LUPUS SCIENCE & MEDICINE™

LLDAS (lupus low disease activity state) and/or remission are associated with less damage accrual in patients with systemic lupus erythematosus from a primarily Mestizo population: data from the Almenara Lupus Cohort

Manuel Francisco Ugarte-Gil ,[1,2] Rocio Violeta Gamboa-Cardenas,[1,2] Cristina Reátegui-Sokolova ,[1,3] Victor Román Pimentel-Quiroz ,[1,3] Mariela Medina,[1] Claudia Elera-Fitzcarrald ,[1,2] Francisco Zevallos,[1] Cesar Augusto Pastor-Asurza,[1,4] Jeniffer Lofland,[5] Federico Zazzetti,[6] Chetan S Karyekar,[5] Graciela S Alarcón,[7,8] Risto Alfredo Perich-Campos[1,4]

To cite: Ugarte-Gil MF, Gamboa-Cardenas RV, Reátegui-Sokolova C, *et al*. LLDAS (lupus low disease activity state) and/or remission are associated with less damage accrual in patients with systemic lupus erythematosus from a primarily Mestizo population: data from the Almenara Lupus Cohort. *Lupus Science & Medicine* 2022;**9**:e000616. doi:10.1136/lupus-2021-000616

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/lupus-2021-000616).

Preliminary results were presented at the 2020 American College of Rheumatology Congress: https://acrabstracts.org/abstract/lldas-low-lupus-disease-activity-state-and-remission-prevent-damage-accrual-in-systemic-lupus-erythematosus-sle-patients-in-a-primarily-mestizo-cohort/.

Received 12 November 2021
Accepted 4 February 2022

For numbered affiliations see end of article.

Correspondence to
Dr Manuel Francisco Ugarte-Gil; mugarte@cientifica.edu.pe

ABSTRACT

Objective To determine if achieving lupus low disease activity state (LLDAS) or remission prevents damage accrual in a primarily Mestizo population.

Methods Patients with SLE from a single-centre cohort with at least two visits occurring every 6 months were included. The definitions used were the following: for remission, the 2021 Definition Of Remission In SLE; and for LLDAS, the Asia Pacific Lupus Collaboration. Damage accrual was ascertained with the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). Univariable and three multivariable interval-censored survival regression models were done: (1) remission versus not on remission; (2) LLDAS/remission versus active; and (3) remission and LLDAS (not on remission) versus active. Three similar multivariable models were also examined considering the duration on each state. Possible confounders included in these analyses were gender, age at diagnosis, socioeconomic status, educational level, disease duration, antimalarial use and SDI at baseline.

Results Two hundred and eighty-one patients were included. Eighty-three patients (29.5%) showed increased SDI during the follow-up. In the analyses of remission, being on remission predicted a lower probability of damage (HR=0.456; 95% CI 0.256 to 0.826; p=0.010). In the analyses of LLDAS/remission, being on LLDAS/remission predicted a lower damage (HR=0.503; 95% CI 0.260 to 0.975; p=0.042). When both states were considered, remission but not LLDAS (not on remission) predicted a lower probability of damage (HR=0.423; 95% CI 0.212 to 0.846; p=0.015 and HR=0.878; 95% CI 0.369 to 2.087; p=0.768, respectively). When the duration of these states was taken into account, remission, LLDAS/remission and LLDAS not on remission were associated with a lower probability of damage accrual.

Conclusions LLDAS and/or remission were associated with a lower probability of damage accrual.

Key messages

What is already known about this subject?

- Remission and lupus low disease activity state (LLDAS) have been proposed as targets in SLE treatment.

What does this study add?

- This is the first study to use the original definition of remission and LLDAS in a Latin American population.
- Remission and LLDAS are associated with lower probability of damage in Latin American patients with SLE.

How might this impact on clinical practice or future developments?

- This study reinforces the relevance of remission and LLDAS as potential targets in the management of patients with SLE.

INTRODUCTION

SLE is a complex inflammatory autoimmune disease characterised by flares, damage accrual and diminished survival.[1] A treat-to-target strategy has been proposed for SLE[2]; however, for this approach to work, a uniform definition of the target, validated in several populations, is required.

The 2021 Definition Of Remission In SLE (DORIS) included the absence of clinical disease activity (clinical Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI-2K)=0 and physician global assessment (PGA) <0.5), with no or minimal intake of glucocorticoids (prednisone daily dose not higher than 5 mg/day) and/or

immunosuppressive drugs on stable maintenance dose.[3] However, as this target is not frequently achieved, an alternative outcome (lupus low disease activity state, LLDAS) has been proposed by the Asia Pacific Lupus Collaboration (APLC). This definition includes the following: SLEDAI-2K ≤4, which allows a low level of disease activity, without activity in major organ systems or new disease activity, PGA ≤1, prednisone daily dose not higher than 7.5 mg/day and/or immunosuppressive drugs on maintenance dose.[4] Of note, antimalarials are allowed for both remission and LLDAS.

In Hispanic populations (from the USA and Latin America), remission and LLDAS have been evaluated in the Grupo Latino Americano De Estudio del Lupus (GLADEL) and LUpus in MInorities: NAture vs. Nurture (LUMINA) cohorts[5 6]; however, in both cases, the definitions had to be somewhat modified due to the fact that same variables were just not available in these cohorts. The main missing variable in both cohorts was the PGA, a variable that allows the evaluation of some less frequent manifestations not included in the disease activity indices.

This study evaluates the impact of the original definitions of remission and LLDAS on damage accrual in a primarily Mestizo Peruvian population.

METHODS

The Almenara Lupus Cohort has been previously described.[7] In short, this cohort was started in 2012 at the Rheumatology Department of the Hospital Guillermo Almenara Irigoyen in Lima, Peru. Patients who signed the informed consent were recruited and followed every 6 months. Evaluations included an interview, medical records review, physical examination and laboratory tests. In these analyses, we have included patients with at least two visits and with all the variables needed to define disease activity states.

SLE was defined using the 1997 revised American College of Rheumatology criteria. Remission and LLDAS were defined according to the 2021 DORIS[3] and APLC[4] definitions. Disease activity states were ascertained at each visit. Damage was ascertained with the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI).[8]

Statistical analyses

Categorical variables were reported as numbers and percentages, and numerical variables as mean and SD. Univariable and multivariable interval-censored survival regression models were used. Three models were done: (1) remission versus not on remission; (2) LLDAS (including those on remission) versus not on LLDAS; and (3) remission and LLDAS (not on remission) versus active. Possible confounders included in the multivariable analyses were gender, age at diagnosis, socioeconomic status, educational level, disease duration at baseline, antimalarial use and SDI. Confounders were determined at the same visit as disease activity state, but SDI was assessed at the subsequent visit.

Alternative models including the number of years (consecutively or not) the patient was on remission or on LLDAS at the index visit were performed.

Antimalarial use and disease activity state were included as time-dependent covariables in all models.

P<0.05 was considered significant in all analyses. All analyses were performed using SPSS V.27.0.

Table 1 Characteristics of the patients at baseline

Characteristics	n (%) or mean (SD)
Female gender	260 (92.5)
Age at diagnosis, years	35.8 (13.3)
Disease duration, years	7.0 (3.9)
SLEDAI-2K	1.4 (2.5)
SDI	1.3 (1.5)
Prednisone daily dose, mg/day	2.1 (3.4)
Antimalarial use	
Never	10 (3.6)
Past	19 (6.8)
Current	252 (89.7)
Immunosuppressive drug use	
Never	61 (21.7)
Past	70 (24.9)
Current	150 (53.4)

SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2K.

RESULTS

Two hundred and eighty-one patients were included, of whom 260 (92.5%) were female, with a mean (SD) age at diagnosis of 35.8 (13.3) years and a mean disease duration at baseline of 9.1 (7.0) years. Patients had a mean of 4.8 (1.9) visits and a mean follow-up of 2.7 (1.1) years. Eighty-three patients (29.5%) showed increased SDI during the follow-up. The characteristics of the patients are depicted in table 1.

Five-hundred and eighty visits (54.6%) were categorised as being on remission and 482 (45.4%) as not on remission. Based on LLDAS, 726 (68.4%) visits corresponded to LLDAS and 336 (31.6%) not on LLDAS. The proportion of the visits the patients were on remission or LLDAS is depicted in online supplemental table 1.

In the first approach, when we evaluated the impact of the disease state at a given visit on the probability of damage accrual, we found that being on remission was associated with a lower probability of damage accrual (HR=0. 456; 95% CI 0.256 to 0.826; p=0.010) (table 2, model 1); being on LLDAS (remission included) was also associated with a lower probability of damage accrual (HR=0. 503; 95% CI 0.260 to 0.975; p=0.042) (table 2,

Table 2 Impact of disease activity state on damage accrual

	Univariable	P value	Model 1 HR (95% CI)	P value	Model 2 HR (95% CI)	P value	Model 3 HR (95% CI)	P value
Not on remission	Ref		Ref					
Remission	0.471 (0.273 to 0.815)	0.007	0.456 (0.252 to 0.826)	0.010				
Active	Ref				Ref			
LLDAS/remission	0.509 (0.282 to 0.920)	0.025			0.503 (0.260 to 0.975)	0.042		
Active	Ref						Ref	
LLDAS (not on remission)	0.871 (0.374 to 2.027)	0.748					0.878 (0.369 to 2.087)	0.768
Remission	0.444 (0.240 to 0.824)	0.010					0.423 (0.212 to 0.846)	0.015
Age at diagnosis	1.003 (0.981 to 1.026)	0.778	1.016 (0.990 to 1.042)	0.238	1.017 (0.991 to 1.044)	0.208	1.017 (0.991 to 1.044)	0.204
Gender, female	0.637 (0.213 to 1.903)	0.419	0.631 (0.229 to 1.738)	0.373	0.653 (0.226 to 1.887)	0.431	0.646 (0.227 to 1.835)	0.412
Educational level, years	0.936 (0.847 to 1.003)	0.189	0.877 (0.748 to 1.030)	0.110	0.889 (0.756 to 1.045)	0.155	0.879 (0.749 to 1.031)	0.113
Socioeconomic status								
Low	Ref		Ref		Ref		Ref	
Medium	1.411 (0.759 to 2.622)	0.276	0.882 (0.405 to 1.919)	0.759	0.908 (0.410 to 2.013)	0.813	0.871 (0.397 to 1.910)	0.871
High	0.72 (0.418 to 2.263)	0.948	0.337 (0.080 to 1.423)	0.139	0.349 (0.090 to 1.514)	0.166	0.340 (0.081 to 1.432)	0.141
Disease duration at baseline, years	1.052 (1.011 to 1.095)	0.012	1.062 (1.017 to 1.109)	0.006	1.061 (1.016 to 1.108)	0.008	1.064 (1.018 to 1.111)	0.006
Antimalarial use								
Current	Ref		Ref					
Past	0.983 (0.358 to 2.695)	0.973	0.870 (0.281 to 2.696)	0.809	0.921 (0.293 to 2.892)	0.888	0.872 (0.274 to 2.780)	0.818
Never	1.614 (0.259 to 10.051)	0.608	1.629 (0.237 to 11.192)	0.620	1.607 (0.234 to 11.026)	0.629	1.601 (0.229 to 11.213)	0.635
SDI	1.177 (1.005 to 1.378)	0.043	1.044 (0.859 to 1.269)	0.668	1.052 (0.863 to 1.282)	0.614	1.038 (0.852 to 1.264)	0.711

Model 1: remission versus not on remission.
Model 2: LLDAS (including remission) versus active.
Model 3: remission, LLDAS (not on remission) and active.
LLDAS, lupus low disease activity state; Ref, reference; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

model 2). When the three states were included (remission, LLDAS (not on remission) and active), remission was associated with a lower probability of damage accrual (HR=0.423; 95% CI 0.212 to 0.846; p=0.015) but LLDAS (not on remission) was not (HR=0.878; 95% CI 0.369 to 2.087; p=0.768) (table 2, model 3).

In the alternative approach, when we evaluated the time in years a patient was on each state, we found that the higher the number of years on remission, the lower the probability of damage accrual (HR=0.554; 95% CI 0.364 to 0.843; p=0.006) (table 3, model 1). Also, the higher the number of years on LLDAS (remission included), the lower the probability of damage accrual (HR=0.458; 95% CI 0.300 to 0.700; p<0.001) (table 3, model 2). When the three states were included, the number of years on remission (HR=0.495; 95% CI 0.316 to 0.776; p=0.002) and on LLDAS (not on remission) (HR=0.343; 95% CI 0.161 to 0.7311; p=0.006) was associated with a lower the probability of damage accrual; these analyses are depicted in table 3 (model 3).

DISCUSSION

In this primarily Mestizo prevalent lupus cohort, remission and LLDAS were associated with less damage accrual, independent of other well-known risk factors for this endpoint; this is consistent with other reports.[5 6 9 10]

The rate of remission and LLDAS in this cohort was higher than the ones reported in the GLADEL and LUMINA cohorts.[5 6] This could be due to the use of different definitions of remission and LLDAS (eg, in the GLADEL cohort, the analyses included complete remission (SLEDAI including serology=0) with treatment) or due to differences in treatments given the characteristics of the cohorts or the time at which patients were recruited into them (the GLADEL and LUMINA cohorts recruited patients towards the end of the 1990s and early 2000s, whereas the Almenara patients were recruited only over the last 10 years or so). Additionally, remission is less likely to be achieved early in the course of the disease,[11] and the GLADEL and LUMINA cohorts included patients with a shorter disease duration. Our rates, however, are similar to those from Europe[9] and Asia.[12]

The DORIS group has recently proposed that duration should not be included in the definition of remission[3]; nevertheless, a durable remission should be the ideal treatment target. Our results showed that the longer the patient remains on remission or LLDAS, the lower the probability of accruing damage, which is consistent with

Table 3 Impact of number of years on each disease activity state on damage accrual

	Model 1 HR (95% CI)	P value	Model 2 HR (95% CI)	P value	Model 3 HR (95% CI)	P value
Not on remission	Ref					
Remission	0.554 (0.364 to 0.843)	0.006				
Active			Ref			
LLDAS/remission			0.458 (0.300 to 0.700)	<0.001		
Active					Ref	
LLDAS (not on remission)					0.343 (0.161 to 0.731)	0.006
Remission					0.495 (0.316 to 0.776)	0.002
Age at diagnosis	1.012 (0.986 to 1.039)	0.368	1.017 (0.991 to 1.042)	0.218	1.017 (0.992 to 1.043)	0.190
Gender, female	0.652 (0.232 to 1.831)	0.417	0.721 (0.266 to 1.954)	0.520	0.711 (0.268 to 1.890)	0.495
Educational level, years	0.868 (0.731 to 1.031)	0.108	0.876 (0.742 to 1.035)	0.120	0.878 (0.746 to 1.034)	0.118
Socioeconomic status						
Low	Ref		Ref		Ref	
Medium	0.964 (0.439 to 2.119)	0.928	0.969 (0.412 to 2.125)	0.937	0.959 (0.441 to 2.086)	0.916
High	0.323 (0.074 to 1.406)	0.132	0.383 (0.092 to 1.586)	0.185	0.398 (0.098 to 1.627)	0.200
Disease duration at baseline, years	1.058 (1.015 to 1.104)	0.008	1.064 (1.020 to 1.111)	0.004	1.065 (1.020 to 1.112)	0.004
Antimalarial use						
Current	Ref					
Past	0.904 (0.297 to 2.747)	0.858	0.877 (0.299 to 2.571)	0.810	0.886 (0.305 to 2.573)	0.824
Never	1.677 (0.238 to 11.825)	0.604	1.450 (0.187 to 11.241)	0.722	1.396 (0.184 to 10.602)	0.747
SDI	1.085 (0.902 to 1.306)	0.387	1.102 (0.914 to 1.042)	0.307	1.197 (0.916 to 1.337)	0.294

Model 1: remission versus not on remission.
Model 2: LLDAS (including remission) versus active.
Model 3: remission, LLDAS (not on remission) and active.
LLDAS, lupus low disease activity state; Ref, reference; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

previous reports.[6 13 14] Additionally, remission, regardless of its duration, was associated with a lower probability of damage accrual, but LLDAS, excluding remission, was not associated with damage accrual in the original model (definition at each visit); however, it was associated with a lower probability of damage accrual when the duration of LLDAS was taken into account. These results are consistent with data reported by other groups of investigators, including the Hopkins Lupus Cohort and the Padua Lupus Clinic.[13–15]

Our study has, however, some limitations. First, as this is a prevalent cohort, we cannot exclude the impact of disease characteristics before the baseline or intake visit. Second, the relatively small sample size precludes us from making stronger conclusions. The main strength of this study is that it is the first to evaluate the impact of the 2021 DORIS definition of remission and the original APLC definition of LLDAS on damage in a primarily Mestizo Latin American population.

In conclusion, being on LLDAS and/or remission is associated with a lower probability of damage accrual. For LLDAS, a minimum duration on such a state seems to be necessary in order for the risk of damage accrual to be diminished.

Author affiliations
[1]Rheumatology, Hospital Nacional Guillermo Almenara Irigoyen, EsSalud, Lima, Peru
[2]Grupo Peruano de Estudio de Enfermedades Autoinmunes Sistémicas, Universidad Cientifica del Sur, Lima, Peru
[3]Unidad de Investigación Para La Generación y Síntesis de Evidencias en Salud, Universidad San Ignacio de Loyola, Lima, Peru
[4]School of Medicine, Universidad Nacional Mayor de San Marcos, Lima, Peru
[5]Janssen R&D, Spring House, Pennsylvania, USA
[6]Medical Affairs, Jan-Cil Argentina, Buenos Aires, Argentina
[7]Heersink School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA
[8]School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru

Twitter Manuel Francisco Ugarte-Gil @mugartegil

Contributors All authors were involved in drafting or revising this article critically for important intellectual content, and all authors approved the final version to be published. MFU-G has full access to all of the data from the study and takes responsibility for their integrity and the accuracy of the analyses performed.

Funding These analyses were done as part of a research grant from Janssen. Additionally the Almenara Lupus Cohort was partially supported by institutional grants from EsSalud (1483-GCGP-ESSALUD-2013, 1733-GCGP-ESSALUD-2014 and 2015 Kaelin Prize 04-IETSI-ESALUD-2016), Pan American League of Associations for Rheumatology (PANLAR) (2015 PANLAR Prize and 2018 H Ralph Schumacher MD/JCR/PANLAR Prize), and Fundación Instituto Hipólito Unanue.

Competing interests MFU-G has grant support from Janssen and Pfizer. RVG-C has grant support from Pfizer. CR-S and VRP-Q have grant support from Janssen. JL, FZ and CSK are employees of Janssen Scientific Affairs. All other authors declare no other conflicts of interest.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the Hospital Guillermo Almenara Irigoyen Institutional Review Board (3474-OCID-G-RAA-ESSALUD-11, 271-CEI-CIDG-RAA-ESSALUD-13, 302-CEI-ICD-G-RAA-14, 3027-OCID-G-RAA-ESSALUD-15 and 4072-OCID-G-HNGAI-ESSALUD-2017). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs

Manuel Francisco Ugarte-Gil http://orcid.org/0000-0003-1728-1999
Cristina Reátegui-Sokolova http://orcid.org/0000-0003-3421-2717
Victor Román Pimentel-Quiroz http://orcid.org/0000-0002-3638-7054
Claudia Elera-Fitzcarrald http://orcid.org/0000-0001-7271-2523

REFERENCES

1 Pons-Estel GJ, Ugarte-Gil MF, Alarcón GS. Epidemiology of systemic lupus erythematosus. *Expert Rev Clin Immunol* 2017;13:799–814.
2 van Vollenhoven RF, Mosca M, Bertsias G, *et al*. Treat-to-target in systemic lupus erythematosus: recommendations from an international Task force. *Ann Rheum Dis* 2014;73:958–67.
3 van Vollenhoven RF, Bertsias G, Doria A, *et al*. 2021 DORIS definition of remission in SLE: final recommendations from an international Task force. *Lupus Sci Med* 2021;8:e000538.
4 Franklyn K, Lau CS, Navarra SV, *et al*. Definition and initial validation of a lupus low disease activity state (LLDAS). *Ann Rheum Dis* 2016;75:1615–21.
5 Ugarte-Gil MF, Wojdyla D, Pons-Estel GJ, *et al*. Remission and low disease activity status (LDAS) protect lupus patients from damage occurrence: data from a multiethnic, multinational Latin American lupus cohort (GLADEL). *Ann Rheum Dis* 2017;76:2071–4.
6 Alarcón GS, Ugarte-Gil MF, Pons-Estel G, *et al*. Remission and low disease activity state (LDAS) are protective of intermediate and long-term outcomes in SLE patients. results from LUMINA (LXXVIII), a multiethnic, multicenter US cohort. *Lupus* 2019;28:423–6.
7 Ugarte-Gil MF, Gamboa-Cárdenas RV, Zevallos F, *et al*. High prolactin levels are independently associated with damage accrual in systemic lupus erythematosus patients. *Lupus* 2014;23:969–74.
8 Gladman D, Ginzler E, Goldsmith C, *et al*. The development and initial validation of the systemic lupus international collaborating Clinics/American College of rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996;39:363–9.
9 Saccon F, Zen M, Gatto M, *et al*. Remission in systemic lupus erythematosus: testing different definitions in a large multicentre cohort. *Ann Rheum Dis* 2020;79:943–50.
10 Ugarte-Gil MF, Mendoza-Pinto C, Reátegui-Sokolova C, *et al*. Achieving remission or low disease activity is associated with better outcomes in patients with systemic lupus erythematosus: a systematic literature review. *Lupus Sci Med* 2021;8:e000542.
11 Drenkard C, Villa AR, Garcia-Padilla C, *et al*. Remission of systematic lupus erythematosus. *Medicine* 1996;75:88–98.
12 Golder V, Kandane-Rathnayake R, Huq M, *et al*. Evaluation of remission definitions for systemic lupus erythematosus: a prospective cohort study. *The Lancet Rheumatology* 2019;1:e103–10.
13 Zen M, Iaccarino L, Gatto M, *et al*. The effect of different durations of remission on damage accrual: results from a prospective monocentric cohort of Caucasian patients. *Ann Rheum Dis* 2017;76:562–5.
14 Zen M, Iaccarino L, Gatto M, *et al*. Lupus low disease activity state is associated with a decrease in damage progression in Caucasian patients with SLE, but overlaps with remission. *Ann Rheum Dis* 2018;77:104–10.
15 Petri M, Magder LS. Comparison of remission and lupus low disease activity state in damage prevention in a United States systemic lupus erythematosus cohort. *Arthritis Rheumatol* 2018;70:1790–5.