



MONASH University

Treat to target in systemic lupus erythematosus: validation of the lupus low disease activity state.

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This thesis is dedicated to my loving parents, who moved halfway around the world to give me a chance at a better life.

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Abstract

Treat to target (T2T) approaches have had profound impact in the management of many chronic diseases, especially those in which treatment endpoints are measurable in single organ systems, such as hypertension or diabetes. Systemic Lupus Erythematosus (SLE), in contrast, is the quintessential autoimmune multi-organ disease, and the inherent clinical complexity and heterogeneity of SLE has hindered the development of treatment endpoints and hence adoption of T2T strategies. While remission remains the ultimate goal of treatment, with current therapies, sustained remission in SLE is rare. In contrast, a low disease activity endpoint could be potentially more attainable than remission. The Asia Pacific Lupus Collaboration (APLC) proposed such an endpoint, the Lupus Low Disease Activity State (LLDAS), which was subsequently defined operationally via a nominal consensus approach, and includes domains capturing the absence of threatening disease activity and harmful treatment burden. The broad aim of this thesis was to complete the validation studies of LLDAS to ensure that it represents a robust and valid treatment target for SLE that is associated with improved patient outcomes.

Chapter 1 reviews the literature and summarises the success of T2T strategies in other chronic conditions, the need for such strategies in SLE, and the process of defining a T2T endpoint based on the currently available instruments used to measure disease activity levels. It also outlines the steps needed to assess the utility and psychometric properties of clinical and research instruments. The methodology chapter describes the study design for the APLC prospective cohort. This is applicable to all of the results chapters with the exception of the construct validity study, the methodology for which is described under a subsection.

The studies presented in chapters 3 and 4 were conducted using the baseline visit data from the prospective APLC cohort. In chapter 3 I confirm that LLDAS is sufficiently prevalent to have utility as a T2T endpoint and identify important disease and socioeconomic factors that predict the attainment of LLDAS. In chapter 4 I demonstrate that LLDAS is independently associated with improved health related quality of life (HR-QoL). In chapter 5 I assess the construct validity of LLDAS by testing its operational definition against SLE expert opinion. I demonstrate that there is good overall agreement between LLDAS and expert opinion, with LLDAS remaining more stringent at defining a low disease activity state compared to expert assessment, whilst not inappropriately capturing patients with high disease activity.

Finally, chapters 6 and 7 present the results of the longitudinal studies of the APLC cohort with over 12,700 individual patient visits and a mean of 2.2 years of follow up. Attainment of LLDAS at a single visit resulted in a 35% reduction in relative risk of subsequent visit flares, and almost halving of relative risk of subsequent damage, compared to patients not in LLDAS, thus validating LLDAS as a treatment target for SLE. The protective effect of LLDAS increased with longer durations of both cumulative and sustained time spent in LLDAS. In chapter 7 I compared the DORIS remission definitions for their effects on disease flares and damage accrual. Remission attainment was markedly affected by definition stringency, and LLDAS was more attainable than any remission definition. The least stringent remission definition, clinical remission on treatment, had the greatest overlap with LLDAS limiting its utility as a standalone measure.

In summary, the work done in this PhD addresses the utility of LLDAS as a T2T endpoint, and completes the validation studies focusing on construct and criterion validity. My findings support the use of LLDAS as a treatment target for SLE, and as an outcome measure for clinical trials and treat-to-target strategies.

Publications during enrolment

The following manuscripts were published or submitted to a peer reviewed journal during the PhD candidature.

Publications included in the thesis

Golder V., Kandane-Rathnayake R., Hoi A.Y., Huq M., et al. *Frequency and Predictors of the Lupus Low Disease Activity State in a Multi-National and Multi-Ethnic Cohort*. Arthritis Research & Therapy. 2016;18(1):260

Golder V., Kandane-Rathnayake R., Hoi A.Y., Huq M., et al. *Association of the lupus low disease activity state (LLDAS) with health-related quality of life in a multinational prospective study*. Arthritis research & therapy. 2017; 19(1):62

Golder V., Huq M., Franklyn K., Calderone A., Lateef A., et al. *Does expert opinion match the operational definition of the Lupus Low Disease Activity State (LLDAS)? A case based construct validity study*. Seminars in Arthritis and Rheumatism, 2017; 46(6):798

Golder V., Kandane-Rathnayake R., Huq M., Nim H. et al. *Lupus Low Disease Activity State: prospective validation study*. Lancet Rheumatology, accepted for publication July 2019.

Golder V., Kandane-Rathnayake R., Huq M., Louthrenoo W., et al. *Evaluation of Remission Definitions in Systemic Lupus Erythematosus*. Lancet Rheumatology, under revision August 2019.

Publications during candidature not included in the thesis

Golder V., Morand E.F, Hoi A.Y. *Quality of Care of Systemic Lupus Erythematosus – Mind the Knowledge Gap*, Journal of Rheumatology, 2017; 44(3):271

Golder V., Hoi A.Y. *What's New in Systemic Lupus Erythematosus*, Medical Journal of Australia, 2017; 206(5):215

Golder V, Ooi J., Antony AS, Ko T, et al. *Discordance of patient and physician health status concerns in systemic lupus erythematosus*. Lupus, 2018; 27(3):501

Kandane-Rathnayake R, **Golder V**, Louthrenoo W, et al. *Development of the Asia Pacific Lupus Collaboration cohort*. Int J Rheum Dis. 2018 Nov 5. doi: 10.1111/1756-185X.13431. [Epub ahead of print]

Oon S, Huq M, **Golder V**, et al. *Lupus Low Disease Activity State (LLDAS) discriminates responders in the BLISS-52 and BLISS-76 phase III trials of belimumab in systemic lupus erythematosus*. Annals of Rheumatic Diseases, Published Online First: 24 January 2019. doi: 10.1136/annrheumdis-2018-214427

Yeo AI, Koelmeyer R, Kandane-Rathnayake R, **Golder V**, et al. *Lupus Low Disease Activity State is Associated with Reduced Direct Healthcare Costs in Patients with Systemic Lupus Erythematosus*. Revision submitted March 2019, Arthritis and Rheumatism.

Morand E, **Golder V**. *Treat-to-target endpoint definitions in lupus: more is less?* The Journal of Rheumatology, *in press*.

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes 3 original papers published in peer reviewed journals and 2 submitted publications. The core theme of the thesis is the validation of the Lupus Low Disease Activity State as a treatment endpoint for systemic lupus erythematosus. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Department of Medicine, School of Clinical Sciences at Monash Health under the supervision of Dr Alberta Hoi and Prof Eric Morand.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of chapters 3 to 7 my contribution to the work involved the following:

Thesis Chapter	Publication Title	Status (published, in press, accepted or returned for revision, submitted)	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student Y/N*
3	<i>Frequency and predictors of the lupus low disease activity state in a multi-national and multi-ethnic cohort</i>	Published	55%. Concept and design; data collection, cleaning and analysis; writing of manuscript	R. Kandane-Rathnayake 5% A.Y. Hoi 5% M. Huq 5% W. Louthrenoo 1% Y. An 1% Z.G. Li 1% S.F. Luo 1% S. Sockalingam 1% C.S. Lau 1% A.L. Lee 1% M.Y. Mok 1% A. Lateef 1% K. Franklyn 1% S. Morton 1% S.V. Navarra 1% L. Zamora 1% Y.J. Wu 1% L. Hamijoyo 1% M. Chan 1% S. O'Neill 1% F. Goldblatt 1% E.F. Morand 6% M. Nikpour 6%	No
4	<i>Association of the lupus low disease activity state (LLDAS) with health-related quality of life in a multinational prospective study.</i>	Published	55%. Concept and design; data collection, cleaning and analysis; writing of manuscript	R. Kandane-Rathnayake 5% A.Y. Hoi 5% M. Huq 5% W. Louthrenoo 1% Y. An 1% Z.G. Li 1% S.F. Luo 1% S. Sockalingam 1% C.S. Lau 1% A.L. Lee 1% M.Y. Mok 1% A. Lateef 1% K. Franklyn 1% S. Morton 1% S.V. Navarra 1%	No

				L. Zamora 1% Y.J. Wu 1% L. Hamijoyo 1% M. Chan 1% S. O'Neill 1% F. Goldblatt 1% M. Nikpour 6% E.F. Morand 6%	
5	<i>Does expert opinion match the operational definition of the Lupus Low Disease Activity State (LLDAS)?</i>	Published	60%. Concept and design; data collection, cleaning and analysis; writing of manuscript	M. Huq 5% K. Franklyn 2% A. Calderone 2% A. Lateef 2% C.S. Lau 2% A.L. Lee 1% S.V. Navarra 2% T. Godfrey 2% S. Oon 2% A.Y. Hoi 5% E.F. Morand 5% M. Nikpour 10%	No
6	<i>Lupus Low Disease Activity State: a prospective validation study</i>	Accepted	55%. Concept and design; data collection, cleaning and analysis; writing of manuscript	R. Kandane-Rathnayake 5% M. Huq 5% H.T. Nim 4% W. Louthrenoo 1% S.F. Luo 1% Y.J. Wu 1% A. Lateef 1% S. Sockalingam 1% S.V. Navarra 1% L. Zamora 1% L. Hamijoyo 1% Y. Katsumata 1% M. Harigai 1% M. Chan 1% S. O'Neill 1% F. Goldblatt 1% C.S. Lau 1% Z.G. Li 1% A.Y. Hoi 4% M. Nikpour 6% E.F. Morand 6%	No
7	<i>Evaluation of Remission Definitions in Systemic Lupus Erythematosus</i>	Under revision	55%. Concept and design; data collection, cleaning and analysis; writing of manuscript	R. Kandane-Rathnayake 5% M. Huq 5% W. Louthrenoo 1% S.F. Luo 1% Y.J. Wu 1% A. Lateef 1%	No

				S. Sockalingam 1% S.V. Navarra 1% L. Zamora 1% L. Hamijoyo 1% Y. Katsumata 1% M. Harigai 1% M. Chan 1% S. O'Neill 1% F. Goldblatt 1% C.S. Lau 1% Z.G. Li 1% A.Y. Hoi 4% M. Nikpour 8% E.F. Morand 8%	
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I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

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provide me with opportunities and continuously support me in all my endeavours, words of gratitude are not enough.

Chapter 1

Introduction and literature review

Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease resulting in significant morbidity and loss of life expectancy. Compared to other rheumatic conditions where new targeted therapies are achieving high rates of remission or low disease activity, the effect sizes of currently available targeted therapies for SLE have been small. The majority of patients are still treated with chronic glucocorticoids and non-specific immunosuppressants. Despite overall improvement in mortality rates, ten-year mortality from SLE is estimated at up to 1 in 8 for patients with renal involvement,¹ and thus premature death remains a risk for the young women who comprise the majority of patients affected by SLE. Those patients that do survive are often burdened with problems of chronic disease, which includes not only activity of the disease itself, adverse effects of treatment and complications such as irreversible end organ damage, but also impact on quality of life, employment and disability – all of these representing measurable outcomes for SLE patients.

SLE is a heterogeneous disease with a broad spectrum of manifestations ranging from mild cutaneous disease to severe vital organ involvement. Additionally, the disease has a fluctuating nature with periods of relative inactivity contrasted by disease flare, as well as a proportion of patients with persistently active disease,² making it difficult to predict the course of disease for any individual patient. Because of this clinical diversity, the current instruments used to measure

disease states are flawed,³ resulting in mixed results from clinical trials attempting to find new targeted therapies.⁴

As prolonged remission occurs in only 2-4% of SLE patients,^{5,6} using this as a treatment target in research or clinical practice is not pragmatic. In other autoimmune disease, mainly rheumatoid arthritis, achieving a minimally active disease state has been proven to translate into improved patient outcomes.⁷ The need for attainable clinical treatment targets for SLE has been recently described by an international treat-to-target taskforce, and defining an acceptable minimal disease activity state has been set as a research agenda.⁸ If attainment of a low disease activity state is proven to translate into less disease related morbidity such as damage accrual; the new treatment target could serve as novel benchmark for clinical trials and have the potential to improve patient outcomes.

Treat to target strategies for chronic disease

What is chronic disease?

Chronic disease can be defined as any condition that is long lasting, negatively impacts individuals and communities, and requires ongoing interaction with the health system. The worldwide burden of chronic disease is huge, killing millions of people every year⁹ and putting a large economic strain on individual health systems.¹⁰ Because of this there has been a great push to manage chronic disease in a more proactive way.

Traditional lifestyle and age related chronic conditions such as heart disease and type 2 diabetes predominantly affect an older population. However, chronic conditions caused by immune system dysfunction tend to be diagnosed in younger patients. The most common example of these is type

1 diabetes mellitus, with a prevalence of approximately 5.7/1000 in Australia.¹¹ Other notable examples such as multiple sclerosis, autoimmune thyroid disease and SLE have much lower prevalence in comparison;^{12,13} none-the-less the lifetime morbidity associated with a diagnosis at a younger age in all these immune mediated conditions is considerable.

What is treat to target?

In the clinical context “treat to target” implies a process of initiating and adjusting or escalating therapy to achieve and maintain a predefined treatment goal (clinical state, laboratory marker, or combination of both in a measurement index) . Conceptually these goals, also referred to as treatment targets or endpoints, must have utility - that is be attainable and sustainable by the majority of patients, and must have validity - that is have empirical evidence of their association with desired patient outcomes.

Effective treat to target approaches in other chronic diseases

Treat to target (T2T) approaches have had profound impact in the management of many chronic diseases, especially those in which treatment endpoints are measurable in single organ systems – with initial studies focusing on conditions encompassing traditional cardiovascular risk factors such as hypertension, hypercholesterolemia and diabetes.¹⁴⁻¹⁷ In cardiovascular medicine treatment targets can be quantified by a single laboratory or clinical measure with an explicit benchmark to reach, such as blood pressure, low density lipo-protein level or haemoglobin-A1C. The pivotal T2T trials in type 1 and type 2 diabetes demonstrated a substantial reduction in the frequency of complications as well as overall mortality with adherence to threshold blood glucose levels,^{15,18} and hence encouraged the adoption of a T2T approach in other cardiovascular conditions.

The success of T2T in reducing cardiovascular risk factors has prompted the adoption of T2T strategies in inflammatory joint disease, based on the recognition that in chronic conditions, poorly controlled disease activity leads to irreversible end organ damage, a set of outcomes that is also shared with SLE.¹⁹ No inflammatory rheumatic condition, perhaps with the exception of uric acid in gout, has a standardised single stand-alone biomarker that accurately corresponds to clinical disease activity or can be undisputedly linked to improved outcomes. Likewise, clinical improvement of a patient does not necessarily rule out absence of underlying inflammatory activity. As such, composite instruments using both clinical and laboratory measures are relied on to quantify a treatment response or a treatment target state. In rheumatoid arthritis (RA), T2T approaches, based on the attainment of low disease activity or remission defined by number of inflamed joints, physician and/or patient global assessment and measurement of serum inflammatory markers, have resulted in dramatically improved outcomes even prior to the introduction of biological therapies,²⁰ and have been adopted in treatment guidelines and the assessment of novel therapies.²¹ Moreover, there is evidence that attainment of a target state, rather than measuring treatment response as a predefined change in disease activity from baseline, confers greater protection from accrual of joint damage,²² and as such there is a move to change the primary outcome endpoints in clinical trials of RA to 'time to attainment of low disease activity and/or remission' and 'time in low disease activity and/or remission'.²¹ More recently, attainment of low disease activity and/or remission have emerged as treatment targets for psoriatic arthritis,²³ and T2T strategies have been proposed for future spondyloarthritis clinical trials.²⁴

SLE, in contrast, is the quintessential complex multi-organ disease with inherent biological and clinical heterogeneity, which has hindered the development of treatment endpoints and hence adoption of T2T strategies.^{8,25,26}

The need for adoption of treat to target strategies in SLE

The economic and personal burden of SLE

SLE is a prototypical multi-organ chronic disease with significant morbidity and loss of life expectancy,²⁷ requiring frequent interaction with different aspects of the health system even in asymptomatic patients.²⁸ In cardiovascular medicine, the proof of concept that T2T vastly improves outcomes has resulted in healthcare stakeholders implementing changes in health policy to deploy algorithm driven treatment protocols.²⁹ And whilst there are international guidelines on monitoring and treatment strategies for SLE,³⁰⁻³² these are difficult to adopt into clinical practice, in part due to the phenotypic heterogeneity of the disease, and at least in part due to the lack of validated treatment endpoints making it impossible to derive standardised approaches to care. As such, there is wide variation in routine SLE care – and indeed there is no optimal chronic disease program for SLE.

Similarly to other chronic diseases, disease activity, treatment and damage contribute to economic and personal burden on patient and families. Numerous studies have looked at the direct costs of healthcare for SLE patients with estimates of mean annual costs of \$20,000 US per patient.³³ Indirect costs, measured as loss of productivity as a result of the disease, are estimated to be just as substantial in SLE.³⁴ An estimated 20-30% of previously employed SLE patients are unable to do any work within 12 months of diagnosis.^{35,36} Those patients that do continue to work reduce their working hours³⁷ and take longer sick leave³⁸ compared to population averages.

In addition to the monetary costs associated with loss of employment, SLE patients with work disability are much more likely to experience worse pain, fatigue, cognitive dysfunction and

depression.³⁹ Irrespective of employment, patients with SLE report worse health related quality of life compared to the general population,⁴⁰ more so in patients with concomitant fibromyalgia.⁴¹ Moreover, quality of life in SLE is as poor as it is in coronary artery disease, end stage airways disease, human immunodeficiency virus and rheumatoid arthritis.⁴² Perhaps what makes this worse is that in general SLE, patients report feeling misunderstood by their families, the community and even the specialists treating them.⁴³ Consequently, evidence suggests that patients feel that their needs are not being adequately met by treating teams.⁴⁴

Measurable outcomes for SLE patients

High morbidity in SLE is driven predominantly by poorly controlled disease activity and accrual of irreversible organ damage, both of which impact on health related quality of life – thus making disease activity, damage and quality of life the three most important outcomes studied in SLE.⁴⁵ Damage in SLE refers to the diagnosis of irreversible end organ manifestations such as stroke, end stage renal failure or osteoporosis – it is therefore not surprising that damage accrual increases the likelihood of early mortality.⁴⁶ Whilst some predictors of damage are not modifiable, such as older age and non-Caucasian ethnicity,^{47,48} there are strong associations of high disease activity levels and glucocorticoid use as independent and modifiable risks for damage accrual.

SLE has a fluctuating nature with periods of relative inactivity contrasted by disease flares, as well as some patients with persistently active disease despite best efforts at management, making it difficult to predict the course of disease for any individual patient.² There is evidence that both persistent disease activity and disease flares can individually contribute to irreversible damage,^{49,50} therefore reduction of overall activity levels and prevention of disease flares are valuable conceptual treatment targets. Disease activity in SLE can be measured as clinical activity – reflecting inflammation in end organs, or serological activity – elevation of antibodies to double

stranded DNA levels (dsDNA) or lowering of complement 3 and/or 4 levels. Whilst there is no doubt that untreated end organ inflammation leads to damage accrual, the role of serological activity in contributing to outcomes is less clear. ‘Serologically active clinically quiescent’ (SACQ) disease is a well-described entity in SLE,⁵¹ with some literature suggesting a proportion of SACQ patients can spend years without emergence of new disease features,⁵² whilst others may flare.^{53,54} Certain clinical manifestations such as lupus nephritis are more frequent in patients with elevated anti-dsDNA levels. Patients with serologically active disease, particularly the classic markers described above, are more likely to respond to some targeted therapy, as recently seen in post-hoc analysis of the belimumab trials, a monoclonal antibody directed at BAFF, which has been approved for the treatment of active SLE.⁵⁵ The same group of patients was also found to be more likely to flare.⁵⁶

Despite evidence that prednisolone doses of ≥ 7.5 mg are associated with adverse outcomes and independently predict damage accrual,⁵⁷ glucocorticoids continue to be relied upon by SLE physicians in the absence of alternate effective therapies. The minimum “safe” dose of prednisolone is not known, with only one large cohort study showing that doses of 6mg or less were associated with freedom from damage accrual.⁵⁸ More recently, glucocorticoids have also been shown to independently contribute to damage not traditionally associated with steroid use.⁵⁹ Therefore use and dosing of glucocorticoids must be considered when thinking about target clinical states in SLE. Perhaps most importantly, it is now known that once damage is established it propagates further damage, irrespective of disease activity control,¹⁹ further highlighting the need to control the disease and reduce activity levels early in the treatment course to minimise the risk of damage accrual in the first place.

Both disease activity and accrued damage affect health related quality of life (HR-QoL) in SLE patients.^{42,60} As recently highlighted, the impact of SLE on HR-QoL are comparable to other chronic diseases such as chronic heart failure, coronary artery disease, end stage airways disease, human immunodeficiency virus and rheumatoid arthritis.^{42,61,62} HR-QoL is a multi-dimensional construct that evaluates different health perceptions and self-reported functional status, and is often included as a key patient reported outcome (PRO) in studies of chronic disease. PROs are increasingly recognised as an integral part of assessment in clinical trials and routine practice,^{63,64} as they measure domains not captured by physician-assigned disease activity scores. In order to have value in clinical practice and clinical trials, measures of a desirable disease outcome state for use in treat-to-target strategies should associate not only with physician-applied measures of disease activity and outcome, but also with PROs.

The failure of clinical trials

In contrast to other rheumatic diseases, such as RA and ankylosing spondylitis, there has been a considerable lag in finding a suite of effective targeted biological therapies for treatment of SLE. The reasons for this are multifactorial, including a more complex immunopathogenesis, clinical and biological disease heterogeneity, debate about optimal trial design with criticisms regarding the dose of concomitant glucocorticoids and immunosuppression allowed, and most importantly problematic outcome measures that may have hindered the ability to differentiate responders from non-responders.^{25,65} Many therapeutic agents showing great potential in pre-clinical studies and phase II trials have failed to show clinical efficacy in phase III clinical trial settings. The most notable examples are abatacept, ⁶⁶ which blocks co-stimulation of T-cells, and rituximab, a B-cell depleting therapy.⁴ Two pivotal phase III clinical trials of rituximab in SLE have failed to reach their primary efficacy end-points,^{67,68} despite widespread anecdotal experience suggesting positive

results in at least some patients. As such, rituximab is still used off-label as rescue therapy based on observational data.

Belimumab has been shown to be efficacious in phase III clinical trials and is currently registered as an add-on therapy for use in moderate to severe SLE by multiple therapeutic governing agencies worldwide.⁶⁹ Two multinational phase III trials showed clinical and serological improvement compared to placebo, particularly in patients with active musculoskeletal and mucocutaneous disease,^{70,71} and belimumab was demonstrated in post hoc analysis to be more effective in patients with serologically active disease (low complement and high anti-dsDNA).⁷² Although statistically significant, the absolute effect size of belimumab over placebo as measured by the SLE responder index (SRI) appeared to be small, suggesting both the need for a more robust endpoint to better discriminate responders from non-responders and the need for more powerful therapies.

Indices currently used to measure outcomes in SLE

Multisystem involvement and heterogeneity of SLE make assessment of current disease state at a given point in time difficult, and hence measuring change in disease activity in response to an intervention is highly problematic. Indeed there are six SLE disease activity indices and three damage indices available for use in research and clinical practice.⁷³ There are also many patient reported outcome measures, mostly covering health related quality of life; and yet no single one that captures the overall impact of SLE on an individual patient.⁷⁴ The available tools to measure disease activity and other outcomes in SLE are summarised in Table 1.

Table 1: Indices to measure outcomes in SLE patients

Measurable outcome	Tool	Use	Strengths	Weaknesses
Disease Activity	BILAG	Physician tool. Activity across organ systems.	Able to capture change in activity from previous assessment. Sensitive to small changes	Cumbersome to use in routine practice – developed for research purposes. Reliance on change from previous assessment can mean imprecise estimation of current activity. Floor and ceiling effect.
	SLEDAI	Physician tool. Weighted presence of activity across organ systems.	Activity must be attributable to disease. Easy to use. Validated for clinical and research use.	Binary assessment of activity, may not capture change. Floor and ceiling effect.
	ECLAM	Physician tool Global score	Easy to use, can be computerised. Correlates well with physician global assessment. Can be used in retrospective analysis.	Less validation studies compared to SLEDAI and BILAG Misses changes in severity over time
	SLAM	Physician tool Evaluates specific manifestations in organ systems	Can be computerised	Includes subjective measures such as fatigue and pain Cumbersome to use Not used in trials
	LAI	Physician tool Global physician assessment in 4 systems – neurological, renal, pulmonary and haematological	Short time to complete	Not comprehensive Misses changes in severity over time
	SLAQ	Patient tool Measures activity across organ systems	Only self-report activity measure Useful for questionnaire/survey studies	Subjective
	Physician global assessment	Physician tool Visual analogue scale	Useful for recording activity not captured by numerical activity indices	Subjective
	Patient global assessment	Patient tool Visual analogue scale	Useful as a companion tool to numerical indices	Subjective
Disease flares	SELENA-SLEDAI	Physician tool Based on components of	Stand-alone instrument Responsive to change	Lacks thorough validation Inconsistent at capturing mild flares

	Flare Index (SFI)	SLEDAI and treatment response to new activity		Overscores moderate flares
	BILAG flares	Physician tool Based on inbuilt grading of severity in the BILAG	Does not require additional assessment if BILAG already completed	Same as BILAG Can capture persisting activity as flare
Treatment response	SRI	Physician tool Measures predefined change from baseline Driven by reduction in SLEDAI with lack of worsening captured by BILAG and PGA	Discriminatory in belimumab clinical trials	Responders remain heterogenous Cumbersome to use
	BICLA	Physician tool Measures predefined change from baseline Driven by improvement in BILAG with lack of worsening captured by SLEDAI and PGA	Discriminatory in clinical trials	Responders remain heterogenous Cumbersome to use
	ACR lupus nephritis response criteria	Physician tool Measures change in different domains of renal activity – renal function, proteinuria and active sediment	Validated for clinical trials	Organ specific Not all recommendations are evidence based
Damage	SLICC/ACR-damage index (SDI)	Physician tool Measures irreversible organ damage regardless of cause	Accounts for impact of disease activity, treatment burden (especially glucocorticoids) and comorbidities Good validation	Definition of some items open to interpretation
	LDIQ and BILD	Patient tool Measures self-reported irreversible damage across organ systems	Correlates well with SDI	Subjective

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BILAG – British Isles Lupus Assessment Group; SLEDAI – Systemic Lupus Erythematosus Activity Index; ECLAM – European Consensus Lupus Activity Measurement; SLAM – Systemic Lupus Activity Measure; LAI – Lupus Activity Index; SLAQ – Systemic Lupus Activity Questionnaire; SELENA – Safety of Estrogen in Lupus Erythematosus National Assessment; SRI – Systemic Lupus Erythematosus Responder Index; BICLA – BILAG based Composite Lupus Assessment, ACR – American College of Rheumatology; SLICC – Systemic Lupus International Collaborating Clinics; LDIQ – Lupus Damage Index Questionnaire; BILD – Brief Index of Lupus Damage.

Measures of activity

Six disease activity indices are available for use in SLE with varying degrees of validation.⁷³ The most frequently used in clinical trials and observational studies are the SLE Disease Activity Index (SLEDAI) or British Isles Lupus Assessment Group Index (BILAG) – the former using weighted scores in organ systems to provide a single summary score for overall activity level, and the latter assessing current and worsening activity in individual organ systems. Originally developed in 1992 and modified to the currently used version in 2002,⁷⁵ the SLEDAI-2K measures the presence of new and persisting clinical and serological activity, weighted most heavily in CNS disease, vasculitis and nephritis, with less points per item in serositis and mucocutaneous disease. Items are only scored if they can be reasonably attributed to disease activity rather than another cause, such as fever in infection, or existing damage, such as chronic proteinuria in class VI nephritis. The main limitations of the SLEDAI stem from the binary description and therefore scoring of each item as either present or absent. This does not allow for measurement of partial worsening or improvement, for example a patient with arthritis who has gone from 20 swollen and tender joints to 4 will retain the same score on the SLEDAI. There is also no room for assessment of degree of activity, such that a patient with severe profuse rash will score less than a patient with mild

proteinuria. None the less, the SLEDAI has cross-cultural validity and good inter-rater reliability, is sensitive to change and can be completed in a short amount of time with minimal training.^{76,77}

The BILAG on the other hand, uses an intention-to-treat approach to scoring items within individual organ systems, therefore allowing for assessment of severity within each item ranging from severe disease requiring high dose prednisolone ('A') to no current or prior disease activity ('E') for that item requiring no change in treatment.⁷⁸ This characterisation of severity can also be useful in capturing disease flares. The comprehensive nature of BILAG is both its greatest advantage, as well as its main limitation. Whilst being able to stratify patients based on organ involvement and severity of activity, as well as being shown to be the most sensitive to change,⁷⁷ the BILAG is also the most cumbersome and time consuming activity index for those not using it on a regular basis, thereby limiting its use in clinical practice and potentially affecting precision and reproducibility when used by investigators in pharmaceutical trials.

Both SLEDAI and BILAG suffer from floor and ceiling effects,⁶⁴ can miss certain clinical manifestations.⁴⁵ In light of this, the Physician Global Assessment (PGA) is often deployed alongside the SLEDAI and BILAG. Typically measured using a visual analogue scale, the PGA is a descriptor of the overall disease activity levels taking into account all of the information available during physician assessment.⁷⁹ The PGA is not without criticism – it is inherently subjective and has wide interrater variability; therefore as a stand-alone tool it is rarely used to assess activity levels. However, in combination with numerical indices it is useful in capturing those aspects of disease activity that would have otherwise been missed. As such the PGA is included as a measure in clinical trials and forms part of the composite measures of treatment response.

Definitions of flare

Disease flares have been defined conceptually by an international working group as "... a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by the assessor and usually there would be at least consideration of a change or an increase in treatment."⁸⁰ Whilst this particular definition is yet to be operationalised, researchers have leaned on existing activity indices to build flare instruments, including the SELENA-SLEDAI Flare Index (SFI) based on the SLEDAI,⁸¹ and BILAG flares using the aforementioned categories of severity.⁸² The SFI was developed specifically as the primary endpoint for the SELENA randomised controlled trials,⁸³ and as such has received criticism that it has not undergone a rigorous validation process prior to being employed. The updated version of the BILAG (BILAG 2004),⁷⁸ has inbuilt scores of severity that have been proposed as surrogate measures of flares – severe flare denoted as ‘new activity’ or score of ‘A’ in any system, and moderate flare as ‘worsening activity’ or score of ‘B’ in at least two systems.

Whilst being able to discern severe flares, the main drawback of both flare indices is the inconsistency at capturing mild to moderate flares,⁸⁴ as well as overscoring of moderate flares as severe, and scoring persistent activity as a flare.⁸⁵ In the absence of alternate measures for disease flares the SFI and BILAG continue to be used in observational studies and clinical trials, often as a secondary endpoint.

Measures of treatment response

As is the case for trial design in any inflammatory disease, to enter a clinical trial patients must have at least moderate disease activity at baseline, in order to show improvement in response to the studied treatment. These patients have often failed at least one conventional therapy prior to

trial entry and as such by definition form a group with more difficult to control disease. Given that remission occurs infrequently in general in SLE,^{5,6} this is particularly pertinent in the case of the clinical trial population, thus lowering the utility of remission as an endpoint in the trial design for a heterogeneous disease requiring large multicentre trials. This has also been echoed by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA), who have acknowledged that whilst 'complete response' to treatment should be the ultimate goal in SLE, it may not be a practical measure for clinical trials.^{86,87} As such, the use of composite endpoints has been encouraged by both agencies to define a minimally acceptable treatment response, prompting the evolution of several such measures over the past decade.

These composite measures or responder indices define those who have improved or responded to the tested treatment versus those who have not. The SLE Responder Index (SRI)⁸⁸ and the BILAG-based Combined Lupus Assessment (BICLA)⁸⁹ were developed based on the data from phase II trials of belimumab and epratuzumab respectively, and have subsequently gone on to be used in phase III trials of these drugs. Both utilise components of the SLEDAI and BILAG, the SRI being driven by improvement in the SLEDAI, and BICLA being driven by improvement in the BILAG. Measured using other elements of the composite outcome including PGA, and BILAG (in the case of SRI) or SLEDAI (in the case of BICLA). Both require no worsening of disease activity as well as a minimum pre-defined improvement from baseline. More recently, the SRI has been used as an outcome measure in trials targeting the interferon pathway and has been shown to correlate with improvements in other short term outcome measures including reduction in prednisolone dose and PGA, and improvement in patient reported outcomes.⁹⁰

The SRI or BICLA have not been independently validated, or shown to be reliable or sensitive to change – it is therefore unknown whether they associate with improved long term outcomes such

as reduction in damage accrual or mortality. These indices rely on the use of both the SLEDAI and BILAG in one assessment tool, thereby making them complex and time consuming to use even in the clinical trial setting. And most importantly, these are designed to measure a minimally clinically relevant change from baseline, which whilst meeting the needs of demonstrating treatment response in a clinical trial as defined by regulatory agencies, do not fulfil the requirement of an absolute target state for the adoption of T2T strategies.

In addition to the multisystem measures of treatment response, the American College of Rheumatology has published treatment response criteria for use in clinical trials of lupus nephritis.⁹¹ These measure change in three domains of lupus nephritis – change in renal function, proteinuria and active sediment, and are useful for a very specific subgroup of SLE patients. However, it should be noted that the majority of non-organ specific clinical trials in SLE consist of patients with musculoskeletal and/or cutaneous phenotypes, and in fact for some trials active renal disease is an exclusion criterion.⁹² As such organ specific response criteria are not fit for purpose for a global treat to target approach for SLE.

Measures of damage

Unlike the measures of activity, there is relative consensus in the SLE research community on the use of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index⁹³ (SDI) as the primary physician scored tool for capturing accrual of irreversible end organ damage. By definition damage is permanent, it therefore must be present for at least 6 months, and once an item is scored it cannot be crossed off in future assessments. Contrasting to scoring in measures of activity, damage does not have to be directly attributable to SLE, but can be secondary to treatment, such as osteoporosis or diabetes from chronic

glucocorticoid use, or associated with a co-morbidity, such as malignancy. The SDI has been shown to have validity, reliability and feasibility, and as such has been widely used in SLE research.⁶⁴

Patient reported outcome measures

A large array of PROs exist to capture activity, damage, fatigue, disability and health related quality of life (HR-QoL).⁷⁴ These include both generic instruments used in a variety of chronic conditions, as well as those designed specifically for SLE. Of these important outcomes for patients, the one that lends itself best to testing the ideals of a treat-to-target strategy is HR-QoL, as it describes the impact of disease on the physical, psychological, mental and social aspects of patient health. Attainment of a T2T endpoint should ideally therefore be associated with improved aspects of HR-QoL.

Of the generic HR-QoL measures the Medical Outcomes Study 36-item Short Form Health Survey (SF-36v2),⁹⁴ has been used in a number of SLE observational cohorts and clinical trials, and cross-culturally validated in several languages.^{41,61,95-98} The SF-36 is divided into 8 domains including physical function (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), role emotional (RE), and mental health (MH); as well as two summary scores including the physical component score (PCS) and mental component score (MCS). The individual domain scores are expressed on a scale of 0 to 100, and the component summary scores are standardized around a US normal population mean of 50, with higher scores representing better HR-QoL. Whilst capturing domains that are common to many chronic diseases including SLE, SF-36 does not account for specific concerns of patients associated with chronic pain and/or inflammatory disease. The lack of measurement for presence of fibromyalgia is one of the main limitations of SF-36 as a generic instrument, as pain and fatigue have been shown to independently influence HR-QoL in SLE patients.^{41,99,100} Disease specific HR-QoL instruments such

as LupusQoL and LupusPRO are better at capturing features such as fatigue, pain and depression, and are in the process of being cross-culturally validated.⁷⁴

Challenges in delineating treatment endpoints in SLE

Heterogeneity of disease

By far the greatest challenge in defining a treatment target suitable for all SLE patients is the clinical heterogeneity of the disease, with a wide spectrum of manifestations ranging from mucocutaneous, musculoskeletal and constitutional symptoms, to potentially life threatening manifestations such as lupus nephritis or central nervous system (CNS) involvement. Genetic variables clearly modify susceptibility, cytokine expression and resultant clinical phenotype in SLE. The disease is between two and four times more common in non-whites, including African Americans, Asians, Hispanics and various indigenous populations.¹⁰¹ Non-Caucasian patients have significant differences in autoantibody profiles and distinct patterns of end organ disease.²⁷ African Americans and Hispanics have more severe disease and accrue damage faster,⁴⁷ and Asian patients are more likely to have persistently active disease and lupus nephritis compared to their Caucasian counterparts.¹⁰² Specific genes that influence clinical phenotypes are being studied across the world. While non-inherited factors no doubt also contribute significantly to clinical disease heterogeneity, the example of genetic and ethnic variation serves to illustrate the problems to measurement posed by the heterogeneity of SLE.

One interesting observation is that the degree of heterogeneity is related to the level of disease activity of the patient.²⁵ The more activity there is across different organ systems, the more likely patients are to differ. In a disease activity score such as the SLEDAI, as disease activity levels diminish, patients become more homogenous and easier to group together. In the clinical setting,

this is exemplified by the patient who has had a major response to treatment, in whom evidence of what organs were previously actively involved may be absent. Therefore, defining a state based on low levels or absence of disease activity may be intrinsically more achievable than attempting to quantify active disease across multiple systems. This allows for outcome measurement in a binary fashion – a patient is either in the desired low or absent activity state or not, and ensures that the endpoint or outcome achieved is consistent across all patients versus instruments that measure change from baseline which still allow for clinical heterogeneity to remain in those achieving the target.

Adoption into routine care

A second challenge is being able to deploy a T2T strategy into routine clinical practice in SLE. Unlike hypertension and diabetes, where target blood pressure and blood glucose levels can be readily measured, SLE is a complex disease. The structured indices used to measure activity were all developed with the primary purpose of observational or clinical research, and are therefore largely limited to use in academic research centres and are less likely to be used in routine clinical practice. Furthermore, as T2T in principle requires escalation of therapy in the face of failing to meet predefined goals, it becomes difficult for healthcare stakeholders to roll out a T2T strategy unless measurement can be widely deployed.

On the other hand, successful deployment of a T2T strategy can prove cost-effective and even cost saving to health care systems, as has been shown in the case of diabetes and hypertension.^{103,104} In rheumatoid arthritis, where biologic therapy is now routinely used to achieve and maintain remission or low disease activity, the cost of medication alone can be \$10,000-20,000 per year for each patient.¹⁰⁵ Despite this, treating to target in early rheumatoid arthritis not only improves patient outcomes but has been shown to be cost-effective compared to usual therapy.¹⁰⁶ Even in

established RA there is a cost-benefit to adherence to a T2T approach.¹⁰⁷ In SLE, the cost of care increases exponentially with increasing disease activity, compared to patients with mild disease and no recent flares.^{108,109} Thus the adoption of a T2T approach for SLE may also prove cost-effective and offset the cost of expensive biologic therapy, making the adoption and application of T2T strategies more attractive to healthcare policymakers.

Setting the benchmark

Assessing where on the continuum of disease activity to place the benchmark for a T2T endpoint in SLE requires quantification of remission and low disease activity states, and testing of these targets against patient outcomes. This proves difficult in SLE due to lack of universal consensus on the available measures of activity, a problem yet again stemming from the complexity and multiorgan involvement of the disease. Therefore, when choosing an instrument to set the benchmark for activity levels in order to define the target treatment state, conflicting factors such as thoroughness versus ease of use must be considered. Additionally, most of the available physician scored instruments do not include a patient assessment of activity, which is potentially problematic in a disease with known discordance between physical and patient assessments.¹¹⁰⁻¹¹² What may be considered as 'target met' by a physician, may not be so by a patient, an issue that may be impossible to overcome as multiple other factors can influence patients' perception of disease state.¹¹²

SLE patients are able to identify their perceived unmet needs for care,^{113,114} with themes such as inadequate education, lack of support at the time of diagnosis, emotional and physical barriers to care and difficulty navigating the health system identified as key deficiencies.¹¹⁵ It is known that shared-decision making or patient centred care leads to improvement in treatment adherence and allegiance to healthcare providers, leading to better clinical outcomes and improved HR-QoL.¹¹⁶ The

T2T in SLE taskforce recommendations include shared decision making between the patient and physician as one of the topmost overarching principles.⁸ Therefore, patient assessment should form part of the development of a T2T endpoint, and if it is impossible to include a direct patient assessment as part of the T2T endpoint, at the very least attainment of the target should align with improvement in patient reported outcomes.

Perhaps most importantly of all, especially given the variable history of validation of measurement tools used in SLE, endpoints for T2T, such as definitions of low disease activity or remission, should undergo very thorough validation, ideally in prospective studies. Only with robust empirical validation can such tools be recommended for adoption into clinical practice, or as endpoints in clinical trials. Studies to validate T2T endpoints for SLE, including remission and low disease activity, form the purpose of this thesis.

Remission in SLE

When thinking conceptually about disease activity states, as activity diminishes so does the risk of adverse outcome, therefore there is no argument that remission or the absolute absence of activity should be the gold standard treatment target state in any inflammatory disease. For remission to have utility as an endpoint it must be attainable in a significant proportion of patients, which unfortunately is not the case for the historically described very strict definitions of remission in SLE. An earlier study of remission, defined as absence of all activity (clinical and serological) and off all treatment, showed that only 1.7% of patients were able to sustain this stringent state for any prolonged period of time.¹¹⁷ More recent analysis of the same cohort, similarly showed that 2.4% of patients were able to sustain complete remission and 2.1% of patients were able to sustain remission on treatment.⁵ One version of clinical remission, allowing serological activity, also known as serologically active clinically quiescent (SACQ) disease, was

achieved in 6.1% of the above cohort for 2 years,⁵² which whilst being more attainable than complete remission, is still not frequent enough to have utility as a treatment target.

In a monocentric cohort of Caucasian patients with established disease, complete remission was seen somewhat more frequently at 7.1%, which increased to 14.7% when serological activity was allowed.¹¹⁸ Another group further loosened the definition of remission, allowing mild stable clinical disease (C, D or E on the BILAG) and antimalarial use. The authors showed that 14.5% of patients were able to achieve this version of remission for 3 years, but disease flares continued to occur even beyond 10 years of follow up.⁶ In a smaller study of lupus nephritis patients, it was shown that renal flares can occur in patients up to 15 years after attainment of remission.¹¹⁹

The Definitions of Remission in SLE (DORIS) Group definitions

In recognition of the previously ad-hoc nature of defining remission and the variability of what was considered to be 'absence of activity', a definitions of remission in SLE (DORIS) international task force was set up to form a consensus on the definitions to be used in research and clinical practice.¹²⁰ Based on four domains deemed to be critical, including clinical activity, serological activity, duration and treatment, the DORIS taskforce came up with 8 potential definitions of remission. All definitions require the absence of any clinical activity as measured by a clinical SLEDAI of 0 and a PGA \leq 0.5, but vary in allowing for serological activity, use of immunosuppression and prednisolone of up to 5mg. The most stringent of the definitions requires absence of all activity and no treatment, and conversely the least stringent allows for serological activity, immunosuppression and low dose prednisolone. This latter state, also known as remission on treatment. The frequency and duration of the DORIS remissions were tested in a large retrospective cohort with a significant proportion of African-American patients, demonstrating that the median duration of any of the remission definitions was only 3 months, with the percent

of patients in remission for 5 years ranging from 0.6% to 2.0% , the low overall rates even for remission on treatment likely reflecting that serological activity was not allowed in this study.¹²¹

The low frequency of attainment of all the various definitions of remission has prompted the search for a treatment target with greater attainability whilst still retaining association with desired outcomes. In rheumatoid arthritis, another disease with fluctuating levels of activity and a linear relationship between activity and damage, achieving a minimally active disease state has been shown to be comparable to complete clinical remission in preventing joint damage.⁷ That the same could be true for SLE prompted another research group to develop a definition for low disease activity in SLE.

Definition and retrospective validation of the Lupus Low Disease Activity State

In response to the need for a more attainable treatment target than remission, prominent SLE researchers from the Asia-Pacific region combined to form the Asia-Pacific Lupus Collaboration, whose primary goal was to develop and validate the Lupus Low Disease Activity State (LLDAS) as the first attainable treatment endpoint for SLE proven to be associated with improved outcomes.¹²² The definition and initial validation of LLDAS was subsequently published by *Franklyn et al.*,¹²³ and is described in further detail below.

A panel of 6 SLE experts defined LLDAS conceptually as follows: ‘A state which, if sustained, is associated with a low likelihood of adverse outcome, considering both disease activity and medication safety’. Delphi and nominal consensus methods were then used to set thresholds at which the conceptual definition of LLDAS would be attained. The panel was invited to contribute

individually generated items for potential inclusion in an operational definition of LLDAS.

Considerable experience and a review of current literature generated fifty-six unique items, in two domains: (i) disease activity, and (ii) medication use. The experts then individually scored these items on a five-point Likert scale (ranging from 1 = strongly disagree, to 5 = strongly agree). Items with a mean score of greater than three were retained.

The second phase of the definition process involved eleven experts across the Asia Pacific. The nominal group technique was used – a structured group technique that provides an orderly procedure for obtaining qualitative information from a group of experts. A second round of Delphi was then undertaken, and the remaining items were again scored out of five. Items with a mean score of greater than four were retained.

This process unanimously produced the final five item composite LLDAS definition as follows: (1) A SLEDAI-2K ≤ 4 , with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, haemolytic anaemia, fever) and no gastrointestinal activity; (2) no new features of lupus disease activity compared to the previous assessment; (3) a SELENA-SLEDAI physician global assessment (PGA, scale 0-3) ≤ 1 ; (4) a current prednisolone(or equivalent) dose ≤ 7.5 mg daily and (5) well-tolerated standard maintenance doses of immunosuppressive drugs and approved biologic agents, excluding investigational drugs. A patient is considered to be in LLDAS if they fulfil all of the above criteria.

The resultant operational definition of LLDAS was then assessed against patient outcomes in a retrospective single centre cohort. In a dataset comprising 192 SLE patients followed longitudinally for a mean of almost 4 years the authors showed that patients who spent greater than 50% of their observed time in LLDAS accrued significantly less damage compared to patients who spent

less than 50% of their observed time in LLDAS.¹²³ Patients with the majority of observed time in LLDAS also had significantly less disease flares and lower mean doses of prednisolone. LLDAS defines a clinical state to be used as a treatment target in both routine care of SLE as well as in future clinical research. In what is inherently a heterogeneous disease LLDAS provides a measurable composite tool to stratify clinically diverse phenotypes into either active disease or LLDAS. By combining different measures of clinical activity as well as those of medication burden the LLDAS is a more encompassing measure of the overall clinical state of the patient.

LLDAS criteria - rationale for inclusion

Measures of activity

When choosing an instrument to measure levels of activity the relative benefits and shortcomings of a number of disease activity instruments were considered. Given the aim of LLDAS is to be used in T2T approaches in SLE care, the SLEDAI was felt to be the most applicable in both clinical and research settings. The BILAG was also considered, however, its comprehensive format and therefore cumbersome nature, made it less feasible for routine clinical use. The universal consensus of setting the SLEDAI threshold to ≤ 4 with the caveat of no activity in any major organ system forms the starting point of assessing a patient for LLDAS. However, given the inability of the SLEDAI to measure severity within an organ, and in some cases not detect organ involvement, it was important to specify gastrointestinal involvement and haemolytic anaemia in criterion one, and to include a criterion with PGA as a measure of overall activity and surrogate for severity of activity within an allowable organ system, thus accounting for the patient with profuse rash or arthritis that may score ≤ 4 on the SLEDAI but should not be considered in low disease activity.

One important omission from the definition of LLDAS is the inclusion of a patient reported assessment of activity. However, given the lack of concordance with disease activity measures

between patients and physicians, and the difficulty deploying a formal patient reported measure in a busy clinical practice it was thought to be impractical to include a PRO at the outset in the definition of LLDAS. None the less, making sure that attainment of LLDAS aligns with improvement in other patient reported outcomes such as HR-QoL is crucial.

Measures of treatment burden

The experts involved in defining LLDAS felt it important to include current use of medication as part of the desired state, as a patient should not be considered to have reached a treatment target if it is at the cost of medication related toxicity or morbidity. Whilst the definition of tolerated and standard doses of immunosuppressive drugs was reasonably straightforward given the conventional dosing of most established medications, there was much debate regarding the dose of prednisolone in defining LLDAS. Although the optimal dose of prednisolone is of course none, LLDAS is not a definition of remission. Given the paucity of disease specific therapies, a low dose of prednisolone was considered an acceptable treatment burden for a patient in a state of low disease activity. The choice of ≤ 7.5 mg prednisolone was largely chosen based on available literature of glucocorticoid associated damage in SLE.⁵⁷⁻⁵⁹ In the preliminary validation of LLDAS, the choice of 7.5mg of prednisolone as a 'reasonable' dose at which medication toxicity is mitigated by disease activity was tested in further analyses by modifying the prednisolone dose cut off to ≤ 5 mg. Although the absolute difference in the risk ratios for damage accrual between the two versions of LLDAS was small, a prednisolone cut off of ≤ 5 mg was associated with greater protection from damage, prompting the need to further test both definitions in future validation studies.

LLDAS in other cohorts

Since the publication of the first paper on LLDAS and papers comprising chapters 3-5 of this PhD, other international research groups have undertaken retrospective studies of data in existing cohorts. Using similar analysis to the initial validation paper, several groups looked at the effect of proportion of observed time spent in LLDAS. Studies performed by Petri *et al.*¹²⁴ and Tsang-A-Sjoe *et al.*¹²⁵ both demonstrated that LLDAS in $\geq 50\%$ of observations was associated with protection from new damage; and Tani *et al.*¹²⁶ demonstrated that patients with $< 50\%$ of observed time in LLDAS accrue more damage. In an analysis of an inception cohort of SLE patients it was demonstrated that failure to achieve LLDAS within 6 months of diagnosis was associated with 5 times the odds of damage accrual by 18 months, compared to patients for whom LLDAS was achieved within the timeframe.¹²⁷ In an established cohort of all Caucasian patients with SLE, Zen *et al.* demonstrated that the proportion of patients with damage accrual progressively decreased with longer time spent in LLDAS, however 2 years in LLDAS was required for a significant protective effect to be demonstrated in this small cohort.¹²⁸

LLDAS has been also been tested as an outcome measure in several therapeutic trials.^{129,130} In a recent post-hoc analysis of a phase II trial of anifrolumab, a monoclonal antibody to the Type I interferon receptor, LLDAS was attained in significantly more patients in the treatment group vs those treated with placebo, demonstrating its utility as a response measure in clinical trials.¹³⁰ LLDAS also has potential implications for therapies that have previously not shown efficacy in phase III trials based on primary outcomes measures looking at change in disease activity from baseline, such as SRI and BICLA. For example, an observational study of patients treated with belimumab found that 40% achieved LLDAS by 9 months, although the authors did not use a placebo group to compare treatment response.¹³¹ A recent post-hoc analysis of the original phase

III belimumab trials showed that LLDAS is a better discriminator of treatment responders than the SRI.¹³² Similar findings were reported in the same dataset by Parodis *et al.*¹³³

Other definitions of low disease activity

Other research groups have also attempted to quantify a low disease activity state to study in existing longitudinal SLE cohorts. The Latin American Lupus Cohort (GLADEL) group used a similar definition to LLDAS but omitted the PGA and requirement for no new activity,¹³⁴ presumably because these data were lacking in their dataset. Using this definition the authors were able to show that low disease activity (termed LDAS) was associated with lower risk of damage accrual, however only 10% of observed time intervals fulfilled this status.¹³⁴ The researchers behind the Toronto SLE cohort defined a low disease activity (LDA) as a SLEDAI<3, allowing for 1 of rash, alopecia, mucosal ulcers, pleurisy, pericarditis, fevers, thrombocytopaenia or leukopenia, and allowing patients to have serological activity and to be on antimalarials.¹³⁵ Again new activity and PGA were excluded, therefore not accounting for potential severity of activity in one of the allowable systems (e.g. severe thrombocytopaenia). On the other hand because maintenance immunosuppression was not allowed, only 12.9% of patients attained this definition of LDA. None the less, LDA was associated with low SDI scores at 2 and 4 years of follow up.¹³⁵ Importantly, both of the above definitions of low disease activity were created to fit available data already collected in retrospective cohorts, rather than being created based on empiric methodology, thereby automatically lowering the face and content validity of these measures. Moreover, the Toronto LDA definition, as it allows for serology, could include patients with SLEDAI as high as 7, a cut-off which includes many patents recruited into clinical trials for active disease.

The validation process for clinical and research instruments

Clinical and/or research instruments are frequently assessed and accepted into practice based on their utility and psychometric properties – a term referring to the reliability and validity of the instrument in question.¹³⁶ This is done to ensure that instruments measure and perform in the way they are intended to, and to minimise errors, which is particularly important in the healthcare setting where errors or inconsistencies in measurement can have dire consequences for patients.

Utility or feasibility broadly refers to how useful and practical an instrument is. In the case of LLDAS, a target clinical state, utility would mainly be addressed by assessing the attainability and sustainability of LLDAS as a T2T endpoint. The reliability of the instrument assesses the degree of precision and ability to measure repeatedly without error, and include aspects such as intra-rater and inter-rater reliability, as well as internal consistency.¹³⁷ For LLDAS, this was partly addressed in the initial validation study where inter-rater agreement on the final items included in the LLDAS operational definition was tested using Delphi methods.¹²³

Validity on the other hand refers to the ability of an instrument to measure what it is intended to measure through aspects including face, content, construct and criterion validity.¹³⁷ Face and content validity ensure that the instrument truthfully reflects what it is intended to measure and that it represents all the facets of its conceptual definition. The Delphi and nominal consensus techniques used in the initial validation study of LLDAS support its face and content validity, and criterion validity was partially addressed by assessing the association of LLDAS with disease flares and damage accrual in this single centre retrospective cohort,¹²³ as well as other multiple retrospective studies referred to earlier. As well as testing the association of a measure against important outcomes, criterion validity can also be tested by comparing the new measure to an existing validated instrument or a gold standard. Whilst there is no other validated definition of a

low disease activity state, a conceptual gold standard for comparison could be remission, but even this proves problematic given no consensus on a single remission definition and validation of eight proposed definitions for remission currently in evolution.¹²⁰ Lastly, construct validity pertains to the degree in which two measures of a construct are related, or the operational accuracy to the conceptual definition, and is yet to be tested for LLDAS.

Prior to acceptance into clinical practice or as a research tool, any new measure or instrument should undergo these series of validation steps, and whilst the majority of currently available measures used to assess patients with SLE have undergone some degree of validity and reliability studies, very few indices have actually completed the full validation process or have been found lacking in one or more aspects of their psychometric properties.^{64,73} To ensure that LLDAS represents a robust and valid treatment target for SLE the work done in this PhD addresses the utility of LLDAS as T2T endpoint, further assesses inter-rater reliability and completes the validity studies focusing on construct and criterion validity.

Summary

The adoption of T2T strategies has revolutionised the care of several chronic disease giants such as diabetes, hypertension and rheumatoid arthritis, with proven short and long term improvement in patient outcomes. No such strategy exists for SLE, the prototypical multiorgan chronic inflammatory disease that is associated with significant morbidity and mortality in a patient population consisting predominantly of women of childbearing age. For T2T strategies to come to fruition in SLE, treatment targets or endpoints that have both utility (attainable and sustainable in a large proportion of patients) and validity (empiric studies of face, content, construct and criterion validity) are needed. Several barriers in the development of T2T endpoints are present,

including inherent heterogeneity of the disease, flawed instruments to measure disease activity, and lack of consensus on levels of allowable activity; but these can be overcome with a composite definition of a desired clinical target state. Whilst remission remains the gold standard for any chronic disease, it is rarely attained for any considerable length of time in SLE and as such may lack utility as a T2T endpoint. LLDAS on the other hand may represent a more attainable treatment target that, if proven to be associated with improved outcomes, may evolve as a desirable endpoint for T2T approaches in SLE.

This thesis aims to complete the validation studies of LLDAS as a T2T endpoint, thereby making LLDAS the first T2T endpoint in SLE with robust evidence for adoption into research and clinical practice. Five studies were conducted to achieve this, with the hypothesis and individual study aims outlined below.

Project hypothesis and aims

Hypothesis

LLDAS represents a feasible treatment target (utility), attainment of which is associated with less disease flares and damage accrual, and improved health related quality of life (validity).

Aims

- To determine the frequency and predictors of attaining LLDAS
- To assess the association of LLDAS with patient reported outcomes
- To assess the construct validity of LLDAS by comparing it to expert opinion
- To prospectively validate LLDAS against morbidity related patient outcomes including disease flares and damage accrual

- To prospectively compare LLDAS to remission as a conceptual gold standard treatment target

Chapter 2

Methodology

Introduction

In chapter 1, I described the need for treat to target approaches to improve outcomes for SLE patients. LLDAS was introduced as a potential treat to target endpoint, and its creation and initial retrospective validation was described. In order for LLDAS to become a routinely used target measure, a series of validation studies need to be completed. The most robust methodology for validation studies of new measures uses prospectively collected data, in a study designed specifically for this purpose. This thesis reports the findings of studies in which this was done for LLDAS, with the methods described in detail in this chapter.

The construct validity study (chapter 5) was conducted with a group of SLE experts using paper cases and the methods of this are therefore described as a separate subsection below.

The APLC prospective cohort

Participating countries/institutions

Since the initial meeting of the founding members in 2012, the APLC has grown to include 23 sites from 13 countries by the end of 2018.¹²² Each site has signed a Memorandum of Understanding that states the rules under which APLC operates. In addition, each institute has signed a legally binding collaborative research agreement to conduct the LLDAS study. The APLC has formalised a steering committee to ensure transparency and accountability, oversee resource utilisation,

provide research focus and optimise outputs. The APLC has established policies including a Publication Policy and Data Access Policy to manage a range of contingencies.

Given that the validation studies of LLDAS were conducted at different points of time in my PhD, the number of centres, patients and patient visits in the datasets used is different and the contribution of each centre is outlined in Table 2 below. The studies described in chapters 3 and 4 used a dataset comprising baseline visit data only, and the studies described in chapters 6 and 7 used a longitudinal dataset. Two of the centres who contributed data to the baseline dataset were not able to provide data in a timely manner for the longitudinal study, however two new centres contributed to the longitudinal study to offset this.

Table 2: Patients and visits contributed to datasets per centre

Centre, Country	Baseline dataset	Longitudinal dataset	
	1 visit per patient	Multiple visits per patient	
	2015	2017	
	Patients	Patients	Visits
Royal Adelaide H./Flinders Medical Centre, SA, Australia	33	44	170
Monash H./Uni., VIC, Australia	169	189	1,576
Liverpool H., NSW, Australia	38	40	190
St. Vincent's H., VIC, Australia	-	58	176

Peking Uni. Health Science Center, Beijing, China	235	-	-
The University of Hong Kong, Hong Kong	190	-	-
Padjadjaran Uni., Indonesia	98	107	905
Tokyo Women's Medical Uni., Japan	-	97	461
Uni. Malaya, Malaysia	193	184	919
Uni. Santo Tomas H., Philippines	124	124	571
National University H., Singapore	179	201	1,570
Tan Tock Seng H., Singapore	42	54	387
Chang-Gung Memorial Hospital, Taiwan	295	300	2,373
Chiang Mai Uni., Thailand	250	337	3,419
TOTAL	1846	1735	12,337

Ethics

Individual centres were responsible for obtaining ethics approval from the relevant local authority for research involving humans, with overarching ethics approval for collation and storage for data from Monash University.

Funding

To support ongoing data collection, entry and cleaning, particularly in centres from countries with a lower socioeconomic status, the APLC sought project funding support from several pharmaceutical companies. This funding was distributed on an as needed case by case basis.

The APLC received unrestricted project support grants in support of the LLDAS validation studies from UCB, GlaxoSmithKline, Janssen, Bristol-Myers Squibb and AstraZeneca. These funders had no role in data collection, analysis, preparation, review or approval of any of the studies presented in this thesis.

Target patient population, patient identification and consent

Patient identification, recruitment and follow up occurred during routine ambulatory care at each centre. Patients were eligible to partake in the cohort study if they were at least 18 years of age and met either the 1997 American College of Rheumatology Modified Classification Criteria for SLE,¹³⁸ with at least four of the 11 items; or alternatively, fulfilled the Systemic Lupus International Collaborating Clinics 2012 Classification Criteria,¹³⁹ with at least four of the 17 items (at least one clinical and one immunological criterion) or with lupus nephritis in the presence of at least one immunological criterion. Disease duration was not part of the recruitment criteria and patients

with either newly diagnosed or longstanding disease could be included. Unlike a clinical trial where active disease is a prerequisite for study entry, patients any level of disease activity were eligible to enter; effectively patients were unselected other than for fulfilling classification criteria for SLE and providing informed consent. Participants were excluded if they were *under 18 years of age, were unable to give consent or did not meet ACR or SLICC classification criteria for SLE*.

Principal Investigators at each site were responsible for identifying eligible patients, and individual centres obtained valid written informed consent in accordance with local authority regarding ethical conduct of human research.

Visit frequency

Each centre aimed to recruit between 50 and 200 consecutive patients. A minimum routine visit frequency was pre-defined as 6 months, in order to allow capture of variability in disease activity and therefore LLDAS status per patient. More frequent visits were allowed based on clinical need and were recorded into the dataset. Therefore the mean (\pm SD) frequency of visits or the interval between visits in the longitudinal dataset was 0.34 ± 0.17 years. An annual visit was mandated for collection of additional data (see data collection – annual visit).

Data collection

All data were collected using standardised Case Report Forms (CRF) in Excel format (see Appendix). Patient identifiers were removed at time of data pooling, with the exception of the unique study identification number of each patient to allow for data querying. The principal researcher at each site was responsible for maintaining a record of patients with matched study identification numbers. This was kept in a secure location within each hospital or university.

Baseline

Data collected at the enrolment visit included demographic and diagnostic information, in addition to all information collected at routine visits **and** annual visits. The demographic data collected included: date of birth, gender, year of onset of SLE symptoms, year of confirmed SLE diagnosis, ethnicity (self-report), smoking status, family history of SLE, and highest attained education level. Diagnostic criteria required completion of the ACR and SLICC classification criteria (see Appendix for details).

Routine visit

At every routine visit the following data were collected (see Appendix for details):

- Measures of activity
 - SLEDAI-2K⁷⁵
 - measures clinical and serological activity (either present or absent) across organ systems
 - does not measure improving or worsening activity within a system
 - scores range from 0 to 105, with higher scores indicating more active disease
 - SELENA flare index (SFI)⁸¹
 - Based on the SLEDAI
 - Measures mild/moderate and severe flares based on clinical, laboratory and medication criteria
 - For the purposes of the study if a patient fulfilled any of the severe flare criteria, they were considered to have a severe flare irrespective of whether they also fulfilled mild/moderate flare criteria. If a patient fulfilled

mild/moderate flare criteria but not severe flare criteria, they were considered to have a mild/moderate flare

- PGA⁷⁹
 - Visual analogue scale from 0 to 3, where 0 is no activity and 3 is high activity
 - PGA=0 is no disease activity, PGA >0 to 1 is considered mild disease activity, PGA >1 to 2 is considered moderate disease activity (e.g. requiring consideration of change to treatment), and PGA >2 to 3 is considered severe disease activity (e.g. requiring hospitalisation).
- Laboratory results within 30 days of the study visit as allowable by the SLEDAI-2K
 - full blood count
 - renal function and electrolytes
 - serum albumin
 - urine protein:creatinine ratio and microscopy
 - erythrocyte sedimentation rate
 - complement 3 and 4
 - double stranded DNA (dsDNA) antibody titre
- Use and dose of medications
 - Prednisolone or equivalent
 - Antimalarial (hydroxychloroquine or chloroquine)
 - Immunosuppressive medication (including methotrexate, azathioprine, mycophenolate, leflunomide, cyclosporine, cyclophosphamide, tacrolimus, rituximab and/or belimumab)

Annual visit

Every 12 months the following additional data were collected (see Appendix for details)

- SLICC damage index (SDI)⁹³
 - Measures irreversible damage across organ systems
 - Scores range from 0 to 46, with higher scores indicating greater disease-related damage
- SF-36⁹⁴
 - A generic HR-QoL instrument validated in a number of SLE observational cohorts and clinical trials, and validated in each of the languages used by patients in this study ^{41,61,95-98}
 - Comprises 8 domains including physical function (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), role emotional (RE), and mental health (MH), as well as two summary scores defined as the physical component score (PCS) and mental component score (MCS). The individual domain scores are expressed on a scale of 0 to 100, and the component summary scores are standardized around a US normal population mean of 50, with higher scores representing better HR-QoL.

Outcomes

The primary outcome measure in this study was accrual of irreversible damage measured annually using the SLICC damage index (SDI). Secondary outcome measures included disease flares measured at every visit using the SELENA flare index (SFI); and patient reported health related quality of life measured annually using the Medical Outcomes Study 36-item Short Form Health Survey (SF-36v2).

Data management and cleaning

Each centre was responsible for securely storing collected data. De-identified data were pooled and cleaned every 6-12 months to ensure integrity and accuracy of ongoing data collection.

Cleaning of data was performed in a two stage process: missing values, typographical and numerical errors were identified using STATA v15.1 (StataCorp, College Station, Texas, USA); additionally manual cleaning to identify clinical errors (e.g. medication dose outside allowable range, likely representing a transcription error) was performed as an extra measure to ensure data accuracy. Data query reports with missing or incomplete data, and any potential errors were then sent back to each centre for completion and correction prior to inclusion in the final dataset.

Handling of missing data

For the longitudinal dataset less than 5% of visits had missing values, the majority of these were laboratory results particularly in centres where investigations may incur an out of pocket cost for the patient. Less than 5% of visits had missing SLEDAI-2K data and were excluded from the analyses requiring SLEDAI-2K data.

As SDI was collected yearly, for visits in between, the closest previous or next visit SDI value was used.

Scoring of LLDAS attainment

Scoring of LLDAS was based on the published definition and is outlined in table 2 below.

Table 2: Scoring of the Lupus Low Disease Activity State

Operational definition	Scoring
------------------------	---------

1. SLEDAI-2K ≤ 4 , with <i>no</i> activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no haemolytic anaemia or gastrointestinal activity	<ul style="list-style-type: none"> - SLEDAI-2K ≤ 4 - score of 0 in SLEDAI domains for renal, CNS, cardiopulmonary, vasculitis, fever - score of 0 for haemolytic anaemia or gastrointestinal activity (additional on CRF)
2. No <i>new</i> features of lupus disease activity compared to the previous assessment	<ul style="list-style-type: none"> - Assessment of two consecutive visits required - If any SLEDAI domain (including serological) is marked 0 on a given visit, it must also be marked 0 on the subsequent visit
3. SELENA-SLEDAI physician global assessment (PGA, scale 0-3) ≤ 1	<ul style="list-style-type: none"> - PGA ≤ 1
Immunosuppressive Medications	
4. Current prednisolone (or equivalent) dose ≤ 7.5 mg daily	<ul style="list-style-type: none"> - Prednisolone ≤ 7.5mg
5. Standard maintenance doses of immunosuppressive drugs and approved biologic agents*	<ul style="list-style-type: none"> - Hydroxychloroquine ≤ 400mg/day - Chloroquine ≤ 150mg/day - Methotrexate ≤ 30mg/week - Azathioprine ≤ 200mg/day - Mycophenolate ≤ 3000mg/day - Mycophenolic acid ≤ 2160mg/day - Leflunomide ≤ 20 mg/day - Tacrolimus – adjusted for serum levels

	- Cyclosporine ≤ 200 mg/day - Cyclophosphamide, Rituximab and Belimumab as per treatment protocols
LLDAS achieved if all 5 criteria fulfilled	

Handling of time dependent relationships

For analyses that incorporated length of time in LLDAS, if a patient was in LLDAS on two consecutive visits, she/he was 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 subsequent visit, the duration of LLDAS was calculated based on visit time interval divided by 2. The percentage of follow-up in LLDAS per patient was determined as the sum of all intervals in LLDAS, divided by total length of follow-up.

The same calculations were performed for time spent in remission (Chapter 7).

Statistical analysis

For all of the results chapters descriptive statistics were reported as mean (standard deviation (SD)) for normally distributed continuous variables and median (inter-quartile range (IQR)) for skewed continuous data. Chi-squared tests were used for categorical comparisons.

Chapter 3 - Frequency and predictors of the lupus low disease activity state in a multi-national and multi-ethnic cohort

Univariate simple logistic regression was used to identify predictors of LLDAS. Variables with $p \leq 0.2$ in simple logistic regression analysis were then checked for confounding and multicollinearity, prior to inclusion in stepwise multivariable logistic regression analysis for LLDAS. Model properties were tested including sensitivity and specificity, ROC curve analysis and p-value of the Hosmer-Lemeshaw test for goodness of fit.

Chapter 4 - Association of the lupus low disease activity state (LLDAS) with health-related quality of life in a multinational prospective study

To allow for linear regression analysis, domain and summary scores were log transformed prior to inclusion into models in order to fulfil the assumption of 'normality'. The exponentiated regression coefficients (coeff) are reported in results to allow ease of clinical interpretation. This represents (coeff-1)*100 percent increase or decrease in PCS or MCS scores for every one-unit change in continuous independent variables or a change in category for categorical independent variables. Variables with a $p \leq 0.1$ in simple linear regression analysis were checked for multicollinearity prior to inclusion into backward stepwise multiple linear regression models for PCS and MCS scores. LLDAS is a composite measure comprising the SLEDAI, PGA, flare index, prednisolone dose and medication use. In addition to assessing the relationship between LLDAS and HR-QoL (model 1), a separate multiple linear regression model was used to ascertain to what degree individual LLDAS components contributed to this relationship (model 2). A third model of the LLDAS components was also tested, but using organ system activity rather than the total SLEDAI-2K score (model 3). Model adequacy was evaluated using adjusted R^2 , residual and normality plots.

Chapter 6 - Lupus Low Disease Activity State: a prospective validation study

Repeated failures Cox proportional hazard models were used to assess the time- dependent relationship between LLDAS and disease flares at each subsequent visit, as well as subsequent damage accrual (increase in SDI of at least 1 point), with proportionality of hazard ensured. Kaplan-Meier survival curves with log-rank test for significance were used to determine the relationship between proportion of time spent in LLDAS (at the 50% cut- off) and time to flare and new damage accrual. Generalized linear models were used to determine the association of (1) various cut-offs for proportion of time spent in LLDAS and (2) duration of 'sustained LLDAS', with flare and damage accrual. Subgroup analyses were performed to assess the effect of LLDAS on damage accrual in patients with existing damage at baseline ($SDI \geq 1$), and patients with active disease at baseline ($SLEDAI-2K \geq 6$). Sensitivity analyses were performed on treatment-related criteria of LLDAS (4 and 5), and I also assessed the effect of adding the SFI to the assessment of criterion 2 of LLDAS (no new activity) on damage accrual.

Chapter 7 – Prospective Evaluation of Remission Definitions in Systemic Lupus Erythematosus

Univariable analyses using Mann Whitney tests and Chi Square tests as appropriate were performed to compare the characteristics of patients based on percentage of time spent in LLDAS and remission. Cross tabulation and Chi Square tests were used to assess the overlap between LLDAS and remission definitions across all visits.

Repeated failures Cox proportional hazard models were used to assess the time-dependent relationship between LLDAS or remission and disease flares at each subsequent visit, as well as subsequent damage accrual (increase in SDI of at least 1 point), after ensuring proportionality of hazard. Time dependent proportional hazard models were also used to assess the relationship of proportion of time spent in LLDAS or remission (at the 50% cut-off) and disease flares and damage

accrual. The effect of sustained LLDAS and remission on flares and damage accrual was assessed using generalized linear models.

Construct Validity Study

In order to test the construct validity of LLDAS I needed to assess if LLDAS captured the concept originally defined. To achieve this I tested the concordance/agreement between SLE experts' 'gut feeling' / 'clinical judgement' regarding whether a patient is 'doing well' based on the conceptual definition of LLDAS, and the fulfilment of the operational definition of LLDAS, which at the time of the survey had not been published. .

Sample size calculation

The sample size calculation was based on an estimate of desired agreement of Kappa 0.8. I calculated the number of paired case-expert responses needed for different levels of agreement, taking into account the proportion of expected patients in each category of disease activity (e.g. remission (20 %), low (40%), moderate (20%) and high (20%)). Based on this, 50 cases and 50 independent responders gave the study 80% power at the 5% level of significance to reliably estimate an overall agreement of 40% or higher and a Cohen's Kappa of at least 0.2.

SLE vignette creation

Fifty SLE case summaries based on real de-identified patients and without manipulation of any details were prepared by five experts from the APLC, with each expert contributing 10 cases. Each case was based on a current adult patient attending routine ambulatory care who fulfilled criteria for SLE (either the 1997 American College of Rheumatology (ACR) criteria ¹³⁸ or the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria ¹³⁹), thus having the same selection

criteria as the patients enrolled in the APLC cohort. The cases were selected to represent the breadth of SLE clinical presentations. Each case was presented in the same format and included basic demographic descriptors (sex, age, occupation), detailed past history of SLE, current disease features, current treatment and investigation results. Each of the cases is available in the Appendix of the thesis.

SLE expert selection

Contact details for rheumatologist with expertise in SLE were sourced from the Systemic Lupus Erythematosus International Collaborating Clinics group and the international Treat to Target taskforce.⁸ None of the respondents were involved with the APLC or had knowledge of the operational definition of LLDAS at the time of the survey. The survey responses were collected in October 2015, prior to the publication of the operational definition of LLDAS. A total of 116 invitations were sent, over a period of 3 weeks multiple email reminders were sent until the desired sample of 50 completed responses were obtained.

Expert opinion survey

The survey was presented to the experts in electronic format using SurveyMonkey. The full transcript of the survey is available in the Appendix. The responders were given the conceptual (not the operational) definition of LLDAS in the introduction of the survey, as well as detailed instructions for completion. The conceptual definition of LLDAS was given as follows: *“a state which if sustained, is associated with a low likelihood of adverse outcome, considering both disease activity and medication safety.”*

The responders were first asked to complete contact and demographic details such as years of experience, type of clinical practice and number of SLE patients seen per annum. Each of the case

summaries was then presented in random order to each expert. After reading a case summary, each responder was asked to complete two questions: first to assess the patient's current disease *activity* using a PGA on a scale of 0-3, where 0 is no disease activity and 3 is severe disease activity; and second to rate the patient's current *state* as either remission, low, moderate or high, taking into account both current disease manifestations and treatment burden.

Assessment of the cases took approximately one hour to complete, and experts were able to move forward and back between cases, and login multiple times until full completion of the survey. Only completed surveys were used in data analysis, and reminders were sent until 50 complete responses were collected.

Data analysis

Two investigators from the APLC independently assessed whether each case met the operational definition of LLDAS. First, the SLEDAI-2K and presence of any new disease activity was calculated for each case based on the clinical information provided. The PGA was taken as the median score of expert survey responses, as the PGA responses were not normally distributed. Current treatment including prednisolone dose and other immunosuppressive mediations were available in each case summary. The investigators then independently classified each case as either being in LLDAS or not using the operational definition. There was no disagreement between the assessors.

Pooled data were analysed using STATA v13 (StataCorp, College Station, Texas, USA). Given that the operational definition of LLDAS sets the ceiling for maximal allowable disease activity, both 'remission' and 'low activity' are subsumed within LLDAS, and I considered expert designation of disease state of either remission or low to be equivalent to LLDAS. Therefore, expert responses on global disease activity state were grouped into remission/low or moderate/high, and compared to

the operational definition of LLDAS in a two by two table. Agreement between expert opinion and the operational definition of LLDAS was assessed using Cohen's Kappa.

Cases where there was >20% disagreement between expert opinion assessment and LLDAS were further analysed to assess which of the LLDAS criteria contributed most to the disagreement.

Subsequently two of the LLDAS criteria were adjusted to see if agreement could be improved.

Prednisolone dose ≤ 7.5 mg daily was adjusted to prednisolone dose ≤ 10 mg daily; and SLEDAI-2K ≤ 4 was adjusted to SLEDAI-2K ≤ 3 excluding serological activity (hypocomplementaemia and/or elevated anti-dsDNA).

Chapter 3

Frequency and predictors of the lupus low disease activity state in a multi-national and multi-ethnic cohort

Introduction

As explained in Chapter 1, one of the key desired characteristics of any treatment endpoint is utility – that is attainability in a sizeable proportion of patients. Without utility an endpoint has limited application in research or clinical practice, even if associated with desired outcomes, as is the case with the previously published studies of remission.

Prior to this study the attainability of LLDAS had only been tested in the pilot retrospective study of a relatively small cohort of SLE patients. Therefore the prevalence of attainment of LLDAS in a larger more representative population of SLE patients was not established. Additionally, it was important to identify the factors that may increase or reduce the likelihood of a patient being in LLDAS, as even though these antecedent characteristics are unlikely to be modifiable, they can be useful in identifying patients with a higher likelihood of active disease and therefore higher risk of damage accrual.

Therefore the objectives of this study were to describe the frequency and identify the predictors of attaining LLDAS in a large multinational cohort of patients with SLE.

Findings

The published manuscript in this chapter “Frequency and predictors of the lupus low disease activity state in a multi-national and multi-ethnic cohort”, describes the results in detail. A summary of the key findings is outlined below:

- 44% of the cohort in this cross sectional study of prospectively recruited patients were in LLDAS at a single point in time.
- Shorter disease duration, discoid rash, renal disease and serological activity were associated with lower LLDAS attainment.
- Higher national social wealth as a surrogate for socioeconomic status was associated with higher LLDAS attainment.

Implications

In this study I was able to show that LLDAS was sufficiently prevalent to have potential utility as a treatment endpoint in SLE, as well as identify antecedent factors associated with LLDAS attainment potentially helping to identify patients at higher risk of damage accrual.

The results of this study were presented at multiple national and international scientific meetings, as well as being published in a peer reviewed journal:

Golder V., Kandane-Rathnayake R., Hoi A.Y., Huq M., et al. *Frequency and predictors of the lupus low disease activity state in a multi-national and multi-ethnic cohort*. Arthritis research & therapy. 2016;18(1):260

Future direction


Whilst confirming the utility of LLDAS as a treatment endpoint for SLE, this study was not designed to test the association of LLDAS attainment with patient outcomes. Such studies are described in the following chapters.

RESEARCH ARTICLE

Open Access



Frequency and predictors of the lupus low disease activity state in a multi-national and multi-ethnic cohort

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Abstract

Background: Systemic lupus erythematosus (SLE) is a chronic heterogeneous disease with considerable burden from disease activity and damage. A novel clinical treatment target in the form of the lupus low disease activity state (LLDAS) has been recently reported, with retrospective validation showing that time spent in LLDAS translates to reduced damage accrual. The objectives of this study were to describe the frequency and identify the predictors of attaining LLDAS in a large multinational cohort of patients with SLE.

Methods: Data were collected at the recruitment visit in patients with SLE enrolled in a longitudinal study in nine countries. Data were analysed cross-sectionally against the recently published definition of LLDAS, and the frequency and characteristics associated with presence of LLDAS were determined. Stepwise multivariable logistic regression was used to determine predictors of LLDAS.

Results: Of the 1846 patients assessed, criteria for LLDAS were met by 44 %. Patients with shorter disease duration were less likely to be in LLDAS (OR 0.31, 95 % CI 0.19–0.49, $p < 0.001$). Likewise, patients with a history of discoid rash (OR 0.66, 95 % CI 0.49–0.89, $p = 0.006$), renal disease (OR 0.60, 95 % CI 0.48–0.75, $p < 0.001$), elevated double stranded DNA (OR 0.65, 95 % CI 0.53–0.81, $p < 0.001$) or hypocomplementaemia (OR 0.52, 95 % CI 0.40–0.67, $p < 0.001$) were less likely to be in LLDAS. When countries were compared, higher national social wealth (OR 1.57, 95 % CI 1.25–1.98, $p < 0.001$) as measured by the gross domestic product per capita was positively associated with LLDAS, but ethnicity was not.

Conclusion: The lupus low disease activity state is observed in less than half of patients with SLE at a single point in time. Disease duration and phenotype, and national social wealth, are predictive of LLDAS.

Keywords: Systemic lupus erythematosus, Disease activity, Treatment target, Low disease activity

Background

Systemic lupus erythematosus (SLE) is a chronic multi-organ autoimmune disease with a broad spectrum of manifestations. Despite global advances in translational research, effective targeted therapies in SLE are lacking [1], and a large proportion of patients are treated with

long-term glucocorticoids and non-specific immunosuppressants, which fail to prevent significant morbidity and reduction in life expectancy [2]. The course of SLE is variable, in some cases characterized by periods of relative inactivity punctuated by disease flare, whilst others have persistently active disease [3]. Current instruments used to measure disease activity are complex [4], contributing to mixed results in clinical trials of new targeted therapies [5]. This state of affairs has led to a call for definitions of treatment target states that can be used in clinical trials and clinical practice [6].

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Given that definitions of remission remain under debate [7], and a recently reported stringent definition of remission occurs in only 2 % of patients with SLE [8], using remission as a treatment target is not pragmatic. In other autoimmune diseases, mainly rheumatoid arthritis (RA), achieving a minimally active disease state has been proven to translate into improved patient outcomes [9]. The value of a treatment target for SLE has been recently described in an international consensus statement, in which defining a low disease activity state to use as a treatment target was set as a research agenda [10].

Using consensus methods, the Asia-Pacific Lupus Collaboration has recently developed and retrospectively validated the lupus low disease activity state (LLDAS) definition [11]. The conceptual definition of LLDAS is a state, which if sustained, is associated with good long-term outcomes. The operational definition of LLDAS is fulfilled when all of the following criteria are met: (1) SLE Disease Activity Index (SLEDAI-2 K) ≤ 4 , with no activity in major organ systems (renal, central nervous system (CNS), cardiopulmonary, vasculitis, fever) and no haemolytic anaemia or gastrointestinal activity; (2) no new features of lupus disease activity compared to the previous assessment; (3) a Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI physician global assessment (PGA) (scale 0–3) ≤ 1 ; (4) a current prednisolone (or equivalent) dose ≤ 7.5 mg daily; and (5) well-tolerated standard maintenance doses of immunosuppressive drugs and approved biologic agents, excluding investigational drugs. In a retrospective cohort analysis, Franklyn et al. showed that patients who spent greater than 50 % of their disease duration in LLDAS accrued significantly less damage compared to patients who did not [11], suggesting this definition has a role in the identification of treatment responses associated with improved long-term outcomes.

Currently, work is underway to prospectively validate and refine this definition of LLDAS in a large multinational cohort followed over several years, with the hypothesis that attainment of LLDAS results in less damage accrual. The objective of the current study is to determine the frequency and correlates of LLDAS in a cross-sectional analysis of data collected at recruitment for this study.

Methods

Study population

Patients were recruited at 12 centres in nine countries, commencing in May 2013. Each institution obtained ethics approval and written informed patient consent for the study. Patients over the age of 18 years who fulfilled criteria for SLE (either the 1997 American College of Rheumatology (ACR) criteria [12] or the 2012 Systemic

Lupus International Collaborating Clinics (SLICC) criteria [13]) were eligible. Data collection took place during the routine ambulatory care of each SLE patient, using a standardized paper or electronic case report form.

Variables

At recruitment, demographics, disease characteristics and clinical variables were collected from each patient. Demographic variables included gender, ethnicity (self-report based on Australian Standard Classification of Cultural and Ethnic Groups [14]), date of birth, year of definite SLE diagnosis, smoking status, and highest attained education level. Disease manifestations were determined from the ACR classification criteria on an “ever present” basis. Current use and doses of glucocorticoids and immunosuppressive medications were captured for each patient. Disease activity was measured using SLEDAI-2 K [15], and a PGA on a scale of 0–3. Disease flares compared to the previous routine clinical visit were captured using the SLE flare index (SFI) [16]. Irreversible disease damage was captured using the SLICC damage index (SLICC-DI) [17]. Additionally, laboratory results for each patient were obtained within 30 days of the visit, including full blood count, renal function and electrolytes, serum albumin, urine protein/creatinine ratio and microscopy, erythrocyte sedimentation rate, complement 3 and 4, and double stranded DNA (dsDNA) antibody titre.

Determination of LLDAS

A patient was considered to be in LLDAS if they fulfilled all five predefined criteria [11], with the following modifications. Given the cross-sectional nature of the baseline visit, data collected at recruitment, and hence the absence of data from the previous visit, patients were deemed to be on stable doses of immunosuppressive medications if they did not exceed the maximum recommended dose (Table 3); the criterion for “no new disease activity” was deemed to be met if patients did not meet any SFI criteria.

Data analysis

Given the young mean age of the patients (Table 1), age at diagnosis ≤ 30 years was used as a binary variable. Given the likelihood of higher disease activity in the period immediately after diagnosis of SLE [18], disease duration ≤ 1 year was also used as a binary variable. Patients from different countries were grouped according to gross domestic product (GDP) purchasing power parity per capita [19] in order to account for international differences in socioeconomic status.

Pooled data from all sites were analysed using STATA v13 (StataCorp, College Station, TX, USA). Data are

Table 1 Patient demographics and disease characteristics

	Number (%) ^c or mean (SD) or median (IQR 25–75) (n = 1846 patients)
Country	
Australia	240 (13.00 %)
China	235 (12.73 %)
Hong Kong	190 (10.29 %)
Indonesia	98 (5.31 %)
Malaysia	193 (10.46 %)
Philippines	124 (6.72 %)
Singapore	221 (11.97 %)
Taiwan	295 (15.98 %)
Thailand	250 (13.54 %)
Ethnicity	
Caucasian	126 (6.73 %)
Chinese	1008 (54.60 %)
Filipino	132 (7.15 %)
Indonesian	102 (5.53 %)
Thai	255 (13.81 %)
Malay	98 (5.31 %)
Vietnamese/Cambodian	24 (1.30 %)
Indian/Sri Lankan	64 (3.47 %)
Other ^a	37 (2.00 %)
Female gender	1723 (93.34 %)
Age at diagnosis (years)	29.34 (12.35)
Age at diagnosis ≤30 years	973 (52.71 %)
Disease duration at enrollment (years)	8.64 (8.50)
Disease duration at enrollment ≤1 year	149 (8.07 %)
Current smoker	67 (3.63 %)
First-degree relative with SLE	117 (6.34 %)
Highest attained education level	
Primary	242 (13.11 %)
Secondary	572 (30.99 %)
Tertiary	618 (33.48 %)
ACR criteria ^b	
Malar rash	1087 (58.88 %)
Discoid rash	290 (15.71 %)
Photosensitivity	537 (29.09 %)
Mouth ulcers	670 (36.29 %)
Arthritis	1205 (65.28 %)
Serositis	313 (16.96 %)
Renal	803 (43.50 %)
Neurologic	160 (8.67 %)
Haematologic	1118 (60.56 %)
Immunologic	1547 (83.80 %)

Table 1 Patient demographics and disease characteristics (Continued)

ANA	1627 (88.14 %)
Number of ACR criteria for SLE	5.07 (1.39)
Number of SLICC criteria for SLE	5.70 (2.47)
SLICC-DI score at enrollment	0 (0–1)
Damage present at enrollment ^d	694 (37.59 %)
PGA at enrollment	0.6 (0.3–1)
Mild flare since last clinical review	210 (11.38 %)
Severe flare since last clinical review	111 (5.94 %)
SLEDAI-2 K score	4 (2–6)
SLEDAI-2 K no complement or dsDNA	0 (0–4)

^aOther includes Hispanic, African, other South-East Asian, Pacific Islander and mixed ethnicity. ^bEver present arthritis (two or more joints with tenderness, swelling or effusion), serositis (pleuritis or pericarditis), renal disorder (persistent proteinuria >0.5 g/day, or presence of cellular casts), neurologic disorder (seizures or psychosis not attributable to other causes), haematologic disorder (haemolytic anaemia, leukopenia, lymphopenia or thrombocytopenia), immunologic criteria (presence of anti-dsDNA antibody, anti-Sm antibody, or positive finding of antiphospholipid antibodies). ^cPercent present shown in table, percent absent and missing not shown in table. ^dSLICC-DI >0. SLE systemic lupus erythematosus, ACR American College of Rheumatology, SLEDAI SLE disease activity index, SLICC Systemic Lupus International Collaborating Clinics, DI damage index, PGA Physician Global Assessment, ANA antinuclear antibody, dsDNA double-stranded DNA

reported as mean (standard deviation (SD)) for normally distributed continuous variables and median (interquartile range (IQR)) for skewed continuous data. The chi-squared test was used for categorical comparisons. Univariate simple logistic regression was used to identify predictors of LLDAS. Variables with *p* value ≤0.2 in simple logistic regression analysis were then checked for confounding and multicollinearity, prior to inclusion in stepwise multivariable logistic regression analysis for LLDAS. Model properties including sensitivity and specificity, receiver operating characteristic (ROC) and *p* value for the Hosmer-Lemeshaw test for goodness of fit are available in Additional file 1: Table S1.

Results

Demographics and disease characteristics

A total of 1846 patients were recruited. In this cohort, 93 % of patients were female, with a mean age at diagnosis of 29 (SD ± 12.4) years and mean disease duration of 8.6 (SD ± 8.5) years at the time of recruitment. There were 149 patients (8 %) recruited within 12 months of disease diagnosis. More than 50 % of patients were of Chinese ethnicity, 7 % of patients were Caucasian, and the remainder represented other ethnic groups native to the region (Table 1). Other baseline demographics are presented in Table 1.

Disease manifestations were determined from the ACR criteria on an “ever present” basis (Table 1). More than half of the patients had a history of malar rash, arthritis and haematologic and immunologic

manifestations, and 803 patients (44 %) had a history of renal disease. The median SLEDAI-2 K at enrollment was 4 (IQR 2–6) (Table 1). There were 694 patients (38 %) had irreversible damage at recruitment (SLICC-DI >0), and the median SLICC-DI score was 0 (IQR 0–1). In total, 1430 patients (77.5 %) were on prednisolone, with a mean dose of 11 mg (SD \pm 12.8 mg) per day (Table 2).

Frequency of meeting criteria for LLDAS

All of the patients fulfilled at least one criterion of LLDAS (Table 3). The most frequently present criterion (n = 1838 patients (99.6 %)) was the criterion relating to immunosuppressive medications, with only eight patients exceeding a maximum recommended dose. The least frequently present criterion (1171 patients (63.4 %)) was SLEDAI-2 K \leq 4 without activity in a major organ system, followed by the glucocorticoid dose criterion (68.2 %). A higher proportion of patients achieved PGA \leq 1 than achieved SLEDAI \leq 4 (76 % vs. 63 %, p < 0.001). Despite a high frequency of attainment of individual criteria, only 810 patients (43.9 %) fulfilled all five criteria for LLDAS.

Determinants of presence of LLDAS

Multiple independent variables had a significant association with LLDAS in univariate analysis (Table 4). Younger age at diagnosis (OR 0.77, 95 % CI 0.64–0.93, p = 0.006) and shorter disease duration (OR 0.34, 95 % CI 0.23–0.51, p < 0.001) were negatively associated with LLDAS. A history of discoid rash (OR 0.73, 95 % CI 0.57–0.95, p = 0.02) or renal disease (OR 0.63, 95 % CI 0.53–0.77, p < 0.001), or current anti-

dsDNA positivity (OR 0.55, 95 % CI 0.46–0.68, p < 0.001) and hypocomplementaemia (low C3 and/or C4; OR 0.45, 95 % CI 0.37–0.55, p < 0.001) were all negatively associated with LLDAS. No significant differences were observed in ethnicity, gender or educational level. In multivariable logistic regression analysis, variables that remained significantly negatively associated with LLDAS included disease duration \leq 1 year (OR 0.31, 95 % CI 0.19–0.49, p < 0.001), history of discoid rash (OR 0.66, 95 % CI 0.49–0.89, p = 0.006) or renal disease (OR 0.60, 95 % CI 0.48–0.75, p < 0.001); and current elevated anti-dsDNA (OR 0.65, 95 % CI 0.53–0.81, p < 0.001) or hypocomplementaemia (OR 0.52, 95 % CI 0.40–0.67, p < 0.001). Patients from countries with a high GDP (PPP) per capita were significantly more likely to be in LLDAS than patients from countries with a lower GDP (PPP) per capita (OR 1.57, 95 % CI 1.25–1.98, p < 0.001). Model properties for the aforementioned variables are presented in Additional file 1: Table S1.

Analysis of the effect of disease manifestations as defined by ACR criteria [12] on individual LLDAS criteria (Additional file 1: Table S2) revealed that patients with immunologic manifestations were less likely to have SLEDAI-2 K \leq 4 (OR 0.73, 95 % CI 0.56–0.96, p = 0.02). A history of renal disease was significantly associated with lower odds of meeting any of the individual LLDAS criteria. The presence of damage (SLICC-DI >0) at recruitment was significantly associated with lower frequency of meeting several LLDAS criteria including SLEDAI \leq 4 (OR 0.79, 95 % CI 0.65–0.96, p = 0.02), absence of flare (OR 0.67, 95 % CI 0.52–0.88, p = 0.003) and PGA \leq 1 (OR 0.64, 95 % CI 0.51–0.79, p < 0.001).

Table 2 Medication taken at enrollment

Medication	Number (%)	Mean dose (SD)	Dose range
Prednisolone	1430 (77.46 %)	11.08 mg (12.78)	0.50–200 mg
Antimalarial	1333 (72.21 %)	291.19 mg (104.56) ^a	28.57–600 mg ^a
Methotrexate	75 (4.06 %)	13.79 mg (6.73)	2.50–50 mg
Azathioprine	412 (22.32 %)	73.99 mg (30.29)	12.50–200 mg
Mycophenolate mofetil	306 (16.58 %)	1247.70 mg (546.96)	50–3000 mg
Mycophenolic acid	41 (2.22 %)	1102.93 mg (645.86)	180–2160 mg
Leflunomide	38 (2.06 %)	15.53 mg (5.49)	10–30 mg
Cyclosporine	35 (1.90 %)	126.43 mg (65.29)	50–300 mg
Cyclophosphamide ^b	73 (3.95 %)	N/A	N/A
Rituximab ^b	13 (0.70 %)	N/A	N/A
Belimumab ^b	15 (0.81 %)	N/A	N/A
Any Immunosuppressant ^c	940 (50.92 %)	N/A	N/A

^aBased on hydroxychloroquine dosing - Indonesia and Thailand predominantly use chloroquine. ^bTaken in the last 6 months. ^cEither methotrexate, azathioprine, mycophenolate, leflunomide, cyclosporine, cyclophosphamide, rituximab and/or belimumab. Maximum recommended dose: hydroxychloroquine \leq 400 mg; methotrexate \leq 30 mg; azathioprine \leq 200 mg; mycophenolate mofetil \leq 3000 mg; mycophenolic acid \leq 2160 mg; leflunomide \leq 20 mg
N/A - dosing not applicable

Table 3 Lupus low disease activity state (LLDAS) frequency

Descriptors of disease activity	Number (%) (n = 1846)
1. SLEDAI-2 K ≤ 4 , with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, haemolytic anaemia, fever) and no gastrointestinal activity	1171 (63.43 %)
2. No new features of lupus disease activity compared to the previous assessment	1574 ^a (85.27 %)
3. SELENA-SLEDAI Physician Global Assessment (PGA, scale 0–3) ≤ 1	1400 (75.84 %)
Immunosuppressive medications	
4. Current prednisolone (or equivalent) dose ≤ 7.5 mg daily	1258 (68.15 %)
5. Well-tolerated standard maintenance doses of immunosuppressive drugs and approved biologic agents, excluding investigational drugs ^b	1838 (99.57 %)
All 5 criteria present	810 (43.88 %)

^aBased on flares (see “Methods”). ^bCalculated as not exceeding maximum recommended dose: hydroxychloroquine ≤ 400 mg; methotrexate ≤ 30 mg; azathioprine ≤ 200 mg; mycophenolate mofetil ≤ 3000 mg; mycophenolic acid ≤ 2160 mg; leflunomide ≤ 20 mg. SLE systemic lupus erythematosus, SELENA Safety of Estrogens in Lupus Erythematosus National Assessment trial, SLEDAI SLE disease activity index, CNS central nervous system, PGA Physician Global Assessment

Discussion

The authors have commenced a large prospective longitudinal study to validate the recently reported definition of LLDAS as being predictive of protection from damage accrual in SLE [11]. In the current cross-sectional study of data collected at recruitment into this large multinational cohort, we have shown that 44 % of patients with SLE met LLDAS criteria for low disease activity at a single point in time. This is the first multinational study to focus on the recent definition of LLDAS, and the frequency of LLDAS observed closely matches the 41 % frequency of LLDAS attainment in our initial retrospective single-centre validation study [11]. If LLDAS attainment or maintenance is shown to translate into improved patient outcomes, such as is the case for attainment of minimal disease activity in RA [9], this frequency of attainment, especially compared to more stringent cutoffs such as remission, suggests that LLDAS could represent a treatment target to use in SLE strategy trials and in clinical trials of novel therapies. Conversely, the fact that the majority of patients did not meet criteria for LLDAS speaks to the inadequate state of current treatment of SLE.

The definition of LLDAS [11] incorporates cutoffs for both disease activity and treatment burden. It refers to a desired clinical state, rather than a treatment response or change in disease activity, therefore representing a tool with which to stratify clinically diverse disease manifestations in a binary fashion, i.e. a patient is either in

LLDAS or not. LLDAS was designed to take into account validated measures of disease activity [20] and treatment variables, in view of the fact that treatment, especially with glucocorticoids, is known to contribute to poor long-term outcomes in SLE [21, 22]. In the current study, the second most frequent reason for not attaining LLDAS was glucocorticoid dose >7.5 mg/day. Although it is clear that higher disease activity over time is associated with worse outcomes [23], measures of disease activity alone, such as the SLEDAI-2 K or the British Isle Lupus Assessment Group (BILAG) measure, do not take into account treatment burden and therefore omit consideration of a major contributor to long-term harm in SLE. Similarly, measures of treatment response such as the SLE Responder Index [24], although they combine different measures of disease activity, do not represent a target state and do not include treatment variables.

Our finding that 99 % of patients met at least one LLDAS criterion, but only 44 % of patients met all five criteria, supports the value of including multiple variables in the definition of LLDAS. A higher proportion of patients achieved PGA ≤ 1 than achieved SLEDAI ≤ 4 , potentially because of the inclusion of serological and clinical activity in the SLEDAI-2 K; the presence of dsDNA antibodies and hypocomplementaemia equates to 4 points on the SLEDAI-2 K, therefore any additional manifestation will result in the patient exceeding the SLEDAI-2 K cutoff for LLDAS.

The size of this cohort allowed us to evaluate factors associated with the presence of LLDAS. Some of the most common clinical manifestations of active disease in SLE are immunologic, cutaneous and renal disease [3], each of which was significantly negatively associated with LLDAS in multivariable regression. Disease duration of less than one year was also negatively associated with LLDAS, consistent with the observation that newly diagnosed patients are more likely to have active disease [18].

Our study has shed some further light on treatment practices in tertiary lupus centres. The lower frequency of use of immunosuppressants in this cohort may be related to issues with access to or availability of medications in some Asian countries, which has been previously described [26]; certainly in our recent single centre report based on an Australian cohort, the frequency of immunosuppressant use was considerably higher than in the present study [11]. The mean daily dose of prednisolone of 11 mg/day is higher than doses reported in recent studies in single-centre cohorts with similar mean disease duration [11, 22]. As prolonged prednisolone use is known to contribute to significant morbidity in SLE [27], the consequences of high glucocorticoid dosing in this cohort

Table 4 Determinants of lupus low disease activity state (LLDAS)

Independent variable	Number (%) in LLDAS	Univariable logistic regression for LLDAS		Multivariable logistic regression for LLDAS	
		OR (95 % CI)	<i>p</i>	OR (95 % CI)	<i>p</i>
Ethnicity ^a					
Caucasian	63 (50.00)	Reference		Reference	
Asian	700 (43.24)	0.76 (0.53–1.09)	0.14	1.23 (0.82–1.86)	0.31
Gender					
Female	758 (43.99)	Reference		N/A	
Male	52 (42.28)	0.93 (0.64–1.35)	0.71		
Education					
Primary	113 (46.69)	Reference		N/A	
Secondary	229 (40.03)	0.76 (0.56–1.03)	0.21		
Tertiary	254 (41.10)	0.80 (0.59–1.07)	0.30		
Age at diagnosis					
>30 years	407 (47.22)	Reference		Reference	
≤30 years	397 (40.80)	0.77 (0.64–0.93)	0.006	0.86 (0.70–1.06)	0.16
Disease duration					
>1 year	765 (46.48)	Reference		Reference	
≤1 year	34 (22.82)	0.34 (0.23–0.51)	<0.001	0.31 (0.19–0.49)	<0.001
Clinical features ^b					
Malar rash					
No	331 (43.61)	Reference		N/A	
Yes	479 (44.07)	1.02 (0.82–1.23)	0.85		
Discoid rash					
No	701 (45.05)	Reference		Reference	
Yes	109 (37.59)	0.73 (0.57–0.95)	0.02	0.66 (0.49–0.89)	0.006
Photosensitive					
No	562 (42.93)	Reference		Reference	
Yes	248 (46.18)	1.14 (0.93–1.40)	0.20	1.18 (0.93–1.50)	0.16
Mouth Ulcers					
No	527 (44.81)	Reference		N/A	
Yes	283 (42.24)	0.90 (0.74–1.09)	0.28		
Arthritis					
No	263 (41.03)	Reference		Reference	
Yes	547 (45.39)	1.19 (0.98–1.45)	0.07	0.98 (0.78–1.23)	0.87
Serositis					
No	673 (43.90)	Reference		N/A	
Yes	137 (43.77)	0.99 (0.78–1.27)	0.97		
Renal					
No	508 (48.71)	Reference		Reference	
Yes	302 (37.61)	0.63 (0.53–0.77)	<0.001	0.60 (0.48–0.75)	<0.001
Neurologic					
No	732 (43.42)	Reference		Reference	
Yes	78 (48.75)	1.24 (0.90–1.72)	0.20	1.31 (0.90–1.91)	0.16

Table 4 Determinants of lupus low disease activity state (LLDAS) (Continued)

Haematologic						
No	289 (39.70)	Reference		Reference		
Yes	521 (46.60)	0.22 (0.03–1.76)	0.09	1.21 (0.97–1.51)	0.09	
Immunologic						
No	145 (48.59)	Reference		N/A		
Yes	665 (42.99)	0.80 (0.63–1.03)	0.08			
ANA						
No	101 (46.12)	Reference		N/A		
Yes	709 (43.58)	0.90 (0.68 – 1.20)	0.48			
Baseline damage						
SLICC-DI = 0	505 (44.84)	Reference		N/A		
SLICC-DI >0	308 (42.95)	1.00 (0.83–1.21)	0.96			
Current high anti-dsDNA						
No	434 (51.12)	Reference		Reference		
Yes	341 (36.43)	0.55 (0.46–0.68)	<0.001	0.65 (0.53–0.81)	<0.001	
Current low complement						
No	636 (49.88)	Reference		Reference		
Yes	142 (29.83)	0.45 (0.37–0.55)	<0.001	0.52 (0.40–0.67)	<0.001	
GDP ≤ \$25,000 ^c	324 (36.00)	Reference		Reference		
GDP > \$25,000	486 (51.37)	1.89 (1.56–2.26)	<0.001	1.57 (1.25–1.98)	<0.001	

Multivariable model choice - variables with a *p* value ≤0.20 or clinical association in univariable regression were tested for multicollinearity and confounding. Final variable list - GDP (PPP) per capita, ethnicity, age at diagnosis, disease duration, discoid rash, photosensitivity, arthritis, renal disease, neurologic disease, haematologic disease, dsDNA and complement. ^aEthnicity - no significant differences were seen between Asian ethnicity subgroups. ^bEver present, arthritis (two or more joints with tenderness, swelling or effusion), serositis (pleuritis or pericarditis), renal disorder (persistent proteinuria >0.5 g/day, or presence of cellular casts), neurologic disorder (seizures or psychosis not attributable to other causes), haematologic disorder (haemolytic anaemia, leukopenia, lymphopenia or thrombocytopenia), immunologic criteria (presence of anti-dsDNA antibody, anti-Sm antibody, or positive finding of antiphospholipid antibodies). ^cCountries with GDP < \$25,000 - China, Indonesia, Malaysia, Philippines, Thailand; countries with GDP > \$25,000 - Australia, Hong Kong, Singapore, Taiwan. GDP measured in US dollars. N/A variable not included in multivariable regression model

LLDAS lupus low disease activity state, SLICC Systemic Lupus International Collaborating Clinics, DI damage index, dsDNA double-stranded DNA, ANA antinuclear antibody, GDP gross domestic product

with mean disease duration at recruitment close to 9 years will need to be further assessed.

It is well-established that personal socioeconomic status contributes to disease activity [28] and disease damage [29] in SLE. A recent study from the Asia Pacific region has also shown that national social wealth and development has a very strong association with 5-year survival among patients with SLE [25]. As such, we believed it important to include an index of socioeconomic wealth in analyzing predictors of LLDAS. Indeed, in our study, patients from countries with higher GDP per capita (PPP) were significantly more likely to meet all criteria for LLDAS. The GDP (PPP) per capita is adjusted for the cost of living and is therefore useful for comparing standards of living rather than just national wealth [19]. The main drawback of this measure is that it does not measure personal socioeconomic status, which would also vary from patient to patient. However, education level, a potential surrogate marker of individual socioeconomic standing, was not predictive of LLDAS.

Certain limitations apply to the current study. Because of the cross sectional nature of the current analysis, we are unable to ascertain whether time spent in LLDAS is associated with less damage accrual, as was shown in the original retrospective single-centre validation of LLDAS [11]. The cohort described here is the subject of a longitudinal study intended to determine the association of LLDAS attainment with outcomes including damage accrual. Additionally, the published definition of LLDAS requires the absence of new disease manifestations, which is not possible to measure in a cross-sectional study; we replaced this with a requirement for the absence of flare as measured using SFI, which is likely to have been more rather than less stringent. In addition, identification of the “well-tolerated immunosuppressive” component of LLDAS was modified due to the inability to determine dose change or tolerance at recruitment. This resulted in a high proportion of patients fulfilling this criterion, and use of the original definition in our longitudinal

study may result in a lower overall frequency of LLDAS.

Conclusions

In conclusion, a validated definition of low disease activity has transformed both clinical care and clinical trial design in RA. Defining a treatment outcome that is attainable in an achievable proportion of patients and associated with improved long-term outcomes is something that has eluded SLE researchers until recently. Here, we have shown in a large multi-national and multi-ethnic cohort that LLDAS is attainable in a significant proportion of patients analysed at a single point in time, suggesting this definition is practical for use in long-term studies. We have also identified clinical variables associated with reduced likelihood of LLDAS, which if confirmed in longitudinal studies, may help with early identification of patients at higher risk. The next step in validation of LLDAS as an outcome measure in SLE is the definitive evaluation of whether LLDAS attainment or maintenance is associated with protection from long-term adverse outcomes such as damage accrual. This validation study, which will also allow for potential refinement of the LLDAS definition based on identifying variables that are most predictive of good outcomes, as was done for the recently described re-definition of remission in RA [30], is underway. That less than half of patients studied met the definition of LLDAS serves to underline the need for advances in the care of SLE, for which new strategies and new drugs are needed.

Additional file

Additional file 1: Table S1. Multiple logistic regression model properties. **Table S2.** Effect of disease manifestations and damage at recruitment on LLDAS components. (DOCX 59 kb)

Abbreviations

ACR: American College of Rheumatology; ANA: antinuclear antibody; APLC: Asia Pacific Lupus Collaboration; CNS: central nervous system; DI: Damage Index; dsDNA: double-stranded DNA; GDP: gross domestic product; LLDAS: lupus low disease activity state; PGA: Physician Global Assessment; RA: rheumatoid arthritis; ROC: receiver operating characteristic; SELENA: Safety of Estrogens in Lupus Erythematosus National Assessment; SFI: systemic lupus erythematosus flare index; SLE: systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC: Systemic Lupus International Collaborating Clinics

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Availability of data and material

Reasonable requests to view the dataset used in this manuscript can be made in writing to the project manager for the Asia Pacific Lupus Collaboration - Dr Rangsi Kandane-Rathnayake, rangi.kandane-rathnayake@monash.edu.

Authors' contributions

VG made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting and revising the manuscript. RKR made substantial contributions to analysis and interpretation of data and revising the manuscript critically for important intellectual content. AYBH made substantial contributions to acquisition of data and revising the manuscript critically for important intellectual content. MH made substantial contributions to analysis and interpretation of data and revising the manuscript critically for important intellectual content. WL made substantial contributions to acquisition of data and revising the manuscript critically for important intellectual content. YA made substantial contributions to acquisition of data and revising the manuscript critically for important intellectual content. ZGL made substantial contributions to acquisition of data and revising the manuscript critically for important intellectual content. SFL made substantial contributions to acquisition of data and revising the manuscript critically for important intellectual content. SS made substantial contributions to acquisition of data and revising the manuscript critically for important intellectual content. CSL made substantial contributions to conception and design, acquisition of data and revising the manuscript critically for important intellectual content. ALL made substantial contributions to acquisition of data and revising the manuscript critically for important intellectual content. MYM made substantial contributions to acquisition of data and revising the manuscript critically for important intellectual content. AL made substantial contributions to acquisition of data and revising the manuscript critically for important intellectual content. KF made substantial contributions to acquisition of data and revising the manuscript critically for important intellectual content. SM made substantial contributions to acquisition of data and revising the manuscript critically for important intellectual content. STVN made substantial contributions to conception and design, acquisition of data and revising the manuscript critically for important intellectual content. LZ made substantial contributions to acquisition of data and revising the manuscript critically for important intellectual content. YJW made substantial contributions to acquisition of data and revising the manuscript critically for important intellectual content. LH made substantial contributions to acquisition of data and revising the manuscript critically for important intellectual content. MC made substantial contributions to acquisition of data and revising the manuscript critically for important intellectual content. SON made substantial contributions to acquisition of data and revising the manuscript critically for important intellectual content. FG made substantial contributions to acquisition of data and revising the manuscript critically for important intellectual content. EFM made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and drafting and revising the manuscript. MN made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and drafting and revising the manuscript. All authors have given approval for the final version of the manuscript to be published. All authors have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Overarching ethics approval for data collection, analysis and publication of data collected by the Asia Pacific Lupus Collaboration was given by the Monash University Human Research Ethics Committee (Project Number: CF15/1617 – 2015000817).

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Chapter 4

Association of the lupus low disease activity state (LLDAS) with health-related quality of life in a multinational prospective study

Introduction

In chapter 3, I explored the utility of LLDAS as a treatment endpoint and found that it was prevalent in just under half of the APLC cohort at a single point in time. The work in this chapter begins to address the criterion validity of LLDAS by assessing its association with patient reported outcomes, in particular health-related quality of life (HR-QoL). As well as aligning with hard physician measured clinical outcomes such as reduction in disease flares or damage accrual, a treat to target endpoint should also correlate with improvements in HR-QoL reflective of the physical, psychological, mental and social aspects of patient health.

HR-QoL in SLE is known to be poor, and is known to change with disease activity levels and damage. Whilst practical constraints may limit the ability to incorporate a patient reported outcome measure directly into a treatment endpoint, attainment of this endpoint should align with improvement in patient reported outcomes.

The instrument used to assess HR-QoL in this study was the SF-36, which captures the physical and mental aspects of HR-QoL over the preceding 28 days of a patient's life. This timeframe of capture is very similar to the activity measure used when defining LLDAS – the SLEDAI-2K, which captures activity levels over the preceding 30 days. This allowed us to perform this study in a cross-sectional manner, as attainment of LLDAS will be relevant to a patient's current perception of his/her health status.

The main objective of this study was to assess the association of LLDAS with HR-QoL. Having such a large cohort of patients also allowed us to assess additional correlates of HR-QoL.

Findings

The published manuscript in this chapter “Association of the lupus low disease activity state (LLDAS) with health-related quality of life in a multinational prospective study”, describes the results in detail. A summary of the key findings is outlined below:

- Patients in LLDAS had significantly better physical and mental summary scores, as well as in multiple individual domains of the SF-36, compared to patients not in LLDAS.
- Antecedent patient characteristics such as ethnicity, level of education, age and disease duration had a significant impact on the physical components of SF-36.
- Musculoskeletal activity was associated with poor physical scores, and cutaneous activity was associated with poor mental health. In contrast, renal activity appeared clinically silent from the perspective of patient reported HR-QoL, with no impact on either physical or mental HR-QoL status.

Implications

In this study I was able to demonstrate that LLDAS status was associated with better HR-QoL, thus supporting its criterion validity and making sure that LLDAS fulfils one of the key overarching principles of the treat-to-target vision in SLE.

The results of this study were presented at multiple national and international scientific meetings, as well as being published in a peer reviewed journal:

Golder V., Kandane-Rathnayake R., Hoi A.Y., Huq M., et al. *Association of the lupus low disease activity state (LLDAS) with health-related quality of life in a multinational prospective study.* Arthritis research & therapy. 2017; 19(1):62

Future directions


This study partly addresses criterion validity of LLDAS as a treatment endpoint. Further validation studies testing LLDAS against clinical outcome measures such as flares and damage were completed in the following chapters. A further study of the impact of LLDAS attainment on improvements in HR-QoL is underway but is beyond the scope of this thesis.

RESEARCH ARTICLE

Open Access



Association of the lupus low disease activity state (LLDAS) with health-related quality of life in a multinational prospective study

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Abstract

Background: Systemic lupus erythematosus (SLE) is associated with significant impairment of health-related quality of life (HR-QoL). Recently, meeting a definition of a lupus low disease activity state (LLDAS), analogous to low disease activity in rheumatoid arthritis, was preliminarily validated as associated with protection from damage accrual. The LLDAS definition has not been previously evaluated for association with patient-reported outcomes. The objective of this study was to determine whether LLDAS is associated with better HR-QoL, and examine predictors of HR-QoL, in a large multiethnic, multinational cohort of patients with SLE.

Methods: HR-QoL was measured using the Medical Outcomes Study 36-item short form health survey (SF-36v2) in a prospective study of 1422 patients. Disease status was measured using the SLE disease activity index (SLEDAI-2 K), physician global assessment (PGA) and LLDAS.

Results: Significant differences in SF-36 domain scores were found between patients stratified by ethnic group, education level and damage score, and with the presence of active musculoskeletal or cutaneous manifestations. In multiple linear regression analysis, Asian ethnicity ($p < 0.001$), a higher level of education ($p < 0.001$), younger age ($p < 0.001$) and shorter disease duration ($p < 0.01$) remained significantly associated with better physical component scores (PCS). Musculoskeletal disease activity ($p < 0.001$) was negatively associated with PCS, and cutaneous activity ($p = 0.04$) was negatively associated with mental component scores (MCS). Patients in LLDAS had better PCS ($p < 0.001$) and MCS ($p < 0.001$) scores and significantly better scores in multiple individual SF-36 domain scores. Disease damage was associated with worse PCS ($p < 0.001$), but not MCS scores.

Conclusions: Ethnicity, education, disease damage and specific organ involvement impacts HR-QoL in SLE. Attainment of LLDAS is associated with better HR-QoL.

Keywords: Systemic lupus erythematosus, Health-related quality of life, Patient-reported outcomes, Treatment target, Low disease activity

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Background

Systemic lupus erythematosus (SLE) is a chronic multi-system autoimmune disease resulting in significant morbidity and reduced quality of life. With the improvement in overall survival of patients with SLE compared to historical outcomes [1], a growing number of young adults face the burden of chronic disease, which includes not only the activity of the disease itself, the adverse effects of treatment and the complications such as organ damage [2], but also the impact of disease on physical function, quality of life and employment. Health-related quality of life (HR-QoL) is a multi-dimensional construct that evaluates different health perceptions and self-reported functional status, and is often included as a key patient-reported outcome (PRO) in studies of chronic disease.

Both generic and disease-specific instruments have been developed to facilitate measurement of PROs, resulting in an increase in the number of studies assessing HR-QoL in SLE [3–6]. PROs are increasingly recognized as an integral part of assessment in clinical trials and in routine practice [7, 8], as they measure domains not captured by physician-assigned disease activity scores. Patients with SLE perform poorly on HR-QoL measures when compared to the general population [9], especially those with concomitant fibromyalgia [10] or fatigue [6, 11]. The effects of SLE on HR-QoL are comparable to other chronic diseases such as chronic heart failure, coronary artery disease, end-stage airways disease, human immunodeficiency virus and rheumatoid arthritis [12–14]. In addition, it has been reported that patients with SLE feel misunderstood by their families, the community and even the specialists treating them [15]. Consequently, patients feel that their quality of life needs are not being met by treating teams [16, 17].

As recently highlighted, measures of a treatment outcome status for use in clinical trials, or in treat-to-target strategy studies, have been lacking in SLE [18, 19]. Definitions of remission may be too stringent for use in routine practice or clinical trials [20], highlighting the need for a definition of low disease activity [18, 19]. Recently, we reported the definition and preliminary validation of a lupus low disease activity state (LLDAS), combining disease activity and treatment domains, attainment of which was shown in a longitudinal cohort study to be protective against damage accrual [21]. For such a measure to have value in clinical practice and clinical trials, it should be associated not only with physician-applied measures of disease activity and damage, but also with PROs. The objectives of this study were to determine whether LLDAS is associated with better HR-QoL, and to determine other predictors of HR-QoL in a large multiethnic multinational cohort of patients with SLE.

Methods

Study population

Ten centers from seven countries took part in this study. Patients over the age of 18 years, who fulfilled the classification criteria for SLE (either the 1997 American College of Rheumatology (ACR) criteria [22] or the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria [23]) were eligible. The study centers are members of the Asia Pacific Lupus Collaboration (APLC), involved in a multicenter prospective longitudinal study of SLE outcomes; data reported here represent all patients with complete data acquisition from the enrollment visit. Data collection took place between May 2013 and August 2015, during the routine ambulatory care of each patient, using either a standardized paper or electronic case report form.

Measurement of HR-QoL

HR-QoL was measured using the Medical Outcomes Study 36-item short form health survey (SF-36v2) [24], a generic instrument validated in a number of SLE observational cohorts and clinical trials, and validated in each of the languages used by patients in this study [3, 4, 10, 13, 25, 26]. The SF-36 comprises eight domains including physical function (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), role emotional (RE) and mental health (MH), and two summary scores defined as the physical component score (PCS) and mental component score (MCS). The individual domain scores are expressed on a scale of 0 to 100, and the component summary scores are standardized around a USA normal population mean of 50, with higher scores representing better HR-QoL.

Other variables

Demographic information, disease characteristics and data on clinical variables were collected from each patient at the study visit date. Demographic variables included gender, ethnicity (self-reported based on the Australian Standard Classification of Cultural and Ethnic Groups [27]), date of birth, year of SLE diagnosis, smoking status, and highest-attained education level. Disease manifestations were determined from the ACR and SLICC classification criteria [22, 23], recorded at study entry on an ever-present basis. Current doses of glucocorticoids and immunosuppressive medications were recorded for each patient. Disease activity was measured using the SLE disease activity index (SLEDAI-2 K) [28], with specific organ system activity derived from components of the SLEDAI-2 K.

Additional disease status measures included a physician global assessment (PGA) of disease activity on a scale of 0 to 3 [29], and fulfillment of the criteria for

LLDAS [21]. The operational definition of LLDAS is fulfilled when all of the following criteria are met: (1) SLEDAI-2 K ≤ 4 , with no activity in major organ systems (renal, central nervous system (CNS), cardiopulmonary, vasculitis or fever) and no hemolytic anemia or gastrointestinal activity; (2) no new features of lupus disease activity compared to the previous assessment; (3) a Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI PGA (scale 0–3) ≤ 1 ; (4) a current prednisolone (or equivalent) dose ≤ 7.5 mg daily and (5) well-tolerated standard maintenance doses of immunosuppressive drugs and approved biologic agents, excluding investigational drugs. Disease flares compared to the previous visit were measured using the SELENA-SLE flare index (SFI) [29]. Irreversible disease damage was measured using the SLICC damage index (SLICC-DI) [30].

Data analysis

Pooled cross-sectional data from all centers were analyzed using STATA v13 (StataCorp, College Station, TX, USA). Individual domain and component summary scores are expressed as median and interquartile range, as the data were not normally distributed. To allow for linear regression analysis, domain and summary scores were log-transformed prior to inclusion into models in order to fulfill the assumption of a normal distribution. The exponentiated regression coefficients (coeff) are reported in results for ease of clinical interpretation. This represents (coeff-1)*100% increase or decrease in PCS or MCS scores for every one-unit change in continuous independent variables or a change in category for categorical independent variables.

Variables with a p value ≤ 0.1 in simple linear regression analysis were checked for multicollinearity prior to inclusion into backward stepwise multiple linear regression models for PCS and MCS scores. LLDAS is a composite measure comprising the SLEDAI, PGA, flare index, prednisolone dose and medication use. In addition to assessing the relationship between LLDAS and HR-QoL (model 1), a separate multiple linear regression model was used to ascertain to what degree individual LLDAS components contributed to this relationship (model 2). A third model of the LLDAS components was also tested, but using organ system activity rather than the total SLEDAI-2 K score (model 3). Model adequacy was evaluated using adjusted R^2 , residual and normality plots.

Results

Demographic and disease characteristics

A total of 1422 patients were studied. The majority of patients were female (93%), with a mean (\pm SD) age at diagnosis of 31.2 (\pm 12.2) years and mean (\pm SD) disease duration of 9.2 (\pm 7.7) years. Caucasians formed 8% of

the sample, with the rest of the patients representing Asian ethnicities native to the region (Table 1). Other demographic characteristics are also shown in Table 1. More than half of patients had a history of malar rash, arthritis, hematologic or immunologic manifestations, and 46% had a history of renal disease (Additional file 1: Table S1). The median score in the SLEDAI-2 K was 4 (IQR 2–6). There were 369 patients (26%) with active renal disease, 273 (19%) with cutaneous activity and 119 (8.4%) with musculoskeletal activity; 593 patients (42%) fulfilled criteria for LLDAS (Table 1). The median SLICC-DI score was 0 (IQR 0–1), with 498 patients (35%) having some damage (SLICC-DI >0).

Individual domain and component summary scores of the SF-36v2 are presented in Table 2. Overall, domains with the highest (best) median, IQR (25th–75th) scores included physical functioning (85, 65–95), role physical (75, 50–100), role emotional (83.3, 58.3–100), and social functioning (75, 50–100). The lowest (worst) medians were observed in vitality (62.5, 50–75) and general health (57, 40–72).

Determinants of HR-QoL

Significant differences in the scores for individual SF-36 domains were seen in relation to ethnicity, education, damage and active disease manifestations. Patients of Asian ethnicity had higher (better) scores in domains including role physical, bodily pain, general health, vitality, and social function (Fig. 1a; Additional file 1: Table S2). Higher education was also associated with higher domain scores, while the presence of damage, or active musculoskeletal or cutaneous manifestations, were associated with lower (worse) scores across multiple domains (Fig. 1b, c, d; Additional file 1: Table S2). The presence or absence of renal activity did not significantly impact on SF-36 domain scores.

Higher disease activity as measured by the SLEDAI-2 K and PGA, and higher prednisolone dose, were each significantly associated with lower (worse) PCS and MCS scores in simple linear regression analysis (Table 3). With regard to organ domains of disease activity as measured using SLEDAI-2 K, patients with active musculoskeletal manifestations had significantly poorer PCS scores (coeff 0.89, $p < 0.001$), whereas patients with cutaneous manifestations had significantly worse MCS (coeff 0.94, $p < 0.001$). Neither PCS nor MCS scores were significantly different between patients with or without active renal disease. The presence of damage was associated with significantly worse PCS scores, but no differences in MCS scores were observed. Older age at diagnosis (coeff 0.997, $p < 0.001$) and longer disease duration (coeff 0.997, $p < 0.001$) were also associated with poorer PCS but not MCS scores.

We also analyzed the effect of country of study site and education level as variables. Australian patients

Table 1 Patient demographics and disease characteristics

	Number (%) or mean (SD) or median (IQR: 25th–75th)
Country, <i>n</i> (%)	
Australia	217 (15%)
China	222 (16%)
Indonesia	98 (7%)
Philippines	124 (9%)
Singapore	219 (15%)
Taiwan	294 (21%)
Thailand	250 (18%)
Ethnicity, <i>n</i> (%)	
Caucasian	116 (8%)
Chinese	699 (49%)
Filipino	132 (9%)
Indonesian	101 (7%)
Thai	254 (18%)
Malay	37 (3%)
Vietnamese/Cambodian	22 (2%)
Indian/Sri Lankan	35 (2%)
Other ^a	28 (2%)
Gender, <i>n</i> (%)	
Female	1329 (93%)
Highest attained education level ^b	
Primary	241 (17%)
Secondary	548 (38%)
Tertiary	607 (42%)
Age at diagnosis (years)	31.1 (12.2)
Disease duration (years)	9.2 (7.7)
SLICC-DI score	0 (0–1)
Damage present ^c	498 (35%)
PGA at enrollment	0.5 (0.2–1)
Mild flare	170 (12%)
Severe flare	100 (7%)
SLEDAI-2 K	4 (2–6)
Current CNS activity ^d	9 (0.6%)
Current vasculitis ^d	23 (1.6%)
Current renal activity ^d	369 (25.9%)
Current musculoskeletal activity ^d	119 (8.4%)
Current cutaneous activity ^d	273 (19.2%)
Current serositis ^d	12 (0.8%)
Lupus low disease activity state (LLDAS)	593 (42%)

Table 1 Patient demographics and disease characteristics (Continued)

Number (%) of patients taking prednisolone ^g	1167 (82%)
Taking immunosuppressant ^e	762 (53.5%)
Taking antimalarial ^f	1044 (73.3%)

^aOther includes Hispanic, African, other South-East Asian, Pacific Islander and mixed ethnicity. ^bPercent present shown in table, percent absent and missing not shown in table. ^cSLICC-DI >0. ^dActive based on non-zero SLEDAI-2 K scores in organ domains as indicated. ^eEither methotrexate, azathioprine, mycophenolate, leflunomide, cyclosporine, cyclophosphamide (in the last 6 months), rituximab (in the last 6 months) and/or belimumab (in the last 6 months). ^fEither hydroxychloroquine or chloroquine. Abbreviations: *SLE* systemic lupus erythematosus, *SLEDAI* SLE disease activity index, *SLICC* Systemic Lupus International Collaborating Clinics, *DI* damage index, *PGA* physician global assessment, *CNS* central nervous system, *CVA* cerebrovascular accident ^gMean dose (SD) 12 mg (13.7)

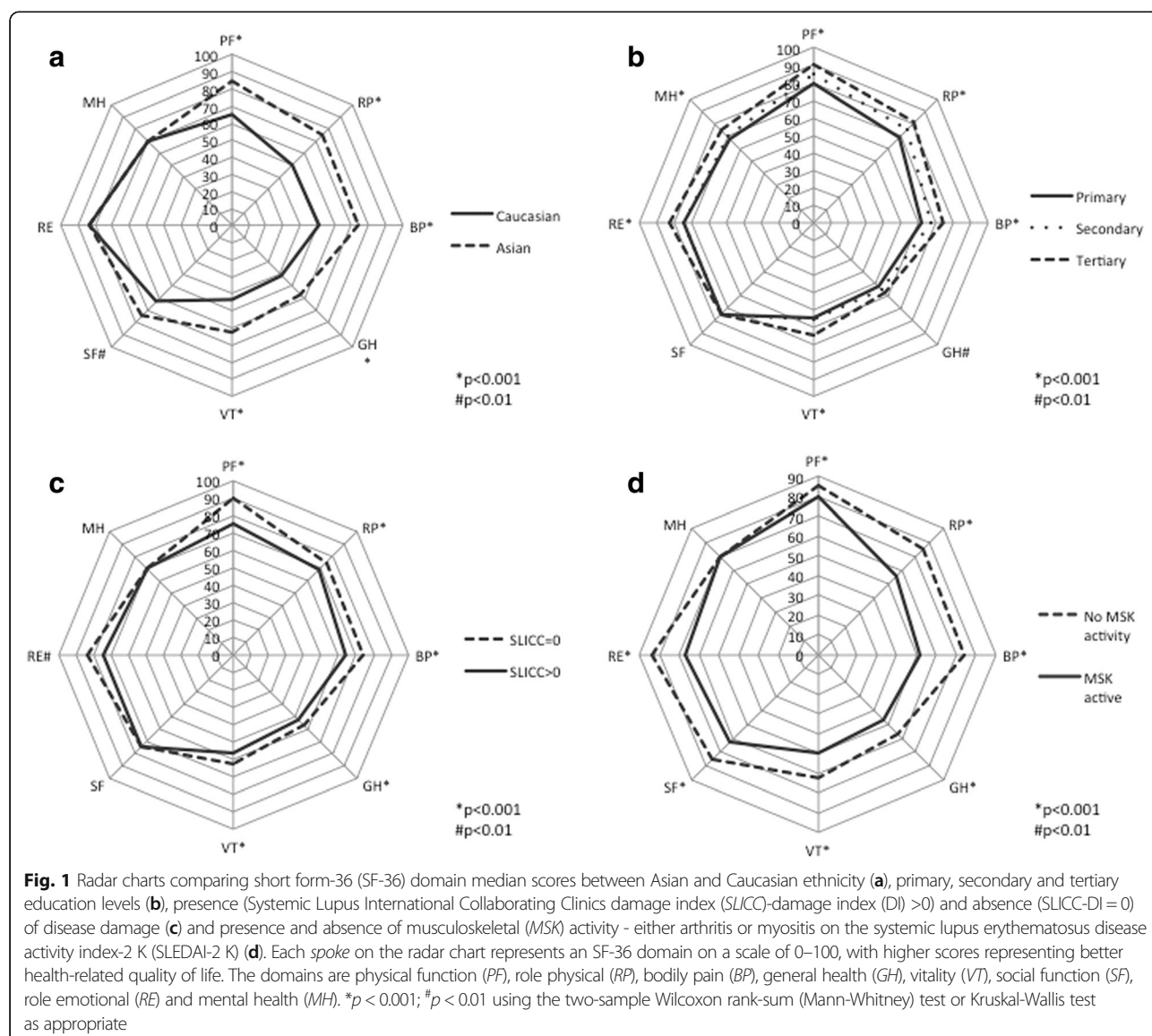
recorded the worst PCS scores (43.5, 36.1–52.3), and Chinese patients the worst MCS scores (44.9, 38.5–55.8). In simple linear regression analysis, Asian patients had significantly better PCS scores than their Caucasian counterparts (coeff 1.22, $p < 0.001$) regardless of the country of residence. Both PCS and MCS scores were significantly higher in patients with higher levels of education (Table 3). In backward stepwise multiple linear regression, multiple variables remained significantly associated with PCS (Table 4). The presence of damage remained negatively associated with PCS scores ($p < 0.001$). In contrast, shorter disease duration, younger age at diagnosis, Asian ethnicity, and higher level of education remained significantly positively associated with PCS. Patients with tertiary education ($p < 0.01$) had better MCS scores. The model set-up and properties are shown in Table 4.

Association between LLDAS or disease activity measures and HR-QoL

Patients who fulfilled criteria for LLDAS had significantly higher scores in individual SF-36 domains including role

Table 2 Short form-36 domain and component summary scores

	Median (IQR: 25th–75th)
Physical functioning	85 (65–95)
Role physical	75 (50–100)
Bodily pain	74 (51–84)
General health	57 (40–72)
Vitality	62.5 (50–75)
Social functioning	75 (50–100)
Role emotional	83.3 (58.3–100)
Mental health	70 (56–80)
Physical component summary score	49.73 (42.74–54.67)
Mental component summary score	48.34 (40.7–53.32)



physical, bodily pain, general health, vitality, social function, role emotional and mental health (Fig. 2). The only domain not significantly higher (better) in patients who met the criteria for LLDAS was physical function. Patients in LLDAS also had higher PCS and MCS scores (Table 3). After backward stepwise multiple linear regression adjustment for other variables, patients in LLDAS retained higher PCS scores ($p < 0.001$) and MCS scores ($p < 0.001$) (model 1, Table 4). These findings support the utility of LLDAS and its association with HR-QoL. Analysis of LLDAS individual components in multiple linear regression (model 2, Table 4) showed that a higher SLEDAI-2 K score ($p = 0.05$), PGA ($p < 0.001$) and prednisolone dose ($p = 0.01$) remained negatively associated with PCS scores, whereas disease flares did not have a significant association.

Only the PGA ($p = 0.02$) remained significantly negatively associated with MCS scores. Assessing individual organ activity instead of total SLEDAI-2 K score (model 3, Table 4) showed after adjustment that musculoskeletal activity ($p < 0.001$) remained negatively associated with PCS scores, and active cutaneous disease ($p = 0.04$) remained negatively associated with MCS scores.

Discussion

The ability to define an achievable treatment goal that is predictive of improved outcomes is essential for the implementation of treat-to-target strategies in SLE, and potentially has utility in the analysis of trials of current and novel therapies [19, 31]. Recently, the need to define

treatment goals for SLE has received increased attention [20], consequent upon which we reported the definition of a low disease activity treatment outcome state, LLDAS [21]. When disease activity and treatment domains are combined, both of which have been shown to contribute to an adverse long-term outcome in SLE, sustained attainment of LLDAS is associated with protection from accrual of damage over time, as measured using the SLICC-DI, in retrospective analysis of prospectively collected data [21]. Whether LLDAS is associated with measures of HR-QoL has not previously been assessed.

An important finding in the present study is the association between LLDAS and better HR-QoL, even after adjustment for other variables that were associated with HR-QoL. The LLDAS definition represents a composite tool with which patients with clinically diverse phenotypes can be stratified in a binary fashion, as either meeting criteria for LLDAS or not. This “reductionistic” approach takes advantage of the fact that the heterogeneity of disease expression in active SLE is, by definition, lessened as the disease activity lessens [18]. By combining different measures of clinical activity, and those of medication burden, the LLDAS is an encompassing measure of the overall clinical state of the patient, and emerging data confirm that the domains of LLDAS contribute independently to the stringency of the measure [32]. This means that LLDAS, rather than simply representing a description of mild disease, represents a composite treatment target state. Non-attainment of LLDAS could therefore reflect flare, refractory disease or insufficient treatment intensity, just as is the case with low disease activity definitions in RA. Given that improvement in HR-QoL is recognized as an important outcome measure in clinical trials [3, 8], the association between LLDAS and better SF-36 scores further supports its utility as a treatment target. Prospective studies showing that attainment of LLDAS is associated with improvements in HR-QoL over time are required, and are in progress.

In order to scrutinize the effects of the LLDAS components on HR-QoL, we utilized separate multiple linear regression models. SLEDAI-2 K, PGA and prednisolone dose (potentially a surrogate for activity) were each significantly and negatively associated with PCS scores, but only the PGA was negatively associated with MCS scores. Interestingly, disease flares as measured by the SFI were not significantly associated with either PCS or MCS scores. Of note, due to the cross-sectional nature of the analyses in this study, the SFI was used as a surrogate for the third criterion of LLDAS, which is that there must be no new features of lupus disease activity compared to the previous assessment [21]. It is possible that with longitudinal analysis, this LLDAS criterion may be significantly associated with HR-QoL.

The relationship between disease activity and HR-QoL in SLE remains controversial in the published literature [12, 25, 33–35], likely due to a combination of varying study designs, an inherently heterogeneous disease, different measures of activity and fluctuating disease states. Our study is the first to analyze HR-QoL in relation to individual organ system activity based on the SLEDAI. We observed a negative association between active musculoskeletal disease and poorer PCS, and between active cutaneous disease and poorer MCS scores. We consider that it makes clinical sense that active joint and muscle disease affects physical function, while cutaneous disease influences mental wellbeing; young women with SLE who comprise the majority of patients are known to suffer from poor body image [36]. An effect of renal activity on HR-QoL has been described by Appenzeller et al., who reported that patients with active renal disease had slightly poorer physical function, albeit with wide confidence intervals [37]. In contrast we found no significant association between active renal disease and any domains of the SF-36. Some organ involvement, such as lupus nephritis, may be inherently clinically silent in terms of HR-QoL, despite reflecting a serious threat to health.

Although undertaken in order to evaluate the association between LLDAS and HR-QoL, this is one of the largest studies to date of HR-QoL in patients with SLE, and as such it affords the opportunity to investigate other factors associated with HR-QoL in SLE. Patient characteristics, such as ethnicity, have previously been shown to be associated with various aspects of disease burden in SLE [38, 39], with Caucasian patients having lower disease activity but reporting poorer HR-QoL compared to their non-Caucasian counterparts [35, 40]. Studies from individual countries within the Asia Pacific region report poorer HR-QoL in patients with SLE compared to national averages [33], and negative associations with poorer socioeconomic status [26]. However, to date, between-country comparisons have been lacking.

We have demonstrated important regional and ethnic differences in HR-QoL. In our study, compared to Caucasians, patients of Asian ethnicity reported better PCS, even when adjusted for other variables, but no significant differences in MCS scores. Similar findings have been reported in different ethnic groups in Canada and the USA, with white ethnicity associated with poorer physical, but not mental function [4, 35]. The SF-36 has been cross-culturally validated to allow global comparisons, but it is unlikely that it is sensitive to all cultural and ethnic nuances. The significant difference in PCS and MCS scores between countries in our cohort, even when adjusted for ethnicity and disease factors, further highlights the importance of cultural differences in perception of the impact of disease and patients' coping strategies, which have been suggested to be just as important as

Table 3 Association of patient and disease characteristics with short form-36 component summary scores in simple linear regression

Variable	Physical component summary			Mental component summary		
	Coeff ^a	p	95% CI	Coeff ^a	p	95% CI
Country						
Australia	reference	-	-	1.06	0.01	1.01–1.10
China	1.14	<0.001	1.10–1.18	reference		
Indonesia	1.11	<0.001	1.06–1.16	1.06	0.04	1.01–1.12
Philippines	1.23	<0.001	1.18–1.28	1.20	<0.001	1.14–1.26
Singapore	1.14	<0.001	1.10–1.18	1.13	<0.001	1.08–1.18
Taiwan	1.14	<0.001	1.11–1.18	1.05	0.01	1.01–1.10
Thailand	1.12	<0.001	1.09–1.16	1.04	0.10	0.99–1.08
Ethnicity						
Caucasian	reference	-	-	reference	-	-
Asian	1.22	<0.001	1.18–1.26	1.03	0.19	0.99–1.08
Gender						
Female	reference	-	-	reference	-	-
Male	1.02	0.42	0.98–1.06	0.99	0.95	0.95–1.05
Education						
Primary	reference	-	-	reference	-	-
Secondary	1.05	0.001	1.02–1.08	1.01	0.47	0.98–1.05
Tertiary	1.09	<0.001	1.06–1.13	1.06	0.002	1.02–1.09
Age at diagnosis (years)	0.997	<0.001	0.996–0.998	1.00	0.76	0.998–1.001
Disease duration (years)	0.997	<0.001	0.996–0.999	1.00	0.07	0.999–1.003
SLEDAI score	0.994	<0.001	0.992–0.996	0.997	0.03	0.994–0.999
Current organ activity						
CNS	0.82	0.003	0.73–0.93	0.93	0.32	0.79–1.08
Renal	0.98	0.12	0.96–1.00	0.99	0.37	0.96–1.02
MSK	0.89	<0.001	0.86–0.93	0.95	0.03	0.91–0.99
Vasculitis	0.90	0.02	0.83–0.98	0.96	0.46	0.88–1.06
Cutaneous	0.97	0.02	0.94–0.99	0.94	0.001	0.92–0.98
Serositis	0.86	0.01	0.77–0.96	1.04	0.58	0.91–1.18
PGA (0–3)	0.94	<0.001	0.93–0.96	0.94	<0.001	0.93–0.96
Mild flare	0.95	0.002	0.92–0.98	0.98	0.25	0.94–1.02
Severe flare	0.89	<0.001	0.86–0.93	0.95	0.03	0.90–0.99
Prednisolone dose (mg)	0.998	<0.001	0.997–0.999	0.998	<0.001	0.997–0.999
LLDAS	1.04	<0.001	1.02–1.06	1.06	<0.001	1.04–1.09
SLICC-DI score	0.95	<0.001	0.94–0.96	0.99	0.43	0.99–1.01

^aCoefficient (Coeff) is based on the log-linear model and back-transformed using the exponential function. This represents (coeff-1)*100% increase/decrease in physical component summary or mental component summary scores for change in category (categorical variables), or (coeff-1)*100% change per one unit (continuous variables). Abbreviations: *SLEDAI* systemic lupus erythematosus disease activity index, *MSK* musculoskeletal, *PGA* physician global assessment, *LLDAS* lupus low disease activity state, *SLICC* Systemic Lupus International Collaborating Clinics, *DI* damage index, *CNS* central nervous system

disease states in determining HR-QoL in SLE [41]. The ability to cope better with illness was potentially reflected in the association between higher education and better summary scores, a finding supported by previous studies [4, 33]. However, this may also be indicative of patients with higher levels of education being employed in less

manually labor-intensive jobs, therefore with potentially a less noticeable impact on physical function.

Studies assessing the association between organ damage and HR-QoL have reported discrepant results. We identified significant association between greater damage and PCS scores, but not MCS scores, which is also seen

Table 4 Backward stepwise multiple linear regression for physical component summary (PCS) and mental component summary (MCS)

Model	Variable	Model 1				Model 2				Model 3			
		PCS		MCS		PCS		MCS		PCS		MCS	
		Coeff	<i>p</i>	Coeff	<i>p</i>	Coeff	<i>p</i>	Coeff	<i>p</i>	Coeff	<i>p</i>	Coeff	<i>p</i>
Model 1	Country												
	Australia	reference	-	1.05	0.10	reference	-	1.04	0.19	reference	-	1.06	0.08
	China	1.04	0.09	reference	-	1.06	0.02	reference	-	1.05	0.04	reference	-
	Indonesia	1.01	0.73	1.06	0.04	1.02	0.40	1.07	0.03	1.02	0.45	1.07	0.02
	Philippines	1.10	<0.001	1.17	<0.001	1.12	<0.001	1.18	<0.001	1.12	<0.001	1.19	<0.001
	Singapore	1.08	<0.01	1.12	<0.001	1.09	<0.001	1.12	<0.001	1.09	<0.001	1.13	<0.001
	Taiwan	1.06	0.01	1.04	0.08	1.07	<0.01	1.03	0.15	1.06	0.01	1.03	0.14
	Thailand	1.04	0.11	1.02	0.33	1.05	0.06	1.02	0.39	1.04	0.12	1.02	0.30
	Ethnicity												
	Caucasian	reference	-	reference	-	reference	-	reference	-	reference	-	reference	-
	Asian	1.10	<0.001	1.02	0.50	1.10	<0.001	1.02	0.62	1.10	<0.001	1.02	0.53
	Education												
	Primary	reference	-	reference	-	reference	-	reference	-	reference	-	reference	-
	Secondary	1.03	0.03	1.03	0.12	1.03	0.03	1.03	0.16	1.03	0.04	1.03	0.13
	Tertiary	1.05	0.002	1.06	<0.01	1.05	0.001	1.06	<0.01	1.05	0.001	1.06	<0.01
	Age at diagnosis (years)	0.997	<0.001	1.00	0.39	0.997	<0.001	1.00	0.39	0.997	<0.001	1.00	0.37
	Disease duration (years)	0.998	0.05	1.00	0.06	0.998	<0.01	1.00	0.08	0.998	<0.01	1.00	0.10
	SLICC-DI score	0.96	<0.001	0.99	0.13	0.96	<0.001	0.99	0.21	0.97	<0.001	0.99	0.15
	LLDAS	1.06	<0.001	1.05	<0.001	-	-	-	-	-	-	-	-
Model 2	SLEDAI score	-	-	-	-	0.997	0.05	1.00	0.35	-	-	-	-
	PGA (0–3)	-	-	-	-	0.95	<0.001	0.97	0.02	-	-	-	-
	Mild flare	-	-	-	-	0.98	0.26	0.98	0.25	-	-	-	-
	Severe flare	-	-	-	-	0.97	0.11	0.97	0.33	-	-	-	-
	Prednisolone (mg)	-	-	-	-	0.998	0.01	0.999	0.13	-	-	-	-
Model 3	Current organ activity												
	Renal	-	-	-	-	-	-	-	-	1.00	0.43	1.02	0.29
	MSK	-	-	-	-	-	-	-	-	0.93	<0.001	0.99	0.55
	Vasculitis	-	-	-	-	-	-	-	-	0.99	0.84	1.02	0.74
	Cutaneous	-	-	-	-	-	-	-	-	0.95	0.70	0.94	0.04
	Serositis	-	-	-	-	-	-	-	-	0.96	0.34	1.04	0.49
	PGA (0–3)	-	-	-	-	-	-	-	-	0.99	<0.001	0.97	0.03
	Mild flare	-	-	-	-	-	-	-	-	0.99	0.59	0.99	0.58
	Severe flare	-	-	-	-	-	-	-	-	0.96	0.04	0.98	0.36
	Prednisolone (mg)	-	-	-	-	-	-	-	-	0.998	<0.01	0.999	0.19

Variables with *p* values ≤ 0.1 in simple linear regression analysis were checked for multicollinearity prior to inclusion in the models. To account for different measures of disease activity and disease state that were collinear and to ascertain which of the LLDAS criteria contributed to the relationship with health-related quality of life, three models were used: Model 1 - disease state measured as lupus low disease activity state (LLDAS); Model 2 - breakdown of LLDAS into its individual components/criteria representing measures of disease activity – the systemic lupus erythematosus disease activity index (SLEDAI) score, physician global assessment (PGA), flare index and prednisolone dose; Model 3 - breakdown of SLEDAI score by current organ activity, and PGA, flare index and prednisolone dose. Common independent variables used in all three models are at the top of the table and include: country, ethnicity, education, age at diagnosis, disease duration and Systemic Lupus International Collaborating Clinics (SLICC)-damage index (DI) score. Coefficient (Coeff) is based on log-linear model and back-transformed using the exponential function. This represents (coeff-1)*100% increase/decrease in PCS or MCS scores for change in category (categorical variables), or (coeff-1)*100% change per one unit (continuous variables). Abbreviations: CNS (cntral nervous system, MSK musculoskeletal). *P* values in italics are significant

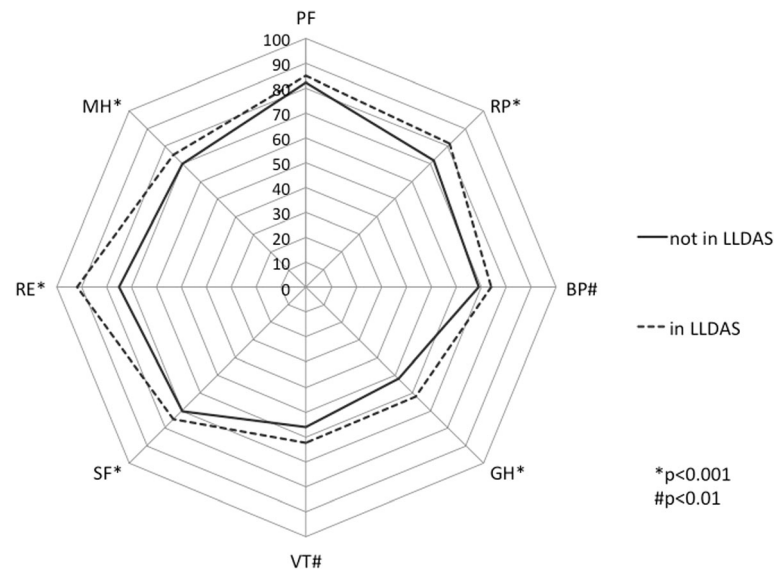


Fig. 2 Radar chart comparing short form-36 (SF-36) domain scores between patients in lupus low disease activity state (LLDAS) and those not in LLDAS. Each spoke on the radar chart represents an SF-36 domain on a scale of 0–100, with higher scores representing better health-related quality of life. The domains are: physical function (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), role emotional (RE), and mental health (MH). * $p < 0.001$; # $p < 0.01$ using the two-sample Wilcoxon rank-sum (Mann-Whitney) test

in the ethnically diverse LUMINA cohort [4]. Similarly, in a longitudinal study of Chinese patients from Hong Kong, Mok et al., showed that accrual of new damage predicted a decline in SF-36 scores [33]. In contrast, in a predominantly Caucasian population with low damage accrual over 8 years, no disease features were associated with decline in physical functioning except for the presence of fibromyalgia [35].

The lack of measurements to identify fibromyalgia and other comorbidities is one of the limitations of this study, as pain and fatigue have been shown to independently influence HR-QoL in patients with SLE [6, 10, 11]. Two domains of the SF-36, bodily pain and vitality, are potential surrogate measures for pain and fatigue respectively. Patients in LLDAS had significantly higher (better) scores in both of these domains, with the inference that LLDAS may be associated with a reduction in pain and fatigue. A disease-specific HR-QoL tool could further address the additional issues pertinent to patients with SLE and assess the effect of LLDAS on these; however, the currently available disease-specific instruments have not been validated in all the spoken languages of this multicultural cohort of patients.

Additionally, clear evidence of superiority is lacking among the multiple disease-specific HR-QoL tools [5]. The cross-sectional nature of the analyses does not allow the assessment of changes in HR-QoL with fluctuating disease states. However, given that the SF-36 is designed to capture HR-QoL in the preceding 4 weeks, the same

time frame as the evaluation of disease activity, it should be relevant to disease activity measures captured at the same time. A longitudinal study is underway, which will enable analysis of the association between LLDAS and transitions in HR-QoL measured by the SF36. Assessment of the effect of LLDAS on other PRO measures, such as patient assessment of disease activity, could form the basis of future validation studies.

Conclusions

In summary, we have shown for the first time that LLDAS is associated with better HR-QoL. This supports the validity of this definition of treatment outcome state for potential use in clinical practice, treat-to-target studies and clinical trials. This conclusion would be further supported by longitudinal studies, of which at least one is underway. In addition, we have described important ethnic, socioeconomic and disease-specific associations with HR-QoL in one of the largest multiethnic SLE cohorts ever studied. Attention to reversible or preventable precipitants of poor HR-QoL should be included in the management of SLE.

Additional file

Additional file 1: Table S1. Disease manifestations ever present. **Table S2.** Comparison of SF-36 domain scores by patient and disease characteristics (DOCX 19 kb)

Abbreviations

ACR: American College of Rheumatology; APLC: Asia Pacific Lupus Collaboration; BP: Bodily pain; CNS: Central nervous system; coeff: Coefficient; DI: Damage index; GH: General health; HR-QoL: Health-related quality of life; LLDAS: Lupus low disease activity state; MCS: Mental component score; MH: Mental health; MSK: Musculoskeletal; PCS: Physical component score; PF: Physical function; PGA: Physician global assessment; PRO: Patient-reported outcome; RE: Role emotional; RP: Role physical; SELINA: Safety of Estrogens in Lupus Erythematosus National Assessment; SF: Social function; SFI: Safety of Estrogens in Lupus Erythematosus National Assessment- systemic lupus erythematosus Erythematosus flare index; SLE: Systemic lupus erythematosus; SLEDAI: Systemic lupus erythematosus disease activity index; SLICC: Systemic Lupus International Collaborating Clinics; VT: Vitality

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Availability of data and materials

Reasonable requests to view the dataset used in this manuscript can be made in writing to the project manager for the Asia Pacific Lupus Collaboration - Dr Rangi Kandane-Rathnayake (rangi.kandane-rathnayake@monash.edu)

Authors' contributions

VG made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and drafting and revising the manuscript. RKR made substantial contributions to analysis and interpretation of data and to revising the manuscript critically for important intellectual content. AYBH made substantial contributions to acquisition of data and to revising the manuscript critically for important intellectual content. MH made substantial contributions to analysis and interpretation of data and revising the manuscript critically for important intellectual content. WL made substantial contributions to acquisition of data and to revising the manuscript critically for important intellectual content. YA made substantial contributions to acquisition of data and to revising the manuscript critically for important intellectual content. ZGL made substantial contributions to acquisition of data and to revising the manuscript critically for important intellectual content. SFL made substantial contributions to acquisition of data and to revising the manuscript critically for important intellectual content. SS made substantial contributions to acquisition of data and to revising the manuscript critically for important intellectual content. CSL made substantial contributions to conception and design, acquisition of data and revising the manuscript critically for important intellectual content. MYM made substantial contributions to acquisition of data and to revising the manuscript critically for important intellectual content. AL made substantial contributions to acquisition of data and to revising the manuscript critically for important intellectual content. KF made substantial contributions to acquisition of data and to revising the manuscript critically for important intellectual content. SM made substantial contributions to acquisition of data and to revising the manuscript critically for important intellectual content. STVN made substantial contributions to conception and design, acquisition of data and revising the manuscript critically for important intellectual content. LZ made substantial contributions to acquisition of data and to revising the manuscript critically for important intellectual content. YJW made substantial contributions to acquisition of data and to revising the manuscript critically for important intellectual content. LH made substantial contributions to acquisition of data and to revising the manuscript critically for important intellectual content. MC made substantial contributions to acquisition of data and to revising the manuscript critically for important intellectual content. SON made substantial contributions to acquisition of data and to revising the manuscript critically for important intellectual content. FG made substantial contributions to acquisition of data and to revising the manuscript critically for important intellectual content. MN made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and drafting and revising the manuscript. EFM made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and drafting and revising the manuscript. All authors have given approval for the final version of the manuscript to be published. All

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Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Each center obtained ethics committee approval for the study and written informed consent from each patient. Overarching ethics approval for data collection, analysis and publication of data collected by the Asia Pacific Lupus Collaboration was given by the Monash University Human Research Ethics Committee (Project Number: CF15/1617 – 2015000817).

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Chapter 5

Does expert opinion match the operational definition of the Lupus Low Disease Activity State (LLDAS)? A case-based construct validity study.

Introduction

As well as criterion validity which was tested in chapters 4, 6 and 7 of this thesis, testing of construct validity contributes to the assessment of the overall robustness of LLDAS as a treat to target endpoint. Construct validity describes the degree to which an instrument measures what it claims to measure. In the case of LLDAS it is the degree to which the operational definition matches the conceptual definition.

In order to be able to quantify whether the conceptual definition of LLDAS was well captured by the operation definition, we presented it to 50 SLE experts who were not aware of the operational definition. We asked the experts to assess 50 clinical scenarios whilst keeping the conceptual definition in mind and grade the disease activity of each case as remission, low, moderate or high. These same cases were independently assessed to see if they met the operational definition of LLDAS, thus allowing assessment of the agreement between expert opinion, as a quantified surrogate of the conceptual definition, and the operational definition of LLDAS.

Findings

The published manuscript in this chapter “Does expert opinion match the operational definition of the Lupus Low Disease Activity State (LLDAS)? A case-based construct validity study”, describes the results in detail. A summary of the key findings is outlined below:

- The overall agreement between expert opinion and the operational definition of LLDAS approached 80%, supporting the construct validity of LLDAS.
- Of the cases that met the operational definition of LLDAS only 5.34% of responses classified disease activity as moderate/high. This suggests that LLDAS does not inappropriately capture patients with active disease. In contrast, of the cases that did not fulfill the operational definition of LLDAS, 35.14% of responses classified the cases as remission/low activity state. This suggests that LLDAS is more stringent than expert opinion.
- Common reasons for disagreement were expert acceptance of higher corticosteroid doses for cases they classified as remission/low disease activity than is defined in LLDAS (prednisolone $\leq 7.5\text{mg}$) and the importance of serological disease activity when evaluating overall disease status.

Implications

This study supports the construct validity of LLDAS as a treat to target endpoint. Moreover, I was able to show that LLDAS was a more stringent measure than expert opinion whilst not inappropriately capturing patients who should not be considered to have a low disease activity state.

The results of this study were presented at multiple national and international scientific meetings, as well as being published in a peer reviewed journal:

Golder V., Huq M., Franklyn K., Calderone A., Lateef A., et al. *Does expert opinion match the operational definition of the Lupus Low Disease Activity State (LLDAS)? A case based construct validity study.* Seminars in Arthritis and Rheumatism, 2017; 46(6):798

Future directions

An interesting observation in this study was the threshold of glucocorticoid dose deemed acceptable by SLE experts in patients they assigned to remission or low disease activity states, despite known evidence of the independent contribution of steroid use to damage accrual. Whether this is a reflection of the current therapeutic climate in SLE and the reliance on glucocorticoids to control disease activity is not known.



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journal homepage: www.elsevier.com/locate/semarthritDoes expert opinion match the operational definition of the Lupus Low Disease Activity State (LLDAS)? A case-based construct validity study[☆]

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ABSTRACT

Objective: To evaluate the construct validity of the Lupus Low Disease Activity State (LLDAS), a treatment target in systemic lupus erythematosus (SLE).

Methods: Fifty SLE case summaries based on real patients were prepared and assessed independently for meeting the operational definition of LLDAS. Fifty international rheumatologists with expertise in SLE, but with no prior involvement in the LLDAS project, responded to a survey in which they were asked to categorize the disease activity state of each case as remission, low, moderate, or high. Agreement between expert opinion and LLDAS was assessed using Cohen's kappa.

Results: Overall agreement between expert opinion and the operational definition of LLDAS was 77.96% (95% CI: 76.34–79.58%), with a Cohen's kappa of 0.57 (95% CI: 0.55–0.61). Of the cases (22 of 50) that fulfilled the operational definition of LLDAS, only 5.34% (59 of 22 × 50) of responses classified the cases as moderate/high activity. Of the cases that did not fulfill the operational definition of LLDAS (28 of 50), 35.14% (492 of 28 × 50) of responses classified the cases as remission/low activity. Common reasons for discordance were assignment to remission/low activity of cases with higher corticosteroid doses than defined in LLDAS (prednisolone ≤ 7.5 mg) or with SLEDAI-2K > 4 due to serological activity (high anti-dsDNA antibody and/or low complement).

Conclusions: LLDAS has good construct validity with high overall agreement between the operational definition of LLDAS and expert opinion. Discordance of results suggests that the operational definition of LLDAS is more stringent than expert opinion at defining a low disease activity state.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic multi-organ autoimmune disease that has historically lacked clear definitions with which to guide treat-to-target approaches. SLE has a broad spectrum of clinical manifestations and a variable disease course with periods of relative inactivity contrasted by disease flare, as well as a proportion of patients with persistently active disease [1]. The heterogeneous nature of disease makes disease activity more difficult to define than for other autoimmune conditions. Current instruments used to measure disease activity and treatment

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response are complex [2], contributing to mixed results from clinical trials of new targeted therapies [3]. Moreover, the lack of a clear treatment target state has implications for routine clinical care of SLE with a high degree of variation in treatment regimens, particularly with regard to long-term use of glucocorticoids [4]. This has led to a call for new definitions of treatment target states for use both in clinical trials and routine clinical practice [5].

Using the strict definition of remission as a treatment target in SLE is not pragmatic, given that only 2–4% of patients achieve this for any prolonged period of time [6,7]. In contrast, a minimally active disease state in SLE may be more achievable than remission, yet still associated with improved long-term outcomes, as has been shown in rheumatoid arthritis (RA) [8]. Additionally, SLE patients with low or minimal disease activity on stable therapy become clinically more homogenous and easier to define as a group, making a low disease activity state an attractive treatment target for SLE [5]. Defining a low disease activity state to use as a treatment target for SLE was recently set as a research agenda in an international consensus statement [9].

The Asia-Pacific Lupus Collaboration (APLC) has recently developed and retrospectively validated the Lupus Low Disease Activity State (LLDAS) definition [10]. The conceptual definition of LLDAS is a state, which if sustained, is associated with a low likelihood of adverse outcomes, considering both disease activity and medication safety. The operational definition of LLDAS is fulfilled when all of the following criteria are met: (i) SLE Disease Activity Index (SLEDAI-2K) ≤ 4 , with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, and fever) and no hemolytic anemia or gastrointestinal activity; (ii) no new features of lupus disease activity compared to the previous assessment; (iii) a SELENA-SLEDAI physician global assessment (PGA, scale 0–3) ≤ 1 ; (iv) a current prednisolone (or equivalent) dose ≤ 7.5 mg daily, and (v) well-tolerated standard maintenance doses of immunosuppressive drugs and approved biologic agents, excluding investigational drugs. In a retrospective cohort analysis, Franklyn et al. [10] showed that patients who spent greater than 50% of their disease duration in LLDAS accrued significantly less damage compared to patients who did not, with current work underway to prospectively validate the association of LLDAS with improved long-term outcomes.

Before acceptance in clinical practice and research, any new measure should undergo rigorous validation including face, content, construct, and criterion validity. The objective of this study was to assess the construct validity of LLDAS by testing its operational definition against SLE expert opinion.

Materials and methods

Sample size calculation

We calculated the number of paired case-expert responses needed for different levels of agreement, taking into account the proportion of expected patients in each category of disease activity state (e.g., remission (20%), low (40%), moderate (20%), and high (20%)). With 50 cases and 50 independent raters, the study had 80% power at the 5% level of significance to reliably estimate an overall agreement of 40% or higher and a Cohen's kappa of 0.2 or higher.

SLE cases summaries

Fifty de-identified SLE case summaries, based on real patient information, summarized without manipulation, were prepared by five experts from the APLC. Ethics approval for this study was obtained from the Human Research Ethics Committee of St.

Table 1
Patient and respondent characteristics

Patients (n = 50)	n (%) or mean (SD) or median (IQR: 25th–75th)
Female gender	41 (82)
Age (years)	38.2 (13.8)
Disease duration (years)	10.2 (7.4)
Disease manifestations (ever present) ^a	
Malar rash	27 (54)
Discoid rash	6 (12)
Photosensitivity	15 (30)
Mouth ulcers	19 (38)
Arthritis	30 (60)
Serositis	10 (20)
Renal	25 (50)
Neurologic	8 (16)
Hematologic	26 (52)
Immunologic	45 (90)
ANA	49 (98)
SLEDAI-2K	5.6 (5.5)
PGA	0.5 (0.3–1.4)
Current hypocomplementaemia ^b	29 (58)
Current elevated dsDNA ^c	35 (70)
Prednisolone (n taking)	34 (68)
Prednisolone (dose, mg)	7.8 (11.6)
Hydroxychloroquine (n taking)	38 (76)
Other immunosuppressant (n taking)	34 (68)
Respondents (n = 50)	n (%)
Continent	
North America	11 (22)
South America	4 (8)
Europe	24 (48)
Asia	5 (10)
Australia	6 (12)
Years of medical practice	
0–10 years	6 (12)
11–20 years	11 (22)
21–30 years	21 (42)
> 30 years	12 (24)
Number of SLE patients seen in the last 12 months	
0–30	2 (4)
31–50	6 (12)
51–100	10 (20)
> 100	32 (64)

Abbreviations: SLE, systemic lupus erythematosus; ACR, American College of Rheumatology; SLEDAI, SLE disease activity index; PGA, physician global assessment; ANA, antinuclear antibody; dsDNA, double stranded DNA.

^a Ever present based on ACR criteria. Arthritis (two or more joints with tenderness, swelling or effusion), serositis (pleuritis or pericarditis), renal disorder (persistent proteinuria > 0.5 g per day, or presence of cellular casts), neurologic disorder (seizures or psychosis not attributable to other causes), hematologic disorder (hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia), immunologic criteria (presence of anti-dsDNA antibody, anti-Sm antibody, or positive finding of antiphospholipid antibodies).

^b Hypocomplementaemia—decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.

^c Elevated dsDNA— $> 25\%$ Farr assay or above normal range for testing laboratory.

Vincent's Hospital Melbourne (approval number LRR071/15). Each case was based on a current adult patient attending routine ambulatory care, who fulfilled criteria for SLE [either the 1997 American College of Rheumatology (ACR) criteria [11] or the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria [12]]. The cases included all common clinical presentations of SLE (Table 1). Each case was presented in the same format and included basic demographic descriptors (sex, age, and occupation), detailed past history of SLE, current disease features, current

treatment, and investigation results. Each of the cases is available in the [Supplementary material](#).

Survey respondents

Contact details for rheumatologists with expertise in SLE were sourced from the SLICC group and an international treat-to-target task force [9]. An invitation to participate was emailed to 116 SLE experts, with 50 experts from multiple centres and countries across the world providing complete responses (see list of contributors). None of the respondents were previously involved with the APLC and the survey responses were collected in October 2015, prior to the publication of the operational definition of LLDAS [10].

Expert opinion survey

The survey was presented to the experts in electronic format using SurveyMonkey. The full transcript of the survey and the cases is available as [Supplementary material](#). The respondents were given the conceptual but not the operational definition of LLDAS in the introduction of the survey, as well as detailed instructions for completion. The conceptual definition of LLDAS was given as follows: “a state which if sustained, is associated with a low likelihood of adverse outcome, considering both disease activity and medication safety.” The respondents were first asked to complete contact and demographic details including years of experience, type of clinical practice, and number of SLE patients seen per annum. The case summaries were then presented in a unique random order to each expert. After reading a case summary, each respondent was asked to complete two questions: first to assess the patient's current disease *activity* using a PGA on a scale of 0–3, where 0 is no disease activity and 3 is severe disease activity; and second to rate the patient's current *state* as remission, low, moderate, or high, taking into account both current disease manifestations and treatment burden.

Assessment of the cases took approximately 1 h to complete, and respondents were able to move forward and back between cases, and login multiple times until full completion of the survey. Only completed surveys were used in data analysis, and reminders were sent until 50 complete responses were collected.

Data analysis

Two investigators from the APLC independently assessed whether each case met the operational definition of LLDAS. First, the SLEDAI-2K and presence of any new disease activity was calculated for each case based on the clinical information provided. The PGA was taken as the median score of expert survey responses, as the PGA responses were not normally distributed. Current treatment including prednisolone dose and other immunosuppressive medications were available in each case summary. The investigators then independently classified each case as either being in LLDAS or not using the operational definition. There was no disagreement between the assessors.

Pooled data were analyzed using STATA v14 (StataCorp., College Station, TX). Given that the operational definition of LLDAS sets a ceiling for disease activity, remission is subsumed under this definition, and therefore we considered respondent designation of either remission or low to be equivalent to LLDAS. Therefore, respondent assessments of global disease activity state were grouped into remission/low or moderate/high, and compared to the operational definition of LLDAS in a two-by-two table. Agreement between expert opinion and the operational definition of LLDAS was assessed using Cohen's kappa. Cases where there was > 20% disagreement between respondent assessment and LLDAS were further analyzed to determine which of the LLDAS criteria

Table 2

Expert classification of SLE disease state

Disease state, n = 2500 unique responses	n (%)
Remission	568 (23%)
Low activity	965 (39%)
Moderate activity	646 (26%)
High activity	318 (13%)

Abbreviation: SLE, systemic lupus erythematosus.

contributed most to the disagreement ([Supplementary Tables 1 and 2](#)). Subsequently, two of the LLDAS criteria were adjusted to see if agreement was affected: prednisolone dose ≤ 7.5 mg daily was adjusted to prednisolone dose ≤ 10 mg daily; and SLEDAI-2K ≤ 4 was adjusted to SLEDAI-2K ≤ 3 excluding serological activity (hypocomplementemia and/or elevated ds-DNA).

Results

Patient and respondent characteristics

In total, 50 SLE expert respondents assessed 50 case summaries each, providing 2500 unique responses. Of the case summaries, 82% of patients were female, with a mean (\pm standard deviation) age of 38.2 (± 13.8) years and mean disease duration of 10.2 (± 7.4) years ([Table 1](#)). More than half of the cases had a previous history of cutaneous (malar, discoid, or photosensitive rash), musculoskeletal, hematologic, and immunologic manifestations; and exactly half of the cases had a history of lupus nephritis. The mean SLEDAI-2K as calculated from the cases by the independent assessors was 5.6 (± 5.5), with a median respondent generated PGA of 0.5 (0.3–1.4). Thirty-four (68%) of the cases were taking prednisolone, with a mean daily dose of 7.8 mg (± 11.6).

A total of 30% of the respondents were from the Americas, 48% from Europe, and the remainder from Asia (10%) and Australia (12%) ([Table 1](#)). The vast majority of respondents had been

Table 3

Lupus Low Disease Activity State (LLDAS) frequency

Descriptors of disease activity	n (%), n = 50 cases
1. SLEDAI-2K ≤ 4 , with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, hemolytic anemia, and fever) and no gastrointestinal activity	30 (60%)
2. No new features of lupus disease activity compared to the previous assessment	34 (68%)
3. SLENA-SLEDAI physician global assessment (PGA, scale 0–3) $\leq 1^a$	32 (64%)
Immunosuppressive medications	
4. Current prednisolone (or equivalent) dose ≤ 7.5 mg daily	34 (64%)
5. Well-tolerated standard maintenance doses of immunosuppressive drugs and approved biologic agents, excluding investigational drugs ^b	44 (88%)
All five criteria present (LLDAS)	22 (44%)

Abbreviations: CNS, central nervous system; LLDAS, Lupus Low Disease Activity State; PGA, physician global assessment; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index.

^a Based on the median PGA of survey respondents for each case.

^b Calculated as not exceeding maximum recommended dose: hydroxychloroquine ≤ 400 mg; methotrexate ≤ 30 mg; azathioprine ≤ 200 mg; mycophenolate mofetil ≤ 3000 mg; mycophenolic acid ≤ 2160 mg; leflunomide ≤ 20 mg.

Table 4
Cross-tabulation of expert assessment of disease state and LLDAS

Expert assessment of disease state (n = 2500)	LLDAS ^a	
	Yes	No
Remission/low	1041 (94.66%)	492 (35.14%)
Moderate/high	59 (5.34%)	908 (64.86%)

Abbreviations: LLDAS, Lupus Low Disease Activity State.

^a For operational definition of LLDAS please see Table 3.

in practice for > 10 years and saw > 100 SLE patients per annum each.

Respondent assessment of disease activity and disease state

There was variation in respondents' assessment of PGA, with an interquartile range of > 1 for 33 (66%) cases (Supplementary Table 1). Overall, 568 responses (23%) classified cases as remission, 956 (39%) as low activity state, 646 (26%) as moderate activity state, and 318 (13%) as high activity state (Table 2).

Frequency of meeting operational criteria for LLDAS

All of the cases fulfilled at least one criterion for LLDAS. The frequency of individual criteria ranged from 60% for SLEDAI-2K ≤ 4 and no activity in major organ systems, to 88% for well-tolerated standard doses of immunosuppressive medications. All five criteria for LLDAS were fulfilled in 44% of cases (Table 3).

Agreement

Overall agreement between expert opinion and the operational definition of LLDAS was 77.96% (95% CI: 76.34–79.58%), with a Cohen's kappa of 0.57 (95% CI: 0.55–0.61) (Table 5). Of the cases (22 of 50) that fulfilled the operational definition of LLDAS, only 5.34% (59 of 22 × 50) of responses classified the cases as moderate/high activity state. In contrast, of the cases that did not fulfill the operational definition of LLDAS (28 of 50), 35.14% (492 of 28 × 50) of responses classified the cases as remission/low activity state (Table 4).

Individual cases with > 20% discordance among respondents were further assessed to ascertain which of the LLDAS criteria

Table 5
Agreement between expert opinion and operational definition of LLDAS

	Agreement (95% CI)	Cohen's kappa (95% CI)
LLDAS original operational definition ^a	77.96% (76.34–79.58%)	0.57 (0.55–0.61)
LLDAS modified (a) SLEDAI-2K ≤ 3 excluding serology	80.44% (78.89–81.99%)	0.60 (0.59–0.66)
LLDAS modified (b) prednisolone ≤ 10 mg	82.76% (81.28–84.24%)	0.65 (0.64–0.70)
LLDAS modified (a) and (b) ^b	84.28% (82.85–85.71%)	0.68 (0.67–0.73)

(a) LLDAS criterion 1 modified to: SLEDAI-2K ≤ 3 excluding serological activity (complement and dsDNA), with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, hemolytic anemia, and fever) and no gastrointestinal activity.

(b) LLDAS criterion 4 modified to: current prednisolone (or equivalent) dose ≤ 10 mg daily.

Abbreviations: CNS, central nervous system; dsDNA, double stranded DNA; LLDAS, Lupus Low Disease Activity State; SLEDAI, systemic lupus erythematosus disease activity index.

^a For operational definition of LLDAS please see Table 3.^b LLDAS criteria 1 and 4 modified as above.

respondents disagreed with. Common reasons for discordance were respondent assignment to remission/low activity states of cases with higher corticosteroid doses than defined in LLDAS (prednisolone ≤ 7.5 mg) or where SLEDAI-2K in the case exceeded 4 due to presence of accompanying serological activity (high anti-dsDNA antibody and/or low complement) (Supplementary Table 1). Five of the cases (10%) were not in LLDAS based on prednisolone dose only, and 2 cases (4%) were not in LLDAS based on serological activity and minor clinical activity (Supplementary Table 2).

Adjusting the LLDAS prednisolone criterion from ≤ 7.5 mg to ≤ 10 mg increased the agreement from 77.96% to 82.76% (95% CI 81.28–84.24%), and adjusting the LLDAS SLEDAI criterion from ≤ 4 to ≤ 3 excluding serological activity increased the agreement to 80.44% (95% CI 78.89–81.99%) (Table 5). Combining these two adjustments to the LLDAS definition increased the agreement to 84.28% (95% CI: 82.85–85.71%).

Discussion

A treat-to-target approach through attainment of target clinical states has become the gold standard of treatment for many chronic conditions such as heart disease, diabetes, and RA [5]. Attainment of a predefined clinical target in the form of a low disease activity state for RA, has been shown to be associated with improved long-term outcomes [8]. The ability to clearly define an attainable treatment goal that is predictive of improved outcomes is essential for the implementation of treat-to-target strategies in SLE, as well as potentially being useful as an endpoint measure in the analysis of clinical trials of new therapies [9,13]. Using a definition combining disease activity and treatment domains, both of which have been shown to contribute to irreversible damage in SLE [14,15], the attainment of LLDAS was shown to be associated with protection from accrual of damage [10]. Damage accrual is an appropriate endpoint for the assessment of a proposed treatment target, as pre-existing damage propagates further damage accrual [14], and this is known to be associated with increased mortality [16]. However, prior to acceptance as a treatment target in clinical research and patient care, any new endpoint should undergo thorough validation. In this study, the authors assessed the construct validity of LLDAS by comparing its operational definition against expert opinion.

The overall agreement between expert opinion and the operational definition of LLDAS was very good, approaching 80% in this study. This suggests that expert perception or “gut feeling” of disease state is not dissimilar to our criteria-driven definition. On the other hand, we have shown that the definition of LLDAS is more stringent than expert opinion, with the majority of disagreement observed in cases where experts assigned cases to a low disease activity state or remission, but patients did not meet criteria for LLDAS. Despite being more stringent than expert opinion, LLDAS remains a considerably more frequently attained treatment endpoint than remission [10]. Perhaps most importantly, there were very few instances where respondents classified cases as moderate/high activity state when the definition of LLDAS was fulfilled. This is a desirable attribute for a measure that is by definition designed to encompass a low activity state associated with improved outcomes, and exclude patients with unacceptable disease activity or treatment burden.

Analysis of cases with a high percentage of disagreement revealed that in many instances, respondents accepted a higher dose of prednisolone than is defined in the criteria for LLDAS. In the five cases where LLDAS was not met based solely on the prednisolone dose criterion, the dose was between 7.5 and 10 mg, suggesting that up to 10 mg of prednisolone was deemed

acceptable by many respondents. Because of their rapid and broad anti-inflammatory and immunosuppressive effects [17], and the lack of highly efficacious targeted therapies for SLE, patients are often treated long-term with maintenance glucocorticoids in addition to non-specific immunosuppressive medication. While a “safe” maintenance prednisolone dose in SLE remains under debate, studies assessing prednisolone use in rheumatic disease have shown that doses as little as 5 mg daily significantly increase the risk of osteoporosis [18], impaired glucose tolerance [19], and infections [20]. Recent literature and studies underway are challenging the need for long-term glucocorticoid use in SLE [4,21,22]. Given that prednisolone doses of > 7.5 mg have been shown to be associated with increased cardiovascular risk and independently contribute to damage accrual in SLE [14,15,23,24], and that only doses of 6 mg or less were associated with freedom from significant impact on damage accrual in one large cohort study [25], we consider doses of prednisolone > 7.5 mg as not being in line with good long-term outcomes.

Another area in which respondents did not agree with LLDAS criteria was serological activity. Serological activity in the form of hypocomplementemia and elevated dsDNA results in a SLEDAI-2K score of 4, meaning that the presence of any other manifestation in the same patient will exceed the threshold for fulfilling LLDAS. Our findings suggest that respondents placed lower weight on serological than on clinical phenomena in their assignment to low disease activity state or remission. “Serologically active clinically quiescent” (SACQ) disease is a well-described entity in SLE [26], with some literature suggesting a proportion of SACQ patients can spend years without emergence of new disease features [27], while others may flare [28,29]. It is not known whether attainment of LLDAS or SACQ is superior with regard to protection from damage accrual. The APLC is undertaking a large multicenter prospective validation study of the LLDAS operational definition, and future analyses may shed further insights into this discrepancy.

An important observation in this study is the wide spread of PGA scores among respondents, suggesting high inter-rater variability. Additionally, a recent study has shown that intra-rater PGA assessment differs when assessed before vs. after knowledge of laboratory results [30]. While subjective, the inclusion of PGA has been useful in capturing aspects of activity not measured by the SLEDAI-2K, and has been shown to correlate with other indices of disease activity [31], which is why it remains included as a criterion for LLDAS and in many composite measures [5]. This study has illustrated that the interpretation of PGA must be done with caution, taking into account the high inter and intra rater variability. Further analysis of the value of inclusion of PGA in an outcome measure such as LLDAS is required, ideally based on analysis of hard outcomes data.

Individual interpretation of case summaries by respondents and resultant attribution to disease severity are limitations of this study. Likewise, respondent assignment of disease state was based on paper case summaries. In real life, clinicians will have the patient and clinical records to provide additional or historical information that may influence their final assessment of disease state. However, expert assessment of real patients would be logistically impossible to perform as a validity study in order to achieve the required sample size.

In conclusion, we have shown in a large study that the operational definition of LLDAS has excellent construct validity when compared to expert opinion. Very few patients who met LLDAS criteria were assigned to high disease activity states by respondents, and the LLDAS criteria were more stringent than expert opinion. The discrepancies between operationally based and respondent assignment of low disease activity relate mostly to variability in SLE clinicians' threshold of acceptability for

glucocorticoid doses and serological activity in evaluating disease status. Further validation of the LLDAS definition based on its ability to be associated with protection from long-term adverse outcomes such as damage accrual is under way in a large prospective longitudinal study. Data from this study will also be used to determine whether any refinement of the LLDAS definition meaningfully improves its ability to predict protection from damage accrual. Until then, demonstration of construct validity is another milestone in the journey toward the employment of empirically derived treatment outcomes in SLE.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.semarthrit.2017.01.007>.

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Chapter 6

Lupus Low Disease Activity State: a prospective validation study.

Introduction

In the preceding chapters I described studies assessing the construct and criterion validity of LLDAS as a treat to target endpoint. Notwithstanding validation in numerous retrospective analyses of high-quality cohorts, only a prospective study, designed specifically for the purpose of validation against hard outcomes, would ensure that the LLDAS definition is stringently validated, allowing it to be accepted for use in clinical practice as a T2T goal, and in SLE clinical trials as an outcome measure.

The study presented in this chapter is the 'pièce de résistance' in the validation process of LLDAS to date, providing evidence that attainment of LLDAS is associated with reduced disease flares and damage accrual in a large multinational cohort of patients with SLE.

Findings

The submitted manuscript in this chapter "Prospective Validation of the Lupus Low Disease Activity State - a Treat to Target Endpoint for Systemic Lupus Erythematosus", describes the results in detail. A summary of the key findings is outlined below:

- 1,707 patients were followed for (mean \pm SD) 2.2 ± 0.9 years, totalling 12,689 visits
- 78% of patients were able to attain LLDAS at least once, with just under half of all visits (48%) fulfilling criteria for LLDAS. Two thirds of patients were able to sustain LLDAS for ≥ 3 months.

- Attainment of LLDAS at any timepoint was associated with protection against subsequent flare and damage accrual.
- Patients who spent $\geq 50\%$ of their observed time in LLDAS had a highly significant reduction in risk of flare and damage accrual, compared to those with $< 50\%$ of observed time in LLDAS. A threshold of only $\geq 20\%$ was identified as significantly protective.
- Increased durations of sustained LLDAS were associated with incremental reductions in the risk of damage accrual.
- LLDAS attainment was associated with significant protection from damage accrual even in patients who were enrolled with active disease (SLEDAI2K ≥ 6). Despite the expected lower attainment of LLDAS in patients with higher disease activity at baseline, the magnitude of association of LLDAS with protection against damage was greater in this subgroup of patients compared to those with less active baseline disease.

Implications

With the completion of this study, LLDAS represents a robustly validated treatment endpoint.

Aiming to achieve and maintain LLDAS in clinical practice has the potential to improve outcomes for lupus patients, and use of LLDAS as an end-point in clinical trials of novel therapies or in treatment target studies may change the landscape of therapeutic approaches for SLE.

The results of this study have been presented at multiple national and international scientific meetings, including a plenary presentation at the 2018 American College of Rheumatology annual scientific meeting. It has been accepted for publication at a peer reviewed journal:

Golder V., Kandane-Rathnayake R., Huq M., Nim H. et al. *Lupus Low Disease Activity State: a prospective validation study*. Lancet Rheumatology, accepted July 2019.

Future direction

Longer term studies assessing the relationship between LLDAS attainment and maintenance and patient outcomes are currently in process. Moreover, with ongoing data collection the APLC cohort now represents one of the largest contemporary SLE cohorts in the world, with vast amount of available data that can be used to research questions beyond that of LLDAS validation. A comprehensive list of possible future studies is described in Chapter 8.

Lupus Low Disease Activity State: a prospective validation study.

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Research in context

Evidence before this study

Treat to target (T2T) strategies, whereby disease status is measured against predefined endpoints in order 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 lack a single clinical or laboratory marker, and consequently no treatment endpoint required for the adoption of T2T approaches has previously been defined for systemic lupus erythematosus (SLE).

The Asia Pacific Lupus Collaboration (APLC) was established to generate evidence supporting new endpoints for SLE. Previously, we 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’, and used Delphi and nominal consensus techniques to derive a composite measure with strong face and content validity. 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 T2T or trial endpoint, definitive evidence is required that attainment of LLDAS is associated with improved patient outcomes.

Added value of this study

This is the first prospective study designed specifically to validate a low disease activity endpoint in SLE.

In a large multinational cohort (n=1,707 patients enrolled, with n=12,717 visits), we have demonstrated that LLDAS has both utility – it is attainable; and validity – attainment of LLDAS 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 analysis 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 T2T strategies in complex multiorgan disease, and paves the way for LLDAS to become a standard measure in future SLE clinical trials, T2T studies, and clinical practice.

Abstract

Background: Treat-to-target (T2T) strategies have improved outcomes in single organ diseases with simple clinical or laboratory endpoints. A lack of validated endpoints has prevented adoption of T2T for complex multi-organ conditions, such as systemic lupus erythematosus (SLE). We report the first prospective study undertaken to specifically validate a T2T endpoint for SLE.

Methods: A multinational cohort of adults with SLE was enrolled and followed prospectively by protocol between 2013-2016. The association of Lupus Low Disease Activity State (LLDAS) attainment with flare or accrual of irreversible end-organ damage was assessed using time-dependent hazard regression models and generalised linear models.

Findings: 1,707 patients were recruited and followed for (mean \pm SD) 2.2 ± 0.9 years, totalling 12,689 visits. Attainment of LLDAS at any timepoint was associated with reduction in subsequent flare (HR 0.65, 95%CI 0.56-0.75, $p < 0.001$) and damage accrual (HR 0.59, 95%CI 0.45-0.76, $p < 0.001$). Cumulative time in LLDAS was associated with improved outcomes; compared to patients with $< 50\%$ of observed time in LLDAS, those with $\geq 50\%$ of observed time in LLDAS had reduced risk of flare (HR 0.41, $p < 0.001$) and damage accrual (HR 0.59, $p < 0.001$). 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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GlaxoSmithKline, Janssen, Bristol-Myers Squibb and AstraZeneca.

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with a significant morbidity and mortality burden driven by accrual of irreversible end-organ damage. In contrast to 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 (T2T) approaches have had significant impact in the management of chronic diseases such as hypertension, diabetes and rheumatoid arthritis (RA), with attainment of treatment endpoints measurable in single organ systems shown to associate with improved outcomes.^{3,4} In 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 T2T 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 While remission remains the ultimate goal of treatment, with current therapies, sustained remission in SLE is rare,⁶ and hence remission definitions remain in evolution.⁷ In 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, more simply measured than existing disease activity scales. The Asia Pacific Lupus Collaboration (APLC) has proposed such an endpoint, the Lupus Low Disease Activity State (LLDAS), which includes domains capturing the absence of organ threatening disease activity and harmful treatment burden.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 for its adoption 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 population and design

We conducted a prospective cohort study (NCT03138941) from 2013 to December 2016. Consecutive prevalent SLE patients aged ≥ 18 who fulfilled standardised criteria for classification of SLE,^{11,12} were recruited from 13 centres of the APLC, and patients with ≥ 2 visits were included in longitudinal analysis. Data were collected during routine patient follow-up using standardised data-collection forms. Minimum required visit frequency was six-monthly, with the majority of patients having more frequent visits based on clinical need. Loss to follow-up was defined as no visit within the last year of study. Each institution obtained ethics approval and informed patient consent.

Variables

At the baseline visit, demographic and disease characteristics were collected, including gender, 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 (SLEDAI-2K),¹³ modified as per Thanou *et al.*,¹⁴ and a physician global assessment (PGA) 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. LLDAS requires all five of the following criteria: a SLEDAI-2K ≤ 4 with the absence of any disease activity in major organ systems; absence of new-onset disease activity in any system (measured as any new SLEDAI-2K item compared to the previous visit); a PGA ≤ 1 ; prednisolone ≤ 7.5 mg daily and standard doses of immunosuppressants;⁸ anti-malarial medications are permitted.

Scoring of LLDAS is provided in Table 1. Mild/moderate and severe flares were captured using the SELENA flare index (SFI), 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 SLICC-ACR Damage Index (SDI),¹⁶ with any increase in SDI reflecting damage accrual.

Exposures and Measured Outcomes

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

Statistical analysis

Less than 5% of visits had missing SLEDAI-2K data and these were excluded from analyses requiring SLEDAI-2K data. As SDI was collected yearly, for other visits, the closest previous or next visit SDI value was used. For analyses that incorporated length of time in LLDAS, if a patient was in LLDAS on two consecutive visits, she/he was 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 subsequent visit, the duration of LLDAS was calculated based on visit time interval divided by 2. 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 greater or less than 50% of observed time in LLDAS for each patient was used, 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 ≥ 2 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.

Data were analysed using STATA v15.1 (StataCorp, College Station, Texas, USA). Repeated failures Cox proportional hazard models were used to assess the time- dependent relationship between LLDAS and disease flares at each subsequent visit, as well as subsequent damage accrual (≥ 1 point increase in SDI), with proportionality of hazard ensured (Supplementary Table 1). Kaplan-Meier survival curves with log-rank test for significance were used to determine the relationship between proportion of time spent in LLDAS (at the 50% cutoff) and time to flare and new damage accrual. Generalised linear models with log-binomial regression were used to determine the association between (1) various cutoffs for percentage of time spent in LLDAS and (2) duration of 'sustained LLDAS', with flare and damage accrual (Supplementary Table 1). Subgroup analyses were performed to assess the association between LLDAS and damage accrual in patients with existing damage at baseline ($SDI \geq 1$), and patients with active disease at baseline using a cutoff commonly used as a selection criterion for entry into clinical trials¹ (SLEDAI-2K ≥ 6). Sensitivity analyses were performed on treatment-related criteria of LLDAS (Table 1 - criteria 4 and 5).

Results

Patient demographics and cohort characteristics

A total of 1,707 patients (93% female) were recruited, with a median (IQR 25th-75th) age at diagnosis of 29 (21-40) years. The majority of patients were Asian. Over half of the patients had a history of renal disease, mucocutaneous, musculoskeletal or haematologic manifestations. Patients were followed for a mean (\pm SD) of 2.2 (\pm 0.9) years (longest follow-up 3.6 years), totalling 12,689 visits (with median (IQR 25th-75th) visit interval of 0.28 (0.23-0.46) years). Twenty-eight patients had a baseline visit only and were excluded from longitudinal analysis, such that 1,707 patients were included, and data on 304 patients (18%) 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 median (IQR 25th-75th) SLEDAI-2K at enrolment was 4 (2-6), and 520 (30%) patients had SLEDAI-2K \geq 6 at study entry. Organ damage (SDI \geq 1) was present in 714 (41%) of patients at baseline. Other baseline characteristics are presented in Table 2 and Supplementary Table 2.

LLDAS attainment

The LLDAS definition was met in 6,081 (47.9%) visits, with 1,332 (78%) patients having at least one episode of LLDAS during follow-up (Table 2). Although the mean (\pm SD) duration of LLDAS episodes was 0.3 (\pm 0.2) years, 1071 (62.7%) patients achieved at least one episode of sustained LLDAS, with 517 (30.2%) sustaining LLDAS for \geq 12 months. Patients who spent \geq 50% of their observed time in LLDAS (n=803 (47.0%)) had a lower SLEDAI-2K at recruitment and lower mean prednisolone dose during follow-up, and were significantly less likely to have ever had vasculitis or renal disease (Supplementary Table 3).

Effect of LLDAS on disease outcomes

Attainment of LLDAS at any visit was associated with significant reduction in flare at the subsequent visit (HR 0.65, 95%CI 0.56-0.75, $p<0.001$) and subsequent accrual of damage (HR 0.59, 95%CI 0.45-0.76, $p<0.001$) (Table 3). Patients who spent $\geq 50\%$ of their observed time in LLDAS had a significant reduction in flare (HR 0.41, 95% CI 0.35-0.48, $p<0.001$) and damage accrual (HR 0.54, 95% CI 0.42-0.70, $p<0.001$) across the entire observation period compared to patients with $<50\%$ of observed time in LLDAS, and time to first flare and first damage accrual were significantly different between these two groups (log rank $p<0.001$) (Figure 1). There was greater reduction in risk of flare with larger proportion of time in LLDAS (Supplementary Table 4).

Damage accrual was observed in 31/1071 (2.9%) of patients who had experienced sustained LLDAS, compared to 113/664 (17%) who never experienced sustained LLDAS ($p<0.001$). Although any period of sustained LLDAS was associated with significant reduction in risk of subsequent damage accrual (Supplementary Table 5), increasing duration of sustained LLDAS was associated with incremental reduction in risk of subsequent new damage (Figure 2). Sustained LLDAS for ≥ 12 months was associated with an almost 90% reduction in risk of subsequent damage (RR 0.14, 95% CI 0.07-0.30, $p<0.001$).

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 performed subgroup analysis. LLDAS attainment was less frequent in patients with active disease at baseline (SLEDAI-2K ≥ 6) (901 of 3835 visits in LLDAS, 23.5%), compared to patients with SLEDAI-2K < 6 at baseline (5190 of 8845 visits in LLDAS, 58.7%), $p<0.001$. Compared to patients with baseline SLEDAI-2K < 6 , patients with active disease at baseline demonstrated a stronger association between LLDAS attainment and reduction in damage accrual in visit by visit analysis (HR 0.49 vs 0.72)

and in relation to cumulative time in LLDAS (HR 0·52 vs 0·65), despite lower rates of attainment of LLDAS in these patients (Table 4). Among the subset of patients with existing damage at study entry ($SDI \geq 1$), a significant reduction in risk of further damage accrual was observed if they were able to attain LLDAS at any visit (HR 0·52, $p < 0·001$) or if they spent $\geq 50\%$ of their observed time in LLDAS (HR 0·53, $p < 0·001$) (Table 4).

Sensitivity analysis of LLDAS definition

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 cutoff from $\leq 7.5\text{mg}$ to $\leq 5\text{mg}$ resulted in associations of LLDAS attainment at any visit with subsequent disease flares (HR 0·62, 95% CI 0·53-0·72, $p < 0·001$) and damage accrual (HR 0·58, 95% CI 0·43-0·72, $p < 0·001$) that were not meaningfully different from those observed with the original definition (see Table 3). Similarly, changing the SLEDAI-2K cutoff to 3, taking out haematological or gastrointestinal activity from criterion 1, or using the SFI 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 impact on reduction in disease flares or damage accrual.

Discussion

The use of T2T approaches, based on evidence that endpoint attainment impacts positively on outcomes, has transformed clinical practice and the efficiency of clinical trials in such diseases as hypertension, diabetes, and RA.^{3,4} The application of the T2T 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 In this study, we sought to address the utility and validity of a low disease activity endpoint in SLE. In this prospective multi-centre study, we demonstrate that LLDAS is an attainable treatment target in SLE, which is nonetheless robustly associated with protection from disease flares and the accrual of irreversible end-organ damage, two factors known to directly impact on mortality.

To improve treatment response measurement in SLE, the development of endpoints that have both utility (that is, are feasible and attainable) and validity (that is, 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 are highly correlated with one another.^{17,18} However, no threshold level of disease activity measured using these instruments has been demonstrated to improve outcomes, thereby enabling use as a T2T endpoint in trials or clinical practice. Likewise, measures of treatment response seen in clinical trials thus far detect change from baseline rather than describing attainment of a defined target state. Moreover, unlike in diseases such as RA, 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.

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 either clinical or laboratory activity fall under the disease activity threshold (SLEDAI-2K ≤ 4) in LLDAS, but the combination of both does not. 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, using visit by visit analysis, 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 in analyses demonstrating that spending more than half of observed time in LLDAS was associated with significant protection against both flares and damage. Retrospective studies by Petri *et al.*²² and Tsang-A-Sjoe *et al.*²⁵ similarly demonstrated that LLDAS in $\geq 50\%$ of observations was associated with around 50% reduction in damage accrual. Importantly, as little as $\geq 20\%$ 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 whilst 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 conducted a subgroup analysis of patients with active disease at baseline. Despite the expected lower frequency of attainment of LLDAS among patients with higher disease activity at baseline, the magnitude of association of LLDAS attainment with protection against damage was in fact greater in this subgroup of

patients compared to those with less active baseline disease. This 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 SLE patients, failure to achieve LLDAS within 6 months of diagnosis was associated with 5 times the odds of damage accrual by 18 months, compared to patients achieving LLDAS within this timeframe.²⁷ The majority of our cohort had established disease, and at baseline 41% of patients had organ damage, 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, >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 Caucasian patients with SLE, Zen *et al.* also demonstrated that the proportion of patients with damage accrual progressively decreased with longer time spent in LLDAS, although longer periods in LLDAS were required for a statistically significant protective effect to be observed in this smaller cohort.²³

The 'dose dependent' effect of sustained LLDAS 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 recent *post hoc* analyses of clinical trials, LLDAS was more stringent than currently-used outcome measures in discriminating

active treatment from placebo.^{9,10} Moreover, sustained LLDAS for >3 months could be demonstrated, with significantly higher proportions of patients on active treatment meeting this goal.⁹ Although rates of LLDAS attainment in the trial setting vary, in a recent Phase II trial in which LLDAS was included *a priori* as a secondary outcome measure, LLDAS attainment approached 40% in active treatment arms.²⁸ Additionally, rates of attainment of LLDAS and disease flares over time described here may have value in the design of future clinical trials.

As part of our validation process we performed 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 showing that doses of 6mg or less were associated with freedom from damage accrual.²⁹ In our study, reducing the allowable prednisolone dose in the LLDAS definition to ≤ 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 absence of flare defined using the SFI to the definition of 'no new disease activity', had no impact on the magnitude of protective effect of LLDAS. Removing the criterion of LLDAS relating to background immunosuppressants also did not significantly impact on outcomes in the sensitivity analysis. This is likely due to the fact that patients recruited from routine clinical practice mostly fulfilled the criteria for standard doses of immunosuppressant medications.

Potential 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 RA.³ Damage in SLE is accrued slowly. Our study had a mean duration of follow-up of just over 2 years. Whilst 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 rates of LLDAS attainment in patients with activity in some organ systems impacts on the protective associations of LLDAS. Just under 20% of patients failed to complete a study visit in the last 12 months of the study, potentially creating drop-out bias, however this is considered 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 generalizability of results. However, ethnicity had no impact on the protective effect of LLDAS on damage accrual in subgroup analysis of our cohort (data not shown), and prior retrospective studies including Caucasian, Hispanic, and African-American subjects showed that LLDAS was similarly associated with reduced accrual of damage.^{8,22-27} The majority of our cohort had prevalent disease, with only 12% of patients reporting a disease duration of <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 specifying the absence of gastrointestinal involvement and haemolytic anaemia, and including the PGA as a means to capture activity within organ systems both present in and omitted from the SLEDAI-2K. Sensitivity analysis for addition of the SFI as a means to capture new activity 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 multi-centre study demonstrates 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 T2T strategies in SLE.

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Author Contributions

V.G. – study planning and design, data collection, data analysis and interpretation, writing of the manuscript, editing of the manuscript, approval of final manuscript

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E.M. - study planning and design, data collection, data analysis and interpretation, editing of the manuscript, approval of final manuscript

Conflicts of interest

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Ethics approval

Approval for this study was granted by the Monash University Human Research Ethics Committee: CF15/1617 – 2015000817.

Table 1: Scoring of the Lupus Low Disease Activity State (LLDAS)

Descriptors of Disease Activity	YES/NO
1. SLEDAI-2K ≤ 4 , with <i>no</i> activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever)	
2. No <i>new</i> features of lupus disease activity compared to the previous assessment [#]	
3. SELENA-SLEDAI physician global assessment (PGA, scale 0-3) ≤ 1	
Immunosuppressive Medications	
4. Current prednisolone (or equivalent) dose ≤ 7.5 mg daily	
5. Standard maintenance doses of immunosuppressive drugs and approved biologic agents [†]	
LLDAS achieved if all 5 criteria fulfilled	

[#] Defined as any new SLEDAI-2K component which was not present at the previous assessment.

[†] Includes methotrexate, azathioprine, mycophenolate mofetil, mycophenolic acid, leflunomide, cyclosporine, cyclophosphamide, tacrolimus, rituximab and belimumab. Antimalarials are permitted.

Abbreviations: SLE (systemic lupus erythematosus); SLEDAI (SLE disease activity index); CNS (central nervous system); PGA (physician global assessment, scale 0-3 where 0 is no disease activity and 3 is maximum disease activity).

Table 2: Characteristics of study cohort (n=1,707)

	Mean \pm SD, Median (25th-75th) or n (%)
Female	1591 (93.2%)
Age at SLE diagnosis (years)	29 (21 – 40)
Age at recruitment (years)	40.44 (31.15 – 50.64)
Ethnicity	
Caucasian	172 (10.1%)
Asian	1497 (87.7%)
Other	38 (2.2%)
<i>Medication use (during follow-up)</i>	
Daily prednisolone dose (mg)	5 (1.95 – 8.8)
Immunosuppressant use [§]	1193 (69.9%)
Anti-malarial use ^β	1217 (71.3%)
Disease duration at recruitment (years)	8 (4 - 14)
Disease duration at recruitment \geq 15 months	1510 (88.5%)
SLEDAI-2K [*] at recruitment	4 (2 – 6)
SDI [#] at recruitment	0.80 \pm 1.32 [^]
Duration of follow-up (years)	2.20 \pm 0.88
Number of visits observed	12,689
Visits per patient	7.32 \pm 3.38
Interval between visits (years)	0.28 (0.23 – 0.46)
AMSt	3.32 (1.48 – 5.29)
PGA†	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 (47·9%)
Number of visits in LLDAS (per patient)	3·56 ± 3·11
Total LLDAS duration per patient (years)	1·05 ± 0·91
Percentage follow-up time in LLDAS per patient	48·3 ± 36·7%

* 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

§ include methotrexate, azathioprine, mycophenolate mofetil, mycophenolic acid, leflunomide, cyclosporine, cyclophosphamide, tacrolimus, rituximab and belimumab

β include chloroquine and hydroxychloroquine

† averaged across all visits

SLEDAI – Systemic Lupus Erythematosus Disease Activity Index; SDI - Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; AMS – time adjusted mean SLEDAI; PGA – Physician Global Assessment (scale of 0-3, where 0 is no activity and 3 is maximum activity); LLDAS – Lupus Low Disease Activity State

^ median(25th-75th) for SDI: 0 (0 - 1)

Table 3: Association of LLDAS at each visit with subsequent flare and damage accrual

	Time-dependent proportional hazards model (independent variable: in LLDAS (Yes/No)) n = 12,689 visits		
Outcome	HR	95% CI	<i>p</i> value
Flare (any) at subsequent visit	0·65	0·56 - 0·75	<0·001
Flare (mild-moderate) at subsequent visit	0·74	0·63 - 0·86	<0·001
Flare (severe) at subsequent visit	0·45	0·37 - 0·56	<0·001
Damage accrual (Increase in SDI \geq 1)	0·59	0·45 - 0·76	<0·001

LLDAS – Lupus Low Disease Activity State

Table 4: Effect of LLDAS at any visit, or cumulative LLDAS $\geq 50\%$ of time, on damage accrual in subgroups of patients with or without active disease or existing damage at baseline.

	Subgroup*	Patients with characteristic at baseline n = 1707	Time-dependent proportional hazards models	
			Visit by visit in LLDAS HR for damage 95% CI p value	$\geq 50\%$ time in LLDAS HR for damage 95% CI p value
Activity	SLEDAI-2K<6	1215 (70.0%)	0.72 0.52 – 0.99 0.047	0.65 0.47 – 0.91 0.011
	SLEDAI-2K ≥ 6	520 (30.0%)	0.49 0.28 – 0.86 0.013	0.52 0.33 – 0.83 0.006
Damage	SDI=0	1020 (58.8%)	0.71 0.49 – 1.01 0.060	0.61 0.43 – 0.87 0.007
	SDI ≥ 1	714 (41.2%)	0.52 0.36 – 0.76 0.001	0.53 0.37 – 0.75 <0.001

*Defined based on 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 to visits not in LLDAS). $\geq 50\%$ 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 – Systemic Lupus Erythematosus Disease Activity Index; SDI - Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index;
LLDAS – Lupus Low Disease Activity State

Figure 1 A

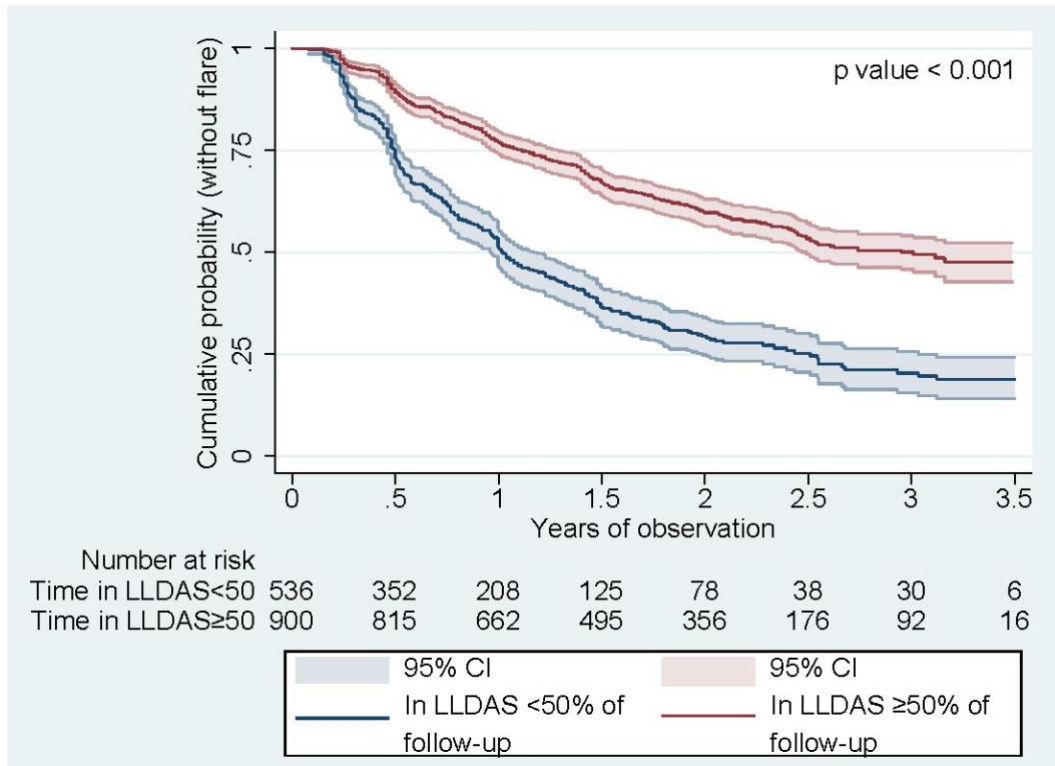


Figure 1B

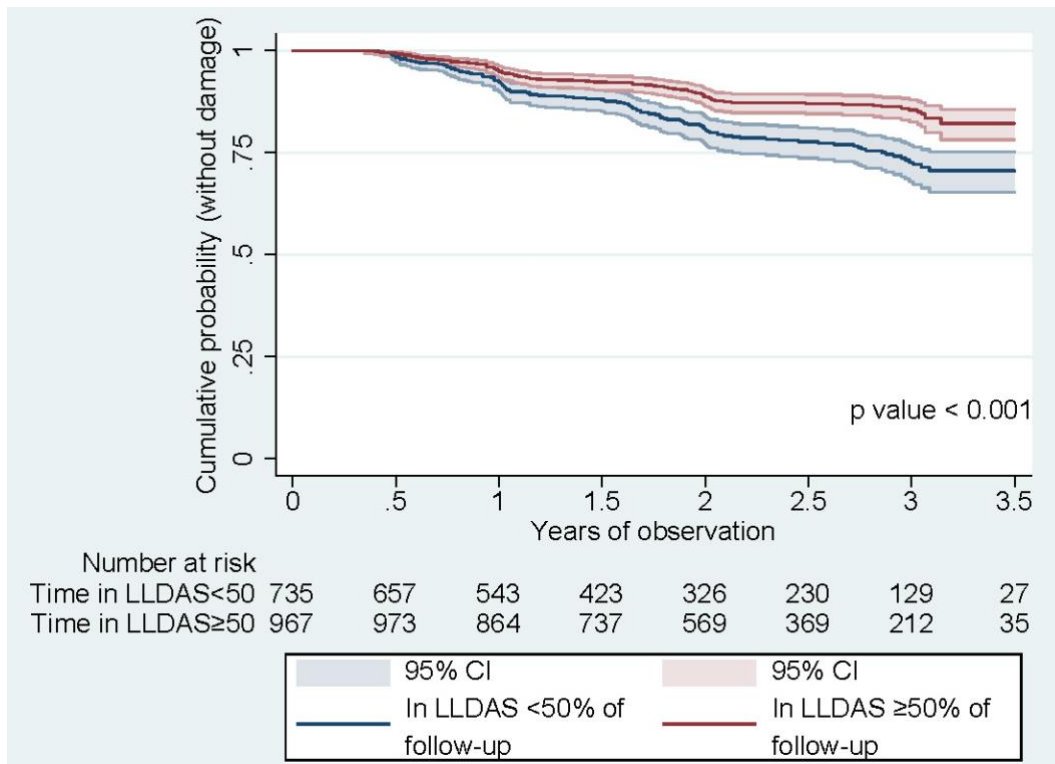


Figure 1: Kaplan-Meier plots of time flare-free (A) and damage accrual free (B) for patients who spent more than half of their observed time in LLDAS (red) compared to patients who spent less than half of their observed time in LLDAS (blue). Time in LLDAS was associated with reduced flare and damage accrual.

Figure 2

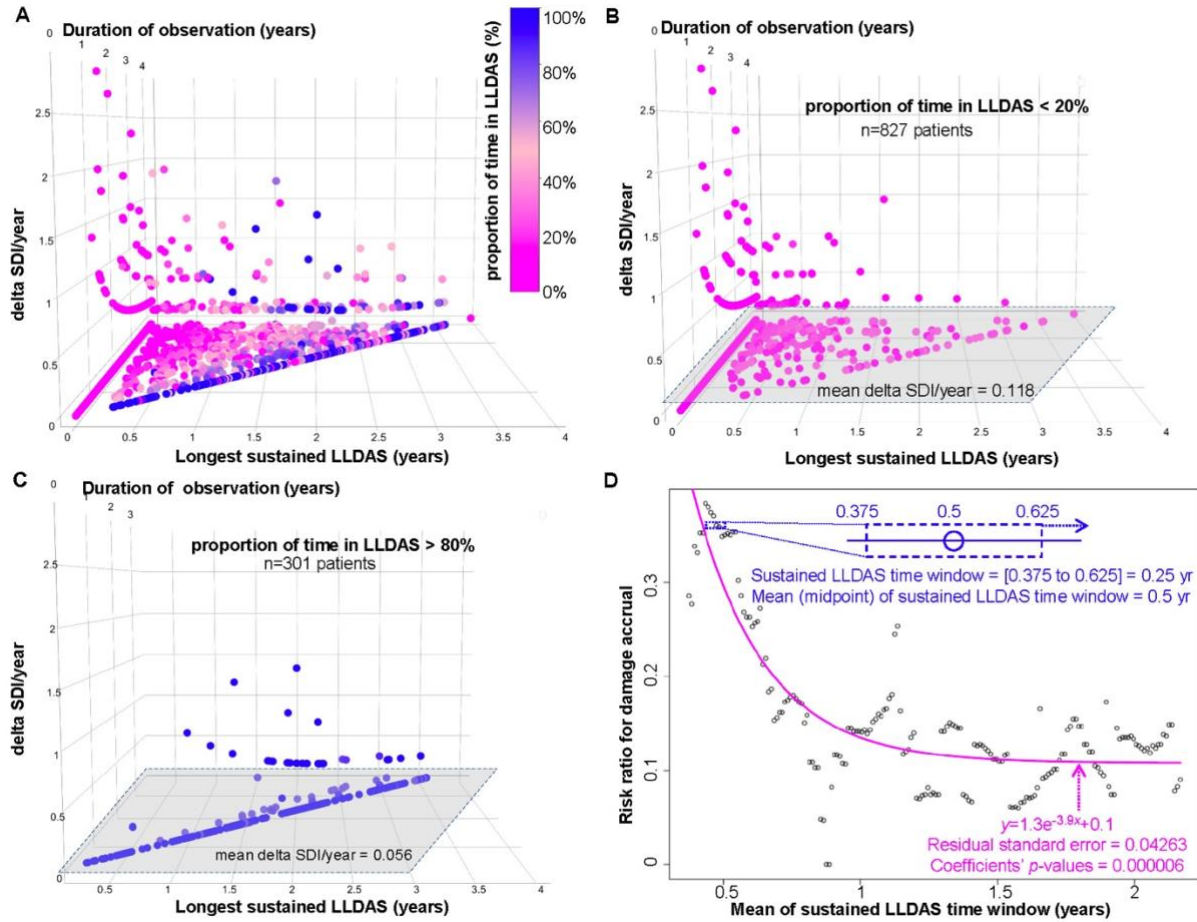


Figure 2: Multi-variate visualisation of longitudinal data. (A) 3D scatter plot of all study participants, each represented by a single point on the plot, showing for each patient the longest period of sustained LLDAS (x-axis), cumulative proportion of observed period in LLDAS (colour change), total duration of observation (z-axis) and change in SDI (y-axis), shown as delta SDI/year, i.e. the average yearly increase in SDI during the duration of observation. The same information is shown for (B) only patients who spent <20% of their observed time in LLDAS, and (C) only patients who spent >80% of their observed time in LLDAS. (D) Association of sustained LLDAS duration with damage accrual. A 3-month (0.25-year) time window moves continuously over the sustained LLDAS data, and the risk ratio for damage accrual is computed over the data in the window. An exponential regression curve is fitted over the risk ratios.

Supplementary Table 1: Summary of Statistical Analyses

	Visit by visit analysis		Percentage of observed time in LLDAS	Sustained LLDAS
	Time dependent Cox proportional hazards model (visit by visit analysis of the entire observation period)	Time dependent Cox proportional hazards model (visit by visit analysis of the entire observation period)	Generalised Linear Model (Log-binomial regression)*	Generalized Linear Model (Log-binomial regression)*
Unit of analysis	Visits: 12,689	Visits: 12,689	Participants: 1,707	Participants: 1,707
Exposure	In LLDAS at each visit or not	Spent at least 50% of followup time in LLDAS vs less than 50% of followup time in LLDAS	Spent at least X%*** of followup time in LLDAS, vs. not Percentage of time in LLDAS = (Sum of all time periods in LLDAS/total time observed)*100	Sustained LLDAS (defined as longest consecutive time during observation period spent in LLDAS, categorised as 0-3 months, 3-6 months, 6-12 months, 12-24 months and >24 months) vs never in sustained LLDAS
Outcome	Primary: Damage accrual Secondary: Flare	Primary: Damage accrual Secondary: Flare	Primary: Damage accrual at the end of follow up Secondary: Flare ever	Primary: Damage accrual in the next annual visit where SDI recorded, after period of sustained LLDAS
Measure of association**	Hazard Ratio (HR)	Hazard Ratio (HR)	Risk Ratio (RR)	Risk Ratio (RR)
Interpretation	Hazard of damage accrual/flare in subsequent visit if in LLDAS compared to not in LLDAS in current visit	Hazard of damage accrual/flare if 50% or more of followup time in LLDAS compared to if not in LLDAS for at least 50% of followup time	Risk of damage accrual/flare at the end of study period if in LLDAS for $\geq X\%$ of followup time compared to $< X\%$ of followup time	Risk of damage accrual/flare in subsequent visit if sustained LLDAS present for given period of time, compared to those who never had sustained LLDAS

*Generalised Linear Model with Poisson regression did not alter the results

**Predefined statistical significance $p \leq 0.05$, with 95% confidence intervals presented

*** X% was either 20%, 30%, 40%, 50%, 60%, 70% or 80% (please see Supplementary Table 4)

LLDAS – Lupus Low Disease Activity State; SDI – SLICC Damage Index

Supplementary Table 2: Additional patient and disease characteristics

	Mean \pm SD, Median (25 th -75 th) or n (%)
	n=1707
Number of ACR Classification criteria met at recruitment	5 (4 - 6)
Neurological manifestations ever†	185 (10.8%)
Musculoskeletal manifestations ever†	1161 (68.0%)
Nephritis ever†	1044 (61.2%)
Muco-cutaneous manifestations ever†	1428 (83.7%)
Cardio-pulmonary manifestations ever†	331 (19.4%)
Hematological manifestations ever†	1155 (67.7%)
ANA positive (at recruitment)	1592 (93.3%)
Anti-dsDNA positive (at recruitment)	1327 (77.7%)
Hypocomplementaemia (at recruitment)	386 (22.6%)
<i>Medication use during follow up</i>	
Azathioprine	493 (28.9%)
Mycophenolate mofetil	641 (37.6%)
Mycophenolic acid	86 (5.0%)
Methotrexate	137 (8.0%)
Leflunomide	9 (0.5%)
Cyclosporine	89 (5.2%)

†determined as present if patients met the ACR classification criteria in the relevant domains, or had active disease (SLEDAI-2K) in the relevant domain during follow-up ANA – Antinuclear antibody

Supplementary Table 3: Univariable analysis of characteristics associated with LLDAS* (n=1707)

	Mean (SD), Median (25 th – 75 th) or n (%) Time in LLDAS		<i>p</i> value
	<50% n=904 (53.0%)	≥50% n=803 (47.0%)	
Sex (Female:Male)	836:68	755:48	0.206
Age at diagnosis (years)	28 (21 – 37)	31 (22 – 42)	<0.001
Disease duration at recruitment (years)	8 (4 – 14)	8 (4 – 15)	0.715
Duration of follow up (years)	2.2 (1.5 – 3.0))	2.2 (1.5 – 3.0)	0.571
Ethnicity:			
Caucasian	83 (9.2%)	89 (11.1%)	0.389
Asian	802 (88.7%)	695 (86.6%)	
Other	19 (2.1%)	19 (2.4%)	
SLEDAI-2K at recruitment	6 (4 – 8)	2 (0 – 3)	<0.001
Mean PNL dose during follow-up	7.5 (4.9 – 10.6)	3.0 (0 – 5)	<0.001
Number of immunosuppressants during follow-up	5 (1 – 8)	2 (0 – 5)	<0.001
<i>Lupus Manifestations (ever)</i>			
Vasculitis†	53 (5.9%)	8 (1.0%)	<0.001
Neurological†	92 (10.2%)	93 (11.6%)	0.351
Musculoskeletal†	624 (69.0%)	537 (66.9%)	0.341
Nephritis†	650 (71.9%)	394 (49.1%)	<0.001
Muco-cutaneous†	767 (84.9%)	661 (82.3%)	0.158
Cardio-pulmonary †	188 (20.8%)	143 (17.8%)	0.119

Haematological †	604 (66.8%)	551 (68.6%)	0.427
Fever†	24 (2.7%)	10 (1.3%)	0.037
Serological activity†	759 (84.0%)	573 (71.4%)	<0.001
<i>Outcome measures</i>			
Flare - Severe	105 (11.6%)	7 (0.9%)	<0.001
Flare - Mild/mod	177 (19.6%)	35 (4.4%)	<0.001
Flare - Any	232 (25.7%)	39 (4.9%)	<0.001
Any Change in SDI	161 (17.8%)	89 (11.1%)	<0.001

* Mann Whitney test and Chi Square test were performed for this table

†Determined as positive if patients ever met the ACR classification criteria in the relevant domains, or had active disease (SLEDAI-2K) in the relevant domain during the observed period of followup.

Supplementary Table 4: Association of percentage of time in LLDAS with flare and damage accrual*

Percentage time in LLDAS**	Mild-moderate flare RR (95% CI) (p value)	Severe flare RR (95% CI) (p value)	Any flare RR (95% CI) (p value)	Damage accrual RR (95% CI) (p value)
20%	0.52 (0.40 – 0.66) (p<0.001)	0.37 (0.26 – 0.53) (p<0.001)	0.48 (0.39 – 0.59) (p<0.001)	0.67 (0.53 – 0.84) (p=0.001)
30%	0.54 (0.42 – 0.70) (p<0.001)	0.37 (0.25 – 0.53) (p<0.001)	0.49 (0.40 – 0.62) (p<0.001)	0.65 (0.51 – 0.81) (p=0.001)
40%	0.54 (0.42 – 0.69) (p<0.001)	0.35 (0.24 – 0.52) (p<0.001)	0.49 (0.39 – 0.61) (p<0.001)	0.64 (0.51 – 0.80) (p<0.001)
50%	0.51 (0.39 – 0.67) (p<0.001)	0.30 (0.20 – 0.46) (p<0.001)	0.45 (0.36 – 0.57) (p<0.001)	0.64 (0.50 – 0.80) (p<0.001)
60%	0.51 (0.39 – 0.68) (p<0.001)	0.24 (0.14 – 0.40) (p<0.001)	0.44 (0.34 – 0.57) (p<0.001)	0.65 (0.51 – 0.83) (p=0.001)
70%	0.49 (0.36 – 0.67) (p<0.001)	0.14 (0.07 – 0.28) (p<0.001)	0.39 (0.29 – 0.52) (p<0.001)	0.70 (0.54 – 0.91) (p=0.007)
80%	0.42 (0.29 – 0.61) (p<0.001)	0.10 (0.04 – 0.26) (p<0.001)	0.34 (0.24 – 0.49) (p<0.001)	0.60 (0.44 – 0.81) (p=0.001)

* n=1707 patients

**determined as the sum of all time intervals during followup in LLDAS divided by total duration of followup and multiplied by 100

LLDAS – Lupus Low Disease Activity State

Supplementary Table 5: Effect of sustained LLDAS on damage accrual

Longest duration of sustained LLDAS	n (%)	Risk ratio for damage accrual	95% CI	p
>3 to ≤6 months	185 (10·8%)	0·27	0·14-0·53	<0·001
>6 to ≤12 months	292 (17·1%)	0·14	0·07-0·29	<0·001
>12 to ≤24 months	341 (20·0%)	0·13	0·07-0·27	<0·001
>24 months	176 (10·3%)	0·13	0·05-0·34	<0·001

Groups are mutually exclusive.

Total n=1,707 patients, 636 (37·3%) patients never experienced sustained LLDAS, 77 (4·5%) patients experienced sustained LLDAS for ≤3 months.

LLDAS – Lupus Low Disease Activity State

Chapter 7

Evaluation of Remission Definitions in Systemic Lupus Erythematosus

Introduction

An important piece of the puzzle in the validation of LLDAS is comparison to an alternate target state, representing another way to test criterion validity. Given no other robustly validated definition of a low disease activity state exists in SLE, the nearest closest conceptual target state is remission. Whilst remission should be the ultimate goal in any disease, studies of existing remission definitions in SLE suggest it is seldom achieved, thus lowering its utility. Additionally, head to head comparison of the effect of remission and LLDAS on disease flares or damage accrual in a prospective study has not been done. In this chapter, I describe studies evaluating the Definitions of Remission in SLE (DORIS) group definitions of remission, and comparing the attainability and validity of these definitions, using LLDAS as a comparator.

LLDAS and remission are, conceptually, concentric states, with remission subsumed within LLDAS (i.e., patients in remission also fulfil the definition of LLDAS). Some studies comparing LLDAS and remission in retrospective cohorts have proposed that at least some of the protective effects of LLDAS may be attributable to remission. In this study I wanted to determine whether the protective effects of LLDAS seen in the longitudinal validation study described in chapter 6 were not driven by the overlap of LLDAS with remission. To achieve this I performed additional analyses looking only at those visits that fulfilled LLDAS and not remission.

Findings

The submitted manuscript in this chapter “Evaluation of Remission Definitions in Systemic Lupus Erythematosus”, describes the results in detail. A summary of the key findings is outlined below:

- Depending on definition, remission was achieved in 4.6% to 35.8% of visits, indicating a stepwise effect of definition stringency on attainability. In contrast, LLDAS was achieved in 47.9% of visits.
- All but the most stringent definitions of remission were associated with significantly reduced damage accrual, likely due to the low frequency of attainment of these more stringent definitions of remission.
- The magnitude of protection from damage accrual (hazard ratio) for remission overall was very similar to that of LLDAS.
- Remission definitions disallowing serological activity had the greatest magnitude of protection against disease flares.
- Sustained remission (2 or more visits) was demonstrated to be significantly protective against damage accrual across all definitions, suggesting that sustaining rather than just attaining a target state yields greater protective effects.
- When assessing data on attainment of LLDAS excluding overlap with remission, a significant association of LLDAS with protection from damage accrual remained, with a magnitude of protection largely unchanged, for all definitions except clinical remission on treatment which had the greatest overlap with LLDAS.

Implications

This first prospective study comparing all the DORIS remission definitions confirms that variation in stringency has a major impact on attainability of remission. Highly stringent remission

definitions were attained so seldom that significant association with protection from damage accrual could not be demonstrated in visit by visit analyses or cumulative time analyses. LLDAS was more achievable than remission, and distinct from all but the least stringent remission definition. Remission definitions lacking stringency may be insufficiently distinct from LLDAS, and further studies are needed to distinguish the protective effects of the various remission definitions.

The results of this study have been presented at multiple national and international scientific meetings, and are currently under review in a peer reviewed journal:

Golder V., Kandane-Rathnayake R., Huq M., Louthrenoo W., et al. *Evaluation of Remission Definitions in Systemic Lupus Erythematosus*. Lancet Rheumatology, Submitted May 1st 2019.

Future direction

A limitation of this study is the duration of follow up which may have been insufficient to detect protective associations of the most stringent definitions of remission that are attained infrequently. Analysis of longer duration of follow up would potentially increase the power to detect significant associations and allow comparison of the more and less stringent definitions of remission for their association with protection from adverse outcomes.

Evaluation of Remission Definitions in Systemic Lupus Erythematosus

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Research in context

Evidence before this study

Remission is the goal of therapy for all chronic disease. Adoption of empirically validated definitions of remission as part of a treat to target strategy in diseases like rheumatoid arthritis has resulted in paradigm shifts in treatment approaches and patient outcomes. In complex multi-organ diseases like systemic lupus erythematosus (SLE), remission is potentially difficult to define; historical studies have reported variable but mostly low rates of remission attainment with various definitions. No definition of remission for SLE has been widely adopted, in part because of a lack of high quality prospective studies evaluating the alternative remission definitions for their utility and validity.

The DORIS (Definitions of Remission in SLE) group published a framework for remission definitions in SLE, giving rise to 8 potential remission definitions, which need to be empirically evaluated before one or more can be recommended for adoption; to date, this has not been done. Ideally, a remission state in SLE would be highly, or even completely, protective from adverse outcomes such as end-organ damage accrual, and clearly distinct from low disease activity.

Added value of this study

This is the first prospective study designed specifically to evaluate the utility and validity of competing remission definitions in SLE. In a large multinational cohort (n=1,707 patients enrolled, with n=12,689 visits), we have demonstrated that the DORIS remission definitions vary widely in their attainability, from as few as 4.6% to up to 35.8% of visits, depending on

stringency. Among the definitions, all but the two most stringent definitions could be demonstrated to be associated with significantly reduced damage accrual in this study, albeit with little difference in protective effect. In contrast, when sustained, all remission definitions were protective, with greater spread across the magnitude of the protective effect depending on the stringency of remission. Interestingly, remission definitions disallowing serological activity were associated with the greatest reductions in flare. In comparison, Lupus Low Disease Activity State (LLDAS) was more readily attainable, yet had comparable protective associations. Importantly, LLDAS attainment remained highly associated with protection from adverse outcomes even after excluding patients in remission, except for the least stringent remission definition.

Implications of all the available evidence

This prospective multicentre study confirms that while definition stringency has a major impact on the attainability of remission in SLE, most proposed definitions were associated with reduction in flare and damage accrual, although excess stringency constrained the ability to demonstrate validity for some definitions, and remission was poorly separated from the protective associations of LLDAS. The effects of sustained remission were more widely separated among the definitions, suggesting that longer periods of study, focusing on sustained remission, will be needed to identify a preferred remission definition for SLE. The least stringent definition was poorly separated from LLDAS, which sets the ceiling of an acceptable disease activity state, suggesting it lacks sufficient additional stringency to be recommended as a 'working' definition of remission pending such future studies.

Abstract

Background: Thus far no definition of remission has been widely adopted for systemic lupus erythematosus (SLE). The objective of this study was to evaluate the attainability and effect on outcomes of the Definitions of Remission in SLE (DORIS) group remission states .

Methods: 1,707 SLE patients were prospectively recruited, and followed for (mean \pm SD) 2.2 \pm 0.9 years, totalling 12,689 visits. Time dependent Cox proportional hazards models and generalized linear equations were used to assess DORIS definitions of remission in terms of impact on disease flares and damage accrual, and to also compare them with the Lupus Low Disease Activity State (LLDAS).

Findings: Remission was achieved in between 4.6% and 35.8% of visits. Spending \geq 50% of observed time in any defined remission was associated with a significant reduction in damage accrual, with the exception of the two most stringent remission definitions, that had the lowest frequency of attainment. Remission definitions disallowing serological activity were associated with the greatest reductions in flare. LLDAS was more attainable, and was associated with a similar magnitude of protection to remission. Sustained remission and LLDAS were associated with a wider spread of effect sizes for reduction in risk of damage. By analysing patients who met the definition for LLDAS but not remission, we found that LLDAS was significantly associated with reduction in damage accrual independently of remission for all definitions except the least stringent.

Interpretation: Attainment of remission was associated with significant reductions in damage accrual and disease flare. LLDAS was more achievable than remission, and distinct from all but the least stringent remission definition. Remission definitions lacking stringency may be insufficiently distinct from LLDAS, and further studies are needed to distinguish the protective effects of the various remission definitions.

Funding: The Asia Pacific Lupus Collaboration received project support grants from UCB, GlaxoSmithKline, Janssen, Bristol-Myers Squibb and AstraZeneca.

Introduction

The use of treat-to-target (T2T) approaches based on validated outcome measures has transformed clinical trials and practice in chronic diseases such as diabetes and hypertension.¹ T2T has become standard of care in rheumatoid arthritis (RA), with the demonstration that achievement of the treatment targets of remission or low disease activity is associated with significant reduction in structural joint damage.² Addressing the need for validated outcome measures from which to derive treatment strategies in SLE was highlighted by an international working group as an urgent priority.³ Mortality in SLE is strongly associated with damage accrual, contributed to by poorly controlled disease activity, glucocorticoid use and complications of long term immunosuppression.^{4,5} Reduction in damage accrual is therefore a highly sought-after goal in SLE, with remission and low disease activity identified as the potential target states to achieve this.³

The Definitions of Remission in SLE (DORIS) group has proposed a framework encompassing multiple potential definitions of remission,⁶ which until now have awaited formal evaluation. Whilst the optimal treatment goal for any chronic disease should be remission, in SLE sustained remission occurs only in a small proportion of patients.⁷ A less stringent low disease activity outcome, the Lupus Low Disease Activity State (LLDAS), has been shown to be attainable whilst associated with reduction in disease flares and damage accrual, and improved health related quality of life.⁸⁻¹¹ Recently, two DORIS remission definitions and LLDAS were compared in a large retrospective study, which confirmed that remission was more stringent (less frequently attained) than LLDAS and was associated with protection from damage accrual at a lower exposure than LLDAS,¹² consistent with desired characteristics of these concentric but step-wise states.¹³

The objective of this multinational prospective study was to formally evaluate for the first time all DORIS definitions of remission. We examined their attainability, and association with reductions in the primary outcome measure of damage accrual and key secondary outcome measure of disease flare, to test the hypothesis that remission would be associated with protection against these adverse outcomes. A second objective was to compare remission and LLDAS in terms of these outcomes, to test the hypothesis that remission was less attainable but more protective than LLDAS.

Methods

Study population and design

We conducted a prospective cohort study (NCT03138941) of SLE patients from 13 international centres which are part of the Asia Pacific Lupus Collaboration (APLC), with enrolment commencing in 2013. Patients over the age of 18 who fulfilled the classification criteria for SLE (either the 1997 American College of Rheumatology criteria¹⁴ or the 2012 Systemic Lupus International Collaborating Clinics criteria¹⁵) were eligible to be enrolled in the study. Each participating institution obtained informed patient consent and ethics approval from the relevant governing bodies. Data were collected during routine ambulatory care using standardised paper or electronic case report forms. Visit frequency was based on clinical need, with a minimum visit frequency set at an interval of six months. Patients with <2 visits were excluded.

Variables

At recruitment, demographic and disease characteristics were collected from each patient including gender, ethnicity and year of definite SLE diagnosis. Disease manifestations ever present were collected using ACR and SLICC criteria at recruitment, and disease activity at each visit was captured using the SLE Disease Activity Index (SLEDAI-2K)¹⁶ modified as per Thanou *et al.*,¹⁷ and a physician global assessment (PGA) on a scale of 0 to 3, where 0 is no activity and 3 is high disease activity. Laboratory results were obtained within 30 days of each visit. Use and dose of glucocorticoids and immunosuppressive medication were captured at each visit.

Attainment of remission was determined for each visit based on the eight definitions published by the DORIS group (Table 1).⁶ In brief, all definitions require the absence of clinical activity as measured by a clinical SLEDAI of 0 and a PGA ≤ 0.5 , and allow use of antimalarials; but vary in allowing for serological activity, glucocorticoid use up to 5mg/day prednisolone equivalent, and use of immunosuppression. Attainment of LLDAS at each visit was determined as previously described⁸ and summarised in Table 1. Disease flares were captured using the SELENA flare index (SFI).¹⁸ Irreversible disease damage was recorded at enrolment and annually until the conclusion of data collection, using the SLICC damage index (SDI).¹⁹

Exposures and Measured Outcomes

To address the main objective of this study, we assessed exposure of patients to each of the remission definitions, and disease outcomes. Several measures of remission exposure were studied – attainment at a single visit, percentage of overall observed time in remission (cumulative remission), and amount of consecutive time in remission (sustained remission). The primary outcome measure assessed was accrual of irreversible organ damage (change in SDI score), with disease flares a key secondary outcome (Supplementary Table 1). We also compared attainment rates of remission and LLDAS, and the effects of these states on damage and flares. Lastly, we assessed the independence of the effects of LLDAS from those of remission by analysing the same outcomes measuring exposure to LLDAS excluding remission.

Statistical Analysis

Less than 5% of visits had missing SLEDAI-2K data, and these were excluded from analyses requiring SLEDAI-2K data. As SDI was collected yearly, for other visits, the closest previous or next visit SDI value was used. For duration of remission, if a patient was in a given state of remission on two consecutive visits, she/he was considered to have stayed in remission for the time interval in between the visits. If a patient was not in remission on a previous visit, but in remission on a current visit, duration of remission was calculated based on the time interval divided by 2. As patients had varying lengths of follow-up, we also assessed percentage of follow-up time spent in remission using a cutoff of greater or less than 50%, based on previously published sensitivity analyses.⁸ Sustained remission was defined as at least 2 consecutive visits meeting each respective definitions. LLDAS was analysed similarly.

Data were analysed using STATA v15.1 (StataCorp, College Station, Texas, USA). Univariable analyses using Mann Whitney tests and Chi Square tests as appropriate were performed to compare the characteristics of patients based on percentage of time spent in LLDAS and remission. Cross tabulation and Chi Square tests were used to assess the overlap between LLDAS and remission definitions across all visits. Repeated failures Cox proportional hazard models were used to assess the time-dependent relationship between remission (or LLDAS) and disease flares at each subsequent visit, as well as subsequent damage accrual (increase in SDI of at least 1), after ensuring proportionality of hazard (Supplementary Table 1). Time-dependent proportional hazard models were also used to assess the relationship of proportion of time spent in remission (or LLDAS) (at the 50% cutoff) and disease flares and damage accrual. The effect of sustained remission (or LLDAS) on flares and damage accrual was assessed using generalized linear models (Supplementary Table 1).

In additional analyses, we assessed whether the effects of LLDAS on flares and damage were independent of the effects of remission subsumed within LLDAS, by assessing those visits that fulfilled the criteria for LLDAS but not for remission, for each of the remission definitions.

Results

Demographics and cohort characteristics

A total of 1,707 patients were studied, of whom 93% were female with a median (IQR 25th-75th) age at diagnosis of 29 (21-40) years and median disease duration of 8 (4-14) years. The majority of patients in this cohort were of Asian ethnicity. Patients were followed for (mean \pm SD) 2.2 \pm 0.9 years (longest follow up 3.6 years), totalling 12,689 visits. Data on 304 patients (18%) who did not have a visit in the last 12 months of the observation period were censored from their last visit. The median SLEDAI-2K at enrolment was 4 (2-6). Over half of the patients had a history of mucocutaneous, musculoskeletal, hematologic or renal manifestations. Other patient and disease characteristics are presented in Table 2.

Attainment of remission and LLDAS during follow-up

Remission was achieved in 581 (4.6%) to 4546 (35.9%) visits depending on definition, with 11.0% to 60.2% of patients achieving a definition of remission on at least one occasion during follow-up (Table 3). In contrast, LLDAS was achieved in 6081 visits (47.9%), with 77.4% of patients having at least one episode of LLDAS during follow-up. The least stringent remission definition (definition 3), which allows serological activity, antimalarials, prednisolone and immunosuppressives, had the greatest overlap with LLDAS, with 68.1% of the visits in LLDAS also fulfilling this definition (Figure 1C). Remission definition 6 (complete clinical and serological remission, off all treatment except antimalarials) had the least overlap with LLDAS attainment (Figure 1F).

Effect of remission on disease flares and damage accrual

In time-dependent analysis considering every visit, only definitions describing clinical remission (definitions 1-4) could be demonstrated to be associated with significantly reduced subsequent damage accrual (Table 4). In contrast, all remission definitions were significantly associated with reduction in subsequent flares, with the greatest protective effect (lowest hazard ratios) seen with definitions requiring the absence of both serological activity and prednisolone use (definitions 5 and 6) (Table 4). Analysing effects of cumulative time in remission using a cutoff of $\geq 50\%$ of observed time meeting a given definition, most of the remission definitions were similarly significantly protective against damage accrual, with the exception of the most stringent remission definitions (definitions 5 and 6) which had the lowest frequency of attainment (Table 4). In relation to flares, all remission definitions attained for $\geq 50\%$ of observed time were significantly associated with reduced flares, again with the lowest hazard ratios seen for definitions 5 and 6 (Table 4). In comparison, LLDAS attainment at any visit was associated with significantly reduced subsequent flare and damage accrual, while LLDAS for $\geq 50\%$ of observed time was associated with a two-fold reduction in risk of flare and damage accrual, with the magnitude of these protective effects similar to those of remission (Table 4).

Sustained remission (≥ 2 consecutive visits) was seen in 7.1% to 47.2% of patients, depending on definition stringency. Damage accrual was observed in 0.5% to 2.5% of patients who experienced sustained remission (Table 5). In comparison, 61.7% of patients experienced at least one episode of sustained LLDAS, and damage accrual was observed in 31/1071 (2.9%) of those. Attainment of all of remission definitions or LLDAS, when sustained, could be shown to be significantly associated with reduction in risk of damage accrual, with the greatest reduction in risk seen for remission definitions 2 and 6, neither of

which allow immunosuppressant or prednisolone use, but differ in serological activity (Table 5).

As remission is effectively concentric within LLDAS, the aggregate of patients in LLDAS includes a subset of patients who also meet definitions for remission (Figure 1). To evaluate whether LLDAS confers protection from adverse outcomes independently of its capture of remission, we assessed only the subset of visits that fulfilled the criteria for LLDAS but not remission. Attainment of LLDAS excluding remission at any visit remained significantly associated with reduction in subsequent disease flares and damage accrual for all definitions except the least stringent (definition 3), which had the greatest overlap with LLDAS (Table 6). Similarly, cumulative attainment of LLDAS excluding remission for $\geq 50\%$ of observed time remained significantly associated with reduction in both disease flares and damage accrual for all definitions except definition 3 (Table 6).

Discussion

For treatment strategies to be able to improve outcomes in SLE, treatment endpoints used in such strategies must have both utility (attainability and sustainability) and validity (association with improved outcomes).¹³ Remission remains the goal of SLE therapy, but to evaluate the ability of novel treatment approaches to deliver remission, definitions of remission must be evaluated empirically against these standards. In this prospective multi-centre study, we have evaluated the recently proposed DORIS definitions of remission for SLE.⁶ With regard to attainability, we demonstrate that these definitions vary widely depending on stringency, ranging from 4·6% to 35·9% of visits representing 5·78% to 36·1% of observed time spent. Therefore, the most stringent definitions appear to have least utility, at least with current treatments, similar to historical reports of stringent remission attainment being very infrequent in SLE.²⁰

With regard to validity, the most important association of any treatment endpoint in SLE is reduction in damage accrual. Of the DORIS remission definitions, we found that only the 'clinical remission' definitions (1-4), not requiring serological remission, had a significant association with reduction in damage accrual in visit by visit analysis. This is likely due to the low frequency of attainment of the more stringent definitions, reducing the power to detect significant associations when attained at a single visit. Similarly, when considering cumulative time in remission the two most stringent definitions could not be shown to be significantly associated with protection from damage. These findings argue against the utility of very stringent remission definitions in SLE, at least with current standards of care. Importantly for the design of future studies, however, the protective associations of remission were more readily demonstrated across all definitions when remission was

sustained, consistent with sustained remission intuitively being the more impactful goal than episodic or cumulative remission. Moreover, a greater spread between the remission definitions in the magnitude of associations with protection from damage was observed for sustained remission, with those definitions disallowing any prednisolone and immunosuppressant use having the lowest risk of damage accrual. Of note, the frequency of damage accrual events in these most stringent states was very low, meaning some caution is needed in interpretation of these findings.

In regard to the secondary outcome of flare, in both visit by visit and cumulative time analyses, all remission definitions were associated with significant reduction in flare, with definitions excluding serological activity as well as disallowing prednisolone having the greatest protective associations. The temporal relationship between serological and clinical disease activity remains controversial, as evidence regarding whether serological activity predicts clinical features varies.^{21,22} A *post-hoc* analysis of the placebo arm of the phase III belimumab trials showed that raised anti-dsDNA levels and hypocomplementemia significantly increased the risk of clinically meaningful flare, consistent with our finding that exclusion of serological activity was associated with reduced flares.²³

The concentric nature of the stepwise more stringent response states means that a proportion of patients in LLDAS will also meet definition of remission; this is an intentional feature of the relationship between such endpoints, but the endpoints need to be sufficiently distinguished from one another. Here, LLDAS was attained in 47.9% of visits, representing 61.8% of observed time, indicating LLDAS is more attainable than even the most lenient definition of remission. The findings are similar to those of previous reports

from retrospective studies,¹² in which the percentages of observed time in LLDAS, clinical remission on treatment (definition 3) and clinical remission off treatment (definition 2) approximately halves with stepwise increases in stringency.¹² In contrast, the overlap of low-stringency remission with LLDAS was considerably lower than that described in another study, in a much smaller single centre European cohort using a less stringent definition that does not include the PGA.²⁴ Interestingly, for some definitions there were visits that fulfilled the criteria for remission but not for LLDAS, as LLDAS but not the DORIS remission definitions exclude activity, including serological activity, that is new compared to the previous assessment.

In contrast to the differences in attainability, but consistent with retrospective cohort studies,^{12,25,26} remission and LLDAS had similar protective effects on flare and damage accrual. These findings suggest that remission as currently defined may not be associated with greater protection from adverse outcomes compared to LLDAS, although limitations of the current study including length of follow-up, discussed below, limit the ability to draw this conclusion. To explore this further, we assessed the independent effects of LLDAS on flares and damage by removing from consideration those visits that fulfilled criteria for both LLDAS and remission. With one exception, 'LLDAS without remission' retained a highly significant association with reduction in damage accrual, and the magnitude of this effect was largely unchanged, consistent with LLDAS having an important and independent association with improved outcomes. In contrast, the least stringent remission definition, which also had the highest proportional overlap with LLDAS, could not be separated from LLDAS. As LLDAS represents the ceiling for an acceptable treatment outcome state, this

suggests that 'clinical remission on treatment' may be insufficiently stringent to be useful as a standalone endpoint.

A limitation of this study is the duration of follow-up. Whilst an average follow-up of 2.2 years was sufficient to demonstrate the broad protective associations of remission and LLDAS, it is possible that over longer followup these protective effects are not sustained. Studies of longer followup, which are underway in this cohort, may provide greater confidence regarding the protective associations of remission, and may reveal a greater spread in protective associations akin to what was seen in our sustained analysis that allows a more definitive recommendation on an SLE remission definition. A further limitation is that the majority of our patients had prevalent disease, and this study should be repeated in an inception cohort, to evaluate whether attaining remission is associated with reductions in damage accrual in patients with early severe disease; such protective effects of LLDAS have been reported in two inception cohort studies.^{27,28}

In summary, in this large prospective cohort study, we have demonstrated wide variation between the attainability and utility of 8 possible remission definitions from the DORIS framework. Remission was significantly associated with protection from damage accrual, but as similar magnitudes of protection were seen across the definitions in our analysis, other than when analysing the associations of sustained remission, it remains unclear which definition is the most useful. A state in between the most stringent definitions, which lack utility through low attainability, and the most lenient, which have excess overlap with and poor separation from LLDAS, is likely to emerge as the optimum definition of remission for SLE. Further studies, using longer periods of observation to assess sustained remission, will

be needed to illuminate the optimum remission definition for SLE in terms of utility, validity, and separation from LLDAS.

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Author Contributions

V.G. – study planning and design, data collection, data analysis and interpretation, writing of the manuscript, editing of the manuscript, approval of final manuscript

R.K.R. – data analysis and interpretation, editing of the manuscript, approval of final manuscript

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E.M. - study planning and design, data collection, data analysis and interpretation, editing of the manuscript, approval of final manuscript

Conflicts of interest

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Ethics approval

Approval for this study was granted by the Monash University Human Research Ethics Committee: CF15/1617 – 2015000817.

Table 1: Operational definitions of remission and LLDAS

	Disease Activity			Treatment*		
	PGA	SLEDAI	Serological activity allowed*	PNL (mg)	IS allowed	AM allowed
Clinical remission without steroids						
IS allowed (definition 1)	≤0.5	Clinical=0	✓	0	✓	✓
Without IS (definition 2)	≤0.5	Clinical=0	✓	0	x	✓
Clinical remission with steroids						
IS allowed (definition 3) [#]	≤0.5	Clinical=0	✓	≤5	✓	✓
Without IS (definition 4)	≤0.5	Clinical=0	✓	≤5	x	✓
Complete remission without steroids						
IS allowed (definition 5)	≤0.5	Clinical=0	x	0	✓	✓
Without IS (definition 6) [‡]	≤0.5	Clinical=0	x	0	x	✓
Complete remission with steroids						

IS allowed (definition 7)	≤ 0.5	Clinical=0	x	≤ 5	✓	✓
Without IS (definition 8)	≤ 0.5	Clinical=0	x	≤ 5	x	✓
LLDAS[†]	≤ 1	≤ 4	✓	≤ 7.5	✓	✓

*For remission definitions, serological activity where marked '✓' is permitted but not required; treatments marked '✓' are permitted but not required. Where a treatment is permitted, that definition includes patients using or not using that treatment at a given visit.

[†]LLDAS additionally requires no activity in any major organs (renal, CNS, cardiopulmonary, vasculitis or fever), and no activity since the previous clinical assessment (no new item on the SLEDAI-2K).

[#]Remission 3 is alternatively known as 'clinical remission on treatment' and is the least stringent of the remission definitions.

[¥]Remission 6 is alternatively known as 'complete remission off treatment' and is the most stringent.

Abbreviations: AM – antimalarial; IS – immunosuppression; PNL – prednisolone; serological activity – presence of elevated dsDNA antibodies and/or low levels of complement 3 and/or 4.

Table 2: Patient demographics and disease characteristics (n=1707)

	Mean \pm SD, Median (25th-75th) or n (%)
Sex (Female)	1591 (93.2%)
Age at SLE diagnosis (years)	29 (21 – 40)
Age at recruitment (years)	40.44 (31.15 – 50.64)
Ethnicity	
Caucasian	172 (10.1%)
Asian	1497 (87.7%)
Other	38 (2.2%)
Disease duration at recruitment (years)	8 (4 - 14)
Disease duration at recruitment ≥ 2 years	1510 (88.5%)
Duration of follow-up (years)	2.19 (1.51 – 2.99)
Number of visits observed	12,689
Visits per patient	7.43 \pm 3.30
Interval between visits (years)	0.28 (0.23 – 0.46)
Number of ACR Classification criteria met at recruitment	5 (4 – 6)
SLEDAI-2K* at recruitment	4 (2 – 6)
SLEDAI across observation period†	3.32 (1.48 – 5.29)
PGA†	0.44 (0.24 – 0.84)
SDI# at recruitment	0.80 \pm 1.32^
<i>Medication use (during follow-up)</i>	
Daily prednisolone dose (mg)	5 (1.4 – 10)

Immunosuppressant use [§]	1193 (69·9%)
Anti-malarial use ^β	1217 (71·3%)

* scores range from 0 to 105, with higher scores indicating more active disease

#scores range from 0 to 46, with higher scores indicating greater disease-related damage

†time-adjusted mean across all visits

[§]immunosuppressives include methotrexate, azathioprine, mycophenolate mofetil, mycophenolic acid, leflunomide, cyclosporine, cyclophosphamide, tacrolimus, rituximab and belimumab

^βinclude chloroquine and hydroxychloroquine

[^]median(25th-75th) for SDI: 0 (0 - 1)

Abbreviations: SLEDAI – Systemic Lupus Erythematosus Disease Activity Index; SDI - Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; PGA – Physician Global Assessment (scale of 0-3, where 0 is no activity and 3 is maximum activity)

Table 3: Remission and LLDAS attainment during follow-up (n patients=1707, n visits=12689)

	Remission								LLDAS
	Def 1	Def 2	Def 3	Def 4	Def 5	Def 6	Def 7	Def 8	LLDAS
Patients with at least one episode of Remission/LLDAS	425 (24.5%)	316 (18.2%)	1044 (60.2%)	656 (37.8%)	246 (14.2%)	190 (11.0%)	590 (34.0%)	367 (21.2%)	1342 (77.4%)
Number of visits where Remission/LLDAS achieved	1548 (12.2%)	1131 (8.9%)	4546 (35.9%)	2628 (20.7%)	769 (6.1%)	581 (4.6%)	2156 (17.0%)	1242 (9.8%)	6081 (47.9%)
Total Remission/LLDAS duration per patient (years)	1.3 ± 0.9	1.3 ± 0.8	1.3 ± 0.9	1.3 ± 0.8	1.1 ± 0.8	1.1 ± 0.7	1.1 ± 0.8	1.1 ± 0.8	1.4 ± 1.0
Percentage time in Remission/LLDAS per patient	14.4 ± 30.0	10.8 ± 26.9	36.1 ± 38.2	21.8 ± 34.2	7.4 ± 22.1	5.78 ± 19.8	17.7 ± 31.2	10.8 ± 25.7	61.8 ± 34.5

LLDAS – Lupus Low Disease Activity State; operational definitions of remission and LLDAS are available in Table 1.

Table 4: Association of remission or LLDAS with flare and damage accrual (n patients=1707, n visits=12689)

Independent Variable	Outcome					
	Visits by visit analysis			% time (≥50% vs <50%)		
	n (%) visits	Flare at subsequent visit HR (95% CI) p value	Damage Accrual HR (95% CI) p value	n (%) patients with ≥50% time	Flare HR (95% CI) p value	Damage Accrual HR (95% CI) p value
Definition 1	1548 (12.2%)	0.50 (0.39-0.64) <0.001	0.60 (0.38-0.92) 0.020	175 (10.3%)	0.39 (0.31-0.50) <0.001	0.64 (0.44-0.93) 0.020
Definition 2	1131 (8.9%)	0.45 (0.34-0.60) <0.001	0.58 (0.35-0.96) 0.034	146 (8.6%)	0.36 (0.27-0.47) <0.001	0.60 (0.39-0.93) 0.022
Definition 3	4546 (35.8%)	0.75 (0.64-0.87) <0.001	0.55 (0.41-0.73) <0.001	472 (27.7%)	0.54 (0.46-0.63) <0.001	0.49 (0.38-0.65) <0.001
Definition 4	2628 (20.7%)	0.68 (0.57-0.81) <0.001	0.57 (0.40-0.80) 0.001	309 (18.0%)	0.52 (0.44-0.62) <0.001	0.57 (0.42-0.78) <0.001
Definition 5	769 (6.1%)	0.38 (0.26-0.56) <0.001	0.69 (0.38-1.23) 0.205	76 (4.5%)	0.28 (0.19-0.41) <0.001	0.62 (0.37-1.05) 0.076
Definition 6	581 (4.6%)	0.36 (0.23-0.56) <0.001	0.66 (0.34-1.29) 0.223	68 (4.0%)	0.26 (0.17-0.40) <0.001	0.59 (0.32-1.07) 0.083
Definition 7	2156 (17.0%)	0.56 (0.45-0.70) <0.001	0.70 (0.48-1.0) 0.059	207 (12.1%)	0.43 (0.35-0.53) <0.001	0.63 (0.45-0.89) 0.008

Definition 8	1242 (9·8%)	0·55 (0·43-0·72) <0·001	0·72 (0·46-1·14) 0·160	136 (8·0%)	0·41 (0·32-0·53) <0·001	0·65 (0·43-0·99) 0·043
LLDAS	6081 (47·9%)	0·65 (0·56-0·75) <0·001	0·59 (0·43-0·75) <0·001	813 (47%)	0·41 (0·35-0·48) <0·001	0·54 (0·42-0·70) <0·001

LLDAS – Lupus Low Disease Activity State; operational definitions of remission and LLDAS are available in Table 1

Visit by visit analysis refers to the effect of being in LLDAS/remission at a single visit on subsequent flare or damage accrual (compared to visits not in LLDAS/remission). % time analysis refers to comparison of damage accrual and flare across the observation period in patients who spent $\geq 50\%$ vs $< 50\%$ of total observed time in LLDAS/remission.

Table 5: Effect of sustained remission or LLDAS on damage accrual ((n patients=1707, n visits=12689)

	Patients with ≥ 2 consecutive visits n (%)	Observed period (years) Median (IQR)	Damage accrual		RR for damage accrual (95% CI)	<i>p</i>
			No n (%)	Yes n (%)		
Definition 1	303 (17.8%)	2.52 (1.81 – 3.00)	298 (98.3%)	5 (1.7%)	0.11 (0.04-0.26)	<0.001
Definition 2	222 (13.0%)	2.35 (1.70 – 2.99)	221 (99.5%)	1 (0.5%)	0.03 (0.00-0.21)	<0.001
Definition 3	806 (47.2%)	2.51 (1.78 – 3.03)	787 (97.6%)	19 (2.4%)	0.14 (0.08-0.22)	<0.001
Definition 4	490 (28.7%)	2.58 (1.86 – 3.05)	478 (97.5%)	12 (2.5%)	0.15 (0.09-0.27)	<0.001
Definition 5	160 (9.4%)	2.22 (1.79 – 2.99)	157 (98.1%)	3 (1.9%)	0.13 (0.04-0.39)	<0.001
Definition 6	121 (7.1%)	2.12 (1.67 – 2.93)	120 (99.2%)	1 (0.8%)	0.06 (0.01-0.39)	0.004
Definition 7	402 (23.6%)	2.36 (1.71 – 3.00)	394 (98.0%)	8 (2.0%)	0.13 (0.06-0.26)	<0.001
Definition 8	235 (13.8%)	2.25 (1.81 – 2.99)	231 (98.3%)	4 (1.7%)	0.11 (0.04-0.30)	<0.001
LLDAS	1071	2.30	1040	31	0.17 (0.12-0.24)	<0.001

	(61.7%)	(1.74 – 2.99)	(97.1%)	(2.9%)	0.25)	
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LLDAS – Lupus Low Disease Activity State; operational definitions of remission and LLDAS available in Table 1.

Sustained defined as 2 or more consecutive visits.

Table 6: Effect of LLDAS excluding remission on disease flares and damage accrual (n**patients=1707, n visits=12689)**

Independent Variable	Outcome					
	Visits by visit analysis			% time (<50% or ≥50%)		
	N (%) visits	Flare at subsequent visit HR (95% CI) p value	Damage Accrual HR (95% CI) p value	N (%) patients	Flare HR (95% CI) p value	Damage Accrual HR (95% CI) p value
LLDAS including overlap with remission	6081 (47.9%)	0.65 (0.56 – 0.75) <0.001	0.59 (0.45 – 0.76) <0.001	803 (47.0%)	0.41 (0.35 – 0.48) <0.001	0.54 (0.42-0.70) <0.001
LLDAS excluding remission (definition 1)*	4664 (36.8%)	0.70 (0.60 – 0.82) <0.001	0.58 (0.44 – 0.78) <0.001	628 (36.8%)	0.44 (0.38 – 0.51) <0.001	0.60 (0.46 – 0.78) <0.001
LLDAS excluding remission (definition 2)*	5045 (39.8%)	0.70 (0.60 – 0.81) <0.001	0.59 (0.44 – 0.78) <0.001	657 (38.5%)	0.44 (0.38 – 0.51) <0.001	0.59 (0.45 – 0.76) <0.001
LLDAS excluding remission (definition 3)*	1928 (15.2%)	0.61 (0.49 – 0.75) <0.001	0.74 (0.51 – 1.06) 0.099	331 (19.4%)	0.36 (0.30 – 0.44) <0.001	0.81 (0.59 – 1.12) 0.210
LLDAS excluding remission (definition 4)*	3674 (29.0%)	0.65 (0.55 – 0.78) <0.001	0.64 (0.47 – 0.87) 0.004	494 (28.9%)	0.37 (0.32 – 0.44) <0.001	0.63 (0.47 – 0.83) 0.001
LLDAS excluding remission (definition 5)*	5312 (41.9%)	0.70 (0.61 – 0.82) <0.001	0.59 (0.45 – 0.78) <0.001	727 (42.6%)	0.46 (0.40 – 0.54) <0.001	0.58 (0.45 – 0.75) <0.001
LLDAS excluding remission (definition 6)*	5500 (43.3%)	0.70 (0.60 – 0.81) <0.001	0.60 (0.46 – 0.78) <0.001	735 (43.1%)	0.45 (0.39 – 0.53) <0.001	0.58 (0.45 – 0.75) <0.001
LLDAS excluding remission (definition 7)#	3925 (30.9%)	0.73 (0.63 – 0.86) <0.001	0.59 (0.44 – 0.80) 0.001	596 (34.9%)	0.46 (0.40 – 0.54) <0.001	0.58 (0.44 – 0.77) <0.001
LLDAS excluding remission (definition 8)*	4839 (38.1%)	0.71 (0.60 – 0.83) <0.001	0.59 (0.44 – 0.78) <0.001	667 (39.1%)	0.45 (0.38 – 0.52) <0.001	0.58 (0.44 – 0.75) <0.001

LLDAS – Lupus Low Disease Activity State; operational definitions of LLDAS and remission available in Table 1.

*Defined as those visits that meet the operational definition of LLDAS but not the specified remission definition

Visit by visit analysis refers to the effect of being in LLDAS/remission at a single visit on subsequent flare or damage accrual (compared to visits not in remission). % time analysis refers to comparison of damage accrual and flare across the observation period in patients who spent $\geq 50\%$ vs $< 50\%$ of total observed time in LLDAS/remission.

Figure 1

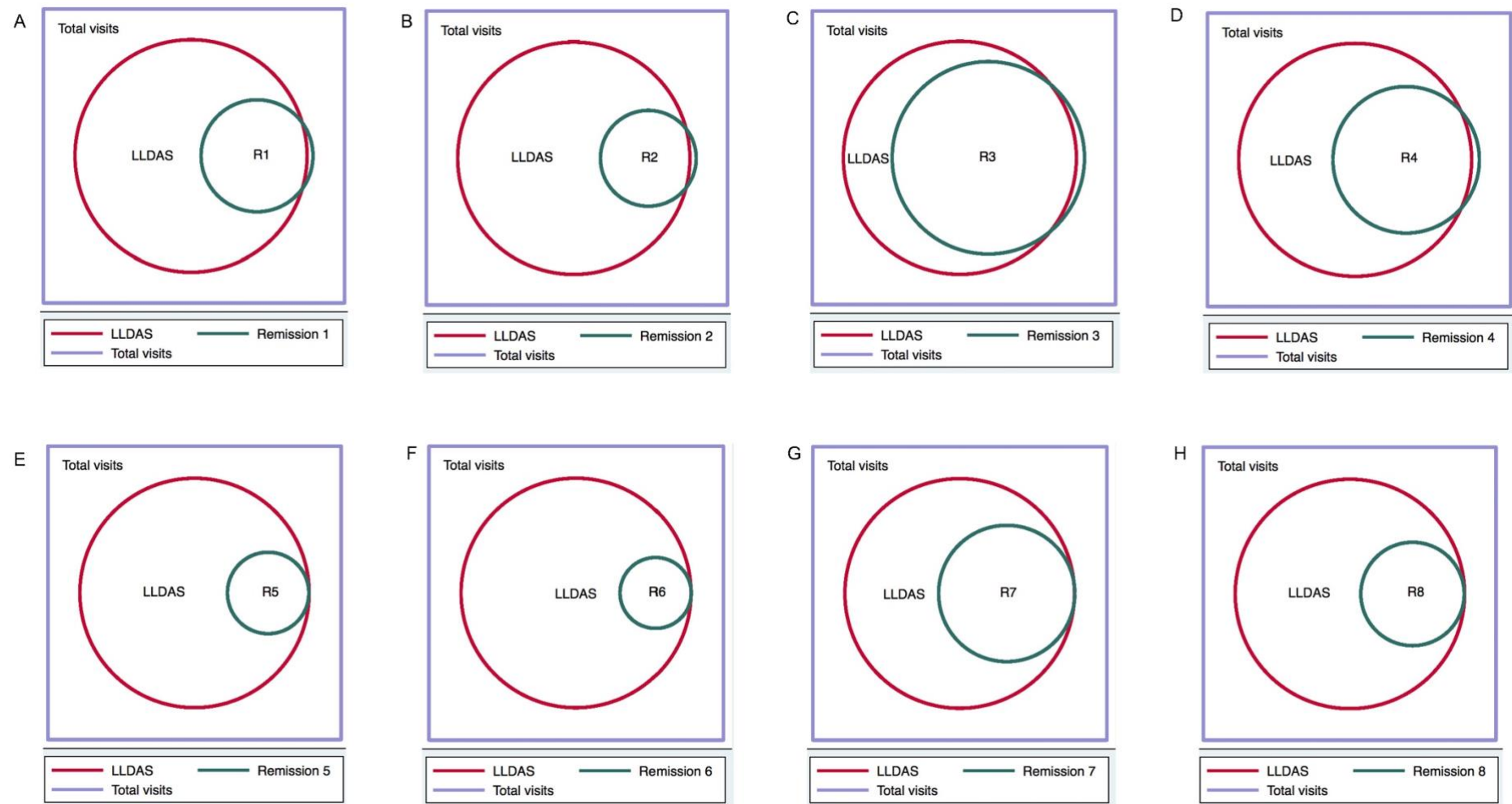


Figure 1 Caption: Venn diagrams depicting overlap between each remission definition and LLDAS. Of the visits that fulfilled LLDAS criteria (n=6091) 23·25% also fulfilled remission definition 1 (Figure 1A), 17·01% also fulfilled definition 2 (Figure 1B), 68·10% also fulfilled definition 3 (Figure 1C), 39·50% also fulfilled definition 4 (Figure 1D), 12·64% also fulfilled definition 5 (Figure 1E), 9·56% also fulfilled definition 6 (Figure 1F), 35·43% also fulfilled definition 7 (Figure 1G), and 20·42% also fulfilled definition 8 (Figure 1H). For remission definitions 1 to 4, 1·45% to 6·08% of visits that were not in LLDAS (n=6626) fulfilled the criteria for remission.

Supplementary Table 1: Summary of Statistical Analyses

	Visit by visit analysis		Sustained LLDAS/remission
	Time dependent Cox proportional hazards model (visit by visit analysis of the entire observation period)	Time dependent Cox proportional hazards model (visit by visit analysis of the entire observation period)	Generalized Linear Model (Log-binomial regression)*
Unit of analysis	Visits: 12,717	Visits: 12,717	Participants: 1,707
Exposure	In LLDAS/remission at each visit or not	Spent at least 50% of followup time in LLDAS/remission vs less than 50% of followup time in LLDAS/remission	Sustained LLDAS/remission (defined as 2 or more consecutive visits in LLDAS/remission) vs never in sustained LLDAS/remission
Outcome	Primary: Damage accrual Secondary: Flare	Primary: Damage accrual Secondary: Flare	Primary: Damage accrual in the next annual visit where SDI recorded, after period of sustained LLDAS/remission
Measure of association**	Hazard Ratio (HR)	Hazard Ratio (HR)	Risk Ratio (RR)
Interpretation	Hazard of damage accrual/flare in subsequent visit if in LLDAS/remission compared to not in LLDAS/remission in current visit	Hazard of damage accrual/flare if 50% or more of followup time in LLDAS/remission compared to if not in LLDAS/remission for at least 50% of followup time	Risk of damage accrual/flare in subsequent visit if sustained LLDAS/remission present for given period of time, compared to those who never had sustained LLDAS/remission

*Generalised Linear Model with Poisson regression did not alter the results

**Predefined statistical significance $p \leq 0.05$, with 95% confidence intervals presented

LLDAS – lupus low disease activity state, remission – 8 definitions as described by the DORIS taskforce. For operational definitions of LLDAS and remission please see Table 1.

Chapter 8

Integrative Discussion and Conclusion

Summary of research findings

The broad aim of this thesis was to undertake the validation studies required to evaluate whether LLDAS is suitable as the first ever tangible treat to target endpoint for SLE. In order to achieve this, members of the Asia Pacific Lupus Collaboration set up one of the largest prospective SLE cohorts that followed 1735 patients for just over 2 years.

The following is a summary of the key findings of this thesis:

- First, I was able to show that LLDAS has utility as a T2T endpoint – it is attainable and sustainable. Both in cross-sectional and longitudinal analysis, LLDAS was attained in just under half of all visits, with almost 80% of the cohort being able to attain LLDAS on at least one occasion and two thirds of the patients being able to sustain LLDAS for a minimum of three months.
- Second, I was able to identify important patient and disease characteristics that are associated with LLDAS attainment. Shorter disease duration, discoid rash, renal disease and serological activity were associated with lower frequency of LLDAS attainment. Patients from countries with higher national social wealth were more likely to attain LLDAS, highlighting the importance of access to medical specialists, diagnostic tests and immunosuppressants as crucial for successful disease management.
- Third, I demonstrated that attainment of LLDAS was associated with improved HR-QoL. Current disease activity measures do not consider HR-QoL, and PRO instruments do not specifically take into account disease activity and organ damage. Thus, these two domains

of assessment of SLE patients' health status remain separate. Being able to provide a link between LLDAS and better HR-QoL further adds to its validity as a treatment target.

- Fourth, I studied the construct validity of LLDAS by comparing it to SLE expert assessment of target treatment states. These studies demonstrated that there was overall good agreement between the operational definition of LLDAS and expert opinion of a conceptual low activity state. Importantly, LLDAS did not inappropriately capture patients with higher disease activity. At the same time LLDAS was more stringent than expert opinion, particularly in the domain of allowable glucocorticoid dose.
- Fifth, in a prospective analysis of association of LLDAS with morbidity-driving outcomes such as disease flares and damage accrual, I demonstrated that attainment of this target state even at a single visit resulted in a 30-40% reduction in subsequent disease flare and damage accrual. Furthermore, the magnitude of the protective effect increased incrementally with increasing durations of both cumulative and sustained time spent in LLDAS. These findings provide robust criterion validity for LLDAS as a T2T endpoint.
- Sixth, not only was the protective association of LLDAS with reduced damage accrual also present in patients with active disease at baseline, the magnitude of this association was greater in this subgroup of patients compared to those with less active baseline disease.
- Lastly, I describe the first prospective evaluation of DORIS remission, a conceptual gold standard treatment endpoint. The remission definitions differed greatly in relation to their utility, reflected in rates of attainment, indicating the importance of specific definitions to the study of remission states. LLDAS was more attainable and more sustainable than any of the proposed DORIS remission definitions. Significant protection from damage accrual was seen for all but the most stringent definitions of remission, likely due to low rates of attainment, with hazard ratios very similar to that of LLDAS. Importantly, exclusion of patients in remission from the subset in LLDAS did not confer any loss of the protection

associated with LLDAS, except for the least stringent definition of remission – clinical remission on treatment. In sustained analysis of ≥ 2 consecutive visits remission was associated with reduced risk of damage, with significant associations and greater magnitude of protection seen for the more stringent definitions of remission. This suggests that sustaining rather than just attaining a target state yields greater protective effects.

Comparison to other work

Since the publication of the original paper describing the operational definition of LLDAS, several international research groups have studied this endpoint in their respective cohorts of SLE patients.^{124-128,140} Remarkably similar associations of attainment of LLDAS with significant reduction in damage accrual have been found, with a ‘dose dependent’ relationship between time spent in LLDAS and reduction in risk of damage. In particular, three separate studies have shown that $\geq 50\%$ of observed time in LLDAS corresponds to a 35-63% reduction in damage accrual, consistent with my findings presented in chapter 6.^{124,125,140}

It is known that there is a correlation between damage accrual and increased risk of mortality in SLE, particularly from causes such as sepsis, malignancy and end organ failure.⁴⁶ Given the proven association of LLDAS attainment with reduced damage accrual, it can be extrapolated that LLDAS will also reduce risk of mortality. Furthermore, a direct link between LLDAS attainment and mortality was very recently demonstrated in a retrospective cohort study of 200 Norwegian SLE patients followed for a mean of 10 years.¹⁴⁰ The authors showed that not only was $\geq 50\%$ observed time spent in LLDAS protective against damage accrual, it was also associated with an almost 70% reduction in mortality (HR 0.31, $p < 0.01$).

Similar to the studies presented in chapter 7 of this thesis, others have compared LLDAS to remission and their respective effects on patient outcomes.^{124-126,128} In all but one study, LLDAS was more attainable than any remission definition, the only exception found in a small cohort of Caucasian patients with high rates of remission, where 84% of patients in LLDAS were also in remission.¹²⁸ The largest of these studies was done in the Hopkins Lupus Cohort, a longitudinal cohort study that has been recruiting patients for close to 30 years. A longer duration of observation in this study allowed for greater differentiation of the protective effects of the various types of remission, which were not observed in our cohort with shorter follow up. LLDAS was 2-3 times more frequently attained than remission, and whilst both were associated with reduced damage accrual, a shorter duration of remission was required for a significant protective effect, suggesting that albeit being infrequently achieved, remission may in fact have a stronger association with protection from damage.¹²⁴

Other research groups have proposed varying definitions of a low disease activity state. Most notably these have arisen from large and well-established SLE cohorts in Canada and South America.^{134,141,142} The Grupo Latino Americano De Estudio de Lupus (GLADEL) group reported the effects of a 'low disease activity state' (LDAS) defined as SLEDAI \leq 4, prednisolone dose \leq 7.5 mg/day, and immunosuppressants allowed.¹³⁴ The selection of these data points reflected the data available to those investigators, rather than any 'a priori' process to select criteria, as was done for LLDAS. The University of Toronto Lupus Clinic at the Center for Prognostic Studies proposed a 'low disease activity' defined as SLEDAI-2K score <3 (with or without positive serology results), based on the presence of only 1 clinical manifestation of rash, alopecia, mucosal ulcers, pleurisy, pericarditis, fever, thrombocytopenia, or leukopenia, and antimalarials allowed.¹⁴¹ Attainment of either of these states was each associated with significant protection from permanent organ damage,^{134,141} albeit at a smaller magnitude to the APLC LLDAS definition. The

quality of the data, analysis, and conclusions in these studies is not in doubt. However, cautious interpretation is required of SLE endpoints created using data from existing cohorts. Deriving endpoint definitions to fit in with the collected variables in an existing dataset influences the choice of concepts included in the definition and limits the ability to measure all facets of the proposed endpoint, therefore compromising its face and content validity. Both 'LDAS' and 'LDA' have elements that are similar to the LLDAS definition, but neither is as comprehensive. Both solely rely on the SLEDAI as a descriptor of disease activity, and are therefore subject to the inherent limitations of a binary instrument. In comparison, the addition of PGA and requirement for no new activity in the LLDAS definition overcomes the potential floor effects of the SLEDAI. As such, and especially given the 4 prospective studies reported in this thesis, LLDAS currently represents the most methodologically robust endpoint for SLE.

Implications for research and clinical practice

The findings of studies presented in this thesis, further supported by publications from independent research groups, validate LLDAS as a first ever attainable and sustainable treatment endpoint for SLE. This body of evidence supports the use of LLDAS in clinical trials and patient care, and has the potential to change current practice in both.

LLDAS is now being tested as a secondary outcome measure in clinical trials of existing and novel therapies. In a head to head superiority comparison of mycophenolate and azathioprine in patients with active SLE, LLDAS was assessed as a secondary discriminant outcome measure, with more patients in the mycophenolate treatment group attaining and sustaining LLDAS compared to patients treated with azathioprine.¹²⁹ In studies of novel therapies including B-cell targeting drugs such as belimumab and atacicept, and the type I interferon receptor blocker anifrolumab, LLDAS was able to discriminate responders to active drug from placebo.^{130,132,143} Moreover, LLDAS was a

more stringent discriminator compared to currently used responder indices such as SRI and BILCA.^{130,132,143} The implications of this for design of future phase III trials is enormous, as a more discriminatory endpoint may enable smaller trials with more robust findings. Of course for this to come to fruition, LLDAS needs to be approved as a discriminatory outcome measure by governing agencies who decide whether a novel therapy is accepted onto the pharmaceutical market, including the Food and Drug Administration and the European Medicines Agency.

Several important steps need to occur for LLDAS to be adopted as a treatment target in routine clinical practice. First, the ease and practicality of using LLDAS in routine patient assessment needs to be addressed in a pilot study based in a non-research focused rheumatology practice. Further down the track the use of electronic platforms or apps, similar to the DAS-28 calculator for rheumatoid arthritis, can make LLDAS more user friendly. Moreover, LLDAS needs to be recommended as a target in treatment guidelines. The previous guidelines by the European League Against Rheumatism (EULAR) and the current American College of Rheumatology (ACR) were updated 7-9 years ago, respectively.^{30,32} The previous SLE EULAR guidelines provide recommendations on the assessment of disease activity using validated indices, monitoring for damage, co-morbidities and complications, but don't actually provide a benchmark as the goal of treatment.³⁰ The new 2019 EULAR guidelines make specific reference to low disease activity as a goal of treatment when remission cannot be attained, and cite domains 1, 3, and 4 of the LLDAS definition as the appropriate cut-offs for this state.¹⁴⁴ On the other hand, the ACR guidelines pertaining to monitoring and treatment of lupus nephritis, are more direct in defining a treatment response which is measurable in a single organ system.³² Third, in addition to the association with improved outcomes, attainment of LLDAS needs to be an economically attractive, or at least financially viable option for healthcare stakeholders in order to offset the cost of infrastructure and treatment required to deploy LLDAS into clinical practice. In a recent single centre study,

attainment of LLDAS was shown to be associated with lower direct annual medical costs for SLE patients (Yeo A.I., Koelmeyer R., et al., *in press*).

Limitations

As with any study arising from an observational cohort, there are some inherent limitations to the work presented in this thesis. In the studies conducted I was able to demonstrate clear associations of LLDAS attainment with improved patient outcomes, however the observational nature of the cohort limits conclusions on the causal relationship between LLDAS and disease outcomes. In order to test this, an interventional trial using a T2T approach with non-attainment of LLDAS as an inflection point for treatment escalation, compared to conventional management, would need to be designed, as has been done for rheumatoid arthritis.²⁰ Eighteen percent of the prospectively followed cohort forming the basis of studies presented in Chapters 6 & 7 did not have a visit in the last 12 months of the study period, potentially creating drop out bias. However, given the observational rather than interventional nature of the studies, this is less likely to be problematic. The majority of our patients were of Asian ethnicity, potentially questioning the generalisability of the presented results. However, LLDAS has now been studied in multiple multi-ethnic cohorts including Europeans, African-Americans, and Hispanics, with remarkably similar associations between LLDAS attainment and reduced damage accrual reported.^{124-128,140} The majority of our cohort had prevalent disease, with only 12% of patients reporting a disease duration of less than 2 years. Utilising a T2T strategy may be more effective early in disease course, particularly in preventing irreversible damage, as has been shown with a T2T approach in early rheumatoid arthritis.¹⁴⁵ Thus the effects of attaining and sustaining LLDAS in an inception cohort of SLE patients should be studied.

The mean follow up in our study was just over 2 years, and whilst this was sufficient to detect the protective associations of LLDAS, it did not provide enough power to detect significant associations with the most stringent and hence least frequently attained definitions of remission. Recent retrospective analysis of a SLE cohort with a longer duration of follow up showed that compared to LLDAS, less cumulative time was needed to detect a protective effect for the more stringent definitions of remission.¹²⁴ The APLC cohort is being extended, potentially allowing the range of DORIS definitions of remission to be compared.

As well as potential limitations arising from the study design and nature of the cohort there are several points to be made about the LLDAS definition itself. The most contentious of these is the inclusion and allowable cut-off of prednisolone dose. Whilst in the ideal setting treatment endpoints for SLE should steer away from allowing prednisolone, the reality of the currently available therapies means that clinicians have to rely on the use of glucocorticoids to achieve, and sometimes maintain, target states. Therefore, any target state should account for the use of glucocorticoids in its definition, until such time that newer therapies eliminate the need for their use. This creates a circular problem of effective therapies being needed to define target states, and target state definitions needed to evaluate new therapies. As such, at least for the time being, a 'safe' cut-off for prednisolone should remain in the definition of LLDAS. As noted in Chapter 6, altering the dose cut-off from 7.5 to 5 mg/day had no significant impact on the protective effect of LLDAS, suggesting that 7.5 mg/day is an appropriate cut-off for LLDAS.

The second potential limitation of the LLDAS definition is the lack of inclusion of a patient reported assessment of their disease state, which goes against the OMERACT recommendations for patient reported outcome measures to be used in clinical trials of SLE.⁶⁴ We felt that including a PRO from the outset in initial studies of LLDAS to be potentially problematic due to several well known

factors. First and foremost, patients' perceptions of their disease states are influenced by many factors outside of disease activity and as such can be difficult to correlate with physician performed assessments.^{41,99,100} Second, including a PRO would add a degree of complexity to the usability of LLDAS, particularly in routine practice. The decision was therefore taken by the expert panel to use HRQoL/PROs to validate LLDAS, rather to include a PRO in its definition. By showing a clear association of LLDAS with improved HR-QoL in the study described in chapter 4 of this thesis, I have at least in part addressed this limitation of LLDAS. Nonetheless, it may be worthwhile studying the inclusion of a simple and therefore easily deployable PRO such as a patient global assessment, and the consequent impact on the performance of the endpoint.

Future studies

There are a number of future studies that can build on the work produced in this thesis, which are summarised below:

- Ongoing longer follow up of the prospective longitudinal cohort. At the time of submission of this thesis the APLC cohort had close to four and half years of mean follow up with over two thousand patients. This would likely increase the power to detect significant associations with the more stringent definitions of remission and thus allow for stratification of T2T states based on their attainability relative to protective effects.
- The increased number of patients would also allow for an inception cohort subgroup analysis.
- Longitudinal association of LLDAS attainment with improvements in HR-QoL to assess the time dependent relationship between attainment of physician scored target state and impact on HR-QoL.

- Further sensitivity testing of the LLDAS definitions, including addition of a PRO to the definition.
- Subgroup analysis of the effects of LLDAS based on organ system involvement as has been done in retrospective cohorts.^{124,127}
- A randomised trial of T2T versus usual care, which will be pivotal for promoting LLDAS to key pharmaceutical governing agencies. Not only will this address impact on patient outcomes, but may also address the deployability of the instrument with assessment of the resources required for use in clinical practice.
- Lastly, the rich dataset provided by the ongoing follow up of the APLC cohort allows for exploration of multiple other research questions not directly related to LLDAS. Some of the topics that have begun to be investigated include comparison of ACR to SLICC classification criteria, the relationship between leukopaenia and disease activity, and predictors of renal disease outcomes.

Conclusion

In summary, the work presented in thesis provides robust validation of LLDAS as a treatment endpoint for SLE, attainment of which is here proven to be associated with improved patient outcomes. I have shown that LLDAS has utility – it is attainable and sustainable, particularly when compared to remission. Attainment of LLDAS is associated with significant protection from disease flares and irreversible organ damage, with a dose dependent relationship of increasing protective effect seen with increasing durations of time spent in LLDAS. It thus represents the first thoroughly validated treatment target state for SLE to allow the adoption of a T2T approach in routine patient care, and provides a robust and discriminative outcome measure for use in clinical trials. I hope

that the findings of this thesis help to change the approach to management of SLE patients and in time alter the landscape of available therapies.

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