.5	8
Louthrenoo *et al*[42]	Thailand	2020	337	NR	NR	NR	NR	NR	Longitudinal	3.2	8
Kang *et al*[43]	Korea	2021	299	NR	NR	NR	NR	NR	Longitudinal	4.0	8

*These articles were included for remission and LDA.
LDA, low disease activity; NOS, Newcastle-Ottawa Scale; NR, not reported.;

studies for inclusion; the selected articles were then abstracted, also independently, using a predetermined form. Information was collected on the study characteristics (study design, country, sample size), the number of participants, gender, age, major clinical variables (damage), definition of LDA/remission used, flare rates or flares per person-years, HRQoL scores, HRQoL instruments, hospitalisation rates, mortality rates, direct healthcare cost, definitions of cardiovascular disease and rates or risk of cardiovascular disease. If the same article reported more than one definition of the states or more than one outcome, all of them were included in the respective analyses.

Evaluation of the quality of the studies

The quality of the studies identified was assessed using the Newcastle-Ottawa Scale (NOS) for cohort and case–control studies a tool specifically developed to assess the quality of observational studies.[15] The scoring system covers three major domains: selection of cohorts or cases and controls (maximum four points), comparability of selected groups (maximum two points) and ascertainment of either the exposure or the outcome of interest (maximum three points): the resulting score ranges from 0 to 9; a higher score represents a better methodological quality. While there is no validated cut-off value to discern between studies of good or poor quality, studies with a score of ≥7 were arbitrarily defined as being of high quality.[22]

Strategy for analysis synthesis

Due to the diversity of remission and LDA definitions, outcomes, heterogeneity of the results and of the different statistical tests performed in the selected articles, a meta-analysis was felt not to be feasible for most of the outcome variables; therefore, the studies selected were summarised using a narrative synthesis approach. A description and rationale were provided for grouping studies for synthesis (eg, according to outcomes type). Established metrics were used to measure the direction and magnitude effect of association between remission/LDA and outcomes (eg, OR, risk ratio (RR), HR, among others) when they were available. Summary tables and structured narrative were employed to descriptively summarise and compare each included study and to examine the heterogeneity across studies.[23]

RESULTS

Study selection and characteristics of studies included

Our search identified 7497 articles, of which 31 studies met the inclusion criteria.[3–5 7 11 14–18 20 24–43] The study selection process and reasons for exclusion are shown in figure 1. Four studies were cross sectional, 27 were longitudinal, 12 (38.7%) were from Europe, 10 (32.3%) from Asia and Australia, 5 (16.1%) from Latin America and 4 (12.9%) from the USA and Canada. The large majority of studies were of high quality according to NOS (table 1).

Remission and LDA rates

The rates of remission and LDA varied depending on both the definition used and the population studied. Remission was more frequent in European populations being as high as 88.1% in one study, but it was as low as 3.5% when the definition excluded patients under treatment and a duration of the remission of at least 7 years. LDA was also more frequent in European populations; however, the rate depended on the definition used; as expected, the less stringent the definition, the more frequently this outcome was achieved. These data are depicted in online supplemental table 2.

Mortality

Six studies including 3933 patients evaluated mortality as an outcome, two evaluated the impact of remission and LDA on mortality, two only LDA, one only remission and one compared remission and LDA. Among the four studies reporting the impact of LDA on mortality, two of them reported a reduction on mortality (HR 0.3% and 1.4% in those in LDA and 6.9% in those active) and two did not, although the trend was similar (HR 0.30 and 0.81, p: not significant). Among the three studies evaluating the impact of remission (compared with those not on remission) on mortality; two of them reported a reduction on mortality (HR 0.08% and 5% in those in remission and 17.7% in those not in remission), whereas the other did not (HR 0.56, p value not significant). In another report, remission was not statistically different from LDA in terms of the mortality rate. These data are depicted in table 2.

Damage accrual

Sixteen studies including 8288 patients evaluated damage accrual. In the majority of studies, both remission and LDA prevented damage accrual when compared with patients who did not attain these states (risk measures between 0.04 and 0.95 for remission and between 0.07 and 0.90 for LDA, depending on the definition). In most of the studies, LDA also included those patients who were on remission; however, depending on the definition used, there could be a difference between those in remission and those in LDA, being better to be on remission. These data are depicted in tables 3 and 4.

Flare

Five studies including 3033 patients evaluated longitudinally the occurrence of flares after achieving these states. Remission and LDA reduced the probability of flares in all studies included, regardless of the definition used (HR between 0.26 and 0.70 for remission and between 0.41 and 0.74 for LDA); however, the longer the duration of the state, the lower the risk. Only one study compare remission versus LDA and it did not find a statistically significant difference. These data are depicted in table 5.

Table 2 Impact of remission and LDA on mortality*

Authors	Patients	Follow-up years	Remission: Disease activity index	Immunological activity	PGA	PDN daily dose	IS use	AM use	Minimal duration	Impact
Drenkard *et al*[4]	667	11.6	Lack of clinical disease activity (no formal index was used)	Allowed	NR	Not allowed	Not allowed	Not allowed	1 year	HR 0.08, p<0.001
Medina-Quiñones *et al*[5]	532	12	BILAG C, D, E	Not allowed	NR	0	Not allowed	Allowed	3 years	5% vs 17.7% (not on remission), p<0.001
Polachek *et al*[7]	620	4	SLEDAI=0	Not allowed	NR	Not allowed	Not allowed	Allowed	1 year	Remission vs LDA: 0.5% vs 2.5%, p=0.15 year 2
Ugarte-Gil *et al*[14]	1350	2.4	SLEDAI=0	Not allowed	NR	≤5	Allowed	Allowed	At least once	Mortality (reference active) HR 0.56, p=0.2623

Authors	Patients	Follow-up years	LDA: Disease activity index	Exclusion of new activity	Major organ exclusion	PGA	Prednisone daily dose	IS drug use	Antimalarial use	Minimal duration	Impact
Polachek *et al*[7]	620	4	SLEDAI<=2	Yes	No	NR	Not allowed	Not allowed	Allowed	1	Remission +LDA vs active 1.4% vs 6.9, p=0.02 (year 2), 3.6% vs 13.3%, p=0.004
Ugarte-Gil *et al*[14]	1350	2.4	SLEDAI<=4	No	No	NR	<=7.5	Allowed	Allowed	At least once	Excluding remission. Mortality (reference active) HR 0.81, p=0.6476
Alarcon *et al*[2020]	558	NR	SLAM<=3	No	No	NR	<=7.5	Not allowed	Allowed	NR	Duration on LDAS RR 0.303, p=0.1360
Sharma *et al*[40]	206	10	SLEDAI<=4	Yes	Yes	NR	<=7.5	Allowed	Allowed	50%	HR 0.31, p<0.01
Sharma *et al*[40]	206	10	SLEDAI<=4	Yes	Yes	NR	<=7.5	Allowed	Allowed	30%	HR 0.36, p<0.05
Sharma *et al*[40]	206	10	SLEDAI<=4	Yes	Yes	NR	<=7.5	Allowed	Allowed	70%	HR 0.25, p<0.01

*If an article included more than one definition, a row per definition is included.
AM, antimalarials; IS, immunosuppressive drug; LDA, low disease activity; LDAS, low disease activity status; NR, not reported; PDN, prednisone; PGA, Physician Global Assessment; RR, risk ratio; SLAM, Systemic Lupus Activity Measure; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

Table 3 Impact of remission on damage

Authors	Patients	Follow-up years	Remission: Disease activity index	Remission: Immunological activity	Remission: PGA	Remission: PDN daily dose	Remission: IS use	Remission: AM use	Remission: Minimal duration	Impact
Polachek *et al*[7]	620	4	SLEDAI=0	Not allowed	NR	Not allowed	Not allowed	Allowed	1 year	ΔSDI: 0.1 vs 0.2 (remission vs LDA only) at year 2; p=0.18
Zen *et al*[16]*	293	7	C-SLEDAI=0	Allowed	NR	≤5	Allowed	Allowed	1 year	1 year (reference <1 year) OR 0.947, p=0.946
Zen *et al*[16]*	293	7	C-SLEDAI=0	Allowed	NR	≤5	Allowed	Allowed	2 years	2 years (reference <1 year) OR 0.228, p=0.028
Zen *et al*[16]*	293	7	C-SLEDAI=0	Allowed	NR	≤5	Allowed	Allowed	3 years	3 years (reference <1 year) OR 0.116, p=0.001
Zen *et al*[16]*	293	7	C-SLEDAI=0	Allowed	NR	≤5	Allowed	Allowed	4 years	4 years (reference <1 year) OR 0.118, p=0.005
Zen *et al*[16]*	293	7	C-SLEDAI=0	Allowed	NR	≤5	Allowed	Allowed	5 years	≥5 years (reference <1 year) OR 0.044, p<0.001
Ugarte-Gil *et al*[14]*	1350	2.4	SLEDAI=0	Not allowed	NR	≤5	Allowed	Allowed	At least once	New damage (reference active) HR 0.60, p=0.0042
Ugarte-Gil *et al*[14]*	1350	2.4	SLEDAI=0	Not allowed	NR	≤5	Allowed	Allowed	At least once	New damage non-GC (reference active) HR 0.51, p=0.0006
Ugarte-Gil *et al*[14]*	1350	2.4	SLEDAI=0	Not allowed	NR	≤5	Allowed	Allowed	At least once	New severe damage non-GC (reference active) HR 0.31, p=0.0101
Ugarte-Gil *et al*[14]*	1350	2.4	SLEDAI=0	Not allowed	NR	≤5	Allowed	Allowed	At least once	New damage GC (reference active) HR 0.99, p=0.9697
Tsang-A-Sjoe *et al*[15]	183	5	C-SLEDAI=0	Allowed	NR	≤5	Allowed	Allowed	5 years	Prolonged remission (5 years) OR=0.20, p=0.001
Mok *et al*[3]	769	NR	C-SLEDAI=0	Allowed	<0.5	≤5	Allowed	Allowed	5 years	No remission or remission <5 years OR damage 2.42, p<0.001
Petri *et al*[18]*	1356	NR	C-SLEDAI=0	Allowed	<0.5	≤5	Allowed	Allowed	NR	Less than 25% RR 0.54, p<0.0001, 25%–50% on remission RR 0.47, p<0.0001, 50%–75% RR 0.43, p<0.0001, >=75%, RR 0.45, p=0.0019 (reference not remission)
Petri *et al*[18]*	1356	NR	C-SLEDAI=0	Allowed	<0.5	0	Allowed	Allowed	NR	Less than 25% RR 0.60, p<0.0001, 25%–50% on remission RR 0.66, p=0.023, 50%–75% RR 0.63, p=0.035, >=75%, RR=0.58, p=0.12 (reference not remission)
Golder *et al*[27]*	1707	2.2	C-SLEDAI=0	Allowed	<0.5	0	Allowed	Allowed	NR	HR 0.64, p=0.020 (>=50% vs <50%)
Golder *et al*[27]*	1707	2.2	C-SLEDAI=0	Allowed	<0.5	0	Not allowed	Allowed	NR	HR 0.60, p=0.022 (>=50% vs <50%)
Golder *et al*[27]*	1707	2.2	C-SLEDAI=0	Allowed	<0.5	<=5	Allowed	Allowed	NR	HR 0.49, p<0.0001 (>=50% vs <50%)
Golder *et al*[27]*	1707	2.2	C-SLEDAI=0	Allowed	<0.5	<=5	Not allowed	Allowed	NR	HR 0.58, p=0.0005 (>=50% vs <50%)
Golder *et al*[2727]*	1707	2.2	C-SLEDAI=0	Not allowed	<0.5	0	Allowed	Allowed	NR	HR 0.62, p=0.076 (>=50% vs <50%)
Golder *et al*[27]*	1707	2.2	C-SLEDAI=0	Not allowed	<0.5	0	Not allowed	Allowed	NR	HR 0.59, p=0.083 (>=50% vs <50%)
Golder *et al*[27]*	1707	2.2	C-SLEDAI=0	Not allowed	<0.5	<=5	Allowed	Allowed	NR	HR 0.63, p=0.0083 (>=50% vs <50%)
Golder *et al*[27]*	1707	2,2	C-SLEDAI=0	Not allowed	<0.5	<=5	Not allowed	Allowed	NR	HR 0.65, p=0.043 (>=50% vs <50%)
Saccon *et al*[35]*	646	5 years	Any	Allowed	Any	<=5	Allowed	Allowed	1 year	OR 0.952 (p=0.828)
Saccon *et al*[35]*	646	5 years	Any	Allowed	Any	<=5	Allowed	Allowed	2 years	OR 0.858 (p=0.471)

Continued

Table 3 Continued

Authors	Patients	Follow-up years	Remission							
			Disease activity index	Immunological activity	PGA	PDN daily dose	IS use	AM use	Minimal duration	Impact
Saccon *et al*[35]*	646	5 years	Any	Allowed	Any	<=5	Allowed	Allowed	3 years	OR 0.912 (p=0.668)
Saccon *et al*[35]*	646	5 years	Any	Allowed	Any	<=5	Allowed	Allowed	4 years	OR 0.391 (p<0.001)
Saccon *et al*[35]*	646	5 years	Any	Allowed	Any	<=5	Allowed	Allowed	5 years	OR 0.620 (p=0.010)
Saccon *et al*[35]*	646	5 years	Any	Allowed	<0.5	Allowed	Allowed	Allowed	1 year	OR 0.808 (p=0.185)
Saccon *et al*[35]*	646	5 years	Any	Allowed	<0.5	Allowed	Allowed	Allowed	2 years	OR 0.560 (p<0.001)
Saccon *et al*[35]*	646	5 years	Any	Allowed	<0.5	Allowed	Allowed	Allowed	3 years	OR 0.427 (p<0.001)
Saccon *et al*[35]*	646	5 years	Any	Allowed	<0.5	Allowed	Allowed	Allowed	4 years	OR 0.226 (p<0.001)
Saccon *et al*[35]*	646	5 years	Any	Allowed	<0.5	Allowed	Allowed	Allowed	5 years	OR 0.377 (p<0.001)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	Any	Allowed	Allowed	Allowed	1 year	OR 0.766 (p=0.119)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	Any	Allowed	Allowed	Allowed	2 years	OR 0.454 (p<0.001)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	Any	Allowed	Allowed	Allowed	3 years	OR 0.512 (p<0.001)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	Any	Allowed	Allowed	Allowed	4 years	OR 0.173 (p<0.001)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	Any	Allowed	Allowed	Allowed	5 years	OR 0.382 (p<0.001)
Saccon *et al*[35]*	646	5 years	Any	Allowed	<0.5	<=5	Allowed	Allowed	1 year	OR 0.764 (p=0.101)
Saccon *et al*[35]*	646	5 years	Any	Allowed	<0.5	<=5	Allowed	Allowed	2 years	OR 0.495 (p<0.001)
Saccon *et al*[35]*	646	5 years	Any	Allowed	<0.5	<=5	Allowed	Allowed	3 years	OR 0.430 (p<0.001)
Saccon *et al*[35]*	646	5 years	Any	Allowed	<0.5	<=5	Allowed	Allowed	4 years	OR 0.294 (p<0.001)
Saccon *et al*[35]*	646	5 years	Any	Allowed	<0.5	<=5	Allowed	Allowed	5 years	OR 0.363 (p<0.001)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	<0.5	Allowed	Allowed	Allowed	1 year	OR 0.857 (p=0.326)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	<0.5	Allowed	Allowed	Allowed	2 years	OR 0.514 (p<0.001)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	<0.5	Allowed	Allowed	Allowed	3 years	OR 0.459 (p<0.001)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	<0.5	Allowed	Allowed	Allowed	4 years	OR 0.243 (p<0.001)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	<0.5	Allowed	Allowed	Allowed	5 years	OR 0.397 (p<0.001)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	Any	<=5	Allowed	Allowed	1 year	OR 0.888 (p<0.471)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	Any	<=5	Allowed	Allowed	2 years	OR 0.497 (p<0.001)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	Any	<=5	Allowed	Allowed	3 years	OR 0.548 (p<0.001)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	Any	<=5	Allowed	Allowed	4 years	OR 0.251 (p<0.001)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	Any	<=5	Allowed	Allowed	5 years	OR 0.411 (p<0.001)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	<0.5	<=5	Allowed	Allowed	1 year	OR 0.800 (p=0.167)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	<0.5	<=5	Allowed	Allowed	2 years	OR 0.479 (p<0.001)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	<0.5	<=5	Allowed	Allowed	3 years	OR 0.438 (p<0.001)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	<0.5	<=5	Allowed	Allowed	4 years	OR 0.296 (p<0.001)
Saccon *et al*[35]*	646	5 years	C-SLEDAI=0	Allowed	<0.5	<=5	Allowed	Allowed	5 years	OR 0.384 (p<0.001)

Continued

Table 3 Continued

Authors	Patients	Follow-up years	Remission						Impact
			Disease activity index	Immunological activity	PGA	PDN daily dose	IS use	AM use	Minimal duration	
Jakez-Ocampo *et al*[36]	NR (case control)	NR	C-SLEDAI=0	Allowed	NR	Not allowed	Not allowed	Not allowed	10 years	Remission group: 0.68±0.67, control group 1.05±0.87 (p=0.016). No difference between those on remission with or without serological activity.
Floris *et al*[34]	116	1.5	C-SLEDAI=0	Allowed	<0.5	Allowed	Allowed	Allowed	NR	OR=0.07, p=0.015
Nikfar *et al*[37]	193	8	C-SLEDAI=0	Allowed	<0.5	<=5	Not allowed	Allowed	5 years	OR=0.62, p=0.047

*If an article included more than one definition, a row per definition is included.
AM, antimalarials; C-SLEDAI, Clinical Systemic Lupus Erythematosus Disease Activity Index; IS, immunosuppressive drug; LDAS, low disease activity status; LLDAS, lupus low disease activity state; NR, not reported; PDN, prednisone; PGA, Physician Global Assessment.;

Health-related quality of life (HRQoL)

Ten manuscripts including 4480 patients evaluated HRQoL. Remission and LDA were associated with a better HRQoL being this impact more consistent on the physical components of HRQoL, and less so on the mental components of HRQoL. These data are depicted in tables 6 and 7.

Other outcomes

Three manuscripts including 802 patients evaluated other outcomes. Being on remission and LDA was associated with a lower hospitalisation rate; LDA was associated with lower medical cost and prolonged remission with lower cardiovascular risk. These data are depicted in table 8.

DISCUSSION

Our systematic literature search showed that being in remission or LDA, regardless of the definitions used, was associated with better outcomes in patients with SLE, the most commonly reported outcomes being lower damage accrual, fewer flares and a better HRQoL. The association with a lower mortality rate was less consistently reported.

In terms of mortality, LDA was associated with lower mortality in two studies, one from the Toronto Lupus Cohort,[7] which had a more stringent definition of LDA (SLEDAI ≤2 without treatment) and the other from Norway[40] (which allowed a SLEDAI ≤4, excluding new activity and major organ activity, and allowing prednisone ≤7.5 mg/day and immunosuppressive drugs on maintenance dose); similarly, remission was associated with lower mortality in a study from Mexico[4] and in one from the UK.[5] However, in the GLADEL[14] and the LUMINA[20] cohorts, the association between remission and LDA and mortality was not statistically significant, although the trend was in the protective direction. This lack of association between achieving these outcomes and mortality could be due to a relatively short follow-up time in these cohorts. The Toronto Lupus Cohort compared remission and LDA and found no statistically significant difference between the two states in terms of mortality.[7]

Remission was associated with a lower risk of damage accrual in several cohorts from Asia, Europe, North America (USA-Canada) and Latin America[3 7 14–16 18 27 34–37]; however, the minimum time on remission needed to prevent damage accrual has yet to be determined. According to the Padua cohort, being in remission for less than 1 year was not protective against damage,[16] whereas according to the Hopkins cohort, being in remission even less than 25% of the follow-up time prevented the accrual of damage.[1818] According to the GLADEL cohort, being in remission prevented not only the accrual of any damage but also the accrual of severe damage (an increase in the SDI of at least 3 points) and from non-glucocorticoid (GC)-related damage and severe damage.[14] Additionally, the longer the duration of remission, the lower the probability of damage accrual.[16] Similarly, LDA (regardless of how it was defined) has been associated with less damage

Table 4 Impact of LDA on damage

Authors	Patients	Follow-up years	LDA								Impact
			Disease activity index	Exclusion of New activity	Major Organ Exclusion	PGA	PDN daily dose	IS use	AM use	Minimal duration	
Polachek *et al*[7]	620	4	SLEDAI<=2	No	No	NR	Not allowed	Not allowed	Allowed	1 year	Remission +LDA vs active: 0.15 vs 0.52, p<0.001 (year 2); 0.25 vs 0.88, p<0.001 (year 4)
Ugarte-Gil *et al*[14]*	1350	2.4	SLEDAI<=4	No	No	NR	<=7.5	Allowed	Allowed	At least once	Excluding remission new damage (reference active) HR 0.66, p=0.0158
Ugarte-Gil *et al*[14]*	1350	2.4	SLEDAI<=4	No	No	NR	<=7.5	Allowed	Allowed	At least once	Excluding remission new severe damage (reference active) HR 0.54, p=0.0614
Ugarte-Gil *et al*[14]*	1350	2.4	SLEDAI<=4	No	No	NR	<=7.5	Allowed	Allowed	At least once	Excluding remission new severe damage (reference active) HR 0.54, p=0.0614
Ugarte-Gil *et al*[14]*	1350	2.4	SLEDAI<=4	No	No	NR	<=7.5	Allowed	Allowed	At least once	Excluding remission new damage non-GC (reference active) HR 0.62, p=0.0067
Ugarte-Gil *et al*[14]*	1350	2.4	SLEDAI<=4	No	No	NR	<=7.5	Allowed	Allowed	At least once	Excluding remission new severe damage non-GC (reference active) HR 0.35, p=0.0206
Ugarte-Gil *et al*[14]*	1350	2.4	SLEDAI<=4	No	No	NR	<=7.5	Allowed	Allowed	at least once	Excluding remission new damage GC (reference active) HR 1.34, p=0.3333
Tsang-A-Sjoe *et al*[15]	183	5	SLEDAI<=4	No	Yes	<=2/10	<=7.5	Allowed	Allowed		>50% on LLDAS: OR=0.52, p=0.046
Tani *et al*[11]*	115	At least 5	SLEDAI<=4	No	Yes	<=1	<=7.5	Allowed	Allowed	100% of the follow-up	ΔSDI: 0.11 vs 0.63; p<0.001
Tani *et al*[11]*	115	at least 5	SLEDAI<=4	No	Yes	<=1	<=7.5	Allowed	Allowed	50%	ΔSDI: 0.25 vs 0.78; p=0.004
Zen *et al*[17]*	293	7	SLEDAI<=4	Yes	Yes	<=1	<=7.5	Allowed	Allowed	1 year	1 year (reference <1 year) OR 0.899, p=0.877
Zen *et al*[1717]*	293	7	SLEDAI<=4	Yes	Yes	<=1	<=7.5	Allowed	Allowed	2 years	2 years (reference <1 year) OR 0.279, p=0.036
Zen *et al*[17]*	293	7	SLEDAI<=4	Yes	Yes	<=1	<=7.5	Allowed	Allowed	3 years	3 years (reference <1 year) OR 0.252, p=0.025
Zen *et al*[17]*	293	7	SLEDAI<=4	Yes	Yes	<=1	<=7.5	Allowed	Allowed	4 years	4 years (reference <1 year) OR 0.122, p=0.001
Zen *et al*[1717]*	293	7	SLEDAI<=4	Yes	Yes	<=1	<=7.5	Allowed	Allowed	5 years	≥5 years (reference <1 year) OR 0.071, p<0.001

Continued

Table 4 Continued

Authors	Patients	Follow-up years	LDA								Impact
			Disease activity index	Exclusion of New activity	Major Organ Exclusion	PGA	PDN daily dose	IS use	AM use	Minimal duration	
Petri *et al*[18]	1356	NR	SLEDAI<=4	Yes	Yes	<=1	<=7.5	Allowed	Allowed	NR	Less than 25% RR 0.80, p=0.12, 25%–50% on remission RR 0.63, p=0.0012, 50%–75% RR 0.47, p<0.0001, >=75%, RR 0.39, p<0.0001 (reference not LLDAS)
Alarcon *et al*[20]	558	NR	SLAM<=3	No	No	NR	<=7.5	Not allowed	Allowed	NR	Duration on LDAS RR: 0.1773, p<0.0001 LDAS prevented from GC-related and non-GC-related damage
Golder *et al*[38]*	1707	2.2	SLEDAI<=4	Yes	Yes	<=1	<=7.5	Allowed	Allowed	NR	HR 0.54, p<0.0001
Golder *et al*[38]*	1707	2.2	SLEDAI<=4	Yes	Yes	<=1	<=7.5	Allowed	Allowed	NR	HR 0.59, p<0.0001
Golder *et al*[38]*	1707	2.2	SLEDAI<=4	Yes	Yes	<=1	<=7.5	Allowed	Allowed	NR	RR 0.14 p<0.0001
Sharma *et al*[40]*	206	10	SLEDAI<=4	Yes	Yes	NR	<=7.5	Allowed	Allowed	50%	HR 0.37, p<0.01 (SDI>=3)
Sharma *et al*[40]*	206	10	SLEDAI<=4	Yes	Yes	NR	<=7.5	Allowed	Allowed	30%	HR 0.57, p=0.08 (SDI>=3)
Sharma *et al*[40]*	206	10	SLEDAI<=4	Yes	Yes	NR	<=7.5	Allowed	Allowed	70%	HR 0.38, p<0.01 (SDI>=3)
Floris *et al*[34]	116	1.5	SLEDAI<=4	Yes	Yes	<=1	<=7.5	Allowed	Allowed	NR	LLDAS (not in remission) OR 0.25, p=0.049
Kang *et al*[43]*	299	4	C-SLEDAI<=1	NR	NR	NR	5	Allowed	Allowed	NR	B=–0.033, p=0.368
Kang *et al*[43]*	299	4	C-SLEDAI<=2	NR	NR	NR	0	Not allowed	allowed	NR	B=–0.093, p=0.390
Kang *et al*[43]*	299	4	SLEDAI<=4	Yes	Yes	<=1	<=7.5	Allowed	Allowed	NR	B=–0.064, p=0.050

*If an article included more than one definition, a row per definition is included.
AM, antimalarials; C-SLEDAI, Clinical Systemic Lupus Erythematosus Disease Activity Index ; IS, immunosuppressive drug; LDA, low disease activity; LDAS, low disease activity status; LLDAS, lupus low disease activity state; ;NR, not reported; PDN, prednisone; PGA, Physician Global Assessment; SLAM, Systemic Lupus Activity Measure.

Table 5 Impact of remission and LDA on flare*

Authors	Country/ region	Year of publication	Patients	Follow-up years	Remission							Impact
					Disease activity index	Immunological activity	PGA	PDN daily dose	IS use	AM use	Minimal duration	
Polachek *et al*[7]	Canada	2017	620	4	SLEDAI=0	Not allowed	NR	Not allowed	Not allowed	Allowed	1 year	Remission vs LDA 5% vs 4.4%, p=0.8, year 2
Mathian *et al*[26]	France	2019	407	1	C-SLEDAI=0	Allowed	NR	<=5	Allowed	Allowed	NR	For each year remission, HR 0.7, p=0.02
Golder *et al*[27 38]	Asia Pacific	2019	1707	2.2	C-SLEDAI=0	Allowed	<0.5	0	Allowed	Allowed	NR	HR 0.39, p<0.0001 (>=50% vs<50%)
Golder *et al*[2727]	Asia Pacific	2019	1707	2.2	C-SLEDAI=0	Allowed	<0.5	0	Not allowed	Allowed	NR	HR 0.36; p<0.0001 (>=50% vs<50%)
Golder *et al*[27]	Asia Pacific	2019	1707	2.2	C-SLEDAI=0	Allowed	<0.5	<=5	Allowed	Allowed	NR	HR 0.54 p<0.0001 (>=50% vs<50%)
Golder *et al*[27]	Asia Pacific	2019	1707	2.2	C-SLEDAI=0	Allowed	<0.5	<=5	Not allowed	Allowed	NR	HR 0.52 p<0.0001 (>=50% vs <50%)
Golder *et al*[27]	Asia Pacific	2019	1707	2.2	C-SLEDAI=0	Not allowed	<0.5	0	Allowed	Allowed	NR	HR 0.28 p<0.0001 (>=50% vs <50%)
Golder *et al*[27]	Asia Pacific	2019	1707	2.2	C-SLEDAI=0	Not allowed	<0.5	0	Not allowed	Allowed	NR	HR 0.26, p<0.0001(>=50% vs <50%)
Golder *et al*[27]	Asia Pacific	2019	1707	2.2	C-SLEDAI=0	Not allowed	<0.5	<=5	Allowed	Allowed	NR	HR 0.43, p<0.0001 (>=50% vs <50%)
Golder *et al*[2727]	Asia Pacific	2019	1707	2.2	C-SLEDAI=0	Not allowed	<0.5	<=5	Not allowed	Allowed	NR	HR 0.41, p<0.0001 (>=50% vs <50%)

Authors	Country/ region	Year of publication	Patients	Follow-up years	LDA							
					Disease activity index	Exclusion of new activity	Major organ exclusion	PGA	PDN daily dose	IS use	AM use	Minimal duration	Impact
Polachek *et al*[7]	Canada	2017	620	4	SLEDAI<=2	Yes	No	NR	Not allowed	Not allowed	Allowed	1	Remission +LDA vs active: 4.8 vs 14.6, p<0.001 (year 2), 3.7 vs 14.8, p=0.007 (year 4)
Golder *et al*[38]	Asia Pacific	2019	1707	2.2	SLEDAI<=4	Yes	Yes	<=1	<=7.5	Allowed	Allowed	Any visit	HR 0.65 (any flare), p<0.0001
Golder *et al*[38]	Asia Pacific	2019	1707	2.2	SLEDAI<=4	Yes	Yes	<=1	<=7.5	Allowed	Allowed	Any visit	HR 0.74 (mild-moderate flare), p<0.0001
Golder *et al*[38]	Asia Pacific	2019	1707	2.2	SLEDAI<=4	Yes	Yes	<=1	<=7.5	Allowed	Allowed	Any visit	HR 0.59 (severe flare), p<0.0001
Golder *et al*[38]	Asia Pacific	2019	1707	2.2	SLEDAI<=4	Yes	Yes	<=1	<=7.5	Allowed	Allowed	50% of the follow-up	HR 0.41, p<0.0001 (any flare)
Kang *et al*[43]	Korea	2021	299	4	C-SLEDAI<=1	NR	NR	NR	5	Allowed	Allowed	NR	B=0.419, p=0.109
Kang *et al*[43]	Korea	2021	299	4	C-SLEDAI<=2	NR	NR	NR	0	Not allowed	Allowed	NR	B=0.960, p=0.969
Kang *et al*[43]	Korea	2021	299	4	SLEDAI<=4	Yes	Yes	<=1	<=7.5	Allowed	Allowed	NR	B=0.090, p<0.001

*If an article included more than one definition, a row per definition is included.
AM, antimalarials; C-SLEDAI, Clinical Systemic Lupus Erythematosus Disease Activity Index; IS, immunosuppressive drug; LDA, low disease activity; NR, not reported; PDN, prednisone; PGA, Physician Global Assessment.

Table 6 Impact of remission on HRQoL*

Authors	Country/ region	Year of publication	Patients	Follow-up years	Remission							Domains positively associated	Domains not associated
					Disease activity index	Immunological activity	PGA	PDN daily dose	IS use	AM use	Minimal duration		
Mok *et al*[3]	Hong Kong	2017	769	Cross-sectional	C-SLEDAI=0	Allowed	<0.5	≤5	Allowed	Allowed	5 years	SF-36: >5 years vs <5 years and >5 years vs no remission role physical, vitality, social functioning, PCS >5 years vs no remission bodily pain, general health, role emotional, mental health, MCS LupusPRO: >5 years vs <5 years and >5 years vs no remission role physical, vitality, social functioning, PCS >5 years vs no remission bodily pain, general health, role emotional, mental health, MCS, remission >5 vs no remission desire/goal	SF-36: >5 years vs <5 years and >5 years vs no remission symptoms, medications, procreation, physical health, emotional, HRQoL total. >5 years vs <5 years remission pain, image LupusPRO: >5 years vs <5 years and >5 years vs no remission cognition, social support, coping, satisfaction with medical care, non-HRQoL total. >5 years vs <5 years remission pain, image, remission >5 vs remission <years desire/goal
Margiotta *et al*[29]	Italy	2019	136	Cross-sectional	C-SLEDAI=0	Allowed	NR	<=5	Allowed	Allowed	5 years	SF-36: >5 years vs <5 years and no remission physical functioning, role physical, bodily pain, general health and social functioning	SF-36: >5 years vs <5 years and no remission vitality, role emotional, mental health
Goswami *et al*[31]	India	2019	126	Cross-sectional	C-SLEDAI=0	Allowed	<0.5	Allowed	Allowed	Allowed	NR	SF-36: Complete remission was associated with a better PCS than clinical remission	

Continued

Table 6 Continued

Authors	Country/ region	Year of publication	Patients	Follow-up years	Remission							Domains positively associated	Domains not associated
					Disease activity index	Immunological activity	PGA	PDN daily dose	IS use	AM use	Minimal duration		
Poomsalood *et al*[24]	Thailand	2019	237	Cross-sectional	C-SLEDAI=0	Allowed	NR	<=5	Allowed	Allowed	1 year	SLEQOL: Remission vs not on remission activities, symptom, treatment, mood, self-image, total QoL univariable	SLEQOL: Remission vs not on remission. Physical, remission vs LDA NS all univariable
Tsang-A-Sjoe *et al*[15]	The Netherlands	2019	154	2	C-SLEDAI=0	Allowed	<=2/10	<=5	Allowed	Allowed	NR	SF-36: Remission on and off therapy and PCS	SF-36: Remission on and off therapy and MCS

*If an article included more than one definition, a row per definition is included.
AM, antimalarials; C-SLEDAI, Clinical Systemic Lupus Erythematosus Disease Activity Index; HRQoL, health-related quality of life; IS, immunosuppressive drug; LDAS, low disease activity; LLDAS, lupus low disease activity state; ;MCS, Mental Component Summary; NR, not reported; PCS, Physical Component Summary; PDN, prednisone; PGA, Physician Global Assessment; SF-36, 36-Item Short Form Health Survey; SLEQOL, Systemic Lupus Erythematosus Quality of Life.

accrual[7 11 14 15 17 18 20 34 38 40 43]; however, in the Padua cohort, being on LDA for less than 1 year did not prevent the accrual of damage.[17] In the Hopkins cohort, being in LDA for less than 25% of the follow-up did not prevent the accrual of damage.[18] Being in LDA prevented also severe damage accrual, non-GC and GC-related damage[14]; furthermore, the longer the duration of LDAS, the less the damage accrued.[20] In the Toronto cohort, being on remission and LDA (SLEDAI ≤2 without treatment) did not differ in terms of the risk of damage accrual[7]; however, in the Padua cohort, being in remission was associated with a lower risk of damage that being on LLDAS (which allowed a SLEDAI ≤4, excluding new activity and major organ activity, and allowing prednisone ≤7.5 mg/day and immunosuppressive drugs on maintenance dose).[17] Probably, the difference in the definitions used in both cohorts could explain these results. Consistent with these results, prolonged remission was associated with a lower probability of cardiovascular events.[30]

Being in remission or LDA reduced the risk of any flares, being those mild-moderate or severe.[7 26 27 38 43] Only in the Toronto cohort remission and LDA (SLEDAI ≤2 without treatment) were compared, but no differences were found.[7]

Patient perspective is important in defining the optimal treatment target. In previous reports, the association between disease activity and HRQoL has been low or absent.[44] Notably, remission and LDA have been found to be associated with a better HRQoL in cross-sectional and longitudinal studies regardless of whether generic or lupus-specific measures were used.[3 24 25 29 31–33 39 42 43] These associations were more consistently reported in the physical than in the mental domains, probably because the mental domains are affected also by comorbid conditions such as depression, fibromyalgia and anxiety. It has been suggested that specific measures may ascertain better QoL dimensions specific to patients with SLE.[44]

Finally, remission and LDA could reduce hospitalisation rate; this has been reported in the Peruvian Almenara Lupus cohort[28]; LDA could also reduce annual medical cost as reported in a study from an Australian cohort.[41] It is important to point out that this information needs to be confirmed in other populations.

Taking together, being on remission or on LDA, regardless of the definitions used, is associated with better outcomes, including mortality, damage, flares, HRQoL, hospitalisation and cost. It is important, however, to point out that a uniform definition of both states is desirable in order to make these results comparable. The current definition of remission, as proposed by the DORIS group, takes into account two physician disease activity measures (clinical SLEDAI=0 and PGA<0.5) as well as treatment (prednisone daily dose not higher than 5 mg/day and/or immunosuppressive drugs on maintenance dose),[1] and, even not all the studies used this definition, the large majority used 2015 or 2021 DORIS definitions[1 2] or a very similar definition. LDA should be different enough from remission in order to define a group of patients

Table 7 Impact of remission and LDA on HRQoL*

Authors	Country/ region	Year of publication	Patients	Follow-up years	LDA								Domains positively associated	Domains not associated
					Disease activity index	Exclusion of New activity	Major Organ Exclusion	PGA	PDN daily dose	IS use	AM use	Minimal duration		
Golder *et al*[39]	APLC	2017	1707	2.2	SLEDAI<=4	Yes	Yes	<=1	<=7.5	Allowed	Allowed	NR	SF-36: PCS and MCS Multivariable role physical, bodily pain, general health, social functioning, role emotional, vitality, mental health univariable	SF-36: Physical function univariable
Poomsalood *et al*[24]	Thailand	2019	237	Cross-sectional	C-SLEDAI=0	Allowed	NR	<=5	Allowed	Allowed	1 year	1 year	SLEQOL: Physical, activities, symptom, treatment, mood, self-image, total QoL univariable, LLDAS vs no LDA b: 20.02, p=0.003 Multivariable	
Ugarte-Gil *et al*[25]	USA	2019	472	NR	SLAM<=3	No	No	NR	<=7.5	Not allowed	Allowed	NR	SF-36: PCS, MCS, physical functioning, role physical, bodily pain, general health, social functioning, role emotional, vitality, mental health	

Continued

Table 7 Continued

Authors	Country/ region	Year of publication	Patients	Follow-up years	LDA								Domains positively associated	Domains not associated
					Disease activity index	Exclusion of New activity	Major Organ Exclusion	PGA	PDN daily dose	IS use	AM use	Minimal duration		
Ugarte-Gil *et al*[33]	Peru	2020	243	2	SLEDAI<=4	No	No	NR	<=7.5	Allowed	Allowed	at least once	LupusQoL: Physical health, pain, planning, burden to others, emotional health, fatigue	LupusQoL: Intimate relationship, body image
Louthrenoo *et al*[42]	Thailand	2020	337	3.2	SLEDAI<=4	Yes	Yes	<=1	<=7.5	Allowed	Allowed	NR	Global and all domains of SLEQOL, PCS and MCS SF-36	
Kang *et al*[43]	Korea	2021	299	4	C-SLEDAI<=1	NR	NR	NR	5	Allowed	Allowed	NR		PCS and MCS SF-36
Kang *et al*[43]	Korea	2021	299	4	C-SLEDAI<=2	NR	NR	NR	0	Not allowed	Allowed	NR		PCS and MCS SF-36
Kang *et al*[43]	Korea	2021	299	4	SLEDAI<=4	Yes	Yes	<=1	<=7.5	Allowed	Allowed	NR	PCS and MCS SF-36	

*If an article included more than one definition, a row per definition is included.
AM, antimalarials; HRQoL, health-related quality of life; IS, immunosuppressive drug; LDAS, low disease activity; LLDAS, lupus low disease activity state; ;MCS, Mental Component Summary; NR, not reported; PCS, Physical Component Summary; PDN, prednisone; PGA, Physician Global Assessment; SF-36, 36-Item Short Form Health Survey; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

Table 8 Impact of remission and LDA on other outcomes*

Authors	Country/ region	Year of publication	Patients	Follow-up years	Remission: Disease activity index	Immunological activity	PGA	PDN daily dose	IS use	AM use	Minimal duration	Impact
Reátegui-Sokolov *et al*[28]	Peru	2019	308	NR	SLEDAI=0	Not allowed	NR	≤5	Allowed	Allowed	At least once	Outcome: Hospitalisation HR 0.45, p=0.001
Fasano *et al*[30]	Italy	2019	294	9	C-SLEDAI=0	Allowed	NR	≤5	Allowed	Allowed	5 years	Cardiovascular event: HR 0.18, p=0.023

Authors	Country/ region	Year of publication	Patients	Follow-up years	LDA: Disease activity index	Exclusion of new activity	Major organ exclusion	PGA	Prednisone daily dose	IS drug use	Antimalarial use	Minimal duration	Impact
Reátegui-Sokolov *et al*[28]	Peru	2019	308	NR	SLEDAI<=4	No	No	NR	<=7.5	Allowed	Allowed	At least once	Excluding remission. Outcome: Hospitalisation HR 0.50, p=0.001
Yeo *et al*[41]	Australia	2020	200	2.1	SLEDAI<=4	Yes	Yes	<1	<=7.5	Allowed	Allowed	50%	Outcome: Direct health cost. Ratio of geometric means 0.53, p<0.001

*If an article included more than one definition, a row per definition is included.
AM, antimalarials; IS, immunosuppressive drug; LDA, low disease activity; NR, not reported; PDN, prednisone; PGA, Physician Global Assessment; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

with a better prognosis than those with active disease, but, not as good as the prognosis of those on remission; in this context, the definition proposed by APLC is a good option as it allows a higher level of disease activity (SLEDAI ≤4 and PGA≤1), excludes activity in major organs and new activity, and also allows a higher dose of prednisone (7.5 mg/day) and keeping the immunosuppressive drugs on maintenance dose.[6] Additionally, in the KORNET cohort from Korea, LLDAS, but not LDA (SLEDAI ≤2 without treatment) or MDA (minimal disease activity) were predictive of good outcomes.[43] However, more information is needed in order to determine if being on remission is better than being on LDA. About the duration of these states, it seems that achieving these states even for a short period of time is associated with better outcomes, but the longer the patient remains on these states, the better the outcomes will be.

These analyses have some limitations; first, as the studies included used different definitions for remission and LDA, a meta-analysis could not be performed. Second, the duration of follow-up in some studies reviewed was not long enough for the assessment of mortality. Third, there are only a few studies for some of the outcomes assessed; this precludes us from making stronger conclusions.

The main strength of this report is the inclusion of several different populations from across the world and several outcomes, allowing us to evaluate the real impact of remission and LDA in the prognosis of patients with SLE.

In conclusion, being in remission or LDA (regardless of the definition) is associated with improved outcomes in patients with SLE. These results reinforce the relevance of these outcomes for the management of patients with SLE.

In order to facilitate the implementation of a T2T strategy in SLE, it is important to have an uniform definition of remission[1] and LDA.

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