CLINICAL SCIENCE

Remission and low disease activity (LDA) prevent damage accrual in patients with systemic lupus erythematosus: results from the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort

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ABSTRACT

Objective To determine the independent impact of different definitions of remission and low disease activity (LDA) on damage accrual.

Methods Patients with ≥2 annual assessments from a longitudinal multinational inception lupus cohort were studied. Five mutually exclusive disease activity states were defined: remission off-treatment: clinical Systemic Lupus Erythematosus Disease Activity Index (cSLEDAI)-2K=0, without prednisone or immunosuppressants; remission on-treatment: cSLEDAI-2K score=0, prednisone ≤5 mg/day and/or maintenance immunosuppressants; low disease activity Toronto cohort (LDA-TC): cSLEDAI-2K score of ≤2, without prednisone or immunosuppressants; modified lupus low disease activity (mLLDAS): Systemic Lupus Erythematosus Disease Activity Index-2K score of 4 with no activity in major organ/systems, no new disease activity, prednisone ≤7.5 mg/day and/or maintenance immunosuppressants; active: all remaining visits. Only the most stringent definition was used per visit. Antimalarials were allowed in all. The proportion of time that patients were in a specific state at each visit since cohort entry was determined. Damage accrual was ascertained with the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). Univariable and multivariable generalised estimated equation negative binomial regression models were used. Time-dependent covariates were determined at the same annual visit as the disease activity state but the SDI at the subsequent visit.

Results There were 1652 patients, 1464 (88.6%) female, mean age at diagnosis 34.2 (SD 13.4) years and mean follow-up time of 7.7 (SD 4.8) years. Being in remission off-treatment, remission on-treatment, LDA-TC and mLLDAS (per 25% increase) were each associated with a lower probability of damage accrual (remission off-treatment: incidence rate ratio (IRR)=0.75, 95% CI 0.70 to 0.81; remission on-treatment: IRR=0.68, 95% CI 0.62 to 0.75; LDA:

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Remission off-treatment and on-treatment, low disease activity Toronto cohort (LDA-TC) and lupus low disease activity (LLDAS) have been proposed as targets in systemic lupus erythematosus (SLE) treatment.

WHAT THIS STUDY ADDS

⇒ This is the first study examining the independent impact of remission off-treatment and on-treatment, LDA-TC and LLDAS on damage accrual.

⇒ Remission off-treatment and on-treatment, LDA-TC and LLDAS are associated with lower probability of damage in a multinational multiethnic inception cohort.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study reinforces the relevance of remission off-treatment and on-treatment, LDA-TC and LLDAS as potential targets in the management of patients with SLE.

IRR=0.79, 95% CI 0.68 to 0.92; and mLLDAS: IRR=0.76, 95% CI 0.65 to 0.89)).

Conclusions Remission on-treatment and off-treatment, LDA-TC and mLLDAS were associated with less damage accrual, even adjusting for possible confounders and effect modifiers.

INTRODUCTION

Remission and low disease activity (LDA) have been proposed as targets for the management of systemic lupus erythematosus (SLE).[1] These states have been associated with a lower probability of mortality, damage, flares, hospitalisation, costs and cardiovascular events and with a better health-related quality of life.[2] However, there are various definitions of these states.

The Definition of Remission in Systemic Lupus Erythematosus (DORIS) group is an international task force whose aim was to provide a validated definition of remission. Its 2021 version includes a clinical Systemic Lupus Erythematosus Disease Activity Index (cSLEDAI)=0, Physician Global Assessment (PGA) score of <0.5 (0–3), prednisone ≤5 mg/day, and/or immunosuppressive drugs and biologics at maintenance dose. The group acknowledged that remission off-treatment is the ultimate goal but infrequently achieved; thus, remission on-treatment was recommended.[3]

LDA has several definitions. The Toronto Cohort definition of LDA (low disease activity Toronto cohort (LDA-TC)) includes a cSLEDAI ≤2, without prednisone or immunosuppressive drugs,[4] while the Asia-Pacific Lupus Collaboration (APLC) definition of lupus low disease activity state (LLDAS) includes a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) of ≤4, with no activity in major organ systems (renal, neurological, cardiopulmonary, vasculitis and fever), with no new features of disease activity compared with previous assessment, PGA score ≤1.0, prednisone of ≤7.5 mg/day and/or immunosuppressive drugs at maintenance dose.[5] All states allow antimalarials.

DORIS remission off-treatment and on-treatment, LDA-TC and LLDAS have been associated with lower probability of damage accrual in several cohorts[4 6–21]; however, the independent impact of each state has rarely been evaluated. Therefore, it is possible that at least part of the protective effect of a less stringent definition resulted from the inclusion of patients fulfilling a more stringent definition of a disease activity state.

Thus, we aimed to determine the independent impact of these states on damage accrual, as well as their impact on specific organ damage. We conducted these analyses in a large multinational, multiethnic disease inception cohort.

METHODS

The Systemic Lupus International Collaborating Clinics (SLICC) cohort is a multinational, multiethnic inception cohort which includes patients recently diagnosed with SLE recruited from 33 centres in Asia, Europe and North America from 1999 to 2011. These patients met the American College of Rheumatology revised classification criteria and were enrolled within 15 months of diagnosis. Data were collected per protocol at enrolment and annually and entered in a centralised database. At each annual visit, disease activity (Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)-2K[22]), damage accrual (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)[23]) and the average medications doses were recorded. Laboratory tests necessary for assessing disease activity and damage variables were performed locally.[24]

Study population

We selected all patients with at least two visits.

Disease activity states

Disease activity states were categorised based on DORIS,[3] the Toronto Cohort (TC)[4] and APLC[18] definitions; however, remission and LLDAS were defined without the inclusion of PGA because this measure was not collected in the SLICC cohort, hence modified lupus low disease activity (mLLDAS). Definitions of remission not including the PGA have previously been proposed by the Padova group.[16] Five mutually independent disease activity states are thus included:

1. Remission off-treatment: cSLEDAI-2K (excluding serology)=0, without prednisone and immunosuppressive drugs at the visit date.
2. Remission on-treatment: cSLEDAI-2K=0, prednisone of ≤5 mg/day and/or immunosuppressive drugs at maintenance dose at the visit date.
3. LDA-TC, defined as a cSLEDAI-2K≤2, without prednisone or immunosuppressive drugs at the visit date.
4. mLLDAS: SLEDAI-2K score of ≤4, with no activity in major organ systems, with no new features of disease activity compared with the previous assessment, prednisone of ≤7.5 mg/day and/or immunosuppressive drugs at maintenance dose at the visit date.
5. Active: all other visits.

If more than one definition was met, the most stringent definition fulfilled per visit was used.

Antimalarials were allowed in all groups.

The outcome was an increase in the total SDI score between two consecutive visits and an increase in the score per organ system included in the SDI.

Covariates

As achieving a disease activity state could be driven by patient or clinical characteristics that are also associated with the outcome, the following potential confounder or effect modifiers were included: sociodemographic variables including age at diagnosis, sex, race/ethnicity (classified as white from the USA, white (other), black, Asian, Hispanic and other), years of formal education, disease and treatment related variables including disease duration at baseline, the highest dose of prednisone before baseline and antimalarial use (antimalarial use was recorded at every visit).

Statistical analyses

We described the mean (SD) for continuous variables and the number (percentage) for categorical variables at baseline.

To determine the impact on the increase of the SDI, univariable and multivariable generalised estimated equation (GEE) negative binomial regression models were used. To create mutually exclusive groups, disease activity was categorised into five states, as noted, with the most stringent definition fulfilled per visit selected. The proportion of the time that patients were in the specific state at each visit since cohort entry was determined by dividing the number of years in a given state by the total follow-up at each visit for each patient. Possible effect modifiers and confounders adjusted for included the aforementioned covariates. Time-dependent covariates were determined at the same annual visit as the disease activity state; the outcome SDI was assessed at the subsequent visit. The interval between visits were included as an offset variable. The association with damage accrual is reported as incidence rate ratio (IRR) compared to

those with active disease. Sensitivity analysis including only those patients with at least 5 and 10 years of follow-up was performed. Additionally, two alternative models were considered: the first one included remission off-treatment, remission on-treatment, LDA (LDA-TC and mLLDAS together as one state) and active; the second one included remission (on-treatmentand off-treatment as one state), LDA (LDA-TC and mLLDAS as one state) and active.

To determine the impact on the increase of damage within each organ, univariable and multivariable GEE logistic regression models were used. In these cases, the outcome was the increase (or not) per organ damage, and visits were included until the maximum score per organ was achieved. Additionally, for premature gonadal failure, only women aged younger than 40 at diagnosis were included. Possible effect modifiers and confounders adjusted for included sex, age at diagnosis, race/ethnicity, education, baseline disease duration, follow-up time, the highest-ever glucocorticoid dose prior to cohort entry, antimalarials and the score of the same organ damage.

For these analyses, we have chosen 25% of the follow-up time as the unit; that is, a significant IRR should be interpreted as a patient staying in a given state 25% longer time has a probability (IRR) of preventing damage (25% vs 0% or 30% vs 5%, etc) compared with those with active disease.

All analyses were performed using SPSS V.28.0.

RESULTS

There were 1652 patients; 1464 (88.6%) were female; median age at diagnosis was 34.2 (SD 13.4) years; and mean baseline disease duration was 5.6 (SD 4.2) months. Patients had a mean follow-up of 7.7 (SD 4.8) years, 7.5 (4.8) visits per patient, and a total of 12 236 follow-up visits were included. Seven hundred and sixty-two patients (46.1%) had an increase in SDI score of ≥1 during follow-up. The SDI increased in 1267 visits, in 992 by 1 point, in 194 by 2 points, in 61 by 3 points, in 16 by 4 points and in 4 by 5 points. Two thousand five hundred and fifty-five (20.9%) of the visits were classified as remission off-treatment, 2419 (19.8%) as remission on-treatment, 556 (4.5%) as LDA-TC, 680 (5.6%) as mLLDAS and 6026 (49.2%) as active. These data are depicted in table 1.

In the multivariable model, being in remission off-treatment, remission on-treatment, LDA-TC and mLLDAS (per 25% increase in time spent in a specified state vs the active state) were predictive of a lower probability of damage accrual: remission off-treatment, IRR=0.75 (95% CI 0.70 to 0.81); remission on-treatment, IRR=0.68 (95% CI 0.62 to 0.75); LDA-TC, IRR=0.79 (95% CI 0.68 to 0.92); and mLLDAS, IRR=0.76 (95% CI 0.65 to 0.89). Univariable and multivariable models are depicted in table 2. Similar results were found in the sensitivity analysis including those patients with at least 5 or 10 years of follow-up (data not shown). The alternative models are depicted in online supplemental table 1.

Neuropsychiatric damage was accrued in 196 (11.9%) patients, musculoskeletal damage in 195 (11.8%), ophthalmological damage in 186 (11.3%) and renal damage in 159 (9.6%) patients (table 3). In the multivariable models, remission off-treatment and on-treatment and LDA-TC were associated with a lower probability of ophthalmological and renal damage; remission off-treatment and on-treatment were associated with lower probability of neuropsychiatric, cardiovascular, musculoskeletal and skin damage; remission off-treatment was associated with a lower probability of lung and gonadal damage; LDA-TC was associated with a lower probability of peripheral vascular damage; and mLLDAS was associated with a lower probability of diabetes. Univariable and multivariable models of the impact of disease activity states on organ damage accrual are depicted in table 4.

Table 1 Characteristics of SLICC patients included in this study

Characteristic	Number (%) or mean (SD)
At baseline	
Female sex	1464 (88.6)
Age at diagnosis (years)	34.2 (13.4)
Ethnicity	
White, USA	512 (31.0)
White, other	304 (18.4)
Black	277 (17.7)
Asian	251 (15.2)
Hispanic	259 (15.7%)
Other	49 (3.0)
Education level (years)	11.5 (2.0)
Disease duration at baseline (months)	5.6 (4.2)
Highest prednisone dose before baseline (mg/day)	27.4 (25.7)
SDI baseline	0.2 (0.6)
Follow-up (visits=12 236)	
Disease activity state	
Remission off-treatment	2555 (20.9)
Remission on-treatment	2419 (19.8)
LDA-TC	556 (4.5%)
mLLDAS	680 (5.6)
Active	6026 (49.2)
Antimalarials use	8771 (71.7)

LDA-TC, low disease activity Toronto cohort; mLLDAS, modified lupus low disease activity state; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLICC, Systemic Lupus International Collaborating Clinics.

DISCUSSION

In this large multinational, multiethnic cohort, we have examined, for the first time, the independent impact of remission off-treatment and on-treatment, LDA-TC and mLLDAS on damage accrual after adjustment for possible confounders. Achieving any of these possible targets was associated with a lower probability of damage accrual. The more annual visits the patient remained in a state, the lower the probability of damage accrual. In the alternative models, when visits were classified into four states (remission off-treatment, remission on-treatment, LDA (including LDA-TC and mLLDAS) and active) and in three states (remission (on-treatment and off-treatment), LDA (including LDA-TC and mLLDAS) and active), similar results were found.

Rates of remission and LDA vary around the world, with remission being most frequent in European populations (almost 90% for at least 1 year in the Padova cohort)[25] but less frequent in Latin American (20% achieved remission at least once during the follow-up).[6] As the SLICC cohort is a multinational, multiethnic cohort, the proportion of patients in remission on and off-treatment is consistent with the literature.[2] However, the relatively low proportion of visits in LDA-TC and mLLDAS but not in remission suggests that a better gradation of response state between remission and active is needed.

Our results are consistent with those from other cohorts; for example, in the GLADEL, Almenara and the Cagliari cohorts, LLDAS (excluding those in remission off-treatment and on-treatment) was associated with lower damage,[6 13 26] while in the Padova cohort,[21] those in remission accrued less damage than those in LLDAS; however, in the Toronto cohort,[4] those in

Table 2 Univariable and multivariable models of the impact of disease activity states on overall damage accrual

	Univariable model	Multivariable model
	IRR (95% CI)	IRR (95% CI)
Disease activity state		
Remission off-treatment	**0.74 (0.69 to 0.80)**	**0.75 (0.70 to 0.81)**
Remission on-treatment	**0.69 (0.63 to 0.76)**	**0.68 (0.62 to 0.75)**
LDA-TC	**0.76 (0.66 to 0.89)**	**0.79 (0.68 to 0.92)**
mLLDAS	**0.75 (0.64 to 0.89)**	**0.76 (0.65 to 0.89)**
Male sex	**1.62 (1.35 to 1.95)**	**1.29 (1.09 to 1.52)**
Age at diagnosis	**1.02 (1.02 to 1.02)**	**1.03 (1.02 to 1.03)**
Ethnicity		
White, USA	Ref.	Ref.
White, other	1.08 (0.87 to 1.34)	1.05 (0.87 to 1.27)
Black	**1.68 (1.36 to 2.08)**	**1.50 (1.23 to 1.83)**
Asian	0.81 (0.64 to 1.04)	0.83 (0.66 to 1.05)
Hispanic	1.33 (1.09 to 1.62)	1.27 (1.04 to 1.55)
Other	1.06 (0.69 to 1.61)	1.10 (0.72 to 1.68)
Educational level (years)	**0.95 (0.92 to 0.98)**	0.98 (0.95 to 1.01)
Disease duration at baseline	0.86 (0.71 to 1.04)	0.97 (0.80 to 1.16)
Antimalarial use	**0.65 (0.56 to 0.74)**	**0.76 (0.65 to 0.87)**
Highest prednisone dose before baseline	**1.01 (1.01 to 1.01)**	**1.00 (1.00 to 1.01)**
SDI before	**1.12 (1.08 to 1.16)**	1.03 (0.99 to 1.07)

Bold indicates values which are statistically significant.
IRR, incidence rate ratio; LDA-TC, low disease activity Toronto cohort; mLLDAS, modified lupus low disease activity state; Ref., reference; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

LDA-TC (and not in remission) and those in remission accrued damage similarly.

While different definitions of remission were evaluated in the Padova cohort, the more stringent the definition, the lower the probability of damage accrual.[11] However, in the APLC cohort, several definitions of remission were evaluated (with or without prednisone, with or without immunosuppressive drugs, with or without serological activity) and the HRs were similar for all definitions.[10] Additionally, LLDAS was significantly associated with reduction of damage accrual, independent of the definition of remission used, except for the least stringent definition. It probably reflects the small number of patients in LLDAS but not in remission according to the least stringent definition.[18] Similarly, in the Hopkins cohort, remission with or without prednisone presented similar risk ratios for damage accrual.[9]

Table 3 Proportion of patients with an increase in organ damage

Organ	Number (%)
Ophthalmological	186 (11.3)
Neuropsychiatric	196 (11.9)
Renal	159 (9.6)
Lung	91 (5.5)
Cardiovascular	101 (6.1)
Peripheral vascular	68 (4.1)
Gastrointestinal	49 (3.0)
Musculoskeletal	195 (11.8)
Skin	103 (6.2)
Gonadal	31/1032 (3.0)
Diabetes	45 (2.7)
Cancer	68 (4.1)

Table 4 Univariable and multivariable models of the impact of disease activity states on specific organ damage accrual

	Univariable	Multivariable*
	OR (95% CI)	OR (95% CI)
Ophthalmological		
Remission off-treatment	0.88 (0.77 to 1.01)	**0.84 (0.72 to 0.97)**
Remission on-treatment	**0.79 (0.64 to 0.96)**	**0.72 (0.59 to 0.88)**
LDA-TC	**0.71 (0.52 to 0.96)**	**0.69 (0.50 to 0.94)**
mLLDAS	0.91 (0.71 to 1.17)	0.88 (0.69 to 1.13)
Neuropsychiatric		
Remission off-treatment	**0.80 (0.68 to 0.99)**	**0.85 (0.73 to 0.99)**
Remission on-treatment	**0.55 (0.42 to 0.72)**	**0.66 (0.53 to 0.82)**
LDA-TC	0.75 (0.51 to 1.09)	0.76 (0.54 to 1.05)
mLLDAS	**0.63 (0.40 to 1.00)**	0.75 (0.53 to 1.05)
Renal		
Remission off-treatment	**0.52 (0.39 to 0.67)**	**0.71 (0.54 to 0.92)**
Remission on-treatment	**0.43 (0.31 to 0.61)**	**0.54 (0.38 to 0.78)**
LDA-TC	**0.12 (0.03 to 0.51)**	**0.27 (0.10 to 0.77)**
mLLDAS	**0.43 (0.22 to 0.87)**	0.65 (0.36 to 1.17)
Lung		
Remission off-treatment	**0.59 (0.44 to 0.80)**	**0.71 (0.53 to 0.95)**
Remission on-treatment	**0.77 (0.59 to 0.99)**	0.85 (0.68 to 1.07)
LDA-TC	**0.52 (0.29 to 0.92)**	0.63 (0.40 to 1.01)
mLLDAS	0.58 (0.34 to 1.00)	0.68 (0.43 to 1.07)
Cardiovascular		
Remission off-treatment	**0.79 (0.64 to 0.99)**	**0.73 (0.58 to 0.92)**
Remission on-treatment	**0.70 (0.53 to 0.93)**	**0.66 (0.51 to 0.92)**
LDA-TC	0.97 (0.73 to 1.30)	0.89 (0.68 to 1.17)
mLLDAS	0.64 (0.36 to 1.10)	0.62 (0.36 to 1.05)
Peripheral vascular		
Remission off-treatment	0.89 (0.69 to 1.15)	0.97 (0.75 to 1.25)
Remission on-treatment	**0.66 (0.45 to 0.98)**	0.75 (0.52 to 1.08)
LDA-TC	**0.03 (0.00 to 0.83)**	**0.06 (0.00 to 0.87)**
mLLDAS	1.07 (0.68 to 1.67)	1.16 (0.78 to 1.72)
Gastrointestinal		
Remission off-treatment	1.02 (0.79 to 1.33)	1.05 (0.81 to 1.37)
Remission on-treatment	1.12 (0.81 to 1.56)	1.17 (0.86 to 1.59)
LDA-TC	0.99 (0.58 to 1.70)	1.01 (0.60 to 1.69)
mLLDAS	1.14 (0.66 to 1.96)	1.27 (0.77 to 2.09)
Musculoskeletal		
Remission off-treatment	**0.89 (0.83 to 0.96)**	**0.70 (0.58 to 0.84)**
Remission on-treatment	0.93 (0.84 to 1.02)	**0.77 (0.62 to 0.94)**
LDA-TC	0.96 (0.85 to 1.08)	0.82 (0.62 to 1.09)
mLLDAS	1.04 (0.92 to 1.17)	0.92 (0.69 to 1.22)
Skin		
Remission off-treatment	**0.66 (0.52 to 0.85)**	**0.69 (0.53 to 0.90)**
Remission on-treatment	**0.47 (0.32 to 0.70)**	**0.52 (0.36 to 0.75)**
LDA-TC	1.07 (0.85 to 1.36)	1.06 (0.82 to 1.37)
mLLDAS	0.71 (0.44 to 1.13)	0.72 (0.46 to 1.12)
Gonadal		
Remission off-treatment	**0.43 (0.22 to 0.84)**	**0.48 (0.25 to 0.94)**
Remission on-treatment	0.68 (0.39 to 1.19)	0.77 (0.45 to 1.32)
LDA-TC	1.07 (0.63 to 1.83)	1.12 (0.66 to 1.89)
mLLDAS	0.48 (0.11 to 2.09)	0.65 (0.18 to 2.30)
Diabetes		
Remission off-treatment	0.73 (0.50 to 1.05)	0.73 (0.51 to 1.05)
Remission on-treatment	0.60 (0.35 to 1.02)	0.61 (0.37 to 1.02)
LDA-TC	0.67 (0.24 to 1.83)	0.66 (0.25 to 1.74)
mLLDAS	**0.28 (0.11 to 0.69)**	**0.32 (0.16 to 0.64)**
Cancer		

Continued

Table 4 Continued

	Univariable	Multivariable*
	OR (95% CI)	OR (95% CI)
Remission off-treatment	1.24 (1.00 to 1.53)	1.10 (0.87 to 1.40)
Remission on-treatment	1.36 (1.05 to 1.76)	1.19 (0.90 to 1.56)
LDA-TC	1.10 (0.71 to 1.70)	1.03 (0.65 to 1.63)
mLLDAS	1.28 (0.86 to 1.89)	1.17 (0.79 to 1.73)

*Adjusted for included sex, age at diagnosis, race/ethnicity, education, baseline disease duration, follow-up time the highest-ever glucocorticoid dose prior to cohort entry, antimalarials and the score of the same organ damage.
LDA-TC, low disease activity Toronto cohort; mLLDAS, modified lupus low disease activity state.

Remission off-treatment and on-treatment and LDA-TC but not mLLDAS were associated with a lower probability of renal and ophthalmological damage. In the case of renal damage, this may be related to better control of disease activity, as it has been associated with renal damage in other cohorts[27 28] and/or to the self-selection of a greater number of non-renal lupus in the remissions and LDA groups. Similar to our results, a longer percentage of the follow-up on remission on-treatment and LLDAS (including remission) were associated with a lower rate of some items of renal damage (end-stage renal disease and glomerular filtration rate <50%) in the Hopkins cohort.[9] Regarding ophthalmological damage, our results are consistent with previous reports that found an association between disease activity and glucocorticoid dose and cataracts.[29 30]

Remissions off-treatment and on-treatment were associated with lower probability of neuropsychiatric, cardiovascular, musculoskeletal and skin damage. In the Hopkins cohort, remission on-treatment and LLDAS (including remission) were associated with a lower probability of neuropsychiatric damage (remission with cranial or peripheral neuropathy and LLDAS with seizures). Nevertheless, in the Hopkins cohort, remission was not associated with a lower risk of cardiovascular damage, but LLDAS (including remission) was associated with a lower probability of myocardial infarction.[9] In the Hopkins cohort, a longer duration of remission was associated with a lower probability of several items of musculoskeletal damage (avascular necrosis and osteoporosis with fracture), and the LLDAS (including remission) was associated with lower probability of musculoskeletal damage (deforming or erosive arthritis, avascular necrosis, osteomyelitis and osteoporosis with fracture).[9] In a recent metaregression, glucocorticoid dose was associated with a higher risk of cardiovascular events, osteonecrosis and osteoporosis with fracture.[31] In the LUpus in MInorities: NAture versus nurture (LUMINA) cohort, disease activity was associated with skin damage.[32]

Remission off-treatment was associated with a lower probability of lung and gonadal damage, and this is consistent with a report from the Hopkins cohort in which a longer duration of remission on-treatment and LLDAS (including remission) was associated with a lower probability of gonadal failure.[9] In the LUMINA cohort, disease activity and glucocorticoids were associated with lung damage in the univariable models but not in the multivariable model.[33]

LDA-TC was associated with a lower probability of peripheral vascular damage; however, in the LUMINA cohort, disease activity and glucocorticoid dose were not statistically significantly associated with peripheral vascular damage.[34]

mLLDAS was associated with a lower probability of diabetes; similarly, in the Hopkins cohort, LLDAS (including remission) was associated with lower probability of diabetes.[9]

Remission off-treatment and on-treatment, LDA-TC and mLLDAS are associated with a lower probability of damage accrual. It would be expected that remission, in particular remission off-treatment, was associated with a lower probability of damage accrual; nevertheless, according to these data, LLDAS and LDA could be good targets in SLE management. These data are relevant to propose treat-to-target strategies and to define outcomes for clinical trials.[1] However, there are some domains that seem to require a more stringent definition of LDA, probably due to the deleterious effect of glucocorticoids. These data could reinforce the partial safety of low dose of prednisone,[35] which is important as glucocorticoid withdrawal is not always possible, and, in some patients, a prednisone dose of ≤5 mg/day could be acceptable.[36–38] Based on the results of remission on-treatment and LDA-TC, it seems that allowing a relatively safe dose of glucocorticoids and/or immunosuppressive drugs is better than allowing LDA but without treatment. These results are consistent with the notion that prednisone should be tapered as quickly as possible but withdrawn only when disease activity is under control and slowly.[38–40] However, these results should be interpreted carefully as they have overlapping CIs. Additionally, these results suggest that the longer the patient remains in remission or an LDA state, the better the outcome, in line with observations from several other cohorts.[9 11 17 21 26] According to these data, remission could be an achievable state in many patients, and it should remain as the ideal target in SLE treatment. However, as more stringent definitions (remission off-treatment and on-treatment) are less frequently achieved in patients with a higher risk of poorer outcomes (like non-white populations or with more severe manifestations), less stringent definitions could be more realistic outcomes for the treatment of SLE patients.[2 41–43] For example, European Alliance of Associations for Rheumatology (EULAR) and Pan American League of Associations of Rheumatology (PANLAR) guidelines recommended remission or LDA as the therapeutic goal.[44 45]

This study has some limitations. First, as the PGA was not included in the SLICC cohort, we could not use the original definition of remission and LLDAS. We believe the PGA is relevant for the definition of remission and LLDAS; however, the PGA has not been consistently reported by different investigators, as reported in a recent systematic review,[46] leading to some problems in its interpretation. However, the recent effort to standardise it (the Physician Global Assessment International Standardisation COnsensus in Systemic Lupus Erythematosus (PISCOS) study) should solve this problem.[47] Nevertheless, based on our results, definitions of remission and LDA without the PGA could be useful, particularly by physicians not properly trained in scoring it. Additionally, as recommended by the group for the PISCOS study, it is important to point out that the PGA should be scored by the same physician at all visits. Second, as visits were performed annually, it is possible that we have missed some fluctuations in disease activity occurring between the scheduled visits, however, as we have recorded the treatment between two visits, it is likely that an increase in disease activity would have been captured as it would have led to an increase in the treatment. Third, we do not know if achievement of remission or LLDAS is related to the underlying disease or more aggressive therapy. Also, we do not know how achievement of remission

or LLDAS mediates decreased damage accrual - is it related to more mild underlying disease, more aggressive therapy, or other factors. Fourth the average duration of follow-up (7.7 years), may have resulted in an overrepresentation of damage occurring earlier versus later in in the disease course. Fifth, as we have examined several outcomes and alternative models, it is possible that some associations have been influenced by multiple comparisons. However, it is important to point out that the lack of a gold standard approach for multiple test adjustment could lead to different results using the same information; based on this, some researchers have suggested to not overcorrect the data but rather to make use of the effect size in these cases.[48]

However, the main strength of this study is the inclusion of a large multinational, multi-ethnic inception cohort, with a relatively long follow-up which allowed us to evaluate the independent impact of each disease activity state on global damage accrual as well as on specific organ damage accrual.

In conclusion, remission on- and off-treatment, LDA-TC and mLLDAS were associated with less damage accrual, even after adjusting for possible confounders and effect modifiers. This highlights the importance of treating-to-target in SLE. If we want to use remission and LDA as treatment goals, their definitions should allow adequate differentiation between these states. The high rate of remission should encourage the use of remission on-treatment or off-treatment as our ideal target, with LDA (LDA-TC and LLDAS) being only an alternative target.

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REFERENCES

1 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.
2 Ugarte-Gil MF, Mendoza-Pinto C, Reátegui-Sokolova C, *et al*. Achieving remission or low disease activity is associated with better outcomes in patients with systemic lupus erythematosus: a systematic literature review. *Lupus Sci Med* 2021;8:e000542.
3 van Vollenhoven RF, Bertsias G, Doria A, *et al*. 2021 DORIS definition of remission in SLE: final recommendations from an international Task force. *Lupus Sci Med* 2021;8:e000538.
4 Polachek A, Gladman DD, Su J, *et al*. Defining low disease activity in systemic lupus erythematosus. *Arthritis Care Res* 2017;69:997–1003.
5 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.
6 Ugarte-Gil MF, Wojdyla D, Pons-Estel GJ, *et al*. Remission and low disease activity status (LDAS) protect lupus patients from damage occurrence: data from a multiethnic, multinational Latin American lupus cohort (GLADEL). *Ann Rheum Dis* 2017;76:2071–4.
7 Tsang-A-Sjoe MWP, Bultink IEM, 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.
8 Mok CC, Ho LY, Tse SM, *et al*. Prevalence of remission and its effect on damage and quality of life in Chinese patients with systemic lupus erythematosus. *Ann Rheum Dis* 2017;76:1420–5.
9 Petri M, Magder LS. Comparison of remission and lupus low disease activity state in damage prevention in a United States systemic lupus erythematosus cohort. *Arthritis Rheumatol* 2018;70:1790–5.
10 Golder V, Kandane-Rathnayake R, Huq M, *et al*. Evaluation of remission definitions for systemic lupus erythematosus: a prospective cohort study. *Lancet Rheumatol* 2019;1:e103–10.
11 Saccon F, Zen M, Gatto M, *et al*. Remission in systemic lupus erythematosus: testing different definitions in a large multicentre cohort. *Ann Rheum Dis* 2020;79:943–50.
12 Jakez-Ocampo J, Rodriguez-Armida M, Fragoso-Loyo H, *et al*. Clinical characteristics of systemic lupus erythematosus patients in long-term remission without treatment. *Clin Rheumatol* 2020;39:3365–71.
13 Floris A, Piga M, Perra D, *et al*. Treatment target in newly diagnosed systemic lupus erythematosus: the association of lupus low disease activity state and remission with lower Accrual of early damage. *Arthritis Care Res* 2020;72:1794–9.
14 Nikfar M, Malek Mahdavi A, Khabbazi A, *et al*. Long-Term remission in patients with systemic lupus erythematosus. *Int J Clin Pract* 2021;75:e13909.
15 Tani C, Vagelli R, Stagnaro C, *et al*. Remission and low disease activity in systemic lupus erythematosus: an achievable goal even with fewer steroids? real-life data from a monocentric cohort. *Lupus Sci Med* 2018;5:e000234.
16 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.
17 Alarcón GS, Ugarte-Gil MF, Pons-Estel G, *et al*. Remission and low disease activity state (LDAS) are protective of intermediate and long-term outcomes in SLE patients. results from LUMINA (LXXVIII), a multiethnic, multicenter US cohort. *Lupus* 2019;28:423–6.
18 Golder V, Kandane-Rathnayake R, Huq M, *et al*. Lupus low disease activity state as a treatment endpoint for systemic lupus erythematosus: a prospective validation study. *Lancet Rheumatol* 2019;1:e95–102.
19 Sharma C, Raymond W, Eilertsen G, *et al*. Association of achieving lupus low disease activity state fifty percent of the time with both reduced damage Accrual and mortality in patients with systemic lupus erythematosus. *Arthritis Care Res* 2020;72:447–51.
20 Kang J-H, Shin M-H, Choi S-E, *et al*. Comparison of three different definitions of low disease activity in patients with systemic lupus erythematosus and their prognostic utilities. *Rheumatology* 2021;60:762–6.
21 Zen M, Iaccarino L, Gatto M, *et al*. Lupus low disease activity state is associated with a decrease in damage progression in Caucasian patients with SLE, but overlaps with remission. *Ann Rheum Dis* 2018;77:104–10.
22 Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002;29:288–91.
23 Gladman D, Ginzler E, Goldsmith C, *et al*. The development and initial validation of the systemic lupus international collaborating Clinics/American College of rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996;39:363–9.
24 Bruce IN, O'Keeffe AG, Farewell V, *et al*. Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the systemic lupus international collaborating clinics (SLICC) inception cohort. *Ann Rheum Dis* 2015;74:1706–13.
25 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.
26 Ugarte-Gil MF, Gamboa-Cardenas RV, Reátegui-Sokolova C, *et al*. LLDAS (lupus low disease activity state) and/or remission are associated with less damage accrual in patients with systemic lupus erythematosus from a primarily Mestizo population: data from the Almenara lupus cohort. *Lupus Sci Med* 2022;9:e000616.
27 Reátegui-Sokolova C, Ugarte-Gil MF, Harvey GB, *et al*. Predictors of renal damage in systemic lupus erythematous patients: data from a multiethnic, multinational Latin American lupus cohort (GLADEL). *RMD Open* 2020;6:e001299.
28 Kandane-Rathnayake R, Kent JR, Louthrenoo W, *et al*. Longitudinal associations of active renal disease with irreversible organ damage accrual in systemic lupus erythematosus. *Lupus* 2019;28:1669–77.
29 Alderaan K, Sekicki V, Magder LS, *et al*. Risk factors for cataracts in systemic lupus erythematosus (SLE). *Rheumatol Int* 2015;35:701–8.
30 Carli L, Tani C, Querci F, *et al*. Analysis of the prevalence of cataracts and glaucoma in systemic lupus erythematosus and evaluation of the rheumatologists' practice for the monitoring of glucocorticoid eye toxicity. *Clin Rheumatol* 2013;32:1071–3.
31 Ugarte-Gil MF, Mak A, Leong J, *et al*. Impact of glucocorticoids on the incidence of lupus-related major organ damage: a systematic literature review and meta-regression analysis of longitudinal observational studies. *Lupus Sci Med* 2021;8:e000590.
32 Pons-Estel GJ, Alarcón GS, González LA, *et al*. Possible protective effect of hydroxychloroquine on delaying the occurrence of integument damage in lupus: LXXI, data from a multiethnic cohort. *Arthritis Care Res* 2010;62:393–400.
33 Bertoli AM, Vila LM, Apte M, *et al*. Systemic lupus erythematosus in a multiethnic US cohort LUMINA XLVIII: factors predictive of pulmonary damage. *Lupus* 2007;16:410–7.
34 Burgos PI, Vilá LM, Reveille JD, *et al*. Peripheral vascular damage in systemic lupus erythematosus: data from LUMINA, a large multi-ethnic U.S. cohort (LXIX). *Lupus* 2009;18:1303–8.
35 Thamer M, Hernán MA, Zhang Y, *et al*. Prednisone, lupus activity, and permanent organ damage. *J Rheumatol* 2009;36:560–4.
36 Tselios K, Gladman DD, Su J, *et al*. Gradual glucocorticosteroid withdrawal is safe in clinically quiescent systemic lupus erythematosus. *ACR Open Rheumatol* 2021;3:550–7.
37 Fasano S, Coscia MA, Pierro L, *et al*. Which patients with systemic lupus erythematosus in remission can withdraw low dose steroids? results from a single inception cohort study. *Lupus* 2021;30:991–7.
38 Ji L, Xie W, Zhang Z. Low-Dose glucocorticoids should be withdrawn or continued in systemic lupus erythematosus? A systematic review and meta-analysis on risk of flare and damage accrual. *Rheumatology* 2021;60:5517–26.
39 Ji L, Gao D, Hao Y, *et al*. Low-Dose glucocorticoids withdrawn in systemic lupus erythematosus: a desirable and attainable goal. *Rheumatology* 2022. doi:10.1093/rheumatology/keac225. [Epub ahead of print: 12 Apr 2022].
40 Ruiz-Irastorza G. Prednisone in systemic lupus erythematosus: taper quickly, withdraw slowly. *Rheumatology* 2021;60:5489–90.
41 Wilhelm TR, Magder LS, Petri M. Remission in systemic lupus erythematosus: durable remission is rare. *Ann Rheum Dis* 2017;76:547–53.

42 Ugarte-Gil MF, Wojdyla D, Pons-Estel GJ, *et al*. Predictors of remission and low disease activity state in systemic lupus erythematosus: data from a multiethnic, multinational Latin American cohort. *J Rheumatol* 2019;46:1299–308.
43 Yang Z, Cheng C, Wang Z, *et al*. Prevalence, predictors, and prognostic benefits of remission achievement in patients with systemic lupus erythematosus: a systematic review. *Arthritis Care Res* 2022;74:208–18.
44 Pons-Estel BA, Bonfa E, Soriano ER, *et al*. First Latin American clinical practice guidelines for the treatment of systemic lupus erythematosus: Latin American Group for the Study of Lupus (GLADEL, *Grupo Latino Americano de Estudio del Lupus*)-Pan-American League of Associations of Rheumatology (PANLAR). *Ann Rheum Dis* 2018;77:1549–57.
45 Fanouriakis A, Kostopoulou M, Alunno A, *et al*. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019;78:736–45.
46 Chessa E, Piga M, Floris A, *et al*. Use of physician global assessment in systemic lupus erythematosus: a systematic review of its psychometric properties. *Rheumatology* 2020;59:3622–32.
47 Piga M, Chessa E, Morand EF, *et al*. Physician global assessment international standardisation consensus in systemic lupus erythematosus: the PISCOS study. *Lancet Rheumatol* 2022;4:e441–9.
48 Huisingh C, McGwin G. An analysis of the use of multiple comparison corrections in ophthalmology research. *Invest Ophthalmol Vis Sci* 2012;53:4777.