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-Cárdenas,1,2 Cristina Reátegui-Sokolova 1,3 Victor Román Pimentel-Quiroz,1,3 Mariela Medina,1 Claudia Elena-Aslerry,1,2 Francisco Zevallos,1 Cesar Augusto Pastor-Asurza,1,4 Jeniffer Lofland,5 Federico Zazzetti,6 Chetan Karyekar,5 Graciela S Alarcón,7,8 Risto Alfredo Perich-Campos1,4

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=0.538; 95% CI 0.295 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=0.122; 95% CI 0.061 to 0.242; p=0.015 and HR=0.273; 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.
- Remission and LLDAS are associated with lower probability of damage in Latin American patients with SLE.

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 accrual 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, LLADS) has been proposed by the Asia Pacific Lupus Collaboration (APLC). This definition includes the following: SLEDAI-2K \(\leq 4\), which allows a low level of disease activity, without activity in major organ systems or new disease activity, PGA \(\leq 1\), 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 LLADS.

In Hispanic populations (from the USA and Latin America), remission and LLADS 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 LLADS 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 LLADS 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 time-censored survival regression models were used. Three models were done: (1) remission versus not on remission; (2) LLADS (including those on remission) versus not on LLADS; and (3) remission and LLADS (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 LLADS at the index visit were performed.

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

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

**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 LLADS, 726 (68.4%) visits corresponded to LLADS and 336 (31.6%) not on LLADS. The proportion of the visits the patients were on remission or LLADS 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 LLADS (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, model 2).

**Table 1** Characteristics of the patients at baseline

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

SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2K.
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 0.731; 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...
previous reports. 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.

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.
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-ESALUD-11, 271-CE-IDIG-RAA-ESALUD-13, 302-CE-IDG-G-RAA-14, 3027-OCID-G-RAA-ESALUD-15 and 4072-OCID-G-HNGAI-ESALUD-2017). Participants gave informed consent to participate in the study before taking part.

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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-Quiróz http://orcid.org/0000-0002-3638-7054
Claudia Elena-Fitzcarrald http://orcid.org/0000-0001-7271-2523

REFERENCES