Lupus low disease activity state as a treatment endpoint for systemic lupus erythematosus: a prospective validation study

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Summary

Background **Treat-to-target strategies have improved outcomes in single-organ diseases with simple clinical or laboratory endpoints. A lack of validated endpoints has prevented adoption of treat to target for complex multiorgan conditions, such as systemic lupus erythematosus (SLE). We report the first prospective study undertaken to specifically validate a treat-to-target endpoint for SLE.**

Methods **In this prospective cohort study, patients aged 18 years or older with SLE were recruited from 13 centres in eight countries and followed prospectively. Patients with at least two visits over the study period no more than 6 months apart were included in the longitudinal analysis. Patients with no visits in the final year of the study were censored from their last visit. Attainment of the lupus low disease activity state (LLDAS) was assessed at each visit. The primary outcome measure was accrual of irreversible end-organ damage, defined as at least a 1-point increase in the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index. We used time-dependent hazard regression models and generalised linear models to measure the association between LLDAS (attainment at any timepoint, cumulative time in LLDAS, and sustained LLDAS) with accrual of irreversible end-organ damage or flare (key secondary outcome). This study is registered with ClinicalTrials.gov, NCT03138941.**

Findings **Between May 1, 2013, and Dec 31, 2016, 1707 patients were recruited and followed for a mean of 2·2 years (SD 0·9), totalling 12 689 visits. Attainment of LLDAS at any timepoint was associated with reduction in damage accrual (0·59, 0·45–0·76; p<0·0001) and subsequent flare (hazard ratio 0·65, 95% CI 0·56–0·75; p<0·0001). Cumulative time in LLDAS was associated with improved outcomes: compared with patients with less than 50% of observed time in LLDAS, those with at least 50% of observed time in LLDAS had reduced risk of damage accrual (0·54, 0·42–0·70; p<0·0001) and flare (0·41, 0·35–0·48; p<0·0001). Similarly, increased durations of sustained LLDAS were associated with incremental reductions in the risk of damage accrual. The association of LLDAS with reduced damage accrual was observed regardless of pre-existing damage or disease activity at study entry.**

Interpretation **LLDAS attainment is associated with significant protection against flare and damage accrual in SLE. These findings validate LLDAS as an endpoint for clinical studies in SLE.**

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with a substantial morbidity and mortality burden driven by accrual of irreversible end-organ damage. In contrast with other rheumatic conditions, only one targeted therapy has been approved for SLE,[1] with issues relating to study design contributing to multiple trial failures.[2] Treat-to-target approaches have had substantial impact in the management of chronic diseases such as hypertension, diabetes, and rheumatoid arthritis, with attainment of treatment endpoints measurable in single-organ systems shown to associate with improved outcomes.[3,4] By contrast, the inherent clinical complexity and heterogeneity of SLE has hindered the development of treatment endpoints, which are required for the development and eventual adoption of treat-to-target strategies.[5]

The need for a treatment endpoint for SLE that is feasible, readily deployable, and reliably associated with improved patient outcomes has been highlighted as a priority by an international taskforce.[5] Although remission remains the ultimate goal of treatment, sustained remission in SLE is rare with current therapies[6] and hence remission definitions continue to evolve.[7] By contrast, a low disease activity endpoint could be potentially more attainable than remission and, by exploiting the observation that disease heterogeneity diminishes with lower states of disease activity, easier to define and assess than existing disease activity scales. The Asia Pacific Lupus Collaboration has proposed such an endpoint, the lupus

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Research in context

Evidence before this study

Treat-to-target strategies, whereby disease status is measured against predefined endpoints to influence treatment changes, have changed the management of many chronic conditions such as diabetes, hypertension, and rheumatoid arthritis. A prerequisite for this approach is definitive evidence that a treatment endpoint is associated with improved outcomes. Treatment endpoints are more elusive for complex multiorgan diseases, which do not have a single clinical or laboratory marker, and consequently no treatment endpoint required for the adoption of treat-to-target approaches has previously been defined for systemic lupus erythematosus (SLE).

We searched PubMed for previous validation studies of low disease activity definitions for SLE, from Jan 1, 1990, to Jan 1, 2013, using search terms "systemic lupus erythematosus", "low disease activity", "treatment target", and "patient outcomes". The Asia Pacific Lupus Collaboration previously defined the lupus low disease activity state (LLDAS) conceptually as a state, which if sustained, is associated with a low likelihood of adverse outcome, considering disease activity and medication safety. Construct and criterion validity studies were subsequently published, and multiple groups have since reported the associations of LLDAS with improved outcomes in existing retrospective cohorts. Additionally, LLDAS is now being tested as a discriminatory measure of treatment response in post-hoc analyses of clinical trials. Prior to formal adoption as a treat-to-target or trial endpoint, definitive evidence is required that attainment of LLDAS is associated with improved patient outcomes. No prior prospective studies of the association of LLDAS with SLE outcomes has been published.

Added value of this study

To our knowledge, this is the first prospective study designed specifically to validate a low disease activity endpoint in SLE. In a large multinational cohort of 1707 patients with 12 689 visits, we have shown that LLDAS has both utility and validity—ie, LLDAS is attainable and is associated with marked reduction in flares and irreversible end-organ damage, with a dose-dependent relationship of reduction in damage accrual with longer durations of time spent in LLDAS. LLDAS was associated with these improved outcomes regardless of baseline damage, or of higher baseline disease activity, and sensitivity analyses revealed no superior definition of LLDAS.

Implications of all the available evidence

This prospective multicentre study confirms the validity of LLDAS as a treatment endpoint for SLE. This provides proof of concept that it is possible to derive endpoints for the development of treat-to-target strategies in complex multiorgan disease and paves the way for LLDAS to become a standard measure in future SLE clinical trials, treat-to-target studies, and clinical practice.

low disease activity state (LLDAS), which includes domains that capture the absence of organ-threatening disease activity and harmful treatment burden (eg, prednisolone no more than 7·5 mg per day).[8] LLDAS is now being tested as an endpoint in SLE clinical trials[9,10] but definitive evidence that it is associated with improved patient outcomes is required before it is adopted as a treatment endpoint. The primary objective of this study was to assess the association of LLDAS with accrual of irreversible end-organ damage and disease flare, testing the hypothesis that LLDAS attainment would be associated with protection against these outcomes.

Methods

Study design and participants

In this prospective cohort study, consecutive patients with prevalent SLE aged 18 years or older who fulfilled standardised criteria for classification of SLE[11,12] were recruited from 13 centres of the Asia Pacific Lupus Collaboration in eight countries; patients with at least two visits during the study period were included in longitudinal analysis. Minimum required visit frequency was once every 6 months, with most patients having more frequent visits based on clinical need. Loss to follow-up was defined as no visits within the last year of study. Each institution obtained ethics approval and written informed patient consent. Approval for this study was granted by the Monash University Human Research Ethics Committee: CF15/1617 – 2015000817.

Procedures

Data were collected during routine patient follow-up using standardised data collection forms. At the baseline visit, demographic and disease characteristics were collected, including sex, ethnicity, date of birth, year of SLE diagnosis, and disease manifestations ever present. Disease activity was measured at each visit using the SLE Disease Activity Index 2000 (SLEDAI-2K),[13] modified as per Thanou et al,[14] and a physician global assessment on a scale of 0 to 3 where 0 is no activity and 3 is maximum activity. Use and doses of glucocorticoids and immunosuppressive medications were recorded for each visit. Laboratory results for each patient were obtained within 30 days of each visit for the purposes of completing the SLEDAI-2K.

Attainment of LLDAS was determined for each visit. The components of LLDAS[8] are shown in the panel. Antimalarial medications were permitted. Mild to moderate flares and severe flares were assessed using the SELENA flare index, modified for the use of the SLEDAI-2K.[15] Irreversible end-organ damage was recorded annually, and at the conclusion of data collection, using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI),[16] with any increase in SDI reflecting damage accrual.

Outcomes

To address the primary objective of this study, we assessed the relationship between exposure of patients to LLDAS and disease outcomes. The primary outcome measure assessed was accrual of irreversible end-organ damage (change in SDI score), and disease flares was the key secondary outcome (appendix 1 p 2). Several measures of LLDAS exposure were studied: attainment at any single visit, percentage of overall observed time in LLDAS (cumulative LLDAS), and amount of consecutive time in LLDAS (sustained LLDAS).

Statistical analysis

Visits missing SLEDAI-2K data were excluded from analyses requiring SLEDAI-2K data. As SDI was collected yearly, for other visits, the SDI value of the closest visit (previous or following) was used. For analyses that incorporated length of time in LLDAS, if a patient was in LLDAS on two consecutive visits, they were considered to have stayed in LLDAS for the time interval between these visits. If a patient was not in LLDAS on one visit but in LLDAS on the previous visit or subsequent visit, the duration of LLDAS between visits was calculated as half the visit time interval. The percentage of follow-up in LLDAS was determined as the sum of all intervals in LLDAS, divided by total length of follow-up and multiplied by 100. A cutoff of 50% of observed time in LLDAS for each patient was used (ie, <50% *vs* ≥50%), and in supplementary analyses, the effect of lower and higher cutoffs was assessed.[8] For each patient, the maximum duration of sustained LLDAS (defined as at least two consecutive visits in LLDAS) was recorded. For those who experienced sustained LLDAS, damage at the first annual recording of the SDI subsequent to the longest period of sustained LLDAS was evaluated. For those who never experienced sustained LLDAS, any increase in SDI during follow-up was considered damage accrual.

Repeated-failures Cox proportional hazard models were used to assess the time-dependent relationship between being in LLDAS and disease flares at each subsequent visit, as well as subsequent damage accrual (≥1-point increase in SDI), with proportionality of hazard ensured (appendix 1 p 2). Cox proportional hazard models were also used to assess the relationship between proportion of time spent in LLDAS (at the 50% cutoff) and subsequent flares and damage accrual. This relationship and time to flare and new damage accrual were also tested using Kaplan-Meier survival curves with log-rank test for significance. Generalised linear models with log-binomial regression were used to determine the association between various cutoffs for percentage of time spent in LLDAS and duration of sustained LLDAS, with flare and damage accrual (appendix 1 p 2). We did subgroup analyses to assess the association between LLDAS and damage accrual in patients with existing damage at baseline (SDI ≥1), and patients with active disease at baseline using a cutoff of SLEDAI-2K of at least 6, which is commonly used as a selection criterion for entry into clinical trials.[1] Sensitivity analyses were done on several criteria of LLDAS (criteria 1, 2, 4, and 5; panel). Data were analysed using STATA version 15.1. This study is registered with ClinicalTrials.gov, NCT03138941.

***Panel:* Scoring of the LLDAS**

The following criteria are scored 'yes' or 'no'; LLDAS is achieved if all five criteria are fulfilled.

Descriptors of disease activity

- Criterion 1: SLEDAI-2K ≤4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever)
- Criterion 2: No new features of lupus disease activity compared with the previous assessment*
- Criterion 3: SELENA-SLEDAI physician global assessment ≤1†

Immunosuppressive medications

- Criterion 4: Current prednisolone (or equivalent) dose ≤7·5 mg daily
- Criterion 5: Standard maintenance doses of immunosuppressive drugs and approved biological agents‡

LLDAS=lupus low disease activity state. SLE=systemic lupus erythematosus. SLEDAI-2K=SLE Disease Activity Index 2000. CNS=central nervous system. *Defined as any new SLEDAI-2K component that was not present at the previous assessment. †Scale 0–3 where 0 is no disease activity and 3 is maximum disease activity. ‡Includes methotrexate, azathioprine, mycophenolate mofetil, mycophenolic acid, leflunomide, cyclosporine, cyclophosphamide, tacrolimus, rituximab and belimumab. Antimalarials are permitted.

Role of the funding source

The funders had no role in study design; data collection, analysis, preparation, or review; or approval of the manuscript for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 1, 2013, and Dec 31, 2016, 1735 patients were recruited. 28 patients had a baseline visit only and were excluded from longitudinal analysis, such that 1707 patients were included, and data on 304 patients (17·8%) who did not have a visit in the last 12 months of the observation period were censored from the date of their last annual visit. The 1707 patients (93% female) had a median age at diagnosis of 29 years (21–40). Most patients were Asian. More than half of the patients had a history of renal disease or mucocutaneous, musculoskeletal, or haematological manifestations. Patients were followed for a mean of 2·2 years (SD 0·9) years, with the longest follow-up 3·6 years, totalling 12 689 visits with a median visit interval of 0·28 years (IQR 0·23–0·46 ; 37 [0·3%] of the 12 689 visits were missing LLDAS status). The median SLEDAI-2K at enrolment was 4 (IQR 2–6), and 506 (29·6%) of 1707 patients had SLEDAI-2K of at least 6 at study entry. Organ damage (SDI ≥1) was present in 706 (41·4%) of 1707 patients at baseline. Other baseline characteristics are presented in table 1 and appendix 1 (p 3).

See Online for appendix 1

	Value
Baseline characteristics and demographics	
Sex	
Female	1591 (93·2%)
Male	116 (6·8%)
Age at SLE diagnosis, years	29 (21–40)
Age at recruitment, years	40·44 (31·15–50·64)
Ethnicity	
Asian	1497 (87·7%)
White	172 (10·1%)
Other	38 (2·2%)
Disease duration at recruitment, years	8 (4–14)
Patients with disease duration ≥15 months at recruitment	1510 (88·5%)
SLEDAI-2K at recruitment*	4 (2–6)
SDI at recruitment†	0·80 (1·32)
Follow-up data	
Duration of follow-up, years	2·20 (0·88)
Number of visits observed	12 689
Visits per patient	7·32 (3·38)
Interval between visits, years,	0·28 (0·23–0·46)
Medication use during follow-up	
Daily prednisolone dose, mg	5·0 (1·4–10·0)
Patients using immunosuppressants‡	1193 (69·9%)
Patients using anti-malarial drugs§	1217 (71·3%)
Time-adjusted mean SLEDAI¶	3·32 (1·48–5·29)
Physician global assessment¶‖	0·44 (0·24–0·84)
Patients with at least one episode of LLDAS	1332 (78·0%)
Number of visits where LLDAS was achieved	6081/12 689 (47·9%)
Number of visits in LLDAS per patient	3·56 (3·12)
Total LLDAS duration per patient, years	1·40 (0·94)
Percentage of follow-up time in LLDAS per patient	61·84% (34·46)

Data are n (%), mean (SD), or median (IQR). SLEDAI-2K=Systemic Lupus Erythematous Disease Activity Index 2000. SDI=Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index. LLDAS=lupus low disease activity state. *Scores range from 0 to 105, with higher scores indicating more active disease. †Scores range from 0 to 46, with higher scores indicating greater irreversible damage. Median values 0 (IQR 0–1). ‡Includes methotrexate, azathioprine, mycophenolate mofetil, mycophenolic acid, leflunomide, cyclosporine, cyclophosphamide, tacrolimus, rituximab, and belimumab. §Includes chloroquine and hydroxychloroquine. ¶Averaged across all visits. ‖Scale of 0–3, where 0 is no activity and 3 is maximum activity.

Table 1: **Characteristics of study cohort (n=1707)**

See **Online** for appendix 2

The LLDAS definition was met in 6081 (47·9%) visits, with 1332 (78·0%) of 1707 patients having at least one episode of LLDAS during follow-up (table 1). Although the mean duration of LLDAS episodes was 0·3 years (SD 0·2), 1071 (62·7%) patients achieved at least one episode of sustained LLDAS (ie, at least 2 consecutive visits in LLDAS), with 517 (48·2%) of this group sustaining LLDAS for at least 12 months. The 803 (47·0%) patients who spent at least 50% of their observed time in LLDAS had a lower SLEDAI-2K at recruitment, lower mean prednisolone dose during follow-up, and were significantly less likely to have ever had vasculitis or renal disease compared with those who spend less than 50% of the observed time in LLDAS (appendix 1 pp 4–5).

Attainment of LLDAS at any visit was associated with significant reduction in flare at the subsequent visit (hazard ratio [HR] 0·65, 95% CI 0·56–0·75; p<0·0001) and subsequent accrual of damage (0·59, 0·45–0·76; p<0·0001; table 2). Patients who spent at least 50% of their observed time in LLDAS had a significant reduction in flare (0·41, 0·35–0·48; p<0·0001) and damage accrual (0·54, 0·42–0·70; p<0·0001) across the entire observation period compared with patients with less than 50% of observed time in LLDAS. In Kaplan-Meier survival curve analysis, time to flare and damage accrual were significantly different between these two groups (both log-rank p<0·0001; figure 1). There was greater reduction in risk of flare with a larger proportion of time in LLDAS (appendix 1 p 6).

Damage accrual was observed in 31 (2·9%) of 1071 patients who experienced sustained LLDAS compared with 113 (17·8%) of 636 patients who never experienced sustained LLDAS (p<0·0001). Although any period of sustained LLDAS was associated with significant reduction in risk of subsequent damage accrual (appendix 1 p 7), increasing duration of sustained LLDAS was associated with incremental reduction in risk of subsequent new damage (figure 2). Sustained LLDAS for at least 12 months was associated with a large reduction in risk of subsequent damage (RR 0·14, 95% CI 0·07–0·30; p<0·0001).

Data for each individual patient are illustrated in interactive three-dimensional plots: one plot for all individuals, one for patients with less than 20% of observed time in LLDAS, and one for those with more than 80% of observed time in LLDAS (appendix 2). Individual patients with longer periods of sustained LLDAS (shown by position on the *x*-axis) or higher proportions of observed time in LLDAS (shown by colour progression from pink to purple) had lower rates of damage accrual (shown by position on the *y*-axis), regardless of duration of follow up (*z*-axis). This is highlighted when patients with less than 20% of observed time in LLDAS are compared with those with more than 80% of observed time in LLDAS (appendix 2).

To ensure the effect of LLDAS on damage and flares seen in the whole cohort was not driven by patients with intrinsically mild disease phenotypes, we did subgroup analyses. LLDAS attainment was less frequent in patients with active disease (SLEDAI-2K ≥6) at baseline (901 [23·6%] of 3821 visits in LLDAS) compared with patients with SLEDAI-2K less than 6 at baseline (5180 [58·7%] of 8831 visits in LLDAS; p<0·0001). However, compared with patients with baseline SLEDAI-2K less than 6, patients with active disease at baseline showed a stronger association between LLDAS attainment and reduction in damage accrual in visit-by-visit analysis and in relation to cumulative time in LLDAS, despite a smaller proportion of these patients achieving LLDAS (table 3).

Among the subset of patients with existing damage at study entry (SDI ≥1), a significant reduction in risk of further damage accrual was observed if they were able to attain LLDAS at any visit or if they spent at least 50% of their observed time in LLDAS compared with patients without existing damage at baseline (SDI=0; table 3). In a further subgroup analysis, ethnicity had no effect on the protective effect of LLDAS on damage accrual (data not shown).

To determine whether the cutoffs in the LLDAS definition domains are optimal, we analysed the effects of LLDAS attainment on outcomes using revised definitions. Reducing the allowable prednisolone dose to no more than 5 mg resulted in associations of LLDAS attainment at any visit with subsequent disease flares (HR 0·62, 95% CI 0·53–0·72; p<0·0001) and damage accrual (0·58, 0·43–0·72; p<0·0001) that were not meaningfully different from those observed with the original cutoff of no more than 7·5 mg (table 2). Similarly, changing the SLEDAI-2K cutoff to 3, specifying the absence of haematological or gastrointestinal activity in criterion 1, or using the SELENA flare index to corroborate the definition of criterion 2 (no new disease activity), had no significant effect on the association of LLDAS with reductions in flare or damage (data not shown). Deletion of criterion 5 (standard doses of immunosuppressants allowed) had no effect on reduction in disease flares or damage accrual (data not shown).

	Hazard ratio (95% CI)	p value
Flare (any) at subsequent visit	0·65 (0·56–0·75)	<0·0001
Flare (mild–moderate) at subsequent visit	0·74 (0·63–0·86)	<0·0001
Flare (severe) at subsequent visit	0·45 (0·37–0·56)	<0·0001
Damage accrual (increase in SDI ≥1)	0·59 (0·45–0·76)	<0·0001

Model results are based on 12 689 visits. LLDAS=lupus low disease activity state. SDI=Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

Table 2: **Association of LLDAS at each visit with subsequent flare and damage accrual**

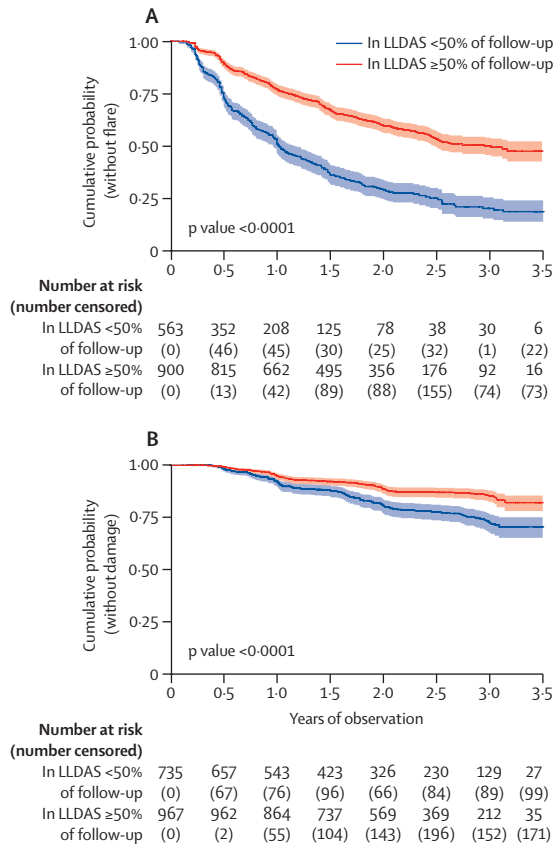

Figure 1: **Kaplan-Meier plots of time flare-free (A) and damage accrual-free (B) by observed time in LLDAS**

Plots compare patients who spent at least half of their observed time in LLDAS with patients who spent less than half of their observed time in LLDAS. Shaded areas represent 95% CIs. LLDAS=lupus low disease activity state.

Discussion

The use of treat-to-target approaches, based on evidence that endpoint attainment positively affects outcomes, has transformed clinical practice and the efficiency of clinical trials in diseases such as hypertension, diabetes, and rheumatoid arthritis.[3,4] The application of the treat-to-target paradigm to multisystem disease is more difficult because of the absence of a single-organ system on which to base a treatment endpoint. Indeed, issues with treatment response endpoints have hampered the success of novel therapy trials for SLE.[2] We sought to address the utility and validity of a low disease activity endpoint in SLE. In this prospective multicentre study, we show that LLDAS is an attainable treatment target in SLE that is robustly associated with protection from disease flares and the accrual of irreversible end-organ damage, two factors known to directly affect mortality.

To improve treatment response measurement in SLE, the development of endpoints that have both utility (ie, are feasible and attainable) and validity (ie, are associated with meaningful improvements in outcome) is required. Several instruments exist for measuring disease activity in SLE; these are reliable, sensitive to change, and highly correlated with one another.[17,18] However, no threshold level of disease activity measured using these instruments has been shown to improve outcomes, which is required for their use as a treat-to-target endpoint in trials or clinical practice. Likewise, measures of treatment response seen in clinical trials thus far detect changes from baseline rather than attainment of a defined target state. Moreover, unlike diseases such as rheumatoid arthritis, the major treatment for active SLE, glucocorticoids, contributes independently to long-term adverse outcomes including end-organ damage.[19] Therefore, treatment burden needs to be accounted for in any target state in SLE.

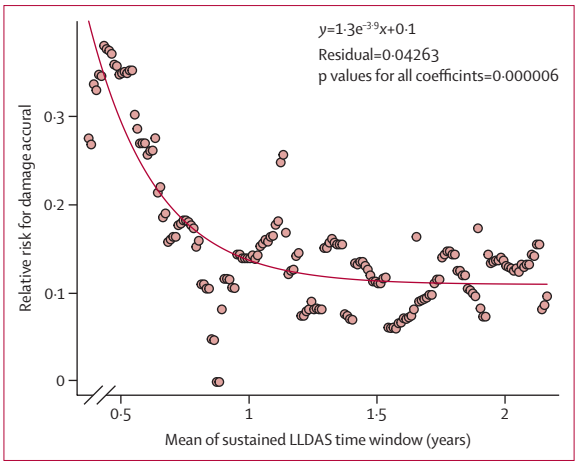

Figure 2: **Association of sustained LLDAS duration with damage accrual**
Relative risk for damage accrual was calculated on all sustained LLDAS data falling within a 3-month time window and plotted against the mean (ie, midpoint) of this time window. For example, the risk ratio of 0·5 years of sustained LLDAS is calculated with all data between 0·375 years and 0·625 years of sustained LLDAS. The 3-month time window was moved continuously over the sustained LLDAS data and 181 relative risks generated for all periods with 3 months of sustained LLDAS. An exponential regression curve is fitted over the risk ratios. LLDAS=lupus low disease activity state. SDI=Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

	Patients with characteristic at baseline (n=1707)	Hazard ratio (95% CI); p value	
		Visit by visit in LLDAS	≥50% time in LLDAS
Activity			
SLEDAI-2K <6	1201 (70·4%)	0·72 (0·52–0·99); p=0·047	0·65 (0·47–0·91); p=0·011
SLEDAI-2K ≥6	506 (29·6%)	0·49 (0·28–0·86); p=0·013	0·52 (0·33–0·83); p=0·0059
Damage			
SDI=0	1001 (58·6%)	0·71 (0·49–1·01); p=0·059	0·61 (0·43–0·87); p=0·0069
SDI ≥1	706 (41·4%)	0·52 (0·36–0·76); p=0·0006	0·53 (0·37–0·75); p=0·0004

Subgroups are defined by characteristic at cohort enrolment. Visit-by-visit analysis refers to the effect of being in LLDAS at a single visit on subsequent damage accrual (compared with visits not in LLDAS). ≥50% time analysis refers to comparison of damage accrual across the observation period in patients who spent ≥50% *vs* <50% of total observed time in LLDAS. SLEDAI-2K=Systemic Lupus Erythematous Disease Activity Index 2000. SDI=Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index. LLDAS=lupus low disease activity state.

Table 3: **Effect of LLDAS at any visit, or cumulative LLDAS ≥50% of time, on damage accrual in subgroups of patients with or without active disease or existing damage at baseline**

The development of the LLDAS definition built on previously validated SLE instruments, resulting in a composite endpoint that can be readily deployed in the clinical or research setting. Low levels of clinical activity with no laboratory activity, or vice versa, will fall under the disease activity threshold (SLEDAI-2K ≤4) in LLDAS, but low levels of both together will exceed this threshold (ie, SLEDAI-2K >4). Previous studies have suggested that LLDAS has face, content, construct, and criterion validity as an endpoint, as well as being associated with improved patient-reported health-related quality of life outcomes.[8,18,20,21] Moreover, retrospective studies of large cohorts suggest LLDAS is attainable in clinical practice and is associated with improved patient outcomes.[8,22–27]

We have shown that attainment of LLDAS at any timepoint was associated with reduction in both mild and severe flares at subsequent visits. Likewise, our data show that LLDAS at any visit was associated with protection against subsequent organ damage accrual. Given the varying lengths of follow-up and disease duration in our study, we used percentage of observed time spent in LLDAS to show that spending more than half of observed time in LLDAS was associated with significant protection against both flares and damage. Retrospective studies[22,25] have similarly shown that LLDAS in at least 50% of observations was associated with around 50% reduction in damage accrual. Importantly, we showed that as little as 20% or more of observed time in LLDAS was associated with significantly improved outcomes.

SLE is typically a disease with waxing and waning activity; however, some patients inherently have milder phenotypes whereas others have persistently active disease. To ensure that the protective association of LLDAS with damage accrual did not simply reflect better prognosis in patients with intrinsically milder disease, we did a subgroup analysis of patients with active disease at baseline. Despite the lower frequency of attainment of LLDAS among patients with higher disease activity at baseline, which was expected, the magnitude of association of LLDAS attainment with protection against damage was greater in this subgroup of patients compared with those with less active disease at baseline. This result supports the validity of LLDAS as an outcome measure in patients similar to those typically selected into clinical trials, and further highlights the impact of achieving a target outcome in patients with active disease.

In an inception cohort of patients with SLE,[27] lack of achievement of LLDAS within 6 months of diagnosis was associated with five times the odds of damage accrual by 18 months compared with patients achieving LLDAS within this timeframe.[27] The majority of our cohort had established disease and 41% of patients had organ damage at baseline, which is a known risk factor for further damage independent of disease activity.[19] We therefore assessed the effect of baseline damage on the relationship between LLDAS and further damage accrual; the protective association of LLDAS attainment with reduced damage accrual was present regardless of pre-existing damage.

In our study, more than 3 months of sustained LLDAS was associated with significant reduction in risk of damage accrual. Importantly, there were incremental further reductions in risk with longer durations of

sustained LLDAS, plateauing beyond the 12-month mark at an almost 90% reduction in risk of damage accrual. In an established cohort of white patients with SLE,[23] the proportion of patients with damage accrual progressively decreased with longer time spent in LLDAS, although longer periods in LLDAS (ie, 2 consecutive years) were required for a significant protective effect to be observed in this smaller cohort.

The incremental effect of time in sustained LLDAS on our study outcomes has important implications in clinical trial design, helping to guide the optimum study duration in which to measure periods of LLDAS attainment associated with protective effects. In two post-hoc analyses of clinical trials,[9,10] LLDAS was more stringent than the currently used outcome measures in discriminating active treatment from placebo. Moreover, sustained LLDAS for at least 3 months was achievable in a trial setting, and was more likely to be achieved with active treatment.[9] Although proportions of patients achieving LLDAS vary in the trial setting, in a phase 2 trial[28] in which LLDAS was included as an a-priori secondary outcome measure, LLDAS attainment approached 40% of patients in active treatment groups.[28] Additionally, rates of attainment of LLDAS and disease flares over time described here might have value in the design of future clinical trials.

As part of our validation process, we did a sensitivity analysis on the original operational definition of LLDAS. The minimum safe dose of prednisolone is not known, with only one large cohort study[29] showing that doses of 6 mg or less were associated with freedom from damage accrual. In our study, reducing the allowable prednisolone dose in the LLDAS definition to no more than 5 mg did not meaningfully improve the protective effect on flares or damage. Similarly, changing the SLEDAI-2K threshold from 4 to 3, or adding the criterion of absence of flare defined using the SELENA flare index to the definition of no new disease activity, had no effect on the magnitude of protective effect of LLDAS. Removing the criterion of LLDAS relating to background immunosuppressants also did not significantly affect outcomes in the sensitivity analysis. This is probably due to the fact that patients recruited from routine clinical practice mostly fulfilled the criteria for standard doses of immunosuppressant medications.

Limitations of this study include its observational nature. Future interventional studies could test the causal relationship between LLDAS attainment and protection from flares and damage using a design similar to treatment strategy studies done in rheumatoid arthritis.[3] Damage in SLE is accrued slowly. Our study had a mean duration of follow-up of just over 2 years. Although this was sufficient to detect the protective associations of LLDAS, a longer period of observation would allow for more thorough evaluation of the effects of LLDAS on damage accrual and other disease outcomes, including assessment of whether the protective associations of LLDAS attainment are sustained, and whether lower proportions of visits with LLDAS attainment in patients with activity in certain organ systems attenuates the protective associations of LLDAS. Less than 20% of patients did not complete a study visit in the last 12 months of the study, potentially creating dropout bias; however, this is less likely to be problematic given the observational rather than interventional nature of the study. Our cohort consisted predominantly of Asian patients, potentially affecting the generalisability of results. However, ethnicity had no effect on the protective effect of LLDAS on damage accrual in subgroup analysis of our cohort, and prior retrospective studies including white, Hispanic, and African-American patients showed that LLDAS was similarly associated with reduced accrual of damage.[8,22–27] Most of our cohort had prevalent disease, with only 12% of patients reporting a disease duration of less than 2 years, limiting extrapolation of these results to patients with early severe disease; however, protective effects of LLDAS attainment on damage accrual and death have been reported in retrospective analyses of two independent inception cohorts.[27,30] Finally, two of the five LLDAS criteria are dependent on the SLEDAI-2K, which has inherent limitations including limited ability to measure severity of activity within an organ system and omitting several important SLE manifestations. The LLDAS definition seeks to overcome these shortcomings by including the physician global assessment as a means to capture activity within organ systems both present in and omitted from the SLEDAI-2K. Sensitivity analyses of addition of the SELENA flare index as a means to capture new activity, specifying the absence of gastrointestinal involvement and haemolytic anaemia as in the original definition of LLDAS, or adjusting the cutoffs in activity and treatment criteria did not improve the association of LLDAS with improved outcomes. In addition, the binary scoring of disease activity using SLEDAI-2K is less limiting when applied in LLDAS, wherein the absence of organ activity is the main consideration.

In conclusion, this prospective multicentre study shows that LLDAS attainment is associated with reduction in flare and end-organ damage in SLE, thus validating it as an endpoint for clinical studies and development of treat-to-target strategies in SLE.

Contributors

VG, CSL, ZL, AH, MN, and EFM contributed to study planning and design. VG, WL, SFL, Y-JJW, AL, SS, SVN, LZ, LH, YK, MHa, MC, SO, FG, AH, MN, and EFM contributed to data collection. VG, RK-R, MHu, HTN, MN, and EFM contributed to data analysis and interpretation. VG wrote the manuscript. VG, RK-R, MHu, HTN, WL, SFL, Y-JJW, AL, SS, SVN, LZ, LH, YK, MHa, MC, SO, FG, CSL, ZL, AH, MN, and EFM contributed to editing and approval of the final manuscript.

Declaration of interests

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The remaining authors declare no competing interests.

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