Remission and Low Disease Activity (LDA) Prevent Damage Accrual in Systemic Lupus Erythematosus Patients. Results from the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort

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

Methods: Patients with ≥ two annual assessments from a longitudinal multinational inception lupus cohort were studied. Five mutually exclusive disease activity states were defined: Remission off-treatment: clinical (c) SLEDAI-2K=0, without prednisone or immunosuppressants; Remission on-treatment: cSLEDAI-2K=0, prednisone≤5mg/d and/or maintenance immunosuppressants; LDA-Toronto Cohort (TC): cSLEDAI-2K≤2, without prednisone or immunosuppressants; modified lupus LDA (mLLDAS): SLEDAI-2K≤4 with no activity in major organ/systems, no new disease activity, prednisone≤7.5mg/d 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 SLICC/ACR damage index (SDI). Univariable and multivariable generalized 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) (95%CI)=0.75 (0.70-0.81); remission on-treatment IRR(95%)=0.68 (0.62-0.75) LDA: IRR (95%CI)=0.79 (0.68-0.92); mLLDAS IRR (95%)=0.76 (0.65-0.89)].

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

Keywords: remission, low disease activity, low lupus disease activity state, systemic lupus erythematosus, damage, outcome

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What is already known about this subject?

Remission off and on treatment, LDA-TC and LLDAS have been proposed as targets in SLE treatment.

What does this study add?

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

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

How might this impact on clinical practice or future developments?

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

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, hospitalization, costs, cardiovascular events and with a better health-related quality of life (HRQoL) (2). However, there are various definitions of these states.

The Definition Of Remission In SLE (DORIS) group is an international task force whose aim was to provide a validated definition of remission. Its 2021 version includes a clinical SLE Disease Activity Index (cSLEDAI) = 0, Physician Global Assessment (PGA) <0.5 (0-3), prednisone ≤5mg/d, 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 (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 SLEDAI≤4, with no activity in major organ systems (renal, neurologic, cardiopulmonary, vasculitis, fever), with no new features of disease activity compared to previous assessment, PGA≤1.0, prednisone ≤7.5 mg/d, and/or immunosuppressive drugs at maintenance dose (5). All states allow antimalarials.

DORIS Remission off- 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 recently diagnosed SLE patients recruited from 33 centers in Asia, Europe and North America from 1999 to 2011. These patients met the American College of Rheumatology (ACR) revised classification criteria and were enrolled within 15 months of diagnosis. Data were collected per protocol at enrolment and annually and entered in a centralized database. At each annual visit, disease activity [SLEDAI-2K (22)], damage accrual [SLICC/ACR damage index (SDI) (23)], and the average medications doses were recorded. Laboratory tests necessary for assessing disease activity and damage variables were performed locally. The study was approved by the Institutional Research Ethics Boards of participating centers in accordance with the Declaration of Helsinki's guidelines for research in human subjects (24).

Study population

We selected all patients with at least two visits.

Disease activity states

Disease activity states were categorized based on DORIS (3), the 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 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:

Remission off-treatment: cSLEDAI-2K (excluding serology) = 0, without prednisone and immunosuppressive drugs at the visit date.

Remission on-treatment: cSLEDAI-2K = 0, prednisone $\leq$5 mg/d and/or immunosuppressive drugs at maintenance dose at the visit date.

LDA-TC, defined as a cSLEDAI-2K $\leq$2, without prednisone or immunosuppressive drugs at the visit date.

mLLDAS: SLEDAI-2K $\leq$4 with no activity in major organ systems, with no new features of disease activity compared to the previous assessment, prednisone $\leq$7.5 mg/d and/or immunosuppressive drugs at maintenance dose at the visit date.

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 US, 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 generalized estimated equation (GEE) negative binomial regression models were used. To create mutually exclusive groups, disease activity was categorized 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 was included as an offset variable. The association with damage accrual is reported as incidence rate ratio (IRR) comparted to those with active disease. Sensitivity analysis including only those patients with at least 5- and 10-years follow-up were 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 and 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 of (IRR) of preventing damage (25% vs. 0% or 30% vs. 5%, and so on) compared to those with active disease.

All analyses were performed using SPSS 28.0 (IBM, Chicago, IL).

Results

There were 1,652 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 12236 follow-up visits were included. Seven hundred and sixty-two patients (46.1%) had an increase in SDI score ≥1 during follow-up. The SDI increased in 1267 visits, in 992 by one point, in 194 by two points, in 61 by three points, in 16 by four points and in four by five 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 versus the active state) were predictive of a lower probability of damage accrual: remission off-treatment IRR=0.75, [95% confidence interval (CI) 0.70-0.81]; remission on-treatment IRR=0.68 (95% CI 0.62-0.75); LDA-TC: IRR=0.79 (95% CI 0.68-0.92); mLLDAS IRR=0.76 (95% CI 0.65-0.89). Univariable and multivariable models are depicted in table 2. Similar results were found in the sensitivity analysis including those patients with at least five or ten years of follow-up (data not shown). The alternative models are depicted in the supplementary table 1.

Neuropsychiatric damage was accrued in 196 (11.9%) patients, musculoskeletal damage in 195 (11.8%), ophthalmologic damage in 186 (11.3%) and renal damage in 159 (9.6%) patients (table 3). In the multivariable models, remission off- and on-treatment and LDA-TC were associated with a lower probability of ophthalmologic and renal damage; remission off- 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.

Discussion

In this large multinational, multi-ethnic cohort, we have examined, for the first time, the independent impact of remission off- 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- 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 one 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 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 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 hazard ratios 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).

Remission off- and on-treatment and LDA-TC but not mLLDAS were associated with a lower probability of renal and ophthalmologic 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 ophthalmologic damage, our results are consistent with previous reports that found an association between disease activity and glucocorticoid dose and cataracts (29, 30).

Remission off- 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 meta-regression, glucocorticoid dose was associated with a higher risk of cardiovascular events, osteonecrosis and osteoporosis with fracture (31). In the 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- 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 $\leq$5mg/d 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 interpretated carefully as they have overlapping confidence intervals. Additionally, these results suggest that the longer the patient remains in remission or a 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- 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, EULAR and 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 standardize it (the 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-or off treatment as our ideal target, with LDA (LDA-TC and LLDAS) being only an alternative target.

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CONTRIBUTORSHIP

All authors were involved in building and maintaining the study cohort, drafting or revising this article critically for important intellectual content, and all authors approved the final version to be published. Dr. Manuel F. Ugarte-Gil had full access to all relevant data from the study and takes responsibility for their integrity and the accuracy of the analyses performed.

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DATA SHARING STATEMENT

Upon a reasonable request.

ETHICAL APPROVAL INFORMATION

This study involves human participants and was approved by the institutional review boards of all SLICC participating sites. This study complies with the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

PATIENT AND PUBLIC INVOLVEMENT

This study was initiated in the mid 1990's before patients and public involvement were customary. So, there was no involvement from either patients or the public in the conceptualization of this study.

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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, US	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/d	27.4 (25.7)
SDI baseline	0.2 (0.6)
Follow-up (Visits=12236)	
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%)

SLICC: Systemic Lupus International Collaborating Clinics. LDA-TC: Low disease activity Toronto Cohort definition. mLLDAS: modified Lupus low disease activity state. SDI: SLICC/ACR: damage index.

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

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

LDA-TC: Low disease activity Toronto Cohort definition. mLLDAS: modified Lupus low disease activity state. SDI: SLICC/ACR: damage index.

Table 3: Proportion of patients with an increase in organ damage

Organ	Number (%)
Ophthalmologic	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 Odds Ratio, OR (95% CI)	Multivariable* OR (95% CI)
Ophthalmologic		
Remission off treatment	0.88 (0.77-1.01)	**0.84 (0.72-0.97)**
Remission on treatment	**0.79 (0.64-0.96)**	**0.72 (0.59-0.88)**
LDA-TC	**0.71 (0.52-0.96)**	**0.69 (0.50-0.94)**
mLLDAS	0.91 (0.71-1.17)	0.88 (0.69-1.13)
Neuropsychiatric		
Remission off treatment	**0.80 (0.68-0.99)**	**0.85 (0.73-0.99)**
Remission on treatment	**0.55 (0.42-0.72)**	**0.66 (0.53-0.82)**
LDA-TC	0.75 (0.51-1.09)	0.76 (0.54-1.05)
mLLDAS	**0.63 (0.40-1.00)**	0.75 (0.53-1.05)
Renal		
Remission off treatment	**0.52 (0.39-0.67)**	**0.71 (0.54-0.92)**
Remission on treatment	**0.43 (0.31-0.61)**	**0.54 (0.38-0.78)**
LDA-TC	**0.12 (0.03-0.51)**	**0.27 (0.10-0.77)**
mLLDAS	**0.43 (0.22-0.87)**	0.65 (0.36-1.17)
Lung		
Remission off treatment	**0.59 (0.44-0.80)**	**0.71 (0.53-0.95)**
Remission on treatment	**0.77 (0.59-0.99)**	0.85 (0.68-1.07)
LDA-TC	**0.52 (0.29-0.92)**	0.63 (0.40-1.01)
mLLDAS	0.58 (0.34-1.00)	0.68 (0.43-1.07)
Cardiovascular		
Remission off treatment	**0.79 (0.64-0.99)**	**0.73 (0.58-0.92)**
Remission on treatment	**0.70 (0.53-0.93)**	**0.66 (0.51-0.92)**
LDA-TC	0.97 (0.73-1.30)	0.89 (0.68-1.17)
mLLDAS	0.64 (0.36-1.10)	0.62 (0.36-1.05)
Peripheral vascular		
Remission off treatment	0.89 (0.69-1.15)	0.97 (0.75-1.25)
Remission on treatment	**0.66 (0.45-0.98)**	0.75 (0.52-1.08)
LDA-TC	**0.03 (0.00-0.83)**	**0.06 (0.00-0.87)**

mLLDAS	1.07 (0.68-1.67)	1.16 (0.78-1.72)
Gastrointestinal		
Remission off treatment	1.02 (0.79-1.33)	1.05 (0.81-1.37)
Remission on treatment	1.12 (0.81-1.56)	1.17 (0.86-1.59)
LDA-TC	0.99 (0.58-1.70)	1.01 (0.60-1.69)
mLLDAS	1.14 (0.66-1.96)	1.27 (0.77-2.09)
Musculoskeletal		
Remission off treatment	**0.89 (0.83-0.96)**	**0.70 (0.58-0.84)**
Remission on treatment	0.93 (0.84-1.02)	**0.77 (0.62-0.94)**
LDA-TC	0.96 (0.85-1.08)	0.82 (0.62-1.09)
mLLDAS	1.04 (0.92-1.17)	0.92 (0.69-1.22)
Skin		
Remission off treatment	**0.66 (0.52-0.85)**	**0.69 (0.53-0.90)**
Remission on treatment	**0.47 (0.32-0.70)**	**0.52 (0.36-0.75)**
LDA-TC	1.07 (0.85-1.36)	1.06 (0.82-1.37)
mLLDAS	0.71 (0.44-1.13)	0.72 (0.46-1.12)
Gonadal		
Remission off treatment	**0.43 (0.22-0.84)**	**0.48 (0.25-0.94)**
Remission on treatment	0.68 (0.39-1.19)	0.77 (0.45-1.32)
LDA-TC	1.07 (0.63-1.83)	1.12 (0.66-1.89)
mLLDAS	0.48 (0.11-2.09)	0.65 (0.18-2.30)
Diabetes		
Remission off treatment	0.73 (0.50-1.05)	0.73 (0.51-1.05)
Remission on treatment	0.60 (0.35-1.02)	0.61 (0.37-1.02)
LDA-TC	0.67 (0.24-1.83)	0.66 (0.25-1.74)
mLLDAS	**0.28 (0.11-0.69)**	**0.32 (0.16-0.64)**
Cancer		
Remission off treatment	1.24 (1.00-1.53)	1.10 (0.87-1.40)
Remission on treatment	1.36 (1.05-1.76)	1.19 (0.90-1.56)
LDA-TC	1.10 (0.71-1.70)	1.03 (0.65-1.63)
mLLDAS	1.28 (0.86-1.89)	1.17 (0.79-1.73)

*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 definition. mLLDAS: modified Lupus low disease activity state.